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Dietary patterns affecting cardiovascular health

Edited by
Iain Brownlee, Amedeo Amedei, Galya Bigman and Stefano Fumagalli

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Dietary patterns affecting cardiovascular health

Topic editors
Iain Brownlee — Northumbria University, United Kingdom
Amedeo Amedei — University of Florence, Italy
Galya Bigman — University of Maryland, United States
Stefano Fumagalli — University of Florence, Italy

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EDITED AND REVIEWED BY
Michael Mathai,
Victoria University, Australia

*CORRESPONDENCE
Galya Bigman
gbigman@som.umaryland.edu

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Editorial: Dietary patterns affecting cardiovascular health

Galya Bigman[1]* and Amedeo Amedei[2]

[1]Department of Epidemiology and Public Health, School of Medicine, University of Maryland, Baltimore, MD, United States, [2]University of Florence, Florence, Italy

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Editorial on the Research Topic
Dietary patterns affecting cardiovascular health

Over half a billion people globally are affected by cardiovascular diseases (CVDs), which caused 20.5 million deaths in 2021—nearly a third of all global deaths and a significant increase from previous estimates of 12.1 million deaths in 1990. Ischaemic heart disease (IHD) and stroke account for approximately 85% of all CVD deaths (1). This burden disproportionately affects low- and middle-income countries, where four out of five CVD deaths occur (1).

Poor dietary habits such as high sodium intake, low whole grain consumption, and inadequate fruit intake significantly impact cardiovascular health globally. Addressing these habits through global public health strategies, including food- and nutrient-based guidelines, is crucial for CVDs prevention and management (2). However, the specific mechanisms linking dietary components to cardiovascular function require further elucidation and recent decades have seen a shift toward assessing overall dietary patterns rather than isolated food components.

Therefore, this Research Topic, "*Dietary Patterns Affecting Cardiovascular Health*," aims to consolidate new research on dietary patterns and their impact on cardiovascular health, especially in underrepresented populations, to deepen our understanding of diet-health interactions.

Overall, we received 62 submissions, with 40 being rejected following initial editorial assessment. Ultimately, 22 articles underwent one or more rounds of peer review, exploring various dietary factors such as dietary risks, low fruit consumption, sodium intake, lycopene, and supplements like thiamine and folic acid. The studies also investigated different dietary patterns such as carbohydrate restriction, ketogenic-like diets, and ultra-low-fat diets. Additional topics included ultra-processed foods, high-fat meals, and the effects of three diet interventions on weight loss (low carbohydrate, low fat, and low calorie). Furthermore, research covered plant-based vs. animal-based protein intake, dietary intake of live microbes, and the dietary inflammation index.

Data sources encompassed the Global Burden of Disease (GBD) 2019, national surveys from the USA, Korea, the UK Biobank and the FinnGen, as well as data from Tehran, China, and Pakistan and Belt and Road (B&R) countries. Studies employed different methodologies including observational epidemiological studies, randomized controlled trials, Mendelian randomization analyses, and reviews.

The studies explored diverse aspects of cardiovascular health (CVH) such as CVDs, IHD, stroke, myocardial infarction (MI), vascular function, cardiometabolic outcomes, heart failure (HF), abdominal aortic calcification (AAC), severe coronary artery disease (CAD), atherosclerotic cardiovascular disease (ASCVD), acute coronary syndrome (ACS), hypertension (HTN), H-type hypertension and dyslipidemia. Our summary focuses on the main dietary factors investigated in these studies as follows:

Three studies utilized the GBD 2019 data to examine the global burden of CVDs from 1990 to 2019 and the relationships with different dietary risks. Pan et al. found that the number of deaths and disability-adjusted life years (DALYs) due to a diet low in fruits increased by 31.5% and 27.4%, respectively. Among the tertiary diseases, IHD, stroke, and diabetes and kidney disease were the top three contributors to that increase, with the burden being significantly higher in the elderly. In Zhang Y. et al. although there was a significant overall reduction in stroke mortality and DALYs attributable to dietary risk across Belt and Road (B&R) countries, there were geographical disparities in age-standardized rates (ASR) for stroke mortality and DALYs, with some regions experiencing rapid declines (e.g., Estonia in Eastern Europe) while others observed increases (e.g., the Philippines). Yan et al. focused on regional and country levels across China and Pakistan and found that the all-ages CVD burden attributable to dietary risks and high BMI increased by ~2–3-fold in China and by 3–5-fold in Pakistan.

Two studies have examined sodium intake and CVDs using Mendelian randomization analysis. This approach relies on genetic variants as instrumental variables, providing more robust results compared to traditional observational studies, which have shown inconsistent outcomes. Fu et al. measured the sodium intake by the urinary sodium/creatinine ratio (UNa/UCr), which showed a significant positive relationship with seven specific CVDs types. In contrast, Yuan et al. also suggest that higher sodium intake is associated with an increased risk of HF as well as with HTN. However, they noted that excessively low sodium intake may not necessarily be beneficial, with maximum benefits observed at a sodium intake level of around 3,000 mg/day.

Three studies focused on a specific nutrient, where two administrated supplementations and one by analyzing FFQ data. Chen et al. conducted a randomized clinical trial with 1,567 Chinese adults aged ≥45 years with H-type HTN, defined as essential HTN with an increased plasma homocysteine level (≥10 μmol/L), which accounts for about 75% of HTN among Chinese patients. They showed that 0.8 mg of folic acid is the optimal dosage for balancing efficacy (increasing 5-methyl tetrahydrofolic acid [5-MTHF] and lowering homocysteine) while minimizing the undesirable elevation of unmetabolized folic acid (UMFA), which is due to excessive intake of folic acid based on previous research. Yue et al. aimed to determine the survival benefit of thiamine supplementation in critically ill patients with MI in the ICU using a retrospective cohort analysis of medical records. The results showed that thiamine supplementation significantly decreased the risk of in-hospital, 30-day, and 90-day mortality, suggesting that thiamine use might be associated with better survival outcomes in critically ill MI patients. Finally, Amjadi et al. conducted a Tehran-based case-control study using a 237-item FFQ to assess dietary lycopene intake. They analyzed data from 443 IHD patients and 443 controls, finding 33% lower odds of IHD in the highest vs. lowest quartile of lycopene intake ($p = 0.036$).

Five studies examined the association between different macronutrients and CVDs. Angelotti et al. analyzed a nationally representative sample of over 35,000 US individuals followed for an average of 10 years. They found that carbohydrate restriction (<45% of energy intake) was not associated with increased or decreased mortality from all causes, CVD, or cardiometabolic disease. This held true even after stratifying the analysis by different fat types and amounts. Aronica et al. analyzed the DIETFITS trial, which compared weight loss and cardiometabolic outcomes between participants following either a ketogenic-like diet (KLD) or an ultra low-fat diet (ULF) for 3 and 12 months. Less than 10% of participants maintained strict KLD or ULF diets at 3 months. Overall, extreme dietary restriction of fat or carbohydrates led to substantial initial benefits in weight loss and improvement in insulin sensitivity, with slight advantages in diet quality and blood lipid parameters favoring KLD over ULF after 12 months despite dietary relapse.

Losavio et al. examined factors influencing weight loss success across three diet interventions (low carbohydrate, low fat, and low calorie) among obese patients. Despite similar average weight loss of -5.1 ± 4.0 kg over 12–16 weeks across all diets, significant inter-individual variation was observed in weight loss outcomes. Each diet type demonstrated unique cardiometabolic health benefits, highlighting the importance of personalized diet interventions to enhance weight loss and improve overall cardiometabolic outcomes. Jung et al. analyzed data from Korean adults aged 40 years and older to examine the association between the percentage of energy intake from ultra-processed foods (UPFs) and CVH metrics defined by the American Heart Association. It was found that individuals in the highest quartile of UPF intake had a 26% higher likelihood of having inadequate CVH compared to those in the lowest quartile. The study highlights the potential benefits of limiting UPF consumption as a preventive measure against CVDs. Lastly, Szczepańska et al. assessed dietary habits among MI patients, highlighting frequent consumption of refined carbohydrates like white bread and pasta. Despite insights from the pro-Healthy Diet Index, the study suggests potential dietary errors needing further investigation due to limitations in sample size and assessment methods.

Two studies focused on amino acids intake. Gao and Hou reviewed the recent evidence linking branched-chain amino acids (BCAAs)—leucine, isoleucine, and valine—with HF, a critical stage in cardiovascular diseases with high mortality and limited treatment options. They explore complex metabolic pathways, revealing how disrupted BCAA metabolism is associated with conditions such as hypertension, obesity, and atherosclerosis, contributing to HF progression. They discusses therapeutic strategies, the potential of modulating BCAAs metabolism to treat heart failure, and consider BCAAs and their metabolites as biomarkers for assessing cardiac metabolic risk. Chung et al. investigated the association between amino acid intake and dyslipidemia in Korean adults using data from the Ansan and Ansung Study and the Health Examinee Study. They analyzed data from over 35,000 participants initially without dyslipidemia, with an average follow-up of 5.7 years. Higher intake of essential

and nonessential amino acids was associated with a reduced risk of dyslipidemia. Plant-based protein intake showed a negative association, while animal-based protein intake did not significantly affect dyslipidemia risk after adjusting for energy-adjusted fat intake. These findings suggest that amino acid intake, regardless of protein source, may have a protective effect against dyslipidemia.

Two other studies examine the potential of gut microbiota in relations with CVDs. Huo et al. explored the association between dietary intake of live microbes and AAC, using data from the National Health and Nutrition Examination Survey (NHANES). The results showed that higher intake of dietary live microbes was significantly associated with a lower risk of severe AAC and decreased AAC scores after adjusting for covariates and suggested a potential protective effect of dietary live microbes against AAC. Jiao et al. reviewed the growing evidence on the therapeutic potential of gut microbiota (GM) in addressing HTN. Using bibliometric analysis tools like CiteSpace and VOSviewer, the study identified 1,730 articles published from 2014 to 2023. The research spans 88 countries and involves 9,573 authors across 593 journals, highlighting the global interest and collaboration in this field. Key topics include GM metabolites, high-salt diet, and the impact of conditions like metabolic syndrome and chronic kidney disease on HTN.

Two studies address anti-inflammatory properties in relation with CVDs. Dadaei et al. explored the relationship between the dietary inflammation index (DII) and severe CAD. Using data from 275 adults undergoing elective angiography, DII was measured using a valid semi-quantitative 168-item food frequency questionnaire (FFQ). The study found that individuals with higher DII scores (indicating higher intake of pro-inflammatory foods) had significantly increased odds of severe CAD, hypercholesterolemia, reduced HDL-cholesterol levels, and hypertension compared to those with lower DII scores (indicating higher intake of anti-inflammatory foods). Zhang J. et al. investigated the relationship between composite dietary antioxidant index (CDAI) and estimated 10-year ASCVD risk among U.S. adults using data from the NHANES. It included 10,984 adults aged 18 years and above. The study found that higher CDAI scores, indicating greater dietary antioxidant intake, were associated with a lower 10-year ASCVD risk after adjusting for potential confounders.

Lastly, there were two studies that focused on psychological factors. So et al. assessed dietary and psychological factors in Korean patients with an ACS compared to controls. ACS patients showed higher intake of sweets and fish/seafood, higher levels of depressive symptoms, and lower life satisfaction across various domains. High sweet intake and low total life satisfaction scores independently contribute to increased risk of ACS, with a synergistic interaction further amplifying their impact on ACS development. Baynham et al. investigated how consuming a high-fat meal exacerbates the negative impact of mental stress on vascular function. The results showed that the high-fat meal significantly increased plasma triglyceride levels compared to the low-fat meal. Both groups experienced similar acute impairments in endothelial function immediately after stress, but those who consumed the high-fat meal showed prolonged impairment 90 min post-stress.

In summary, all the studies included in this Research Topic either provided insight on well-established nutrients such as sodium and folic acids to establish optimal intake, or they offered new insights on popular dietary patterns such as carbohydrate restriction, ketogenic-like diets, ultra-low-fat diets, and plant-based protein diet, along with different approaches for weight loss. Additionally, specific mechanisms linking dietary components were examined, including live microbes and the dietary inflammation index. Finally, they explored the interplay between psychological disorders, diets, and CVDs, an area that warrants further investigation. Clearly, additional research is necessary to replicate these findings and to solidify their implications.

To conclude, we would like to express our profound gratitude to "Frontiers in Nutrition" for the opportunity to serve as editors for this Research Topic. This challenging and motivating experience has been highly educational, and we look forward to continuing this endeavor. We extend our heartfelt thanks to the contributing authors for sharing their valuable research, which we believe will significantly impact clinical practice. Lastly, we are deeply appreciative of our reviewers for their time and insights, which have undoubtedly enhanced the quality of these studies.

Author contributions

GB: Conceptualization, Writing – original draft, Writing – review & editing. AA: Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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EDITED BY
Iain Brownlee,
Northumbria University, United Kingdom

REVIEWED BY
Muhammad Fawad,
Zhejiang University, China
Abbas Khan,
Lahore College for Women University, Pakistan

*CORRESPONDENCE
Xiuzhen Yan
✉ 378767014@qq.com
Nawsherwan
✉ nawshermkd177@gmail.com

†These authors have contributed equally to this work and share first authorship

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Epidemiological trend and age-period-cohort effects on cardiovascular disease mortality and disability-adjusted life years attributable to dietary risks and high body mass index at the regional and country level across China and Pakistan

Wu Yan[1†], Xiuzhen Yan[2*†], Sumaira Mubarik[3] and Nawsherwan[4*]

[1]Department of Information, Zhongshan Hospital of Xiamen University, School of Medicine, Xiamen University, Xiamen, China, [2]Department of Hematology, Zhongshan Hospital of Xiamen University, School of Medicine, Xiamen University, Xiamen, China, [3]Department of Epidemiology and Biostatistics, School of Public Health, Wuhan University, Wuhan, Hubei, China, [4]Xiamen Cardiovascular Hospital of Xiamen University, School of Medicine, Xiamen University, Xiamen, China

Background: Modifiable risk factors are major drivers of cardiovascular disease (CVD). We aimed to determine the epidemiological trend and age-period-cohort effects on CVD burden attributable to dietary risks and high body mass index (BMI) across China and Pakistan from 1990 to 2019.

Methods: Data on the all-ages and age-specific CVD burden, age-standardized CVD mortality and disability-adjusted life years (DALYs) rates were obtained from the Global Burden of Disease Study 2019. Joinpoint regression analysis was conducted to find temporal trends and age-period-cohort (APC) modeling was used to estimate age, period, and cohort effects on CVD burden.

Results: Between 1990 and 2019, the all-ages CVD burden attributable to dietary risks and high BMI increased by ~2-3-fold in China and by 3-5-fold in Pakistan. The diet-related CVD age-standardized mortality rate (ASMR) and age-standardized disability-adjusted life years (DALYs) rate significantly decreased in China but increased in Pakistan. Both countries showed a marked increasing trend of CVD ASMR and the age-standardized DALYs rate attributable to high BMI. Taiwan in China showed a remarkable reduction in CVD burden. However, in Pakistan, all regions observed a significantly increasing trend of CVD burden attributable to modifiable risk factors. A higher risk ratio of premature CVD mortality (<70years) was observed among Chinese attributable to high BMI and among Pakistani attributable to dietary risks. In China, early birth cohorts showed a higher risk ratio and recent birth cohorts experienced a lower risk ratio of CVD burden compared with Pakistan.

Conclusion: In conclusion, dietary risks and high BMI caused a huge CVD burden across China and Pakistan.

KEYWORDS

cardiovascular diseases, mortality, dietary risks, high body mass index, nursing care, China, Pakistan

Introduction

Cardiovascular disease (CVD) caused 18.6 million deaths worldwide and is considered the leading cause of premature mortality in 2019. Cardiovascular diseases (CVDs), particularly ischemic heart disease (IHD) and stroke accounted for 9.1 million and 6.5 million deaths in the year 2019, respectively (1). By 2030, CVD-related deaths would be more than 23 million across the globe (2). World Health Organization (WHO) estimated that more than three-quarters of CVDs deaths occurred in low- and middle-income countries (LMICs) which is considered a growing epidemic problem (3). Among LMICs, China and Pakistan are home to 1.45 billion and 0.23 billion people and ranked first and fifth with the largest population in 2022 in the world, respectively (4). Both China and Pakistan experiencing an increasing trend of CVD burden (5). The number of CVD deaths increased in China (2.42 million to 4.58 million) and Pakistan (0.17 million to 0.34 million) from 1990 to 2019 (1).

The huge increasing CVD burden in China and Pakistan could be attributed to several modifiable risk factors (1). The United Nations set a target to reduce premature CVD mortality by 25% at the end of 2025 attributable to behavioral and biological risk factors (6). Behavioral and metabolic risk factors such as dietary risks and high body mass index (BMI) are major drivers of CVD. In the GBD study 2019, dietary risks are either an over-consumed diet (sodium, trans-fatty acids, sugar-sweetened beverages, red meat, and processed meat) or an under-consumed diet (whole grains, legumes, vegetables, fruits, nuts and seeds, milk, fiber, calcium, omega-3 fatty acids from seafood, and polyunsaturated fatty acids) (1, 7). High BMI ($\geq$25 kg/m^2) is considered an epidemic worldwide. High BMI exacerbates CVD risk factors including blood pressure, lipids, blood sugars, and inflammation, and has a linear association with coronary heart diseases. Globally, dietary risks and high BMI caused 6.8 million and 3.2 million deaths and 153 million and 86 million disability-adjusted life years (DALYs) in 2019, respectively (1).

Several epidemiological studies reported a temporal trend of CVD attributable to smoking, low physical activity, air pollution, and dietary risks in the high socio-demographic index (SDI) and low SDI countries from 1990 to 2017 (8–10). However, no or limited studies (1, 5, 7, 11, 12) observed the recent times trends and age-period-cohort effects on CVD burden attributable to the dietary risk and high BMI at the regional and country level across China and Pakistan. In the age-period-cohort analysis, period and cohort effects would assist public health policymakers to determine the success of earlier health-policy interventions and identifying future targets (13). To provide advice and references for health policymakers, an accurate and comparable analysis of long-term CVD trends at the regional and country level is required. Therefore, we aimed to determine the epidemiological trend and age-period-cohort effect on CVD burden attributable to dietary risks and high BMI across China and Pakistan from 1990 to 2019.

Materials and methods

Data source

In this study, the data were extracted by sex (male, female, and both sex combined) from the global burden of diseases (GBD) free online database (GBD 2019)[1] (14) (accessed on July 7, 2022) from 1990 to 2019. In addition, all-ages deaths, the age-standardized mortality rate (ASMR), and age-specific data (i.e., from 25–29 years to 85–89 years) on CVD mortality and disability-adjusted life years (DALYs) attributable to dietary risks and high BMI were extracted. GBD is an international cooperative project that estimates the disease burden at regional, national, and global levels. GDB estimates the burden of disease indices including, prevalence, incidence, mortality rate, years of life lost (YLL), years lived with disability (YLD), and DALYs for several diseases and injuries. Moreover, the GBD data are provided by different organizations like World Bank Open Data, WHO, and Global Health Observatory for different political and social research. The GBD data is managed by the Institute for Health Metrics and Evaluation (IHME), University of Washington. Therefore, a waiver of informed consent was reviewed and approved by the University of Washington Institutional Review Board (15, 16).

Variables understudy

In the present study, the considered modifiable risk factors were dietary risks and high BMI ($\geq$25 kg/m^2). The dietary risk factor was a composite of an over-consumed diet (sodium, trans-fatty acids, sugar-sweetened beverages, red meat, and processed meat) and an under-consumed diet (whole grains, legumes, vegetables, fruits, nuts and seeds, milk, fiber, calcium, omega-3 fatty acids from seafood, and polyunsaturated fatty acids) (1). The outcome variables were ASMR, all-ages death numbers, and DALYs of CVD, ischemic heart disease (IHD), and ischemic stroke (IS) for China and Pakistan at the regional and country level from 1990 to 2019. Regions in Pakistan were Islamabad, Punjab, Sindh, Khyber Pakhtunkhwa (KPK), Balochistan, Azad Jammu & Kashmir (AJ& K), Gilgit-Baltistan (GB), and Taiwan in China. DALYs are defined as the sum of years lived with disability (YLDs) and years of life lost (YLLs) (16).

Statistical analysis

Joinpoint regression for trend analysis (1990–2019)

To assess the temporal trends of CVD, IHD, and IS burden, we estimated the average annual percentage change (AAPC) for CVD, IHD, and IS mortality and DALYs with joinpoint regression analysis. AAPC represents the trend of CVD, IHD, and IS burden in the whole period from 1990 to 2019. Additionally, AAPC is a weighted average of the yearly percentage change determined by the joinpoint model, with weights corresponding to the duration of the annual percentage change (APC) interval. The APC shows the CVD, IHD, and IS burden trend in each segment determined by using joinpoint regression software. From 1990 to 2019, we produced AAPCs and their 95% confidence intervals (CIs) for each trend segment identified by the model. Furthermore, we estimated AAPCs of CVD, IHD, and IS deaths for both sexes combined, males, and females. AAPC is considered significant when it is different from 0 at the alpha of 0.05.

1 http://ghdx.healthdata.org/gbd-results-tool

This analysis was conducted using the joinpoint regression program version 4.9.1.0 (April 2022) from the Surveillance Research Program of the U.S. National Cancer Institute (NCI).

Age-period-cohort analysis

The aim of the age-period-cohort (APC) analysis is to estimate the effects of age, period, and cohort on CVD burden attributable to modifiable risk factors. The age effect represents the association of CVD burden with different age groups. Period effect represents influencing factors, such as a series of historical events and environmental factors, and it reflects variation in the CVD burden over time that influences all age groups simultaneously. The cohort effect shows variations of CVD burden across birth cohorts born in the same year and changes in different lifestyles (17). The common problem associated with the APC analysis is collinearity (i.e., birth cohort = period - age). The APC model is affected by the linearity between two variables, so it is impossible to determine the three independent linear APC variables of age, period, and cohort. We used the APC model with the intrinsic estimator (IE), which is a new method to estimate the coefficients and solve the collinearity problem by generating a distinctive set of trend estimates independent of any arbitrary assignment of identifying limitations on age, period, or cohort coefficients that may not be verified in the data itself (18). Estimated coefficients for the age, period, and cohort effects were produced by the APC analysis using the IE method. The exponential value [exp(coef.) = ecoef.] was created from these coefficients, which denotes the risk ratio (RR) of a particular age, period, or birth cohort relative to the reference group.

In the APC model using the IE method, the age-specific CVD rates were appropriately categorized into 13 age groups (from 25–29 years to 85–89 years). It has 6 periods with 5-year intervals (from 1990–1994 to 2015–2019) and 18 birth cohorts (period-age) (from1905-1909 to 1990–1994). The general form of the APC model is written as $Y = \log(M) = \mu + \alpha age_i + \beta period_i + \gamma cohort_i + \varepsilon$; where, M is defined as the incidence rate in the age groups, α, β, and γ indicates the functions of age, period, and cohort effect, μ, and ε are the intercept item and the random error. The APC model was used to decompose the three trends and estimate efficient results (19). Moreover, the Akaike information criterion (AIC), and Bayesian information criterion (BIC) were used to estimate and analyze the degree of fitting of the model. The APC analysis was done using Stata 15.0 software (College Station, TX, USA).

Results

CVD burden attributable to dietary risks

For both sexes, the all-ages CVD deaths due to dietary risks significantly increased in China (0.9 million to 1.7 million) and in Pakistan (0.06 million to 0.15 million) by 89 and 150%, respectively during the study period. The CVD ASMR and the age-standardized DALYs rate in China significantly decreased by −1.2% (95%CI: −1.5, −0.9) and by −1.4% (95%CI: −1.7, −1.2) per year. However, in Pakistan, the ASMR of CVD and the age-standardized DALYs rate significantly increased by 0.7% (95%CI: 0.6, 0.7) and by 0.7% (95%CI: 0.6, 0.8) per year. At the regional level in China, Taiwan showed a remarkable reduction in CVD ASMR by −3.2% (95%CI: −3.5, −2.9) and age-standardized DALYs rate by −2.9% (95%CI, −3.1, −2.7). However, in Pakistan, all regions observed significantly increasing trends of CVD ASMR and age-standardized DALYs rate with the highest in KPK. Overall, male showed less improvement in CVD, IHD, and IS ASMR and age-standardized DALYs rate attributable to dietary risks than the female population across China and Pakistan (Tables 1–3; Supplementary Tables S1–S6; Figure 1; Supplementary Figure S1).

CVD burden attributable to high BMI

For both sexes, the all ages-CVD deaths attributable to high BMI remarkably increased in China by 4.0% (95%CI: 3.6, 4.3) and in Pakistan by 5.5% (95%CI: 5.4, 5.7) per year. Similarly, the ASMR of CVD and the age-standardized DALYs rate significantly increased in both China and Pakistan. At the regional level in China, Taiwan experienced a pronounced reduction in CVD ASMR by −2.3% (95%CI: −2.6, −2.0) and age-standardized DALYs rate by −1.7 (95%CI: −2.0, −1.5) per year. On the other hand, in Pakistan, all regions showed a significantly increasing trend of CVD ASMR and age-standardized DALYs rates notably in Sindh, Balochistan, and AJ&K. Moreover, Islamabad experienced higher CVD ASMR and DALYs rates during the study period. The male population showed the fastest increasing trend of CVD, IHD, and IS ASMR and age-standardized DALYs rate than the female population in both countries (Tables 1–3; Supplementary Tables S1–S6; Figure 1; Supplementary Figure S1).

Age-period-cohort effect on CVD burden attributable to dietary risks and high BMI

The risk ratio of CVD mortality and DALYs due to dietary risks and high BMI markedly increased with age. China had the highest risk of CVD mortality across all age groups, particularly at older ages than Pakistan. The risk ratio of premature CVD mortality (<70 years) attributable to dietary risks was higher among Pakistanis. However, the Chinese population showed a higher risk ratio of premature CVD mortality attributable to high BMI. Period effects were generally higher for CVD mortality and DALYs attributable to high BMI with the most remarkable in Pakistan. Compared to the reference cohorts, the risk ratio of cohort effect on CVD burden attributable to dietary risks and high BMI showed a similar downward trend among the Chinese and Pakistani populations. Early birth cohorts in China had a higher risk ratio of CVD mortality and DALYs than in Pakistan. However, recent birth cohorts in China showed relatively a lower risk ratio of CVD burden attributable to modifiable risk factors (Tables 4, 5; Figures 2, 3; Supplementary Figures S2, S3).

Discussion

The present GBD study 2019 provides the epidemiological trend (1990–2019) and age-period-cohort effect on CVD mortality and DALYs attributable to dietary risks and high BMI at the regional and country level across China and Pakistan. We observed that the all-ages CVD deaths and DALYs due to dietary risks and high BMI significantly increased in China and Pakistan during the study period. The diet-related CVD ASMR and the age-standardized DALYs rate significantly decreased in China.

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TABLE 1 The temporal trend in the burden of CVD mortality attributable to the dietary risk and high BMI for both sexes across China and Pakistan from 1990 to 2019.

Dietary risks	ASMR/100,000			Deaths, *n*×10,000		
CVD	1990 (95%UI)	2019 (95%UI)	AAPC (95%CI)	1990 (95%UI)	2019 (95%UI)	AAPC (95%CI)
China	143 (185, 107)	101 (132, 74)	−1.2 (−1.5, −0.9)	99 (126, 74)	176 (230, 130)	2.0 (1.7, 2.3)
Taiwan	76 (102, 54)	29 (42, 19)	−3.2 (−3.5, −2.9)	0.9 (1.3, 0.7)	1.2 (1.7, 0.7)	0.6 (0.3, 0.9)
Pakistan	127 (159, 98)	153 (193, 121)	0.7 (0.6, 0.7)	6.7 (8.3, 5.2)	15 (19, 12)	2.9 (2.7, 3.1)
Islamabad	110 (143, 79)	125 (161, 92)	0.5 (0.4, 0.6)	0.02 (0.03, 0.01)	0.08 (0.1, 0.06)	4.7 (4.6, 4.8)
Punjab	135 (169, 104)	156 (201, 122)	0.5 (0.5, 0.6)	4.2 (5.3, 3.3)	8.9 (11.4, 6.9)	2.6 (2.4, 2.7)
Sindh	117 (152, 85)	147 (193, 110)	0.8 (0.7, 0.9)	1.2 (1.5, 0.8)	3.1 (4.1, 2.2)	3.4 (3.4, 3.5)
KPK	109 (151, 76)	150 (201, 106)	1.1 (1.0, 1.2)	0.8 (1.1, 0.5)	2.2 (3.1, 1.5)	3.5 (3.3, 3.6)
Balochistan	122 (165, 86)	162 (217, 119)	1.0 (0.9, 1.1)	0.2 (0.3, 0.1)	0.6 (0.8, 0.4)	3.1 (3.0, 3.2)
AJ&K	122 (163, 90)	152 (197, 111)	0.8 (0.7, 0.9)	0.2 (0.2, 0.1)	0.3 (0.4, 0.2)	2.6 (2.5, 2.7)
GB	121 (167, 85)	161 (220, 112)	1.0 (0.8, 1.2)	0.03 (0.04, 0.02)	0.1 (0.1, 0.07)	4.3 (4.2, 4.5)
High BMI						
China	22 (50, 5)	29 (51, 12)	0.9 (0.4, 1.4)	17 (38, 4)	54 (94, 24)	4.0 (3.6, 4.3)
Taiwan	29 (47, 12)	15 (24, 7)	−2.3 (−2.6, −2.0)	0.4 (0.7, 0.2)	0.5 (0.9, 0.2)	1.0 (0.7, 1.3)
Pakistan	23 (49, 6)	55 (87, 29)	3.1 (2.9, 3.2)	1.3 (2.7, 0.3)	6.3 (9.8, 3.4)	5.5 (5.4, 5.7)
Islamabad	41 (68, 20)	77 (110, 50)	2.2 (2.1, 2.4)	0.01 (0.01, 0.004)	0.06 (0.09, 0.04)	6.6 (6.4, 6.8)
Punjab	25 (52, 6)	57 (89, 30)	2.9 (2.7, 3.1)	0.8 (1.7, 0.2)	3.6 (5.7, 1.9)	5.2 (5.0, 5.4)
Sindh	22 (48, 6)	63 (99, 36)	3.7 (3.5, 3.8)	0.2 (0.5, 0.1)	1.5 (2.3, 0.8)	6.5 (6.4, 6.6)
KPK	15 (37, 3)	30 (63, 9)	2.4 (2.2, 2.5)	0.1 (0.3, 0.1)	0.5 (1.1, 0.1)	4.8 (4.6, 5.0)
Balochistan	23 (51, 6)	65 (106, 34)	3.6 (3.4, 3.7)	0.1 (0.1, 0.01)	0.3 (0.5, 0.1)	5.9 (5.7, 6.0)
AJ& K	25 (51, 7)	70 (107, 40)	3.6 (3.5, 3.8)	0.03 (0.06, 0.01)	0.1 (0.2, 0.09)	5.7 (5.6, 5.8)
GB	22 (51, 5)	61 (101, 29)	3.5 (3.4, 3.6)	0.01 (0.01, 0.001)	0.05 (0.08, 0.02)	6.9 (6.8, 7.1)

KPK, Khyber Pakhtunkhwa; AJ&K, Azad Jammu & Kashmir; GB, Gilgit Baltistan; CVD, cardiovascular disease; ASMR, age-standardized mortality rate; BMI, body mass index; AAPC, average annual percent change.

However, the ASMR of CVD and the age-standardized DALYs rate attributable to dietary risks significantly increased in Pakistan. Both countries showed a marked increasing trend of CVD ASMR and the age-standardized DALYs rate attributable to high BMI. At the regional level in China, Taiwan showed a remarkable reduction in CVD ASMR and age-standardized DALYs rate attributable to dietary risks and high BMI. However, in Pakistan, all regions observed significantly increasing trends of CVD ASMR and age-standardized DALYs rate attributable to aforementioned modifiable risk factors.

Age-period-cohort analysis revealed that the risk ratio of premature CVD mortality (<70 years) attributable to dietary risks was higher among Pakistanis. On the other hand, the Chinese population showed a higher risk ratio of premature CVD mortality attributable to high BMI. The risk ratio of period effect on CVD burden attributable to modifiable risk factors significantly increased across both countries. In China, early birth cohorts showed a higher risk and recent birth cohorts experienced a lower risk of CVD burden compared with Pakistan.

Temporal trend in CVD burden attributable to dietary risks

CVDs are the primary consequences of dietary risks and one-third of global CVD deaths are attributed to dietary risks (1). Our study found that the all-ages CVD deaths and DALYs due to dietary risks nearly doubled in China and tripled in Pakistan. The upward trend in all-ages CVD burden could be explained by population growth and aging across China and Pakistan (1). Aging has a profound impact on heart health and the arterial system and has been linked with a higher risk of CVD (20). Globally, adults aged ≥65 years increased by 3-fold over the last four decades. The older population in China and Pakistan is increasing and is projected to double by 2050 (4). It suggests that both countries are needed to significantly invest in the primary and secondary prevention of CVD among the older population.

Our findings show that ASMR of CVD and the age-standardized DALYs rate attributable to dietary risks significantly decreased in China as well as at the regional level in Taiwan. The reduction in CVD burden attributable to dietary risks could be explained by improvements in diet quality and changes in diet patterns among the Chinese population. The diet quality as measured by China Dietary Guidelines Index 2018 (CDGI-2018) improved from 41.7 to 52.4 during 1991–2015 among Chinese adults aged 18 years or older. Energy intake from high-quality protein and high-quality fats significantly increased whereas consumption of low-quality carbohydrates significantly decreased (21). A lower risk of CVD mortality was observed among Chinese adults having higher diet index scores and optimal consumption of vegetables, fruits, and lower consumption of red meat (22).

Moreover, the increasing trend in urbanization, higher education level, and socioeconomic status have improved diet quality among the

TABLE 2 The temporal trend in the burden of CVD DALYs attributable to the dietary risk and high BMI for both sexes across China and Pakistan from 1990 to 2019.

Dietary risks	Age-standardized DALYs/100,000			DALYs, *n*×10,000		
CVD	1990 (95%UI)	2019 (95%UI)	AAPC (95%CI)	1990 (95%UI)	2019 (95%UI)	AAPC (95%CI)
China	3,061 (3,839, 2,345)	2,011 (2,572, 1,505)	−1.4 (−1.7, −1.2)	2,604 (3,242, 2008)	3,904 (4,970, 2,918)	1.5 (1.2, 1.7)
Taiwan	1,556 (2045, 1,133)	660 (917, 456)	−2.9 (−3.1, −2.7)	24 (31, 17)	25 (35, 17)	0.1 (−0.1, 0.3)
Pakistan	2,950 (3,625, 2,321)	3,602 (4,516, 2,839)	0.7 (0.6, 0.8)	177 (216, 140)	450 (564, 354)	3.3 (3.2, 3.4)
Islamabad	2,387 (3,126, 1,680)	2,650 (3,541, 1888)	0.4 (0.3, 0.5)	0.6 (0.8, 0.4)	2.5 (3.5, 1.6)	5.0 (4.8, 5.1)
Punjab	3,154 (3,918, 2,471)	3,691 (4,708, 2,868)	0.6 (0.5, 0.6)	109 (135, 86)	258 (331, 200)	3.0 (2.9, 3.1)
Sindh	2,700 (3,493, 1977)	3,425 (4,515, 2,547)	0.9 (0.8, 1.0)	31 (41, 23)	91 (122, 67)	3.8 (3.7, 3.9)
KPK	2,551 (3,514, 1810)	3,525 (4,751, 2,514)	1.1 (1.0, 1.2)	22 (30, 15)	64 (87, 45)	3.7 (3.5, 3.9)
Balochistan	2,863 (3,926, 1965)	3,880 (5,208, 2,796)	1.1 (1.0, 1.2)	7 (10, 5)	20 (27, 14)	3.5 (3.4, 3.6)
AJ&K	2,798 (3,764, 2082)	3,422 (4,519, 2,500)	0.7 (0.6, 0.8)	3.9 (5.2, 2.9)	8.9 (11, 6.4)	2.9 (2.8, 3.0)
GB	2,877 (4,004, 2003)	3,881 (5,319, 2,687)	1.1 (0.9, 1.3)	1.0 (1.4, 0.6)	3.5 (4.9, 2.4)	4.5 (4.3, 4.7)
High BMI						
China	576 (1,251, 141)	747 (1,253, 343)	0.9 (0.5, 1.3)	532 (1,129, 132)	1,500 (2,494, 694)	3.6 (3.3, 4.0)
Taiwan	744 (1,188, 342)	450 (699, 247)	−1.7 (−2.0, −1.5)	12 (19, 5)	16 (25, 9)	0.9 (0.7, 1.2)
Pakistan	642 (1,325, 176)	1,539 (2,384, 842)	3.1 (3.0, 3.3)	40 (83, 11)	206 (317, 113)	5.8 (5.6, 6.0)
Islamabad	1,093 (1,804, 540)	1,955 (2,787, 1,269)	2.1 (1.9, 2.2)	0.3 (0.5, 0.1)	2.1 (3.1, 1.2)	6.8 (6.5, 7.1)
Punjab	698 (1,436, 190)	1,601 (2,467, 862)	3.0 (2.8, 3.1)	25 (51, 6)	119 (184, 65)	5.6 (5.4, 5.7)
Sindh	617 (1,276, 171)	1,740 (2,683, 998)	3.7 (3.5, 3.9)	7.7 (16, 2.1)	50 (77, 28)	6.7 (6.6, 6.9)
KPK	440 (1,050, 86)	853 (1,717, 261)	2.3 (2.1, 2.5)	4.1 (9.7, 0.8)	16 (33, 5)	4.9 (4.8, 5.1)
Balochistan	658 (1,421, 175)	1,839 (2,988, 966)	3.7 (3.4, 3.9)	1.8 (4.1, 0.4)	10 (17, 5)	6.2 (6.1, 6.3)
AJ&K	688 (1,412, 203)	1,878 (2,845, 1,112)	3.6 (3.3, 3.9)	1.1 (2.1, 0.2)	5.3 (8.1, 3.1)	5.9 (5.8, 6.0)
GB	629 (1,417, 152)	1,721 (2,866, 842)	3.6 (3.5, 3.7)	0.2 (0.5, 0.1)	1.7 (2.8, 0.8)	7.1 (7.0, 7.2)

KPK, Khyber Pakhtunkhwa; AJ&K, Azad Jammu & Kashmir; GB, Gilgit Baltistan; CVD, cardiovascular disease; DALYs, disability-adjusted life years; BMI, body mass index; AAPC, average annual percent change.

Chinese population and resulted in lower CVD deaths (23, 24). The most recently launched public health and nutrition-related policy "Healthy China Action Plan (2019–2030)" including the popularization of health knowledge and promotion of a balanced diet could further improve diet quality and reduce diet-related CVD mortality and morbidity (25). The diet quality and dietary habits in Taiwan significantly improved such as higher consumption of vegetables, fruits, whole grains, fish, soy products, nuts, and seeds (26, 27). These positive changes in dietary habits could explain the remarkable reduction in the CVD burden at the regional level in Taiwan.

We observed significantly increasing trends of CVD ASMR and age-standardized DALYs rate attributable to dietary risks in Pakistan and across all regions with the highest in KPK. Pakistan is a country with a low socioeconomic status (SES). Poverty and low SES affect diet quality and are associated with adverse health outcomes (28). Moreover, Pakistan is an agricultural country with a large population that lives in rural areas with a lower *per capita* income (31%) than in urban areas. One-fifth of the population is malnourished and one-third of the population has no access to adequate nutrition (28). All these interrelated factors could explain a marked increase in CVD burden attributable to dietary risks. A previous study also reported that the Pakistani traditional diet was associated with high cardiovascular risk factors (29). The majority of Pakistani people eat deep-frying foods and foods high in saturated fats which ultimately increased the risk of CVD (30).

Pakistan is also initiated public health and nutrition-related policy to promote health knowledge and awareness about healthy food choices as adopted by China (25). Over the last few years, several nutritional programs have been launched by the government and non-government organizations to raise nutritional awareness among the Pakistani population. The government of Pakistan has initiated health and nutrition programs at the school level to provide relevant nutritional information to students (31, 32). At the community level, Nutrition International (NI) works with the Pakistani government to combat micronutrient malnutrition such as deficiency of iron, zinc, folic acid, and vitamin A (32). In the coming years, these nutritional intervention and awareness programs will gradually decrease the CVD burden attributable to dietary risks among the Pakistani population.

Temporal trend in CVD burden attributable to high BMI

Obesity or high BMI is a growing public health epidemic problem and its prevalence increased by 3-fold over the last four and half decades across the globe. High intake of energy-dense foods, lower energy expenditure, and low physical activity lead to obesity (1, 33).

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TABLE 3 The temporal trend in the burden of CVD AMSR and DALYs attributable to the dietary risk and high BMI in males and females across China and Pakistan from 1990 to 2019.

CVD ASMR	Male (AAPC) (95%CI)		Female (AAPC) (95%CI)	
	Dietary risks	High BMI	Dietary risks	High BMI
China	−0.8 (−1.1, −0.5)	1.5 (1.3, 1.7)	−1.7 (−1.9, −1.4)	0.2 (−0.1, 0.6)
Taiwan	−2.6 (−2.9, −2.2)	−1.3 (−1.7, −1.0)	−3.9 (−4.2, −3.6)	−3.4 (−3.7, −3.2)
Pakistan	1.0 (0.9, 1.1)	3.5 (3.4, 3.7)	0.3 (0.3, 0.4)	2.6 (2.4, 2.7)
Islamabad	0.9 (0.8, 1.0)	3.0 (2.7, 3.2)	−0.1 (−0.2, −0.1)	1.4 (1.3, 1.6)
Punjab	0.9 (0.8, 1.0)	3.4 (3.3, 3.5)	0.1 (0.1, 0.2)	2.4 (2.3, 2.5)
Sindh	1.0 (0.9, 1.1)	4.0 (3.8, 4.2)	0.6 (0.6, 0.7)	3.2 (3.1, 3.3)
KPK	1.4 (1.3, 1.5)	2.6 (2.4, 2.7)	0.8 (0.7, 0.9)	2.1 (1.9, 2.3)
Balochistan	1.2 (1.1, 1.3)	4.0 (3.7, 4.3)	0.8 (0.7, 0.9)	3.3 (3.1, 3.4)
AJ&K	1.1 (1.0, 1.2)	4.2 (4.0, 4.4)	0.4 (0.4, 0.5)	3.0 (2.8, 3.1)
GB	1.2 (1.0, 1.4)	3.9 (3.8, 4.0)	0.9 (0.7, 1.1)	3.3 (3.1, 3.4)
CVD DALYs				
China	−1.0 (−1.3, −0.7)	1.5 (1.2, 1.9)	−2.1 (−2.3, −1.8)	0.1 (−0.2, 0.2)
Taiwan	−2.3 (−2.6, −2.0)	−0.9 (−1.4, −0.5)	−3.7 (−3.9, −3.5)	−2.8 (−3.0, −2.6)
Pakistan	1.1 (1.0, 1.2)	3.6 (3.4, 3.8)	0.3 (0.2, 0.3)	2.6 (2.4, 2.7)
Islamabad	0.8 (0.7, 1.0)	2.8 (2.4, 3.1)	−0.3 (−0.4, −0.1)	1.2 (1.0, 1.4)
Punjab	1.0 (0.9, 1.1)	3.4 (3.3, 3.6)	0.1 (−0.1, 0.1)	2.5 (2.2, 2.7)
Sindh	1.1 (1.0, 1.2)	4.0 (3.8, 4.3)	0.6 (0.5, 0.6)	3.3 (3.1, 3.4)
KPK	1.5 (1.4, 1.7)	2.6 (2.5, 2.8)	0.7 (0.6, 0.8)	2.1 (1.9, 2.3)
Balochistan	1.4 (1.2, 1.5)	4.1 (3.8, 4.4)	0.8 (0.7, 0.9)	3.3 (3.1, 3.4)
AJ& K	1.2 (1.0, 1.3)	4.2 (4.0, 4.4)	0.3 (0.2, 0.4)	2.9 (2.7, 3.1)
GB	1.3 (1.2, 1.5)	4.0 (3.9, 4.1)	0.8 (0.6, 1.0)	3.2 (3.1, 3.4)

KPK, Khyber Pakhtunkhwa; AJ&K, Azad Jammu & Kashmir; GB, Gilgit Baltistan; CVD, cardiovascular disease; ASMR, age-standardized mortality rate; DALYs, disability-adjusted life years; BMI, body mass index; AAPC, average annual percent change.

High BMI exacerbates cardiovascular risk factors and increased the risk of CVD including hypertension, heart failure, and coronary heart disease (34). We observed that the all-ages CVD deaths and DALYs attributable to high BMI increased by 3-fold in China and by 5-fold in Pakistan. Moreover, the all-ages IHD, IS deaths and DALYs increased by 5-fold in China and by ~6-fold across Pakistan. The ASMR and age-standardized DALYs rate across all CVD categories significantly increased in China and Pakistan. All regions in Pakistan observed significantly increasing trends of CVD ASMR and age-standardized DALYs rate attributable to high BMI notably in Sindh, Balochistan, and AJ& K. However, Taiwan in China showed a marked reduction in CVD ASMR and age-standardized DALYs rate due to high BMI.

High BMI or obesity is a serious public health problem in China. More than half of the adult population and one-fifth of children and adolescents are overweight or obese and the rates are continuously rising in China (35). The continuously increasing burden of obesity could be driven by rapid economic growth. It has reduced poverty and impacted dietary habits, moving away from a traditional and balanced diet and adhering to ultra-processed junk food product. Physical activity substantially decreased with an increasingly sedentary lifestyle in China (36, 37). Such changes in diet patterns and lifestyle and other risk factors including genetic susceptibility, and psychosocial factors are implicated in the increasing trend of obesity in China and associated with a higher risk of CVD (36, 37). In the general Chinese population, obesity was associated with higher odds of CVDs (38).

Over the last two decades, several prevention and interventional programs have been implemented in China, however, obesity and chronic diseases such as CVD have not been effectively prevented and reduced yet (39). Recently in 2020, the National Health Commission of the People's Republic of China (China NHC) formulated a series of policies, guidelines, and recommendations, which aims to effectively control, prevent, and reduce obesity among Children and adolescents. Moreover, in 2021, the China NHC's Bureau of Disease Control and Prevention released a set of guidelines for obesity prevention and control among Chinese adults (40). In 2022, "The Expert Consensus on Obesity Prevention and Treatment" was issued which consisted of prevention and control strategies, and future recommendations (39). It reflects that China has made a great effort for obesity prevention which will ultimately decrease obesity-related CVD burden in the recent future. However, if these obesity-related policies and interventions have not effectively implemented, it is projected that about 65.3% of adults and 31.8% of children and adolescents could become overweight and obese by 2030 in China (35, 40).

Our findings show that the CVD ASMR and age-standardized DALYs rate attributable to high BMI markedly increased in Pakistan and across all regions. Pakistan with 50% of obesity is the tenth most obese nation in the world due to intake of a high-fat diet and

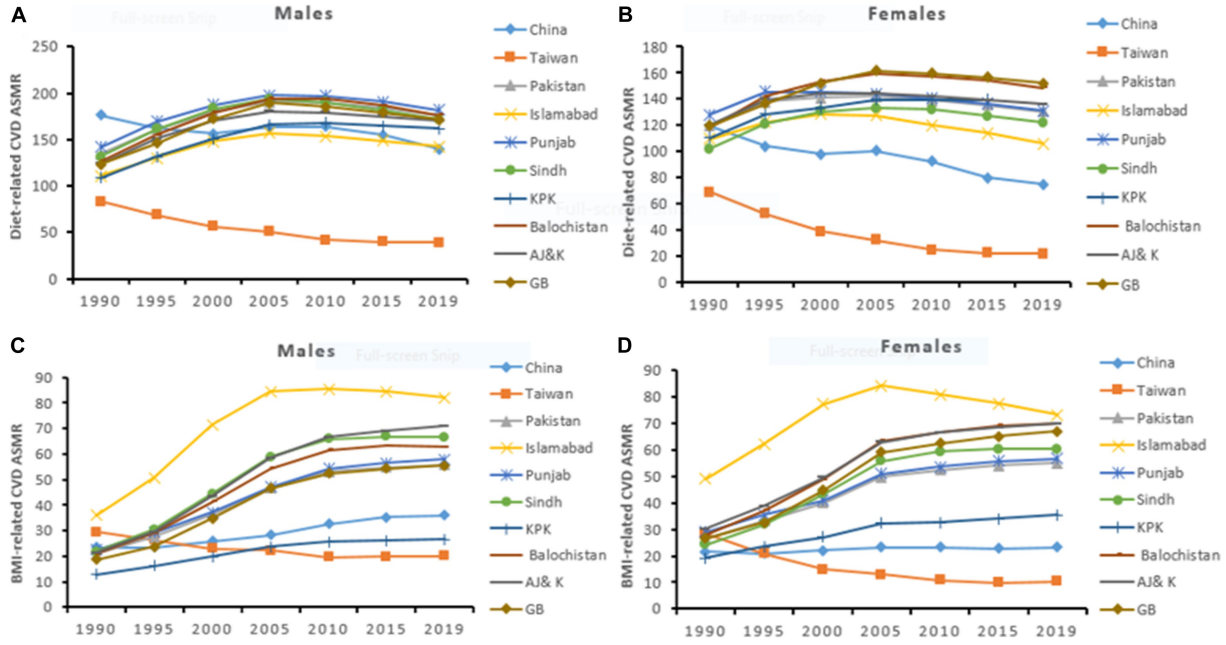

FIGURE 1
Temporal trend of CVD ASMR (per 100,000) attributable to dietary risks **(A,B)** and high BMI **(C,D)** in males and females across China and Pakistan.

sedentary lifestyle (41, 42). Among the Pakistani population, diet mostly consisted of saturated fats and trans fatty acids. The trend of eating fast food, processed foods, and junk food increased among the young population. Moreover, rapid urbanization and modernization have shifted the intake of a traditional low-fat diet to a high-fat diet (43). According to a systematic review and meta-analysis, Pakistani adolescents had a low level of physical activity and less than one-fifth has achieved recommended levels (44). The higher consumption of high-fat and saturated-fat diets, and low physical activity could be the contributing factors to increasing obesity which resulted in high CVD mortality and morbidity among the Pakistani population (45, 46).

Pakistan urgently needs to develop and formulate a prevention and control strategy for obesity at the national level by implementing the World Health Organization (WHO) policies and recommendations for preventing obesity and diabetes in the Eastern Mediterranean Region (47). The government and non-government organizations should initiate and promote public awareness programs about the impact of a healthy diet and physical activity on individual and national health. School and college-based awareness and intervention pogroms should be initiated across the country for promoting healthy dietary habits and physical activity among the younger population. Adopting healthy dietary habits and sufficient physical activity could reduce the high BMI-related CVD burden in Pakistan (48).

Overall, male showed less improvement and high burden in CVD, IHD, and IS ASMR and age-standardized DALYs rate attributable to dietary risks and high BMI than the female population across China and Pakistan. Generally, men showed poor dietary habits and lower Healthy Eating Index (HEI) scores (49), a higher prevalence of obesity (50), and experienced earlier (10–15 years) coronary heart disease than women. Moreover, women had a lower incidence of CVD than men due to estrogen's protective effect on the cardiovascular system (51, 52). Our findings are coinciding with several previous studies (7, 11, 53).

Age-period-cohort effect on CVD burden attributable to dietary risks and high BMI

We found that the risk ratio of CVD mortality and DALYS showed a linear association with age. Age is an independent risk factor of CVD and the proportion of CVD incidence increased with aging among both men and women (54, 55). The age effect on CVD burden attributable to modifiable risk factors was remarkable in China. Moreover, the risk ratio of premature CVD mortality (<70 years) attributable to high BMI was higher among the Chinese population. Between 1993 and 2015, the prevalence of overweight (26.6 to 41.3%), obesity (4.2 to 15.7%), and abdominal obesity (20.2 to 46.9%) increased among Chinese adults aged 18–80 years. The absolute increase in BMI was positively correlated with age and older people showed a marked increasing trend in obesity (56) and a higher risk of CVD mortality and morbidity (20). On the other hand, the Pakistani population showed a higher risk ratio of premature CVD mortality attributable to dietary risk. Several factors such as malnutrition (28) poverty and low diet quality (29) poor dietary habits (30) and a poor healthcare system (57) may contribute to the increased risk of diet-related premature CVD mortality in Pakistan.

In our findings, the risk ratio of period effect on CVD burden attributable to modifiable risk factors significantly increased across both countries. The period effect was generally higher for CVD mortality and DALYs attributable to high BMI notably in Pakistan. Pakistan is facing twin problems of poor nutrition and over-nutrition and around 5.4 million school-aged children will be obese by 2030 (42). The increasing risk of BMI-related CVD burden in Pakistan

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TABLE 4 Age-Period-Cohort effects on CVD mortality attributable to dietary risks and high BMI across China and Pakistan.

Variables	China CVD mortality (RR 95% CI)		Pakistan CVD mortality (RR 95% CI)	
	Dietary risks	High BMI	Dietary risks	High BMI
Age				
25–29	1.00	1.00	1.00	1.00
30–34	1.65 (1.65, 149)	1.74 (2.13, 1.49)	1.93 (2.07, 1.79)	1.46 (1.58, 1.35)
35–39	2.72 (3.01, 2.23)	2.73 (3.56, 2.16)	3.12 (3.46, 2.81)	1.97 (2.20, 1.75)
40–44	4.06 (4.97, 3.32)	4.60 (6.38, 3.46)	5.05 (5.75, 4.45)	2.56 (2.94, 2.22)
45–49	5.48 (6.71, 4.96)	6.47 (9.30, 4.65)	7.21 (8.32, 6.27)	3.27 (3.84, 2.78)
50–54	8.18 (10.01, 6.70)	9.20 (13.79, 6.44)	10.39 (12.16, 8.91)	4.56 (5.48, 3.80)
55–59	10.40 (13.11, 8.18)	11.21 (17.35, 7.72)	13.42 (15.87, 11.39)	5.49 (6.68, 4.52)
60–64	13.49 (16.50, 11.05)	14.60 (23.00, 9.72)	16.93 (20.20, 14.22)	6.95 (8.56, 5.65)
65–69	18.22 (24.62, 14.91)	18.77 (30.19, 12.25)	20.78 (25.01, 17.32)	7.79 (9.68, 6.29)
70–74	30.04 (33.23, 22.25)	25.72 (42.29, 16.47)	25.84 (31.28, 21.43)	9.76 (12.19, 7.82)
75–79	36.69 (44.86, 27.17)	30.79 (50.43, 19.72)	32.17 (39.02, 26.60)	10.02 (12.48, 8.04)
80–84	54.73 (66.93, 40.54)	22.88 (37.07, 14.76)	40.85 (49.45, 33.88)	7.59 (9.36, 6.17)
85–89	90.25 (121.95, 73.88)	40.74 (65.40, 26.62)	50.65 (60.83, 42.26)	11.41 (14.01, 9.30)
Period				
1990–1994	1.00	1.00	1.00	1.00
1995–1999	0.95 (0.95, 0.92)	1.04 (1.06, 1.02)	1.29 (1.30, 1.28)	1.30 (1.32, 1.29)
2000–2004	0.97 (0.99, 0.94)	1.21 (1.25, 1.17)	1.54 (1.56, 1.51)	1.52 (1.55, 1.49)
2005–2009	1.10 (1.12, 1.07)	1.43 (1.47, 1.38)	1.79 (1.81, 1.76)	1.95 (2.01, 1.91)
2010–2014	1.19 (1.22, 1.18)	1.74 (1.78, 1.70)	1.98 (2.01, 1.96)	2.13 (2.18, 2.09)
2015–2019	1.12 (1.14, 1.13)	2.08 (2.10, 2.06)	2.06 (2.07, 2.05)	2.42 (2.46, 2.38)
Cohort				
1905–1909	1.00	1.00	1.00	1.00
1910–1914	1.05 (1.06, 1.03)	0.99 (1.03, 0.96)	0.87 (0.88, 0.85)	0.39 (0.39, 0.39)
1915–1919	1.02 (1.04, 0.98)	0.90 (0.96, 0.85)	0.77 (0.79, 0.75)	0.78 (0.83, 0.74)
1920–1924	0.95 (0.98, 0.91)	0.83 (0.89, 0.77)	0.70 (0.72, 0.67)	0.78 (0.84, 0.73)
1925–1929	0.92 (0.95, 0.87)	0.82 (0.90, 0.75)	0.63 (0.65, 0.60)	1.05 (1.15, 0.96)
1930–1934	0.84 (0.86, 0.80)	0.79 (0.86, 0.72)	0.56 (0.58, 0.54)	1.02 (1.12, 0.93)
1935–1939	0.75 (0.77, 0.72)	0.71 (0.77, 0.66)	0.50 (0.52, 0.49)	1.10 (1.20, 1.01)
1940–1944	0.64 (0.65, 0.63)	0.62 (0.65, 0.58)	0.45 (0.46, 0.44)	1.06 (1.15, 0.98)
1945–1949	0.54 (0.54, 0.54)	0.54 (0.56, 0.52)	0.40 (0.41, 0.40)	0.97 (1.04, 0.91)
1950–1954	0.47 (0.48, 0.46)	0.49 (0.49, 0.49)	0.36 (0.36, 0.36)	0.91 (0.96, 0.86)
1955–1959	0.39 (0.40, 0.37)	0.42 (0.42, 0.41)	0.32 (0.32, 0.31)	0.79 (0.82, 0.76)
1960–1964	0.32 (0.33, 0.30)	0.35 (0.37, 0.33)	0.28 (0.29, 0.27)	0.68 (0.70, 0.66)
1965–1969	0.28 (0.30, 0.26)	0.32 (0.34, 0.29)	0.25 (0.26, 0.24)	0.54 (0.55, 0.54)
1970–1974	0.24 (0.27, 0.22)	0.28 (0.32, 0.24)	0.23 (0.24, 0.21)	0.44 (0.45, 0.43)
1975–1979	0.21 (0.45, 0.24)	0.25 (0.31, 0.21)	0.21 (0.22, 0.19)	0.32 (0.35, 0.30)
1980–1984	0.19 (0.24, 0.15)	0.25 (0.33, 0.21)	0.19 (0.22, 0.17)	0.26 (0.30, 0.23)
1985–1989	0.17 (0.24, 0.11)	0.23 (0.37, 0.14)	0.18 (0.22, 0.15)	0.22 (0.29, 0.18)
1990–1994	0.14 (0.33, 0.06)	0.20 (0.59, 0.06)	0.18 (0.29, 0.11)	0.19 (0.34, 0.10)
AIC	7.90	6.45	8.36	20.63
BIC	−175.66	−184.16	−176.93	880.92

CVD, cardiovascular disease; BMI, body mass index; RR, risk ratio; AIC, Akaike information criterion; BIC, Bayesian information criterion.

TABLE 5 Age-Period-Cohort effects on CVD DALYs attributable to dietary risks and high BMI across China and Pakistan.

Variables	China CVD DALYs (RR 95% CI)		Pakistan CVD DALYs (RR 95% CI)	
	Dietary risks	High BMI	Dietary risks	High BMI
Age				
25–29	1.00	1.00	1.00	1.00
30–34	1.55 (1.56, 1.53)	1.66 (1.70, 1.63)	1.81 (1.83, 1.80)	1.68 (1.70, 1.65)
35–39	2.35 (2.38, 2.32)	2.43 (2.49, 2.37)	2.78 (2.81, 2.74)	2.40 (2.44, 2.35)
40–44	3.44 (3.50, 3.38)	3.81 (3.94, 3.69)	4.22 (4.28, 4.16)	3.65 (3.74, 3.57)
45–49	4.52 (4.62, 4.43)	5.01 (5.21, 4.83)	5.61 (5.70, 5.51)	4.99 (5.12, 4.86)
50–54	6.11 (6.26, 5.97)	6.66 (6.94, 6.39)	7.45 (7.59, 7.32)	7.26 (7.47, 7.05)
55–59	7.37 (7.56, 7.19)	7.53 (7.86, 7.20)	8.76 (8.93, 8.60)	8.31 (8.57, 8.07)
60–64	8.93 (9.18, 8.70)	8.74 (9.16, 8.35)	9.89 (10.08, 9.69)	9.75 (10.07, 9.44)
65–69	10.70 (11.01, 10.40)	9.85 (10.35, 9.39)	10.62 (10.85, 10.40)	10.36 (10.70, 10.01)
70–74	12.96 (13.37, 12.60)	11.44 (12.04, 10.89)	11.24 (11.49, 11.00)	10.07 (10.41, 9.74)
75–79	14.49 (14.93, 14.07)	11.18 (11.76, 10.63)	11.50 (11.76, 11.25)	8.81 (9.11, 8.52)
80–84	16.68 (17.19, 16.21)	6.58 (6.90, 6.28)	11.64 (11.89, 11.39)	4.52 (4.66, 4.38)
85–89	22.40 (23.06, 21.81)	9.21 (9.66, 8.79)	11.38 (11.61, 11.13)	4.60 (4.74, 4.47)
Period				
1990–1994	1.00	1.00	1.00	1.00
1995–1999	0.92 (0.92, 0.92)	1.03 (1.03, 1.03)	1.26 (1.27, 1.26)	1.34 (1.35, 1.34)
2000–2004	0.92 (0.92, 0.92)	1.18 (1.18, 1.17)	1.46 (1.46, 1.46)	1.79 (1.79, 1.78)
2005–2009	1.01 (1.01, 1.01)	1.35 (1.35, 1.34)	1.63 (1.63, 1.63)	2.39 (2.39, 2.38)
2010–2014	1.05 (1.05, 1.05)	1.56 (157, 1.56)	1.73 (1.73, 1.73)	2.75 (2.76, 2.74)
2015–2019	0.98 (0.98, 0.98)	1.81 (1.82, 1.81)	1.72 (1.72, 1.72)	3.05 (3.06, 3.04)
Cohort				
1905–1909	1.00	1.00	1.00	1.00
1910–1914	1.06 (1.07, 1.06)	1.01 (1.02, 1.01)	0.89 (0.89, 0.89)	0.90 (0.91, 0.89)
1915–1919	1.05 (1.06, 1.05)	0.94 (0.96, 0.93)	0.82 (0.83, 0.81)	0.85 (0.87, 0.83)
1920–1924	1.02 (1.03, 1.01)	0.89 (0.91, 0.87)	0.76 (0.77, 0.76)	0.80 (0.83, 0.78)
1925–1929	1.02 (1.03, 1.01)	0.91 (0.93,0.89)	0.71 (0.72, 0.70)	0.76 (0.78, 0.74)
1930–1934	0.97 (0.97, 0.96)	0.89 (0.91, 0.87)	0.66 (0.67, 0.66)	0.72 (0.75, 0.70)
1935–1939	0.90 (0.90, 0.89)	0.84 (0.86, 0.82)	0.61 (0.62, 0.61)	0.69 (0.71, 0.67)
1940–1944	0.80 (0.80, 0.79)	0.77 (0.78, 0.75)	0.57 (0.57, 0.57)	0.65 (0.67, 0.63)
1945–1949	0.70 (0.71, 0.70)	0.70 (0.71, 0.69)	0.53 (0.53, 0.53)	0.62 (0.64, 0.60)
1950–1954	0.64 (0.64, 0.64)	0.66 (0.67, 0.65)	0.49 (0.50, 0.49)	0.60 (0.61, 0.58)
1955–1959	0.55 (0.55, 0.55)	0.59 (0.59, 0.58)	0.45 (0.46, 0.45)	0.57 (0.58, 0.55)
1960–1964	0.47 (0.47, 0.47)	0.52 (0.52, 0.51)	0.42 (0.42, 0.42)	0.53 (0.54, 0.52)
1965–1969	0.44 (0.44, 0.43)	0.49 (0.49, 0.49)	0.39 (0.39, 0.39)	0.49 (0.50, 0.48)
1970–1974	0.39 (0.40, 0.39)	0.44 (0.44, 0.44)	0.37 (0.37, 0.36)	0.46 (0.47, 0.46)
1975–1979	0.35 (0.36, 0.35)	0.42 (0.43, 0.42)	0.35 (0.35, 0.35)	0.45 (0.46, 0.45)
1980–1984	0.33 (0.34, 0.32)	0.42 (0.43, 0.42)	0.34 (0.34, 0.33)	0.44 (0.44, 0.44)
1985–1989	0.30 (0.32, 0.29)	0.41 (0.43, 0.39)	0.33 (0.34, 0.33)	0.42 (0.43, 0.42)
1990–1994	0.27 (0.29, 0.24)	0.38 (0.42, 0.34)	0.34 (0.36, 0.32)	0.42 (0.44, 0.40)
AIC	16.74	11.99	16.25	11.08
BIC	246.48	−19.42	174.96	−128.28

CVD, cardiovascular disease; BMI, body mass index; DALYs, disability-adjusted life years; RR, risk ratio; AIC, Akaike information criterion; BIC, Bayesian information criterion.

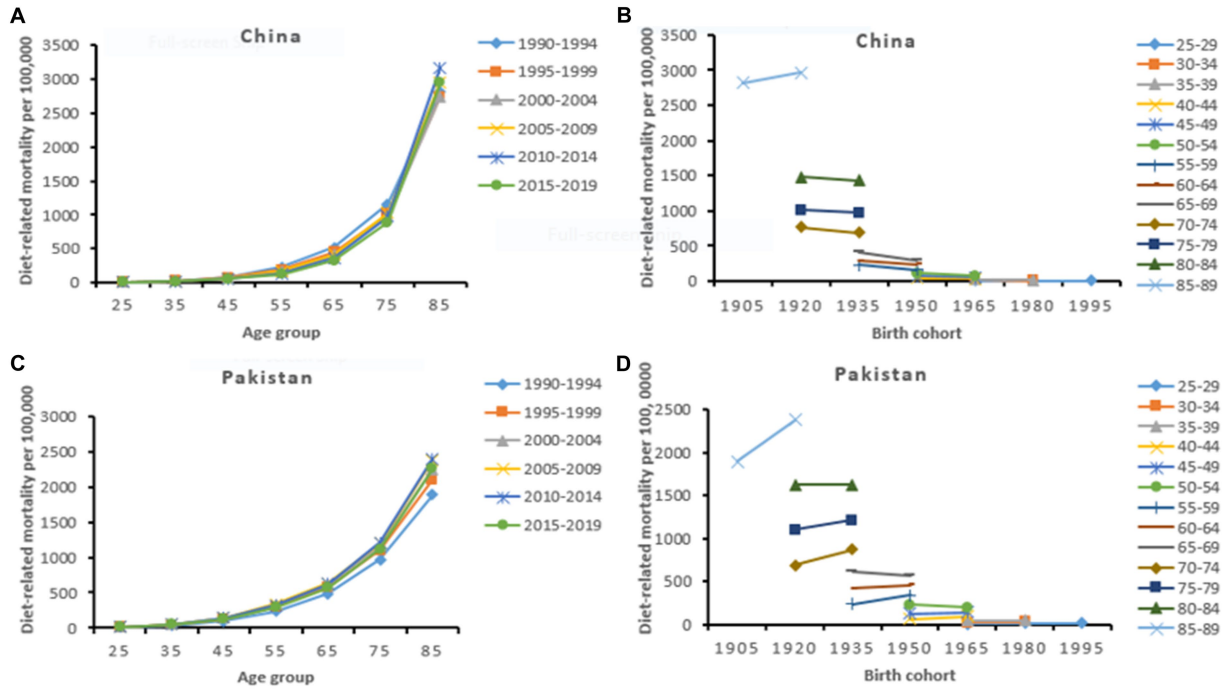

FIGURE 2
Diet-related age-specific CVD mortality rate by period **(A,C)** and cohort-specific CVD mortality rate by age group **(B,D)** across China and Pakistan from 1990 to 2019.

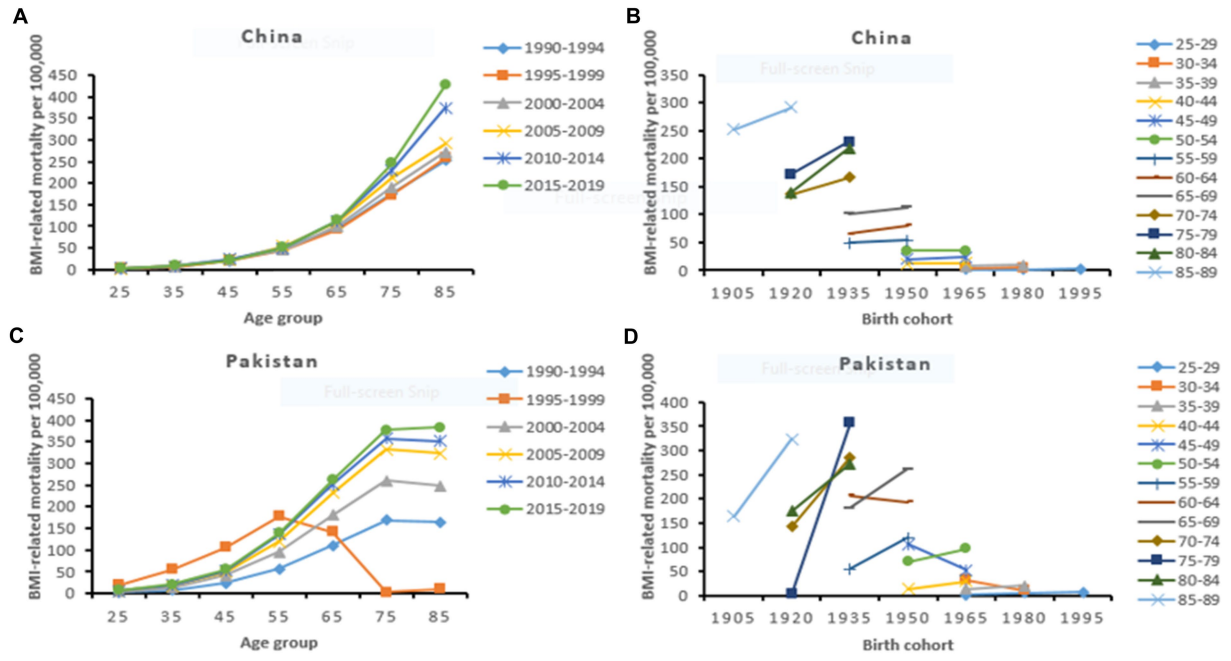

FIGURE 3
High BMI-related age-specific CVD mortality rate by period **(A,C)** and cohort-specific CVD mortality rate by age group **(B,D)** across China and Pakistan from 1990 to 2019.

could be attributed to the high trend of fast food, urbanization, moderation, and low physical activity. The fast food industry is the 2nd largest in Pakistan with 180 million consumers (58). The trend of fast food consumption is tremendously increasing among the young population (43). Due to rapid urbanization and modernization people have adopted a westernized high-fat diet over a traditional low-fat diet (43). Moreover, Pakistani adolescents had a low level of physical activity, and less than one-fifth achieved recommended levels (44).

We observed that compared to the reference cohort, the risk ratio of cohort effect on CVD burden attributable to dietary risks and high BMI showed a similar monotonic downward pattern among the Chinese and Pakistani populations. Early birth cohorts in China had a higher risk ratio of CVD mortality and DALYs. However, recent birth cohorts in China showed relatively a lower risk ratio of CVD mortality and DALYs than in Pakistan. Advancement in techniques for diagnosis, management, treatment, improvement in healthcare facilities, early-life nutrition, education level, and socioeconomic status may play a critical role in the lower risk ratio of CVD burden in the recent birth cohorts in China (17, 59, 60). In accordance with our findings, several studies observed that early birth cohorts showed higher risk and recent birth cohorts experienced a lower risk of CVD burden in China (17, 59, 61, 62).

Our study has several limitations. First, our findings are obtained from GBD data and all GBD limitations are apply to our results as mentioned previously (63). Second, we observed epidemiological trends of CVD mortality and morbidity attributable to overall dietary risks and could not find for the individual dietary risk factor. Third, the age-period-cohort effect on CVD burden attributable to dietary risks and high BMI was not conducted for different genders and at the regional level across China and Pakistan.

Conclusion

Our findings indicate that the all-ages CVD deaths and DALYs due to dietary risks and high BMI significantly increased across China and Pakistan from 1990 to 2019. The diet-related CVD ASMR and the age-standardized DALYs rate significantly decreased in China. However, the ASMR of CVD and the age-standardized DALYs rate attributable to dietary risks significantly increased in Pakistan. Both countries showed a marked increasing trend of CVD ASMR and the age-standardized DALYs rate attributable to high BMI. Age-period-cohort analysis showed a higher risk ratio of premature CVD mortality (<70 years) among Chinese attributable to high BMI and Pakistani attributable to dietary risks. In China, early birth cohorts showed higher risk and recent birth cohorts experienced a lower risk of CVD burden compared with Pakistan. Besides government-level initiatives, proper nursing care could play a significant role in preventing and controlling premature CVD mortality across China and Pakistan (64). These findings can provide evidence-based references for health-policy makers to priorities strategies for the premature CVD burden attributable to dietary risk and high BMI across China and Pakistan.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

Ethical approval was not provided for this study on human participants because ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The requirement for informed consent was waived. The ethics committee waived the requirement of written informed consent for participation.

Author contributions

XY, WY, and Nawsherwan: study design and critical revision of manuscript and writing— review and editing. XY, SM, and Nawsherwan: data collection and analysis and drafting the manuscript. Nawsherwan and SM: data collection. Nawsherwan and SM: data analysis. WY and Nawsherwan: writing—original draft preparation. Nawsherwan: visualization. XY and WY: supervision. WY: project administration. All authors have read and agreed to the published version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2023.1158769/full#supplementary-material

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EDITED BY
Amedeo Amedei,
University of Florence, Italy

REVIEWED BY
Bret Rust,
Indiana University, United States
Eric Westman,
Duke University, United States

*CORRESPONDENCE
Christopher D. Gardner
✉ cgardner@stanford.edu

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Weight, insulin resistance, blood lipids, and diet quality changes associated with ketogenic and ultra low-fat dietary patterns: a secondary analysis of the DIETFITS randomized clinical trial

Lucia Aronica[1], Matthew J. Landry[1], Joseph Rigdon[2] and Christopher D. Gardner[1]*

[1]Stanford Prevention Research Center, Stanford University School of Medicine, Stanford, CA, United States, [2]Department of Biostatistics and Data Science, Wake Forest University School of Medicine, Quantitative Sciences Unit, Stanford, CA, United States

Background: The DIETFITS trial reported no significant difference in 12-month weight loss between a healthy low-fat and healthy low-carbohydrate diet. Participants were instructed to restrict fat or carbohydrates to levels consistent with a ketogenic or ultra low-fat diet for 2 months and to subsequently increase intakes until they achieved a comfortable maintenance level.

Objective: To compare 3- and 12-month changes in body weight and cardiometabolic risk factors between a subsample of participants who reported 3-month fat or carbohydrates intakes consistent with either a ketogenic-like diet (KLD) or ultra low-fat diet (ULF).

Design: 3-month and 12-month weight and risk factor outcomes were compared between KLD ($n = 18$) and ULF ($n = 21$) sub-groups of DIETFITS participants (selected from $n = 609$, healthy overweight/obese, aged 18–50 years).

Results: Less than 10% of DIETFITS participants met KLD or ULF criteria at 3-months. Both groups achieved similar weight loss and insulin resistance improvements at 3-months and maintained them at 12- months. Significant differences at 3-months included a transient ~12% increase in LDL cholesterol (LDL-C) for KLD with a concomitant greater reduction in log(TG/HDL), a measure of LDL-C's atherogenic potential. The latter was maintained at 12-months, despite substantial diet recidivism for both groups, whereas LDL-C levels were similar for ULF at baseline and 12-months. KLD participants achieved and maintained the greatest reductions in added sugars and refined grains at 3- months and 12-months, whereas ULF participants reported a 50% increase in refined grains intake from baseline to 12-months.

Conclusion: Among the ~10% of study participants that achieved the most extreme restriction of dietary fat vs. carbohydrate after 3 months, weight loss and improvement in insulin sensitivity were substantial and similar between groups. At 12 months, after considerable dietary recidivism, the few significant differences in diet quality and blood lipid parameters tended to favor KLD over ULF.

KEYWORDS

ketogenic diet, ultra low-fat diet, low carbohydrate, low fat, weight loss, triglycerides/HDL ratio, insulin resistance, refined grains

1. Introduction

The consumption of added sugars and refined carbohydrates has significantly grown in the past five decades with a concomitant increase in the global rates of obesity, diabetes and cardiovascular disease (CVD) (1, 2). While a substantial reduction in added sugars and refined carbohydrate intake has become a priority in current public health guidelines (3), there is still little consensus on the optimal ratios of carbohydrates and fats for promoting weight loss and optimizing CVD risk factors. Multiple diets promoting reduction of added sugar and refined grain consumption with varying ranges of carbohydrate and fat content have been associated with significant improvements in body weight and cardiovascular disease (CVD) risk factors (4). At one extreme is the ketogenic diet, which restricts net carbohydrates to ≤20–50 g per day (5–13), and at the opposite end of the spectrum are ultra low-fat diets like the Ornish and Pritikin diets, which recommends a drastic reduction of fat to <10% of total daily calories (14–16).

Several randomized clinical trials (RCTs) have compared weight loss and chronic disease factors on low-carbohydrate (LC) and low-fat diets (LF), with a preponderance of studies reporting greater benefits for LC at 6-months but not at 12-months (17–20). However, these studies displayed a high variability in the definitions of "low-carb" and "low-fat" and in the reporting of adherence to these two dietary approaches (21, 22). We recently reported that there was no significant difference in 12-month weight loss among 609 healthy subjects with overweight/obesity assigned to a Healthy Low Carbohydrate diet (HLC) or Healthy Low Fat diet (HLF) (23). However, both diets minimized added sugar and refined grains and, hence, reduced overall carbohydrate consumption from baseline (23). In addition, with such a large study population, variability in both adherence and weight loss success was substantial. Following the main publication of our findings, we received many queries regarding the outcomes for the subset of participants in the study that had been most adherent and achieved the greatest dietary changes from their baseline diets for both intervention diets. This analysis is a response to those queries.

In order to explore the potential health impacts of diets with greater differentiation in relative carbohydrate and fat content, in this secondary analysis of the DIETFITS study we selected the participants from the HLC group who reported achieving the greatest carbohydrate restriction - a dietary pattern that resembled a ketogenic diet (ketogenic-like diet, KLD), and the participants from the HLF group who reported achieving the greatest fat restriction - a dietary pattern that resembled an ultra low-fat diet (ultra low-fat, ULF). The 3-month intermediate time point was used for selecting these subsets because this was when participant enthusiasm and engagement was assessed to be highest; at the end of the 12-month protocol very few individuals from the original n = 609 DIETFITS participants reported dietary patterns that resembled KLD or ULF. Changes in weight and chronic disease risk factors were contrasted between these two selected subgroups at the 3-month time point, and then longer-term dietary pattern adherence was examined at 12-months, along with weight and risk factor comparisons.

2. Subjects and methods

2.1. Design and participants

The original trial, Diet Intervention Examining The Factors Interacting with Treatment Success (DIETFITS), was a single-site, parallel-group, randomized trial of 609 men ($n = 263$) and women (n = 346) with overweight or obesity conducted at the Stanford Prevention Research Center from January 2013 to May 2016 and designed to whether baseline genetic or cardiometabolic factors would explain differential weight loss for those assigned to either a HLC or a HLF diet (23).The detailed primary study protocol has been reported elsewhere (24). Participants were generally healthy women and men, aged 18–50 years, with body mass index (BMI) 28–40 kg/m^2. The dietary protocol consisted of two phases, *Limbo* and *Titrate*, whose goal was to help participants achieve the lowest intake of fat or carbohydrates they could realistically maintain beyond the end of the trial. During the first eight weeks of *Limbo* phase, participants were instructed to cut back on fat or carbohydrate intake progressively until they achieved a daily intake of no more than 20 g of carbohydrate (HLC) or fat (HLF), which is consistent with a ketogenic or ultra low-fat dietary pattern, respectively. During the *Titrate* phase, participants were instructed to increase their fat or carbohydrate intake slowly, by 5–15 g each week, until they achieved a comfortable maintenance level. In this phase participants were instructed to strive for the lowest intake of fat or carbohydrates they could realistically maintain for the 12-month intervention period, and even beyond the end of the trial should they experience positive benefits from their diet assignment. Emphasis on diet *Quality* was a common feature of both intervention arms. All subjects were instructed to (1) maximize vegetable intake; (2) minimize added sugars, refined grains, and trans fats; and (3) focus on minimally-processed whole foods, prepared at home when possible.

2.2. Dietary assessment

Dietary intake was recorded using unannounced 24-h multiple-pass recall interviews. Diet recalls were collected using Nutrition Data System for Research (NDS-R, University of Minnesota), a computer-based dietary analysis program designed for the collection and analyses of 24-h dietary recalls. Nutrient profiles are compiled using data provided by the NDSR software and sourced from the NCC Food and Nutrient Database (25). Data from 3 dietary recalls for each time point (baseline, 3-, 12-months), 2 on weekdays and 1 on a weekend day, were averaged and used to determine overall dietary intake for each time point. Six-month data were available, but not included in this analysis.

2.3. Anthropometric and laboratory measures

Anthropometric measures and blood samples were captured at baseline, 3-, and 12- months. Body weight was recorded without shoes to the nearest 0.1 kg using a calibrated Scale-tronix clinical scale. Height was measured to the nearest 0.1 cm using a Seca wall-mounted stadiometer. All measurements were taken by a nurse at the Stanford Clinical & Translational Research Unit (CTRU) at each time point. All clinic visits started between 7:00 and 9:30 am, with participants in a fasted state for at least 10–12 h. Blood samples were taken at baseline, 3, 6 and 12 months via venipuncture by trained nurses or phlebotomists. Blood was collected into purple top EDTA vacutainer tubes. Samples were processed, aliquoted, and frozen directly by the CTRU lab after being drawn. Samples were stored in a −80° freezer until the time of

processing for analysis. Lipids were assessed at all four times points (i.e., baseline, 3, 6, and 12 months) from a fasting blood sample. Plasma triglycerides, total- and HDL-cholesterol were measured by enzymatic endpoint analysis on a clinical chemistry analyzer (Liasys 330). LDL-cholesterol was calculated using the Friedewald equation. Triglyceride and cholesterol measurements are standardized through the CDC-NHLBI lipid standardization program. Insulin levels were assessed by radioimmunoassay by the Core Laboratory for Clinical Studies Washington University School of Medicine, St. Louis, Missouri. Glucose levels were analyzed using a Beckman Glucose Analyzer II (BGA II) by electrochemical technique. Insulin resistance status was determined by calculating the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) as described previously (26). 6-month data were available, but not included in this analysis.

2.4. Diet group criteria and outcome analysis

KLD and ULF subjects were selected at 3-months, as this was the timepoint with the highest reported restriction of carbohydrates or fat, and the most complete weight and cardiometabolic data (i.e., least drop-out). Out of 549 subjects with intake data at 3-months, we conservatively excluded those who reported <1,200 kcal per day due to underreporting concerns ($n = 128/549$ subjects excluded, 23%). For KLD, the threshold of net carbohydrates (carbohydrates minus fiber) was set at <30 g per day, based on the recommended range of 20-50 g used in previous studies (27). This resulted in the inclusion of 18/205 subjects in KLD from the HLC group. For ULF the cutoff of fat intake was initially defined as <10% of daily calories from fat based on original recommendations of the Ornish diet (28). However, since only 5 of 216 subjects met the <10% fat cutoff, this was increased to 15% (about 20 g/day) that resulted in the identification of 21 ULF subjects, a number reasonably comparable to the KLD group.

2.5. Statistics

The primary aim of this study was to test whether changes in baseline to 3-month outcomes [weight, HDL-C, triglycerides, log(TG/HDL-C), LDL-C, and HOMA-IR] were different among the two study population subgroups; KLD and ULF. Baseline demographic, anthropometric and cardiometabolic variables data are presented using basic descriptive data. Patterns of nutrition intake at baseline, 3- and 12-months were also summarized descriptively using means and standard errors by diet and timepoint.

Linear mixed effects models (29) with fixed effects for diet, time (baseline, 3-, or 12-months), and all diet by time interactions, and a random intercept for participant were used to test all primary study hypotheses to account for the correlated nature of within participant changes while using all available data. The models allowed estimation of within-diet baseline to 3-month changes and also comparisons (using two-sided Wald tests) between diets of these 3- and 12-month changes. No adjustments for multiple testing were made given that this was a hypothesis generating secondary analysis of a subset of participants from a large, randomized trial. All statistical tests were two-tailed with type 1 error assumed to be 0.05. All analyses were conducted using R version 4.1.2 (30).

3. Results

3.1. Baseline characteristics of the study population

The KLD ($n = 18$) and ULF ($n = 21$) groups included participants exclusively from the HLC and HLF arms, respectively. There were no significant between-group differences in baseline demographic or anthropometric data and laboratory measurements (Table 1). Baseline daily intake of total calories, fats, protein and added sugars and refined grains was also similar between groups (Table 2). The ULF group reported a marginally significantly greater baseline daily intake of total carbohydrates compared to the KLD group (KLD: 250.4 ± 18.3; ULF: 292.4 ± 17.7 grams; $p = 0.047$). However, baseline daily intake of net carbohydrates (total carbohydrates minus fiber) was similar between the two groups.

3.2. Intake of macronutrient, added sugars, and refined carbohydrates

All groups reported similar reductions in caloric intake at 3-months relative to baseline. As expected, and by design, there were significant between group differences in the intake of macronutrients

TABLE 1 Baseline demographics and cardiometabolic variables for KLD and OLD.

	KLD	ULF	*p*-value[a]
	n=18	*n*=21	
Diet			
Healthy Low Carb	18 (100.0%)	0 (0.0%)	<0.0001
Healthy Low Fat	0 (0.0%)	21 (100.0%)	
Sex			
Female	9 (50.0%)	7 (33.3%)	0.60
Male	9 (50.0%)	14 (66.7%)	
Age (years)	42.0 (±6.8)	41.2 (±5.6)	0.50
Weight (kg)	103.8 (±14.3)	102.8 (±15.6)	0.32
Race/ethnicity			
White	16 (88.9%)	14 (66.7%)	0.26
Hispanic	2 (11.1%)	3 (14.3%)	
Asian	0 (0.0%)	3 (14.3%)	
Other	0 (0.0%)	1 (4.8%)	
HDL	47.4 (±10.7)	47.0 (±8.8)	0.35
LDL	121.0 (±33.1)	109.4 (±27.7)	0.53
Triglycerides	219.1 (±29.1)	137.0 (±67.6)	0.22
Log(TG/HDL ratio)	1.2 (±0.9)	1.0 (±0.4)	0.44
HOMA-IR	4.7 (±2.5)	4.3 (±3.6)	0.88
DXA percent fat	36.5 (±6.5)	34.1 (±5.8)	0.55
Missing	6 (33.3%)	9 (42.9%)	
BMI (kg/m^2)	35.0 (±2.7)	33.3 (±3.2)	0.065

[a]Wilcoxon rank-sum for continuous variables, e.g., age, and Fisher's exact test for categorical variables, e.g. race.

TABLE 2 Nutrition variables for KLD and ULF at baseline, 3 months, and 12 months.

	KLD	ULF	*p*-value[a]
	n=18	*n*=21	
Calories (kcal/day)			
Baseline	2265 (±133)[b]	2392 (±136)	0.42
3 Months	1482 (±63)	1543 (±45)	0.70
12 Months	1665 (±118)	1938 (±145)	0.13
Carbohydrates (g/day)			
Baseline	250 (±18)	292 (±18)	0.05
3 Months	38 (±4)	264 (±8)	<0.0001
12 Months	96 (±14)	264 (±20)	<0.0001
Net carb (g/day)			
Baseline	226 (±17)	265 (±17)	0.05
3 Months	16 (±7)	227.3 (±7)	<0.0001
12 Months	77 (±12)	236 (±19)	<0.0001
Fat (g/day)			
Baseline	97 (±7)	86.2 (±6.5)	0.23
3 Months	100 (±6.0)	20 (±1.1)	<0.0001
12 Months	90.3 (±9.3)	51.9 (±5.8)	<0.0001
Protein (g/day)			
Baseline	91 (±5)	100 (±4)	0.33
3 Months	110 (±7)	84 (±6)	0.01
12 Months	109 (±11)	98 (±6)	0.28
Added sugars (g/day)			
Baseline	54 (±8)	45 (±7)	0.25
3 Months	3 (±1)	23 (±4)	0.01
12 Months	10 (±3.4)	32 (±5)	0.01
Refined grains (g/day)			
Baseline	93 (±18.1)	114 (±24)	0.47
3 Months	3 (±1)	81 (±22)	<0.01
12 Months	41(±13)	166 (±30)	<0.001
Fat (%)			
Baseline	37.2 (±1.1)	31.3 (±1.3)	<0.01
3 Months	58.6 (±1.9)	11.1 (±0.5)	<0.001
12 Months	46.9 (±2.8)	22.4 (±1.3)	<0.001
Carbohydrates (%)			
Baseline	43.5 (±1.9)	48.4 (±1.7)	0.07
3 Months	9.8 (±1.3)	66.4 (±1.8)	<0.001
12 Months	22.7 (±3.2)	53.4 (±1.8	<0.001
Protein (%)			
Baseline	16.7 (±0.9)	17.2 (±0.7)	0.76
3 Months	30.9 (±1.4)	21.0 (±1.4)	<0.001
12 Months	27.3 (±2.1)	21.1 (±1.2)	<0.01
Sugar (%calories)			
Baseline	22.6 (±2.9)	18.0 (±2.4)	0.21
3 Months	2.0 (±0.5)	16.2 (±3.4)	<0.001
12 Months	6.0 (±2.1)	17.6 (±2.7)	<0.01
Total sugars (g)			
Baseline	93.6 (±8.6)	105.6 (±11.1)	0.73
3 Months	16.5 (±2.3)	94.7 (±6.0)	<0.001
12 Months	35.2 (±5.1)	95.3 (±11.1)	<0.001

[a]*p*-values for null hypothesis that nutrition variables are equivalent between diets at a given timepoint; from a linear mixed effects model including fixed effects for time, diet, and time*diet interaction, and a random effect for study participant.
[b]Mean (±standard error of mean).

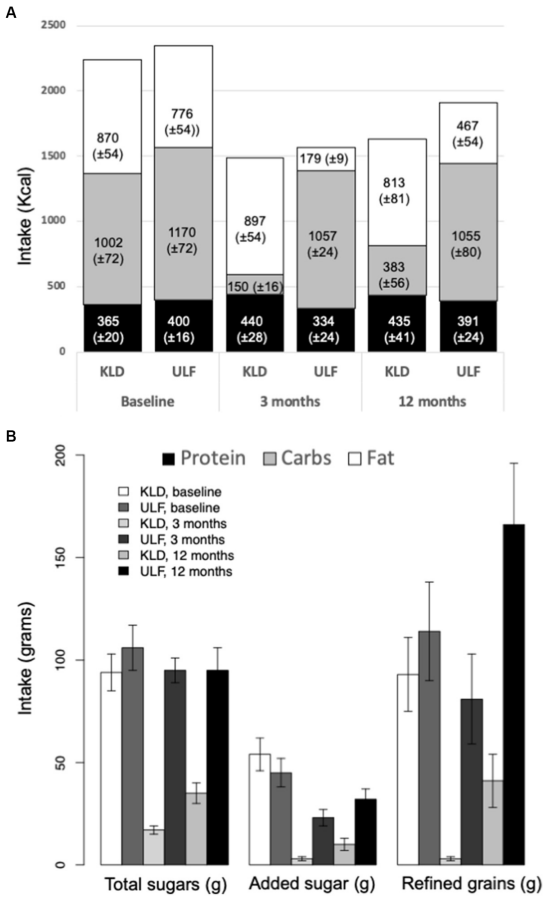

FIGURE 1
Macronutrient, added sugar, and refined grains intake for KLD and ULF. **(A)**: Mean intake (Kcal/day; ± standard error of mean) of protein (black), carbohydrates (gray), and fat (white) for KLD and ULF at baseline, 3 months, and 12 months. **(B)**: Mean intake (grams/day; ± standard error of mean) of total sugar, added sugars, and refined grains for KLD and ULF at baseline, 3 months, and 12 months. *p*-values for null hypothesis that nutrition variables are equivalent between diets at a given timepoint; from a linear mixed effects model including fixed effects for time, diet, and time*diet interaction, and a random effect for study participant.

(Table 2 and Figures 1A,B). Although all DIETFITS participants were instructed to minimize added sugars and refined carbohydrates, their reduction was significantly greater for KLD than ULF at 3-months with an average difference in daily intake of ~20 g of added sugars and ~80 g

TABLE 3 Baseline to 3-month changes in clinical variables for KLD and ULF.

	KLD	ULF	*p*-value[a]
Weight (kg)[a]	-9.8 (-12.8, -6.8)	-8.7 (-11.6, -5.8)	0.59
HDL (mg/dl)	1.7 (-1.8, 5.1)	-3.0 (-6.4, 0.3)	0.05
LDL (mg/dl)	14.9 (3.4, 26.4)	-2.9 (-13.8, 7.9)	0.03
Trig (mg/dl)	-108.6 (-184.8, -32.4)	-25.1 (-97.8, 47.6)	0.12
Log (TG/HDL ratio)	-0.53 (-0.77, -0.28)	-0.13 (-0.36, 0.11)	0.02
HOMA-IR	-1.4 (-2.3, -0.4)	-1.4 (-2.3, -0.4)	0.98
Sugar (%calories)	-20.6 (-25.9, -15.2)	-1.84 (-6.8, 3.1)	<0.001
Total sugars (g)	-77.1 (-97.1, -57.1)	-11.0 (-29.5, 7.5)	<0.001

[a]*p*-values, estimates, and 95% confidence intervals from a linear mixed effects model including fixed effects for time, diet, and time*diet interaction, and a random effect for study participant.

TABLE 4 Baseline to 12-month changes in clinical variables for KLD and ULF.

	KLD	ULF	*p*-value
Weight (kg)[a]	-9.9 (-12.9, -6.9)	-10.5 (-13.3, -7.6)	0.78
HDL (mg/dl)	4.9 (1.3, 8.5)	0.1 (-3.3, 3.5)	0.05
LDL (mg/dl)	5.0 (-6.7, 16.7)	-3.3 (-14.1, 7.6)	0.31
Trig (mg/dl)	-113.7 (-191.2, -36.2)	-13.0 (-85.7, 59.7)	0.06
Log TG/HDL ratio	-0.62 (-0.87, -0.37)	-0.09 (-0.32, 0.15)	<0.01
HOMA-IR	-1.3 (-2.3, -0.30)	-1.6 (-2.5, -0.6)	0.67
Sugar (%calories)	-16.6 (-22.2, -11.1)	-1.1 (-6.2, 4.0)	<0.001
Total sugars (g)	-57.9 (-78.6, -37.1)	-10.8 (-29.9, 8.4)	0.001

[a]*p*-values, estimates, and 95% confidence intervals from a linear mixed effects model including fixed effects for time, diet, and time*diet interaction, and a random effect for study participant.

of refined grains between KLD vs. ULF. As presented in Table 2, net carbohydrate intake (g/day) was significantly lower for KLD vs. ULF (KLD: 15.5 ± 7.2; ULF: 227.3 ± 6.5; $p = <0.001$), whereas fat intake was significantly lower for ULF vs. KLD (KLD: 99.7 ± 6.0; ULF: 19.9 ± 1.1; $p = <0.001$). Protein intake (g/day) was significantly higher for KLD compared to ULF (KLD = 110.1 ± 7.1 g; ULF = 83.5 ± 5.9 g; $p = <0.001$).

The pattern of statistical differences between the two groups persisted at 12-months, although the reported intakes of carbohydrates and fat increased for KLD and ULF, respectively. For KLD, the reported net carbohydrate intakes increased ~60 g/day reaching ~80 g/day, whereas fat intakes remained relatively stable around 90 g/day. For ULF, the reported fat intakes increased ~30 g/day reaching 50 g/day, whereas carbohydrate intakes remained relatively stable at around 230 g/day. At 12-month the reported intakes of refined grains increased for both KLD and ULF from 3-months. However, they remained >50% lower than at baseline for KLD, whereas they were almost 50% higher than at baseline for ULF. The reported 12-month added sugars intake was higher than at 3-months but lower than at baseline for both groups.

3.3. Changes in weight, blood lipids, and insulin resistance

At 3-months, weight loss was similar between KLD and ULF (Table 3). LDL-C decreased by ~3% for ULF, whereas it increased by ~12% for KLD with a significant between-group difference [KLD: 14.9 mg/dL (3.4, 26.4); ULF: −2.9 mg/dL (−13.8, 8.0); $p = 0.03$]. On the other hand, compared to ULF, KLD resulted in a significantly greater reduction in the log(TG/HDL-C) also known as atherogenic index of plasma (AIP), a measure of the atherogenic potential of an individual's LDL profile [KLD: −0.53 (−0.77, −0.28); ULF: −0.13 (−0.36, 0.11); $p = 0.02$]. Both KLD and ULF resulted in a similar ~30% reduction in insulin resistance (HOMA-IR) from baseline that persisted at 12-months with no significant between-group difference.

At 12-months, when substantial dietary recidivism was reported by both the KLD and ULF groups, LDL-C and weight loss were similar for KLD and ULF, whereas KLD maintained significantly greater improvements in log(TG/HDL) compared to ULF [KLD: −0.62 (−0.87, −0.37); ULF: −0.09 (−0.32, 0.15); $p = 0.003$ (Table 4)]. Overall, at 12-months both KLD and ULF lost ~10 kg of body weight and experienced a ~ 30% reduction in insulin resistance, whereas TG and HDL changed similarly and only modestly in the ULF groups at 12-months.

4. Discussion

In this secondary analysis of the DIETFITS study we examined 3-month and 12-month changes in weight loss and CVD risk factors among the <10% of participants who reported consuming a very-low carbohydrate ketogenic-like diet (KLD) or an ultra low-fat diet (ULF) at 3-months. Compared to ULF, KLD resulted in a transient but significantly greater increase in LDL-C at 3-months with a concomitant significantly greater reduction in the log(TG/HDL). At 12-months, LDL-C was similar for KLD and ULF, whereas KLD maintained significantly greater improvements in log(TG/HDL) compared to ULF. In terms of diet quality, refined grain intake was reduced significantly more for KLD than ULF at both 3-months. At 12-months the consumption of refined grains remained less than 50% of baseline levels for KLD, whereas it increased almost 50% from

baseline for ULF, possibly due to compensatory mechanisms for the decreased intake of calories from fat. Both groups substantially reduced added sugars, although these reductions were significantly greater for KLD compared to ULF at both 3-months and 12-months; KLD and ULF reported consuming ~80% and ~ 30% less added sugar than at baseline, respectively.

Our analysis provides a snapshot of the DIETFITS participants assigned to HLC or HLF that most successfully restricted dietary carbohydrates or fat, respectively, at 3-months. Participants were instructed to consume <20 g of carbohydrates or fat for the HLC or HLF, respectively, during the first 2 months of *Limbo* phase, and to subsequently increase intakes until they achieved their lowest level of intake that they could realistically maintain in the long term. Following these instructions, few subjects assigned to either diet arm achieved and maintained at 3-months macronutrient intakes approximating those initial targets: <30 g/day of carbohydrates for the 18 subjects in KLD out of 205 assigned to HLC, and < 15% of fat, equivalent to about 20 g/day, for the 21 subject in ULF out of 216 assigned to HLF. These dietary patterns underscore notable parallels: KLD aligns with the principles of the Atkins induction diet, while ULF shares resemblances with well-known ultra low-fat regimens like the Ornish and Pritikin diets. Even these subjects who most successfully restricted dietary carbohydrates or fat at 3-months reported substantial overall recidivism toward baseline intake values of carbohydrates or fat by 12-months. Nevertheless, ULF maintained an average fat intake of ~50 g/day at 12-months, and KLD maintained an average intake of ~80 g/day of net carbohydrates. Compared to the larger DIETFITS population (23), at 12-months both KLD and ULF lost twice as much weight (~ −10 kg vs. ~ −5 kg) and experienced a two times greater improvement in insulin resistance (30% vs. 15%).

Our finding that a very low-fat diet may lead to a compensatory increase in refined grain intake is in line with what was reported by the Women's Health Initiative (WHI) Dietary Modification Trial, which showed that women who consumed a low-fat diet (<20% daily energy intake) increased intake of refined grains (+0.3 servings/d) (31). This suggests that, while a low fat diet has the potential to be cardioprotective if the total sugar intake is also kept low, more often there is a compensatory increase in the consumption of refined carbohydrates and added sugars. It is estimated that dietary carbohydrate intake among US adults make up 50% of our total energy intake with over 40% of carbohydrates being of low-quality from refined grains, added sugars in foods and beverages, fruit juice, and potatoes (32).

Our data add to previous evidence indicating that very low-carb ketogenic diets can lead to a triad of higher LDL-C, higher HDL-C and lower TGs (5–10, 12, 13, 33–45). This triad is thought to reflect a shift toward an overall less atherogenic LDL profile (46, 47) — from TG-enriched small dense LDL particles (LDL-P, pattern B) to cholesterol-enriched large buoyant LDL-P (pattern A) (5, 11, 42, 48, 49). Specifically, KLD induced a ~ 12% transient increase in LDL-C at 3-months with a concomitant greater decrease in log(TG/HDL), which is a marker of increased LDL-P size and an overall less atherogenic LDL profile (50). At 12-months, KLD maintained this greater improvement in log (TG/HDL), whereas LDL-C was similar for KLD and ULF.

This study has several strengths including a large parent trial ($n = 609$), comprehensive diet assessment, comprehensive set of cardiometabolic risk factors analyzed, and high macronutrient differentiation at 3-months in presence of similar caloric intake and reduction of added sugars and refined grain intake. Our analysis also has a number of important limitations. First, this was a post-hoc analysis that tested hypotheses that were not planned in the parent trial protocol. Most importantly, only a small number of subjects met the criteria for inclusion compared to the broader parent trial, which impairs the significance and generalizability of our findings. In addition, dietary intake data were self-reported even if collected in multiple pass recalls. Therefore, all the reported statistically significant associations or lack thereof must be interpreted with caution. For example, despite non-statistically different baseline values in triglycerides, the physiological differences could still contribute to the observation that triglycerides and the atherogenic index improved in KLD. Finally, it is important to mention the difficulty in discerning the impact of diet versus weight loss on clinical outcomes and that long-term studies on ketogenic diets are limited.

Clinicians can take away a few practical insights from this exploratory analysis. First, patients who successfully establish a very low "anchor" of carbohydrate or fat intake in the initial phase of a low-carb or low-fat intervention may achieve lower maintenance intakes and better outcomes than those who began with a higher anchor. Anchoring is an unconscious process whereby initial exposure to a number serves as a reference point or "anchor" thus influencing subsequent judgments (51–54). Both KLD and ULF participants achieved greater long-term restrictions of carbohydrates and fats, respectively, and greater weight loss and insulin improvements than the overall DIETFITS population. However, KLD and ULF dieters made up less than 10% of our study population, which likely reflects differences in personality, experience, and other socioeconomic factors known to affect the response to anchoring (55, 56). Second, the drastic reduction of dietary fat on an ultra low-fat diet may lead to a compensatory increase in the consumption of refined grains that persist even when people increase their fat intake to moderate levels after an initial ULF phase. In contrast, anchoring patients to a ketogenic diet in the first phase of a low-carb diet may lead to greater long-term reductions in added sugars and refined grains. Third, those who follow a KLD in the first 3-months of a low-carb intervention may experience a transient increase in LDL-C with sustained improvements in TG and HDL that persist even when people increase their carbohydrate intakes to moderate non-ketogenic levels of ~80 g/day after an initial KLD phase. While both dietary approaches appear to reduce cardiometabolic risk factors, further research is needed to compare their effects to a Mediterranean Diet in an outcome study with cardiac endpoints and total mortality.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by Stanford University Human Subjects Committee (Institutional Review Board). The patients/participants provided their written informed consent to participate in this study.

Author contributions

LA, JR, and CG designed research. JR analyzed data. LA, ML, JR, and CG wrote paper. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2023.1220020/full#supplementary-material

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Iain Brownlee,
Northumbria University, United Kingdom

*CORRESPONDENCE
Christopher D. Gardner
✉ cgardner@stanford.edu

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Corrigendum: Weight, insulin resistance, blood lipids, and diet quality changes associated with ketogenic and ultra low-fat dietary patterns: a secondary analysis of the DIETFITS randomized clinical trial

Lucia Aronica[1], Matthew J. Landry[1], Joseph Rigdon[2] and Christopher D. Gardner[1]*

[1]Stanford Prevention Research Center, Stanford University School of Medicine, Stanford, CA, United States, [2]Department of Biostatistics and Data Science, Wake Forest University School of Medicine, Quantitative Sciences Unit, Stanford, CA, United States

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In the published article, there was an error in Figure 1 as published. The KLD and ULF bars were switched, but the numerical values within them, as well as other information presented in the figure and caption, were accurate.

The corrected Figure 1 and its caption appear below.

The authors apologize for this error and state that this does not change the scientific conclusions of the article in any way. The original article has been updated.

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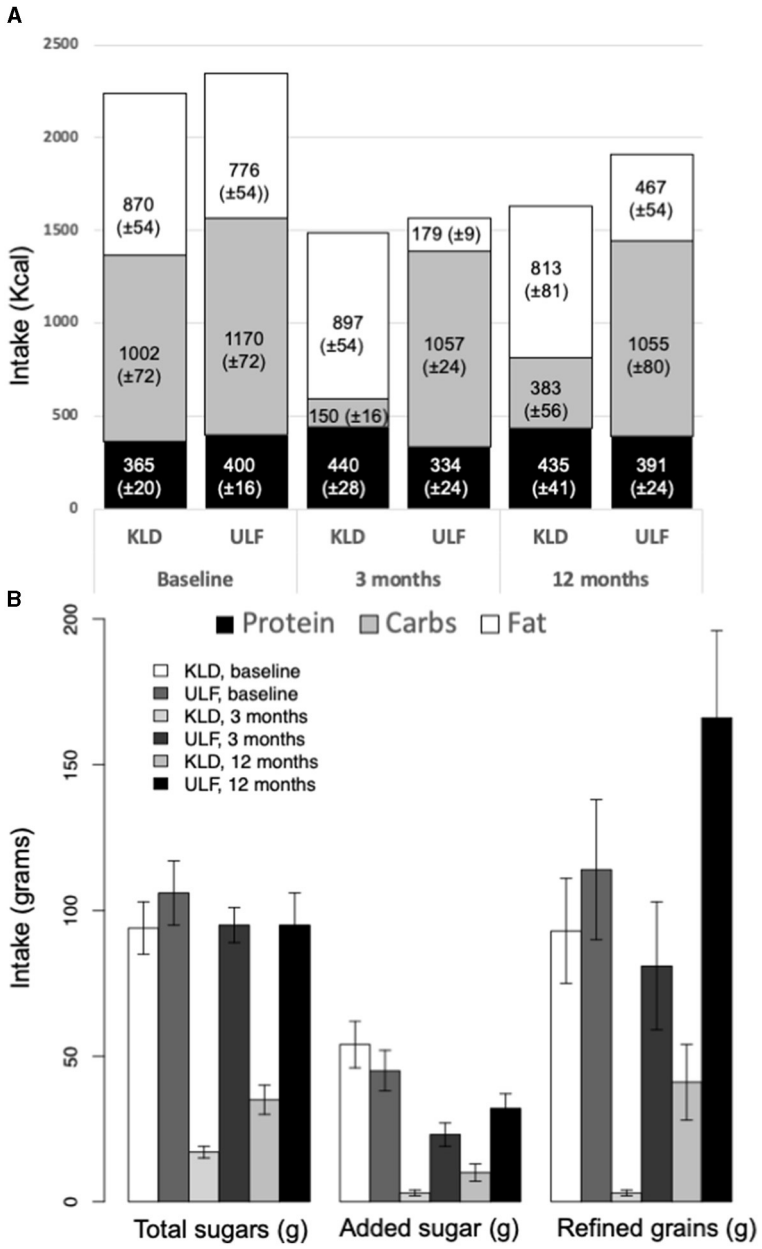

FIGURE 1
Macronutrient, added sugar, and refined grains intake for KLD and ULF. **(A)**: Mean intake (Kcal/day; ± standard error of mean) of protein (black), carbohydrates (gray), and fat (white) for KLD and ULF at baseline, 3 months, and 12 months. **(B)**: Mean intake (grams/day; ± standard error of mean) of total sugar, added sugars, and refined grains for KLD and ULF at baseline, 3 months, and 12 months. *p*-values for null hypothesis that nutrition variables are equivalent between diets at a given timepoint; from a linear mixed effects model including fixed effects for time, diet, and time*diet interaction, and a random effect for study participant.

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EDITED BY
Galya Bigman,
United States Department of Veterans Affairs, United States

REVIEWED BY
Jennifer Ann Nasser,
Drexel University, United States
Rafael De La Torre,
Hospital del Mar Medical Research Institute (IMIM), Spain

*CORRESPONDENCE
Heidi J. Silver
✉ Heidi.j.silver@vumc.org
Elizabeth A. Gollub
✉ egollub@agcenter.lsu.edu

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Factors that predict weight loss success differ by diet intervention type

Jordan Losavio[1], Michael J. Keenan[1], Elizabeth A. Gollub[2]* and Heidi J. Silver[3,4]*

[1]College of Agriculture, Louisiana State University, Baton Rouge, LA, United States, [2]Louisiana State University Agricultural Center, Baton Rouge, LA, United States, [3]Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, United States, [4]Department of Veterans Affairs, Tennessee Valley Healthcare System, Nashville, TN, United States

Background: Many types of diet intervention can achieve negative energy balance and successful weight loss in persons with obesity. However, within any dietary strategy, there is large inter-individual variation in the weight loss response. The aim of this study is to determine factors that predict weight loss success for diet interventions that vary by macronutrient and caloric composition.

Methods: Participants with BMI 30.0 to 49.9kg/m^2 self-selected one of three diet intervention trials for weight loss: low carbohydrate (LOW CHO), low fat (LOW FAT), or low calorie (LOW KCAL). Multivariable regression models were developed to determine the significance of predictor demographic, body composition, metabolic, clinical, and dietary variables for each diet type.

Results: Weight loss over 12–16weeks averaging −5.1±4.0kg from baseline weight, $p<0.001$, was not significantly different among diet types. Several different factors were identified that account for the inter-individual variance in weight loss success. Regardless of diet type, the most robust predictor of weight loss success was completion of the intervention, accounting for 20–30% of the variance. Factors predicting diet intervention completion were age, physical activity level, blood leptin level, blood pressure, and the amount of weight loss occurring. Differences by diet type in cardiometabolic risk factor reduction were identified with LOW CHO decreasing glycemia/insulinemia factors, LOW FAT decreasing lipidemia factors, and LOW KCAL decreasing inflammatory factors.

Conclusion: These data provide evidence to inform more precise and personalized approaches to diet intervention for weight loss and cardiometabolic health.

KEYWORDS

obesity, diet, fat, carbohydrate, weight loss, cardiometabolic

1. Introduction

Overweight and obesity is affecting ~2 billion adults and almost 400 million children and adolescents globally (1). A market research survey of 22,008 individuals from 30 countries showed that 45–60% of people are currently trying to lose weight (2). These statistics underscore the urgent need to identify key determinants for efficacy of weight loss diets (3). While many types of diet interventions can achieve a negative energy balance, a successful dietary strategy is one that facilitates a loss of at least 5% of baseline body weight and improves cardiometabolic

health (4). Common dietary strategies include varying macronutrient composition (e.g., low carbohydrate or low fat) as well as restricting total energy (low calorie) intake. Low carbohydrate diets are often promoted for weight loss based on the hypothesis that they increase satiety and promote lipolysis, as illustrated by the carbohydrate insulin model (5). Low fat diets have been recommended as a means for avoiding positive energy balance and reducing cardiovascular disease risk (6). Low calorie diets promote negative energy balance, but may be thwarted by adaptative thermogenesis that favors weight regain (7).

A meta-analysis of 5 randomized controlled trials that included 447 free-living adults showed that weight loss from low carbohydrate diets was greater than from low fat diets by 3.3 kg at the 6-month timepoint, but this difference was not maintained at 12 months (8). More recently, a meta-analysis of 121 randomized controlled trials that included 21,942 overweight/obese adults, similar in age to those in the prior meta-analysis, was conducted (9). This analysis demonstrated minimal differences in weight loss at 6 months between low carbohydrate and low fat diet types, and no significant differences at 12 months (9). These findings indicate that weight loss can be achieved with adherence to any diet type (10).

However, within any dietary strategy, there is large variation in weight loss response among individuals. For example, in a 12-month randomized trial comparing the efficacy of four popular diets, weight change among participants within a given diet type ranged from −30 to +10 kilograms (11). This inter-individual variability may be accounted for by a range of biological, physiological, psychological, behavioral, and environmental factors. The purpose of the present study is to determine factors that impact weight loss and weight loss success in diet interventions that vary by macronutrient and caloric content. These findings may assist in personalizing dietary approaches for weight loss and optimizing treatment outcomes.

2. Methods

2.1. Recruitment and eligibility

Participants were recruited for dietary weight loss interventions that were conducted at Vanderbilt University Medical Center (VUMC) between 2016–2020 (Supplementary Figure S1) upon responding to flyers posted in the metropolitan Nashville area at college campuses, public libraries, community parks, and community agency offices or responding to a study-specific announcement distributed on the VUMC research email listserv. To be included participants were age 21–60 years, BMI between 30.0 to 49.9 kg/m^2, and weight stable during the 3 months prior to enrollment. Exclusion criteria were diagnosis in the electronic medical record of esophageal disorders, type 1 and 2 diabetes, cancer, liver disease, respiratory disease, kidney disease, cardiovascular disease, uncontrolled hypertension, or a history of esophageal or bariatric surgery. Potential participants were also excluded if they had food allergies or dietary restrictions, gastrointestinal malabsorption, alcohol consumption averaging >2 drinks/day during the 3 months prior to enrollment, had a history of smoking, vaping, or illicit drug use, taking medications that alter appetite or energy metabolism, or were pregnant or lactating. The studies were approved by the Vanderbilt University Medical Center Institutional Review Board and all participants signed written informed consent.

2.2. Diet interventions

To mimic real-world conditions, participants self-selected one of three diet intervention types (Supplementary Figure S1). The diet interventions were 4–6 months in duration (Figure 1) and utilized a dietary strategy with defined macronutrient distributions and/or energy restriction. A 7-day rotation of menus was developed for each diet type by research dietitians at the Vanderbilt Diet, Body Composition and Human Metabolism Core (Core) using Nutrition Data System for Research software (NDS-R version 2015, Nutrition Coordinating Center, Minn., MN) to assure that each diet type met the planned macronutrient and energy goals. To establish individual caloric goals for weight loss, resting energy expenditure was measured by metabolic cart (ParvoMedics TrueOne 2,400®, Sandy, UT) and multiplied by an activity factor determined by a subject's total physical activity score. The low carbohydrate (LOW CHO) diet menus were designed to provide 30% of energy from carbohydrate, 50% of energy from fat, and 20% of energy from protein. The low fat (LOW FAT) and low calorie (LOW KCAL) diet menus were designed to provide 50% of energy from carbohydrate, 30% of energy from fat, and 20% of energy from protein. In addition, the LOW KCAL diet was designed to reduce baseline habitual energy intake by 500 calories per day. During the consent visit, participants agreed to refrain from heavy alcohol consumption and vigorous physical activity during the diet intervention period.

2.3. Diet assessment

Dietary intakes were assessed for energy and nutrient composition by 24-h diet recall interviews conducted by registered dietitians at the Core using the validated U.S. Department of Agriculture five-step multi-pass methodology, a standardized questionnaire, and computer-generated prompts from NDS-R version 2016 (12, 13). Direct entry into NDS-R enabled identifying foods and beverages consumed by name, brand, and preparation method from a database of 18,000 items. Portion sizes of all foods and beverages consumed during the 24-h periods were estimated using standard measuring utensils (plates, cups, bowls, and spoons of various sizes). Data were analyzed for energy (kcal), energy density (kcal/g), macronutrients as percentage of energy, and two micronutrients (sodium and potassium) due to their role in hypertension, the major risk factor for cardiovascular disease (14). Food level data were also categorized into 12 subgroups: juices and sugar sweetened beverages, fruit and non-starchy vegetables, starchy vegetables, fats and fried foods, plant proteins, animal proteins, dairy, snacks and desserts, whole grains, refined grains, artificially sweetened beverages, and alcohol for analysis (Supplementary Table S1).

2.4. Anthropometry, body composition, and resting energy expenditure

Participants were instructed to avoid alcohol, excess caffeine intake, and non-routine physical activities on the day before each testing visit at the Vanderbilt Clinical Research Center, and to fast from 9:00 pm until arrival at 7:00 am. After vital signs were obtained, height (± 0.1 cm), weight (± 0.1 kg), and waist and hip circumferences

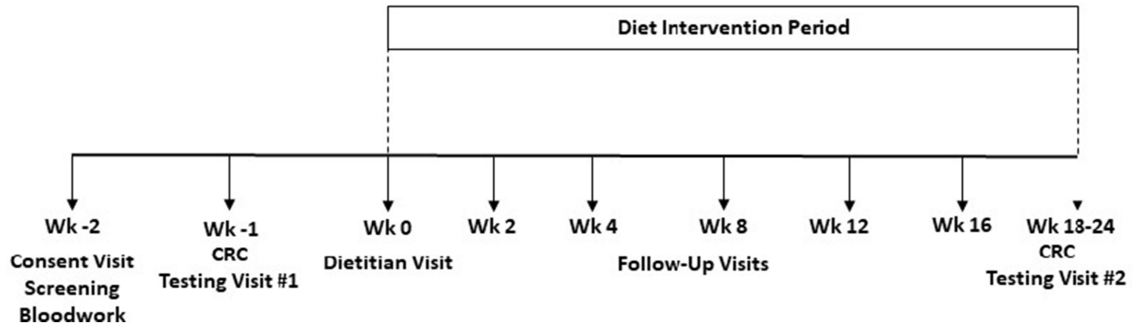

FIGURE 1
Study design.

(± 0.1 cm) were measured in triplicate using standardized procedures. Participants then rested in the supine position for ≥10 min prior to data collection for resting energy expenditure (REE) and substrate oxidation rates. We used a metabolic cart system (ParvoMedics TrueOne 2,400®, Sandy, UT) that was calibrated to room air and a single gas tank prior to data collection. Data was collected for 15 min at steady state under the hood with average change in minute $VO_2 \leq 10\%$ and respiratory quotient (RQ) ≤ 5%. REE was calculated via the Weir equation and substrate oxidation was determined according to the method of Frayn upon adjustment for 24-h urinary urea nitrogen output (15, 16).

Dual energy x-ray absorptiometry (DXA) was used to measure body composition using a Lunar iDXA scanner (GE Healthcare) with Encore software (version 13.6). Measurements were performed by one trained certified densitometrist after machine calibration to a phantom. Outputs included visceral adipose tissue (VAT) mass, total and regional fat mass, total and regional lean mass, and bone mineral area and density. In comparing performance of our DXA protocol *vs* whole body MRI, we show coefficients of variation <1.5% for total fat, trunk fat, total lean, and trunk lean masses, indicating good precision and reliability of the DXA data (17).

2.5. Clinical biomarkers

Whole blood and 24-h urine samples were collected at the clinical research center. A urine β-hCG test confirmed non-pregnancy at each study visit. Plasma glucose (colorimetric timed endpoint method), serum insulin (chemiluminescent immunoassay), plasma lipid profiles (selective enzymatic hydrolysis), and plasma C-reactive protein (CRP via enhanced turbidimetric assay) levels were measured at the Vanderbilt Department of Pathology Diagnostic Laboratory. Plasma leptin levels were measured at the Vanderbilt Hormone Core by radioimmunoassay. HOMA-IR was calculated from measured glucose and insulin levels [(fasting glucose (mg/dL) × fasting insulin (mU/mL)) / 405]. Metabolic syndrome status was determined based on having abnormal levels for ≥3 of the 5 established risk criteria (18).

2.6. Questionnaires

The three subscales of the Eating Attitudes Test (EAT-26) were scored with 20 or higher indicating high eating disorder risk characterized by high level of preoccupation with body weight, body image, and eating (19). Depression was categorized as "none to mild" versus "moderate to severe" based on scoring ≥16 on the Center for Epidemiological Studies Depression (CES-D) scale or ≥ 10 on the Beck Depression Inventory (20). Physical activity levels were established from scores on the Physical Activity during Cancer Treatment Questionnaire (PACT-Q) and the Baecke Physical Activity Questionnaire (21).

2.7. Statistical analysis

Differences in baseline characteristics among the 3 diet types were tested by chi-square or ANOVA. As a result of this testing sex, age, and BMI were included as covariates in all modeling. Potential predictors for each diet type were identified by univariate linear regression analysis with amount of weight loss as the primary outcome. Multivariable linear regression models were developed to determine the significance of predictor variables for each diet type. Prior to analysis, mean imputation was utilized to replace missing values, which comprised <1% of the independent variables (22). Akaike information criterion (AIC) forward-backward stepwise regression was used to remove nonsignificant covariates while achieving the best fit of the data. Initially, food and nutrient variables were excluded, leaving 26 independent variables. Dietary variables that were significant in the univariate analysis were then added to the multivariate model if this improved model performance (R^2 increased by ≥1%). The Variance Inflation Factor (VIF) was capped at 5 to reduce potential multicollinearity. The percentage of the variance explained by each predictor variable was estimated by dividing the individual sum of squares by the total sum of squares for all variables and residuals. This value was used to determine relative influence of each predictive factor on amount of weight loss. Logistic regression models for each diet type were also created for the secondary outcomes of: (a) weight loss success (yes/no), defined as weight loss ≥5% of baseline body weight and (b) diet intervention completer (yes/no). Lastly, we performed exploratory analysis to determine any trends within each diet type for improvements in clinical biomarkers of cardiometabolic health via analysis of covariance (ANCOVA) with the baseline biomarker value as a covariate. RStudio for Windows software (R Foundation for Statistical Computing, Vienna, Austria) was used for all statistical analyses with a type I error of 5% (23).

3. Results

Of the 305 study participants who met enrollment criteria (Supplementary Figure S1), 65% self-identified as white and 35% as Black or other, with no significant differences among diet type groups by race/ethnicity, income, marital status, or educational status (Table 1). Unlike the LOW FAT and LOW KCAL diet groups, the LOW CHO group, comprising 47% of all participants, was 100% female. At baseline, the LOW KCAL group was older, had higher glucose and insulin levels, and had a greater proportion of participants meeting metabolic syndrome criteria compared to the LOW CHO and LOW FAT diet groups (all *ps* < 0.001). Overall, 48% of participants met BMI criteria for Class I obesity (BMI 30.0–34.9 kg/m^2), 42% for Class II obesity (BMI 35.0–39.9 kg/m^2), and 10% for Class III obesity (BMI ≥ 40.0 kg/m^2).

At baseline, prior to any diet intervention, reported intakes of the amount of energy (kcal) consumed differed among the groups ($p < 0.001$), ranging from 1903.0 ± 447.5 kcal/day in the LOW CHO group to 2106.1 ± 970.7 kcal/day in the LOW FAT group to 2349.9 ± 707.4 kcal/day in the LOW KCAL group (Table 2). However, there were no significant differences observed among diet groups for

TABLE 1 Baseline descriptive characteristics of study participants by diet type.

	LOW CHO	LOW FAT	LOW KCAL	ALL	
	N =144	*N* =85	*N* =76	*N* =305	*p*-value
Demographics					
Age (year)	36.8 ± 6.8[a]	38.7 ± 8.2[a]	48.0 ± 7.0[b]	39.9 ± 8.5	< 0.001
Sex (male)	0 (0%)[a]	21 (25%)[b]	23 (35%)[b]	44 (15%)	< 0.001
Race (non-white)	41 (29%)	34 (39%)	29 (44%)	104 (35%)	0.06
Education					0.24
High School or less	22 (15%)	9 (11%)	11 (17%)	42 (14%)	
College or more	120 (85%)	76 (89%)	55 (83%)	251(86%)	
Income					0.65
≤ $50 k/yr.	67 (47%)	38 (45%)	33 (50%)	138 (47%)	
> $50 k/yr.	75 (53%)	47 (55%)	33 (50%)	155 (53%)	
Married (yes)	83 (58%)	47 (55%)	44 (67%)	174 (59%)	0.26
Anthropometrics					
Height (cm)	163.5 ± 6.4[a]	167.4 ± 8.2[b]	169.4 ± 9.4[b]	166.0 ± 8.1	< 0.001
Weight (kg)	93.0 ± 10.6[a]	99.7 ± 13.5[b]	107.1 ± 17.0[c]	98.1 ± 14.2	< 0.001
Body Mass Index (kg/m^2)	34.8 ± 2.7[a]	35.6 ± 3.3[a]	36.9 ± 4.2[b]	35.5 ± 3.3	< 0.001
Body Fat (%)	47.2 ± 3.4[a]	45.5 ± 6.4[b]	45.1 ± 5.6[b]	46.2 ± 5.0	0.006
Clinical Biomarkers					
Glucose (mg/dL)	92.3 ± 12.1[a]	89.6 ± 8.5[a]	144.9 ± 43.0[b]	103.4 ± 30.5	< 0.001
Insulin (mIU/L)	10.7 ± 7.5[a]	10.2 ± 5.9[a]	29.4 ± 14.5[b]	14.8 ± 11.8	< 0.001
HOMA-IR (score)	2.6 ± 2.1[a]	2.3 ± 1.4[a]	10.3 ± 5.3[b]	4.2 ± 4.3	< 0.001
TG/HDL-Cholesterol (ratio)	2.1 ± 1.4[a]	2.1 ± 1.3[a]	3.7 ± 2.3[b]	2.4 ± 1.8	< 0.001
LDL–Cholesterol (mg/dL)	102.3 ± 25.4	106.2 ± 28.1	105.3 ± 33.1	104.1 ± 28.0	0.56
C-Reactive Protein (mg/L)	6.0 ± 6.9	4.8 ± 4.7	6.7 ± 7.1	5.8 ± 6.3	0.18
Systolic Pressure (mmHg)	121.4 ± 11.1	124.6 ± 13	123.1 ± 13.9	122.7 ± 12.1	0.15
Diastolic Pressure (mmHg)	69.9 ± 8.5[a]	74.3 ± 9.5[b]	69.6 ± 9.1[a]	71.1 ± 8.9	< 0.001
Resting Energy Expenditure (kcal)	1608.2 ± 191.9[a]	1638.8 ± 314.1[a]	1890.5 ± 303.4[b]	1680.7 ± 277.3	< 0.001
Respiratory Quotient (VCO_2/VO_2)	0.82 ± 0.05	0.82 ± 0.09	0.80 ± 0.05	0.82 ± 0.06	0.16
Leptin (ng/mL)	33.8 ± 9.8[a]	22.8 ± 9.9[b]	30.1 ± 17.1[a]	29.8 ± 12.0	< 0.001
Risk factors					
Metabolic Syndrome (yes)	40 (28%)[a]	22 (26%)[a]	58 (76%)[b]	117 (38%)	< 0.001
Low Physical Activity (yes)*	36 (25%)	21 (25%)	19 (26%)	76 (25%)	0.94
Mod-Severe Depression (yes)**	11 (8%)	6 (7%)	4 (6%)	21 (7%)	0.91
Eating Behavior (score)***	12.5 ± 7.6[a]	10.0 ± 6.0[b]	10.3 ± 5.1[b]	11.3 ± 6.8	0.009

*Low physical activity is defined as being in the bottom quartile of physical activity scores (21). **Moderate to severe depression is determined by score on the CESD/BDI scales (20). ***Eating behavior score is based on the EAT-26 questionnaire (19). ****Values with different superscript letters ([a b c]) are significantly different.

TABLE 2 Reported dietary intakes at baseline by diet type.*

	LOW CHO	LOW FAT	LOW KCAL	
	N =144	*N* =85	*N* =76	*p*-value
Nutrients				
Total Energy (kcal)	1903.0 ± 447.5[a]	2106.1 ± 970.7[a,b]	2349.9 ± 707.4[b]	< 0.001
Energy Density (kcal/g)	0.7 ± 0.2[a]	0.9 ± 0.4[b]	0.7 ± 0.3[a]	0.01
Fat (%)	38.4 ± 7.4	38.0 ± 11.9	40.8 ± 9.4	0.14
Carbohydrate (%)	44.5 ± 8.8	46.4 ± 14.0	42.5 ± 10.4	0.09
Protein (%)	16.6 ± 4.3	16.1 ± 5.3	16.0 ± 4.3	0.54
Animal Protein (%)	67.1 ± 12.0	66.2 ± 16.5	65.3 ± 26.0	0.69
Saturated Fat (g)	28.0 ± 9.7	30.6 ± 21.5	33.1 ± 11.9	0.05
Polyunsaturated Fat (g)	18.1 ± 8.9[a]	19.1 ± 13.6[a]	37.7 ± 14.5[b]	< 0.001
Monounsaturated Fat (g)	30.2 ± 9.3[a,b]	33.1 ± 19.4[a]	26.5 ± 15.1[b]	0.02
Omega-3 Fatty Acids (g)	1.8 ± 0.9[a]	2.0 ± 1.3[a]	2.5 ± 1.5[b]	< 0.001
Simple Sugars (g)	87.2 ± 44.3[a]	112.4 ± 100.8[b]	97.7 ± 69.1[a,b]	0.03
Starch (g)	103.0 ± 36.8	109.1 ± 60.7	117.8 ± 52.9	0.12
Fiber (g)	15.6 ± 6.0[a]	15.1 ± 8.4[a]	19.4 ± 10.1[b]	0.001
Glycemic Load	121.3 ± 41[a]	142.1 ± 84.7[b]	146.6 ± 69.1[b]	0.01
Sodium (mg)	3412.9 ± 982.3[a]	3450.2 ± 1668.8[a]	4431.9 ± 1711.6[b]	< 0.001
Sodium:Potassium Ratio	1.7 ± 0.7	1.6 ± 0.7	1.8 ± 0.7	0.18
Foods (svgs/day)				
Fruits & Non-Starchy Vegetables	3.2 ± 1.5	2.5 ± 2.4	2.9 ± 3.2	0.15
Starchy Vegetables	0.3 ± 0.3	0.2 ± 0.5	0.4 ± 0.7	0.23
Fats, Fried Foods, Fast Foods	6.9 ± 5.1[a]	4.8 ± 4.2[b]	5.7 ± 4.3[a,b]	0.003
Plant Proteins	1.6 ± 1.0[a]	0.7 ± 1.6[b]	0.9 ± 2.2[b]	< 0.001
Animal Proteins	5.2 ± 2.1	5.0 ± 3.2	5.7 ± 3.8	0.36
Dairy Products	1.3 ± 0.6	1.4 ± 2.0	1.3 ± 1.1	0.72
Whole Grains	0.9 ± 0.9	1.1 ± 1.7	0.9 ± 1.3	0.72
Refined Grains	3.4 ± 2.1[a]	4.6 ± 3.2[b]	5.0 ± 3.1[b]	< 0.001
Snacks & Dessert items	0.9 ± 1.1[a]	2.2 ± 3.0[b]	1.6 ± 1.6[b]	< 0.001
Juice & Sugar-Sweetened Beverages	0.6 ± 1.0[a]	1.3 ± 1.7[b]	1.0 ± 1.8[b]	< 0.001
Artificially Sweetened Beverages	0.8 ± 1.5	0.8 ± 1.6	1.1 ± 2.1	0.32
Alcohol Beverages	0.1 ± 0.4	0.1 ± 0.5	0.0 ± 0.1	0.10

Values with different superscript letters [(a b)] are significantly different.

the macronutrient composition (percentage of energy as fat, carbohydrate, and protein) of habitual dietary intakes. The LOW CHO group reported consuming fewer simple carbohydrates (simple sugars), fewer servings/day of refined grains, fewer servings/day of juice and sugar-sweetened beverages, fewer servings/day of snacks and desserts, and less sodium. The LOW FAT group reported a higher intake of monounsaturated fats and fewer servings/day of total fats, fried foods, and fast foods. The LOW KCAL group reported a higher intake of dietary fiber, more servings/day of refined grains, a higher glycemic load, and higher sodium intake.

3.1. Impact of intervention on body weight by diet type

Participants in all diet types experienced a significant weight loss averaging 5.1 ± 4.0 kg from baseline weight ($p < 0.001$). Neither the amount or rate of weight loss were significantly differently among the diet types: LOW CHO -5.0 ± 4.0 kg; LOW FAT -5.2 ± 3.9 kg; LOW KCAL -4.9 ± 4.2 kg, $p = 0.85$ (Figure 2; Supplementary Figure S2). There was also no significant difference in the proportion of participants who achieved successful weight loss (≥ 5% of baseline weight), with 49% of the LOW CHO group, 51% of the LOW FAT group, and 38% of the LOW KCAL group achieving weight loss success ($p = 0.23$). Yet, participants who completed all weeks of their respective diet intervention type lost more weight than non-completers (LOW CHO -6.7 ± 4.0 *vs* − 2.1 ± 1.9 kg; LOW FAT -6.1 ± 3.5 *vs* − 1.4 ± 2.97 kg; LOW KCAL -6.0 ± 4.2 *vs* − 1.7 ± 2.2 kg, all *p*s < 0.001). Univariate analysis showed that amount of weight loss, older age, higher leptin level, higher physical activity score, and lower depression score were associated with diet intervention completion (Supplementary Table S1). Although diet type was not significantly associated with completion status, there was a difference by diet type

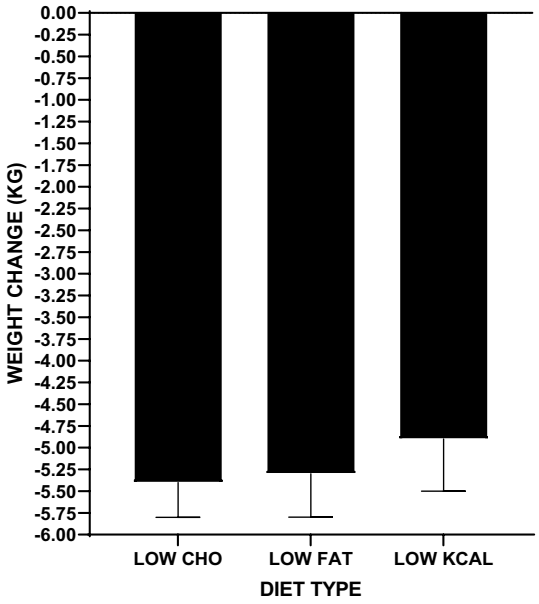

FIGURE 2
Comparison among diet types for total weight change.

in the proportion of participants who completed all study weeks (LOW CHO 64%, LOW FAT 81%, LOW KCAL 74%, $p = 0.02$).

3.2. Predictors of amount of weight loss by diet type

As expected, there was much variability in weight change among participants within each diet type. Linear regression modeling was used to determine the most parsimonious models to predict amount of weight loss for each diet type. For the LOW CHO diet, the factors that accounted for 41% of the inter-individual variance in weight loss were completion status, self-reported race, baseline percent body fat, respiratory quotient, and metabolic syndrome status. For the LOW FAT diet, 51% of the inter-individual variance in weight loss was accounted for by completion status, education level, marital status, baseline percent body fat, LDL-cholesterol level, leptin level, blood pressure, resting energy expenditure, and fruit and vegetable intake. For the LOW KCAL diet, 42% of the inter-individual variability in weight loss was accounted for by completion status, age, education level, LDL-cholesterol level, insulin level, systolic blood pressure, leptin level, eating behavior score, metabolic syndrome status, and protein and simple sugars intake. Completion status accounted for the greatest proportion of the inter-individual variance in all diet types (Table 3).

3.3. Predictors of successful weight loss (≥ 5% baseline weight) by diet type

Logistic regression modeling was used to predict weight loss success by diet type (Table 4). For the LOW CHO diet, completion status, age, self-reported race, baseline percent body fat, and baseline glucose level accounted for 41% of the variance in weight loss success. For the LOW FAT diet, completion status, baseline insulin level, LDL-cholesterol level, physical activity score, and fruit and vegetable intake accounted for 40% of the variance in weight loss success. For the LOW KCAL diet, completion status, age, LDL-cholesterol level, and leptin level accounted for 24% of the variance in weight loss success. As with the linear regression modeling for amount of weight loss, completion of the diet intervention most significantly increased the odds for weight loss success with all three diet types [LOW CHO: OR 44.87 (13.22, 152.26); LOW FAT: OR 64.0 (6.17, 664.4); LOW KCAL: OR 17.42 (1.95, 155.71)]. The strongest predictor for diet intervention completion was the amount of weight loss being achieved [OR 1.58 (CI 1.39, 1.80)]. Other predictors of diet intervention completion were age, physical activity score, leptin level, and systolic blood pressure (Supplementary Table S3). Diet type was not a significant predictor of completion.

3.4. Impact of weight loss on cardiometabolic biomarkers by diet type

Exploratory analysis was performed to uncover trends within each diet type on nine fundamental biomarkers of cardiometabolic health (Table 5). Participants with successful weight loss in the LOW CHO group had significantly improved blood insulin level, HOMA-IR score, LDL-cholesterol level, and systolic and diastolic blood pressure. For participants with successful weight loss in the LOW FAT group, there were significantly improved LDL-cholesterol level, triglyceride level, TG/HDL ratio, and diastolic blood pressure. In the LOW KCAL group, participants with successful weight loss had significantly improved blood glucose level, HDL-cholesterol level, systolic and diastolic blood pressure, and serum CRP level.

4. Discussion

Although some public and scientific debate continues, this study and the cumulative evidence does not support recommending a particular diet type for weight loss – many different types of diets yield significant and clinically meaningful weight loss. Indeed, a meta-analysis of controlled feeding studies evaluating the impact of diet composition (isocaloric low fat *vs* low carbohydrate diets) on daily energy expenditure showed such small differences by diet type that they were physiologically meaningless (26 kcal/day) (24). The present data support the concept that a person can choose a weight loss diet based on individual preference for diet type – indicating that there is no one specific optimal or ideal diet for weight loss. However, the present study provides unique information regarding the demographic, body composition, cardiometabolic, and dietary factors that are associated with the greatest weight loss success within three commonly employed diet types.

The demographic factors of age, self-reported race, and education status were significant predictors of the amount of weight loss and weight loss success (defined as ≥5% of baseline weight). Participant age was associated with weight loss success in both the LOW CHO and LOW KCAL groups. Interestingly, a study in adults age ≥ 25 years showed the amount of weight loss increased with age and older participants were more successful in maintaining weight loss after 3 years (25). Qualitative investigation has provided the insight that engaging in diet change is more likely to be interrupted by lifestyle behaviors, perceived stress, finances, and time challenges in younger

TABLE 3 Results from multivariable linear regression modeling to predict amount of weight change by diet type.*

Predictors	% Variance	Estimate	std. error	Statistic	*p*-value
LOW CHO diet: Adj. $R^2 = 0.40$, $p < 0.001$					
(Intercept)		26.449	6.270	4.22	<0.001
Completion (no/yes)	29.84	4.818	0.579	8.32	<0.001
Race (white/non-white)	4.56	−1.978	0.636	−3.12	0.002
Body Fat (%)	1.01	−0.195	0.086	−2.28	0.024
Respiratory Quotient (VCO_2/VO_2)	3.03	−17.295	5.649	−3.06	0.003
Metabolic Syndrome (no/yes)	2.90	−1.866	0.311	−2.79	0.006
LOW FAT diet: Adj. $R^2 = 0.51$, $p < 0.001$					
(Intercept)		0.737	5.391	0.13	0.892
Completion (no/yes)	23.92	3.664	0.868	4.22	< 0.001
Education (high school/college)	7.28	2.108	1.036	2.04	0.045
Marital Status (no/yes)	0.04	0.982	0.664	1.48	0.143
Body Fat (%)	0.45	0.153	0.076	2.02	0.047
LDL-Cholesterol (mg/dL)	6.58	−0.040	0.012	−3.44	<0.001
Diastolic Pressure (mm Hg)	3.62	−0.130	0.048	−2.74	0.008
Systolic Pressure (mm Hg)	1.43	0.084	0.037	2.25	0.027
Resting Energy Expenditure (kcal)	1.97	−0.003	0.001	−1.99	0.051
Leptin (ng/dL)	10.34	−0.173	0.045	−3.86	< 0.001
Fruit & Vegetable Intake (svgs/day)	3.05	0.346	0.127	2.72	0.008
LOW KCAL diet: Adj. $R^2 = 0.42$, $p < 0.001$					
(Intercept)		−3.350	5.382	−0.62	0.536
Completion (no/yes)	19.54	3.662	0.871	4.21	<0.001
Age (years)	3.01	0.143	0.057	2.52	0.015
Education (high school/college)	3.54	−2.337	1.039	−2.25	0.029
Insulin (mIU/L)	1.04	0.038	0.029	1.31	0.197
LDL-Cholesterol (mg/dL)	3.71	0.035	0.012	2.94	0.005
Systolic Pressure (mm Hg)	2.27	−0.050	0.033	−1.54	0.129
Leptin (ng/dL)	6.59	−0.044	0.027	−1.63	0.110
Metabolic Syndrome (no/yes)	2.76	−0.768	0.442	−1.74	0.088
EAT-26 (score)	4.81	0.118	0.075	1.58	0.121
Protein Intake (% kcal)	2.12	0.170	0.100	1.69	0.096
Simple Sugars Intake (g/day)	8.70	−0.014	0.006	−1.69	0.096

*Multiple linear regression and variable selection were performed to generate the best fitting model for the outcome of amount of weight loss for each diet type.

adults (26). In contrast, social support, diminishing responsibilities, and greater available time facilitate successful weight loss in older adults (27). Further, doubly labeled water studies show that the age-related decline in resting energy expenditure, which would inhibit weight loss and increase risk for weight gain, does not begin until after age 60 (28). The association of self-reported race with weight loss in the LOW CHO diet is consistent with previous research showing that participants who identified as African American, especially females, achieve less weight loss than white participants - despite similar reported dietary intakes (29–31). It is important to recognize that the racial/ethnic category of "African-American" represents a diverse group of people. Differences in response to diet may be influenced by genetics, cultural influences, family support, finances, living environment, and retention rates (29). It is also remains plausible that the difference in weight loss response by racial/ethnic category is a function of metabolic adaptation related resistance to weight change or dietary compliance (32, 33).

As a biological variable, it has been suggested that sex differences may partly explain the variability in weight loss. In the present study, we did not detect differences by sex with regard to adherence to the diet types and sex was not a significant predictor for the amount of weight loss, for having weight loss success, or for diet intervention completion. These findings contrast with a secondary analysis of the DietFits trial which showed that males were more adherent and lost more weight on a low carbohydrate diet than females (34). It is plausible that differences between males and females in body mass and composition, energy expenditure, as well as dietary preferences, were contributing factors. A systematic review of the published evidence identified only 4 studies designed to directly compare diet-induced

TABLE 4 Results from logistic regression modeling to predict achieving successful weight loss (≥ 5% of baseline weight) by diet type.*

Predictors	OR	95% CI	Increment	Wald statistic	*p*-value
LOW CHO diet: $R^2 = 0.41$					
(Intercept)				4.61	0.032
Completion	44.87	13.22, 152.26	Completer	37.23	<0.001
Age	0.93	0.87, 1.00	Year	3.94	0.047
Race (self-reported)	0.20	0.07, 0.58	Non-white	8.81	0.003
Body Fat %	0.80	0.66, 0.91	Percent	7.99	0.005
Glucose	1.03	1.00, 1.07	mg/dL	2.82	0.093
LOW FAT diet: $R^2 = 0.40$					
(Intercept)				1.48	0.401
Completion	64.03	6.17, 664.4	Completer	12.14	<0.001
Insulin	0.89	0.79, 0.99	mIU/L	4.15	0.042
LDL-Cholesterol	0.96	0.94, 0.99	mg/dL	10.16	0.001
Physical Activity	0.03	0.01, 1.56	Score	3.01	0.083
Fruit & Vegetable Intake	1.46	1.06, 2.01	Serving	5.22	0.022
LOW KCAL diet: $R^2 = 0.24$					
(Intercept)				8.05	0.005
Completion	17.42	1.95, 155.71	Completer	6.54	0.011
Age	1.13	1.02, 1.25	Year	5.18	0.023
LDL-Cholesterol	1.02	0.99, 1.04	mg/dL	2.19	0.139
Leptin	0.95	0.91, 1.00	mg/dL	3.50	0.061

*Logistic regression modeling and variable selection were performed to generate the best fitting model for the outcome of weight loss success (≥ 5% of baseline weight) for each diet type.

weight loss between males and females (35). The difference in amount of weight loss was no longer significant when adjusted for baseline weight in two of the 4 studies, and none of the studies showed significant differences when percent weight change was the outcome.

The influence of educational status on health outcomes such as comorbidities and life expectancy has been well-established (36, 37). However, data from 196,000 participants enrolled in work-based online weight loss programs showed that education level was not a predictor of percent weight loss (38). Yet, in the present findings, education status was a more robust predictor than age or self-reported race. The link between education status and weight loss success may be a function of available income and/or having resources to support diet change. Further, the relationship between education and cognitive function may be a factor influencing diet intervention adherence and the amount of weight loss (39). Nevertheless, lower educational status appears to be related to greater risk for weight gain and obesity (40, 41).

The baseline percentage of body fat, indicating whole body adiposity, was associated with weight loss in the LOW CHO and LOW FAT groups. Population-based evidence shows that the probability of achieving weight loss success, as defined in the present study, increases with higher BMI (42). Interestingly, baseline serum leptin level, which is dependent on total body fat (43, 44), was significantly associated with amount of weight loss in the LOW FAT and LOW KCAL diet groups. It is understood that obesity, and thus, high levels of circulating leptin, are associated with being in a state of leptin resistance that impairs sensitivity to the action of leptin on reducing food intake and increasing energy expenditure (45, 46). Hence, leptin resistance has a role in weight gain and maintaining a higher body weight, and circulating levels of leptin decrease with weight loss (47). Thus, in the present study, individuals with higher BMI but lower leptin levels had greater weight loss. Other forces driving leptin resistance include inflammation and high levels of circulating lipids, and reduced circulating leptin is a predictor of changes in oxidized LDL levels (48). In the present data, both baseline LDL-cholesterol levels and blood pressures associated with the amount of weight loss in the LOW FAT and LOW KCAL groups. It is expected that weight loss would reduce LDL-cholesterol, specifically the prevalence of small dense LDL particles (49), and improve blood pressure. However, whether baseline levels of LDL-cholesterol or baseline blood pressure would influence achieving weight loss has not been investigated. It is likely that the type of diet interventions provided attracted participants who are motivated by concern for their cardiometabolic risk and seek the benefits of weight loss on commonly measured clinical risk factors (50).

The most robust predictor of successful weight loss was completion status, accounting for 20–30% of the variance in weight loss. Like other non-surgical interventions for weight management, the attrition rate averaged 20–30% for the three diet types (51, 52). An ongoing challenge for weight management interventions is how to improve participant retention. Indeed, the World Health Organization has deemed adherence to treatments for chronic disease states a critical problem (53). We found that the amount of weight loss being achieved was the most robust predictor of study completion. Consistent with this finding, meta-analysis of 10 studies showed that dissatisfaction with weight loss results was associated with lower adherence (54). As with the present findings, older age was also associated with higher adherence. Given the widespread prevalence of obesity and increasing burden of cardiometabolic disease in younger adults, it remains crucial to identify efficacious treatment approaches for adults in their 20s, 30s and 40s (55).

TABLE 5 Comparison of changes in cardiometabolic biomarkers by diet type.

	Weight loss ≥5%			Weight loss <5%			p for Difference in mean change between groups
	Baseline	Final	*p*-value	Baseline	Final	*p*-value	
Low CHO Diet	*N* =63			*N* =26			
Glucose	93.4 ± 11.5	91.1 ± 7.5	0.07	88.2 ± 7.4	92.4 ± 8.8	0.01	0.04
Insulin	10.7 ± 7.6	8.1 ± 5.3	<0.001	8.6 ± 5.2	8.1 ± 5.1	0.49	0.16
HOMA-IR score	2.6 ± 2.1	1.9 ± 1.3	<0.001	1.8 ± 1.0	1.8 ± 1.2	0.94	0.22
LDL-Cholesterol	104.2 ± 22.5	96.4 ± 20.6	0.001	105.0 ± 31.1	99.81 ± 28.4	0.05	0.41
HDL-Cholesterol	46.6 ± 11.2	46.1 ± 10.1	0.61	50.0 ± 11.4	50.0 ± 8.4	0.89	0.53
Triglycerides	88.9 ± 47.6	81.7 ± 47.7	0.13	85.4 ± 31.9	89.7 ± 39.8	0.46	0.09
TG/HDL ratio	2.1 ± 1.5	1.9 ± 1.4	0.20	1.8 ± 0.9	1.8 ± 0.9	0.99	0.69
Systolic Pressure	120.6 ± 10.7	112.3 ± 10.4	<0.001	123.9 ± 10.8	120.4 ± 9.1	0.03	< 0.001
Diastolic Pressure	69.5 ± 8.4	64.6 ± 7.8	<0.001	71.9 ± 8.1	70.8 ± 5.2	0.38	< 0.001
C-Reactive Protein	6.2 ± 7.1	5.5 ± 5.4	0.33	4.9 ± 3.5	3.9 ± 3.3	0.10	0.33
Metabolic Syndrome Score	2.2 ± 0.9	1.9 ± 0.7	0.03	1.9 ± 0.9	2.0 ± 0.7	0.75	0.16

	Weight loss ≥5%			Weight loss <5%			p for Difference in mean change between groups
	Baseline	Final	*p*-value	Baseline	Final	*p*-value	
Low FAT Diet	*N* =39			*N* =24			
Glucose	89.7 ± 9.1	90.1 ± 8.2	0.81	90.4 ± 8.6	92.0 ± 11.11	0.54	0.46
Insulin	8.5 ± 5.2	7.9 ± 3.6	0.42	10.9 ± 5.6	12.6 ± 7.4	0.19	0.01
HOMA-IR score	1.9 ± 1.4	1.7 ± 0.8	0.40	2.3 ± 1.2	2.5 ± 1.0	0.45	< 0.001
LDL-Cholesterol	107.7 ± 22.8	100.7 ± 22.8	0.002	114.9 ± 28.8	113.0 ± 31.6	0.67	0.04
HDL-Cholesterol	52.4 ± 12.3	51.1 ± 10.8	0.28	50.4 ± 14.3	49.8 ± 14.0	0.70	0.41
Triglycerides	98.7 ± 40.8	85.2 ± 29.9	0.009	99.9 ± 49.0	105.3 ± 53.1	0.48	0.03
TG/HDL ratio	2.1 ± 1.4	1.8 ± 0.8	0.02	2.2 ± 1.6	2.4 ± 1.6	0.35	< 0.001
Systolic Pressure	123.2 ± 11.9	120.6 ± 11.8	0.13	129.9 ± 13.1	125.1 ± 13.9	0.13	0.73
Diastolic Pressure	72.4 ± 8.6	69.6 ± 6.3	0.02	78.5 ± 9.7	78.5 ± 11.6	0.99	0.01
C-Reactive Protein	4.6 ± 4.7	5.0 ± 5.7	0.35	5.3 ± 5.9	4.8 ± 4.1	0.21	0.14
Metabolic Syndrome Score	2.0 ± 0.9	1.7 ± 0.7	0.02	2.5 ± 1.1	2.3 ± 0.9	0.36	0.60

	Weight loss ≥5%			Weight loss ≥5%			p for Difference in mean change between groups
	Baseline	Final	*p*-value	Baseline	Final	*p*-value	
Low KCAL Diet	*N* =24			*N* =25			
Glucose	137.9 ± 43.5	105.8 ± 26.1	0.004	144.6 ± 34.3	113.6 ± 23.5	<0.001	0.40
Insulin	26.1 ± 10.9	37.3 ± 29.4	0.08	30.7 ± 14.3	37.3 ± 28.3	0.40	0.88
HOMA-IR	7.9 ± 3.6	7.6 ± 5.3	0.87	10.1 ± 4.4	11.5 ± 9.1	0.56	0.21
LDL-Cholesterol	108.4 ± 30.2	109.5 ± 28.3	0.89	96.4 ± 28.7	96.8 ± 28.0	0.93	0.64
HDL-Cholesterol	40.8 ± 9.8	43.1 ± 10.9	0.04	43.6 ± 10.9	41.0 ± 9.0	0.04	0.86
Triglycerides	157.3 ± 63.1	136.5 ± 49.8	0.09	141.1 ± 63.1	127.2 ± 57.2	0.20	0.67
TG/HDL	3.9 ± 2.0	3.5 ± 1.5	0.27	3.5 ± 1.9	3.3 ± 1.8	0.61	0.96
Systolic Pressure	120.8 ± 14.3	112.2 ± 10.3	<0.001	125.0 ± 14.5	121.3 ± 14.5	0.21	0.03
Diastolic Pressure	67.5 ± 9.0	63.3 ± 6.2	0.01	70.7 ± 9.6	69.1 ± 9.8	0.43	0.04
C Reactive Protein	4.7 ± 3.6	3.8 ± 3.1	0.04	7.6 ± 8.3	8.1 ± 10.3	0.81	0.20
Metabolic Syndrome Score	3.2 ± 0.9	2.5 ± 0.7	0.006	3.0 ± 1.0	2.7 ± 1.0	0.21	0.35

Notably, participants enrolled in all three diet types demonstrated valuable improvements in several cardiometabolic risk factors, especially those who achieved weight loss success (≥ 5% baseline weight). A modest 5% reduction in weight has been accepted as clinically meaningful as it is associated with improved percentage body fat, reduced intra-abdominal and intra-hepatic fat, reduced circulating levels of glucose, insulin, and triglycerides, as well as reduced HbA1C and blood pressures (56). Participants who achieved weight loss success in the three diet types experienced significant improvements in 4–5 key cardiometabolic risk factors. Weight loss success in all three diet types was associated with reduced blood pressure, although the improvement in the LOW FAT group was detected only for diastolic blood pressure. In addition to improved blood pressure, participants in the LOW FAT group experienced improved LDL-cholesterol, triglycerides, and TG/HDL ratio. Participants in the LOW CHO group experienced improvements in insulin levels, HOMA-IR score, and LDL-cholesterol. Participants in the LOW KCAL group experienced the greatest improvements in circulating glucose, HDL-cholesterol, and C-reactive protein.

This study has several limitations and strengths to be noted. First, the study was not a randomized controlled trial which would limit bias and allow for determination of cause and effect. Instead, participants chose the diet type they preferred, which mimics real-world conditions where almost half of all adults age 20 and over are attempting to lose weight by modifying their dietary intakes and/or physical activity (57). Second, the dataset did not include all the factors that may contribute to predicting the amount of weight loss or weight loss success, including genetic differences and some cognitive, behavioral, and environmental components of eating. Nevertheless, the inclusion of a wide variety of biological, physiological, and psychological factors into predictive modeling enabled accounting for a significant portion of the variance in both the amount of weight loss and achieving weight loss success. Third, we recognize the limitation of under-reporting in diet assessment. To reduce this bias, we train study subjects on portion size estimation using food models and measuring utensils, and we incorporate multi-pass methodology along with NDSR software generated prompts. Fourth, the diet intervention period was 4–6 months which limits extrapolating the findings to long-term intervention or weight loss maintenance. Finally, the addition of exercise combined with diet intervention may provide the stimulus for greater response, and thus, warrants future investigation.

5. Conclusion

The findings from this study support the concept that completion of an intervention to improve weight and health is the most important factor for a successful outcome. The data show that successful weight loss can be achieved through various dietary strategies. However, reducing weight to positively impact specific cardiometabolic risk factors differs by type of diet intervention. These findings indicate that a low carbohydrate diet may be most optimal for individuals at risk for prediabetes or type 2 diabetes. A low-fat diet may be most beneficial for reducing atherogenic dyslipidemia. A calorically restricted diet may improve either condition. Aligning a diet intervention type with an individual's personal risk factors is likely the most efficacious approach for improving cardiometabolic health.

Data availability statement

The raw data supporting the conclusions of this article could be made available by the authors, without undue reservation.

Ethics statement

The studies were approved by the Vanderbilt University Medical Center Institutional Review 66 Board and all participants signed written informed consent. The patients/participants provided written informed consent prior to their study participation.

Author contributions

HS and EG: study concept, study design, and funding. HS: data acquisition and database entry. JL: statistical analysis. JL, EG, and HS: tables, figures and manuscript development. JL, MK, EG, and HS: manuscript revisions and final draft. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2023.1192747/full#supplementary-material

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EDITED BY
Galya Bigman,
United States Department of Veterans Affairs, United States

REVIEWED BY
Pengkun Song,
Chinese Center For Disease Control and Prevention, China
Nazir Ahmad,
Government College University, Faisalabad, Pakistan

*CORRESPONDENCE
Kyungho Ha
✉ kyungho.ha@jejunu.ac.kr
Sangah Shin
✉ ivory8320@cau.ac.kr

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Amino acid intake with protein food source and incident dyslipidemia in Korean adults from the Ansan and Ansung Study and the Health Examinee Study

Sangwon Chung[1], Jae Ho Park[1], Hyojee Joung[2], Kyungho Ha[3]* and Sangah Shin[4]*

[1]Personalized Diet Research Group, Korea Food Research Institute, Wanju-gun, Jeollabuk-do, Republic of Korea, [2]Department of Public Health, Graduate School of Public Health, Seoul National University, Seoul, Republic of Korea, [3]Department of Food Science and Nutrition, Jeju National University, Jeju, Republic of Korea, [4]Department of Food and Nutrition, Chung-Ang University, Ansung-si, Gyeonggi-do, Republic of Korea

Background: Dyslipidemia is a major risk factor for cardiovascular diseases and appropriate intake of amino acids may be helpful for the management of dyslipidemia. However, evidence of an association between amino acid intake and dyslipidemia in Korean adults is limited.

Objective: The purpose of this study was to investigate how the incidence of dyslipidemia in Korean adults is associated with the consumption of amino acids, essential and nonessential types, as well as the sources of these amino acids from food.

Methods: Data from 35,478 study participants without dyslipidemia at baseline from the Ansan and Ansung Study and the Health Examinee Study were used for the analysis. Dyslipidemia and its components such as hypertriglyceridemia, hypercholesterolemia, hyper-low-density lipoprotein (LDL) cholesterolemia and hypo-high-density lipoprotein (HDL) cholesterolemia were the main outcome in this study. The participants were categorized into quartiles, based on the intake of amino acids and plant–/animal-based proteins.

Results: On average, the follow-up period lasted for 5.7 years. The two major food groups that contributed to one-half of the intake for each type of amino acid were whole grain mixed rice and white rice. Compared to the lowest quartile group, the highest quartile groups of essential amino acid intake [men: hazard ratio (HR) = 0.78; 95% confidence interval (CI), 0.63–0.97; *P* for trend = 0.0088; women: HR = 0.86; 95% CI, 0.76–0.99; *P* for trend = 0.0201] and nonessential amino acid intake (men: HR = 0.75; 95% CI, 0.60–0.94; *P* for trend = 0.0069; women: HR = 0.81; 95% CI, 0.71–0.93; *P* for trend = 0.0024) had a decreased risk of dyslipidemia. Plant-based protein intake had a negative association and animal-based protein intake had a nonsignificant association with dyslipidemia after adjustment for energy-adjusted fat intake. Furthermore, the essential and nonessential amino acid intake showed stronger negative associations with dyslipidemia after further adjustment for energy-adjusted fat intake.

Conclusion: To conclude, the intake of amino acids may have a protective effect against dyslipidemia in Korean adults who are aged 40 years or older, regardless of their protein food sources.

KEYWORDS
amino acid, plant-based protein, animal-based protein, dyslipidemia, cohort, Korea

1. Introduction

Dyslipidemia, which can lead to stroke, coronary heart disease, and ischemic heart disease, is a significant risk factor for cardiovascular diseases (CVDs) and can influence their incidence (1). Increased cholesterol levels in 20- to 39-year-old young adults have been associated with a high risk of ischemic heart disease incidence (2). In addition, more than 40 and 20% of global death by ischemic heart disease and stroke, respectively, were attributed to elevated levels of plasma low-density lipoprotein cholesterol (LDL-C) (3). However, the improvement of dyslipidemia, such as lowered triglyceride (TG) levels, has been associated with decreased CVD risk in previous studies (4). Therefore, paying close attention to the management and prevention of dyslipidemia as a means to enhance health and increase longevity is crucial.

Healthy dietary habits are recommended as a strategy for lowering lipid levels and preventing CVD (5, 6). Maintaining a balanced intake of energy sources, including an appropriate proportion of protein in one's diet, has been a long-standing concern for managing various diseases and is crucial for a healthy diet (7). Although the results remain inconclusive, several studies have shown that a high protein intake improves cardiometabolic parameters, including lipid profiles, blood pressure, and glycemic regulation (8–10). Moreover, an appropriate intake of amino acids can be helpful for the management of cardiometabolic health has been reported.

Amino acids are components of proteins and are traditionally categorized as essential and nonessential amino acids. Consuming essential amino acids from dietary sources is essential because the carbon skeletons of these amino acids cannot be synthesized *de novo* or they are inadequately synthesized by cells to meet the metabolic needs of the body (11). In general, animal-based foods have sufficient essential amino acids, and several plant-based foods have a limited quantity of essential amino acids (12, 13). Thus, having sufficient essential amino acids from various food sources is important, especially in the Korean diet, which is primarily composed of plant-based foods.

Each amino acid has different metabolic functions (14, 15). Studies (16–18) have confirmed that the intake of several essential amino acids such as arginine, glutamine, and histidine, and the nonessential amino acids such as cysteine and glycine improve endothelial dysfunction and vascular stiffness and reduces blood pressure. In another study (19), the levels of plasma free essential amino acids including leucine, isoleucine, valine, tyrosine, and phenylalanine were positively associated with metabolic diseases, including dyslipidemia, in a large Asian population study. Investigators have also reported that the physiological effects of amino acids from different protein food sources can differentially affect cardiovascular health (15, 20). Nevertheless, limited evidence exists regarding the impact of amino acid intake, based on their type and food sources and their functions, on dyslipidemia in a large population.

The association between amino acid intake and health has been explored in the elderly Korean population (21–23). In several cross-sectional studies (21, 22), branched-chain amino acid intake was associated with high skeletal muscle mass in older adults aged 50–64 years. However, the amino acid intake of elderly individuals may differ from that of young and middle-aged adults. Based on the findings of previous studies, individuals aged 60 years or older consumed only 30% of their protein from animal-based foods (23, 24), whereas animal-based protein intake among adults aged 30–64 has increased (25). Moreover, the association of other types of amino acid intake and food sources with dyslipidemia in younger adult populations has rarely been estimated. As a result, our objective was to investigate the association between dietary intake of amino acid, based on the amino acid type and food sources, and the occurrence of dyslipidemia in Korean adults who are aged 40 years or older.

2. Methods

2.1. Study population

We used data from the Ansan and Ansung Study and the Health Examinee (HEXA) Study in Korea. In brief, these studies are part of the Korean Genome and Epidemiology Study (KoGES), conducted by the Korea Disease Control and Prevention Agency (Cheongju, Republic of Korea) with the aim of exploring the effects of diet, lifestyle, and environmental factors on chronic diseases in the Korean population. The Ansan and Ansung Study recruited 10,030 participants, aged 40–69 years, from urban and rural regions, Ansan and Ansung, respectively, in Korea. Data were examined from 2001 to 2002. The HEXA study recruited 173,195 participants, aged ≥40 years, from 38 health examination centers or hospitals in urban areas across the country. Baseline data were obtained from 2004 to 2013. Comprehensive information on the cohorts is available elsewhere (26). We used data from the baseline to the follow-up in 2012–2017. Among 71,926 individuals who participated in the baseline and follow-up survey, individuals were excluded who were diagnosed with or were being treated for hypertension, diabetes, CVDs, or any cancer (n = 19,415); had implausible energy intake (<500 kcal/day or > 5,000 kcal/day) or no information on the Food Frequency Questionnaire (FFQ) survey (n = 1,070); or had dyslipidemia, based on health examination data at baseline or had no health examination data at baseline and follow-up (n = 15,963; Figure 1). Finally, the data of 35,478 study participants (10,012 men and 25,466 women) were used for the analysis. The institutional review board of Chung-Ang University (Ansung, Republic of Korea;

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; FFQ, Food Frequency Questionnaire; HEXA, Health Examinee; HR, hazard ratio; KoGES, Korean Genome and Epidemiology Study; TC, total cholesterol; TG, triglyceride.

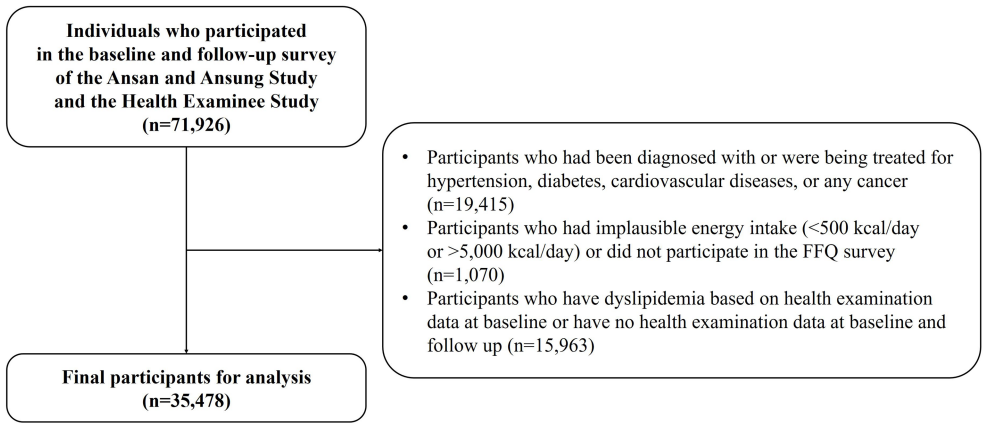

FIGURE 1
Flow chart of the participants used in this study from the Ansan and Ansung Study and the Health Examinee Study in Korea.

approval no., 1041078-202109-HR-278-01) approved this study protocol. Written informed consent was provided by each participant.

2.2. Dietary data assessment

Data from the validated semi-quantitative FFQ (27) were used to estimate amino acids, protein, and food intake. The amino acid database was expanded, using the Korean Food Composition Table of the Rural Development Administration (28), the Food and Nutrition Composition Database of the Ministry of Food and Drug Safety (29), and the database of the Korea Health Industry Development Institute (30). The amino acid database consisted of 19 amino acids. Amino acids were categorized into two types: essential and nonessential. The list of amino acids by type is in Supplementary Table S1. The amino acid database was linked to the recipe database for each FFQ food item. Amino acid intake (g/day) was estimated by multiplying the amino acid content of each food per 1 gram by the amount of food intake. The intake of each type of amino acid was divided into quartiles. Protein intake (g/day) was calculated, based on plant-based protein and animal-based protein, and divided into quartiles.

2.3. Definition of dyslipidemia

Blood samples were obtained from individuals who had fasted for at least 8 h and were promptly stored at −80°C until analysis. Serum levels of total TG, total cholesterol (TC), and high-density lipoprotein cholesterol (HDL-C) were measured using an automated analyzer (ADVIA 1650; Bayer Diagnostics, Leverkusen, Germany), based on the standardized protocol. The level of LDL-C was calculated by using the Friedewald formula: LDL-C = TC − (TG/5 + HDL-C). Participants were diagnosed with dyslipidemia if they satisfied one of the following four factors at follow-up (1): hypertriglyceridemia with a blood TG level ≥ 200 mg/dL (2); hypercholesterolemia with a TC level ≥ 240 mg/dL (3); hyper-LDL cholesterolemia with an LDL-C level ≥ 160 mg/dL; or (4) hypo-HDL cholesterolemia with an HDL-C level < 40 mg/dL. The criteria were based on the 2018 Korean guidelines for the management of dyslipidemia (31).

2.4. Covariate variables

Sociodemographic and lifestyle variables such as age, sex, education, household income, physical activity, alcohol drinking, and smoking status were obtained from the self-administered questionnaires at baseline. Education level was categorized as less than middle school or beyond high school, and household income was categorized as <2,000,000 Korean Won (KRW)/month [approximately 1,525 United States dollars (USD)/month] or ≥ 2,000,000 KRW/month. Physical activity was defined as the amount of time spent engaging in vigorous physical activity per day and was categorized as inactive (i.e., no physical activity) or active (i.e., >30 min per day). Alcohol drinking status was categorized as nondrinker/past drinker or current drinker. Smoking status was categorized as nonsmoker/past smoker or current smoker.

2.5. Statistical analysis

The general characteristics of the study participants were assessed by using the Chi-square test for categorical variables and the generalized linear model for continuous variables. The person-years of each participant were estimated from the enrollment date until the incident date of dyslipidemia and its components for participants with dyslipidemia and its components, or until the date of the most recent follow-up for participants without dyslipidemia and its components. The Cox proportional hazard regression model was used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for dyslipidemia and its components across the quartiles of amino acid and plant-/animal-based protein intake, based on sex.

Multivariable-adjusted analyzes were also conducted. The confounding factors included age, energy intake, body weight, education level, household income, physical activity, alcohol drinking status, and smoking status. In a further analysis, energy-adjusted fat

TABLE 1 Baseline characteristics of the study subjects according to the quartiles of amino acid intake.

	Total amino acid intake (g/day)				
	Q1	Q2	Q3	Q4	*P* value[a]
Total population (*N* = 35,478)	8,869	8,870	8,870	8,869	
Median intake (g/kg/day)	45.9 ± 0.1	62.1 ± 0.1	74.5 ± 0.1	101.8 ± 0.1	
Age (y)	52.1 ± 0.1	52.1 ± 0.1	51.1 ± 0.1	50.3 ± 0.1	<0.0001
Sex (%)					<0.0001
Female	82.0	72.0	69.7	63.5	
Education level (%)[b]					<0.0001
≥ High school	65.0	67.7	72.4	75.6	
Household income (%)[b]					<0.0001
≥2,000,000 KRW/month	60.2	62.4	66.4	66.8	
Physical activity (%)[b]					<0.0001
Active	51.6	53.7	54.1	56.5	
Alcohol drinking status (%)[b]					<0.0001
Current drinker	37.5	42.8	47.1	50.7	
Smoking status (%)[b]					<0.0001
Current smoker	6.8	8.5	9.9	12.4	
Nutrient intake					
Energy intake (kcal/day)	1205.2 ± 3.3	1594.9 ± 3.3	1862.2 ± 3.3	2430.0 ± 3.3	<0.0001
Energy intake from carbohydrate (%E)	74.1 ± 0.1	73.7 ± 0.1	71.1 ± 0.1	66.9 ± 0.1	<0.0001
Energy intake from fat (%E)	12.4 ± 0.1	12.4 ± 0.1	14.4 ± 0.1	17.4 ± 0.1	<0.0001
Energy intake from protein (%E)	12.6 ± 0.0	12.6 ± 0.0	13.5 ± 0.0	15.0 ± 0.0	<0.0001

[a]*p*-values were obtained from the Chi-square test for categorical variables and from the generalized linear model for continuous variables. [b]Education level is categorized as less than middle school and beyond high school; household income is categorized as <2,000,000 KRW (Korean Won)/month and ≥ 2,000,000 KRW/month; physical activity is defined as the time of engaging in vigorous physical activity per day: inactive (i.e., no physical activity) or active (i.e., >30 min per day); alcohol drinking status is categorized as nondrinker/past drinker and current drinker; and smoking status is categorized as nonsmoker/past smoker and current smoker.
Q1–4, quartile 1–4.

intake obtained from the residual method (32) was adjusted. The *p* value for trend was estimated across median amino acid and plant-/animal-based protein intakes of the quartile groups. All statistical analyzes were conducted using SAS 9.4 (SAS Institute, Cary, NC, United States).

3. Results

Among participants without dyslipidemia at baseline, a total of 1,820 (5.1%) cases, 3,828 (10.8%) cases, 2,728 (7.7%) cases, 1,537 (4.3%) cases, and 6,744 (19.0%) cases of incident hypertriglyceridemia, hypercholesterolemia, hyper-LDL cholesterolemia, hypo-HDL cholesterolemia and dyslipidemia, respectively, were reported during a mean follow-up of 5.7 years. Table 1 presents the general characteristics of the study participants without dyslipidemia at baseline ($n = 35,478$), based on the quartile of total amino acid intake. The higher amino acid intake group tended to be younger, drank and smoked more, and had a higher education level ($p < 0.0001$). Compared to the lowest amino acid intake quartile group, the highest amino acid intake quartile group had a higher energy intake and percentage of energy intake from protein and fat, but a lower percentage of energy intake from carbohydrates ($p < 0.0001$).

The intakes of essential amino acids and nonessential amino acids from plant- and animal-based food sources in Korean adults are presented in Figure 2. Korean adults had higher essential and nonessential amino acid intake from plant-based foods (men: essential 21.5 ± 5.3 g/day, nonessential 33.0 ± 8.4 g/day; women: essential 19.2 ± 5.7 g/day, nonessential 29.6 ± 8.8 g/day) than from animal-based foods (men: essential 9.2 ± 6.3 g/day, nonessential 12.2 ± 8.4 g/day; women: essential 8.7 ± 6.3 g/day, nonessential 11.5 ± 8.3 g/day). In addition, nonessential amino acid intake was higher than essential amino acid intake from plant- and animal-based food sources. The top 10 food sources contributing to each type of amino acid intake in Korean adults are described in Table 2. Overall, whole grain mixed rice, white rice, red meat, fish, soybean mixed rice, dairy, noodles, legumes, eggs, white meat, and bread were the major food groups for essential and nonessential amino acid intake. Whole grain mixed rice was the food group that contributed the most to the intake of essential and nonessential amino acids in men (34.9 and 33.4%, respectively) and in women (38.4 and 36.8%, respectively). Koreans obtained nearly one-half of amino acids from plant-based foods, whole grain mixed rice, and white rice (men: essential 51.3%, nonessential 48.9%; women: essential 48.4%, nonessential 46.2%). Detailed information of major food groups consumed by Korean adults is described in Supplementary Table S2.

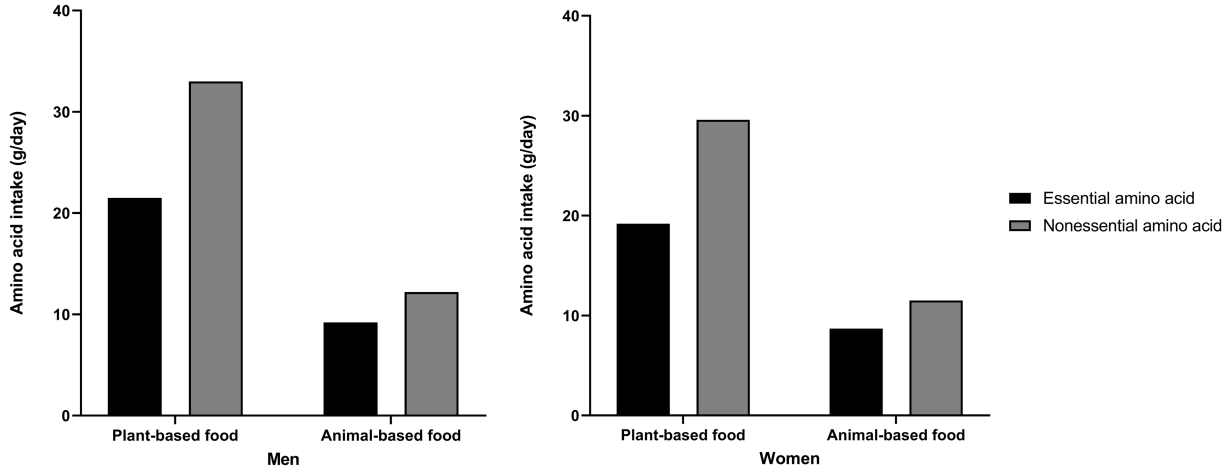

FIGURE 2
Essential and nonessential amino acid intake from plant- and animal-based food sources.

Table 3 shows the association between amino acid intake and dyslipidemia and its components. Essential and nonessential amino acid intake showed inverse relationships with the incidence of dyslipidemia and its components in men and women. Compared to the lowest group, the highest quartile for essential amino acid intake had a 22 and 14% decreased risk of dyslipidemia in men (HR = 0.78; 95% CI, 0.63–0.97; *P* for trend = 0.0088) and in women (HR = 0.86; 95% CI, 0.76–0.99; *P* for trend = 0.0201), respectively. In addition, essential amino acid intake had a negative association with hypercholesterolemia (HR = 0.66; 95% CI, 0.46–0.95; *P* for trend = 0.0157) and hyper-LDL cholesterolemia (HR = 0.69; 95% CI, 0.46–1.02; *P* for trend = 0.0436) in men.

The intake of nonessential amino acids was also inversely associated with the incidence of dyslipidemia in men and women. Compared to the lowest nonessential amino acid intake quartile group, men in the highest quartile group had a 25% reduced risk of dyslipidemia (HR = 0.75; 95% CI, 0.60–0.94; *P* for trend = 0.0069) and women had a 19% reduced risk of dyslipidemia (HR = 0.81; 95% CI, 0.71–0.93; *P* for trend = 0.0024). Furthermore, in men, the nonessential amino acid intake was negatively associated with hypercholesterolemia (HR = 0.57; 95% CI, 0.39–0.83; *P* for trend = 0.0035) and hyper-LDL cholesterolemia (HR = 0.60; 95% CI, 0.40–0.90; *P* for trend = 0.0082). In women, nonessential amino acid intake was also associated with a decreased risk of hypercholesterolemia (HR = 0.83; 95% CI, 0.70–0.99; *P* for trend = 0.0349) and hypo-HDL cholesterolemia (HR = 0.70; 95% CI, 0.51–0.96; *P* for trend = 0.0510). The median intake of amino acids and number of cases and person-years for dyslipidemia and its components, based on the quartile group, are shown in Supplementary Tables S3, S4, respectively.

To further investigate whether the protein food source affects the incidence of dyslipidemia, the association of plant- and animal-based protein intake with dyslipidemia and its components was assessed (Table 4). The median intake of protein and the person-years and number of cases of dyslipidemia and its components, based on quartile group, are shown in Supplementary Tables S3, S5, respectively. As a result, plant-based protein intake had a negative relationship with dyslipidemia in men and in women. The highest quartile group of plant-based protein intake had a 19 and 21% reduced risk of dyslipidemia in men (HR = 0.81; 95% CI, 0.67–0.98; *P* for trend = 0.0157) and in women (HR = 0.79; 95% CI, 0.70–0.89; *P* for trend = 0.0001), respectively, compared to the lowest group. Plant-based protein intake was also inversely associated with hypercholesterolemia and hyper-LDL cholesterolemia in men and women. Contrary to this finding, in women, animal-based protein intake had a positive relationship with hypercholesterolemia (HR = 1.24; 95% CI, 1.11–1.40; *P* for trend = 0.0003) and with dyslipidemia (HR = 1.12, 95% CI, 1.02–1.24; *P* for trend = 0.0173). However, this positive association disappeared after further adjusting for energy-adjusted fat intake, as shown in Supplementary Table S6. In addition, the essential and nonessential amino acid intake with dyslipidemia had a stronger negative relationship, after further adjustment for energy-adjusted fat intake, as shown in Supplementary Table S7.

The association of amino acid and protein intake for each participant's body weight with dyslipidemia was also assessed to evaluate the appropriate intake level with respect to physical condition. The results are presented in Supplementary Tables S8, S9. All types of amino acid intake were inversely associated with all components of dyslipidemia incidence in men and women. Plant-based protein intake was also negatively associated with all components of dyslipidemia incidence in men and women. Animal-based protein intake was negatively associated with hypercholesterolemia, hypo-HDL cholesterolemia, and dyslipidemia in men, and with hypertriglyceridemia, hypercholesterolemia, hyper-LDL cholesterolemia, and dyslipidemia in women.

4. Discussion

The purpose of this study was to investigate whether the incidence of dyslipidemia in Korean adults would be associated with the consumption of essential and nonessential amino acids, as well as with the protein food sources (i.e., plant or animal) of these amino acids. We found that essential and nonessential amino acid intake was

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TABLE 2 Top ten food sources contributing to amino acid intake.

Men				
Rank	Food group	Contribution (%)	*Cum* (%)	Intake (g/day)
Essential amino acids				
1	Whole grain mixed rice	34.9	34.9	10.4 ± 8.6
2	White rice	16.4	51.3	4.8 ± 7.7
3	Red meat	10.1	61.4	3.4 ± 3.4
4	Fish	7.5	68.9	2.4 ± 2.3
5	Soybean mixed rice	4.4	73.3	1.3 ± 4.9
6	Dairy	3.8	77.2	1.2 ± 1.5
7	Legumes	3.4	80.5	1.1 ± 1.0
8	Noodles	3.2	83.7	1.0 ± 1.2
9	Eggs	2.1	85.9	0.7 ± 0.9
10	White meat	2.0	87.8	0.6 ± 0.9
Nonessential amino acids				
1	Whole grain mixed rice	33.4	33.4	14.7 ± 12.1
2	White rice	15.5	48.9	6.6 ± 10.5
3	Red meat	9.3	58.1	4.5 ± 4.6
4	Fish	6.5	64.6	3.1 ± 2.9
5	Noodles	5.1	69.7	2.4 ± 2.7
6	Soybean mixed rice	4.2	74.0	1.9 ± 6.8
7	Legumes	3.8	77.8	1.8 ± 1.6
8	Dairy	3.5	81.3	1.6 ± 2.1
9	Eggs	1.9	83.2	0.9 ± 1.1
10	White meat	1.8	85.0	0.9 ± 1.3
Women				
Essential amino acids				
1	Whole grain mixed rice	38.4	38.4	10.3 ± 7.4
2	White rice	10.0	48.4	2.7 ± 5.8
3	Fish	8.6	57.0	2.5 ± 2.5
4	Red meat	8.4	65.4	2.6 ± 3.0
5	Dairy	5.6	71.0	1.6 ± 1.8
6	Soybean mixed rice	4.7	75.7	1.3 ± 4.6
7	Legumes	3.9	79.6	1.1 ± 1.1
8	Eggs	2.4	82.0	0.7 ± 0.8
9	Noodles	2.3	84.4	0.7 ± 0.9
10	White meat	1.9	86.3	0.6 ± 0.9
Nonessential amino acids				
1	Whole grain mixed rice	36.8	36.8	14.6 ± 10.5
2	White rice	9.4	46.2	3.6 ± 7.9
3	Red meat	7.7	53.9	3.4 ± 4.0
4	Fish	7.5	61.3	3.2 ± 3.2
5	Dairy	5.0	66.4	2.1 ± 2.4
6	Soybean mixed rice	4.6	70.9	1.9 ± 6.4
7	Legumes	4.4	75.4	1.9 ± 1.9
8	Noodles	3.7	79.1	1.6 ± 2.2
9	Bread	2.3	81.3	1.0 ± 1.6
10	Eggs	2.1	83.4	0.9 ± 1.1

Cum: cumulative contribution.

TABLE 3 Hazard ratios and 95% confidence intervals for the incidence of dyslipidemia and its components, based on the amino acid intake quartile[a].

	Amino acid intake (g/day)				
	Q1	Q2	Q3	Q4	*P* for trend
Men					
Essential amino acid					
Hypertriglyceridemia	Ref	1.08 (0.86–1.35)	0.94 (0.72–1.21)	0.92 (0.65–1.31)	0.4645
Hypercholesterolemia	Ref	0.90 (0.72–1.12)	0.75 (0.58–0.97)	0.66 (0.46–0.95)	0.0157
Hyper-LDL cholesterolemia	Ref	0.88 (0.68–1.13)	0.69 (0.52–0.93)	0.69 (0.46–1.02)	0.0436
Hypo-HDL cholesterolemia	Ref	1.01 (0.80–1.26)	0.90 (0.70–1.16)	0.73 (0.51–1.04)	0.0563
Dyslipidemia	Ref	1.00 (0.88–1.15)	0.86 (0.74–1.01)	0.78 (0.63–0.97)	0.0088
Nonessential amino acid					
Hypertriglyceridemia	Ref	1.10 (0.87–1.39)	0.97 (0.75–1.26)	0.91 (0.63–1.32)	0.4409
Hypercholesterolemia	Ref	0.81 (0.65–1.02)	0.72 (0.56–0.93)	0.57 (0.39–0.83)	0.0035
Hyper-LDL cholesterolemia	Ref	0.84 (0.65–1.08)	0.65 (0.48–0.87)	0.60 (0.40–0.90)	0.0082
Hypo-HDL cholesterolemia	Ref	0.95 (0.76–1.20)	0.98 (0.76–1.27)	0.80 (0.56–1.15)	0.2617
Dyslipidemia	Ref	0.96 (0.84–1.10)	0.87 (0.75–1.02)	0.75 (0.60–0.94)	0.0069
Women					
Essential amino acid					
Hypertriglyceridemia	Ref	0.98 (0.82–1.18)	0.88 (0.72–1.08)	0.79 (0.60–1.04)	0.0688
Hypercholesterolemia	Ref	0.98 (0.88–1.09)	0.88 (0.78–0.99)	0.90 (0.77–1.07)	0.1448
Hyper-LDL cholesterolemia	Ref	0.99 (0.87–1.13)	0.90 (0.78–1.05)	0.93 (0.76–1.13)	0.3370
Hypo-HDL cholesterolemia	Ref	0.83 (0.67–1.03)	0.91 (0.72–1.15)	0.75 (0.55–1.02)	0.1207
Dyslipidemia	Ref	0.96 (0.88–1.04)	0.89 (0.80–0.98)	0.86 (0.76–0.99)	0.0201
Nonessential amino acid					
Hypertriglyceridemia	Ref	0.99 (0.83–1.18)	0.87 (0.71–1.08)	0.81 (0.61–1.08)	0.1038
Hypercholesterolemia	Ref	0.92 (0.82–1.02)	0.88 (0.77–0.99)	0.83 (0.70–0.99)	0.0349
Hyper-LDL cholesterolemia	Ref	0.92 (0.81–1.05)	0.92 (0.79–1.06)	0.87 (0.71–1.07)	0.2111
Hypo-HDL cholesterolemia	Ref	0.80 (0.64–0.99)	0.85 (0.68–1.08)	0.70 (0.51–0.96)	0.0510
Dyslipidemia	Ref	0.90 (0.83–0.98)	0.87 (0.78–0.96)	0.81 (0.71–0.93)	0.0024

[a]All values have been adjusted for age, energy intake, body weight, education level, household income, physical activity, alcohol drinking status, and smoking status.
Q1–4, quartile 1–4; LDL, low-density lipoprotein; HDL, high-density lipoprotein; Ref, reference.

associated with a decreased risk of the incidence dyslipidemia and its parameters in this prospective cohort study of Korean adults ≥ 40 years old. Koreans primarily had essential and nonessential amino acid intakes from plant-based foods, whole grain mixed rice, and white rice, which accounted for approximately one-half of the amino acid intake. Thus, plant-based protein intake also had a negative relationship with dyslipidemia, whereas animal-based protein intake had a positive relationship with dyslipidemia. However, plant-based protein intake had a stronger negative association and animal-based protein intake had a nonsignificant association with dyslipidemia, after adjusting for energy-adjusted fat intake. The essential and nonessential amino acid intake also had stronger negative associations with dyslipidemia after adjusting for energy-adjusted fat intake. Amino acid intake may have preventive effects on dyslipidemia, independently of the protein food sources.

Although the mechanisms underlying the relationship between dietary amino acids and metabolic disorders are unclear, a few studies have demonstrated that essential amino acid supplementation lowers plasma levels of TG, LDL, and TC in humans (33, 34). Reports have indicated that various amino acid patterns are implicated in the metabolism related to nonalcoholic fatty liver disease. Synthesis and catabolism of protein and amino acids are involved in metabolic pathways in the liver such as β-oxidation and tricarboxylic acid and have a role in oxidative stress and inflammation. In individuals with nonalcoholic fatty liver disease, investigators have observed increased levels of several essential amino acids such as the branched-chain amino acids such as isoleucine, leucine, and valine and the aromatic amino acids, phenylalanine and tryptophan, and decreased levels of the nonessential amino acids, tyrosine, glutamine, serine, and glycine (35).

Another possibility that other dietary factors may influence amino acid metabolism related to dyslipidemia has been observed in other epidemiological studies (36–40). Higher intake of essential amino acids and better nutrient adequacy have been associated with decreased all-cause and cardiovascular disease mortality in United States adults (36). Contrary to this finding, an amino acid intake dietary pattern, which was highly correlated with essential amino acids such as lysine, methionine, histidine, threonine, and branched-chain amino acids, and meat protein was associated with increased cardiovascular mortality in a prospective study of adults in the United States and Canada (37). In

TABLE 4 Hazard ratios and 95% confidence intervals for the incidence of dyslipidemia and its components, based on the protein intake quartile[a].

	Protein intake (g/day)				
	Q1	Q2	Q3	Q4	*P* for trend
Men					
Plant-based protein					
Hypertriglyceridemia	Ref	1.10 (0.88–1.37)	0.93 (0.73–1.19)	1.03 (0.75–1.40)	0.9743
Hypercholesterolemia	Ref	0.94 (0.76–1.17)	0.83 (0.65–1.05)	0.62 (0.44–0.86)	0.0031
Hyper-LDL cholesterolemia	Ref	0.97 (0.76–1.24)	0.78 (0.59–1.02)	0.59 (0.41–0.85)	0.0027
Hypo-HDL cholesterolemia	Ref	1.06 (0.85–1.33)	1.00 (0.78–1.26)	0.88 (0.64–1.20)	0.3306
Dyslipidemia	Ref	1.01 (0.88–1.15)	0.90 (0.78–1.04)	0.81 (0.67–0.98)	0.0157
Animal-based protein					
Hypertriglyceridemia	Ref	1.05 (0.84–1.31)	1.09 (0.87–1.37)	0.98 (0.76–1.27)	0.7765
Hypercholesterolemia	Ref	1.06 (0.85–1.31)	1.06 (0.84–1.34)	1.14 (0.88–1.48)	0.3472
Hyper-LDL cholesterolemia	Ref	1.01 (0.78–1.29)	1.09 (0.84–1.41)	1.09 (0.81–1.45)	0.5322
Hypo-HDL cholesterolemia	Ref	1.07 (0.87–1.33)	0.97 (0.77–1.21)	1.05 (0.82–1.35)	0.8499
Dyslipidemia	Ref	1.05 (0.92–1.20)	1.05 (0.92–1.21)	1.06 (0.91–1.24)	0.5190
Women					
Plant-based protein					
Hypertriglyceridemia	Ref	0.88 (0.73–1.05)	0.90 (0.74–1.10)	0.82 (0.64–1.05)	0.1331
Hypercholesterolemia	Ref	0.85 (0.76–0.94)	0.81 (0.73–0.91)	0.72 (0.62–0.84)	<0.0001
Hyper-LDL cholesterolemia	Ref	0.86 (0.76–0.98)	0.86 (0.74–0.98)	0.84 (0.70–1.00)	0.0299
Hypo-HDL cholesterolemia	Ref	1.06 (0.85–1.32)	1.09 (0.86–1.38)	1.06 (0.80–1.42)	0.6244
Dyslipidemia	Ref	0.88 (0.80–0.95)	0.86 (0.79–0.95)	0.79 (0.70–0.89)	0.0001
Animal-based protein					
Hypertriglyceridemia	Ref	1.02 (0.86–1.20)	1.01 (0.85–1.20)	1.00 (0.82–1.22)	0.9488
Hypercholesterolemia	Ref	1.10 (0.99–1.22)	1.18 (1.06–1.31)	1.24 (1.11–1.40)	0.0003
Hyper-LDL cholesterolemia	Ref	1.11 (0.98–1.25)	1.19 (1.05–1.35)	1.15 (1.00–1.33)	0.0716
Hypo-HDL cholesterolemia	Ref	1.10 (0.91–1.33)	0.99 (0.81–1.22)	0.93 (0.74–1.17)	0.3505
Dyslipidemia	Ref	1.06 (0.97–1.15)	1.10 (1.01–1.20)	1.12 (1.02–1.24)	0.0173

[a]All values have been adjusted for age, energy intake, body weight, education level, household income, physical activity, alcohol drinking status, and smoking status.
Q1–4, quartile 1–4; LDL, low-density lipoprotein; HDL, high-density lipoprotein; Ref, reference.

addition, the intake of animal-based protein has been positively associated with metabolic diseases, including dyslipidemia and mortality (38–40). The available evidence suggests that undisclosed effects may exist that result from interactions between amino acids and other dietary components, depending on the food sources. Therefore, further research, including structural studies, aimed at examining the relationship between amino acid intake, other food components, and metabolic diseases is needed.

To investigate whether protein food sources and other nutrients affect dyslipidemia, we conducted further analyzes of the association of protein intake by food source and other nutrient intake with dyslipidemia in this study. The results indicated that plant-based protein intake was inversely associated with dyslipidemia, whereas animal-based protein intake was positively associated with dyslipidemia. Nevertheless, we believe that the association was influenced by fat intake because nonsignificant correlations with animal-based protein intake were observed, after adjusting for energy-adjusted fat intake. These findings indicate that amino acids may have an impact on dyslipidemia, regardless of the food source. Furthermore, we hypothesize that food components may interact with amino acids or participate in amino acid metabolism because the inverse relationship between essential and nonessential amino acid intake and dyslipidemia became stronger after adjusting for energy-adjusted fat intake. Future research should aim to investigate the correlation between amino acid intake and other dietary components beyond fat.

Furthermore, the findings also confirmed that appropriate amino acid and protein intake may be helpful for the prevention of dyslipidemia, independently of protein food sources. As shown in Supplementary Tables S8, S9, all types of amino acid and plant-based protein intake per each participant's body weight were inversely associated with all components of dyslipidemia incidence in men and in women. Animal-based protein intake was negatively associated with several dyslipidemia components in women. These findings imply that the effect of amino acid and protein intake on cardiometabolic function should be evaluated by considering the absolute amount of intake and the protein requirements, based on body weight.

To the best of our knowledge, this study is the first prospective study to examine the relationship between amino acid intake and the

likelihood of developing dyslipidemia among Korean adults. However, this study has several limitations.

First, amino acid intake may have been underestimated because the FFQ and the amino acid database did not obtain information on amino acid intake from all food and supplements consumed by the participants. This limitation is an impetus for future studies to develop a detailed amino acid database.

Second, the estimation of amino acid and protein food sources may have been biased because of the food items on the FFQ. The number of plant-based food sources are much higher than that of animal-based food sources (Supplementary Table S2). Moreover, several food lists, for example, pizza/hamburger and jam/honey/butter/margarine could not be individually divided into plant- or animal-based foods. These limitations may induce high amino acid and protein intake from plant-based foods. In addition, cumulative and long-term dietary status and lifestyle factors could not be assessed because we used only baseline data. Thus, changes in diet or lifestyle during the follow-up period were not considered. Although the Korean diet has a higher proportion of plant-based protein than animal-based protein (13) and a rice-based dietary pattern, animal-based protein intake has recently increased since the time the survey of this present study was conducted (41). The disparity in animal-based protein intake data obtained from previous and recent studies may result in inconclusive associations.

Third, although we adjusted for potential confounders, unrevealed or residual confounders may have affected the relationship between amino acid intake and dyslipidemia.

Finally, generalizing the study findings from middle-aged participants to all generations and populations is difficult. Despite these limitations, the findings of this study can offer evidence for suitable amino acid and protein intake when creating dietary guidelines for cardiovascular health.

5. Conclusion

In conclusion, the intake of all types of amino acids, including essential and nonessential amino acids, was inversely associated with the incidence of dyslipidemia and its components in the Korean adults aged ≥40 years, independently of plant- and animal-based protein food sources. Approximately one-half of essential and nonessential amino acids was obtained from plant-based foods, and plant-based protein intake was negatively associated with the incidence of dyslipidemia. Animal-based protein intake was not significantly associated with dyslipidemia and essential and nonessential amino acid intake showed stronger negative associations with dyslipidemia, after adjusting for energy-adjusted fat intake. Our study findings suggest that amino acid intake may be beneficial in the management of dyslipidemia and can offer evidence for the appropriate amount of amino acid and plant- and animal-based protein intake for cardiovascular health in Korean adults.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by Chung-Ang University (Ansung, Republic of Korea; approval no., 1041078-202109-HR-278-01). The patients/participants provided their written informed consent to participate in this study.

Author contributions

SC, KH, and SS designed the study. SC analyzed the data and wrote the first draft of the manuscript. SC, KH, and HJ participated in interpreted the results. JHP, HJ, and SS reviewed and critically edited the manuscript. All authors read and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2023.1195349/full#supplementary-material

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EDITED BY
Iain Brownlee,
Northumbria University, United Kingdom

REVIEWED BY
Biju Soman,
Sree Chitra Tirunal Institute for Medical Sciences and Technology (SCTIMST), India
Akram Hernández-Vásquez,
Universidad San Ignacio de Loyola, Peru

*CORRESPONDENCE
Xiaopan Li
✉ xiaopanli0224@126.com
Yue Zhang
✉ yuezhang@sxmu.edu.cn
Wei Zhang
✉ woaijsf@126.com

†These authors have contributed equally to this work

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Burden and trends of stroke attributable to dietary risk factors from 1990 to 2019 in the Belt and Road Initiative countries: an analysis from the global burden of disease study 2019

Yue Zhang[1*†], Zheng Luo[2†], Juan Yi[3†], Junjie Zhu[4], Yun Qiu[5], Xiaoyun Xu[2], Wanying Xie[6], Jinyi Wu[7], Huihui Lv[8], Changhua Mou[9], Wei Zhang[2*] and Xiaopan Li[10*]

[1]Key Laboratory of Coal Environmental Pathogenicity and Prevention, Ministry Education, Department of Epidemiology, School of Public Health, Shanxi Medical University, Taiyuan, China, [2]Department of Neurology, Shanghai University of Medicine and Health Sciences Affiliated Zhoupu Hospital, Shanghai, China, [3]Department of Neurology, Zhuzhou Central Hospital, Zhuzhou, Hunan, China, [4]Department of Epidemiology and Health Statistics, School of Public Health, Dali University, Dali, China, [5]Department of Public Health, Nanjing University of Chinese Medicine, Nanjing, Jiangsu, China, [6]Department of Traditional Chinese Medicine Encephalopathy, Shanghai Pudong Traditional Chinese Medicine Hospital, Shanghai, China, [7]Department of Public Health, Wuhan Fourth Hospital, Wuhan, China, [8]Department of Neurology, Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine, Shanghai, China, [9]Department of Neurology, Shanghai Children's Medical Center, Shanghai Jiao Tong University School of Medicine, Shanghai, China, [10]Department of Health Management Center, Zhongshan Hospital, Shanghai Medical College of Fudan University, Shanghai, China

Objectives: This study aimed to compare the burden and trends of stroke attributed to dietary risk factors in the Belt and Road ("B&R") countries from 1990 to 2019.

Methods: The 2019 Global Burden of Disease (GBD) Study was used to gather information on the burden of stroke attributable to dietary risk factors. Numbers and age-standardized rates (ASRs) of deaths, disability-adjusted life years (DALYs) were determined in 1990 and 2019 among the "B&R" countries. The average annual percent change (AAPC) was used to analyze the temporal trends of diet-induced stroke DALYs from 1990 to 2019 and in the final decade (2010–2019) by Joinpoint regression analysis.

Results: In 2019, the absolute number of stroke deaths and DALYs attributable to dietary risk factors were 671,872 cases (95% UI 436,354–937,093) and 1.67 million cases (95% UI 1.15–2.24) in China. We found geographical differences in mortality and DALYs of diet-attributable stroke among member countries, with Bulgaria, Hungary and Serbia being the three highest countries in 1990, Bulgaria, North Macedonia and Montenegro in Central Asia in 2019. The ASRs of diet-induced stroke mortality and DALYs were generally declining in most member states from 1990 to 2019, however, the corresponding metrics in Mongolia remained high. The fastest decline in ASR of mortality and DALYs for diet-induced stroke was seen in Estonia, Eastern Europe, with AAPC values of –7.09% (95%CI: –7.72, –6.46%) and – 6.62% (95%CI: –7.20, –6.03%), respectively. We noted a substantial downward trend in ASR of mortality and DALYs from diet-induced stroke changes in the final decade (2010–2019) for most member states. The ASR of DALYs

for diet-induced stroke decreased greater in females than in males. For those aged 50–74, the DALYs for stroke due to dietary risk factors in all other member countries of the "B&R" showed a decreasing trend, except for the Philippines, which rose (AAPC = 2.13, 95%CI: 1.40–2.87%) and Turkmenistan, which remained stable (AAPC = 0.05, 95%CI: −0.43–0.33%).

Conclusion: The burden of diet-induced stroke varies substantially across "B&R" countries and threaten public health, relevant evidence-based policies and interventions should be adopted to address the future burden of stroke in "B&R" countries through extensive collaboration.

KEYWORDS

"B&R" countries, stroke, burden of disease, dietary risk factors, disability-adjusted life years, average annual percent change, trend analysis

Introduction

Stroke is a global public health problem that imposes a heavy disease and financial burden on individuals and society. According to the 2019 Global Burden of Disease, Injury and Risk Factor Study (GBD 2019), stroke was the second-leading cause of death (11.6% of total deaths) and third-leading cause of disability (5.7% of total disability-adjusted life years [DALYs]) worldwide (1). Stroke incidence has maintained stable and mortality have declined over the last 20 year-period, however, DALYs due to stroke and stroke-related survivors have all increased, making stroke prevention a global health priority (2). American Heart Association (AHA) predicts that stroke incidence could reach 4% by 2030 among American adults, resulting in an increase in stroke-related medical costs to $183 billion (3). Additionally, GBD shows that more than 75% of stroke deaths and 80% of DALYs occur in low- and middle-income countries (1).

As we all know, health issues are no longer the responsibility of individual countries with the rapid pace of globalization. In 2013, Chinese government initiates the Belt and Road Initiative (BRI) to accelerate infrastructure, trade development and business partnerships among 66 countries in Asia, Europe, South America and Africa (4, 5). Although the BRI focuses on economic development and infrastructure investment, its impact on global health is emerging (6). In 2017, Chinese government launched the "Health Silk Road" (HSR) initiative to strengthen global health cooperation. Under the framework of HSR, a variety of regional and trans-regional plans have been implemented, including the training of health professionals, the establishment of disease control centers, and the creation of knowledge sharing networks. Through the HSR, China could use BRI transportation networks to provide health care and medical assistance to member countries. Against the backdrop of COVID-19, the BRI provides an important platform for member counties to discuss clinical treatment guidelines and epidemic control strategies (7, 8). Currently, member countries face the threat of stroke to varying degrees, and the distribution of risk factors is constantly changing, so analyzing the differences between member states is essential to allocate resources for prevention strategies (1, 9).

Recent epidemiological evidence has found that the large burden of stroke can be attributed to several modifiable factors, such as obesity, hypertension, diabetes, a sedentary lifestyle, or unhealthy diet (10). Diet is an important risk factor for stroke, a growing number of prospective observational studies have been performed to explore the impact of dietary factors on stroke risk (11). English et al. (12) found that poor diet and nutritional intake were strongly associated with the risk of first stroke, and a Mediterranean-style diet was reported to reduce the risk of first stroke. Baden et al. (13) explored the relationship between plant-based diet quality and total stroke risk and found that people who adhered to a healthy plant-based diet had a lower risk of total stroke.

The GBD 2019 framework, through extensive collection of data sources and statistical modeling, allows for comparable assessment of stroke burden in terms of mortality and DALYs. At present, none of the existing studies on stroke mortality and DALYs attributable to modifiable dietary risk factors had explored differences and the changing trend of DALYs stratified by gender, age and diet-specific risk factors among 66 countries from the BRI. Therefore, this study was conducted to compare the burden and trends of diet-induced stroke from 1990 to 2019 in the "B&R" countries, and to provide the basis for generating prevention and control strategies of stroke for building a healthy "B&R."

Methods

Data sources

In this study, data on annual diet-induced stroke deaths, DALYs, and respective age-standardized rates (ASR) by gender, age and specific diet risk factor in the "B&R" countries from 1990 to 2019 were extracted from the GBD 2019 database.[1] The GBD 2019, which is an international collaborative surveillance system, estimated 369 diseases and injuries, 87 risk factors and combinations of risk factors across 204 countries and territories from 1990 to 2019. It contains a total of 86,249 data input sources from censuses, household surveys, civil registration, vital statistics and other sources. The GBD 2019 Stroke Collaborators has presented methods for processing, standardizing, and modeling stroke mortality and DALYs (1). GBD estimates the burden of disease indices including incidence, prevalence, mortality,

1 https://vizhub.healthdata.org/gbd-results/

years lived with disability (YLD), years of life lost (YLL) and DALYs at regional, national and global levels. Detailed methodology has been published elsewhere (14, 15). The detailed information on the statistical codes for diet-related burden in the GBD study has been previously announced on the following website: http://ghdx.healthdata.org/gbd-2019/code/nonfatal-12. DALYs is a composite indicator to assess the disease burden of disability and premature death, which is obtained by summing YLL and YLD.

The composition of "B&R" countries is mainly based on the GBD classification of global regions and international political and economic organizations (16). BRI include 66 member countries, divided as follows: (1) East Asia: China, (2) Central Asia: Armenia, Azerbaijan, Georgia, Kazakhstan, Turkmenistan, Uzbekistan, Kyrgyzstan, Mongolia, Tajikistan, (3) South Asia: India, Nepal, Bangladesh, Bhutan, Pakistan, (4) Southeast Asia: Philippines, Sri Lanka, Thailand, Indonesia, Vietnam, Cambodia, Laos, Malaysia, Maldives, Burma, (5) High-income Asia pacific: Brunei, Singapore, (6) North Africa and Middle East: Jordan, Kuwait, Lebanon, Oman, Afghanistan, Yemen, Bahrain, Iran, Iraq, United Arab Emirates, Qatar, Saudi Arabia, Syria, Egypt, Palestine, Turkey, (7) Central Europe: North Macedonia, Poland, Romania, Croatia, Czechia, Bosnia and Herzegovina, Montenegro, Albania, Bulgaria, Hungary, Slovakia, Slovenia, Serbia, (8) Eastern Europe: Republic of Moldova, Russia, Ukraine, Estonia, Lithuania, Belarus, Latvia, and (9) Western Europe: Cyprus, Greece, Israel. To ensure replicability and transparency of results, our study follows the Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER) (Supplementary Appendix A) (17).

Statistical analyzes

The absolute numbers and ASR of mortality and DALYs for stroke attributed to dietary risks were calculated in "B&R" countries. For estimated metrics, the 95% uncertainty interval (UI) were reported, and 95% UI was calculated by drawing 1,000 times from each number of posterior distributions, using the 2.5th and 97.5th ordering of the uncertainty distribution (1). ASR, as a weighted mean of the age-specific rates, were estimated using a global age structure from 2019, which allow comparisons across time, countries and subregions. We focused on three specific age groups: 20 to 54 years, 50 to 74 years and ≥ 75 years and 6 dietary risk factors (high in sodium, high in red meat, low in fruits, low in vegetables, low in fiber and low in whole grains). The temporal trends of disease burden were assessed using average annual percent change (AAPC) by using the Joinpoint regression software from 1990 to 2019, 95% confidence intervals (CIs) for trend segment identified. The annual ASR of diet-induced stroke mortality and DALYs was designated as a dependent variable, and the year was assigned as an independent variable. The Heteroscedastic Errors Option was set to constant variance, the maximum number of joinpoints was set at 5, and the Log-linear model ($\ln y = xb$) was chosen. For segmented line regression, the Bayesian information criterion (BIC) was used to calculate the optimal number of change points. The software uses a *Z*-test to check whether the slope for each trend segment is significantly different from prior segment (18).

In addition, we evaluated AAPCs of age-standardized DALYs for stroke, stratified by sex, age and specific dietary factors. Meanwhile, we compared the changes in AAPC of stroke burden attributed to dietary risk factors in the last decade and throughout the study period (1990–2019 and 2010–2019). If both the AAPC estimate and the lower limit of 95% UI were positive, ASR of mortality and DALYs showed an upward trend. Conversely, if both the AAPC estimate and the upper limit of the 95% UI were negative, then ASR of mortality and DALYs exhibited a decreasing trend (setting 3% as the cut-off point and ≥ 3% as a larger decrease). Other than that, ASR was considered to be stable (19). All analysis was conducted using the Joinpoint Regression Program (Version 4.9.0.0, The National Cancer Institute, MD, United States) (20). The map visualization of the "B&R" member states was performed using "ggmap" package in R software (version 4.3.0, R core team). The "ggmap" package is an extension package, which obtains shapefiles from Google Maps.[2] $p < 0.05$ was considered statistically significant.

Results

Absolute number of mortality and DALYs in 1990 and 2019 caused by stroke attributed to modifiable dietary risk factors in the "B&R" member countries are shown in Table 1. In 2019, the number of stroke deaths and DALYs attributable to dietary risks were 671,872 cases (95% UI 436,354–937,093) and 1.67 million cases (95% UI 1.15–2.24) in China. We found geographical differences in mortality and DALYs of diet-attributable stroke among member countries, with Bulgaria, Hungary, and Serbia being the three highest countries in 1990, Bulgaria, North Macedonia, and Montenegro in Central Asia in 2019. The country with the lowest number of mortality and DALYs is the Qatar in North Africa and Middle East (27 cases, 95% UI, 16–42 and 1716 cases, 95% UI, 1112–2,454) in 2019. From 1990 to 2019, the countries with the largest decreases in the number of diet-induced stroke deaths and DALYs were Czechia and Hungary, and the countries with the largest increases were Albania and Mongolia.

Figure 1 illustrated the ASR of diet-induced stroke mortality and DALYs in 1990 and 2019 in member countries of the "B&R" initiative. In 1990, the regions with higher age-standardized mortality and DALYs from diet-related stroke were concentrated in Central Europe, East Asia and Southeast Asia. In 1990, the country with the lowest age-standardized mortality and DALYs of diet-induced stroke was Lebanon (6.76 per 100,000 population and 149.86 per 100,000 population, respectively), the highest in Burma (103.90 per 100,000 population and 2617.69 per 100,000 population, respectively). In 2019, Israel enjoyed the lowest age-standardized mortality and DALYs of diet-induced stroke (13.42 per 100,000 population and 85.08 per 100,000 population, respectively), the highest in Mongolia (90.27 per 100,000 population and 2127.00 per 100,000 population, respectively). The age-standardized mortality and DALYs of stroke attributable to dietary risk factors were generally declining in most member states from 1990 to 2019. However, the mortality and DALYs of diet-induced stroke in Mongolia has remained high. See Supplementary Table S1 for more details.

The temporal trend of ASR of mortality and DALYs due to diet-induced stroke for 1990–2019 and 2010–2019 in "B&R" countries was displayed in Figure 2. From 1990 to 2019, the fastest decline in ASR of

2 https://mapsplatform.google.com

10.3389/fnut.2023.1235271

TABLE 1 The absolute number of mortality and DALYs for stroke attributed to dietary risk factors in the "B&R" countries in 1990 and 2019.

Countries	1990				2019			
	Mortality		DALYs		Mortality		DALYs	
	Number	*95%UI*	Number	*95%UI*	Number	*95%UI*	Number	*95%UI*
East Asia								
China	519,444	365,947–684,456	13,921,162	10,116,646–17,796,087	671,872	436,354–937,093	16,729,078	11,517,379–22,374,535
Central Asia								
Armenia	718	483–990	17,050	11,815–23,033	569	372–832	12,110	8,298–17,357
Azerbaijan	1,399	891–1982	36,209	23,396–50,005	2,135	1,289–3,294	52,449	32,653–78,181
Georgia	3,072	1934–4,377	69,738	44,304–97,106	2,364	1,543–3,446	45,212	29,968–63,855
Kazakhstan	6,667	5,090–8,529	168,353	132,157–207,529	6,656	4,814–9,142	163,128	119,957–219,323
Kyrgyzstan	1,666	1,260–2,149	42,090	32,626–53,248	1,252	889–1731	35,033	25,428–47,156
Mongolia	855	641–1,240	25,107	19,183–34,406	1873	1,333–2,538	57,938	41,807–78,194
Tajikistan	961	606–1,343	23,739	15,739–32,543	1,429	885–2,131	38,296	24,443–56,100
Turkmenistan	785	578–1,019	22,466	16,826–28,601	1,635	1,136–2,265	49,060	34,938–66,409
Uzbekistan	4,277	3,058–5,646	113,905	83,509–147,688	6,583	4,406–9,083	200,534	136,918–273,220
South Asia								
Bangladesh	23,369	17,059–31,023	658,112	474,339–870,935	45,776	30,361–64,458	1,130,114	753,143–1,568,966
Bhutan	55	34–84	1,633	1,024–2,431	78	47–120	1950	1,207–2,894
India	108,806	76,011–149,533	3,193,700	2,266,760–4,261,449	174,510	116,473–245,234	4,878,839	3,303,619–6,726,592
Nepal	2,366	1,542–3,526	68,682	45,629–99,984	3,488	2073–5,294	87,713	53,381–129,061
Pakistan	17,619	11,681–24,627	470,608	321,297–640,398	31,622	21,833–44,086	941,775	664,136–1,308,567
Southeast Asia								
Cambodia	2,825	2058–3,747	82,950	61,408–108,405	5,109	3,401–7,015	135,856	93,442–182,872
Indonesia	54,221	37,097–71,978	1,667,014	1,163,148–2,145,745.	97,556	59,670–138,786	2,721,311	1,691,264–3,808,140
Laos	1,416	938–1969	42,389	29,285–57,404	1967	1,191–2,878	57,057	35,395–82,502
Malaysia	4,630	3,141–6,009	134,520	94,922–171,401	5,660	3,327–8,505	160,675	97,942–236,362
Maldives	35	23–48	1,136	773–1,497	41	25–61	1,222	785–1707
Burma	22,675	15,693–31,437	664,973	467,158–918,224	25,754	16,316–35,697	669,267	436,430–931,955
Philippines	5,899	3,957–7,996	182,098	128,081–239,695	23,588	14,885–33,385	727,040	472,675–1,001,384
Sri Lanka	2,834	1813–3,947	73,671	48,915–99,207	3,446	1932–5,666	86,419	51,348–136,071
Thailand	11,222	7,482–15,119	333,518	231,185–435,191	14,312	8,247–22,373	409,927	253,360–617,746
Vietnam	24,948	16,329–35,322	627,551	420,264–858,595	43,166	27,438–60,949	1,109,704	719,539–1,539,709
High-income Asia pacific								
Brunei	39	26–53	1,235	856–1,614	45	29–63	1,482	1,008–1993
Singapore	483	318–652	13,965	9,403–18,499	390	253–559	12,035	7,905–16,686
North Africa and Middle East								

(Continued)

TABLE 1 (Continued)

Countries	1990				2019			
	Mortality		DALYs		Mortality		DALYs	
	Number	*95%UI*	Number	*95%UI*	Number	*95%UI*	Number	*95%UI*
Afghanistan	3,325	2,163–4,689	96,768	65,406–135,387	4,950	3,288–6,999	167,425	113,188–232,267
Bahrain	17	12–24	611	433–829	34	22–51	1,398	935–1991
Egypt	3,244	2,104–4,720	109,798	72,186–157,112	5,249	2,941–8,653	183,803	108,860–284,020
Iran	3,913	2,872–5,200	114,356	86,128–148,118	5,817	4,128–7,778	144,829	103,456–192,654
Iraq	1,659	1,135–2,340	46,668	32,065–65,410	4,274	2,805–6,140	125,402	81,694–178,735
Jordan	290	205–387	8,296	5,980–10,845	648	455–869	19,217	13,793–25,443
Kuwait	50	36–68	2037	1,504–2,629	185	124–260	6,730	4,743–9,055
Lebanon	116	79–168	3,255	2,157–4,601	247	145–356	6,711	4,382–9,455
Oman	127	83–184	4,165	2,745–5,950	163	113–228	5,979	4,252–8,130
Palestine	277	197–367	6,436	4,618–8,494	393	283–520	9,792	7,142–12,830
Qatar	9	6–14	446	295–638	27	16–42	1716	1,112–2,454
Saudi Arabia	1,028	682–1,499	31,438	20,939–44,957	2,348	1,502–3,373	91,954	60,437–130,780
Syria	1,086	745–1,503	33,414	22,882–45,232	1,672	1,125–2,399	47,512	32,535–66,603
Turkey	2,491	1,690–3,548	69,637	46,884–97,124	5,125	3,403–7,354	117,407	76,754–167,557
United Arab Emirates	102	65–158	4,403	2,932–6,507	533	336–826	26,359	17,108–39,491
Yemen	1,616	1,018–2,377	48,729	31,375–71,113	3,581	2,413–5,184	107,727	73,222–151,603
Central Europe								
Albania	1,071	699–1,454	22,240	15,193–29,147	1,620	914–2,507	27,171	16,031–41,820
Bosnia and Herzegovina	1,501	970–2075	37,006	24,550–49,864	1854	1,013–2,940	34,752	19,262–54,363
Bulgaria	9,895	7,028–12,707	223,459	161,984–283,996	9,204	5,987–12,979	170,587	113,102–238,779
Croatia	3,198	2,159–4,252	70,125	48,450–91,615	2,223	1,363–3,293	39,207	24,901–55,719
Czechia	8,278	5,958–10,889	168,042	124,114–214,304	3,478	2,227–4,962	65,399	44,008–89,638
Hungary	8,708	6,304–11,223	202,197	151,708–251,873	4,160	2,701–5,827	86,770	59,055–118,507
Montenegro	371	235–518	7,577	5,066–10,260	526	299–796	9,357	5,499–14,032
North Macedonia	1,395	913–1963	29,651	19,987–40,241	1848	1,067–2,765	35,011	20,428–51,764
Poland	13,513	9,571–18,021	313,397	231,142–408,272	11,865	7,794–16,992	240,386	165,399–329,341
Romania	16,530	11,197–21,945	369,732	256,820–479,508	15,541	9,644–21,994	284,585	183,930–394,641
Serbia	7,767	5,128–10,468	169,368	115,241–225,429	7,120	4,367–10,752	125,306	78,443–188,322
Slovakia	2,581	1822–3,315	59,980	43,799–75,910	1921	1,232–2,808	41,545	27,580–58,793
Slovenia	976	633–1,424	20,816	14,090–29,112	603	364–910	10,416	6,625–14,989
Eastern Europe								
Belarus	4,037	3,177–5,127	99,149	78,742–123,382	3,678	2,594–5,169	82,302	58,537–114,072

(Continued)

TABLE 1 (Continued)

Countries	1990				2019			
	Mortality		DALYs		Mortality		DALYs	
	Number	*95%UI*	Number	*95%UI*	Number	*95%UI*	Number	*95%UI*
Estonia	693	521–889	15,590	11,893–19,510	199	130–292	4,142	2,828–5,871
Latvia	1,597	1,212–2,102	33,220	25,538–42,669	950	638–1,352	17,136	11,904–23,996
Lithuania	998	726–1,343	24,659	18,635–32,219	957	638–1,390	18,738	12,850–26,167
Republic of Moldova	1,086	723–1,570	27,756	18,524–39,376	998	675–1,436	23,594	16,047–33,420
Russia	86,376	63,584–114,847	1,997,368	1,507,553–2,574,674	73,383	49,738–102,945	1,595,601	1,108,276–2,198,646
Ukraine	25,279	19,213–33,295	555,814	428,147–717,875	18,047	12,353–25,098	417,587	293,387–565,884
Western Europe								
Cyprus	150	106–205	2,977	2,144–4,005	156	108–220	2,912	2078–3,923
Greece	3,716	2,693–5,309	62,659	45,622–88,642	3,818	2,677–5,356	53,746	39,134–72,757
Israel	391	245–639	8,284	5,176–13,062	494	314–757	9,592	6,378–14,118

DALYs, disability-adjusted life-years; UI, uncertainty interval.

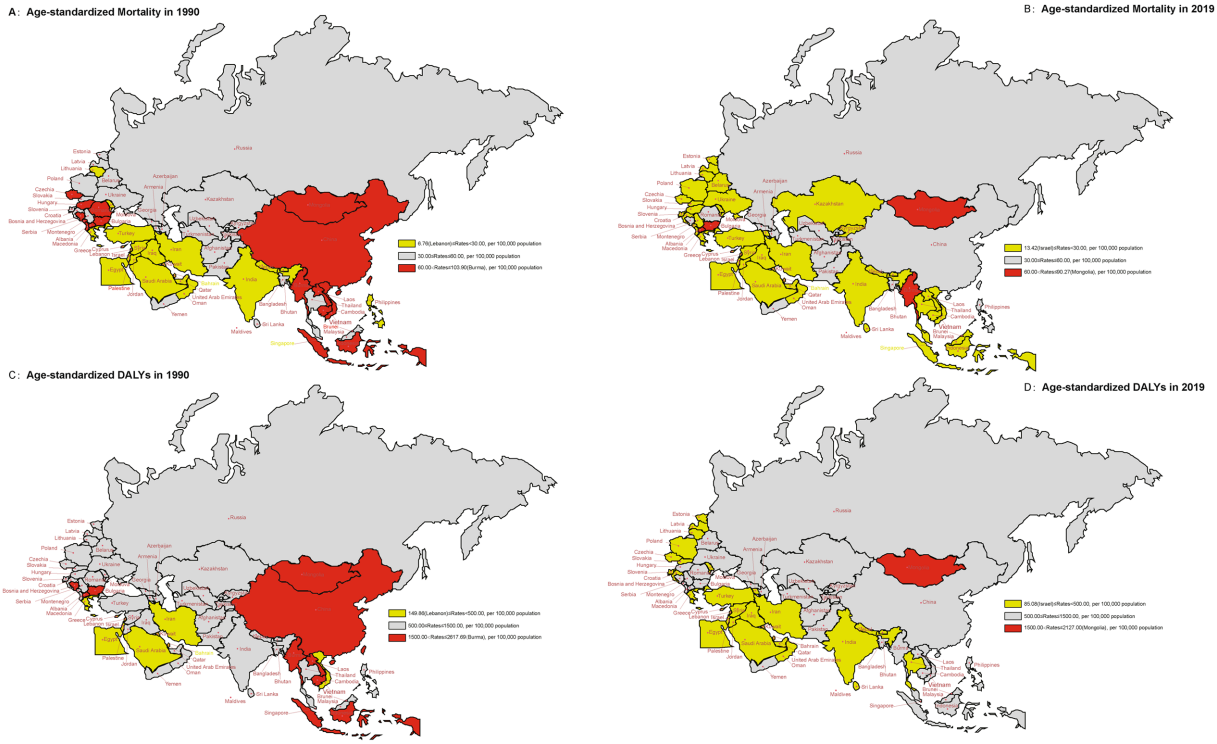

FIGURE 1
The age-standardized rates of mortality and DALYs due to stroke attributed to dietary risk factors for the "B&R" countries in 1990 and 2019. **(A)** Age-standardized mortality rate in 1990. **(B)** Age-standardized mortality rate in 2019. **(C)** Age-standardized DALYs rate in 1990. **(D)** Age-standardized DALYs rate in 2019.

mortality and DALYs for diet-induced stroke was seen in Estonia, Eastern Europe, with AAPC values of −7.09% (95%CI, −7.72, −6.46%) and − 6.62% (95%CI, −7.20, −6.03%), respectively. However, the AAPC of age-standardized metrics showed an increasing trend in Philippines in Southeast Asia (mortality: AAPC = 1.60%; DALYs: AAPC = 2.03%; $p < 0.001$, respectively). We found no statistically significant differences in AAPC for ASR of diet-induced stroke mortality and DALYs in Kuwait, Mongolia and Turkmenistan in Central Asia and North Africa and Middle East for 1990–2019. In addition, we noted a substantial downward trend in ASR of mortality

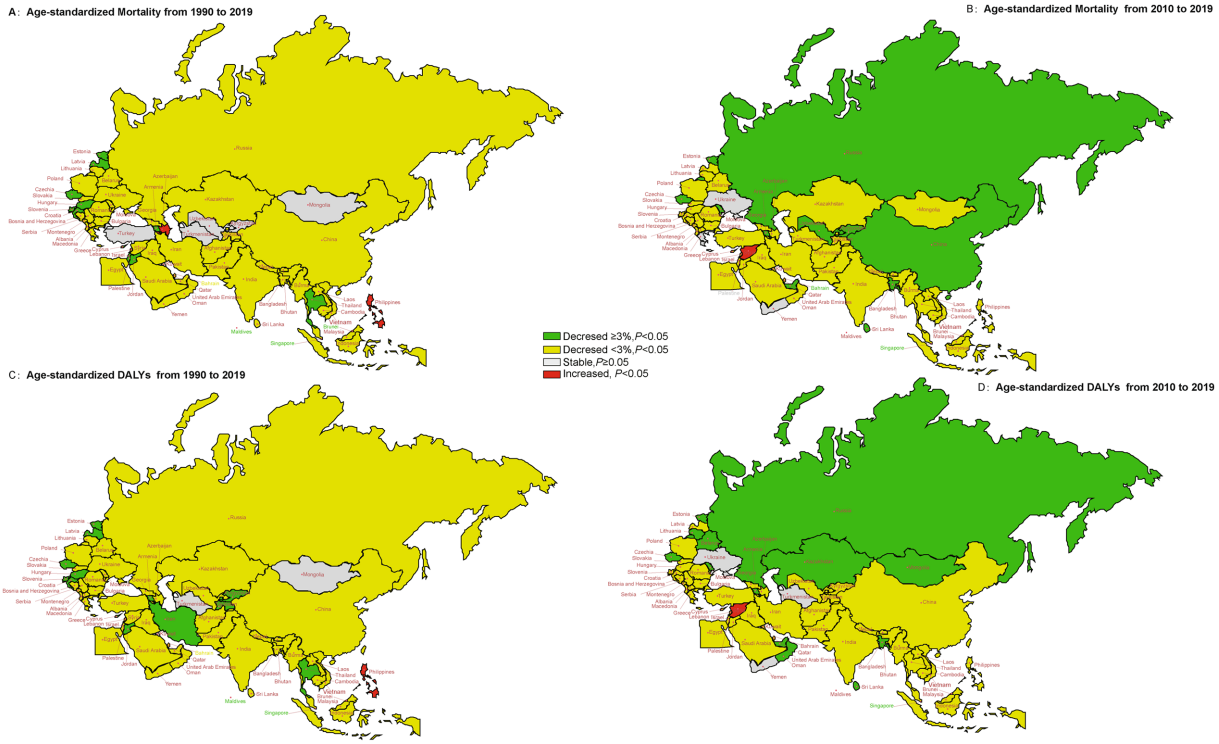

FIGURE 2
The temporal trend in the age-standardized mortality and DALYs rate of stroke attributed to dietary risk factors for 1990–2019 and 2010–2019 in the "B&R" countries. **(A)** The AAPC of age-standardized mortality from 1990 to 2019. **(B)** The AAPC of age-standardized mortality from 2010 to 2019. **(C)** The AAPC of age-standardized DALYs from 1990 to 2019. **(D)** The AAPC of age-standardized DALYs from 2010 to 2019.

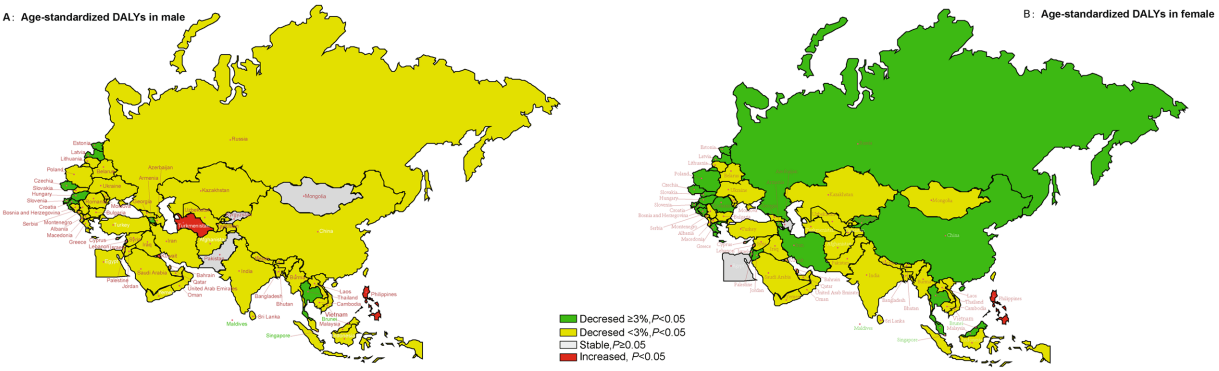

FIGURE 3
The temporal trend in the age-standardized DALYs rate of stroke attributed to dietary risk factors, stratified by gender for 1990–2019 in the "B&R" countries. **(A)** The AAPC of age-standardized DALYs rate in male. **(B)** The AAPC of age-standardized DALYs rate in female.

and DALYs from diet-induced stroke changes in the last decade (2010–2019) for most member states. The ASR of mortality and DALYs due to diet-related stroke in Mongolia remained stable over the full 30 years, yet showed a decreasing trend in the last decade. Trends in age-standardized mortality rates and DALYs for diet-induced stroke in 2010–2019 were not statistically significantly different in Ukraine in Eastern Europe, and Yemen in North Africa and Middle East. See Supplementary Table S2 for more details.

Figure 3 illustrated the AAPC values of age-standardized DALYs rate in each member country of the "B&R" in males and females. Most of countries in the "B&R" countries showed a downward trend in AAPC, Estonia had the highest decline in AAPCs of age-standardized DALYs from 1990 to 2019 (male: AAPC = −6.55, 95%CI: −7.15 to −5.95%; female: AAPC = −6.70, 95%CI: −7.27 to −6.13%). However, an upward trend for both sexes in Philippine was observed (mortality: AAPC = 2.31, 95%CI: 1.64–2.99%; DALYs: AAPC = 1.65, 95%CI: 1.00–2.30%; $p < 0.001$, respectively). The ASR of DALYs for diet-induced stroke decreased more in females than in males. For males, the AAPCs in Mongolia, Tajikistan, Pakistan and Lebanon were stable between 1990 and 2019, while the change trend

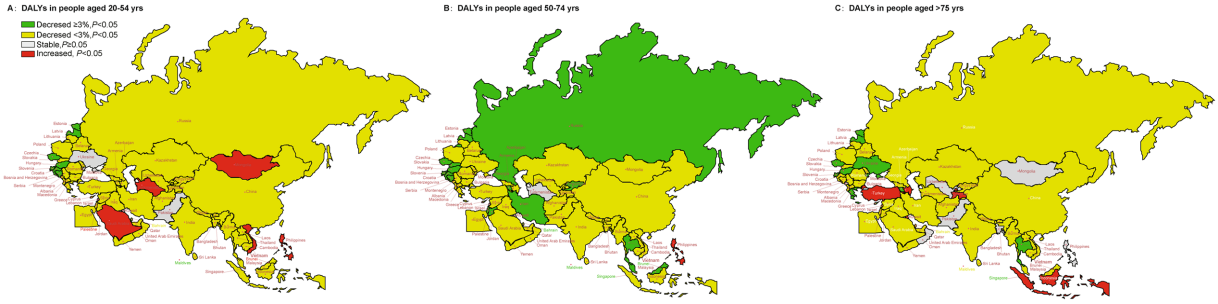

FIGURE 4
The temporal trend in the DALYs rate of stroke attributed to dietary risk factors, stratified by age for 1990–2019 in the "B&R" countries. **(A)** The AAPC of DALYs rate in people aged 20–54 years. **(B)** The AAPC of DALYs rate in people aged 50–74 years. **(C)** The AAPC of DALYs rate in people aged ≥75 years.

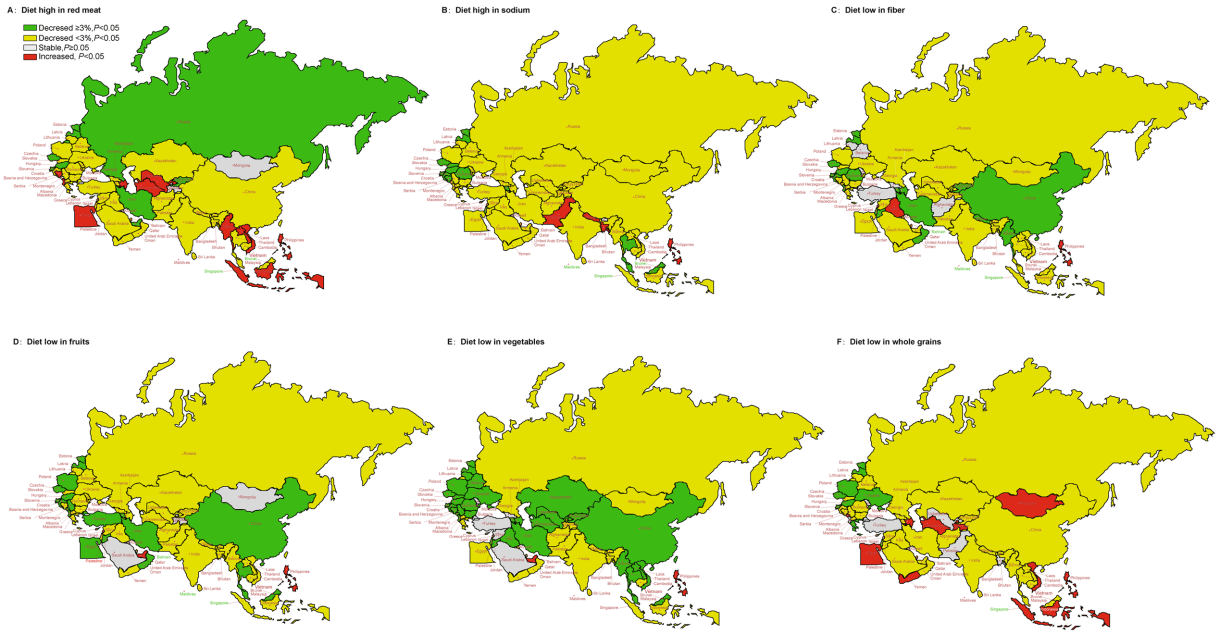

FIGURE 5
The temporal trend in the DALYs rate of stroke attributed to specific dietary risk factors for 1990–2019 in the "B&R" countries. **(A)** Diet high in red meat. **(B)** Diet high in sodium. **(C)** Diet low in fiber. **(D)** Diet low in fruits. **(E)** Diet low in vegetables. **(F)** Diet low in whole grains.

of DALYs was stable for female in Azerbaijan and Egypt ($p \geq 0.05$) (Supplementary Table S3).

Figure 4 showed the long-term trends of DALYs rate due to diet-related stroke, stratified by age for 1990–2019 for the "B&R" countries. The DALYs rate for stroke attributable to dietary risk factors showed a decreasing trend in all age groups among the member countries in Europe from 1990 to 2019. For people aged 20–54 years, DALYs showed an increasing trend in Mongolia and Turkmenistan in Central Asia, Philippines and Vietnam in Southeast Asia, Saudi Arabia in North Africa and Middle East. Overall, for those aged 50–74, the DALYs for stroke due to dietary risk factors in all other "B&R" member countries showed a decreasing trend, except for the Philippines, which rose (AAPC = 2.13, 95%CI: 1.40–2.87%) and Turkmenistan, which remained stable (AAPC = 0.05, 95%CI: −0.43–0.33%). For adults aged 75 years or older, the AAPC value of DALYs caused by diet-related stroke showed an increasing trend in Azerbaijan, Tajikistan, Indonesia, Kuwait, and Turkey, however, the AAPC values varied steadily in Mongolia, Uzbekistan, Bangladesh, Pakistan, Philippines, Oman and Montenegro, with no statistical significance. See Supplementary Table S4 for more details.

The AAPC of age-standardized rates for DALYs due to stroke, attributable to specific dietary risk factors for 1990–2019 in the "B&R" member countries was displayed in Figure 5. The ASR of stroke attributable to modifiable dietary risk factors in Philippines significantly increased. Regions with high red meat consumption showed an increasing trend in the ASR of stroke DALYs, such as Azerbaijan, Uzbekistan and Turkmenistan in Central Asia, Indonesia, Laos, Burma, Philippines, Vietnam in Southeast Asia, Egypt in North Africa and Middle East, Albania and Bosnia and Herzegovina in Central Europe. From 1990 to 2019, regions with low fruit and vegetable intake showed a decreasing trend in the ASR of stroke DALYs in "B&R" member countries, except for Philippines and

United Arab Emirates. Age-standardized DALYs of stroke showed an increasing trend in regions with low intake of whole grains, such as Mongolia, Azerbaijan, Tajikistan and Turkmenistan in Central Asia, Indonesia, Vietnam and Philippines in Southeast Asia, and Egypt in North Africa and Middle East. See Supplementary Table S5 for more details.

Discussion

Based on latest data from the GBD Study 2019, we explored the impact of dietary risks on stroke deaths and DALYs in the member states of the "B&R" over past three decade (1990–2019) and the final decade (2010–2019). The results showed geographical differences in mortality and DALYs of diet-attributable stroke among member countries, the age-standardized mortality and DALYs were generally declining in most member states. The decreases in ASRs of diet-related stroke burden may be attributed to decreases in the improvement of living standard, increased awareness of self-health, improved screening programs, the diagnosis of patients in the early stages of disease and better access to effective therapy (21–23). Bulgaria, Hungary, and Serbia were the three countries with the highest diet-attributable ASR of stroke mortality and DALYs in 1990, and Bulgaria, North Macedonia, and Montenegro in Central Asia in 2019. Central Asian countries have seen a shift from traditional Asian to westernized diets, in addition to dietary risks, diabetes, hypertension and cigarette consumption remain the main risk factors for cardiovascular diseases in this region (24). Another possible explanation for this observation was that the highest percentage of total stroke burden was attributable to YLL, suggesting differences in the quality of acute stroke care in these countries. Lack of education and inadequate preventive measures on the treatment of stroke are also key factors contributing to the progressive stroke burden in Central Asia (25). We also found that the mortality and DALYs of diet-induced stroke in Mongolia remained high. It was reported that in Mongolia, low intake of vegetables and fruits resulted in morbidity and mortality of cardiovascular disease that greatly exceed those of Western countries (26). A substantial downward trend in ASR of mortality and DALYs from diet-induced stroke in the final decade (2010–2019) for most member states, compared to the past 3 decades. This phenomenon may be explained by the improvement of stroke awareness in the community, economic development, increased numbers of neurologists, government insurance coverage and so on.

Findings from this study found that the fastest decline in ASR of mortality and DALYs for diet-induced stroke was seen in Estonia, Eastern Europe. Estonia has established detailed stroke registration and management system since the 1970s, and the results of the third population-based stroke register in 2005 showed a decrease in stroke incidence and 28 days case fatality rates compared to the previous decade (27, 28). Furthermore, we noted that the AAPC of age-standardized metrics showed an increasing trend in Philippines in Southeast Asia. A study found that stroke mortality in Philippines has remained high over the past decade, which is similar to our findings (29). In low- and middle-income countries, dietary patterns are changing considerably, such as the replacement of staple-based diets with increased fat, meat and salt intakes (30). Numerous epidemiological studies have focused on dietary habits, as one of the modifiable risk factors and their impact on stroke risk, found a strong association between low-quality diet and stroke risk, however adherence to Mediterranean-style diet pattern has been pointed out to decrease the risk of first stroke (12, 31). Rosato et al. (32) confirmed that dietary patterns of the "B&R" Mediterranean countries exerted a protective effect on the risk of stroke. The Philippines is constantly facing the enormous burden of malnutrition, especially among adults suffering from various forms of malnutrition, and there has also been a noticeable change in food consumption (33, 34). The 2018 Expanded National Nutrition Survey in Philippines analyzed the relationship between food intake and diet quality, and found that the breakfast that Filipinos regularly eat was not nutritious enough (35). This partly explains the increasing trend of diet-induced stroke DALYs in Philippines over the 30 years period.

Meanwhile, our study found that the temporal trends of diet-induced stroke DALYs varied considerably by sex, age and specific dietary risk factors. Females displayed lower negative AAPCs than males in most member counties, suggesting a higher downturn in ASR in females. Gender is a key risk factor for cardiovascular diseases, with biological sex (determined by sex chromosomes and gonadal hormones) and gender (social and cultural behaviors) influencing differences in disease susceptibility and pathology between men and women (36). Thus, this discrepancy is likely due to the different distribution of stroke risk factors between genders and other pathophysiological factors, such as the protective impact of estrogen for females (37). The DALYs rate for diet-induced stroke showed a decreasing trend in all age groups among the member countries in Europe. Dokova et al. (38) found that ASR of stroke DALY declined in West, Central, and East Europe regions and in all twenty East and Central European countries but at a different pace, which is consistent with our study. For those aged 50–74, the DALYs for stroke due to dietary risk factors in all other "B&R" member countries showed a decreasing trend, except for the Philippines, which rose and Turkmenistan, which remained stable. As we have discussed above, inadequate stroke units and rehabilitation facilities, lack of education on stroke prevention and treatment, and traditional diet pattern (high nutrient and fibrous) contribute to the high DALYs of stroke in Central Asia.

Evidence suggested that the main dietary risk factors for deaths and DALYs were low in whole grains, high in sodium, low in fruits and vegetables globally and in many countries (39). Wang et al. (40) demonstrated that ASR of stroke mortality attributable to high sodium intake showed a downward trend from 1990 to 2019 in China, which was consistent with our results. In China, the daily sodium intake was the highest worldwide and started to decrease from 15 g in 1988 (41) to 4.7 g in 2016 (42), therefore, ASR for stroke mortality due to high sodium intake showed a downward trend. This suggests that the implementation of salt reduction policies has had a significant influence on the reduction of stroke mortality and DALYs. It has been observed that age-standardized DALYs of stroke showed an upward tendency in regions with low intake of whole grains, such as Mongolia, Azerbaijan, Tajikistan and Turkmenistan in Central Asia, Indonesia, Vietnam and Philippines in Southeast Asia, and Egypt in North Africa and Middle East, which belonged to low- and middle-income countries. A review article reports that in low- and middle-income countries, consumption of animal-derived foods, oils and sugar is increasing, while consumption of whole grains is low (43). Additionally, dietary fiber is found in fruits and vegetables, and it has been

shown to reduce the risk of stroke. A balanced diet is one of the essential elements of a healthy lifestyle, according to studies showing that two-fifths of acute ischemic stroke episodes can be prevented (44). Current comparative risk assessments may significantly underestimate the protective effect of fruit and vegetable intake on stroke. In fact, other factors such as economic income, educational level, and dietary environment have an impact on food choice and diet quality (45). In order to improve diet quality, active collaboration in different areas is necessary given the complexity of dietary practices and the diversity of impacts on diet. Besides, the important contribution of potential interactions or synergistic effects between different dietary risk factors to stroke burden should also be considered. By evaluating and comparing the ASR of diet-induced stroke mortality and DALYs in the "B&R" countries, it is found that different countries face different diet-related stroke challenges. Therefore, under the HSR framework, establishing scientific and effective dietary policy applicable to each country, and improving diet quality will remain the key measures of stroke in "B&R" countries.

Based on the broadest epidemiological dataset available to date, this study analyzes estimates of stroke mortality and DALYs attributable to dietary risk factors from 1990 to 2019, and the corresponding changes in the last decade for the first time. Meanwhile temporal trend in diet-induced stroke DALYs were also explored by sex, age, and specific dietary factors. The main strength is the data collection of "B&R" member countries using the same methods and modeling used in the GBD study. Several limitations exist in this study. Firstly, dietary risks from GBD dataset were not strictly categorized, for example vegetables, fruits and whole grains are all rich in fiber, to some extent they overlap with the fiber group. Also, we did not consider potential interactions or synergistic effects between different dietary risk factors. Secondly, underreporting or misclassification of stroke cases existed in each member country due to different diagnostic criteria, definition and measurement of dietary risk are not the same around the "B&R" countries. Thirdly, given the diversity of whole grain products, it is quite difficult to accurately measure intake, which can lead to measurement errors. Fourthly, while certain confounders (smoking, drinking, BMI) were taken into account in the GBD framework, other variables, such as socioeconomic status and access to healthcare, could still be sources of bias. Finally, our study is based on a secondary analysis of GBD, thus GBD all limitations also apply to our study, which is why age groups were not mutually exclusive in this analysis.

Conclusion

This study compared stroke mortality and DALYs attributable to dietary risk factors from 1990 to 2019, and the corresponding changes in the last decade, and explored the temporal trend of ASR for diet-induced stroke DALYs stratified by gender, age and specific dietary risk factors in "B&R" countries in the past three decades. We found geographical differences in mortality and DALYs for diet-induced stroke among member countries, with a general downward trend in these indicators from 1990 to 2019 in most member countries. A substantial downward trend in ASR of mortality and DALYs from diet-induced stroke changes in the final decade. Notably, the AAPCs of age-standardized stroke mortality and DALYs attributable to dietary risk factors significantly increased in Philippines. The ASR of DALYs for diet-induced stroke decreased more in females than in males. Therefore, prioritization of public health interventions among "B&R" member countries should be evidence-based and data-driven to address the risks and challenges posed by diet-induced stroke through enhanced health collaboration and resource sharing.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding authors.

Author contributions

YZ and XL conceived and designed the study. YZ, XL, JW, JZ, and YQ analyzed the data. ZL, JY, WX, HL, CM, XX, and WZ provided advice and consultation. YZ wrote the manuscript. All authors read and approved the submitted manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2023.1235271/full#supplementary-material

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EDITED BY
Iain Brownlee,
Northumbria University, United Kingdom

REVIEWED BY
Yunying Hou,
Soochow University, China
Maria Gacek,
University School of Physical Education in Krakow, Poland

*CORRESPONDENCE
Ick-Mo Chung
✉ ickmo@ewha.ac.kr
Sung Nim Han
✉ snhan@snu.ac.kr

†PRESENT ADDRESS
Jisun So,
Department of Biochemistry and Molecular Biology, Indiana University School of Medicine, Indianapolis, IN, United States

‡These authors have contributed equally to this work and share first authorship

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High intake of sweet foods and low life satisfaction can act as risk factors for acute coronary syndrome through synergistic interaction

Jisun So[1†‡], Kyong-Mee Chung[2‡], Jihyeon Seo[2], Byungmi Kim[3], Hyejin Chun[4], Sung Nim Han[1,5*] and Ick-Mo Chung[6*]

[1]Department of Food and Nutrition, College of Human Ecology, Seoul National University, Seoul, Republic of Korea, [2]Department of Psychology, Yonsei University, Seoul, Republic of Korea, [3]Division of Cancer Prevention, National Cancer Control Institute, National Cancer Center, Goyang-si, Republic of Korea, [4]Department of Family Medicine, Mokdong Hospital, Ewha Womans University School of Medicine, Seoul, Republic of Korea, [5]Research Institute of Human Ecology, Seoul National University, Seoul, Republic of Korea, [6]Division of Cardiology, Mokdong Hospital, Ewha Womans University School of Medicine, Seoul, Republic of Korea

Purpose: Dietary and psychological status contributes to the development of coronary artery disease. However, these lifestyle factors may vary depending on ethnic and environmental background, and secondary prevention programs dealing with these factors in a specific population are not well-established. We aimed to assess dietary and psychological characteristics in Korean patients with acute coronary syndrome (ACS) and analyze their interactions as independent risk factors for ACS.

Methods: Ninety-two patients with ACS (29 acute myocardial infarction and 63 unstable angina) and 69 controls were subjected to dietary and psychological analyses. Dietary intake was assessed by a food frequency questionnaire. Psychological depression and perceived stress were assessed using the Patient Health Questionnaire-9 and the Perceived Stress Scale, respectively. Eight domains of life satisfaction (marital/love relationship, leisure, standard of living, job, health, family life, sex life, and self) were assessed using the Domain Satisfaction Questionnaire (DSQ).

Results: The ACS group had a higher consumption of sweets and fish/seafood, as well as higher levels of depressive symptoms. Additionally, they had lower DSQ scores in total, and all eight individual domains compared with the control group. In multivariate logistic regression analysis, sweet intake (OR 4.57, 95% CI: 1.94–11.40) and total DSQ scores (OR 0.34, 95% CI: 0.14–0.81) were identified as independent risk factors for ACS. Furthermore, these factors, which displayed a significant inverse correlation ($\rho = -0.23$, $p = 0.01$), were determined as having a synergistic contribution to the development of ACS.

Conclusion: High sweet food intake and low life satisfaction can act as risk factors for ACS through a synergistic interaction, which emphasizes a demand for a more comprehensive approach to secondary prevention of ACS. In addition, these data highlight the role of positive psychological wellbeing factors in cardiovascular health.

KEYWORDS

coronary artery disease, sweets, life satisfaction, diet, psychology

Introduction

The mortality rate of coronary artery diseases (CAD), a top leading cause of death and disease burden globally (1), has notably decreased in recent decades in substantial part due to improved medical management strategies for major modifiable risk factors such as high blood pressure or blood cholesterol levels (2). Along with conventional medical interventions, the adoption of therapeutic lifestyle changes has been acknowledged as the essential basis for managing these risk factors (3, 4). Despite the guidelines that emphasize cardiac rehabilitation on comprehensive lifestyle core components, most programs in the field are under-resourced, especially regarding patient-centered nutritional and psychological counseling (5).

According to the recent systematic analysis conducted on the Global Burden of Disease (GBD) Study, cardiovascular disease (CVD) was revealed as the primary cause of mortality and disability-adjusted life-years attributed to diet (6). In that vein, diet is one of the most studied lifestyle factors for cardiovascular risk, as highlighted in international dietary recommendations such as the dietary approaches to stop hypertension (DASH) (7) and the American Heart Association (AHA) guidelines (8). These guidelines recommend a holistic change in the dietary pattern to have more fruits, vegetables, nuts, legumes, fish, vegetable oil, low-fat dairy, and whole grains and to limit red meats, processed meats, refined grains, added sugars, and salts. However, compliance with the guidelines remains poor in many countries, especially in populations with higher CVD risk (9–11). This indicates a demand for more practical strategies of nutritional care on major food sources that contribute most to cardiovascular risk in a particular population of interest.

Psychological health is another emerging risk and prognostic factor for CAD. The role of psychological maladjustments, such as depression (12), anxiety (13), hostility (14), and stress (15), in developing CAD has been reported. However, as "health" is a complete physical, mental, and social wellbeing and not merely the absence of physical illness (16), psychological wellbeing also needs to be focused on to maintain cardiovascular health (17, 18). Indeed, growing evidence of distinct impacts of psychological maladjustment and wellbeing on cardiovascular biomarkers (19) and future events (20) suggests that both aspects should be well considered in the psychological management of CAD patients.

These lifestyle components can be significantly influenced by ethnic, cultural, and environmental backgrounds, and they can affect each other as well. Cardiac rehabilitation programs that incorporate comprehensive core components have been reported more effective in reducing cardiovascular events (21). For such a comprehensive and strategic intervention program, a careful evaluation of the patient's lifestyle should be preceded. To this end, we assessed the lifestyles of patients with acute coronary syndrome (ACS) by targeting their dietary behaviors and psychological status. We focused on identifying major food items or food groups that are mostly associated with ACS risk, and for psychological status, the indices of both psychological maladjustment and wellbeing were studied. Furthermore, an interactive association of diet and psychological status with the risk of developing ACS was determined.

Abbreviations: ACS, acute coronary syndrome; BMI, body mass index; CAD, coronary artery diseases; CVD, cardiovascular diseases; DASH, dietary approaches to stop hypertension; DSM-IV, diagnostic and statistical manual of mental disorders IV; DSQ, domain satisfaction questionnaire; FFQ, food frequency questionnaire; KNHANES, Korea National Health and Nutrition Examination Survey; K-PSS, Korean version of the perceived stress scale; OR, odds ratio; PHQ-9, patient health questionnaire 9; SSB, sugar-sweetened beverages.

Methods

Study design and participants

Ninety-two patients with ACS and 69 control participants, aged 18–70 years, were recruited and completed the study from January 2012 to March 2013 at Ewha Womans University Mokdong Hospital. The ACS patients had been diagnosed with acute myocardial infarction or unstable angina 2–4 weeks before the analysis. Acute myocardial infarction, which encompasses both non-ST segment elevation myocardial infarction and ST segment elevation myocardial infarction, was diagnosed based on the following three criteria: (1) typical ischemic chest pain, (2) increased cardiac enzyme (hs-cardiac troponin T and CK-MB), and (3) EKG change (ST-T change and pathologic Q wave if present). Unstable angina was diagnosed based on the presence of ischemic chest pain with at least one of the following three features: (1) occurrence at rest, (2) recent onset within the past 2 weeks, and (3) a crescendo pattern characterized by increasing severity, frequency, or duration. Coronary angiography and echocardiography were performed for all patients with ACS. The exclusion criteria included active infection, malignant disease, autoimmune disease, $\geq$ stage 4 chronic kidney disease (eGFR $\leq$30 ml/min/1.73 m^2), any other serious medical/surgical illnesses, and a family history of premature CAD or stroke. During the same time period, upon consent, individuals who visited the Health Promotion Center of the hospital for medical check-ups were initially screened for significant CVD or any other medical/surgical conditions based on the record of their annual check-ups. Additionally, participants who were identified to have those conditions through physical examination and laboratory analyses (e.g., EKG, echocardiography, or 3D heart CT angiogram) during the current check-up were subsequently excluded from the study. All participants signed written informed consent, and the study protocol was approved by the Institutional Review Board of Ewha Womans University Mokdong Hospital (ECT 12-01-10).

Data collection

For the ACS patients, anthropometric information and blood samples were collected during the first or second outpatient visit, which occurred after 1–3 weeks of discharge. Subsequently, on the same day, diet and psychological health assessments were conducted by trained dietitians and psychologists in a separate session by collecting demographic information. For the control

participants, all information was collected on the day of their medical check-up visits.

Diet assessment

Dietary intake was assessed using a food frequency questionnaire (FFQ) during an interview conducted by trained dietitians. The FFQ utilized in this study consists of 103 food items and was developed by the Korea Centers for Disease Control and Prevention specifically for the Korean Genome and Epidemiology Study (KoGES). Its validation was conducted on Korean adults (22, 23). Detailed instructions were given to participants to record food intake estimates over the previous one-year period, especially for patients, for the year preceding their diagnosis. The frequency of consumption was divided into 9 categories: never or seldom, once a month, 2–3 times a month, 1–2 times a week, 3–4 times a week, 5–6 times a week, once a day, twice a day, and three times or more per day. Portions were classified as small, medium, and large, according to the median value of each food consumption from the Korea National Health and Nutrition Examination Survey (KNHANES).

To estimate the nutritional composition of the diet and the frequency of food intake, all FFQs were analyzed by the same dietitians using KoGES software and Can-Pro 4.0 (Korean Nutrition Society, Korea) based on the KoGES database. Can-Pro 4.0 was used to generate data on more nutrients and conduct flexible food grouping. The consistency between the data generated by these two tools was confirmed (data not shown). Each food item, except for 8 items, was classified into one of the main food group categories: rice and grains, starch and starchy vegetables, noodles, instant ramen, meat and poultry, fish and seafood, salted fish, eggs, legumes, nuts, fruits, vegetables, salted vegetables, seaweeds, dairy, sweets, and fast foods (Supplementary Table 1).

Psychological health assessment

The Patient Health Questionnaire 9 (PHQ-9) was used to assess the severity of depressive symptoms based on the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) criteria (24). Participants were asked to rate 9 depressive symptoms over the past 2 weeks using a 4-point scale. The total score ranges from 0 to 27 points with a higher score indicating a higher level of depression (clinical depression: $\geq$10 points). Cronbach's alpha is 0.83 in the current study.

To measure the level of perceived stress in daily life, we used a modified Korean version of the Perceived Stress Scale (K-PSS), a 10 item-scale, which was developed from the original version with 14 items (25). Participants were asked to rate the level of experienced stress during the previous month based on a five-point scale. An overall score ranges from 0 to 40 points, and a higher score indicates a higher level of stress. Cronbach's alpha was 0.74 in this study.

Life satisfaction was assessed by the Domain Satisfaction Questionnaire (DSQ) which measures eight domains of satisfaction in life: marital/love relationship, leisure, standard of living, job, health, family life, sex life, and self (26). The level of satisfaction in each life domain was rated using a seven-point Likert scale ranging from 1 (very dissatisfied) to 7 (very satisfied). Satisfaction in health was excluded from the analysis as it can be confounded by the diagnosis of ACS in patients. Cronbach's alpha was 0.92 in the present study.

Assessment of other socioeconomic and lifestyle information

Socioeconomic information, including education, household income, and marital status, as well as other lifestyle components, such as smoking, physical activity, and alcohol consumption, was assessed. Smoking status was determined by smoking experience and daily smoking frequency, resulting in the categorization into 1 of the 4 groups: never smoker, former smoker, and current smoker with <1 pack per day or 1 or more packs per day. The level of alcohol consumption was assessed based on the weekly frequency and the quantity consumed per occasion. Heavy alcohol consumption was defined as both drinking at least twice per week and consuming five or more glasses of alcohol on a single occasion. The assessment of physical activity level took into account the frequency of exercise sessions that are longer than 30 min in duration: light (1–2 sessions per week), moderate (3–5 sessions per week), and heavy (6–7 sessions per week). Low-intensity walking was considered as half a session.

Anthropometric data including waist circumference and body mass index (BMI) were measured. Serum concentrations of glucose, LDL cholesterol, HDL cholesterol, and triglycerides were measured after 12 h of fasting.

Statistical analysis

Data were presented as means $\pm$ SDs or geometric means $\pm$ interquartile range, and all analyses were conducted in R version 4.1.0 (27). In a comparison of variables between ACS patients and controls, generalized linear regression models or logistic regression models were used with adjustment for relevant risk factors: sex, age, total energy intake for diet-related variables, and total household income for psychological variables. Multivariate logistic regression models were used to determine independent dietary or psychological risk factors for the development of ACS with adjustment for sex, age, smoking, and/or total energy intake. To explore the interplay between sweet food consumption and total DSQ scores in relation to the risk of ACS, we initially categorized the participants into four groups based on their sweet food intake and DSQ scores, relative to the median values: "Sweets (low) $\times$ DSQ (high)," "Sweets (low) $\times$ DSQ (low)," "Sweets (high) $\times$ DSQ (high)," and "Sweets (high) $\times$ DSQ (low)". Following that, the risk of ACS development was assessed in comparison to the "Sweets (low) $\times$ DSQ (high)" group through a multivariate logistic regression analysis while controlling for sex, age, smoking, and/or total energy intake. A linear relationship between daily sweet intake and total DSQ scores was assessed using the Spearman correlation coefficient.

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TABLE 1 General characteristics of study participants.

Variable	ACS ($n = 92$)	Control ($n = 69$)	p–value[a]
ACS subtype (%)			
Acute myocardial infarction	29 (31.5)	–	**NA**
Unstable angina	63 (68.5)	–	
Men (%)	73 (79.3)	42 (60.9)	**0.02**
Age, year	53.2 ± 10.2	48.7 ± 6.7	**0.002**
Smoking (%)			
Never	21 (22.8)	29 (42.0)	**0.005**
Former	24 (26.1)	11 (15.9)	
Current (<1 pack/day)	14 (15.2)	7 (10.1)	
Current (≥1 pack/day)	32 (34.8)	11 (15.9)	
No response	1 (1.1)	11 (15.9)	
Alcohol consumption[b] (%)			
None	32 (34.8)	16 (23.2)	0.08
Moderate	28 (30.4)	30 (43.5)	
Heavy	31 (33.7)	21 (30.4)	
No response	1 (1.1)	2 (2.9)	
Physical activity[c] (%)			
None	59 (64.1)	30 (43.5)	**0.02**
Light	17 (18.5)	10 (14.5)	
Moderate	11 (12.0)	18 (26.1)	
Intense	4 (4.3)	9 (13.0)	
No response	1 (1.1)	2 (2.9)	
Waist circumference, cm			
Males	88.4 ± 8.4	84.0 ± 9.1	**0.003**
Females	83.0 ± 10.6	78.6 ± 8.6	0.80
Body mass index, kg/m^2	24.7 ± 3.5	23.8 ± 3.3	0.05
Hypertension[d] (%)	32 (34.8)	4 (5.8)	0.07
Dyslipidemia[e] (%)	39 (42.4)	12 (17.4)	**0.003**
Diabetes[f] (%)	28 (30.4)	3 (4.3)	**0.001**
Metabolic syndrome[g] (%)	30 (32.6)	3 (4.3)	**<0.001**
Systolic blood pressure, mmHg	125 ± 15	121 ± 12	0.13
Diastolic blood pressure, mmHg	76 ± 9	73 ± 8	0.06
Triglycerides[†], mg/dl	116 ± 90	91 ± 75	**0.02**
Total cholesterol, mg/dl	179 ± 40	177 ± 26	0.67
HDL cholesterol, mg/dl	44 ± 11	51 ± 11	**<0.001**
LDL cholesterol, mg/dl	113 ± 40	109 ± 26	0.61
Fasting glucose, mg/dl	114 ± 48	89 ± 9	**<0.001**

Values are presented as means ± SDs or [†]geometric mean ± interquartile range. $n = 161$. Participants who completed either dietary or psychological assessments were included.
ACS, acute coronary syndrome; HDL-C, high-density lipoprotein; LDL, low-density lipoprotein.
[a]p values for the comparison between ACS and control groups, except for sex and age variables, were determined using generalized linear models with adjustment for sex and age.
[b]Heavy alcohol consumption is defined as ≥twice per week and ≥5 glasses at once.
[c]Based on the frequency of exercise per week. Exercise longer than ≥ 30 min counted only. Walking is counted as 0.5. Light = 1–2/week; moderate = 3–5/week; heavy = 6–7/week.
[d]Blood pressure ≥140/90 mmHg or use of antihypertensive drugs.
[e]Adult Treatment Panel (ATP) III of the National Cholesterol Education Program (NCEP) (1); total cholesterol ≥240 mg/dl, LDL cholesterol ≥160 mg/dl, triglycerides ≥200 mg/dl or HDL cholesterol <40 mg/dl.
[f]Fasting blood glucose ≥126 mg/dl, HbA1c ≥6.5, or use of antidiabetics.
[g]Three of the following five criteria were met: waist circumference ≥90 cm (men) or 85 cm (women), triglycerides ≥150 mg/dl, HDL cholesterol < 40 mg/dl (men) or 50 mg/dl (women), blood pressure ≥140/90 mmHg, and fasting blood glucose ≥100 mg/dl.
p-value in bold indicates p-value <0.05.

TABLE 2 Nutrient and food group intakes in male and female ACS patients and controls.

Variable	Men			Women		
	ACS ($n = 72$)	Control ($n = 38$)	p-value	ACS ($n = 19$)	Control ($n = 23$)	p-value
a) Energy intakes[†], kcal	2,083 ± 523	1,863 ± 565	**0.03**	1,998 ± 451	1,842 ± 563	0.89
b) Nutrient intakes						
Macronutrients						
Carbohydrate, g	374 ± 93	337 ± 101	0.78	371 ± 83	334 ± 110	0.31
Dietary fiber, g	19 ± 6	18 ± 8	0.57	22± 5	22 ± 10	0.06
Fat, g	39 ± 17	35 ± 17	0.78	32 ± 22	33 ± 15	0.40
Cholesterol, mg	250 ± 129	202 ± 142	0.22	206 ± 128	212 ± 141	0.86
SFA, g	9.9 ± 5.2	8.4 ± 4.3	0.33	8.5 ± 6.7	8.6 ± 5.4	0.53
MUFA, g	10.5 ± 5.7	8.5 ± 4.0	0.21	9.2 ± 7.8	9.8 ± 6.5	0.86
PUFA, g	5.4 ± 2.9	4.0 ± 1.6	0.05	4.4 ± 2.9	4.5 ± 2.3	0.61
Protein, g	78 ± 24	67 ± 23	0.36	74 ± 25	70 ± 25	0.50
Fat-soluble vitamins						
Vitamin A, μg RAE	547 ± 264	562 ± 318	0.27	646± 285	672 ± 429	0.23
Vitamin D, μg	4.4 ± 3.8	3.1 ± 2.0	0.17	4.0 ± 2.6	2.6 ± 1.5	**0.003**
Vitamin E, mg α-TE	9.5 ± 3.9	7.9 ± 3.2	0.47	8.9 ± 2.6	8.7 ± 3.2	0.20
Vitamin K, μg	178 ± 137	146 ± 111	0.53	205 ± 92	219 ± 185	0.53
Water-soluble vitamins						
Vitamin C, mg	80 ± 44	81 ± 49	0.41	106 ± 36	112 ± 72	0.09
Niacin, mg NE	17 ± 6	15 ± 5	0.51	17 ± 6	16 ± 7	0.92
Vitamin B6, mg	1.6 ± 0.4	1.4 ± 0.5	0.88	1.7 ± 0.4	1.6 ± 0.6	0.46
Folate, μg DFE	481 ± 167	427 ± 193	0.79	533 ± 137	519± 209	0.28
Vitamin B12, μg	7.6 ± 4.2	5.5 ± 3.2	0.10	8.0 ± 5.1	5.7 ± 3.4	**0.02**
Minerals						
Calcium, mg	466 ± 194	425 ± 228	0.84	489 ± 135	451 ± 214	0.92
Phosphorus, mg	1,061 ± 327	907 ± 338	0.38	1,099 ± 278	990 ± 355	0.42
Sodium, mg	3,001 ± 1,269	2,617 ± 1,548	0.42	2,645 ± 1,229	2,446 ± 1,158	0.86
Iron, mg	14 ± 5	12 ± 4	0.87	15 ± 3	14 ± 6	0.41
Selenium, μg	118 ± 34	97 ± 32	**0.01**	106 ± 36	97 ± 32	0.28
c) Food group intakes, serving[‡]						
Rice and grains	2.90 ± 0.83	2.60 ± 0.93	0.61	2.65 ± 0.80	2.26 ± 0.99	0.92
Starch and starchy vegetables	0.46 ± 0.49	0.34 ± 0.42	0.36	0.92 ± 1.23	0.54 ± 0.47	0.48
Noodles	0.22 ± 0.23	0.27 ± 0.37	0.08	0.15 ± 0.30	0.18 ± 0.20	0.18
Instant ramen	0.18 ± 0.20	0.15 ± 0.24	0.65	0.06 ± 0.12	0.08 ± 0.07	0.30
Meat and poultry	0.89 ± 0.66	0.84 ± 0.66	0.81	0.65 ± 0.85	0.76 ± 0.69	0.60
Fish and seafood	1.69 ± 1.19	1.05 ± 0.65	**0.03**	2.28 ± 1.70	1.27 ± 0.83	**0.008**
Salted fish	0.06 ± 0.14	0.04 ± 0.05	0.21	0.04 ± 0.07	0.04 ± 0.06	0.78
Eggs	0.33 ± 0.34	0.29 ± 0.46	0.61	0.21 ± 0.24	0.31 ± 0.40	0.32
Legumes	1.00 ± 1.12	0.73 ± 0.62	0.64	0.72 ± 0.47	1.06 ± 0.78	**0.01**
Nuts	0.13 ± 0.26	0.09 ± 0.16	0.98	0.22 ± 0.39	0.23 ± 0.31	0.57
Fruits	1.18 ± 1.24	1.48 ± 1.70	0.10	1.84 ± 1.53	2.02 ± 2.14	0.27

(Continued)

TABLE 2 (Continued)

Variable	Men			Women		
	ACS ($n = 73$)	Control ($n = 42$)	p-value	ACS ($n = 19$)	Control ($n = 27$)	p-value
Vegetables	3.11 ± 2.38	2.51 ± 2.24	0.53	3.77 ± 2.12	4.87 ± 3.50	0.07
Salted vegetables	2.98 ± 1.98	2.51 ± 2.07	0.36	2.86 ± 1.99	2.69 ± 1.67	0.75
Seaweeds	0.56 ± 0.42	0.50 ± 0.60	0.77	0.79 ± 0.49	0.56 ± 0.65	0.06
Dairy	0.82 ± 0.91	0.93 ± 1.23	0.36	0.59 ± 0.54	0.57 ± 0.51	0.86
Sweets	2.95 ± 2.01	1.55 ± 2.67	**0.005**	1.50 ± 1.41	0.56 ± 0.43	**0.02**
Fast foods	0.06 ± 0.14	0.04 ± 0.05	0.28	0.01 ± 0.01	0.03 ± 0.03	0.08

Values are means ± SDs. $n = 152$. Participants who completed dietary assessment were included in this analysis. p-values for the comparison between ACS and control groups were determined using generalized linear models with adjustment for age and total energy intake.
[†] p value adjusted only for age.
[‡] See Supplementary Table 1 for food grouping details.
p-value in bold indicates p-value <0.05.

TABLE 3 Psychological characteristics of ACS patients and controls.

Variable	ACS ($n = 85$)	Control (n =63)	p-value	
			Model 1[a]	Model 2[b]
Patient health questionnaire-9 (PHQ-9)	5.4 ± 4.7	4.2 ± 3.6	**0.04**	0.07
Perceived stress scale (PSS)	17.4 ± 4.4	17.0 ± 4.1	0.50	0.88
Domain satisfaction questionnaire (DSQ)				
Marital/love relationship	4.37 ± 1.41	4.73 ± 1.32	**0.02**	**0.045**
Leisure	4.22 ± 1.26	4.81 ± 1.12	**0.006**	**0.045**
Standard of living	4.07 ± 1.05	4.80 ± 1.06	**<0.001**	**0.003**
Job	4.20 ± 1.08	4.60 ± 1.16	**0.02**	**0.04**
Health	3.98 ± 1.13	4.59 ± 0.92	**<0.001**	**0.005**
Family life	4.35 ± 1.27	4.84 ± 1.14	**0.004**	**0.03**
Sex life	3.73 ± 1.25	4.60 ± 0.97	**<0.001**	**<0.001**
Self	4.04 ± 1.17	4.72 ± 1.10	**<0.001**	**0.001**
Average	4.16 ± 0.90	4.69 ± 0.96	**<0.001**	**0.001**

Values are means ± SDs. $n = 148$. Participants who completed psychological assessment were included in this analysis.
[a] p-values for the comparison between ACS and control groups were determined using generalized linear models with adjustment for sex and age.
[b] p-values were additionally adjusted for total household income.
p-value in bold indicates p-value <0.05.

Results

Demographic data of subjects

Comparisons of the general characteristics between the ACS patients and controls are presented in Table 1. Compared with the controls, the ACS patients (29 with acute myocardial infarction and 63 with unstable angina) were older, composed of more men, and had heavier smoking habits with lower physical activities. Socioeconomically, the ACS patients belonged to lower household income categories (Supplementary Table 2). The ACS patients tended to have higher BMI and higher waist circumference only in men. The proportion of participants with CAD risk factors, such as dyslipidemia, diabetes, or metabolic syndrome, was higher in the ACS group than controls. Medications taken by the ACS group are shown in Supplementary Table 3.

Comparison of dietary intakes

The nutrient and food group intakes were compared between the ACS patients and the controls, separated by sex (Table 2) or without separation of sex (Supplementary Table 4). The total energy intake of the ACS patients was significantly higher than that of the controls in men but not in women (Table 2a). With age and total energy intake adjusted, men in the ACS group consumed 22% more selenium, and women in the ACS group consumed 54% more vitamin D and 40% more vitamin B12 than in the controls over the past 1 year (Table 2b). Since the content of these nutrients is typically high in foods of animal origin, we analyzed animal-source protein and fat intakes but found no significant inter-group difference in both men and women (data not shown).

Next, we compared food intakes between the two groups by categorizing the food items into 17 different food groups and estimating the total daily servings of each food group (Table 2c).

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This was calculated based on the serving sizes of food items from the KoGES FFQ database. The most notable differences in both men and women were higher intake of sweets and fish/seafood in the ACS patients than in the controls (Table 2c). Among the food items analyzed, the most notable differences between the groups were observed in the consumption of added sugars in coffee/tea, specifically sugars added in coffee mixes, under the sweets category, and mackerel in the fish/seafood category (Supplementary Table 5). The women ACS patients consumed significantly less legumes than the controls (Table 2c).

Comparison of psychological status

While no difference was observed between the groups in perceived stress levels estimated using the K-PSS scores, the levels of depressive symptoms measured using the PHQ-9 scores were significantly higher in the patients than in the controls (Table 3). There was no significant difference in clinical depression (PHQ-9 score $\geq$10) between the ACS patients and the controls (15.3 vs. 8.1%). The total DSQ score, which refers to the average life satisfaction scores across the 8 life domains, was significantly lower in the patients than in the controls, with the lower DSQ scores in all 8 individual domains (marital/love relationship, leisure, standard of living, job, health, family life, sex life, and self; Table 3). These between-group differences remained even after additional adjustment for total household income.

Associations of dietary and psychological factors to ACS development

In this cohort, we determined the risk of developing ACS associated with each of the aforementioned dietary and psychological factors using multivariate logistic regression models with adjustment for sex, age, and smoking. Especially for estimating the risk related to each food group intake, the models were tested with an additional adjustment for total energy intake. Among the food groups that showed significant differences between the groups, only sweet intake had a significant association with ACS risk with an OR of 4.57 (95% CI 1.94–11.40; Table 4a). However, no significant association was observed between fish/seafood intake and ACS risk. Regarding psychological measures, only the total DSQ score showed a significant inverse association with the risk of ACS with an OR of 0.34 (95% CI 0.14–0.81; Table 4b).

Next, we examined an interactive association between sweet food consumption and total DSQ score on the risk of ACS. First, a modest but significant inverse correlation between daily sweet intake and total DSQ score was observed ($\rho = -0.23$, $p = 0.01$, Figure 1), indicating that those with lower life satisfaction tend to consume more sweet foods or vice versa. In addition, a multivariate logistic regression analysis revealed significantly incremental ACS risks depending on four different combinations of sweet food intake and total DSQ score (Table 5). Compared with the participants who consumed sweets less than the median of 1.71 daily servings and had total DSQ scores higher than the median of 4.43, those with lower sweet consumption but lower DSQ scores had increased ACS risks with an OR of 8.64 (95% CI 2.06–43.77). For a group of participants who had higher DSQ scores but consumed larger quantities of sweets, the OR for ACS was 14.99 (95% CI 3.42–85.02). A combination of higher sweet consumption and lower total DSQ score further increased the risk by an OR of 20.72 (95% CI 5.10–111.64).

TABLE 4 Odd ratios of ACS associated with select lifestyle factors.

Variable	OR	95% CI	*p*-value
a) Dietary factors			
Sweet intake (high vs. low)[a]	4.57	(1.94–11.40)	**<0.001**
Fish/seafood intake (high vs. low)[b]	2.18	(0.92–5.34)	0.08
b) Psychological factors			
PHQ-9 score (high vs. low)[c]	2.08	(0.89–5.01)	0.10
Total DSQ score (high vs. low)[d]	0.34	(0.14–0.81)	**0.02**

The odds ratios were determined using logistic regression model adjusted for sex, age, and smoking, and for dietary factors, additionally adjusted for total energy intake. $n = 142$ for dietary factors and 118 for psychological factors. CI, confidence interval; DSQ, domain satisfaction score; OR, odds ratio; and PHQ-9, patient health questionnaire 9.

[a]Divided by the median intake of 1.52 daily servings. high (serving >1.52, $n = 70$); low (serving $\leq$1.52, $n = 72$).

[b]Divided by the median intake of 1.3 daily servings. high (serving >1.3, $n = 71$); low (serving $\leq$1.6, $n = 71$).

[c]Divided by the median score of 4. high (score $\geq$4, $n = 59$); low (score <4, $n = 59$).

[d]Divided by the median score of 4.43. high (score $\geq$4.43, $n = 60$); low (score <4.43, $n = 58$).

p-value in bold indicates *p*-value <0.05.

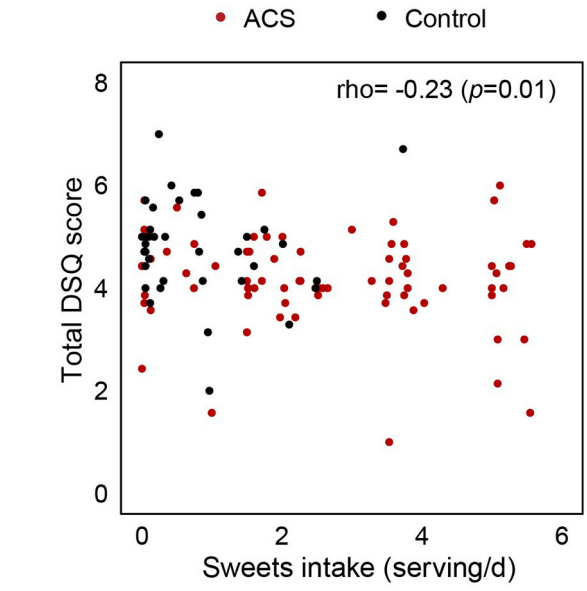

FIGURE 1
A correlation between daily sweet intake and total domain satisfaction score. The correlation was determined using the Spearman rank correlation coefficient (rho, ρ). Each point represents individual participants: ACS (red) and controls (black). The correlation coefficient and its *p*-value are presented in the top right corner.

TABLE 5 Odd ratios of ACS associated with the combinations of select lifestyle factors.

	n	Sweet intake	Total DSQ score	OR (95% CI)	
				Model 1[a]	Model 2[b]
Sweets (low) × DSQ (high)	35	0.50 ± 0.55	5.08 ± 0.58	1	1
Sweets (low) × DSQ (low)	21	0.79 ± 0.61	3.61 ± 0.75	8.19 (2.05–39.65)**	8.64 (2.06–43.77)**
Sweets (high) × DSQ (high)	23	3.71 ± 1.48	5.02 ± 0.58	14.58 (3.53–77.15)***	14.99 (3.42–85.02)***
Sweets (high) × DSQ (low)	35	3.76 ± 2.29	3.67 ± 0.74	26.96 (6.50–149.67)***	20.72 (5.10–111.64)***

Values are presented as means ± SDs. $n = 114$. The odds ratios were determined using logistic regression model with adjustment for sex, age, and smoking. High sweet intake was defined as daily sweet intake more than the median of 1.71 daily servings, and high DSQ score as a total score higher than the median score of 4.43.
CI, confidence interval; OR, odds ratio.
**$p < 0.01$.
***$p < 0.001$.
[a]ORs for developing ACS were determined using generalized linear models with adjustment for sex, age, and smoking.
[b]ORs for developing ACS were determined using generalized linear models with adjustment for sex, age, smoking, and total energy intake.

Discussion

The importance of maintaining healthy lifestyle choices has long been acknowledged in the prevention of CAD (28). However, integrative approaches to managing lifestyle components for CAD prevention and treatment are still limited in the field. In the current study, we identified the most distinguishing nutritional and psychological factors in the lifestyle of Korean ACS patients, which can be useful to understand lifestyle-associated risks in this population. We found that a dietary habit of consuming sweet foods that are high in added sugars and a lower level of overall life satisfaction were most significantly associated with increased risks of developing ACS individually and synergistically. Notably, as for psychological status, the measure of psychological wellbeing, i.e., life satisfaction, is better associated with the risk of ACS rather than that of psychological maladjustments in our study population.

The most noticeable characteristics in the diet of ACS patients, compared with that of the controls, were a high intake of sweets (>1.52 servings/day), which included added sugars in coffee/tea and several dessert foods. It was identified as a significant independent risk factor for ACS (OR 4.57). Intriguingly, the daily consumption of sugars added in coffee mixes was 2.36 servings out of 2.65 servings of overall sweet intake (∼90%) in the ACS patients, which was almost three times higher than that of the controls. The consumption of added sugars has drawn great attention due to its exponential increases over the past few decades in many countries along with the obesity epidemic worldwide (29). According to a recent systematic analysis of the GBD study (6), the consumption of SSB was far higher than the optimal intake, especially in North and Latin America, Europe, and high-income Asia Pacific areas. In Western populations, the influences of consuming high amounts of added sugars or SSB on the risk of obesity/metabolic syndrome (30–32), type 2 diabetes (31, 33), hypertension (34, 35), and CAD (32, 36) have been well-established. Similar trends have been reported in Korean adults: the consumption of SSB is associated with a higher risk of obesity/metabolic syndrome (37, 38), hypertension (39), and CAD (40). While SSB has been identified to account for the largest proportion of added sugar intake in the Korean diet (41), the main source of SSB that drives the association with CAD risk remains relatively unstudied. It has been reported that instant coffee was the top source of sugar intake from SSB for Korean adults aged over 30 years but soft drinks for those under 30 years of age (42). This may be attributed to a distinctive coffee consumption pattern observed among Koreans, particularly in middle-aged or older generations. They prefer instant coffee mixes that come pre-packaged with sugar and non-dairy creamer, contrary to the increasing consumption of brewed black coffee among younger adults (43). Increased sugar intake, coupled with inadequate physical activity, may have contributed to the development of metabolic syndrome or type 2 diabetes in the ACS group, as indicated in their higher prevalence of diabetes (30 vs. 4%) and metabolic syndrome (33 vs. 4%) than the control group. This is in line with the increased risk of metabolic syndrome observed in Korean adults who have a high intake of coffee mixes (at least three times per day) (44). Taken together, our data suggest that high sweet food consumption could contribute significantly to the development of ACS probably, at least in part, through metabolic syndrome or type 2 diabetes.

Eating fish and/or seafood, as good sources of very long-chain omega-3 fatty acids and protein, has long been considered protective against CVD risk, and therefore, dietary recommendations generally encourage consuming a variety of fish, preferably oily fish, at least two servings per week for CVD prevention (45, 46). Unexpectedly, in our study, ACS patients had a higher intake of fish or seafood than the controls, although fish intake was not significantly associated with ACS risk. One thing to be considered is that the favorable associations reported between fish intake and CVD risk factors, such as dyslipidemia or high blood pressure among Korean adults, were specifically for oily fish or omega-3 fatty acid intake (47, 48). Furthermore, recent studies revealed heterogeneity in the associations between fish intake and CVD risk which vary by geographic region or CVD history of individuals (49, 50). The lower CVD risk with high fish intake was observed in CVD patients or high-risk individuals but not in general populations without CVD. Moreover, globally, the trend is neutral in general except for China and Africa (50), which may be attributable to different types of fish consumed, cooking methods, mercury levels, and environmental contaminants in fish.

In addition to diet, psychological factors are known to contribute to the development and prognosis of CAD (51, 52). In this study, we examined the association between psychological health and incident ACS by assessing both psychological maladjustments, including depressive symptoms and perceived stress, and psychological wellbeing such as life satisfaction. The ACS patients had higher levels of depressive symptoms with

lower life satisfaction than the controls. The total DSQ score, which represents overall satisfaction across eight life domains, was inversely associated with ACS risk when adjusted for sex, age, and smoking status. This is consistent with a previous study that showed life satisfaction score as a predictor of physical health outcomes including mortality (53). As psychological health is now denoted as a state of complete wellbeing in various aspects (54), the measures of psychological wellbeing should also be included in the prevention and care of patients with CAD. Nonetheless, while the detrimental effects of psychological maladjustments, such as depression (55) and stress (52), on CAD risk have traditionally been examined, studies on associations between psychological wellbeing and cardiovascular health remain limited. In this context, our findings that life domain satisfaction, rather than depressive symptoms or perceived stress levels, is inversely associated with ACS risk add to the evidence on the beneficial role of maintaining psychological wellbeing in cardiovascular health, especially for individuals with suboptimal levels of psychological maladjustment.

The influence of psychological status on cardiovascular health is beyond its independent effect because psychological maladjustment tends to be accompanied by other unfavorable lifestyle changes, for example, smoking and an unhealthy diet, thereby increasing the risk of CAD (52). We also observed a modest but significant inverse correlation between overall life satisfaction and sweet intake. Reversely, the impact of high sugar intake on increasing the risk of psychological disorders has also been proposed with plausible biological mechanisms (56). Sugar overconsumption can alter neural pathways that are involved in addiction, stress, and depression (56), and several hormone levels that have the potential to affect mood states (57). Based on these links reported between psychological health and diet, we further assessed their interactive association with the risk of developing ACS using a subgroup analysis. Participants with a combination of daily sweet intake higher than 1.71 servings and total DSQ scores lower than 4.43 had a higher ACS risk with an OR of 20.72 compared with those with lower sweet intake and higher DSQ scores. Our data suggest a synergistically interactive role of these lifestyle factors in developing CAD, emphasizing a demand for a more comprehensive approach to secondary prevention.

We acknowledge that this study has several limitations. Our patient data was collected cross-sectionally after the incidence of ACS events. Though we intentionally asked the patients to recall their dietary habits and psychological status for a period of 1 year and 2–4 weeks, respectively, preceding the ACS events, this might have introduced some bias in their answers. In addition, the control group was not perfectly matched with the ACS patients in terms of sex and age due to practical challenges in recruitment. To account for these differences between the groups, we have taken sex, age, and other potential variations as covariates in all our analyses. In addition, because the FFQ used in this study was not strictly designed to assess the amount of added sugars or SSB consumed, we used sweet intake as a proxy variable. Nonetheless, our study provides useful information on the main components that best represent the dietary and psychological status of Korean ACS patients and their potential interaction, which could lay the groundwork for secondary prevention program development. To the best of our knowledge, this is the first study that identifies both dietary and psychological factors associated with CAD risk, especially in Korean adults, and further suggests their synergistic role. Furthermore, the strength of the present study is that psychological wellbeing factors and psychological maladjustment factors were assessed together.

Conclusion

Our data show that high sweet food intake and low life satisfaction can act as risk factors for ACS through a potential synergistic interaction. This urges improvements in current cardiac rehabilitation programs to deal with comprehensive core components including patient-centered diet counseling and psychological factors pertaining to a specific population for greater effectiveness.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Institutional Review Board of Ewha Womans University Mokdong Hospital. The patients/participants provided their written informed consent to participate in this study.

Author contributions

I-MC, K-MC, and SNH designed the research. JSo, JSeo, and HC conducted the data collection. JSo, JSeo, BK, K-MC, SNH, and I-MC conducted the sample and data analyses. JSo and KC wrote the manuscript. JSo, K-MC, SNH, and I-MC had primary responsibility for the final content. All authors have read and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

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EDITED BY
Iain Brownlee,
Northumbria University, United Kingdom

REVIEWED BY
Paraskevi Detopoulou,
General Hospital Korgialenio Benakio, Greece
Mahmoud Rafieian-Kopaei,
Shahrekord University of Medical Sciences, Iran

*CORRESPONDENCE
Yongmei Jin
✉ 13795272016@163.com

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Associations between composite dietary antioxidant index and estimated 10-year atherosclerotic cardiovascular disease risk among U.S. adults

Jia Zhang[1], Xueqin Lu[2], Ruifeng Wu[3], Hanchen Ni[4], Lingli Xu[5], Wenjuan Wu[6], Cheng Lu[1], Jiayi Feng[1] and Yongmei Jin[4]*

[1]Department of Cardiovascular Medicine, Shanghai Seventh People's Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai, China, [2]Department of Nutrition, Shanghai Seventh People's Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai, China, [3]Department of Pediatrics, Shanghai Seventh People's Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai, China, [4]Department of Nursing, Shanghai Seventh People's Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai, China, [5]Intensive Care Unit, Shanghai Seventh People's Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai, China, [6]Department of Gastrointestinal Diagnosis and Treatment, Shanghai Seventh People's Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai, China

Background: Atherosclerotic cardiovascular disease (ASCVD) remains the leading cause of death and disability both in U.S. and worldwide. Antioxidants have been proved critical in mitigating the development of atherosclerosis. This study aimed to investigate the associations between composite dietary antioxidant index (CDAI) and estimated 10-year ASCVD risk among U.S. adults.

Methods: Data extracted from the National Health and Nutrition Examination Survey were analyzed. A total of 10,984 adults aged 18 years and above were included in this study. CDAI was calculated based on the dietary intake reported in their 24-h recall interviews. The estimated 10-year ASCVD risk was calculated via Pooled Cohort Equations (PCE).

Results: After adjusting potential confounders, it was indicated that CDAI score was negatively correlated with 10-year ASCVD risk (OR 0.97, 95% CI 0.95–0.99). Stratify CDAI score by quartile, results showed that participants in the second, third, and fourth quartiles had lower ASCVD odds ratio (Q2: OR 0.87, 95% CI 0.69–1.09; Q3: OR 0.78, 95% CI 0.62–0.98; Q4: OR 0.74, 95% CI 0.59–0.94) than those in the first quartile (Q1, lowest CDAI score group), which was confirmed by the trend test as well ($p < 0.05$). Subgroup analyses stratified by sex, age, race/ethnicity, and smoking status did not show significant effect modification.

Conclusion: Higher dietary antioxidants intake is associated with lower ASCVD risk among U.S. adults, for which policymakers and healthcare professionals may consider increasing the consumption of antioxidant-rich foods as a preventive strategy for ASCVD.

KEYWORDS

composite dietary antioxidant index, atherosclerotic cardiovascular disease, National Health and Nutrition Examination Survey, American, adults (MeSH)

1. Introduction

Atherosclerotic cardiovascular diseases (ASCVD), which involve stroke, myocardial infarction and sudden cardiac death (1), take up a large proportion of healthcare budgets and is a significant financial burden worldwide (2). In the United States, it is also the leading cause of death with an estimated medical cost over $200 billion annually. The reason for this is mainly because prevention strategies are not being implemented effectively, and a significant number of adults have uncontrolled risk factors for ASCVD.2 Therefore, identifying high-risk ASCVD population is significant for its primary prevention. 2013 American College of Cardiology/American Heart Association (ACC/AHA) Guideline proposed Pooled Cohort Equations (PCE) to estimate the 10-year risk of developing a first ASCVD event, which was widely recommended by amount of guidelines as a reliable tool for ASCVD's 10-year risk assessment. PCE's initial risk scoring for ASCVD was also of vital importance. In addition, PCE was also recommended by hypertension guideline (3) to instruct pharmacotherapy usage.

High oxidative stress conditions can cause multiple oxidative modifications to lipoprotein phospholipids, which are closely linked to the onset and progression of ASCVD (4). Thus maintaining oxidative homeostasis and an antioxidant defense system is essential for ASCVD prevention. Diet is known to be a major risk factor for most cardiovascular diseases, and an adequate intake of antioxidants could help reduce oxidative burden (5). The composite dietary antioxidant index (CDAI) comprises vitamins A, C, and E, zinc, selenium, and carotenoids as dietary antioxidants. It is a comprehensive score reflecting an individual's antioxidant profile.6 CDAI was proposed by Wright et al. in 20,047 to evaluate the overall impact of antioxidants on health.

The effect of total dietary antioxidant capacity on health has attracted more and more attention in recent years because of antioxidant's critical role in global diet patterns (6–9). However, only a limited number of studies have investigated the association between CDAI and cardiovascular diseases. These studies focused either on CDAI and all-cause and cardiovascular mortality or on the association between high dietary antioxidant intake (one or more nutrients such as vitamins A, C, and D, zinc, and carotenoid) and ASCVD risk (10–12). The effect of CDAI on estimated 10-year ASCVD risk remains unclear. This study aimed to explore the association between CDAI and estimated 10-year ASCVD risk based on a national sample of U.S. adults.

2. Materials and methods

2.1. Study population

The National Health and Nutrition Examination Survey (NHANES) is a large cross-sectional survey interviewing a group of representative non-institutionalized U.S. civilians. This survey employed a stratified complex multi-stage probability survey design and requested its participants to provide detailed information about their dietary intake for two consecutive 24-h periods. The first dietary recall was completed at a mobile examination center while the second one was accomplished by phone in 3–10 days. To minimize error, all interviewers were intensively trained for one week (10). To ensure the consistency in measurement of food consumption, respondents were provided with a standard set of measuring tools such as cups, spoons, glasses, and bottles. The U.S. Department of Agriculture (USDA) Automated Multiple-Pass Method was utilized to gather two 24-h dietary recalls. The Research Ethics Review Committee of the National Center for Health Statistics has approved the NHANES study, and all participants had been given informed written consent. Data of NHANES 2001–2018 cycle were selected for analysis. In this study, a total of 91,351 participants were selected. Exclusion criteria included: individuals under the age of 18 years old ($n = 37,595$); individuals with missing dietary data ($n = 6,021$); individuals whose data were insufficient for ASCVD 10-year risk calculation ($n = 36,751$). Data of 10,984 patients were ultimately included in this analysis (Figure 1).

2.2. Calculation of CDAI

24-h dietary recall interviews were used to collect information on intake of dietary antioxidant and other food components. During the interview, participants were asked to recall specific food and drinks they consumed within the 24-h period before the interview. To evaluate the overall exposure to dietary antioxidants, a modified version of Composite Dietary Antioxidant Index (CDAI) developed by Wright et al. was used (13, 14). The standardized intake of six antioxidant nutrients (vitamin A, vitamin C, vitamin E, zinc, selenium, and carotenoids) was calculated by dividing the difference between individual intake and mean by the standard deviation, and their sum was used to represent CDAI. The formula was shown as following:

$$\mathrm{CDAI} = \sum_{i=1}^{6} \frac{\text{Individual Intake} - \text{Mean}}{\text{SD}}$$

It should be noted that the dietary antioxidant intake did not include those from supplements, medications, or plain drinking water.

2.3. Assessment of ASCVD risk

Pooled Cohorts Equations model from 2013 ACC/AHA guidelines was applied to assess the 10-year risk of ASCVD.1 This model takes demographics, blood cholesterol, blood pressure, smoking, and diabetes history into consideration to predict the likelihood of a first-time hard ASCVD event. Incorporating several recommendations, 7.5% was taken as the cutoff value for 10-year ASCVD risk in this study.

2.4. Covariates

Covariates were adopted to reduce deviation, which included demographic information such as age, sex, educational level, and poverty income ratio (PIR), lifestyle information such as smoking and drinking habits, physical examination results such as body mass index (BMI), and self-reported health status such as medical and drug history. NHANES calculated BMI based on height and weight measurements. PIR was calculated by dividing the family income by the poverty threshold, and results were categorized into three levels:

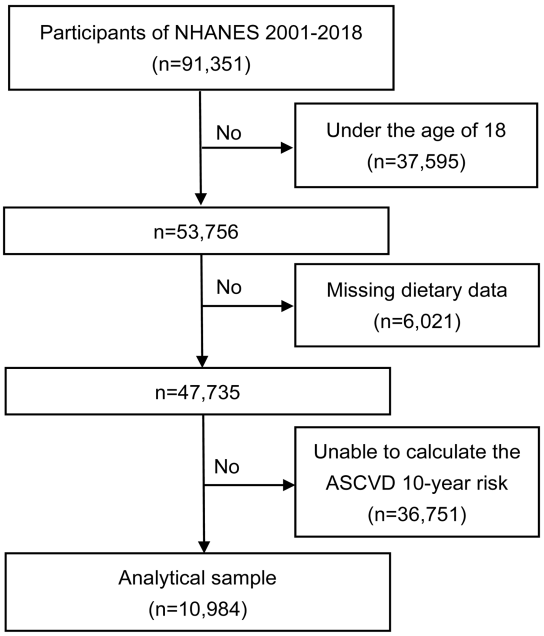

FIGURE 1
Flowchart of the study. ASCVD, atherosclerotic cardiovascular disease.

low income (< 1.3), moderate income (1.3–3.5), and high income (> 3.5). Smoking status was divided into never (less than 100 cigarettes in lifetime), former (more than 100 cigarettes in lifetime and had quit smoking at the time of the survey), and current (more than 100 cigarettes in lifetime and was still smoking every several days at least). Current drinking status was classified into heavy drinking (≥ 3 drinks per day for females; ≥ 4 drinks per day for males; binge drinking for 5 or more days per month), moderate drinking (≥ 2 drinks per day for females; ≥ 3 drinks per day for males; binge drinking ≥2 days per month) (15), and mild drinking (other than the above two). Hypertension was characterized by a blood pressure reading of ≥140/90 mmHg, a medical diagnosis of hypertension, or self-reported use of antihypertensive medication in health questionnaires. Diabetes was confirmed if patients met one or more of the following criteria: (1) diagnosis of diabetes reported by their doctors, (2) glycohemoglobin (HbA1c) > 6.5%, (3) fasting blood glucose ≥7.0 mmoL/L, (4) random blood glucose ≥11.1 mmoL/L, or (5) two-hour blood glucose ≥11.1 mmol/L in oral glucose tolerance test (OGTT). Chronic kidney disease (CKD) was confirmed according to KDIGO guideline (16). We calculated the estimated glomerular filtration rate (eGFR) using the serum creatinine equation from the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) study (17).

2.5. Statistical analysis

Participants were categorized into two groups based on their 10-year ASCVD risks: one group with a risk of less than 7.5% and the other group with 7.5% or higher. Baseline data differences between these two groups were compared. Continuous variables were expressed as means ± standard errors, and categorical variables were represented by percentages. Weighted linear regression was used for continuous variables while weighted chi-squared tests for categorical variables. The relationship between CDAI and 10-year ASCVD risk was investigated by multivariable logistic regression equations. The consistency of the relationship was tested via linear trend tests. Generalized additive models (GAMs) and smooth curve fittings were used to explore non-linear association. Subgroup analyses and interactions were conducted for covariates such as age, sex, hypertension, diabetes, and BMI with controlled variables. All statistical analyses were conducted using R (version 3.5.3) and EmpowerStats,[1] and $p < 0.05$ was taken as statistically significant.

3. Results

3.1. Baseline characteristics

The baseline characteristics were presented in Table 1, which revealed certain difference between two groups. More specifically, participants of "10-year ASCVD risk ≥7.5%" group tended to be older, female, and have higher BMI, worse economic status, lower educational level, smoking and drinking history, diabetes and hypertension, antidiabetic and antihypertensive medications, and lower CDAI.

To investigate the dietary factors causing the variation of CDAI between two groups, we displayed every single component score of CDAI in Table 2. Individuals with a 10-year ASCVD risk ≥7.5% had lower antioxidant dietary scores than the other group regarding all components of CDAI.

3.2. Association between CDAI score and 10-year ASCVD risk

The logistic regression modeling results displayed in Table 3 demonstrated the correlation between CDAI score and 10-year ASCVD risk. After adjusting for covariates (age, sex, PIR, educational level, BMI, smoking, drinking, diabetes, hypertension, CKD, antidiabetic medications and antihypertensive medications), it was indicated that CDAI score was negatively correlated with 10-year ASCVD risk (OR 0.97, 95% CI 0.95–0.99). After stratifying score by quartile, results showed that participants in the second, third, and fourth quartiles had lower ASCVD odds ratio (Q2: OR 0.87, 95% CI 0.69–1.09; Q3: OR 0.78, 95% CI 0.62–0.98; Q4: OR 0.74, 95% CI 0.59–0.94) than those in the first quartile (Q1, lowest CDAI score group), which was confirmed by the trend test as well ($p < 0.05$). We also used generalized additive models and smooth curve fittings to evaluate the associations between these two items. When CDAI was treated as a continuous variable, a negative correlation was observed between CDAI and 10-year ASCVD risk (Figure 2A). When CDAI was treated as a categorical variable with four quartiles, the relationship between CDAI and 10-year ASCVD risk remained unchanged (Figure 2B).

1 http://www.empowerstats.com

TABLE 1 Baseline characteristics of subjects.

Characteristics	Total $n = 10,984$	10-year risk of ASCVD < 7.5% $n = 5,988$	10-year risk of ASCVD ≥ 7.5% $n = 4,996$	*p*-value
Age (years)	58.85 ± 11.37	51.91 ± 8.23	67.17 ± 8.74	<0.05
Sex, *n* (%)				<0.05
Male	5,581 (50.81%)	3,825 (63.88%)	1756 (35.15%)	
Female	5,403 (49.19%)	2,163 (36.12%)	3,240 (64.85%)	
BMI (kg/m^2)	29.35 ± 6.60	28.93 ± 6.47	29.86 ± 6.73	<0.05
PIR[a], *n* (%)				<0.05
Low	2,296 (22.11%)	1,106 (19.43%)	1,190 (25.37%)	
Medium	3,568 (34.36%)	1,574 (27.65%)	1994 (42.52%)	
High	4,519 (43.52%)	3,013 (52.92%)	1,506 (32.11%)	
Education level, *n* (%)				<0.05
Less than high school	1711 (15.58%)	690 (11.53%)	1,021 (20.44%)	
High school	2,899 (26.40%)	1,406 (23.49%)	1,493 (29.90%)	
More than high school	6,369 (58.01%)	3,889 (64.98%)	2,480 (49.66%)	
Smoking, *n* (%)				<0.05
Never	4,856 (44.21%)	2,867 (47.88%)	1989 (39.81%)	
Former	3,815 (34.73%)	1951 (32.58%)	1864 (37.31%)	
Now	2,313 (21.06%)	1,170 (19.54%)	1,143 (22.88%)	
Drinking[b], *n* (%)				<0.05
Never	985 (9.43%)	350 (6.12%)	635 (13.44%)	
Former	2,165 (20.73%)	932 (16.29%)	1,233 (26.10%)	
Mild	4,313 (41.29%)	2,411 (42.14%)	1902 (40.26%)	
Moderate	1,559 (14.92%)	984 (17.20%)	575 (12.17%)	
Heavy	1,424 (13.63%)	1,045 (18.26%)	379 (8.02%)	
Diabetes, *n* (%)	2056 (18.72%)	502 (8.38%)	1,554 (31.10%)	<0.05
Hypertension, n (%)	5,676 (51.68%)	2,237 (37.36%)	3,439 (68.84%)	<0.05
CKD, *n* (%)	2,179 (20.00%)	577 (9.69%)	1,602 (32.42%)	<0.05
Antidiabetic medications, *n* (%)	1,284 (11.69%)	317 (5.29%)	967 (19.36%)	<0.05
Antihypertensive medications (*n*, %)	1,307 (11.90%)	397 (6.63%)	910 (18.21%)	<0.05
CDAI	0.57 ± 3.98	0.94 ± 4.20	0.12 ± 3.66	<0.05

[a]PIR was calculated by dividing the income of the family by the poverty threshold of the family and was categorized on three levels: <1.3 (low income), 1.3–3.5 (moderate income), and > 3.5 (high income); [b]Current drinking is subdivided into three categories: heavy drinking (≥3 drinks per day for females; ≥4 drinks per day for males; binge drinking on 5 or more days per month), moderate drinking (≥2 drinks per day for females; ≥3 drinks per day for males; binge drinking ≥ 2 days per month) and mild drinking (not meet the above). ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; PIR, poverty income ratio; CKD, chronic kidney disease; CDAI, composite dietary antioxidant index.

TABLE 2 Comparison of each component of CDAI scores between individuals with 10-year risk of ASCVD <7.5% and individuals with 10-year risk of ASCVD ≥7.5%.

Characteristics	Total	10-year risk of ASCVD < 7.5%	10-year risk of ASCVD ≥ 7.5%	*p*-value
Vitamin A	474.95 (467.14, 482.90)	483.51 (472.51, 494.76)	464.92 (453.97, 476.13)	<0.05
Vitamin C	44.12 (43.09, 45.17)	44.95 (43.54, 46.40)	43.14 (41.66, 44.68)	0.09
Vitamin E	6.46 (6.37, 6.54)	7.07 (6.95, 7.20)	5.79 (5.68, 5.90)	<0.05
Zinc	9.95 (9.84, 10.06)	10.87 (10.71, 11.04)	8.94 (8.80, 9.08)	<0.05
Selenium	93.42 (92.42, 94.44)	102.87 (101.35, 104.42)	83.24 (82.00, 84.49)	<0.05
Carotenoid	4401.68 (4284.10, 4522.48)	4735.84 (4565.78, 4912.24)	4032.39 (3873.73, 4197.55)	<0.05

Data are presented as the geometric mean and 95% confidence interval. CDAI, composite dietary antioxidant index; ASCVD, atherosclerotic cardiovascular disease.

TABLE 3 Odd ratios and 95% confidence intervals for 10-year risk of ASCVD according to CDAI.

Characteristics	Model 1	Model 2	Model 3
Continuous	0.94 (0.94, 0.95)	0.95 (0.94, 0.97)	0.97 (0.95, 0.99)
Quartile			
Q1	Reference	Reference	Reference
Q2	0.83 (0.74, 0.92)	0.86 (0.72, 1.03)	0.87 (0.69, 1.09)
Q3	0.67 (0.61, 0.75)	0.67 (0.56, 0.80)	0.78 (0.62, 0.98)
Q4	0.55 (0.49, 0.61)	0.61 (0.51, 0.73)	0.74 (0.59, 0.94)
p for trend	<0.05	<0.05	<0.05

Model 1: Non-adjusted. Model 2: Adjusted for age, sex, and PIR. Model 3: Adjusted for age, sex, PIR, education level, BMI, smoking, drinking, diabetes, hypertension, CKD, antidiabetic medications, and antihypertensive medications. ASCVD, atherosclerotic cardiovascular disease; CDAI, composite dietary antioxidant index; PIR, poverty income ratio; BMI, body mass index; CKD, chronic kidney disease.

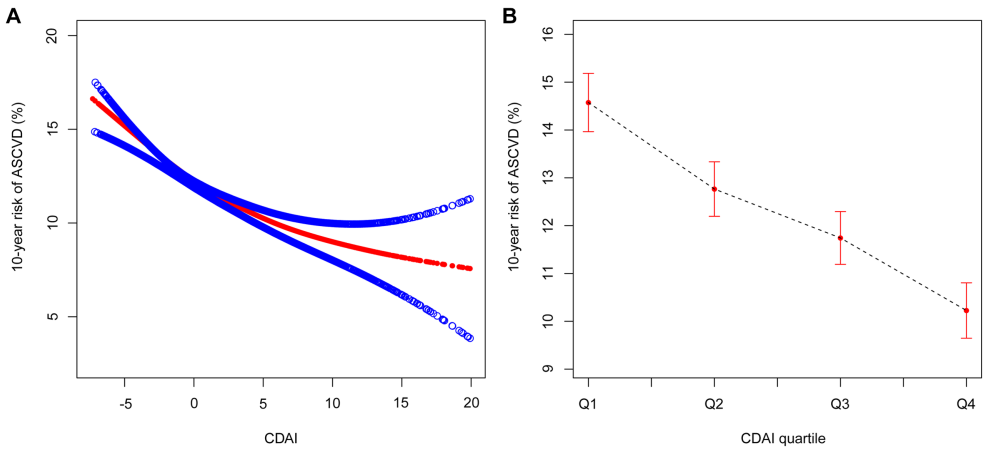

FIGURE 2
The association between CDAI [**(A)** as continuous variable; **(B)** as categorical variable] and 10-year risk of ASCVD. The red line represents the best-fit line, and the blue lines are 95% CI. CDAI, composite dietary antioxidant index; ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval.

The forest plot showed that all stratification variables had consistent interactions, i.e., a negative correlation between CDAI score and 10-year ASCVD risk existing in all stratified analyses (Figure 3). As a sensitivity analysis, the relationship between CDAI score and 10-year risk of ASCVD was also examined in stratified analysis of smooth curve fittings, which suggested a negative correlation between the two variables regardless of gender, age (above or below 65 years), hypertension status, diabetes status, and BMI (above or below 25 kg/m^2) (Figure 4).

4. Discussion

It was demonstrated that overall antioxidant intake, measured by CDAI, was in significant negative association with ASCVD after adjusting for multiple covariates. Participants in the highest CDAI quartile showed a reduced 10-year ASCVD risk than those in the lowest quartile. This study is the first one analyzing the association between CDAI and PCE estimated 10-year ASCVD risk based on a representative group of U.S. adults.

The close correlation between dietary habit and ASCVD risk has been extensively proved. ASCVD risk would be increased by a Western Dietary (WD) pattern and decreased by Mediterranean Diet (MD) pattern and Dietary Approaches to Stop Hypertension (DASH) pattern (18, 19). Oxidative responses mediates the pathogenesis of ASCVD by its different influence on cellular damage, which would vary with aging (20). Such a damage can be relieved by dietary habit's regulation on the redox status of human plasma. It has been shown that recommended, balanced dietary patterns such as MD and Atlantic Diet (AD) can provide all required macro- and micro-nutrients needed to maintain an organism in optimal balance and defend against oxidative damage (21, 22). Proper intake of antioxidants through food could keep our immune system in an optimal antioxidant state (23). In line with this, a recent study by He et al. suggested that high plasma antioxidant level might protect people against age-related diseases (24). Furthermore, growing research studies demonstrate that oxidative stress is closely related to cardiovascular disease and that total dietary antioxidant capacity (TDAC) is negatively associated with markers of inflammation such as C-reactive protein (CRP), platelet-activating factor (PAF), and adiponectin concentration (25–27). Further results from systematic review studies showed substantial associations between DTAC and most cardiovascular disease-related risk factors such as fasting glucose, blood pressure, CRP, and high-density lipoprotein cholesterol

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Characteristics	OR (95% CI)	P-value	P-interaction*
Sex			0.42
Male	0.98 (0.95, 1.01)	0.15	
Female	0.96 (0.94, 0.99)	<0.05	
Age (years)			0.24
<65	1.00 (0.98, 1.02)	0.85	
≥65	0.98 (0.94, 1.01)	0.14	
Hypertension			0.07
Yes	0.99 (0.96, 1.02)	0.46	
No	0.95 (0.93, 0.98)	<0.05	
Diabetes			0.27
Yes	1.00 (0.95, 1.04)	0.86	
No	0.97 (0.94, 0.99)	<0.05	
BMI (kg/m^2)			0.61
<25	0.98 (0.94, 1.02)	0.34	
≥25	0.97 (0.95, 0.99)	<0.05	

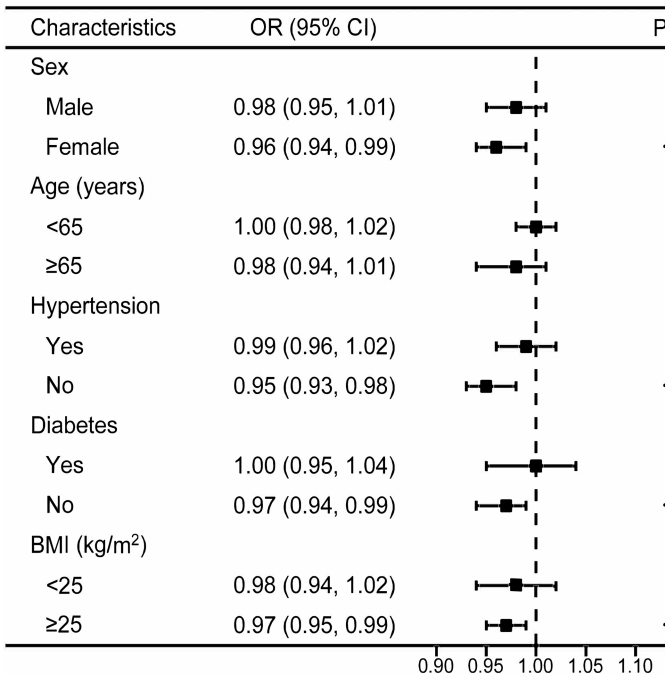

FIGURE 3
Stratified analyses between CDAI and 10-year risk of ASCVD using logistic regression. *Each stratification adjusted for all the factors (age, sex, PIR, education level, BMI, smoking, drinking, diabetes, hypertension, CKD, antidiabetic medications and antihypertensive medications) except the stratification factor itself. OR, odd ratio; CI, confidence interval; ASCVD, atherosclerotic cardiovascular disease; CDAI, composite dietary antioxidant index; PIR, poverty income ratio; BMI, body mass index; CKD, chronic kidney disease.

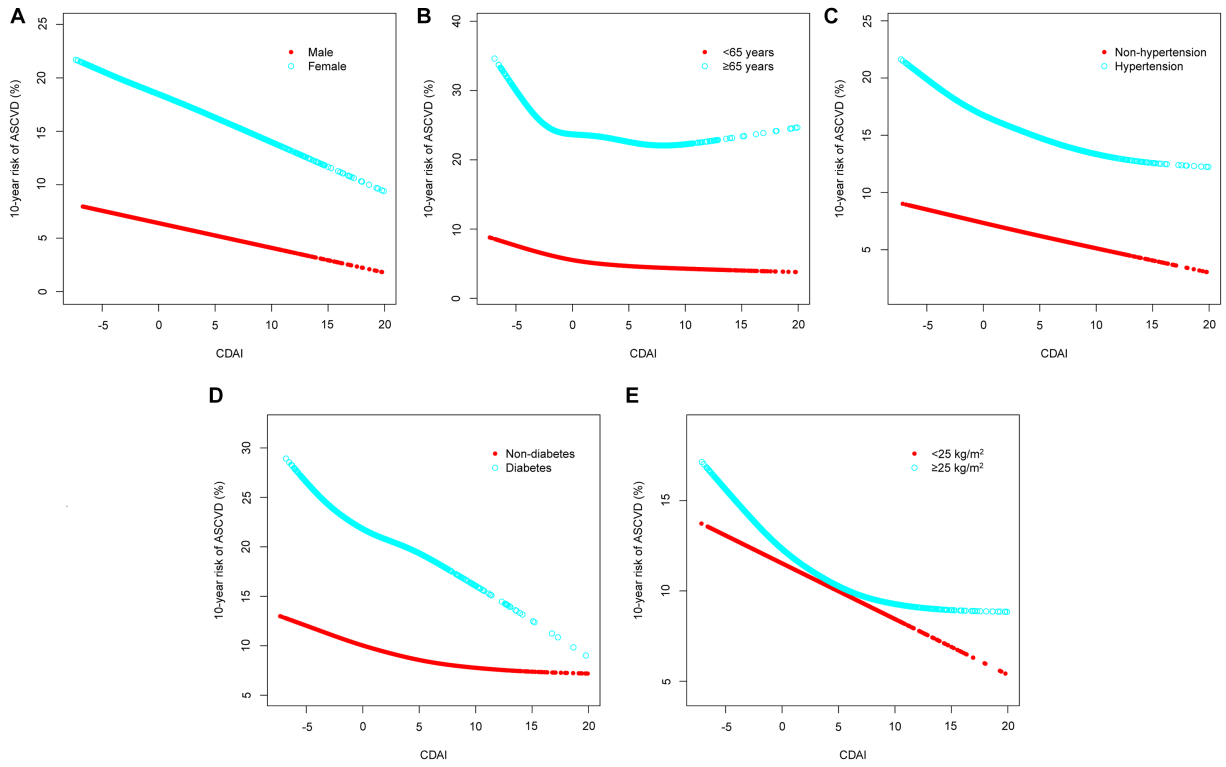

FIGURE 4
Stratified analyses [by **(A)** sex; **(B)** age; **(C)** hypertension; **(D)** diabetes; **(E)** BMI] between CDAI and 10-year risk of ASCVD using generalized additive model and smooth curve fittings. BMI, body mass index; ASCVD, atherosclerotic cardiovascular disease; CDAI, composite dietary antioxidant index.

(HDL-C) (28). In addition, according to Detopoulou et al., PAF is implicated in atherosclerosis, and TDAC and healthy dietary patterns are inversely associated with PAF or its biosynthetic enzymes (29). Another investigator aiming to assess the relationship between adiponectin concentrations and TDAC in adults concluded that antioxidant foods benefit cardiovascular disease through an adiponectin-mediated pathway (27). This highlights the importance of implementing dietary modifications to increase the consumption of antioxidants to better prevent ASCVD risk.

We found that participants with 10-year risk of ASCVD ≥7.5% had lower dietary antioxidants scores in some commonly recognized elements that can alleviate oxidant responses, such as vitamin A, vitamin E, zinc, selenium, and carotenoids. Evidence suggested consumption above the recommended level of certain antioxidants can improve immune functioning and raise resistance to oxidative stress (12, 30). Dietary antioxidants, such as selenium, are beneficial in maintaining the optimal function of intracellular enzyme glutathione peroxide and extracellular protector selenoprotein P against oxidative stress in body (31). Moreover, previous studies have shown that carotenoids act as an essential precursor for the production of retinol such as vitamin A. Carotenoids themselves and their enzymatic products act as antioxidants in lipid-rich environment (32). Other antioxidants, such as vitamin C, can maximize neutrophil concentrations through dietary intake, reduce the production of reactive oxygen species during phagocytosis, and inhibit the oxidation of low-density lipoproteins (33, 34). Vitamin E is a group of fat-soluble compounds whose antioxidant activity mainly derives from α-tocopherol and γ-tocopherol. A lifestyle with Mediterranean diet score > 6 may provide better protection by affecting the oxidant/antioxidant balance in the body (21). Notably, no significant difference detected in vitamin C intake between two groups, which may attributes to the consensus that vitamin C-rich food such as fruits and vegetables may be beneficial to health (35). As the latest U.S. Dietary Guidelines for 2020–2025 emphasizes, there is a need to focus on the importance of healthy dietary patterns as a whole, rather than on individual nutrient, food, or food group in isolation (36).

Considering that these antioxidants might simultaneously affect ASCVD, we further analyzed whether overall potential of dietary antioxidant intake was associated with 10-year ASCVD risk. Present study revealed CDAI's protective effect on 10-year ASCVD risk. As summarized by Senoner et al. (37), reactive oxygen species (ROS) negatively affect myocardial calcium handling and can promote atherosclerotic plaque formation, which was consistent with previous studies. Antioxidants may have a protective effect by modulating immune responses, viral replication, and gene expression to protect against ASCVD (30, 37, 38). Previous studies indicated that dietary total antioxidant capacity (TAC) may impact people with a cardiometabolic risk profile (39). Farhangi et al., indicated that dietary intake of zinc, selenium, and vitamins A, C, and E was inversely related to mortality risk (40). Similarly, Senoner and colleagues presented potential diets that might be beneficial in reducing the burden of oxidative stress in cardiovascular diseases (37). They take into account the difficulty of determining which specific components of food exert antioxidant effects, and therefore also recommend a diet consisting of a variety of foods containing different antioxidants, such as fresh fruits and vegetables and fish, rather than consuming a supplement consisting of a single antioxidant (37). In addition, they suggest that the benefits of antioxidants vary depending on the oxidative status of each individual (41).

After adjusting demographic and clinical covariates associated with ASCVD, the result of logistic regression still demonstrated a significant negative association between CDAI and 10-year ASCVD risk. However, this conclusion did not exclude the influence of other risk factors such as age, sex, hypertension, diabetes, and obesity, which may also be involved in the oxidation process of ASCVD. Age-related vascular endothelial dysfunction is a major antecedent to cardiovascular diseases. Brunt et al. conducted research that found supplementing trimethylamine-N-oxide (TMAO) in the diet increases circulating concentrations of trimethylamine-N-N-oxide, leading to greater oxidative stress caused by superoxides (42). This can result in reduced bioavailability of nitric oxide (NO) and endothelial dysfunction. As a result, healthy middle-aged and older adults have higher plasma TMAO levels compared to young control groups. In addition, accumulating evidence indicates that traditional risk factors for atherosclerosis, including hypertension and diabetes, would induce oxidative stress in blood vessels (43). Moreover, obesity increases the risk of atherogenic dyslipidemia and number of oxidative stress biomarkers. This might provide new ideas for early prevention and treatment of ASCVD. In contrast, some researchers have suggested an association between antioxidant-rich diets and atherosclerosis, but not with insulin, insulin resistance, or total cholesterol (44, 45). Similarly, a study by Kim et al. aimed at investigating the relationship between total antioxidant capacity in diets and supplements and cardiovascular disease risk factors in the NHANES found that intake of antioxidant-rich diets and supplements was beneficial in reducing the risk of cardiovascular disease, but that there were no significant associations between total antioxidant capacity of diets and blood pressure, total cholesterol, and blood glucose (46). The inconsistent results of the above studies regarding the relationship between antioxidant capacity and cardiovascular disease in different subgroups of the population suggest that there is also a strong need to isolate these covariates when exploring the relationship between CDAI and 10-year ASCVD risk. In addition, smoking is well known as a risk factor for cardiovascular disease, and results from a strong heart-based study exploring the potential moderating effects of several dietary nutrients with high antioxidant activity on cardiovascular disease in relation to exposure to environmental tobacco smoke showed that participants exposed to environmental tobacco smoke had a higher risk of cardiovascular disease compared with those not exposed, and a greater risk of cardiovascular disease compared with those who had higher vitamin E intake, as well as a greater risk of cardiovascular disease compared with those who had higher vitamin E intake, as well as a greater risk of cardiovascular disease compared with those who had higher vitamin E intake. The effects of environmental tobacco smoke on cardiovascular disease incidence were greater in those with low vitamin E intake compared to those with high vitamin E intake (47). Of note, the three study centers in the Strong Heart Study reported different smoking prevalence rates and used self-reported exposure to environmental tobacco smoke, making it difficult to differentiate between smoking, secondhand smoke, and thirdhand smoke, which limits the generalization of the results. Additional future studies are recommended to clarify whether smoking or environmental tobacco

smoke exposure mediates the relationship between antioxidant capacity and 10-year ASCVD risk.

A stratified analysis was conducted to isolate the effect of CDAI from forementioned covariates. Interestingly, results of forest plot based-logistic regression and subgroup analysis of the generalized additive models revealed that the negative association between CDAI and 10-year ASCVD risk was robust to sex, age, hypertension, diabetes and BMI, proving the reliability and applicability of our results. This implies that the protective association we observed between dietary antioxidant intake and 10-year risk of ASCVD was independent of sex, age, hypertension, diabetes, and BMI status. Notably, recent medical developments suggest that antioxidants can neutralize free radicals and reduce the risk of disease caused by oxidative stress. However, in some cases, such as at high doses, antioxidants may act as pro-oxidants (48). Hence, the dose–response relationship between antioxidants and the 10-year risk of ASCVD needs further study. In addition, it is interesting to note that a previous study mentioned that there are many antioxidants, especially various safe plants that have antioxidant activity. They found that essential oils (EO) extracted from six chemical components acted as antioxidants and protected fish from oxidative stress (49). This implies that agents with antioxidant activity might be effective against ASCVD related to oxidative stress, and antioxidant drugs might be a new strategy for the prevention of ASCVD, and the relationship between the two and the mechanism of action still needs further study.

As far as we know, this is the initial research to examine the correlation between CDAI and 10-year ASCVD risk in a vast noninstitutionalized U.S. population based on NHANES data. Results suggested that CDAI was in significant negative association with 10-year ASCVD risk, providing clinical references to ASCVD prevention and control. The present study is mainly limited in three aspects. First, it could not construct or confirm any causal inference due to its cross-sectional design nature. Second, data used were all self-reported, which might be subjected to recall bias. Third, there are some potential covariates that are difficult to rule out, which may affect the relationship between CDAI and 10-year ASCVD risk.

5. Conclusion

Higher overall dietary antioxidant consumption was associated with lower 10-year ASCVD risk. The long-term impact of CDAI remains unclear and further analysis of data from longitudinal studies is needed to clarify the causal relationship between CDAI and 10-year ASCVD risk and its underlying mechanisms.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

All data came from NHANES, which was approved by National Centre for Health Statistics Institutional Ethics Review Board, and all the subjects agreed on the survey and signed written consent. The patients/participants provided their written informed consent to participate in this study. The studies were conducted in accordance with the local legislation and institutional requirements.

Author contributions

JZ: writing-most of manuscript, data curation, and processing. XL: writing-part of the manuscript and data curation. RW: writing-part of the manuscript. HN, LX, WW, CL, and JF: software, writing—review and editing, and supervision. YJ: methodology, writing—review and editing, and supervision. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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EDITED BY
Galya Bigman,
Baltimore VA Medical Center, United States

REVIEWED BY
Rahnuma Ahmad,
Medical College for Women and Hospital, Bangladesh
Farhana Akter,
Chittagong Medical College, Bangladesh
Ahmed Mohammed Alwan,
Mashhad University of Medical Sciences, Iran

*CORRESPONDENCE
Yizhong Yan
✉ erniu19880215@sina.com
Yunhua Hu
✉ huyunhua1019@sina.com

†These authors have contributed equally to this work

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Global burden of non-communicable chronic diseases associated with a diet low in fruits from 1990 to 2019

Shijie Pan[1†], Zhihan Lin[1†], Teng Yao[2†], Xiaoli Guo[1], Tongtong Xu[2], Xinyan Sheng[1], Xi Song[2], Zuhai Chen[2], Wanting Wei[2], Yizhong Yan[2,3,4,5*] and Yunhua Hu[2,3,4,5*]

[1]Department of Stomatology, School of Medicine, Shihezi University, Shihezi, Xinjiang, China, [2]Department of Preventive Medicine, School of Medicine, Shihezi University, Shihezi, Xinjiang, China, [3]Key Laboratory for Prevention and Control of Emerging Infectious Diseases and Public Health Security, The Xinjiang Production and Construction Corps, Shihezi, Xinjiang, China, [4]Key Laboratory of Xinjiang Endemic and Ethnic Diseases (Ministry of Education), School of Medicine, Shihezi University, Shihezi, Xinjiang, China, [5]Key Laboratory of Preventive Medicine, Shihezi University, Shihezi, Xinjiang, China

Background: The aim of this study was to assess the global burden of disease from non-communicable chronic diseases (NCD) due to diet low in fruits from 1990 to 2019.

Methods: Based on data from the Global Burden of Disease (GBD) 2019, the global burden of disease due to diet low in fruits was analyzed for each country or region, disaggregated by disease type, age, sex, and year. The number of deaths and disability-adjusted life years (DALYs), population attributable fraction (PAF), age-standardized mortality rate (ASMR) and age-standardized DALY rate (ASDR) were calculated, and the average annual percentage change (AAPC) was calculated to describe trends in ASMR and ASDR from 1990 to 2019.

Results: From 1990 to 2019, the number of deaths and DALYs due to diet low in fruits increased by 31.5 and 27.4%, respectively. Among the tertiary diseases, ischemic heart disease, stroke, and diabetes and kidney disease were the top three contributors to the global increase in deaths and DALYs. However, both ASMR and ASDR showed a decreasing trend. The fastest decline in ASMR and ASDR was in stroke, with AAPC of −2.13 (95% CI: −2.22, −2.05, $p < 0.05$) and −0.56 (95% CI: −0.62, −0.51, $p < 0.05$), respectively. For GBD regions, high PAF occurred mainly in South Asia, Oceania, and sub-Saharan Africa. Age-specific PAF for stroke and ischemic heart disease death attributable to diet low in fruits was significantly negatively associated with age. Diet low in fruits related ASMR and ASDR showed an M-shaped relationship with the socio-demographic index (SDI), but with an overall decreasing trend.

Conclusion: The number of deaths and DALYs due to diet low in fruits continues to increase. Therefore, early nutritional interventions should be implemented by the relevant authorities to reduce the burden of diseases caused by diet low in fruits.

KEYWORDS

global burden, diet low in fruits, epidemiology, disability-adjusted life years, mortality

1. Introduction

Dietary nutrition and health are closely related, and deficiencies in nutrients required to maintain general health, such as protein, carbohydrates, lipids, vitamins and minerals, can affect human health (1). Suboptimal diets can lead to deficiencies of these nutrients and thus increase the disease burden of non-communicable chronic diseases (NCD) in humans (2, 3). The suboptimal diets are mainly due to several poor dietary habits, and diet low in fruits is one of the important ones (2). Diet low in fruits was defined as consuming on average less than 250 g of fruit (fresh, frozen, cooked, canned or dried, but excluding fruit juices and preserved fruits) per day (2). Studies have shown that diet low in fruits is associated with diseases such as lung cancer, esophageal cancer, ischemic heart disease, stroke and diabetes (4–6).

Fruits contain nutrients that benefit human health and are an important part of a healthy diet. Studies have shown that vitamin C in fruits can destroy cancer cells and inhibit tumor growth, so humans can supplement vitamin C and thus reduce cancer risk by consuming appropriate amounts of fruits (7–10) (Figure 1A). In addition, secondary metabolites in fruits, such as flavonoids, alkaloids, carotenoids, essential oils and phenol acids, show antimutagenic and antiproliferative by inhibiting oxidation, protecting DNA from damage and stimulating tumor cell apoptosis (11, 12). Moreover, fruits play an important role in preventing cardio-vascular diseases (13). It has been found that fruit intake shows a negative correlation with cardiovascular burden (14–17). Fruits are one of the main dietary sources of polyphenols (18), which have a high antioxidant capacity and free radical scavenging ability and can inhibit the production of reactive oxygen species, thereby reducing the occurrence of cardiovascular disease (19) (Figure 1B). In addition, high fruit intake can reduce the risk of diabetes by affecting the metabolism and diversity of the gut microbiota (20–24). Diet low in fruits is closely associated with tumors, cardiovascular diseases and diabetes.

Diet low in fruits is receiving increasing attention worldwide as important dietary risk factors. However, the burden of NCD attributable to diet low in fruits has not been systematically and quantitatively assessed. In this study, we counted the age-standardized mortality rate (ASMR) and age-standardized rate of DALY (ASDR) for diseases attributable to diet low in fruits in 204 countries and territories from 1990 to 2019. The mean annual percentage change (AAPC) of ASMR and ASDR was also calculated using a log-linear regression model to analyze trends from 1990 to 2019. And Pearson correlation coefficient was used to explore the relationship between socio-demographic index (SDI) and ASMR, ASDR attributable to diet low in fruits. This study provides a foundation for developing effective health strategies for dietary habits to reduce the future burden of disease attributable to diet low in fruits in different regions.

2. Materials and methods

2.1. Study data

Diet low in fruits is one of the risk factors in the Global Burden of Disease (GBD) Study 2019 database (25). The GBD database provides a suitable data source for consistent comparisons of disease burden by age and sex across different locations from 1990 to 2019, including standard epidemiological measures of mortality and health measures such as disability-adjusted life years (DALYs) in disease burden.

Annual cases and corresponding age-standardized rate and a population-attributable fraction (PAF) of disease burden due to diet low in fruits by disease, sex, age, and location from 1990 to 2019 were collected from the Global Health Data Exchange query tool,[1] a tool that is the most recent estimate of the world's epidemiological data to provide a comparative assessment of the burden of disease for 209 diseases and injuries and 87 risk factors from 1990 to 2019-divided into 15 age groups of 25–29 years, 30–34 years, 35–40 years to 95 years and older in 5-year intervals. The diseases attributable to diet low in fruits identified in GBD 2019 include esophageal cancer, lung cancer, ischemic heart disease, stroke, and diabetes and kidney diseases. Data on epidemiological and geographic conditions from 204 countries and territories, five SDIs (acting as a composite indicator of developmental status strongly associated with health outcomes, including levels of low, low-middle, middle, high-middle, and high), and 21 GBD regions

1 https://vizhub.healthdata.org/gbd-results/

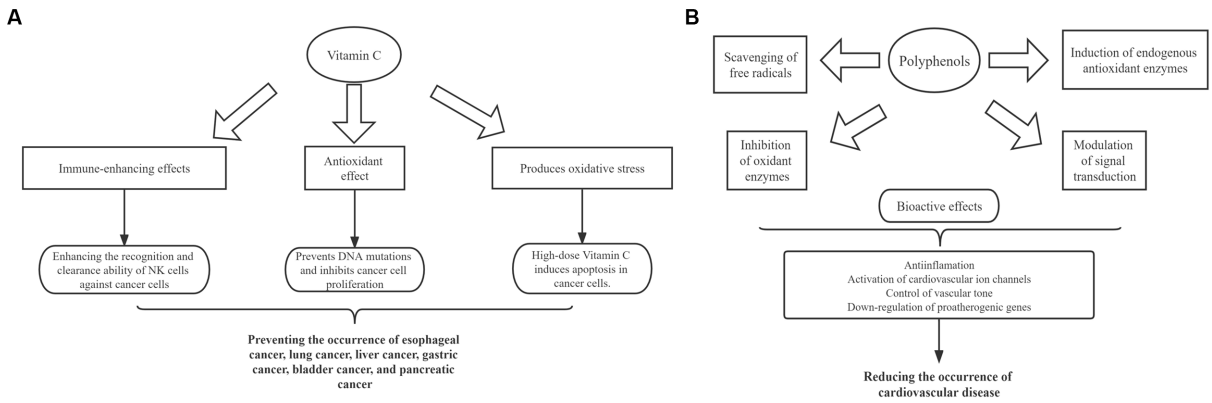

FIGURE 1
Mechanisms of vitamin C and polyphenols in fruits after entering the body. **(A)** Diagram of the role of fruit vitamin C in cancer prevention. **(B)** Schematic representation of the biological activity of fruit polyphenols in the prevention of cardiovascular diseases.

were available and were used to estimate the burden of disease by locations.

2.2. Statistical analysis

To assess the burden of disease and its trends during a specific period, we calculated ASMR/ASDR for mortality and DALYs, and their corresponding AAPC. ASMR/ASDR was calculated by aggregating measures of the rate that a population would have if it had a standard age structure. The weights are taken from the overall distribution of the standard population. The expression was:

$$\mathrm{ASMR}\ /\ \mathrm{ASDR} = \frac{\sum_{i=1}^{A} \alpha i w i}{\sum_{i=1}^{A} w i} \times 100{,}000$$

αi: specific age ratio, wi: number (or weight) of selected standard population. Estimated value was used to describe the burden of disease due to diet low in fruits by age, sex and year. To avoid effects due to the age composition of the populations, we chose the age distribution of the world population from the GBD 2019 study to standardize mortality and DALYs per 100,000 person-years for diseases caused by diet low in fruits.

Based on a log-linear regression model, AAPC was calculated to describe the overall time trend in disease ASMR/ASDR. In the model, $In(R) = a + \beta \bullet T + \varepsilon$, where R is the count or rate, T is calendar year, a is the constant term, β is the regression coefficient, and ε is the random error term. If both the AAPC and the lower limit of 95% CI were higher than 0, the index was considered to have an upward trend. If both the AAPC and the upper limit of 95% CI were less than 0, the estimated was considered to have a downward trend. Otherwise, the index was considered stable over time (26). Log-linear regression model was applied to analyze the temporal trends and AAPC of diseases attributable to diet low in fruits globally. In addition, the Pearson model was used to explore the relationship between SDI and ASMR and between SDI and ASDR for diseases attributed to diet low in fruits.

3. Results

3.1. Global burden of disease caused by diet low in fruits in 2019

Globally, the number of deaths caused by diet low in fruits was 1046.01 thousand (95% UI: 730.09, 1363.86), 459.33 thousand (95% UI: 317.06, 601.72) for female and 586.69 thousand (95% UI: 402.51, 777.78) for male (Table 1). The number of DALYs caused by diet low in fruits was 2767.83 thousand (95% UI: 2022.67, 3592.54), 1128.98 thousand (95% UI: 825.67, 1460.12) and 1638.85 thousand (95% UI: 1178.77, 2156.14) for female and male, respectively (Supplementary Table S1).

At the SDI region level, the middle SDI region had the highest number of deaths attributable to diet low in fruits (325.58 thousand) and the highest number of DALYs (876.18 thousand), but the region with the highest ASMR and ASDR were low-middle SDI region. Among the 21 GBD regions, East Asia and South Asia ranked the top two in terms of deaths or DALYs attributable to diet low in fruits, but the top two ASMR occurred in Central Asia and Oceania, and the top two ASDRs occurred in South Asia and Oceania (Supplementary Tables S2, S3).

Among the five tertiary diseases, the top three diseases in terms of the number of mortality and DALYs attributable to diet low in fruits were: ischemic heart disease, stroke, and diabetes and kidney disease, accounting for 87.7 and 89.2% of the total, respectively (Table 1; Supplementary Table S1). In addition, the three diseases mentioned above also ranked in the top three in ASMR and ASDR (Table 1; Supplementary Table S1).

At the country or territory level, the top three deaths attributable to diet low in fruits were in India, China and Russia (Supplementary Table S4; Figure 2A), while India, China and Indonesia were the top three DALYs attributable to diet low in fruits (Supplementary Table S4; Supplementary Figure S1A). The top three ASMR attributable to diet low in fruits were Solomon Islands, Mongolia and Fiji (Supplementary Table S4; Figure 2B), while Solomon Islands, Kiribati and Fiji were the top three ASDRs attributable to diet low in fruits (Supplementary Table S4; Supplementary Figure S1B).

3.2. Trends in the burden of disease attributable to diet low in fruits from 1990 to 2019

The global number of deaths caused by diet low in fruits increased from 795.57 thousand (95% UI: 566.62, 1034.79) in 1990 to 1046.01 thousand (95% UI: 730.09, 1363.86) in 2019, an increase of 31.5%. However, ASMR showed a decreasing trend overall, males and females with AAPC of −1.70 (95% CI: −1.83, −1.57), −1.62 (95% CI: −1.69, −1.53) and −1.83 (95% CI: −1.93, −1.73), respectively (Table 1; Supplementary Figures S2A, S3A). From 1990 to 2019, the DALYs number in-creased by 27.4%, and ASDR decreased slightly with AAPC of −1.56 (95% CI: −1.69, −1.42). Both male and female ASDR dropped with AAPC of −1.49 (95% CI: −1.63, −1.34) and − 1.66 (95% CI: −1.75, −1.58), respectively (Supplementary Table S1; Supplementary Figures S2B, S3B).

At the SDI region level, ASMR and ASDR decreased in all five SDI regions, with the fastest decrease in ASMR in the high SDI region with AAPC of −2.67 (95% CI: −2.85, −2.49) and the fastest decrease in ASDR in the high-middle SDI region with AAPC of −2.29 (95% CI: −2.57, −2.02). Regarding the GBD region, ASMR in Sub-Saharan Africa and ASDR in Oceania were the fastest growing with AAPC of 0.09 (95% CI: −0.48, 0.66) and 0.09 (95% CI: 0.05, 0.13), respectively. The ASMR and ASDR in Southern Latin America were the fastest de-creasing with AAPC of −3.73 (95% CI: −4.01, −3.46) and −3.65 (95% CI: −3.87, −3.43), respectively (Supplementary Tables S2, S3). At the country or territory level, the fastest decrease in ASMR or ASDR was in Singapore, and the most rapid growth in ASMR or ASDR was in the UAE (Figure 2C, Supplementary Table S4; Supplementary Figure S1C).

Among the 5 level-three diseases, ischemic heart disease, stroke, and diabetes and kidney diseases were the top three contributors to the global increase in deaths due to diet low in fruits, contributing 88.6% of the total increase in deaths from 1990 to 2019. ASMR

TABLE 1 Global deaths attributable to diet low in fruits in 1990 and 2019, and the temporal trend from 1990 to 2019.

Cause of deaths	1990			2019			1990–2019	
	Deaths No. × 10^3 (95% UI)	ASMR per 100,000 (95%UI)	Age-standardized PAF, % (95%UI)	Deaths No. × 10^3 (95% UI)	ASMR per 100,000 (95%UI)	Age-standardized PAF, % (95%UI)	AAPC of ASMR (95%CI)	AAPC of Age-standardized PAF (95%CI)
All causes								
Both	795.57 (560.62, 1034.79)	21.61 (14.98, 28.33)	1.94 (1.34, 2.53)	1046.01 (730.09, 1363.86)	13.12 (9.09, 17.09)	1.79 (1.23, 2.32)	−1.70 (−1.83, −1.57)	−0.28 (−0.38, −0.18)
Female	360.96 (251.35, 473.79)	17.97 (12.44, 23.78)	1.87 (1.31, 2.47)	459.33 (317.06, 601.72)	10.51 (7.25, 13.77)	1.71 (1.19, 2.22)	−1.83 (−1.93, −1.73)	−0.32 (−0.42, −0.21)
Male	434.64 (306.27, 568.38)	25.79 (17.94, 33.76)	1.98 (1.37, 2.57)	586.69 (402.51, 777.78)	16.07 (10.99, 21.38)	1.84 (1.26, 2.41)	−1.62 (−1.69, −1.53)	−0.24 (−0.35, −0.14)
Disease type								
Neoplasms								
Both	100.25 (56.25, 150.31)	2.56 (1.43, 3.83)	1.73 (0.96, 2.58)	128.38 (65.04, 200.43)	1.58 (0.79, 2.46)	1.26 (0.63, 1.95)	−1.67 (−1.78, −1.55)	−1.10 (−1.15, −1.04)
Female	30.84 (16.89, 47.14)	1.46 (0.79, 2.24)	1.24 (0.68, 1.91)	40.44 (21.15, 59.96)	0.92 (0.48, 1.37)	0.92 (0.48, 1.36)	−1.58 (−1.68, −1.47)	−1.04 (−1.12, −0.95)
Male	69.41 (38.87, 104.54)	3.88 (2.15, 5.78)	2.06 (1.14, 3.11)	87.96 (43.14, 141.81)	2.35 (1.16, 3.78)	1.49 (0.74, 2.36)	−1.73 (−1.94, −1.51)	−1.11 (−1.17, −1.04)
Esophageal cancer								
Both	51.87 (17.82, 92.69)	1.32 (0.45, 2.37)	16.14 (5.61, 28.51)	51.21 (15.23, 108.73)	0.63 (0.19, 1.33)	10.27 (3.12, 22.18)	−2.57 (−2.73, −2.41)	−1.54 (−1.59, −1.48)
Female	18.01 (6.63, 32.14)	0.86 (0.31, 1.53)	17.07 (6.34, 29.43)	15.51 (5.19, 30.42)	0.35 (0.12, 0.65)	11.77 (4.06, 23.12)	−3.03 (−3.20, −2.86)	−1.28 (−1.38, −1.18)
Male	33.86 (11.02, 61.13)	1.86 (0.58, 3.39)	15.63 (5.19, 28.01)	35.66 (10.02, 78.76)	0.94 (0.26, 2.09)	9.77 (2.76, 21.98)	−2.36 (−2.60, −2.12)	−1.61 (−1.67, −1.56)
Tracheal, bronchus, and lung cancer								
Both	48.39 (15.86, 71.84)	1.24 (0.39, 1.83)	4.53 (1.47, 6.72)	77.19 (22.55, 115.14)	0.95 (0.28, 1.42)	3.78 (1.09, 5.61)	−0.89 (−1.01, −0.78)	−0.62 (−0.64, −0.60)
Female	12.83 (4.16, 19.21)	0.61 (0.18, 0.91)	4.67 (1.54, 6.94)	24.93 (7.19, 37.41)	0.57 (0.16, 0.85)	3.78 (1.09, 5.66)	−0.23 (−0.29, −0.18)	−0.71 (−0.73, −0.69)
Male	35.55 (11.61, 53.11)	2.01 (0.65, 2.97)	4.47 (1.44, 6.62)	52.26 (15.19, 78.62)	1.41 (0.41, 2.12)	3.77 (1.09, 5.63)	−1.21 (−1.38, −1.04)	−0.58 (−0.61, −0.56)
Cardiovascular diseases								
Both	654.58 (423.35, 897.38)	17.95 (11.58, 24.61)	5.06 (3.28, 6.85)	829.27 (514.63, 1140.66)	10.44 (6.46, 14.41)	4.35 (2.71, 5.93)	−1.84 (−1.98, −1.70)	−0.52 (−0.55, −0.49)
Female	308.28 (204.08, 421.79)	15.44 (10.05, 21.18)	4.91 (3.23, 6.61)	373.39 (230.74, 510.97)	8.54 (5.29, 11.69)	4.19 (2.63, 5.68)	−2.01 (−2.15, −1.87)	−0.54 (−0.58, −0.51)
Male	346.27 (221.36, 479.41)	20.76 (13.16, 28.76)	5.16 (3.34, 7.03)	455.88 (281.51, 635.26)	12.53 (7.71, 17.43)	4.46 (2.76, 6.13)	−1.72 (−1.82, −1.62)	−0.50 (−0.54, −0.46)
Ischemic heart disease								
Both	310.72 (129.32, 458.43)	8.77 (3.66, 12.95)	5.15 (2.15, 7.56)	436.45 (179.36, 659.26)	5.53 (2.28, 8.37)	4.69 (1.91, 6.94)	−1.57 (−1.73, −1.41)	−0.32 (−0.39, −0.25)
Female	137.88 (57.08, 202.43)	7.11 (2.96, 10.49)	5.01 (2.06, 7.35)	189.35 (76.67, 286.58)	4.33 (1.76, 6.55)	4.55 (1.86, 6.76)	−1.68 (−1.85, −1.52)	−0.33 (−0.36, −0.30)
Male	172.84 (72.42, 255.08)	10.64 (4.44, 15.79)	5.18 (2.16, 7.63)	247.11 (102.19, 371.98)	6.86 (2.77, 10.33)	4.75 (1.92, 7.05)	−1.48 (−1.67, −1.29)	−0.31 (−0.39, −0.22)
Stroke								
Both	343.86 (206.87, 528.73)	9.18 (5.44, 14.12)	6.93 (4.16, 10.52)	392.82 (228.22, 604.23)	4.91 (2.84, 7.57)	5.83 (3.43, 8.95)	−2.13 (−2.22, −2.05)	−0.59 (−0.62, −0.56)
Female	170.39 (100.66, 261.82)	8.33 (4.86, 12.85)	6.78 (4.06, 10.31)	184.04 (106.59, 283.78)	4.21 (2.44, 6.49)	5.73 (3.34, 8.65)	−2.32 (−2.42, −2.22)	−0.57 (−0.59, −0.54)
Male	173.47 (103.39, 265.92)	10.12 (5.97, 15.68)	7.06 (4.25, 10.75)	208.77 (121.28, 324.93)	5.67 (3.26, 8.83)	5.88 (3.42, 9.06)	−1.97 (−2.06, −1.88)	−0.63 (−0.69, −0.57)

(Continued)

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TABLE 1 (Continued)

Cause of deaths	1990			2019			1990–2019	
	Deaths No. ×10^3 (95% UI)	ASMR per 100,000 (95%UI)	Age-standardized PAF, % (95%UI)	Deaths No. ×10^3 (95% UI)	ASMR per 100,000 (95%UI)	Age-standardized PAF, % (95%UI)	AAPC of ASMR (95%CI)	AAPC of Age-standardized PAF (95%CI)
Diabetes and kidney diseases								
Both	40.77 (25.66, 56.78)	1.08 (0.69, 1.54)	3.21 (2.02, 4.53)	88.34 (56.09, 126.27)	1.09 (0.7, 1.58)	2.92 (1.81, 4.19)	0.02 (−0.13, 0.16)	−0.34 (−0.42, −0.25)
Female	21.84 (13.34, 31.39)	1.07 (0.65, 1.53)	3.34 (2.07, 4.75)	45.45 (27.92, 65.14)	1.04 (0.64, 1.49)	3.04 (1.88, 4.39)	−0.09 (−0.23, 0.06)	−0.31 (−0.43, −0.19)
Male	18.92 (12.05, 26.12)	1.16 (0.73, 1.61)	3.04 (1.93, 4.25)	42.84 (26.57, 61.46)	1.19 (0.73, 1.71)	2.78 (1.72, 3.98)	0.08 (−0.11, 0.27)	−0.32 (−0.44, −0.19)
Diabetes mellitus								
Both	40.77 (25.66, 56.76)	1.07 (0.69, 1.54)	6.16 (3.89, 8.68)	88.34 (56.09, 126.27)	1.08 (0.69, 1.58)	5.68 (3.47, 8.14)	0.02 (−0.13, 0.16)	−0.28 (−0.43, −0.13)
Female	21.84 (13.34, 31.39)	1.07 (0.65, 1.53)	6.02 (3.77, 8.54)	45.48 (27.92, 65.14)	1.04 (0.64, 1.49)	5.68 (3.55, 8.19)	−0.09 (−0.23, 0.06)	−0.18 (−0.32, −0.05)
Male	18.92 (12.05, 26.12)	1.16 (0.73, 1.61)	6.36 (4.04, 8.87)	42.84 (26.57, 61.46)	1.19 (0.73, 1.71)	5.66 (3.51, 8.13)	0.08 (−0.11, 0.27)	−0.41 (−0.44, −0.37)

ASMR, age-standardized mortality rate; PAF, population attributable fraction; AAPC, average annual percentage change; UI, uncertainty interval; CI, confidence interval.

decreased significantly in patients with stroke and ischemic heart disease, with AAPC of −2.13 (95% CI: −2.22, −2.05) and −1.57 (95% CI: −1.73, −1.41), while ASMR did not change much in patients with diabetes and kidney diseases, with AAPC of 0.02 (95% CI: −0.13, 0.16) (Table 1). Similar to the mortality trend, the main contribution of ischemic heart disease, diabetes and kidney diseases, and stroke to the overall increase in DALYs was 42.2, 36.3 and 14.9%, respectively. Among them, ASDR decreased more rapidly in stroke with AAPC of −0.56 (95% CI: −0.62, −0.51) (Supplementary Table S1).

3.3. PAF of the diseases attributable to diet low in fruits

The PAF of ASMR for five tertiary diseases varied significantly between different regions (Figure 3). In 5 level-three diseases, the top three PAF for esophageal cancer, stroke and ischemic heart disease were 4.7, 5.8, and 10.3%, respectively (Table 1). At the SDI region level, the highest PAF was mainly in low-middle and middle SDI regions. At the GBD region level, the highest PAF was primarily in Eastern Europe, Central Asia and South Asia (Supplementary Table S2).

Trends in PAF for deaths attributable to diet low in fruits varied with age across the 5 level-three disease types (Figure 4). Age-specific PAF for death from stroke and ischemic heart disease was significantly negatively associated with age. Age-specific PAF for esophageal cancer deaths had a slight negative association with age until 60–64. Age-specific PAF for deaths from diabetes and kidney diseases were slightly elevated before 45–49 years and slightly decreased after 80–84 years. A similar trend was observed for PAF in DALYs (Supplementary Figure S4).

3.4. Association of diet low in fruits disease burden with SDI

The ASMR and ASDR showed an overall "M" relationship with SDI, with a negative correlation, reaching the first peak at SDI = 0.4 and the second peak at SDI = 0.7 (Figure 5, Supplementary Figure S5). AAPC of ASMR or ASDR had a weak positive correlation (correlation coefficient around 0.15) (Supplementary Figures S6A, S7A). The AAPC of ASMR had a significant negative correlation in 2019 (correlation coefficient around −0.55), more pronounced when SDI was greater than 0.5 (Figure 6). The AAPC of ASDR had a low negative correlation with SDI in 2019 (correlation coefficient around −0.47), more pronounced when SDI was greater than 0.6 (Supplementary Figure S8B).

4. Discussion

Using GBD study 2019 data, we systematically estimated trends in the burden of NCD due to diet low in fruits from 1990 to 2019. Globally, from 1990 to 2019, the number of deaths and DALYs attributed to diet low in fruits in-creased. But ASMR and ASDR decreased slightly, mainly in ischemic heart disease, stroke, and diabetes and kidney disease. Compared to females, the males had a more severe disease burden. The ASMR and ASDR caused by diet low

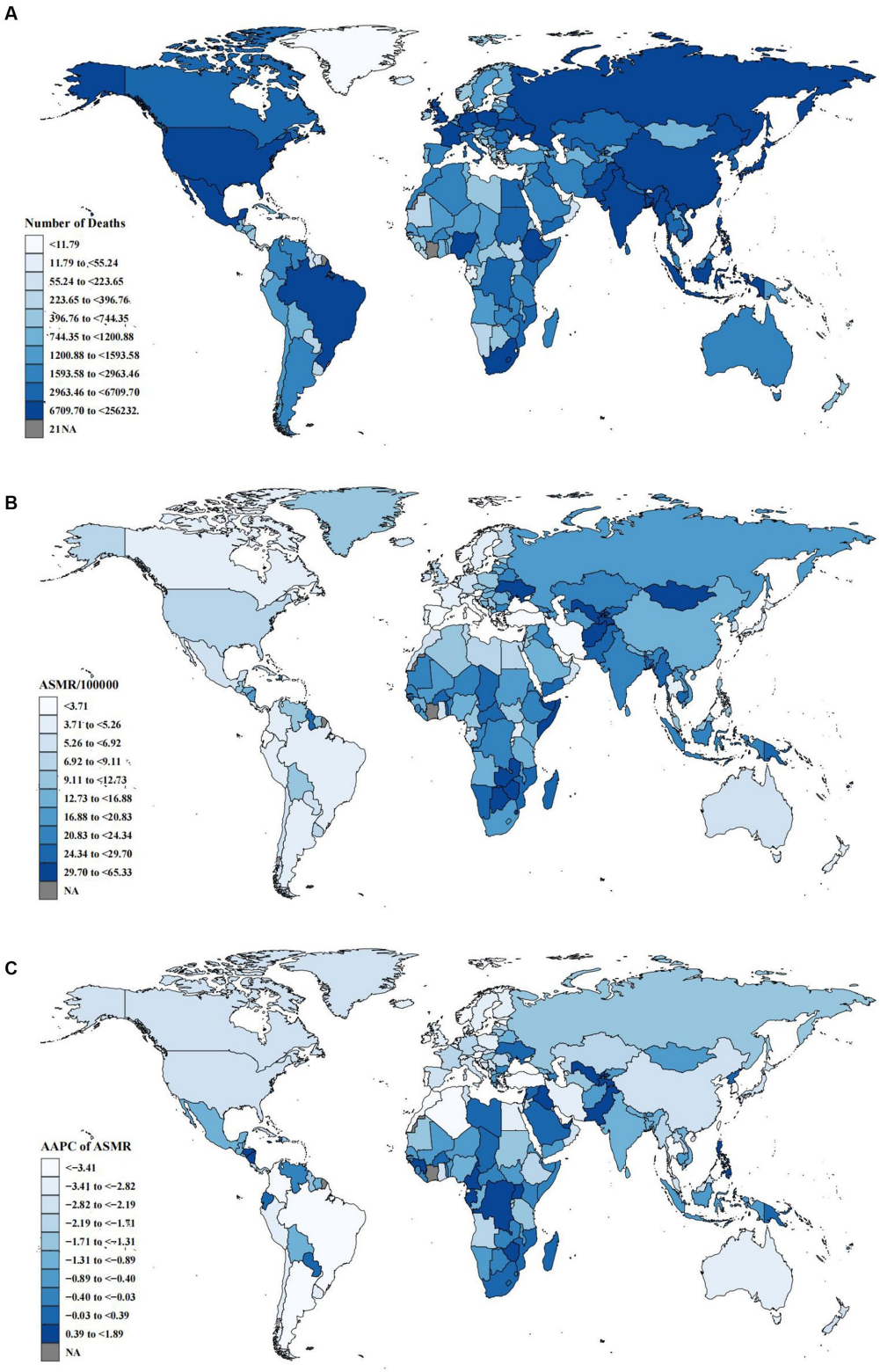

FIGURE 2
Global deaths burden attributable to diet low in fruits for both sexes. **(A)** Number of deaths in 2019. **(B)** ASMR in 2019. **(C)** AAPC of ASMR from 1990 to 2019.

in fruits were more significant in areas with low SDI and high-middle SDI, mainly in South Asia and Eastern Europe. Furthermore, PAF for ASMR or ASDR varied significantly between regions and age groups in the five tertiary diseases. These results help guide public health programs and inform strategies to change eating habits and improve health.

FIGURE 3
Age-standardized PAF of deaths of specific GBD level-three diseases attributable to diet low in fruits by region for both sexes in 2019.

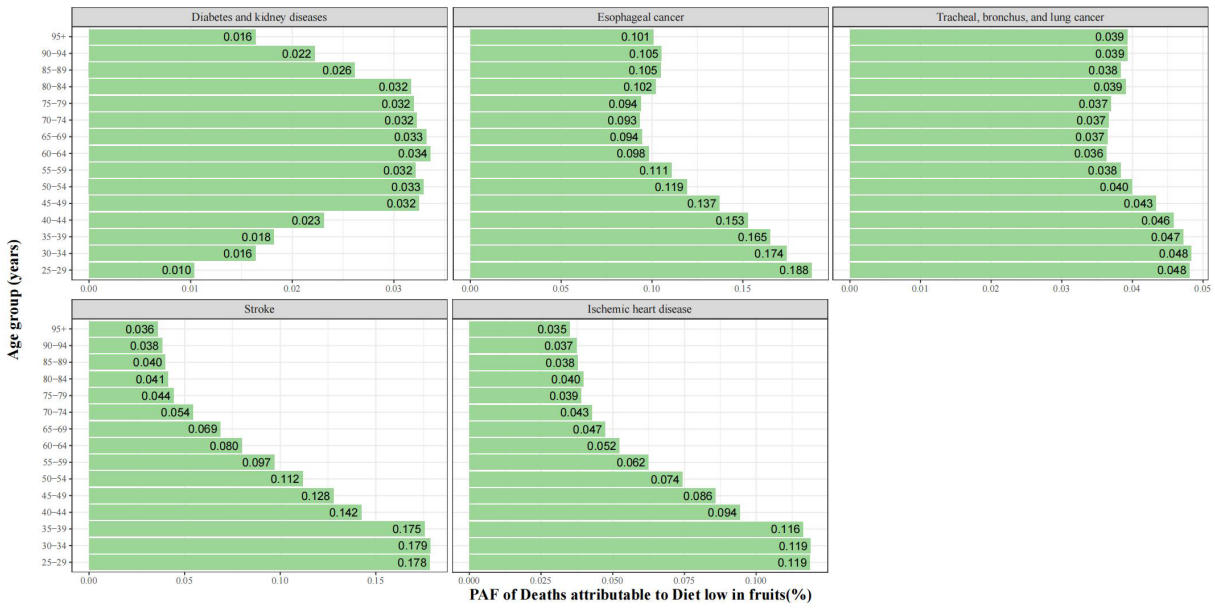

FIGURE 4
PAF of deaths of specific GBD level-three diseases attributable to diet low in fruits by age group for both sexes in 2019.

In this study, it was found that the mortality rate and DALYs rate of elderly individuals due to diet low in fruits were higher than those of young individuals. This trend may be attributed to the weakened metabolism of elderly, which makes them less effective at absorbing and utilizing the nutrients in fruits within the timeframe when adverse effects of low fruit intake occur (27). In addition, energy intake varies by age group and physical activity level and may also play a key role in the mechanism that causes the burden difference between elderly and younger adults (28, 29). Therefore, it is necessary to carry out early nutritional intervention for the elderly population. By encouraging elderly to increase the intake of fruits, strengthening nutritional guidance, increasing physical activities and providing suitable dietary services, and other measures to improve the dietary health and metabolic capacity of elderly, and improve nutritional intake of elderly. Thus, the burden of elderly due to diet low in fruits may be reduced.

Between 1990 and 2019, the burden of disease due to diet low in fruits in-creased in both males and females, with age-wide increases

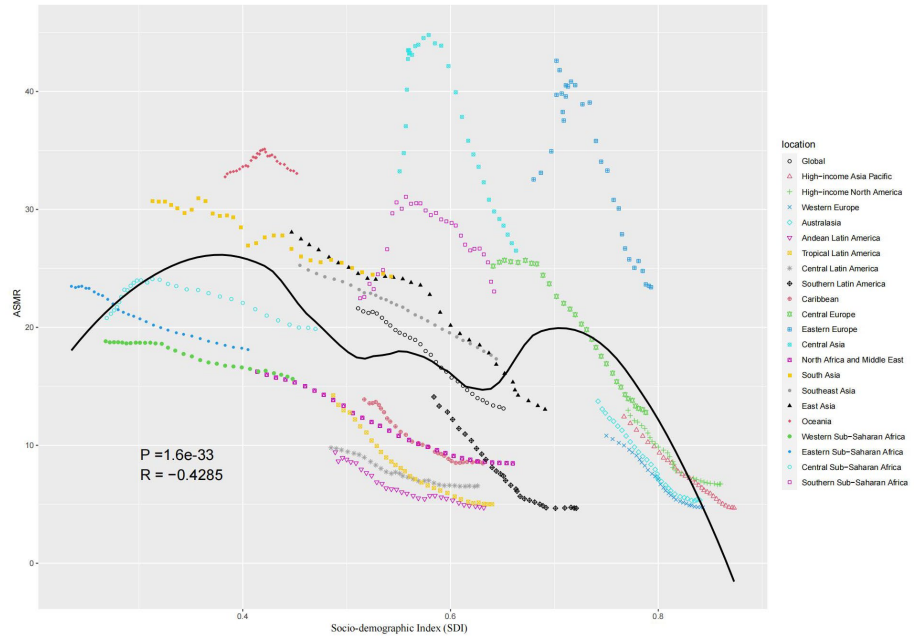

FIGURE 5
Age-standardized burden rate attributable to diet low in fruits across 21 GBD regions by the socio-demographic index for both sexes, 1990–2019.

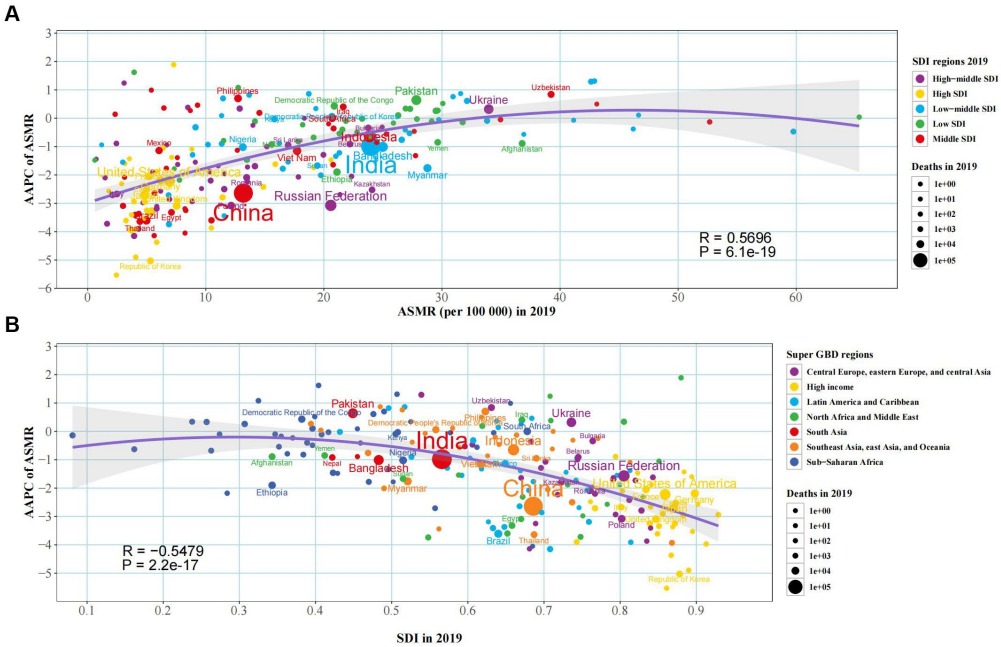

FIGURE 6
The factors associated with the AAPC of ASMR attributable to diet low in fruits from 1990 to 2019, both sexes, at the national level. **(A)** The corresponding ASMR in 2019; **(B)** Socio-demographic index in 2019.

in the number of deaths and DALYs, but corresponding ASMR/ASDR decreased. This may result from the rapid growth of the global population (30). This study revealed a significant sex disparity in the burden of cardiovascular disease caused by diet low in fruits. Specifically, the burden was found to be significantly higher in males compared to females in both 1990 and 2019. This is because there are certain differences in the absorption and function of nutrients in fruits in different sexes, leading to varying impacts on their respective bodies. Studies have shown that polyphenols are a kind of natural antioxidant, which can help reduce the production of free radicals and damage to cells, thus having a protective effect on cardiovascular diseases (31). Although polyphenols are beneficial to both sexes, polyphenols have a more beneficial impact on the cardiovascular health of females compared to males (32). Females have better

absorption and utilization of polyphenols because they have stronger gastric acid secretion and intestinal absorption ability after eating (33). As a result, the females can better obtain nutrients from polyphenols and thus better protect their cardiovascular system.

Around the world, ASMR or ASDR attributed to diet low in fruits showed an M-shaped association with SDI, showing an overall downward trend, while low SDI and high-middle SDI regions had higher disease burdens than other regions. The causes of death from NCD in low SDI regions include poor living environment, infection, inadequate resources and lack of access to health care (34). The disease burden attributed to diet low in fruits is higher in high-middle SDI areas, which may be due to the traditional diet in the area (35). For example, the conventional diet in Eastern Europe is dominated by meat, cereals and bread. The development of modern technology promotes the consumption of conventional diet categories in Eastern Europe, thus reducing the consumption of fruits and indirectly increasing the burden of cardiovascular diseases in the region (36).

In addition, this study found that the number of deaths and DALYs attributable to diet low in fruits were the largest in middle SDI regions, and the middle SDI regions were represented by countries such as China, Albania and Brazil. Studies have shown that young people in China prefer to eat fruit, consuming about twice as much fruit as elderly (37). China has a large population, and in recent years, the aging degree has intensified (38). This may be an important reason for the above results. All five tertiary diseases in this study had higher PAF for deaths and DALYs in low SDI regions and low-middle SDI regions than in the other three SDI regions. Because of this phenomenon, it is speculated that people in low and low-middle-income countries may lack an understanding of the health benefits of fruits, and the fruits cannot enter the fresh food market due to traffic restrictions (39). It is recommended to increase publicity and access to fruit in low and low-middle-income countries, while increasing the availability and import of fruit. This requires the efforts of governments, businesses and society to encourage people to increase their consumption and intake of fruit through various means to improve the health status of low and low-middle-income countries.

At the regional level of GBD, the highest PAFs of ASMR attributed to diet low in fruits in 2019 were in Eastern Europe, Central Asia and South Asia (2.78, 2.66, and 2.65%). The reason may be the low fruit intake caused by the traditional diet culture in Eastern Europe (15). The *per capita* fruit intake in countries represented by Russia, Ukraine and Belarus in Eastern Europe is less than 300 g/d, while the *per capita* fruit intake recommended by WHO is 400 g/d (40, 41). The street food trade is a well-developed activity in Central Asian cities, often organized in typical markets called bazaars. Street food outlets are common, reflecting the high cultural and dietary importance of street food in the region (42–45). In all the cities surveyed, the fruit was the least common street food (46). The gross national income of South Asian countries is low, and the cost of buying fruit is much higher than that of other economic regions (47). In addition, low-income people are more susceptible to the influence of traditional dietary concepts, and prejudice against the mass consumption of fruits, which may lead to the low intake of fruit in South Asian countries (48). We also found that Oceania had higher ASMR and ASDR, consistent with the previous research (49). The diet quality of Australian residents could be further improved by increasing the consumption of fruits and more types of food.

At the national level, the results showed that China and India were the top two countries regarding the number of deaths and DALYs attributable to diet low in fruits. Data show that in South Asia, China and other regions, higher fruit in-take is negatively correlated with the total mortality risk (50). Therefore, diet low in fruits will lead to a higher deaths and DALYs. At the same time, because China and India are both populous countries, the base is larger. These are the key rea-sons for the above results. We also found that the top ranking of ASMR and ASDR attributable to diet low in fruits were both in the Solomon Islands. Studies have shown that the *per capita* fruit intake in the Solomon Islands has decreased, and the consumption of sugar-sweetened beverages is the lowest, but the prevalence of hypercholesterolemia has increased significantly (51). The reason is that energy comes from the three major productive nutrients of protein, carbohydrates and lipids. The intake of diet low in fruits reduces the dietary fiber in carbohydrates. At the same time, due to the total energy demand, excessive intake of proteins and lipids leads to increased disease burden.

The top three deaths, DALYs, ASMR, and ASDR, attributed to diet low in fruits were ischemic heart disease, stroke, and diabetes and kidney disease. This is consistent with the results of a previous study (52), which found that cardiometabolic death was closely related to suboptimal dietary intake (48.6% in males and 41.8% in females). Diet-related cardiometabolic deaths were the highest, with low fruit accounting for 7.5%. Diet low in fruits is therefore strongly associated with the proportion of deaths from ischemic heart disease, stroke, and diabetes and kidney disease. The reason may be closely related to the functions of various vitamins, minerals and other fruit-rich nutrients (53, 54).

Different countries have formulated various policies and strategies to increase people's awareness of fruit consumption. For instance, Australia launched the "Go for 2&5" campaign, which was government-funded and utilized multiple media channels to promote a positive attitude toward consuming more fruits and encourage adults to aim for two servings of fruits per day. The Centers for Disease Control and Prevention in the United States has developed the "Fruits & Veggies - More Matters" program. This program encourages people to increase their fruit intake through methods like educational campaigns, diverse promotions, providing tools and support, and establishing partnerships, aiming to promote a healthy lifestyle. In the United Kingdom, there is a program called "Food Dudes" that aims to enhance children's awareness of fruits through role-playing. This program empowers children with superpowers to fight against villains by tasting various fruits, aiming to inspire them to consume more fruits (55). Due to different levels of economic development in other parts of the world, People's daily intake of fruit content also varies (41). Population-level dietary interventions are needed to reduce the disease burden associated with diet low in fruits in different regions, especially in areas with low SDI regions. Fruit intake can be increased by raising public awareness of healthy eating through the news media. Improve fruit availability to ensure that people in all regions have access to fresh fruit. More appropriate health strategies are proposed according to dietary habits and disease burden in different regions. These initiatives collectively form global efforts aimed at raising public awareness of healthy eating habits and encouraging people to increase their intake of fruits in innovative and proactive ways.

This study has some limitations. The data comes from the GBD 2019 database, and there may be some differences in data quality and accuracy between different regions and countries. The estimated burden of disease will inevitably be somewhat bias. According to the current data, we are unable to discuss the impact of different types of fruit deficiencies on disease burden. The interrelationship between

dietary factors may influence the estimated burden of disease caused by a single dietary component. To address these limitations, we need to design further large-scale epidemiological studies to understand better the burden of NCD caused by diet low in fruits. In addition, intervention studies by providing participants with a variety of fruits are particularly important to explore further the actual size the impact of diet low in fruits on the risk of NCD.

5. Conclusion

ASMR and ASDR from diet low in fruits have decreased globally, but the number of deaths and DALYs has still increased significantly from 1990 to 2019. Reducing the nutritional burden caused by diet low in fruits has become a top priority for national and regional governments. It is noteworthy that the burden is significantly higher in the elderly. Ensuring sufficient nutrition for the elderly becomes particularly important due to factors such as declining physical function and eating disorders. It is recommended to take early nutritional intervention measures for the elderly population. Providing a diverse and balanced diet plan, including increased intake of fruits, can help older adults maintain a healthy nutritional status and reduce the risk of diseases. In order to reduce the disease burden caused by diet low in fruits among different age groups, it is suggested to establish appropriate dietary guidelines and implement relevant strategic measures to encourage increased fruit intake. Especially in low SDI and low-middle SDI countries, it is crucial to enhance the dissemination of knowledge about healthy eating. Activities such as public awareness campaigns, training programs for health educators, and providing easily accessible information resources can enhance people's understanding and awareness of healthy eating, thereby reducing health problems associated with low fruit intake. This requires joint efforts from governments, social organizations, and individuals to promote nutritional health and enhance overall quality of life.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding authors.

Author contributions

SP, ZL, TY, and YY initiated the study. SP, ZL, TY, XG, TX, and XSh collected and processed the data. WW, XSo, and ZC performed the statistical analysis and visualization. SP and ZL drafted the manuscript. YH, TY, and YY revised the manuscript. The corresponding authors attest that all listed authors meet authorship criteria and that no others who meet these criteria have been omitted. All authors read and approved the final manuscript, contributed to the framework construction, result interpretation, manuscript revision, approved the final version of the manuscript, contributed to the article, and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2023.1202763/full#supplementary-material

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EDITED BY
Iain Brownlee,
Northumbria University, United Kingdom

REVIEWED BY
Tao Huang,
Jinan University, China
Ramesh Vishwakarma,
University of East Anglia, United Kingdom

*CORRESPONDENCE
Jiayuan Wu
✉ wujiay@gdmu.edu.cn

†These authors have contributed equally to this work

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Thiamine administration may increase survival benefit in critically ill patients with myocardial infarction

Suru Yue[1,2†], Jia Wang[1,2†], Yumei Zhao[1,2†], Enlin Ye[1], Dongdong Niu[1], Jiasheng Huang[1], Xiaolin Li[1], Yiling Hu[1], Xuefei Hou[1,2] and Jiayuan Wu[1,2*]

[1]Clinical Research Service Center, Affiliated Hospital of Guangdong Medical University, Zhanjiang, Guangdong, China, [2]Guangdong Engineering Research Center of Collaborative Innovation of Clinical Medical Big Data Cloud Service in Western Guangdong Medical Union, Affiliated Hospital of Guangdong Medical University, Zhanjian, Guangdong, China

Background: Myocardial infarction (MI) is a common cardiovascular disease (CVD) in critically ill patients, leading to 17% mortality in the intensive care unit (ICU) setting. Patients with CVD frequently suffer from thiamine insufficiency, thereby thiamine supplements may be helpful. Unfortunately, the relationship between thiamine treatment and survival outcomes in ICU patients with MI is still unknown. The purpose of the research is to demonstrate the survival advantage of thiamine application in these patients.

Methods: The Medical Information Mart of Intensive Care-IV database served as the foundation for this retrospective cohort analysis. Depending on whether patients were given thiamine therapy during the hospital stay, critically ill MI patients were split into the thiamine and non-thiamine groups. The Kaplan–Meier (KM) method and Cox proportional hazard models were used to evaluate the relationship between thiamine use and the risk of in-hospital, 30-day, and 90-day mortality. To validate the results, a 1:2 closest propensity-score matching (PSM) was also carried out.

Results: This study included 1782 patients for analysis with 170 and 1,612 individuals in the thiamine and non-thiamine groups, respectively. The KM survival analyses revealed that the risk of in-hospital, 30-day, and 90-day mortality was significantly lower in the thiamine group than the none-thiamine group. After modifying for a variety of confounding factors, the Cox regression models demonstrated substantial positive impacts of thiamine use on in-hospital, 30-d, and 90-d mortality risk among critically ill patients with MI with hazard ratio being 0.605 [95% confidence interval (CI): 0.397–0.921, $p = 0.019$], 0.618 (95% CI: 0.398–0.960, $p = 0.032$), and 0.626 (95% CI: 0.411–0.953, $p = 0.028$), respectively, in the completely modified model. PSM analyses also obtained consistent results.

Conclusion: Thiamine supplementation is related to a decreased risk of mortality risk in critically ill patients with MI who are admitted to the ICU. More multicenter, large-sample, and well-designed randomized controlled trials are needed to validate this finding.

KEYWORDS

myocardial infarction, cardiovascular disease, thiamine, critically ill patients, mortality risk, MIMIC-IV database

Introduction

Myocardial infarction (MI) is defined as myocardial cell death due to prolonged ischaemia and is a major contributor of mortality in cardiovascular disease (CVD) (1). Given that critically ill patients are vulnerable to myocardial injury from various causes including ischemia and non-ischemia, MI is a common disease in intensive care units (ICUs) and coronary care units. Studies have shown that 66% of patients hospitalized for MI are admitted to the ICU on the first day of admission, and the ICU mortality rate is as high as 25.6% (2). Over the past decades, advances in pharmacology, catheter basis, and surgical reperfusion have made substantial progress in improving the outcomes of critically ill patients with MI. In particular, the incidence of mechanical complications in critically ill patients with MI significantly decreased after the introduction of percutaneous coronary intervention. However, patients with large infarcts or those who do not receive timely revascularization remain at risk for mechanical complications. These complications significantly increase morbidity, mortality, and hospital resource utilization, resulting in up to 60% mortality even with appropriate treatment (3, 4). Moreover, the economic burden caused by MI should not be ignored. The American Heart Association estimates that the direct and indirect costs of CVD in the USA will increase from $272.5 billion and $171.7 billion in 2010 to $818.1 billion and $275.8 billion in 2030, respectively (5). In particular, with the introduction of active treatment such as reperfusion therapy, the overall mortality of MI decreases by 40% and the incidence of in-hospital complications is also substantially reduced (5, 6). Hunziker et al. reported that over the past 20 years, with the implementation of reperfusion therapy, the total mortality of MI patients has decreased from 8.7 to 7.3%, and the incidence of in-hospital cardiogenic shock has decreased from 7.8 to 3.5% with its corresponding in-hospital mortality declining from 62.2 to 36.3% (7). Therefore, finding new therapeutic and cheaper interventions is needed to improve survival outcomes and reduce disease burden in critically ill patients with MI.

Micronutrient deficiency may reduce energy generation in cardiomyocytes and lead to poor clinical outcomes in patients with CVD (8). Thiamine, also known as vitamin B1, is an essential water-soluble vitamin that cannot be synthesized by the human body. In the human body, thiamine has three forms, namely, thiamine monophosphate, thiamine pyrophosphate (TPP), and thiamine triphosphate. TPP is the main bio-active form of thiamine and one of the best markers of the overall nutritional status. Moreover, TPP is a co-factor in the pyruvate and 2-hydroxyvallutarate dehydrogenase complex and is an indispensable coenzyme involved in mitochondrial oxidative decarboxylation, playing an essential role in the synthesis of adenosine triphosphate (ATP) in mitochondria (9). Thiamine also maintains the cellular redox state by participating in the pentose–phosphate cycle for NADPH and glutathione synthesis (10). Recently, thiamine derivatives have been found to have the nonenzymatic functions involved in gene expression, stress response, and regulation of neural signal transduction (10, 11). When thiamine is deficient, the activity of pyruvate dehydrogenase complex, transketolase, and α-ketoglutarate dehydrogenase are reduced, resulting in low ATP synthesis, limited supply and circulation of Krebs cycle, and cell oxidative damage and death (12). Thiamine is primarily transported to organs and tissues with high metabolic requirements and affects high metabolic systems, such as heart, brain, muscle, and nerves (12). Absolute or relative thiamine depletion is reportedly associated with a nearly 50% increase in patient mortality when occurring in adult and pediatric patients with critical illness (13). In conclusion, giving thiamine supplements to individuals who are critically ill can improve their prognosis.

Thiamine supplementation has been studied among severely ill patients. A double-blind randomized controlled trial in patients with septic shock has shown that thiamine supplementation could significantly reduce serum lactate levels for over 24 h and reduce mortality in patients with baseline thiamine deficiency (14). Woolum et al. also found that thiamine treatment could increase the lactate clearance rate and decrease the 28-day mortality in patients with septic shock (15). Other studies have demonstrated that thiamine therapy (also known as HAT therapy), which unites thiamine with hydrocortisone and ascorbic acid, could reverse shock organ dysfunction and decrease mortality in critically ill patients. For example, Iglesias et al. evaluated metabolic resuscitation in sepsis patients and found that the time of shock response of patients who have received HAT treatment is significantly lower than that of patients not treated with HAT therapy (16). Severe pneumonia patients treated with HAT also have a significantly lower in-hospital mortality than those not treated with HAT in the ICU (17). Thiamine deficiency in the body tends to cause lactate accumulation, reducing peripheral resistance, and thereby increasing cardiac preload. Increased cardiac preload combined with myocardial injury and dysfunction may be an etiological basis of cardiovascular events when thiamine deficiency occurs in critically ill patients. Existing evidence suggests that intravenous thiamine may help correct lactic acidosis in critically ill patients, thereby improving heart function and reducing mortality (18). However, no evidence shows whether thiamine supplementation helps improve the outcomes of critically ill patients with MI. Given the convenience and low cost of thiamine administration, it may be an effective approach to treating critically ill patients with MI. Therefore, in order to improve patient treatment and offer evidence for clinical decision-making, the current study intends to explore the impact of thiamine supplementation on the prognosis of MI patients using the Medical Information Mart for Intensive Care (MIMIC)-IV database.

Methods

Data foundation

This study was a single-center retrospective observational study. Data of critically ill patients with MI were extracted from the MIMIC-IV (version 2.2) database. MIMIC-IV, an updated version of MIMIC-III released on January 6, 2023, is an online accessible clinical critical care database containing comprehensive data on over 200,000 patients between 2008 and 2019 in Beth Israel Deaconess Medical Center (19). The database was approved by the Institutional Review Boards of the Massachusetts Institute of Technology and the Beth Israel Deaconess Medical Center. MIMIC-IV used anonymized personal identifier to protect the privacy of all patients, so informed consent was not required. To obtain access, the authors finished the correlative lessons and got the corresponding certificate (no. 9983480).

Participants

The International Classification of Diseases 9 and 10 codes were used to diagnosis MI in all cases. Only the information from the patient's initial admission was chosen if they were admitted to the ICU more than once. Patients suffering fewer than 48 h of hospital or ICU stay, more than 20% missing information, patients under the age of 18, or patients with diseases unsuitable for thiamine therapy were disqualified. Depending on whether or not they had received thiamine treatment during hospitalization (including *via* intravenous and oral methods), MI patients were split into the thiamine and no-thiamine groups.

Data collection

After determining the stay identity of the selected patients, data extraction was performed using the PostgreSQL tool (v.14, PostgreSQL Global Development Group, Berkeley, CA, United States). The following characteristics were extracted: (1) demographic information, containing age, sex, ethnicity, and body mass index (BMI); (2) clinical scores, involving the Glasgow Coma Scale (GCS) and the sequential organ failure assessment (SOFA) score; (3) complications, containing congestive heart failure, diabetes, chronic renal disease, cerebrovascular disease, chronic pulmonary disease, and sepsis; (4) laboratory parameters, containing glucose, hemoglobin, sodium, lactate, blood urea nitrogen (BUN), platelets, creatinine, white blood cell, calcium, hydrogen ion concentration (pH), potassium, prothrombin time, and partial prothrombin time; (5) vital signs, containing heart rate, respiratory rate, body temperature, oxygen saturation (SpO2), systolic blood pressures, diastolic blood pressures, mean blood pressures, and urine output; and (6) clinical therapy, containing vasopressor, renal replacement therapy (RRT), and mechanical ventilation. The first measuring parameter utilized in this investigation were taken 24 h after ICU admission. The primary outcome of this study was in-hospital. Secondary outcomes included 30-day and 90-day mortality. No attempt was made to assess the study's sample size because it was an epidemiological study with a hypothesis. To get the greatest statistical power, all eligible patients in the MIMIC-IV database were enrolled.

Statistical analysis

Normality tests showed that all continuous variables had no normal distribution in this study, so they were shown as medians and quartiles (Supplementary Table S1). The Mann–Whitney U test was used to compare the differences between the two groups. Categorical variables were displayed as numbers and percentages, and the chi-square test or Fisher's exact test was used to identify between-group differences. To determine if thiamine supplementation had an impact on the survival results, Kaplan–Meier (KM) curves and the log-rank test were used.

Cox regression models with hazard ratios (HRs) and 95% confidence intervals (CIs) were built to evaluate the impact of thiamine administration on prognosis by controlling various confounding factors. The crude model only included whether thiamine was used without adjustment of any covariate. In model 1, we adjusted for demographic characteristics. In model 2, we further adjusted for comorbidities. In model 3, we additionally adjusted for clinical scores. In model 4, we further added vital signs into the Cox regression model. In model 5, covariates were additionally adjusted for laboratory tests. Finally, model 6 was additionally adjusted for clinical therapy. The proportional hazard (PH) assumption of the Cox regression model was assessed by the Schoenfeld residual method and deviance residual plot. Multicollinearity between independent variables was tested using variance inflation factors (VIFs) before multivariate Cox regression. This study minimized the baseline disparities between the two groups using a 1:2 closest propensity score matching (PSM) to assure stability. In observational studies, we are unable to achieve the randomization grouping, but PSM can be used to eliminate the imbalance of confounding factors (20). PSM can match the observation and control groups in accordance with the propensity score and then remove the participants who do not match, making sure that the matched participants are comparable in potential confounding factors with the exception of exposure factors (20, 21). Therefore, when there is a difference between the outcomes of the observation group and the control group after matching, we can attribute the difference to the exposure factors. Multiple imputation method was applied with the "mice" package of R software to fill in the missing data based on the random forest method repeated 500 times (22). MI can create multiple datasets with different insert values and perform statistical analysis, thus merging the final results to give a valid synergistic estimate. To validate the robustness and reliability of the results, sensitivity analyses were performed by excluding individuals with missing data. Moreover, subgroup analyses were conducted that took into account age, gender, ethnicity, BMI, and complications. Statistical significance was defined as a two-tailed probability value of $p < 0.05$. R software (version 4.1.0) was used to conduct all of the analyses.

Results

Baseline features

A total of 5,096 patients diagnosed with MI were originally taken from the MIMIC-IV database in ICU. Based on the exclusion criteria, 3,314 patients were excluded (Figure 1). Ultimately, 1,782 patients were included, comprising 170 (9.5%) patients who received thiamine therapy during hospitalization. Table 1 displays the variations in baseline features between the thiamine and non-thiamine groups.

Patients in the thiamine group seemed to be younger compared with non-thiamine group; had a greater proportion of male, a lower GCS score, and a higher SOFA score. Moreover, they had reduced rates of diabetes and chronic renal disease but a greater incidence of sepsis. They also had higher values of heart rate, diastolic blood pressure, temperature, hemoglobin, and lactate, and decreased levels of platelets, creatinine, BUN, and calcium. Moreover, the thiamine group's patients more likely required RRT.

Based on an adjusted PSM, there was no difference in baseline traits among the two groups when 332 cases who did not receive thiamine treatment were contrasted with 166 patients who did. The quality of the matched samples was evaluated by graphing the propensity scores of the two groups (Supplementary Figure S1). In addition, the Standardized mean difference (SMD) was calculated for

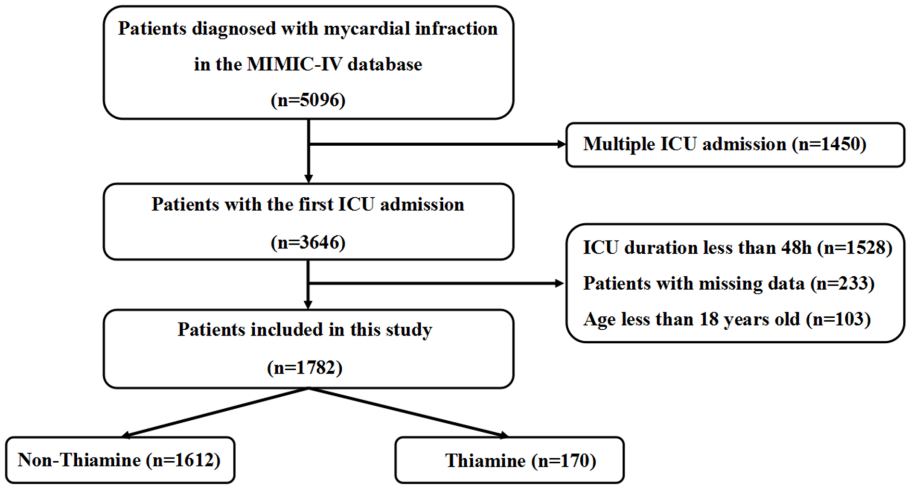

FIGURE 1
Inclusion and exclusion flowchart of the study.

the thiamine and non-thiamine groups for the original and PSM cohorts. Our results showed that 1:2 PSM yielded smaller SMD than the original cohort for all baseline measures and SMD values less than 0.1.

KM survival analysis

KM survival curves suggested that in-hospital, 30-day, and 90-day mortality differed significantly among the thiamine and non-thiamine groups (Figure 2). Figure 2A demonstrated that in the initial population, the thiamine group experienced a smaller in-hospital mortality rate compared with the non-thiamine group ($p < 0.001$). After PSM, the result of KM survival curve in the PSM population was in keep with that in the original population ($p = 0.022$, Figure 2B). Figure 2C demonstrated that in the initial population, the thiamine group possessed a smaller 30-day mortality rate than the non-thiamine group ($p < 0.001$), consistent with the results in the PSM population ($p = 0.029$, Figure 2D). Moreover, the 90-day mortality of the thiamine group was also lower compared with the non-thiamine group in the initial population ($p < 0.001$, Figure 2E) and the PSM population ($p < 0.001$, Figure 2F).

Cox proportional-hazard regression models

The results of the multicollinearity diagnosis are shown in Supplementary Table S2. None of the VIFs exceeded 5 indicates that there was no multicollinearity among the variables. Cox proportional hazards models were further analyzed to reveal the relationship between thiamine supplementation and prognosis, and the results are reported in Table 2.

Thiamine administration was substantially linked with a 49% decrease in the probability of in-hospital mortality in the original group, according to a crude model of univariate Cox regression analysis (HR: 0.507, 95% CI: 0.347–0.741, $p < 0.001$). In the completely adjusted model, multivariate analyses revealed a notable beneficial impact of thiamine supplementation on in-hospital mortality behind adjusting for demographic characteristics, complications, clinical scores, vital signs, laboratory parameters, and clinical interventions ($p = 0.019$). Following PSM, the crude models discovered that thiamine treatment was connected to a 41% decrease among the risk of in-hospital mortality ($p = 0.024$). Likewise, the completely adjusted model based on the PSM population, which is adjusted for a series of confounds, also showed a similar result (HR: 0.559, 95% CI: 0.334–0.935, $p = 0.027$).

With regard to the 30-d mortality, a decreased mortality risk in the original population was observed in the crude (HR: 0.506, 95% CI: 0.337–0.760, $p < 0.001$) and completely adjusted models (HR: 0.618, 95% CI: 0.398–0.960, $p = 0.032$). After PSM, a similar trend was also found in the crude (HR: 0.597, 95% CI: 0.374–0.952, $p = 0.030$) and completely adjusted models (HR: 0.586, 95% CI: 0.330–0.962, $p = 0.035$).

Concerning the 90-d mortality, the crude model demonstrated a significant survival benefit of thiamine supplement in the original (HR: 0.517, 95% CI: 0.354–0.756, $p < 0.001$) and PSM populations (HR: 0.586, 95% CI: 0.369–0.931, $p = 0.024$). After adjustments of various confounders, an important positive impact of thiamine treatment was also observed in the original (HR: 0.626, 95% CI: 0.411–0.953, $p = 0.029$) and PSM populations (HR: 0.559, 95% CI: 0.334–0.935, $p = 0.027$).

According to the Schoenfeld residual plots (Supplementary Figure S2) and the deviance residual plots (Supplementary Figure S3), the formulated Cox regression models conformed to the PH hypothesis, indicating that the HR estimations were valid.

Subgroup analysis

Subgroup analysis was performed for in-hospital, 30-d, and 90-d mortality (Figure 3). Results showed that thiamine use contributed to a survival beneficial in almost all subgroups. Furthermore, there was no discernible interaction, in all strata, when comparing the thiamine and none-thiamine groups.

TABLE 1 Baseline features of the original and PSM populations.

Variable	Original population					PSM population					Missing ratio (%)
	Total (*n* = 1782)	None-Thiamine (*n* = 1,612)	Thiamine (n = 170)	*p* value	SMD	Total (*n* = 498)	None-Thiamine (*n* = 332)	Thiamine (*n* = 166)	*p* value	SMD	
Age, years	73.3 (64.3, 82.0)	73.9 (64.9, 82.6)	68.0 (57.4, 75.5)	< 0.001	0.529	67.3 (58.7, 76.8)	67.1 (58.8, 77.6)	68.1 (58.5, 76.2)	0.753	0.024	0.0
Gender, *n* (%)				< 0.001	0.323				0.864	0.016	0.0
Male	1,078 (60.5)	925 (59.1)	126 (74.1)			368 (73.9)	246 (74.1)	122 (73.5)			
Female	704 (39.5)	660 (40.9)	44 (25.9)			130 (26.1)	86 (25.9)	44 (26.5)			
BMI, kg/m^2	27.5 (23.7, 31.8)	27.5 (23.7, 31.8)	27.7 (23.7, 31.6)	0.785	0.021	27.7 (23.7, 31.8)	27.7 (23.7, 31.9)	27.8 (23.8, 31.6)	0.806	0.014	11.2
Ethnicity, *n* (%)				0.119	0.124				0.949	0.006	0.0
White	1,226 (68.8)	1,118 (69.4)	108 (63.5)			319 (64.1)	213 (64.2)	106 (63.9)			
Others	556 (31.2)	494 (30.6)	62 (36.5)			179 (35.9)	119 (35.8)	60 (36.1)			
Comorbidities, *n* (%)											
Congestive heart failure	1,068 (59.9)	965 (59.9)	103 (60.6)	0.854	0.015	299 (60.0)	200 (60.2)	99 (59.6)	0.928	0.009	0.0
Diabetes	786 (44.1)	729 (45.2)	57 (33.5)	0.003	0.241	174 (34.9)	117 (35.2)	57 (34.3)	0.847	0.019	0.0
Chronic renal disease	614 (34.5)	582 (36.1)	32 (18.8)	< 0.001	0.395	87 (17.5)	55 (16.6)	32 (19.3)	0.474	0.068	0.0
Cerebrovascular disease	266 (14.9)	237 (14.7)	29 (17.1)	0.412	0.065	82 (16.5)	55 (16.6)	27 (16.3)	0.980	0.002	0.0
Chronic pulmonary disease	591 (33.2)	535 (33.2)	56 (32.9)	0.948	0.005	166 (33.3)	111 (33.4)	55 (33.1)	0.964	0.004	0.0
Sepsis	1,145 (64.3)	1,008 (62.5)	137 (80.6)	< 0.001	0.409	396 (79.5)	263 (79.2)	133 (80.1)	0.821	0.022	0.0
Clinical scores											
GCS	14.0 (10.0, 15.0)	14.0 (10.0, 15.0)	12.0 (7.0, 14.0)	< 0.001	0.406	13.0 (7.0, 14.0)	13.0 (7.0, 15.0)	12.0 (8.0, 14.0)	0.164	0.058	0.0
SOFA	6.0 (3.0, 9.0)	6.0 (3.0, 9.0)	7.0 (4.0, 10.0)	< 0.001	0.321	7.0 (4.0, 10.0)	6.0 (4.0, 10.0)	7.0 (4.0, 10.0)	0.596	0.045	0.0
Vital sign											
Heart rate, beats/min	82.4 (72.6, 92.7)	82.2 (72.3, 92.5)	84.8 (75.0, 96.5)	0.036	0.191	84.2 (733, 95.6)	84.0 (71.5, 95.8)	84.4 (74.8, 94.8)	0.824	0.04	0.0
Respiratory rate, beats/min	19.1 (17.1, 21.7)	19.0 (17.1, 21.6)	19.8 (17.1, 22.6)	0.082	0.131	19.8 (17.4, 22.7)	19.8 (17.5, 22.6)	19.7 (17.1, 22.5)	0.551	0.032	0.0
SBP, mmHg	111.4 (103.3, 122.0)	111.7 (103.3, 122.2)	109.5 (1,044, 118.7)	0.425	0.051	109.9 (103.1, 119.9)	109.9 (102.2, 120.4)	1,098 (104.5, 119.1)	0.636	0.052	0.0
DBP, mmHg	58.2 (52.2, 65.6)	58.1 (52.1, 65.5)	59.7 (53.4, 68.6)	0.007	0.249	61.2 (54.5, 68.8)	61.4 (55.0, 69.3)	60.2 (53.5, 68.5)	0.377	0.05	0.0

(Continued)

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TABLE 1 (Continued)

Variable	Original population					PSM population					Missing ratio (%)
	Total (n = 1782)	None-Thiamine (n = 1,612)	Thiamine (n = 170)	p value	SMD	Total (n = 498)	None-Thiamine (n = 332)	Thiamine (n = 166)	p value	SMD	
MBP, mmHg	74.2 (68.1, 80.1)	74.2 (68.0, 80.1)	74.9 (68.3, 81.5)	0.184	0.163	75.6 (69.6, 82.2)	75.8 (70.0, 82.7)	74.9 (683, 81.6)	0.355	0.059	0.0
Temperature, °C	36.8 (36.5, 37.1)	36.8 (36.5, 37.1)	36.9 (36.6, 37.2)	< 0.001	0.171	36.8 (36.6, 37.2)	36.8 (36.5, 37.2)	36.9 (36.6, 37.2)	0.337	0.037	0.0
SpO_2, %	97.4 (96.0, 98.7)	97.4 (96.0 98.7)	97.6 (96.0, 98.7)	0.475	0.060	97.7 (96.1, 98.8)	97.6 (96.1, 98.8)	97.7 (96.0, 98.7)	0.870	0.010	8.6
Urine output, ml	1562.5 (946.5, 2375.0)	1562.5 (950.0, 2368.8)	1552.5 (910.3, 2423.3)	0.896	0.009	1638.5 (993.5, 2348.8)	1643.5 (996.3, 2275.3)	1627.5 (932.5, 2586.0)	0.809	0.004	0.0
Laboratory test											
Hemoglobin, g/dl	10.6 (9.4, 12.2)	10.5 (9.4, 12.1)	11.1 (9.3, 13.0)	0.031	0.191	11.0 (9.7, 12.9)	11.0 (9.8, 12.9)	11.1 (9.3, 12.9)	0.416	0.017	5.4
Platelets, 10^9/L	209.0 (157.5, 268.6)	210.5 (159.0, 271.0)	197.0 (137.9, 250.0)	0.011	0.150	202.5 (147.6, 254.0)	205.0 (153.4, 255.4)	200.0 (139.5, 251.0)	0.407	0.043	7.7
WBC, 10^9/L	11.9 (9.1, 15.5)	11.8 (9.0, 15.3)	12.5 (9.5, 16.8)	0.079	0.089	12.4 (9.4, 16.2)	12.4 (9.4, 16.2)	12.4 (9.3, 16.2)	0.9	0.009	5.1
BUN, mg/dl	25.0 (17.0, 41.5)	25.5 (17.5, 42.0)	21.8 (15.0, 34.3)	0.003	0.175	21.8 (15.6, 34.5)	22.0 (16.1, 34.5)	21.3 (15.1, 34.0)	0.549	0.017	6.3
Calcium, mmol/L	8.4 (7.9, 8.9)	8.4 (8.0, 8.9)	8.2 (7.7, 8.7)	< 0.001	0.404	8.2 (7.8, 8.7)	8.2 (7.8, 8.7)	8.2 (7.7, 8.7)	0.923	0.045	3.7
Creatinine, mg/dl	1.2 (0.9, 2.0)	1.3 (0.9, 2.1)	1.1 (0.8, 1.9)	0.048	0.086	1.1 (0.9, 1.84)	1.1 (0.9, 1.84)	1.1 (0.8, 1.8)	0.499	0.083	0.0
Glucose, mg/dl	143.3 (117.0, 185.1)	142.8 (117.5, 187.0)	144.5 (113.9, 177.6)	0.515	0.102	137.8 (115.0, 175.5)	135.5 (115.0, 173.9)	144.8 (116.0, 178.8)	0.309	0.057	0.0
Sodium, mmol/L	138.0 (135.5, 140.5)	138.0 (135.5, 140.0)	138.0 (135.5, 141.0)	0.606	0.090	138.5 (136.0, 141.0)	138.5 (136.5, 140.9)	138.0 (135.6, 141.0)	0.270	0.029	3.2
Potassium, mmol/L	4.3 (3.9, 4.7)	4.3 (4.0, 4.7)	4.2 (3.8, 4.7)	0.092	0.15	4.2 (3.9, 4.6)	4.2 (3.9, 4.6)	4.2 (3.8, 4.7)	0.858	0.042	10.2
pH	7.38 (7.33, 7.43)	7.38 (7.34, 7.43)	7.38 (7.32, 7.43)	0.434	0.036	7.38 (7.33, 7.43)	7.38 (7.34, 7.43)	7.38 (7.32, 7.43)	0.434	0.092	4.1
Lactate, mmol/L	1.7 (1.3, 2.4)	1.7 (1.3, 2.4)	1.8 (1.3, 2.7)	0.045	0.168	1.8 (1.3, 2.6)	1.7 (1.3, 2.6)	1.8 (1.3, 2.5)	0.405	0.061	6.9
PT, seconds	14.3 (12.8, 16.4)	14.3 (12.8, 16.4)	14.4 (12.6, 16.4)	0.938	0.076	14.3 (12.9, 16.4)	14.3 (12.9, 16.5)	14.3 (12.6, 16.4)	0.554	0.014	0.0
PPT, seconds	41.8 (31.2, 62.5)	41.7 (31.1, 63.2)	42.0 (32.8, 58.5)	0.949	0.064	41.5 (31.1, 61.2)	41.4 (30.5, 64.0)	41.7 (32.8, 57.6)	0.716	0.053	0.0
Clinical Therapy, n (%)											
Vasopressor	726 (40.7)	652 (40.4)	74 (43.5)	0.437	0.062	225 (45.2)	154 (46.4)	71 (42.8)	0.429	0.076	0.0
RRT	180 (10.1)	154 (9.6)	26 (15.3)	0.018	0.175	60 (12.0)	36 (10.8)	24 (14.5)	0.226	0.084	0.0
Mechanical ventilation	1706 (95.7)	1,541 (95.6)	165 (97.1)	0.369	0.078	481 (96.6)	320 (96.4)	161 (97.0)	0.666	0.042	0.0

BMI, body mass index; BUN, blood urea nitrogen; DBP, diastolic blood pressure; MBP, mean blood pressure; GCS, Glasgow Coma Scale; pH, hydrogen ion concentration; PSM, propensity-score matching; PT, prothrombin time; RRT, renal replacement therapy; SBP, systolic blood pressure; SOFA, sequential organ failure assessment; SMD, standardized mean difference; SpO2, oxygen saturation; WBC, white blood cell.

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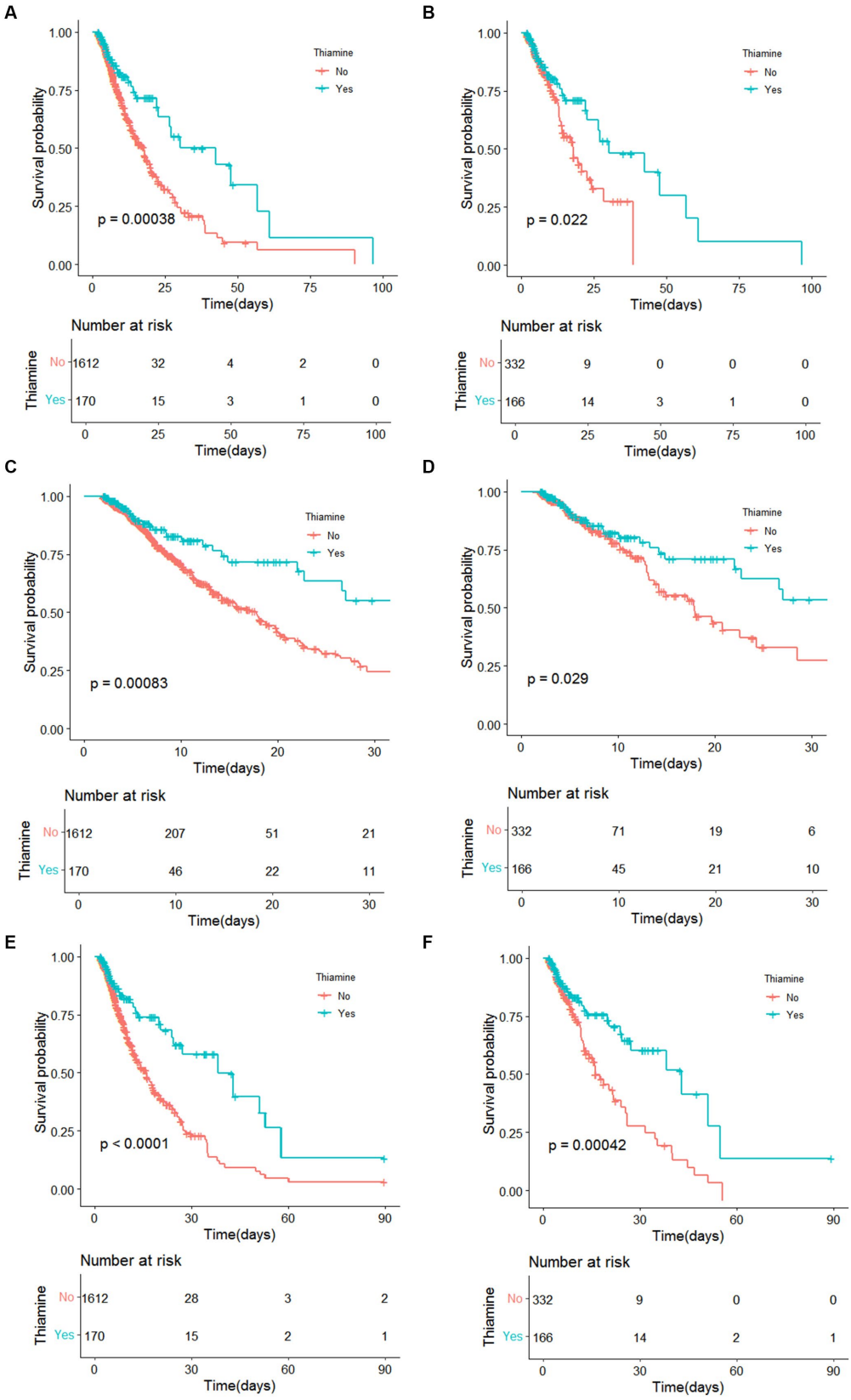

FIGURE 2
Kaplan–Meier survival curves between the thiamine and none-thiamine groups. **(A)** the original population of in-hospital mortality risk; **(B)** After propensity score matching adjustment of in-hospital mortality risk; **(C)** The original population of 30d ICU mortality risk; **(D)** After propensity score matching adjustment of 30d ICU mortality risk; **(E)** the original population of 90d ICU mortality risk; **(F)** After propensity score matching adjustment of 90d ICU mortality risk.

TABLE 2 Results of Cox proportional hazard models.

Category	Models	Original population		PSM population	
		HR (95% CI)	*p* value	HR (95% CI)	*p* value
In-hospital mortality	Crude model	0.507 (0.347–0.741)	< 0.001	0.586 (0.369–0.931)	0.024
	Model 1[a]	0.615 (0.414–0.912)	0.015	0.633 (0.395–0.948)	0.046
	Model 2[b]	0.615 (0.433–0.965)	0.03	0.627 (0.391–0.918)	0.042
	Model 3[c]	0.611 (0.406–0.918)	0.017	0.634 (0.394–0.929)	0.041
	Model 4[d]	0.554 (0.368–0.833)	0.004	0.539 (0.331–0.877)	0.012
	Model 5[e]	0.579 (0.381–0.881)	0.010	0.546 (0.327–0.912)	0.020
	Model 6[f]	0.605 (0.397–0.921)	0.019	0.559 (0.334–0.935)	0.027
30-d mortality	Crude model	0.506 (0.337–0.760)	< 0.001	0.597 (0.374–0.952)	0.030
	Model 1[a]	0.596 (0.391–0.909)	0.016	0.644 (0.401–0.931)	0.028
	Model 2[b]	0.631 (0.412–0.968)	0.034	0.635 (0.394–0.950)	0.041
	Model 3[c]	0.617 (0.401–0.949)	0.028	0.649 (0.402–0.920)	0.037
	Model 4[d]	0.562 (0.364–0.865)	0.008	0.566 (0.347–0.923)	0.022
	Model 5[e]	0.597 (0.385–0.925)	0.021	0.562 (0.337–0.938)	0.027
	Model 6[f]	0.618 (0.398–0.960)	0.030	0.586 (0.330–0.962)	0.035
90-d mortality	Crude model	0.517 (0.354–0.756)	< 0.001	0.586 (0.369–0.931)	0.023
	Model 1[a]	0.631 (0.425–0.937)	0.022	0.633 (0.395–0.923)	0.036
	Model 2[b]	0.665 (0.445–0.993)	0.046	0.627 (0.391–0.945)	0.032
	Model 3[c]	0.631 (0.419–0.948)	0.026	0.634 (0.394–0.921)	0.030
	Model 4[d]	0.573 (0.381–0.862)	0.007	0.539 (0.331–0.877)	0.012
	Model 5[e]	0.603 (0.397–0.916)	0.017	0.546 (0.327–0.912)	0.020
	Model 6[f]	0.626 (0.411–0.953)	0.029	0.559 (0.334–0.935)	0.027

HR, hazard ratio; CI, confidence interval; PSM, propensity-score matching.
[a]Model 1 was adjusted for demographic features, including age, gender, ethnicity, and BMI.
[b]Model 2 was additionally adjusted for comorbidities, including congestive heart failure, chronic renal disease, cerebrovascular disease, chronic pulmonary disease, and sepsis.
[c]Model 3 was additionally adjusted for clinical scores, including GCS, SOFA.
[d]Model 4 was additionally adjusted for vital signs, including heart rate, respiratory rate, SBP, DBP, MBP, temperature, SpO2, and urine output.
[e]Model 5 was additionally adjusted for laboratory tests, including hemoglobin, platelets, white blood cell, BUN, calcium, creatinine, glucose, sodium, potassium, lactate, PT, and PTT; f Model 6 was additionally adjusted for clinical therapy, including renal replacement therapy, mechanical ventilation, and vasopressor.

Sensitivity analysis

After excluding individuals with missing data, a total of 1,426 patients were included in the sensitivity analysis with 139 (9.7%) and 1,287 (90.2%) cases in the thiamine and non-thiamine groups, respectively. The results of sensitivity analyses showed that thiamine usage had a significant survival benefit among critically ill patients with MI, indicating that our results were robust and reliable (Supplementary Table S3; Supplementary Figure S4).

Discussion

Our study was the first to evaluate the effects of thiamine supplementation on the outcome of critically ill patients with MI from the MIMIC-IV database. Results revealed a strong association between thiamine supplementation and reduced risk of ICU, 30-d, and 90-d mortality in MI patients regardless of adjustments for multifarious confounding factors using the Cox regression models. After verification by PSM and subgroup analysis, the results also supported that thiamine supplementation contributed to a survival benefit in critically ill patients with MI.

Thiamine, also known as vitamin B1, was an essential micronutrient and co-factor involved in the important metabolism of the body. Thiamine is essential for the Krebs cycle's oxidative decarboxylation, which takes place in the mitochondria, for the creation of ATP and offers energy for cells. Hence, thiamine deficiency may be limit mitochondrial function and reduce ATP production, leading to severe cardiovascular, metabolic, neurological, respiratory, gastrointestinal, and musculoskeletal system disorders (12, 23). Conversely, thiamine supplementation may improve patient outcomes by restoring mitochondrial function and perfusion in harmed tissues, which will lessen organ dysfunction. Moreover, thiamine defends human infragenicular artery smooth muscle cells from glucose- and insulin-mediated proliferation, which are known to be essential for the formation of the atherosclerotic plaque; thus, thiamine supplementation results in improved cardiac functions and hemodynamic features, as well as decreased in systemic vascular resistance. Thiamine also counteracts the damaging effects of high glucose concentrations on endothelial cells by reducing intracellular protein glycosylation (24). Additionally, thiamine is an antioxidant involved in many redox reactions. Critically ill patients are prone to inflammatory responses and tissue hypoxia, which disrupts the balance of oxidative and antioxidant systems within the body and increases the products of

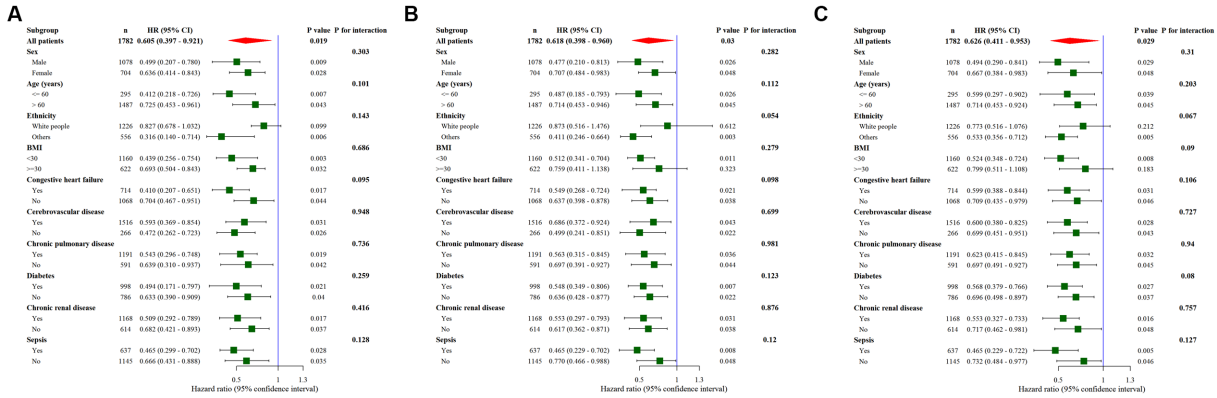

FIGURE 3
Subgroup analysis of the association between thiamine use and outcomes in critically ill patients with myocardial infarction. **(A)** The subgroup analysis of in-hospital mortality risk. **(B)** The subgroup analysis of 30d mortality risk. **(C)** The subgroup analysis of 90d mortality risk. HR, hazard ratio; CI, confidence interval.

oxidative stress, such as reactive oxygen species (25). Based on the inhibition of lipid peroxidation and oleic acid oxidation mechanisms, thiamine supplementation could improve the oxidative stress status (26). Thiamine supplementation also has a promoting effect on the body's immune system and immune cells. For example, it protects macrophages from oxidative stress and has an antioxidant impact on neutrophil cells. Then, by preventing P43's intracellular function, it also further helps the p53 inhibitory protein work as an anti-inflammatory, which is considered as the pathophysiological basis of thiamine in improving poor outcomes among critically ill patients (27).

A large number of evidences shows that 20% critically ill patients often have thiamine deficiency during hospitalization, which may be due to metabolic stress, reduced or poor nutritional intake, and multiple comorbidities (28, 29). Under-nutrition status is common among critically ill patients and may result in inadequate thiamine intake. Notably, thiamine deficiency is difficult to promptly detect in critically ill patients due to the symptomatic lack of sensitivity and specificity. This defect can also lead to peripheral neuropathy, congestive heart failure, gastrointestinal beriberi, Korsarkov's syndrome, and Wernicke's encephalopathy, as well as accelerate the development of complications, such as confusion, unexplained lactic acidosis, and gastrointestinal dysfunction (18). Cardiomyocytes require a sustained energy supply, and abnormalities of the aerobic respiratory pathways caused by thiamine deficiency interrupt normal cardiac function owing to the endovascular dysfunction caused by the thiamine-dependent nitric oxide synthase. Thiamine deficiency is also reportedly associated significantly with CVD such as heart failure, MI, and conduction block, as well as its risk factors (obesity and diabetes) (12). Furthermore, endothelial dysfunction and chronic vascular inflammation are prominent risk factors for the development of atherosclerosis and CVD (23, 30). Thiamine deficiency may aggravate endothelial dysfunction and chronic vascular inflammation, resulting in the loss of arterial vascular resistance that eventually develop into CVD. Therefore, thiamine supplementation may provide an unexpected benefit to the prognosis and outcome in patients with CVD.

Thiamine is transported primarily through red blood cells into organs with high energy and metabolic needs, resulting in the heart being the first to be affected when thiamine deficiency occurs. Moreover, thiamine deficiency interferes with how the regular CV system functions because of the elevated lactate level caused by the accumulation of pyruvate. These lead to raising ventricular filling pressure and oxygen demand (12). Numerous studies have shown how thiamine supplementation can prevent CVD. A meta-analysis summarizing data from two randomized controlled trials has shown that thiamine supplementation induces an overall improvement in left ventricular ejection fraction (LVEF) by 3.28% among patients with systolic heart failure (31). Yang et al. indicated that the probability of in-hospital death in patients with heart failure is dramatically reduced by 26% when thiamine supplementation is used (8). Additionally, Schoenenberger et al. demonstrated an improvement in LVEF among patients with heart failure who have received 300 mg/day thiamine supplementation for 4 weeks (32). Although existing evidence suggests that thiamine supplementation may contribute to increased therapeutic effect of CVD, the recommended reference intake and methods of intake are unclear. The lack of consistent results in clinical trials may explain the low proportion of thiamine supplementation in MI patients in this study.

Similar results have been found in other studies of critically ill patients, indicating that thiamine supplementation may be beneficial for improving outcomes in critically ill patients. For instance, patients with ventilator-associated pneumonia given thiamine supplementation have a significantly decreasing ICU and in-hospital mortality when comparing those untreated with thiamine (10). Another retrospective study has demonstrated that HAT therapy including thiamine supplementation could reduce in-hospital mortality in patients with sepsis (29). Taking the results of this study together with the current evidence, a simple, practical, and risk-free technique to enhance cardiac function is thiamine supplementation. It is worthy of being recommended to enhance survival outcomes in critically ill patients with MI.

To the best of our understanding, this research effort was the first to investigate the relevance between outcomes in MI patients and thiamine and had several strengths. First, our results were validated by PSM and an array of Cox regression models adjusting for various confounders, and the same results were achieved. Second, the MIMIC-IV database embraced quite a few of patient populations that

served as a strong foundation for our study. However, we must acknowledge several limitations. First, single-center retrospective observational studies cannot avoid selection bias. Second, we were unable to determine whether thiamine benefited all MI patients or only thiamine-deficient individuals because MIMIC-IV lacked baseline thiamine levels. Third, this work did not consider the dose and duration of thiamine supplementation. Fourth, studies using MI to fill in the data may deviate from the true value. Therefore, more well-planned clinical trials are required to investigate the prognostic relationship between thiamine and MI in the future.

Conclusion

Thiamine supplementation contributes to a potential survival benefit in critically ill patients with MI. Considering that thiamine is convenient, safe, and low cost, it has an excellent application prospect in critically ill patients. However, the effect of thiamine supplementation requires further multicenter and well-designed clinical trials to provide more convincing evidence and validate the findings.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found at: https://mimic.physionet.org/.

Ethics statement

Ethical approval was not required for the study involving humans in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and the institutional requirements.

Author contributions

JWu, SY, and JWa conceived of and designed the work. SY, YZ, and JWa acquired and check the data. EY, XL, and YH performed statistical and computational analyses. SY, YH, and DN assisted the analysis and explain of statistical methods. JWa, JH, XH, and EY provided professional clinical analyses. SY, JWa, JyW, and YZ drafted the work. All authors read and approved the final manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2023.1227974/full#supplementary-material

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EDITED BY
Iain Brownlee,
Northumbria University, United Kingdom

REVIEWED BY
Jasmina Debeljak Martacic,
University of Belgrade, Serbia
Fabio Fimiani,
Hospital of the Hills, Italy

*CORRESPONDENCE
Agnieszka Białek-Dratwa
✉ abialek@sum.edu.pl

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Lifestyle and the risk of acute coronary event: a retrospective study of patients after myocardial infarction

Elżbieta Szczepańska[1], Agnieszka Białek-Dratwa[1]*, Katarzyna Filipów[2] and Oskar Kowalski[1,2]

[1]Department of Human Nutrition, Department of Dietetics, Faculty of Public Health in Bytom, Medical University of Silesia in Katowice, Zabrze, Poland, [2]Department of Cardiac Surgery, Heart Transplantation and Mechanical Circulatory Support Silesian Centre for Heart Diseases, Zabrze, Poland

Introduction: Unhealthy lifestyle behaviours that may contribute to the development of disorders leading to MI include consuming foods with a high glycaemic load and excessive supply of saturated fats, especially trans fats. Limiting the consumption of simple and refined carbohydrates, such as sweets, sweet drinks, white bread, or white pasta, has a positive effect on the lipid profile by lowering the concentration of triglycerides. Eliminating simple sugars, especially fructose, prevents the deposition of visceral adipose tissue.

Materials and methods: The study included 116 patients of the Silesian Centre for Heart Diseases in Zabrze (SCCS; Poland), with their average age being 59.45 ± 11.54 years, staying in the SCCS due to MI, from March to November 2022. The comprehensive assessment of diet quality included 72 patients: 15 women and 57 men. The research tool was the KomPAN questionnaire for examining dietary views and habits, developed by the Committee on Human Nutrition Science of the Polish Academy of Sciences, evaluating the diet in the year preceding the study. The following three indicators were used to assess the diet quality: pro-Healthy Diet Index (pHDI), non-Healthy Diet Index (nHDI) and Diet Quality Index (DQI).

Results: Most patients ate white wheat bread several times a day (39.66% of patients, with a higher percentage in men than in women – 42.35% vs. 32.26%), and white rice, fine-ground groats and pasta once a week (40.52% of patients, including 41.17% of men and 38.71% of women). Legume seeds were predominantly eaten 1–3 times a month (51.73% of responses, with comparable percentages of men and women, i.e., 51.76% vs. 51.62%), vegetables several times a week (42.25% of responses, including more women than men, i.e., 54.84% vs. 37.64%), and fruit once a day (40.52% of responses, including more men than women: 45.89% vs. 25.81%).

Conclusion: The results of our assessment of individual behaviours of the whole group may indicate errors in the diet. The value of the pro-Healthy Diet Index appears to confirm this fact, while the non-Healthy Diet Index and Diet Quality Index values do not clearly demonstrate its potential adverse impact on health. These limitations of our study may be due to differences in the size of the study population and the size of the population included in the comprehensive diet assessment. Therefore, it seems necessary to conduct further research.

KEYWORDS

lifestyle, diet, myocardial infarction, eating habits, CVD

1. Introduction

Myocardial infarction (MI) is the ischaemia and necrosis of the heart that occur as a result of reduced or completely prevented blood flow in the coronary vessels (1). It is the main cause of deaths globally (2, 3). Restricted blood flow in the vessels is most often the result of coronary artery disease (CAD) caused by atherosclerotic processes (4). The development of abnormalities contributing to MI can be caused by non-modifiable factors, including male sex, as well as modifiable ones, including an unhealthy lifestyle and its consequences in the form of overweight and excessive adipose tissue content (5–7).

Unhealthy lifestyle behaviours that may contribute to the development of disorders leading to MI include consuming foods with a high glycaemic load and excessive supply of saturated fats, especially trans fats (8, 9). Limiting the consumption of simple and refined carbohydrates, such as sweets, sweet drinks, white bread, or white pasta, has a positive effect on the lipid profile by lowering the concentration of triglycerides (8). Eliminating simple sugars, especially fructose, prevents the deposition of visceral adipose tissue (10). By removing the above-mentioned products from the diet, it is possible to lower blood glucose levels, which reduces cardiovascular risk (8, 11). In turn, the unfavourable effect of saturated fats found in butter, meat products, fatty dairy products, fast foods, and fried foods is conducive to increasing the concentration of cholesterol in blood vessels, which results in the development of atherosclerotic processes leading to CAD (12).

A daily diet for limiting the risk of MI should be rich in complex carbohydrates with high fibre content, unsaturated fats, and plant sterols (12–14). It should include an increased amount of vegetables and fruit, wholegrain cereal products, legumes, low-fat dairy products, unprocessed meat, and fish (15–17). The cardioprotective effect of vegetables and fruit consists in providing fibre and anti-inflammatory compounds to the endothelium of blood vessels (12, 18). Fibre has properties that limit the absorption of cholesterol and lower its concentration in the blood (19). Apart from vegetables, it is also present in wholemeal bread, dark pasta, and groats. Other cholesterol-lowering food ingredients are plant sterols, which are found in vegetable fats, vegetables and sprouts (19). Fish are recommended as the most beneficial source of animal protein that is also believed to have cardioprotective effects (20). Fatty sea fish should be eaten at least twice a week (21). As regards meat consumption, it is better to eat white meat than red meat (22, 23).

In addition to dietary factors, other lifestyle elements that have a real impact on the development of CAD and its ischaemic effects include low physical activity, insufficient sleep, smoking, and alcohol consumption. The duration of daily exercise should be at least 30 min (24). Regular moderate physical activity reduces the risk of MI, MI recurrence, and death caused thereby (25). Not getting enough sleep increases the risk of MI; it is beneficial to sleep at least 7 h per day (26–28). When smoking cigarettes, inhalation of toxic substances induces oxidative stress, damaging the endothelium of blood vessels and resulting in the development of vascular diseases; quitting smoking, in turn, significantly reduces the risk of cardiovascular disease (CVD) (29, 30). While the effect of alcohol consumption on the cardiovascular system remains uncertain, binge drinking has been shown to be significantly associated with the risk of MI (31). On the other hand, some studies indicate that the consumption of small amounts of alcohol may have a potentially beneficial effect on the cardiovascular system (31, 32).

Unhealthy behaviours, including dietary and other habits, increase the risk of CVD. Nevertheless, it is necessary to verify whether lifestyle, apart from its proven effect on the cardiovascular system, may also directly contribute to the occurrence of MI.

The primary aim of this study was to assess the lifestyles of patients 1 year before the onset of MI and to attempt to answer the question whether lifestyle could have been one of its causes. The secondary aim was to investigate whether there were lifestyle differences between women and men and the potential impact of lifestyle on MI.

2. Materials and methods

2.1. Study population

The study included 116 patients of the Silesian Centre for Heart Diseases in Zabrze (SCCS; Poland), with their average age being 59.45 ± 11.54 years, staying in the SCCS due to MI, from March to November 2022.

The study was carried out in person, in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the Bioethics Committee of the Medical University of Silesia in Katowice (resolution no. PCN/CBN/0022/KB1/91/21 of July 6, 2021). The patients qualified for participation in the study were informed about the research procedures and gave their informed consent to participate. The criteria for inclusion in the study were: (1) being at least 18 years of age, (2) being hospitalised due to a recent MI (3–30 days after MI; diagnosis according to ICD10: I25.1), (3) functional fitness and motor independence as conditions for independent movement and self-care, and (4) informed consent to participate in the study. The criteria for exclusion from the study were: (1) complicated course of MI, (2) condition preventing independent movement and self-care, (3) psychosocial fitness preventing from independently answering the questions asked, and (4) lack of consent to participate in the study.

The comprehensive assessment of diet quality included 72 patients: 15 women and 57 men, who answered all the questions in the questionnaire. Those patients who could not answer the questions asked, indicating the answer "difficult to assess," were excluded from the assessment.

2.2. Research tool and procedures

The research tool was the KomPAN questionnaire for examining dietary views and habits, developed by the Committee on Human Nutrition Science of the Polish Academy of Sciences, evaluating the diet in the year preceding the study (33). In multicentre studies, the internal reliability (repeatability) of the KomPAN questionnaire was tested, and the results were presented in the publication by Kowalkowska et al. (34). The questionnaire contained four groups of questions, including those concerning eating habits (e.g., the number of meals per day, regularity of eating meals, eating snacks, consumption of salt and sugar), frequency of consumption of certain food products (including potentially healthy and potentially unhealthy

ones), lifestyle (alcohol consumption, smoking, sleep time, physical activity), and personal data.

In assessing the frequency of consumption of food products, the following scale was used: (1) never, (2) 1–3 times a month, (3) once a week, (4) a few times a week, (5) once a day, (6) a few times a day.

In the assessment of leisure physical activity, the following criteria were adopted:

- Low: mostly sitting, watching TV, reading the press or books, light housework, walking for 1–2 h a week
- Moderate: walking, cycling, exercising, gardening or other light physical activity for 2–3 h a week
- High: cycling, running, gardening or other sports recreational activities requiring physical effort for more than 3 h a week (33).

The following three indicators were used to assess the diet quality:

- Pro-Healthy Diet Index (pHDI) – taking into account 10 food groups with a potentially beneficial effect on health (wholemeal bread, wholegrain groats and pasta, milk, fermented milk beverages, curd, white meat, fish, legumes, fruit, and vegetables)
- Non-Healthy Diet Index (nHDI) – taking into account 14 groups of food with a potentially adverse impact on health (white bread, white rice, fine-ground groats and pasta, cheese, cured meat and smoked sausages or hot dogs, red meat, fried foods, butter, lard, fast foods, sweets, tinned (jar) meats, sugar-sweetened beverages, energy drinks, alcoholic drinks)
- Diet Quality Index (DQI) – taking into account the 24 food groups mentioned above (35).

The indices were calculated by summing up the frequency of consumption of the 10 food groups (pHDI), 14 food groups (nHDI), and 24 food groups (DQI), while assigning appropriate ranks to the frequencies (never-1, one to three times a month-2, once a week-3, a few times a week-4, once a day-5, a few times a day-6).

The following formulas were used for the calculations:

$$\text{pHDI}\left(\text{in points}\right) = \left(100 / 20\right) \times \text{sum of frequency of consumption of the 10 food groups } \left(\text{the pHDI range is } 0 - 20\right)$$

$$\text{nHDI}\left(\text{in points}\right) = \left(100 / 28\right) \times \text{sum of frequency of consumption of the 14 food groups } \left(\text{the nHDI range is } 0 - 28\right)$$

Interpretation of pHDI, nHDI and DQI scores is presented in Tables 1, 2.

The DQI was calculated as the sum of all positive-signed pHDI components and all negative-signed nHDI components. Weighting factors were used in the calculations; thus, the share of the 10 pHDI components is the same as the share of the 14 nHDI components. The DQI range is −100 to 100 points.

$$\text{DQI}\left(\text{in points}\right) = \left(100 / 20\right) \times \text{sum of frequency of consumption of the 10 food groups} + \left(-100 / 28\right) \times \text{sum of frequency of consumption of the 14 food groups}$$

TABLE 1 Interpretation pHDI i nHDI (35).

Intensity of eating characteristics	Range (in points)	
	pHDI	nHDI
Small	0–33	0–33
Medium	34–66	34–66
Big	67–100	67–100

The standardised KomPan questionnaire included a question on respondents' subjective assessment toward their financial situation. The explanation for each level is as follows:

- Financial situation below average - the patient lives modestly, has to budget very frugally on a daily basis
- Average financial situation - the patient has enough for daily living but has to save for more serious purchases
- Financial situation above average - the patient lives well (prosperously), there is enough for a lot without saving.

2.3. Statistical analysis

Microsoft Office Word and Microsoft Office Excel programs were used to analyse the collected data. Statistical analysis was performed using Statistica v. 13.3 software (StatSoft Inc., Tulsa, OK, United States). The measured data were represented by mean and standard deviation ($X \pm SD$) as well as minimum and maximum values. Statistical tests were used to analyse the variables for statistical inference. For non-parametric characteristics and two-dimensional tables, Pearson's chi-squared test was used to compare women and men in terms of lifestyle, including diet, alcohol consumption, leisure activities, and sleep. Cramér's V coefficient was also calculated. In the result, Cramér's V coefficient takes values between 0 and + 1 (inclusive); the closer the result is to 0, the weaker the relationship between the examined characteristics, and the closer it is to 1, the stronger the relationship. The statistical significance level of $p \leq 0.05$ was assumed for all calculations.

3. Results

3.1. Characteristics of the study population

The characteristics of the study population are presented in Tables 3, 4.

The examined group of patients consisted of 116 people, including 31 (26.72%) women and 85 (73.28%) men, most often residing in cities with over 100,000 inhabitants (64.66%). The majority of the patients overall (43.10%) and men (48.24%) were part of two-person households, and women were part of one- (32.26%), two- (29.03%) and three-person (25.81%) households. In addition, the majority of patients' households did not include any people under the age of 18 (82.76%). Most participants assessed their financial situation as average (81.9%). Almost half of them were professionally active with permanent employment (49.14%), but another large group (43.1%), including more women than men (61.29% vs. 36.47%), were retired

TABLE 2 Interpretation DQI (35).

Range (in points)	Intensity of eating characteristics	Interpretation
−100–−26	High intensity of unhealthy characteristics	The frequency of consumption of food with potentially adverse effects on health is higher than that of food with potentially beneficial effects on health—the effect of the diet is adverse
−25–25	Low intensity of unhealthy characteristics	The frequency of consumption of foods with potentially adverse effects on health is similar to the frequency of consumption of foods with potentially beneficial effects on health—the effect of the diet is neutral
26–100	High intensity of healthy characteristics	The frequency of consumption of foods with potentially beneficial effects on health is higher than that of foods with potentially adverse effects on health—the effect of the diet is beneficial

TABLE 3 Socioeconomic characteristics of the studied group of post-MI patients by gender.

		Women *N* = 31		Men *N* = 85		Total *N* = 116	
		N	%	*N*	%	*N*	%
Place of residence	City of up to 20.000 inhabitants	3	9.68	5	5.88	8	6.90
	City of 20.000–100.000 inhabitants	8	25.81	18	21.18	26	22.41
	City with over 100.000 inhibitants	20	64.51	55	64.71	75	64.66
	Village	0	0.00	7	8.24	7	6.03
Number of people in the household	1	10	32.26	14	16.47	24	20.69
	2	9	29.03	41	48.24	50	43.10
	3	8	25.81	17	20.00	25	21.55
	4 and more	4	12.91	13	15.29	17	14.65
Number of minors in the household	0	28	90.32	68	80.00	96	82.76
	1	1	3.23	10	11.76	11	9.48
	2	1	3.23	7	8.24	8	6.90
	3	1	3.23	0	0.00	1	0.86
Financial situation	Below the average	2	6.45	2	2.35	4	3.45
	Average	23	74.19	72	84.71	95	81.90
	Above average	6	19.35	9	10.59	15	12.93
	Difficult to assess	0	0.00	2	2.35	2	1.72
Professional work	No. retirement or annuity	19	61.29	31	36.47	50	43.10
	No. unemployed. I run a house	1	3.23	1	1.18	2	1.72
	Yes. Part-time job	0	0.00	2	2.35	2	1.72
	Yes. Permanent employment	10	32.26	47	55.29	57	49.14
	Other	1	3.23	4	4.71	5	4.31
Education	Basic	3	9.68	3	3.53	6	5.17
	Professional	16	51.61	30	35.29	46	39.66
	Medium	6	19.35	33	38.82	39	33.62
	Higher	6	19.35	19	22.35	25	21.55

or received disability pensions. The largest group of the surveyed patients had basic vocational education (39.66%), including more women (51.61%) than men (35.29%; Table 3).

The average height among participants was 171.42 ± 8.23 cm (163.65 ± 7.6 cm for women and 174.25 ± 6.46 cm for men), and the average body weight was 82.49 ± 16.57 kg (74.52 ± 18.08 kg for women and 85.39 ± 15.07 kg for men). The mean BMI in this population was 27.82 ± 4.24 kg/m2 (27.25 ± 3.96 kg/m2 in women and 28.03 ± 4.35 kg/m2 in men; Table 4).

The patients participating in the study most often did not follow a diet (56.90%), which applies to both women and men (58.06 and 56.47%, respectively). Those who followed a diet most often indicated a diet related to diabetes (16 people, i.e., 32.00%), a low-fat diet (11 people, i.e., 22.00%), or a low-calorie diet (13 people, i.e., 26.00%).

Most patients declared that their eating habits had not changed in recent years and that their eating habits on weekdays compared to weekends differed slightly or did not differ at all (47.42% vs. 44.83%). Women most often answered that their diet on weekdays did not differ

TABLE 4 Results of anthropometric measurements of the studied group of post-MI patients by gender.

		Women *N* = 31	Men *N* = 85	Total *N* = 116
WHR [cm]	Mean	0.99 ± 0.18	1 ± 0.12	0.99 ± 0.14
	Min-Max	0.74–1.83	0.77–1.83	0.74–1.83
HEIGHT [cm]	Mean	163.65 ± 7.6	174.25 ± 6.46	171.42 ± 8.23
	Min-Max	153–187	156–187	153–187
WEIGHT [kg]	Mean	74.52 ± 18.08	85.39 ± 15.07	82.49 ± 16.57
	Min-Max	54.5–157.7	57.4–123.7	54.5–157.7
BMI [kg/m^2]	Mean	27.25 ± 3.96	28.03 ± 4.35	27.82 ± 4.24
	Min-Max	22.7–45.1	20.8–39.1	20.8–45.1

TABLE 5 Selected eating behaviours.

Eating behavior		Women		Men		Total	
		N = 31	%	*N* = 85	%	*N* = 116	%
Number of meals *p* = 0.38091 V cr = 0.2136568*	1–2	2	6.45	6	7.06	8	6.90
	3	19	61.29	42	49.42	61	52.59
	4–5	10	32.26	37	43.52	47	40.52
Regular meals *p* = 0.14860 V cr = 0.2145346	No	11	35.48	16	18.82	27	23.28
	Yes. Some	10	32.26	46	54.12	56	48.27
	Yes. All	10	32.26	23	27.06	33	28.45
Salting ready meals** *p* = 0.47691 V cr = 0.1465418	No	19	61.29	45	52.94	64	55.17
	Yes. Sometimes	11	35.48	30	35.29	41	35.34
	Yes. Most foods	1	3.23	10	11.76	11	9.48
Snacking between meals *p* = 0.26787 V cr = 0.2561770	Never	4	12.90	7	8.24	11	9.48
	1–3 times a month	3	9.68	10	11.76	13	11.21
	Once a week	3	9.68	13	15.29	16	13.79
	A few times a week	10	32.26	26	30.59	36	31.03
	Once a day	9	29.03	11	12.94	20	17.24
	A few times a day	1	3.23	13	15.29	14	12.07
	Difficult to assess	1	3.23	5	5.88	6	5.17
Sweetening of hot drinks *p* = 0.68139 V cr = 0.1407063	No	13	41.94	39	45.88	52	44.83
	Yes. 2 or more teaspoons of sugar (or honey)	3	9.68	12	14.12	15	12.93
	Yes. 1 teaspoon of sugar (or honey)	11	35.48	27	31.76	38	32.76
	Yes. Sweeteners	3	9.68	3	3.53	6	5.17
	Difficult to assess	1	3.23	4	4.71	5	4.31

*V cr - Cramér's V coefficient. **Adding salt - Adding salt to prepared foods and sandwiches at the table regardless of where the food was prepared.

from their diet on weekends whatsoever (54.84% of responses), while men that it differed slightly (48.24% of responses).

3.2. Lifestyle of the study population

The lifestyle characteristics of the study population are presented in Tables 5–8.

Patients tended to eat 3 meals a day—this number was indicated by 52.59% of them, including more women (61.29%) than men (49.42%). The tendency to eat certain meals at fixed times was reported by 48.27% of patients, including more men (54.12%) than women (32.26%). Furthermore, in women, not eating meals at fixed times (35.48%) and eating all meals at fixed times (32.26%) were indicated with a similar frequency.

Snacking between meals several times a week was reported by 31.03% of patients, with comparable percentages between women and men (32.26% vs. 30.59%). Most patients declared that they do not add salt to ready meals, as this answer was given by 55.17% of them, including more women (61.29%) than men (52.94%), and that they do not sweeten hot drinks, with 44.83% of the responses, including 41.94% in women and 45.88% in men (Table 5).

The frequency of consumption of wholegrain bread was most often several times a week or never (19.83% each), while for

wholegrain cereal products (groats, pasta), it was several times a week (29.31% of responses). The above-mentioned groups of products were more frequently consumed by women than men, with the frequency still being unsatisfactory.

The most popular frequency of milk consumption was once a day, indicated by 23.28% of patients, including more women (32.26%) than men (20%). 21.18% of men drank milk several times a week. Fermented milk beverages and curd were in most cases consumed several times a week (34.48 and 37.93% of responses, respectively), with this frequency of consumption being indicated by more men than women (Table 6).

The most popular frequency of consumption of white meat was several times a week: this answer was given by 56.9% of patients, including more men than women (61.18% vs. 45.16%). Fish was most often eaten once a week, which was the case for 50.00% of patients, including more women and men (58.06% vs. 47.06%).

Legume seeds were predominantly eaten 1–3 times a month (51.73% of responses, with comparable percentages of men and women, i.e., 51.76% vs. 51.62%), vegetables several times a week (42.25% of responses, including more women than men, i.e., 54.84% vs. 37.64%), and fruit once a day (40.52% of responses, including more men than women: 45.89% vs. 25.81%). Most women (51.61%) ate fruit several times a week. The frequency of consumption is unsatisfactory for both of these groups of products (Table 6).

Most patients ate white wheat bread several times a day (39.66% of patients, with a higher percentage in men than in women—42.35% vs. 32.26%), and white rice, fine-ground groats and pasta once a week (40.52% of patients, including 41.17% of men and 38.71% of women).

The most frequently indicated frequency of consumption of products that are a source of animal fats, including cheese, cured meat, sausages and hot dogs, as well as red meat, was several times a week (38.79, 50.86 and 36.21% of responses, respectively), these answers were given by more men than women for each of the above-mentioned product groups (Table 7).

Most patients ate fried foods several times a week (36.52%, with more responses among men than women, i.e., 37.65% vs. 32.26%), and used butter as an addition to bread or in food preparation several times a day (25.22% of responses, including 27.06% of men and 19.35% of women). 25.81% of women used butter once a day. Lard was typically not used as an addition to bread or in food preparation, as indicated by 57.39% of patients, including comparable percentages in women and in men. Fast foods as well as canned and pickled products were consumed by most patients with a frequency of 1–3 times a month (54.31 and 53.44% of responses, respectively), with the former being eaten with similar frequency by women and men, and the latter more often by women than men.

31.03% of patients indicated that they usually ate sweets 1–3 times a month, with a higher percentage in women than in men (38.71% vs. 28.24%). Most patients declared that they did not consume sugar-sweetened cold drinks or energy drinks (60.34 and 87.07%, respectively). In both product groups, the percentage of women indicating these answers was higher than the percentage of men (77.42% vs. 54.12 and 90.32% vs. 85.88%; Table 7).

The largest group of patients indicated that they consumed alcohol 1–3 times a month (37.93%, including more men than women) or did not consume alcohol at all (37.08%, including more women than men). 85.34% of patients (87.10% of women and 84.71% of men) did not smoke cigarettes, but in the past the percentage of non-smokers was only 24.14%, (29.03% of women and 22.35% of men). Among those who had smoked tobacco in the past, the most frequent amount was more than 10 cigarettes a day (50.86%, with a higher percentage in men than in women—54.12% vs. 41.94%). Most patients slept 7–8 h a day, with similar percentages in women (64.42%) and men (62.35%), and spent 2–4 h a day watching TV or using a computer, with a higher percentage in women than in men (83.87% vs. 70.60%). 53.45% of patients, including 58.06% of women and 51.75% of men, assessed their physical activity as moderate, and as many as 37.07%, including comparable percentages of women and men (38.71% vs. 36.47%), as low (Table 8).

3.3. Diet quality assessment

The results of a comprehensive assessment of the diet quality of the patients participating in the study are presented in Figure 1.

Both in the case of the pro-Healthy Diet Index (pHDI) and the non-Healthy Diet Index (nHDI), the index values indicated a low intensity of beneficial and adverse characteristics of nutrition in women and men. With regard to the general Diet Quality Index (DQI), due to the similar intensity of both pro-health and unhealthy characteristics, it can be assumed that the diet used by women and men most likely had a neutral impact on health (Figure 1).

4. Discussion

The results of many studies allow to link the reduction of CVD risk with a healthy diet, adequate physical activity, being a non-smoker or having quitted smoking, and maintaining a normal body weight (5, 8, 9). A healthy lifestyle can prevent many cases of coronary artery disease, ischaemic strokes, but also premature deaths associated with heart disease (12, 13, 17, 30).

The analysis of the results of this study showed that patients most often consumed 3 meals a day, and they ate only some of those meals regularly. 1/3 of patients ate snacks between meals, approx. 45% added salt to ready meals, and approx. 55% sweetened hot drinks. Similar results were obtained by Mikulska et al., who assessed the eating habits of people with and without CVD. According to the authors, in both groups, the most common errors involved eating irregularly, i.e., having an improper number of meals during the day and snacking between them (36). In turn, Pachocka et al., in their study of the impact of lifestyle on the level of nutrition in elderly people with metabolic syndrome, showed that 36% of people sweetened their beverages and 65.6% added salt to their food (37). As research shows, the quality of diet, including the number and regularity of meals, snacking, or the use of salt and sugar, is strongly associated with an increased risk of morbidity and even mortality due to CVD. Thus, current guidelines recommend eating 4–5 meals regularly, limiting the consumption of beverages and foods with added sugars, and choosing and preparing foods with little or no salt (13, 17, 24).

Studies show that a plant-based diet is associated with better cardiovascular health. Diets that are rich in vegetables, fruits, legumes, whole grains, and nuts contain protective ingredients, including dietary fibre and antioxidants, which reduce the risk of CVD. They are

TABLE 6 Frequency of consumption of the food groups with potentially beneficial effects on health.

Frequency of consumption		Women		Men		Total	
		N = 31	%	*N* = 85	%	*N* = 116	%
Whole wheat bread $p = 0.32311$ V cr = 0.2452231	Never	4	12.90	19	22.35	23	19.83
	1–3 Times a month	1	3.23	9	10.59	10	8.62%
	Once a week	4	12.90	10	11.76	14	12.07
	A few times a week	5	16.13	18	21.18	23	19.83
	Once a day	5	16.13	11	12.94	16	13.79
	A few times a day	5	16.13	11	12.94	16	13.79
	Difficult to assess	7	22.58	7	8.24	14	12.07
Whole grain cereals and pasta $p = 0.77812$ V cr = 0.1671367	Never	3	9.68	12	14.12	15	12.93
	1–3 Times a month	8	25.81	17	20.00	25	21.55
	Once a week	10	32.26	24	28.24	34	29.31
	A few times a month	5	16.13	23	27.06	28	24.14
	Once a day	2	6.45	3	3.53	5	4.31
	A few times a day	0	0.00	1	1.18	1	0.86
	Difficult to assess	3	9.68	5	5.88	8	6.90
Milk $p = 0.37900$ V cr = 0.2350470	Never	6	19.35	13	15.29	19	16.38
	1–3 Times a month	6	19.35	10	11.76	16	13.79
	Once a week	3	9.68	10	11.76	13	11.21
	A few times a week	4	12.90	18	21.18	22	18.97
	Once a day	10	32.26	17	20.00	27	23.28
	A few times a day	1	3.23	13	15.29	14	12.07
	Difficult to assess	1	3.23	4	4.71	5	4.31
Fermented milk beverages $p = 0.47609$ V cr = 0.1975808	Never	4	12.90	5	5.88	9	7.76
	1–3 Times a month	3	9.68	14	16.47	17	14.66
	Once a week	5	16.13	14	16.47	19	16.38
	A few times a week	9	29.04	33	38.83	42	36.2
	Once a day	10	32.26	19	22.35	29	25.00
Curd cheeses $p = 0.64098$ V cr = 0.1917281	Never	2	6.45	6	7.06	8	6.90
	1–3 Times a month	5	16.13	16	18.82	21	18.10
	Once a week	9	29.03	17	20.00	26	22.41
	A few times a week	9	29.03	36	42.35	45	38.79
	Once a day	5	16.13	6	7.06	11	9.48
	A few times a day	1	3.23	4	4.71	5	4.31
White meat dishes $p = 0.22228$ V cr = 0.2452663	Never	0	0.00	1	1.18	1	0.86
	1–3 Times a month	2	6.45	8	9.41	10	8.62
	A few times a week	14	45.16	52	61.18	66	56.90
	Once a week	11	35.48	21	24.71	32	27.59
	A few times a day	1	3.23	0	0.00	1	0.86
	Once a day	3	9.68	3	3.53	6	5.17
Fish $p = 0.04798$ V cr = 0.3104128	Never	2	6.45	2	2.35	4	3.45
	1–3 Times a month	7	22.58	27	31.76	34	29.31
	Once a week	18	58.06	40	47.06	58	47.41
	A few times a week	4	12.90	13	15.29	17	14.66
	Once a day	0	0.00	3	3.53	3	2.59

(Continued)

TABLE 6 (Continued)

Frequency of consumption		Women		Men		Total	
		N = 31	%	*N* = 85	%	*N* = 116	%
Legume dishes *p* = 0.01441 V cr = 0.3498260	Never	4	12.90	9	10.59	13	11.21
	1–3 Times a month	16	51.62	44	51.76	60	51.73
	Once a week	6	19.35	27	31.76	33	28.45
	A few times a week	4	12.90	5	5.88	9	7.76
	Once a day	1	3.23	0	0.00	1	0.86
Fruits *p* = 0.04870 V cr = 0.3304078	Never	1	3.23	1	1.18	2	1.72
	1–3 Times a month	1	3.23	6	7.06	7	6.03
	Once a week	0	0.00	7	8.24	7	6.03
	A few times a week	16	51.61	23	27.06	39	33.62
	Once a day	8	25.80	39	45.89	47	40.52
	A few times a day	5	16.13	9	10.59	14	12.07
Vegetables *p* = 0.23313 V cr = 0.2648791	Never	0	0.00	1	1.18	1	0.86
	1–3 Times a month	1	3.23	7	8.24	8	6.90
	Once a week	0	0.00	7	8.24	7	6.03
	A few times a week	17	54.84	33	37.64	50	42.25
	Once a day	8	25.81	23	27.06	31	26.72
	A few times a day	5	16.13	16	18.82	21	18.10

*V cr - Cramér's V coefficient.

also low in calories and devoid of saturated fats and added sugars that increase this risk (5, 13, 19, 34, 36). Our research has shown an insufficient frequency of consumption of wholegrain cereals, legumes, fruits and vegetables, with differences in the consumption of these products by women and men only regarding legumes and fruits. Similar unhealthy behaviours were also found in the studies by Mikulska et al. (36) and Mrazova et al. (38).

As shown in our research, products potentially beneficial to health, such as milk, fermented milk beverages or curd, were consumed with a varied but insufficient frequency; however, no significant differences in the frequency of their consumption by women and men were found. Milk and milk products are a source of complete protein, calcium, magnesium, potassium, B vitamins, and vitamin D (24). Fermented milk beverages deserve special attention in this group, due to the fact that they contain healthy microflora. As a result of the research, it was found that fermented products—owing to the content of calcium and magnesium, vitamins D and K, as well as bioactive peptides and bioactive lipids, including CLA phospholipids—reduce the risk of CVD and metabolic diseases, lower blood pressure, have an anti-inflammatory effect, reduce the risk of developing diabetes, and positively affect cholesterol levels (5). Although milk and dairy products contain milk fat, which is a source of saturated fatty acids, associated with an increased risk of CVD, meta-analyses of both prospective cohort studies and randomised controlled trials have shown that its effect is inconclusive. The results of these studies indicate that the consumption of dairy products in general, both full-fat and low-fat, does not increase the risk of CVD (39).

Our research has shown a satisfactory frequency of consumption of white meat. This correct behaviour is in line with the scientific evidence supporting the health benefits of its consumption. As demonstrated by Lupoli et al., the results of their study show, for the first time, a strong and inverse relationship between white meat consumption and all-cause mortality, and a neutral relationship with cardiovascular morbidity and mortality. This highlights the importance of differentiating meat types due to their impact on health, and suggests that white meat may be a healthier alternative to red and processed meat (22). Another study, which evaluated the relationship between the consumption of white meat and the occurrence of cardiometabolic risk factors, showed that only the consumption of lean white meat appears to have a potentially beneficial effect in terms of these risk factors (23).

The frequency of fish consumption among the patients surveyed in our study was insufficient, as 14.66% of them ate fish several times a week, and 47.41% once a week. Differences in the frequency of consumption of fish by women and men were found. Low consumption of fish was also indicated in studies conducted by Mikulska et al. (36), Mrazowa et al. (38), Krupa-Kotara et al. (40). Meanwhile, as shown by Petermann-Rocha et al., eating fish instead of meat is associated with a lower risk of adverse cardiovascular effects (20). The protective effect of fish consumption was further demonstrated by the results of a study by Khatun et al. (41). In addition, a study by Mohan et al. showed an association between a minimum fish consumption of 175 g (approx. 2 servings) per week and a lower risk of major CVD and mortality in post-CVD patients. However, such a relationship has not been demonstrated in general populations (21).

Taking into account the frequency of consumption of unhealthy products by the patients participating in our study, with the exception of fast foods and lard, it can be concluded that they are included in the diet more often than they should. Similar conclusions were drawn by Krupa-Kotara et al. (40). At the same time, differences in the

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TABLE 7 Frequency of consumption of the food groups with potentially adverse effects on health.

Frequency of consumption		Women		Men		Total	
		N = 31	%	*N* = 85	%	*N* = 116	%
Wheat bread** *p* = 0.46370 V cr = 0.2206659	Never	0	0.00	3	3.53	3	2.59
	1–3 Times a month	2	6.45	6	7.06	8	6.90
	Once a week	3	9.68	6	7.06	9	7.76
	A few times a week	9	29.03	11	12.94	20	17.24
	Once a day	6	19.35	18	21.18	24	20.69
	A few times a day	10	32.26	36	42.35	46	39.66
	Difficult to assess	1	3.23	5	5.88	6	5.17
White rice. Small groats and pasta *p* = 0.70602 V cr = 0.1597640	Never	0	0.00	1	1.18	1	0.86
	1–3 Times a month	8	25.81	22	25.88	30	25.86
	Once a week	12	38.71	35	41.17	47	40.52
	A few times a week	9	29.03	26	30.59	35	30.17
	Once a day	2	6.45	1	1.18	3	2.59
Cheese *p* = 0.94272 V cr = 0.1221500	Never	1	3.23	4	4.71	5	4.31
	1–3 Times a month	6	19.35	14	16.47	20	17.24
	Once a week	7	22.58	17	20.00	24	20.69
	A few times a week	11	35.48	34	40.00	45	38.79
	Once a day	3	9.68	11	12.94	14	12.07
	A few times a day	1	3.23	3	3.53	4	3.45
	Difficult to assess	2	6.45	2	2.35	4	3.45
Cold cuts. Sausages *p* = 0.06518 V cr = 0.3197451	Never	0	0.00	1	1.18	1	0.86
	1–3 Times a month	4	12.90	7	8.24	11	9.48
	Once a week	9	29.03	6	7.06	15	12.93
	A few times a week	13	41.94	46	54.12	59	50.86
	Once a day	4	12.90	19	22.35	23	19.83
	A few times a day	1	3.23	6	7.06	7	6.03
Red meat dishes *p* = 0.00631 V cr = 0.3935685	Never	2	6.45	5	5.88	7	6.03
	1–3 Times a month	6	19.35	16	18.82	22	18.97
	Once a week	10	32.26	20	23.53	30	25.86
	A few times a week	5	16.13	37	43.53	42	36.21
	Once a day	1	3.23	5	5.88	6	5.17
	A few times a day	2	6.45	1	1.18	3	2.59
	Difficult to assess	5	16.13	1	1.18	6	5.17
Fried dishes *p* = 0.43434 V cr = 0.2255507	Never	4	12.90	4	4.71	8	6.96
	1–3 Times a month	4	12.90	17	20.00	21	18.26
	Once a week	10	32.26	21	24.71	31	26.96
	A few times a week	10	32.26	32	37.65	42	36.52
	Once a day	0	0.00	5	5.88	5	4.35
	A few times a day	1	3.23	1	1.18	2	1.74
	Difficult to assess	2	6.45	5	5.88	7	6.09

(Continued)

TABLE 7 (Continued)

Frequency of consumption		Women		Men		Total	
		N = 31	%	*N* = 85	%	*N* = 116	%
Butter $p = 0.77678$ V cr = 0.1674032	Never	5	16.13	12	14.12	17	14.78
	1–3 Times a month	4	12.90	8	9.41	12	10.43
	Once a week	1	3.23	5	5.88	6	5.22
	A few times a week	5	16.13	20	23.53	25	21.74
	Once a day	8	25.81	14	16.47	22	19.13
	A few times a day	6	19.35	23	27.06	29	25.22
	Difficult to assess	2	6.45	3	3.53	5	4.35
Lard $p = 0.90507$ V cr = 0.1368391	Never	18	58.06	48	56.47	66	57.39
	1–3 Times a month	8	25.81	22	25.88	30	26.09
	Once a week	2	6.45	5	5.88	7	6.09
	A few times a week	0	0.00	2	2.35	2	1.74
	Once a day	1	3.23	1	1.18	2	1.74
	A few times a day	0	0.00	2	2.35	2	1.74
	Difficult to assess	2	6.45	5	5.88	7	6.09
Fast-foods $p = 0.01871$ V cr = 0.3192734	Never	12	38.71	28	32.94	40	34.48
	1–3 Times a month	18	58.06	45	52.94	63	54.31
	Once a week	0	0.00	9	10.59	9	7.76
	A few times a week	1	3.23	3	3.53	4	3.45
Sweets $p = 0.23762$ V cr = 0.2627210	Never	3	9.68%	6	7.06	9	7.76
	1–3 Times a month	12	38.71	24	28.24	36	31.03
	Once a week	5	16.13	11	12.94	16	13.79
	A few times a week	7	22.58	21	24.71	28	24.14
	Once a day	3	9.68	16	18.82	19	16.38
	A few times a day	1	3.23	7	8.24	8	6.90
Tinned (jar) meats $p = 0.00449$ V cr = 0.3828670	Never	8	25.80	13	15.29	21	18.11
	1–3 Times a month	23	74.2	39	45.89	62	53.44
	Once a week	0	0.00	18	21.18	18	15.52
	A few time a week	0	0.00	13	15.29	13	11.21
	Once a day	0	0.00	2	2.35	2	1.72
Sugar-sweetened beverages $p = 0.29444$ V cr = 0.2297476	Never	24	77.42	46	54.12	70	60.34
	A few glasses a month	5	16.13	24	28.24	29	25.00
	A few glasses a week	1	3.23	6	7.06	7	6.03
	1 Glass a day	0	0.00	4	4.71	4	3.45
	2–3 Glasses a day	0	0.00	2	2.35	2	1.72
	Difficult to assess	1	3.23	3	3.53	4	3.45
Energy drinks $p = 0.76171$ V cr = 0.1001624	Never	28	90.32	73	85.88	101	87.07
	A few glasses a month	2	6.45	6	7.06	8	6
	1 Glass a day	0	0.00	3	3.53	3	2.59
	Difficult to assess	1	3.23	3	3.53	4	3.45

*V cr - Cramér's V coefficient. **Whead bread - wheat bread made of refined flour. Toasted bread made of refined wheat flour. Rolls made of refined flour. Baguettes croissants.

frequency of consumption by women and men were observed only in the case of red meat and fast foods. Products such as cheese, sausages, red meat, butter, and fast foods are a significant source of saturated fatty acids. Meanwhile, the results of numerous studies indicate that limiting the supply of saturated fats in the diet has a positive effect in terms of reducing the cardiovascular risk (5, 9, 13).

Furthermore, research suggests that restricting the consumption of saturated fats for at least 2 years results in a potentially significant reduction in total cardiovascular events. In addition, replacing energy from saturated fats with polyunsaturated fats or complex carbohydrates appears to be a correct healthcare strategy (9). The above-mentioned products are also a natural source of sodium, which in combination with adding salt to dishes or meals at the table significantly increases the risk of hypertension and its consequences. Therefore, it seems necessary to implement education to help understand the impact of saturated fats, trans fats, omega-3 and omega-6 polyunsaturated fats, and monounsaturated fats on the risk of atherosclerotic cardiovascular disease (ASCVD) and complications related thereto (12).

Besides nutrition, other lifestyle elements-such as alcohol consumption, smoking, lack of physical activity, or insufficient rest-are recognised as modifiable CVD risk factors (5, 29, 42). The results of our research has shown that most patients consumed alcohol 1–3 times a month or did not consume alcohol at all. 85.34% of patients (87.10% of women and 84.71% of men) did not smoke cigarettes in the last year, while in the past the percentage of non-smokers was only 24.14%, (29.03% of women and 22.35% of men). The largest group who smoked tobacco in the past were people who smoked more than 10 cigarettes/day. Guidelines from many scientific societies, including the American Heart Association (AHA), the American College of Cardiology (ACC) and the National Lipid Association (NLA) or the European Society of Cardiology (ESC), recommend limiting alcohol consumption to a maximum of 100 g per week. Alcohol consumption above this limit reduces life expectancy (17, 29, 43). According to the guidelines, quitting smoking is also recommended, as smoking is strongly and independently associated with ASCVD. Quitting smoking is potentially the most effective preventive method entailing a significant decrease in (recurring) myocardial infarction and mortality (5, 43). As shown in a study by Wang et al., patients with CVD who are smokers are at an increased risk of all-cause mortality, CVD and cancer, and this risk decreases significantly after they quit smoking. These data provide further strong evidence to support the recommendation to quit smoking to prevent premature death among patients with CVD (30).

The analysis of our research results has shown that patients most often slept 7–8 h a day, with comparable percentages in women (64.42%) and men (62.35%). According to Daghlas et al., who studied the relationship between sleep duration and MI, people who slept less than 6 h a day had a 20% higher risk of MI. Thus, their prospective

TABLE 8 Non-dietary lifestyle elements.

Lifestyle elements		Women		Men		Total	
		N = 31	%	*N* = 85	%	*N* = 116	%
Alcohol consumption *p* = 0.23702 V cr = 0.2628	Never	18	58.06	25	29.41	43	37.08
	1–3 Times a month	9	29.03	35	41.18	44	37.93
	Once a week	3	9.68	12	14.12	15	12.93
	A few times a week	1	3.23	8	9.41	9	7.76
	Once a day	0	0	4	4.71	4	3.45
	A few times a day	0	0	1	1.18	1	0.86
Current smoking *p* = 0.76784 V cr = 0.1913	No	27	87.10	72	84.71	99	85.34
	Yes. Less than 5pcs	0	0	2	2.35	2	1.72
	Yes. 5-10pcs	0	0	6	7.06	6	5.17
	Yes. More than10pcs	4	12.90	5	5.88	9	7.76
Smoking in the past *p* = 0.00098 V cr = 0.5952	No	9	29.03	19	22.35	28	24.14
	Yes. Less than 5pcs	2	6.45	3	3.53	5	4.31
	Yes. 5-10pcs	7	22.58	13	15.29	20	17.24
	Yes. More than 10pcs	13	41.94	50	58.82	63	54.31
Hours of sleep *p* = 0.93352 V cr = 0.0610	6 or less hours	7	22.58	22	25.88	29	25.00
	More than 6. less than 9 h	20	64.52	53	62.35	73	62.93
	9 or more hours	3	9.6	6	7.06	9	7.76
	Hard to define	1	3.23	4	4.71	5	4.31
Hours in front of the TV or computer *p* = 0.59192 V cr = 0.1998	Less than 2 h	4	12.9	19	22.36	23	19.89
	2–4 h	26	83.87	60	70.60	86	74.14
	More than 4 h	1	3.23	6	7.06	7	6.03
Physical activity in leisure time *p* = 0.59824 V cr = 0.1272	Low	12	38.71	31	36.47	43	37.07
	Moderate	18	58.06	44	51.76	62	53.45
	High	1	3.23	10	11.76	11	9.48

*V cr - Cramér's V coefficient.

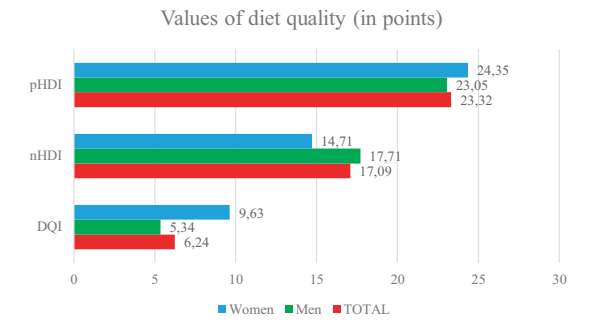

FIGURE 1
Comprehensive diet quality assessment.

observational analyses confirmed that short sleep is a potential risk factor for MI (26). Similarly, in a study assessing the impact of sleep habits on the risk of acute myocardial infarction (AMI) and coronary artery disease (CAD) in a group of post-AMI patients and in a control group, Lian et al. showed that insufficient sleep is an important risk factor for both AMI risk and CAD severity. In addition, late sleeping is associated with an increased risk of AMI (27).

In our study, 53.45% of patients, including 58.06% of women and 51.75% of men, assessed their physical activity as moderate, and as many as 37.07%, including comparable percentages of women and men (38.71% vs. 36.47%), as low. Furthermore, patients usually spent 2–4 h a day watching TV or using a computer, with a higher percentage in women than in men (83.87% vs. 70.60%). In addition, in research by Mrozowa et al. (38), who assessed CVD risk factors in patients hospitalised after MI, and by Pachocka et al., who studied the impact of lifestyle on the level of nutrition in patients with metabolic syndrome, it was shown that physical activity undertaken was insufficient, and a significant proportion of patients did not undertake any activity at all. The guidelines of scientific societies recommend to reduce the time spent in a sedentary position and to undertake at least light activity during the day in order to reduce all-cause mortality and CVD morbidity and mortality (43). Physical activity reduces the risk of numerous adverse clinical events, regardless of age and gender. There is an inverse relationship between moderate to severe physical activity and all-cause mortality, cardiovascular morbidity and mortality, and the incidence of type 2 diabetes. The risk reduction persists throughout the range in terms of amounts of activity. At the same time, the guidelines indicate that physical activity requires an individual approach in terms of frequency, intensity, duration, and type (43–45).

In our study, the intensity of pro-health diet characteristics was assessed as low (pHDI = 23.32), with no significant differences observed between the intensity of these characteristics in women and in men (pHDI = 24.45 and pHDI = 33.05, respectively). This may indicate that the patients did not pay special attention to the appropriate composition of their meals. Their diets were potentially poor in sources of dietary fibre, polyunsaturated fatty acids, antioxidant vitamins, etc., which could have contributed to the lack of cardioprotective effect resulting from the consumption of certain food groups. As in the case of the pro-Healthy Diet Index, the intensity of diet characteristics with potentially adverse effects on health was assessed as low (nHDI = 17.09); however, the group of women was characterised by a lower intensity of unhealthy characteristics (nHDI = 14.71) compared to men (nHDI = 17.71). The Diet Quality Index indicates a low intensity of both unhealthy and healthy characteristics (DQI = 6.24), in both men (DQI = 5.34) and women (DQI = 9.63); thus, it most likely had a neutral impact on their health.

The results of our own and other authors' studies clearly show that in view of dietary errors made by people with and without CVD, there is a constant need to implement preventive measures, including education on nutrition, aimed at increasing patients' awareness of the need to modify their lifestyles.

5. Conclusion

1. The assessment of the diet of patients before the onset of MI indicates that they in fact made certain dietary errors, mainly in the insufficient frequency of consumption of wholegrain products, milk and fermented beverages, fish, vegetables and fruit, as well as the excessive frequency of consumption of products with a high content of saturated fat, such as cheese, red meat, cured meat and sausages, or butter.
2. The results of our assessment of individual behaviours of the whole group may indicate errors in the diet. The value of the pro-Healthy Diet Index appears to confirm this fact, while the non-Healthy Diet Index and Diet Quality Index values do not clearly demonstrate its potential adverse impact on health. These limitations of our study may be due to differences in the size of the study population and the size of the population included in the comprehensive diet assessment. Therefore, it seems necessary to conduct further research.
3. The assessment of non-dietary lifestyle elements indicates a positive change in the reduction of the percentage of smokers. Unhealthy behaviours, on the other hand, concern the number of hours spent sleeping, time spent in front of the TV or computer, or too little physical activity.
4. Few differences in terms of lifestyle were found between women and men.
5. Lifestyle may have been one of the causes of MI.

6. Strengths and limitations of the study

Our study is one of the few in which the diets of patients with a history of MI in the year preceding the study was comprehensively assessed, using the KomPAN standardised questionnaire for examining dietary views, eating habits, and lifestyle. This allowed not only for a detailed analysis of individual behaviours of patients, but also for a comprehensive assessment of the quality of their diet.

The results of our assessment of individual behaviours of the whole group may indicate errors in the diet. The value of the pro-Healthy Diet Index appears to confirm this fact, while the non-Healthy Diet Index and Diet Quality Index values do not clearly demonstrate its potential adverse impact on health. These limitations of our study may be due to differences in the size of the study population and the size of the population included in the comprehensive diet assessment. Therefore, it seems necessary to conduct further research.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The study was carried out in person, in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the Bioethics Committee of the Medical University of Silesia in Katowice (resolution no. PCN/CBN/0022/KB1/91/21 of July 6, 2021). Written informed consent was obtained from the participant/patient(s).

Author contributions

ES: conceptualisation, methodology, analysis of results, writing - preparing and writing an original draft - reviewing and editing. KF, AB-D, and ES: research. AB-D: statistical design, review. OK: supervision. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2023.1203841/full#supplementary-material

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EDITED BY
Iain Brownlee,
Northumbria University, United Kingdom

REVIEWED BY
Keyhan Lotfi,
Tehran University of Medical Sciences, Iran
Guangyun Mao,
Wenzhou Medical University, China

*CORRESPONDENCE
Jie Jiang
✉ jiangjie@jnu.edu.cn
Sha Li
✉ tlisha@jnu.edu.cn

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Association of folic acid dosage with circulating unmetabolized folic acid in Chinese adults with H-type hypertension: a multicenter, double-blind, randomized controlled trial

Ping Chen[1], Linlin Tang[2], Yun Song[3], Binyan Wang[3], Xianhui Qin[4], Nan Zhang[4], Yaping Wei[5], Xiping Xu[5], Ziyi Zhou[6], Qiangqiang He[6], Lishun Liu[7], Sultan Mehmood Siddiqi[7], Xiao Huang[8], Xiaoshu Cheng[8], Genfu Tang[9], Yong Duan[10], Houqing Zhou[11], Jie Jiang[1]* and Sha Li[1]*

[1]College of Pharmacy, Jinan University, Guangzhou, China, [2]State Key Laboratory of Natural Medicines, Research Center of Biostatistics and Computational Pharmacy, China Pharmaceutical University, Nanjing, China, [3]Institute of Biomedicine, Anhui Medical University, Hefei, China, [4]National Clinical Research Center for Kidney Disease, State Key Laboratory for Organ Failure Research, Guangdong Provincial Key Laboratory of Renal Failure Research, Guangzhou Regenerative Medicine and Health Guangdong Laboratory, Division of Nephrology, Nanfang Hospital, Southern Medical University, Guangzhou, China, [5]Key Laboratory of Precision Nutrition and Food Quality, Department of Nutrition and Health, College of Food Sciences and Nutritional Engineering, China Agricultural University, Beijing, China, [6]Shenzhen Evergreen Medical Institute, Shenzhen, China, [7]Graduate School at Shenzhen, Tsinghua University, Shenzhen, China, [8]Department of Cardiology, The Second Affiliated Hospital of Nanchang University, Nanchang, China, [9]School of Health Administration, Anhui Medical University, Hefei, China, [10]Department of Clinical Laboratory, The First Affiliated Hospital of Kunming Medical University, Kunming, China, [11]Department of Clinical Laboratory, Fuwai Hospital Chinese Academy of Medical Sciences, Shenzhen, China

Background: There is growing concern regarding elevated levels of circulating unmetabolized folic acid (UMFA) due to excessive intake of folic acid (FA). However, no randomized clinical trial has been conducted to examine the FA-UMFA dose-response relationship.

Objective: This study aimed to investigate the FA-UMFA dose-response relationship in Chinese adults with hypertension and elevated homocysteine (H-type hypertension), a population with clear clinical indication for FA treatment.

Methods: The data for this study were derived from a randomized, double-blind, multicenter clinical trial of 8 FA dosages on efficacy of homocysteine (Hcy) lowering. The parent trial had three 3 stages: screening period (2–10 days), run-in period (0–2 weeks, baseline visit), and double-blind treatment period (8 weeks) with follow-up visits at the end of the 2nd, 4th, 6th, and 8th weeks of treatment. Participants were randomly assigned to 8 treatment groups corresponding to FA dosages of 0, 0.4, 0.6, 0.8, 1.2, 1.6, 2.0 mg to 2.4 mg.

Results: This study included 1,567 Chinese adults aged ≥45 years with H-type hypertension. There was a positive but non-linear association between FA supplementation and UMFA levels in the dosage range of 0 mg to 2.4 mg. In the regression analysis, the coefficients for the linear and quadratic terms of FA dosage were both statistically significant ($P < 0.001$). Notably, the slope for

UMFA was greater for FA dosages >0.8 mg (ß = 11.21, 95% CI: 8.97, 13.45) compared to FA dosages ≤0.8 mg (ß = 2.94, 95% CI: 2.59, 3.29). Furthermore, FA dosages higher than 0.8 mg did not confer additional benefits in terms of increasing 5-methyl tetrahydrofolic acid (5-MTHF, active form of folate) or reducing homocysteine (Hcy).

Conclusion: In Chinese adults with H-type hypertension, this study showed a positive, non-linear, dosage-response relationship between FA supplementation ranging from 0 to 2.4 mg and circulating UMFA levels. It revealed that 0.8 mg FA is an optimal dosage in terms of balancing efficacy (increasing 5-MTHF and lowering Hcy) while minimizing undesirable elevation of UMFA.

Clinical trial registration: https://clinicaltrials.gov/ct2/show/NCT03472508?term=NCT03472508&draw=2&rank=1, identifier NCT03472508.

KEYWORDS

folic acid, dosage, unmetabolized folic acid, H-type hypertension, safety

Introduction

H-type hypertension, defined as essential hypertension with an increased plasma Hcy level (≥10 μmol/L), accounts for about 75% of hypertension among Chinese patients (1, 2). Many studies have indicated that FA supplementation can effectively lower blood pressure (BP), Hcy levels, and coagulation factors, and remarkably improves prothrombotic status in patients with H-type hypertension (3).

After absorption, however, FA needs to be reduced to tetrahydrofolate (THF) to activate its metabolism, subsequently further metabolized to 5-methyl tetrahydrofolic acid (5-MTHF), which is considered the most biologically active and functional form of FA. This activation process consists of two steps, both catalyzed by dihydrofolate reductase (DHFR). In the first step, FA is transformed into dihydrofolate (DHF); in the second step, DHF is transformed into THF (4). Notably, DHFR activity in humans is inefficient and easily saturated (5). Once the catalytic ability of DHFR has been saturated, UMFA accumulates in biological fluids including plasma. Early studies in adults showed that 0.2 mg of oral FA supplementation can lead to detectable concentrations of UMFA in the bloodstream; a daily dosage of 0.4 mg brought out a continuous occurrence of circulatory FA. However, newer, more sensitive methodologies have detected very low concentrations (~0.8 nmol/L) of UMFA, even in people not taking FA supplementation (6). The presence of UMFA in the circulation is nearly ubiquitous, as it has been detected even in the cord blood of newly delivered infants (7).

Mandatory FA grain fortification in the US (starting in 1998) and in over 50 other countries has raised the circulating levels of UMFA in the general population (8, 9). This practice has also led to a growing concern regarding potential unintended adverse consequences due to high circulating UMFA from FA intake (10). NHANES (the National Health and Nutrition Examination Survey, a US representative sample), a study of elderly participants from 1999 to 2002, showed that UMFA was related to increased odds of anemia among participants who used alcohol (11), alterations in cytokine mRNA expression, a decreased number and weakened cytotoxicity of natural killer (NK) cells (12, 13), and cognitive impairment among seniors (14), as well as showed an association with insulin resistance and metabolic syndrome (15). However, uncertainty remains regarding the exact association between FA supplementation and circulating UMFA levels and what factors may modify the association.

The best study design to address this knowledge gap, is a randomized FA trial. Therefore, we conducted a study using data derived from a randomized, double-blind control, multicenter clinical trial (RCT) to delineate the dosage-response relationship between 8 different FA dosages (ranging from 0 to 2.4 mg daily by mouth) with circulating levels of UMFA. The original trial was conducted in H-type hypertension patients who all had elevated Hcy. As demonstrated in publications from our group (16) and others (17), FA supplementation is a well-established and effective treatment for this patient population. The goal of the current study was to identify the optimal FA dosage that would find the balance between maximizing efficacy in lowering Hcy and minimizing UMFA levels, while considering pertinent individual characteristics. This study represents a significant step toward a future vision of precision nutrition (18).

Methods

Study design

This study used data from a randomized, double-blind control, multicenter clinical study. The primary aim of the trial was to evaluate Hcy reduction efficacy by different dosages of FA among hypertension patients, stratified by MTHFR C677T genotypes (19).

The parent clinical trial consisted of 3 stages: (1) a screening period (2–10 days), (2) a run-in period (0–2 weeks), and (3) a

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; BP, blood pressure; C677T, MTHFR C677T genotype; DBP, diastolic blood pressure; DHF, dihydrofolate; THF, tetrahydrofolate; DHFR, dihydrofolate reductase; eGFR, estimated glomerular filtration rate; FA, folic acid; GLU, fasting glucose; Hcy, homocysteine; HDL-C, high-density lipoprotein cholesterol; 5-MTHF, 5-methyl tetrahydrofolic acid; SBP, systolic blood pressure; TC, total cholesterol; UMFA, unmetabolized folic acid.

double-blind treatment period (8 weeks). There were 6 study visits: the first at the beginning of the run-in period; the second at the beginning of the double-blind treatment period; and the third, fourth, fifth, and sixth at the end of the 2nd, 4th, 6th, and 8th weeks of treatment, respectively. Hypertension patients enrolled in the study who showed good tolerance for and compliance with angiotensin converting enzyme inhibitor (ACEI) drugs, and who had already been genotyped for the MTHFR C677T polymorphism during the run-in period, could directly enter the double-blind randomized treatment period. Drugs that could affect the efficacy evaluation were not permitted to be taken at any stage of the trial.

Participants

Eligible participants were identified from patients presenting at hospitals located in the cities of Wuyuan, Anqing, and Lianyungang between March 2018 and June 2019. The inclusion criteria for the run-in period included patients aged 45 years or older who had been diagnosed with primary hypertension or were currently taking blood pressure medications; or for those who had not taken blood pressure medications within the past 2 weeks, had been newly diagnosed with hypertension, defined as diastolic blood pressure (DBP) $\geq$90 mmHg or systolic blood pressure (SBP) $\geq$140 mmHg; and Hcy $\geq$ 10 μmol/L. For these participants, two BP readings were taken, at least 1 day apart with the patient seated. Three measurements were taken at each visit, and the mean value of the three was used to determine hypertensive status at both visits. The 2nd BP was measured at visit 1. To qualify for the treatment period, patients had to have complete information on the detection of the MTHFR C677T gene polymorphism, and exhibit good tolerance to enalapril and good medication adherence (>80%).

Patients were excluded if they had secondary hypertension, cardiovascular diseases, digestive diseases (viral hepatitis, abnormal liver function, gastrointestinal dysfunction, etc.), urinary diseases, diabetes, corpulmonale, chronic obstructive pulmonary disease (COPD), stroke, malignancy, malnutrition, hematopoietic disorders and other serious diseases. Patients who were taking folate, B12 or B6, as well as those with frequent use of FA supplements or compounds containing FA within the previous 3 months were also excluded. Further exclusion criteria included anyone pregnant and/or lactating, and/or with an allergy or intolerance to enalapril and/or FA. Patients whose mental or nervous system dysfunction, inability to express desire, were excluded.

Ethics approval

The clinical trial was carried out conforming to the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of The Second Affiliated Hospital of Nanchang University Local Ethical Review process (February 4th, 2018) in China. Trial registration was completed before the beginning of recruitment (NCT03472508). All participants provided written, informed consent prior to any data collection. Supporting data will be provided by the corresponding author upon request, after consent from the Ethics Committee of The Second Affiliated Hospital of Nanchang University has been obtained.

Allocation

This study utilized data from a randomized, double blind, clinical trial in order to objectively evaluate the efficacy of different FA dosages on circulating UMFA levels, in addition to circulating folate and Hcy. A total of 5,382 patients were screened for the trial, and ultimately 2,697 patients entered into randomization and the double-blind treatment phase. All patients were first stratified by sex and the MTHFR C677T genotype (CC, CT, TT) for a total of six strata. Each of the six strata was then randomized into eight treatment groups according to a random list generated by SAS software, using quadratic block randomization as the randomization grouping method, consisting of either enalapril only (10 mg), or one of the other 7 treatment combinations with various dosages of FA (see **Figure 1**). All drugs were supplied by AUSA Pharmaceutical Limited; all test drugs were packed into safety capsules that appeared identical. Neither the clinicians/investigators nor the patients knew the contents of the capsules.

As shown in the study flow chart (**Figure 1**), there were 5,382 patients who completed the initial screening, and those who were ineligible for enrollment (n = 1,424) were disqualified. Although 2,697 patients entered into the randomization, only 1,657 patients had biospecimens for the lab analyses. The final sample for this study included 1,567 patients, of whom 218 patients received supplementation with 0.4 mg FA daily (Group 2), 171 with 0.6 mg FA daily (Group 3), 215 with 0.8 mg FA daily Group 4), 160 with 1.2 mg FA daily (Group 5), 209 with 1.6 mg FA daily (Group 6), 163 with 2 mg FA daily (Group 7), 215 with 2.4 mg FA daily (Group 8), and finally, 216 patients who received no FA supplementation who served as a control group (Group 1).

Assessments

Sex, age, and BMI measures

Information on participant sex, age and body mass index (BMI) were collected and recorded at the baseline visit. Males and females were randomized to each group, in which all participants were aged over 45 years. BMI was calculated as the formula BMI = weight in kg/height in meters^2.

Physical examination and lifestyle survey

Each participant completed a physical examination and questionnaire survey, covering lifestyle and disease history and medication use. All participants kept a diary throughout the study in which they reported their daily intake of capsules, any illnesses they experienced, and their use of medication. Habits of smoking and drinking were also recorded.

Biochemical measurements

To determine MTHFR C677T (rs1801133) polymorphisms, an ABI Prism 7900HT sequence detection system (Life Technologies) was used with the TaqMan assay. Detection of serum B12 levels collected at both the baseline visit during the run-in period and the double-blind treatment period was completed by chemiluminescent immunoassay in a commercial laboratory (New Industrial). Serum Hcy, creatinine, fasting lipids, estimated

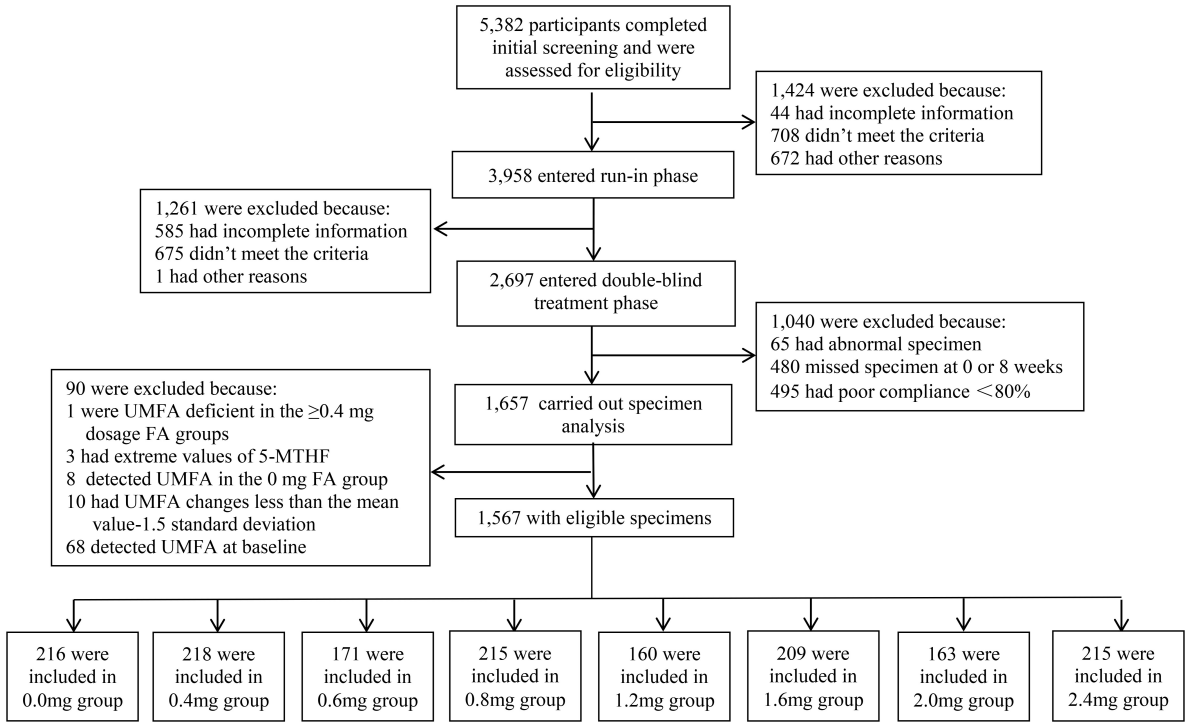

FIGURE 1
Flowchart of the study.

glomerular filtration rate (eGFR), and glucose levels at baseline were measured by automatic clinical analyzers (BeckmanCoulter). Quantification of UMFA and 5-MTHF in plasma was determined by stable-isotope dilution ultra-high performance liquid chromatography-tandem mass spectrometry. All the above measurements were conducted at the central laboratory of the Shenzhen Tailored Medical Laboratory, which obtained certificates of ISO9001:2015, ISO14001:2015, and ISO45001:2018.

Statistical analysis

Continuous variables were presented as means ± SD or medians (IQR); and IQRs were expressed as 25th and 75th percentiles. Categorical variables were presented as numbers (%). The absolute changes in UMFA levels from values at baseline to values at the 8th week of the intervention were calculated. The differences in baseline characteristics between those receiving different dosages of FA in the intervention group were compared by ANOVA tests or Chi square tests. After adjusting for covariables, changes in UMFA for each of the different dosages were determined by graphical smoothing curves using a generalized linear model. The smoothing and regression models were adjusted for center, sex, age, BMI, smoking and drinking status, C677T, baseline eGFR, baseline fasting glucose (GLU), baseline high density lipoprotein cholesterol (HDL-C), baseline total cholesterol (TC), baseline triglycerides (TG), SBP, and DBP. The additive effects of the linear and quadratic terms of the model were tested using chi-square tests (degrees of freedom: 2). The interaction between subgroups of each parameter and FA supplement dosage was assessed by the Wald test, which was used for measuring interactions on a multiplicative scale. Threshold analysis in the correlation of serum folate with UMFA levels was done with a 2-piecewise Cox regression model by a smoothing function, with cutoffs at ≤0.8 and >0.8 mg/day. A likelihood-ratio test and bootstrap resampling methods were employed to confirm the threshold level (i.e., inflection point). All analysis of data were conducted using the statistical package R[1] and Stata software, version 14.0 (Stata Corp). A two-tailed $P < 0.05$ was supposed to have statistical significance.

Results

Many of the baseline characteristics between the eight dosage treatment groups (Table 1) were quite similar, including the MTHFR C677T genotype, baseline folate levels, and Hcy levels. Compared with the control group, the exit folate and exit UMFA levels in the FA groups were significantly higher, and these increased with increasing FA dosage. In comparing eligible patients with ineligible patients, high-density lipoprotein cholesterol (HDL-C) and exit Hcy ($p < 0.001$) differed significantly (Supplementary Table 1).

Figure 2 shows the smoothing curves illustrating the association between different dosages of FA and changes in UMFA (a); folate (b); 5-MTHF (c); and Hcy (d), indicating 0.8 mg/day as the critical FA dosage for stimulating UMFA change. As shown in Figure 2A, as FA dosage increased from 0 to 2.4 mg/day,

1 http://www.r-project.org

TABLE 1 Baseline characteristics of study participants[a].

FA dosage	0 mg	0.4 mg	0.6 mg	0.8 mg	1.2 mg	1.6 mg	2 mg	2.4 mg	*P*-value[b]
Participants (*n*)	216	218	171	215	160	209	163	215	
Center									0.194
Anqing	42 (19.4)	39 (17.9)	32 (18.7)	42 (19.5)	30 (18.8)	42 (20.1)	28 (17.2)	48 (22.3)	
Lianyungang	73 (33.8)	79 (36.2)	49 (28.7)	77 (35.8)	43 (26.9)	76 (36.4)	40 (24.5)	73 (34.0)	
Wuyuan	101 (46.8)	100 (45.9)	90 (52.6)	96 (44.7)	87 (54.4)	91 (43.5)	95 (58.3)	94 (43.7)	
Male	97 (44.9)	103 (47.2)	86 (50.3%)	102 (47.4)	75 (46.9)	96 (45.9)	87 (53.4)	101 (47.0)	0.823
Age, y	65.5 ± 8.1	63.9 ± 7.7	65.1 ± 7.6	65.0 ± 7.9	64.5 ± 8.1	64.6 ± 7.4	64.0 ± 9.0	64.8 ± 9.0	0.527
BMI, kg/m^2	24.9 ± 6.9	24.9 ± 3.5	25.3 ± 11.3	24.9 ± 3.5	24.2 ± 3.5	24.4 ± 3.4	24.7 ± 3.2	24.6 ± 3.4	0.655
Smoking									0.496
Never	140 (64.8)	144 (66.1)	115 (67.3)	131 (60.9)	100 (62.5)	136 (65.1)	95 (58.3)	144 (67.0)	
Former	31 (14.4)	23 (10.6)	25 (14.6)	26 (12.1)	22 (13.8)	28 (13.4)	32 (19.6)	24 (11.2)	
Current	45 (20.8)	51 (23.4)	31 (18.1)	58 (27.0)	38 (23.8)	45 (21.5)	36 (22.1)	47 (21.9)	
Drinking									0.875
Never	135 (62.8)	138 (63.3)	111 (64.9)	140 (65.1)	109 (68.1)	136 (65.1)	112 (68.7)	145 (67.4)	
Former	30 (14.0)	20 (9.2)	23 (13.5)	23 (10.7)	15 (9.4)	28 (13.4)	17 (10.4)	24 (11.2)	
Current	50 (23.3)	60 (27.5)	37 (21.6)	52 (24.2)	36 (22.5)	45 (21.5)	34 (20.9)	46 (21.4)	
C677T									0.861
CC	64 (29.6)	64 (29.4)	55 (32.2)	67 (31.2)	53 (33.1)	57 (27.3)	48 (29.4)	75 (34.9)	
CT	105 (48.6)	105 (48.2)	81 (47.4)	98 (45.6)	70 (43.8)	96 (45.9)	80 (49.1)	85 (39.5)	
TT	47 (21.8)	49 (22.5)	35 (20.5)	50 (23.3)	37 (23.1)	56 (26.8)	35 (21.5)	55 (25.6)	
eGFR, mL/min/1.73 m^2	96.6 (88.0, 104.3)	98.0 (88.8, 104.5)	95.2 (86.8, 104.2)	96.4 (87.8, 104.4)	98.2 (86.4, 107.6)	96.6 (89.1, 104.4)	94.5 (83.9, 104.3)	95.7 (87.9, 105.7)	0.803
GLU, mmol/L	5.7 (5.3, 6.4)	5.8 (5.3, 6.3)	5.7 (5.4, 6.3)	5.9 (5.4, 6.4)	5.8 (5.4, 6.2)	5.8 (5.3, 6.4)	5.9 (5.3, 6.5)	5.7 (5.4, 6.2)	0.670
Hcy, μmol/L	14.4 (11.8, 17.8)	14.3 (12.3, 17.3)	14.6 (11.9, 17.6)	14.1 (12.1, 17.9)	13.3 (11.4, 17.3)	14.5 (11.9, 17.5)	14.3 (12.0, 17.5)	14.5 (12.2, 17.5)	0.897
HDL-C, mmol/L	1.8 (1.4, 2.1)	1.6 (1.4, 1.9)	1.7 (1.4, 2.1)	1.7 (1.4, 2.1)	1.7 (1.4, 1.9)	1.7 (1.4, 2.1)	1.6 (1.4, 1.9)	1.7 (1.4, 2.0)	0.243
TC, mmol/L	5.5 (4.7, 6.1)	5.2 (4.7, 5.9)	5.3 (4.8, 6.1)	5.2 (4.6, 5.9)	5.4 (4.6, 5.9)	5.3 (4.6, 6.0)	5.3 (4.7, 5.9)	5.3 (4.8, 5.9)	0.810

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TABLE 1 (Continued)

FA dosage	0 mg	0.4 mg	0.6 mg	0.8 mg	1.2 mg	1.6 mg	2 mg	2.4 mg	*P*-value[b]
TG, mmol/L	1.4 (1.0, 2.0)	1.4 (1.0, 2.2)	1.6 (1.1, 2.1)	1.4 (1.0, 2.0)	1.4 (1.0, 2.2)	1.4 (1.0, 2.0)	1.4 (1.0, 2.1)	1.4 (1.0, 2.0)	0.703
Folate, ng/mL	12.3 (7.8, 16.9)	10.6 (7.2, 16.6)	11.2 (8.0, 16.3)	10.4 (7.1, 14.5)	12.4 (8.4, 17.8)	10.9 (7.7, 16.4)	11.3 (8.4, 17.3)	11.1 (7.3, 16.5)	0.055
Exit folate, ng/mL	10.1 (7.2, 14.8)	26.9 (17.7, 40.3)	40.7 (23.4, 56.7)	50.0 (25.3, 81.5)	86.1 (32.2, 148.2)	97.5 (23.9, 194.9)	168.8 (45.4, 313.7)	153.6 (40.3, 312.3)	<0.001
Change in folate, ng/mL	−0.8 (−5.8, 1.5)	14.3 (7.0, 26.0)	26.3 (12.1, 44.5)	37.5 (15.0, 69.6)	67.4 (18.5, 132.2)	84.5 (15.0, 177.5)	158.1 (36.0, 299.8)	139.9 (25.8, 303.4)	<0.001
Exit UMFA, ng/mL	0.2 (0.2, 0.2)	1.1 (0.2, 2.9)	3.5 (0.7, 7.1)	6.2 (0.2, 15.1)	20.4 (0.9, 30.8)	27.3 (0.5, 51.3)	41.6 (3.9, 70.0)	54.0 (5.3, 84.9)	<0.001
Change in UMFA, ng/mL	0.0 (0.0, 0.0)	0.9 (0.0, 2.7)	3.2 (0.4, 6.9)	6.0 (0.0, 14.9)	20.2 (0.6, 30.5)	27.0 (0.3, 51.1)	41.3 (3.7, 69.7)	53.8 (5.0, 84.7)	<0.001

[a]Values are the means ± SD, median (interquartile range), and number (percentage) for variables with normal distribution, variables with skewed distribution, and categorical variables, respectively.

[b]Among-group differences were compared using the ANOVA test and the χ 2 test for continuous variables and categorical variables, respectively. BMI, body mass index; *C677T*, MTHFR C677T genotype; eGFR, estimated glomerular filtration rate; FA, folic acid; GLU, fasting glucose; Hcy, homocysteine; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides; UMFA, unmetabolized folic acid.

change in UMFA increased continuously: for FA dosages higher than 0.8 mg/day, UMFA jumped dramatically, while for FA dosages lower than 0.8 mg/day, change in UMFA tended to increase at a much slower rate.

As shown in Figure 2B, changes in folate displayed a positively curved relationship with different dosages of FA. For FA dosages higher than 0.8 mg/day, the slope of the curve was slightly greater than for FA dosages lower than 0.8 mg/day.

As shown in Figure 2C, as the FA dosage increased from 0 to 0.8 mg, changes in 5-MTHF levels rose sharply to 10 ng/mL, after which it remained nearly unchanged. For FA dosages higher than 0.8 mg, the 5-MTHF level appeared to level off at 10 ng/mL.

As shown in Figure 2D, after a sharp initial plunge, the curve flattened out at FA dosage 0.8 mg, and then fell again at FA dosage 1.6 mg. Specifically, as the FA dosage increased from 0 to 0.8 mg, change in Hcy decreased from 2 to −1 μmol/L; and with an FA dosage between 0.8 and 1.6 mg, change in Hcy remained constant at −1 μmol/L, while an FA dosage above 1.6 mg led to a Hcy reduction of −1 to −2 μmol/L.

Combined with Figure 2A, the threshold effect analysis on the effect of FA dosage on UMFA is shown in Table 2. The results of the analysis indicated a positive correlation between the two. All patients were divided into two groups according to FA supplementation with 0.8 mg/day as a new grouping point: low-dosage (≤0.8 mg) and high-dosage FA group (>0.8 mg). For each 0.2, or 0.4 mg/day FA dosage increase, the slope for UMFA was greater for the high-dosage FA group (β = 11.21, 95% CI (8.97, 13.45) compared to the low-dosage FA group (β = 2.94, 95% CI: 2.59, 3.29) (P for interaction, <0.001). The coefficients for the linear and quadratic terms for FA dosages were both statistically significant (P < 0.001) in the total sample regression analysis (Supplementary Table 2).

Table 3 shows the results of a stratified analysis of the effect of FA dosage on UMFA. For those in the low-dosage FA group (≤0.8 mg/day), those with a lower BMI showed a stronger association between FA dosage and UMFA (< 24.5 vs. ≥ 24.5 kg/m^2; P for interaction, <0.001). In addition, hospital center (p for interaction, <0.001) and smoking status (p for interaction, 0.019) positively modified the association between FA dosage and UMFA levels in the low-dosage group, with a stronger correlation found among current smokers and patients from Anqing or Wuyuan. In the high-dosage FA group (1.2–2.4 mg/day) none of the other variables, including age, sex, hospital center, BMI, SBP, DBP, TC, triglycerides, HDL-C, GLU, eGFR, MTHFR C677T, rs70991108 (a polymorphism consisting of a 19-bp deletion in the first intron of the DHFR gene), smoking status, or drinking status, significantly modified the relationship between FA dosage and UMFA levels.

Discussion

To our knowledge, this is the largest study utilizing data from a RCT to assess the dosage-response relationship between FA supplementation (eight different FA dosages) and circulating levels of UMFA, and is the first such study in a Chinese population. The results of this research provide critical insights into the optimal dosage of FA supplementation

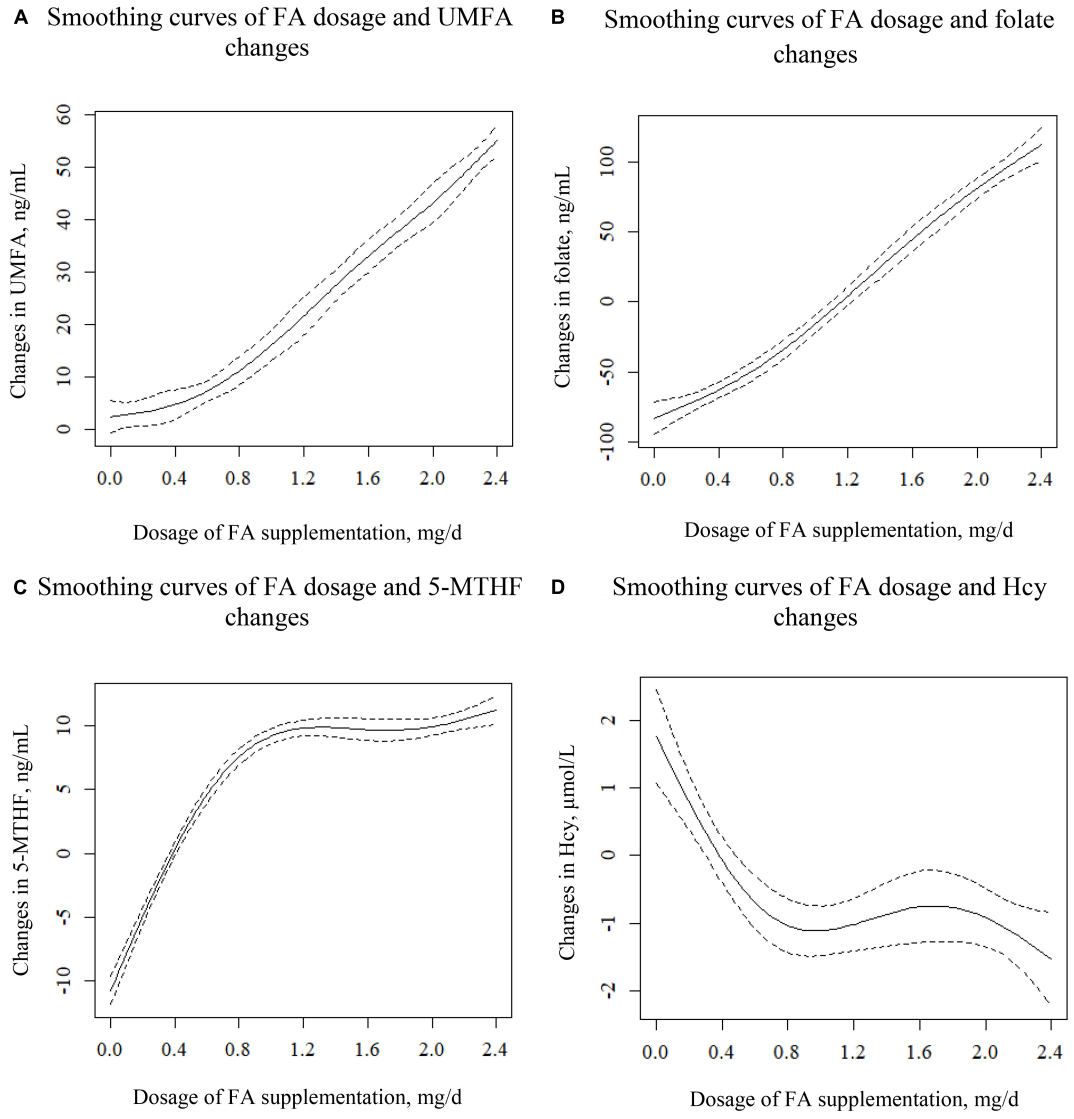

FIGURE 2
Smoothing curves illustrating the association between different dosages of FA and the changes in UMFA **(A)**, folate **(B)**, 5-MTHF **(C)**, and Hcy **(D)**. Adjusted for center, sex, age, BMI, smoking and drinking status, C677T, baseline eGFR, baseline GLU, baseline HDL-C, baseline TC, baseline TG, SBP, and DBP.

TABLE 2 Threshold effect analysis: the dose-response relationship of folic acid supplementation with circulating unmetabolized folic acid (UMFA), stratified by FA dosage subgroups (≤ 0.8 vs. >0.8 mg/day)[a].

FA dosage* mg/day	Crude model		Adjusted model		*P* for interaction
	β (95% CI)	*P*-value	β (95% CI)	*P*-value	
≤0.8	2.93 (2.58, 3.29)	<0.001	2.94 (2.59, 3.29)	<0.001	<0.001
>0.8	11.09 (8.77, 13.41)	<0.001	11.21 (8.97, 13.45)	<0.001	

[a]Adjusted for center, sex, age, BMI, smoking and drinking status, C677T, baseline eGFR, baseline GLU, baseline HDL-C, baseline TC, baseline TG, SBP, and DBP.
*FA dosage: ≤ 0.8 mg/day (0, 0.4, 0.6, 0.8); FA dosage: >0.8 mg/day (1.2, 1.6, 2.0, 2.4 mg/day).

while balancing efficacy and adverse effects. These findings offer practical implications for public health professionals and clinicians.

Our research results show that high intake of FA can lead to the occurrence of UMFA in plasma, which is consistent with that of several previous studies. A study in an elderly Irish cohort of 137 participants with a mean age of 67.4 years demonstrated that an oral FA dosage above 200 μg (threshold dosage) resulted in UMFA in plasma (20). Stamm et al. reported on a study of 117 women who received a daily multivitamin containing 1000 μg FA throughout pregnancy and lactation until 8 weeks postpartum, at which point, UMFA was detected in nearly all non-fasted blood samples (21). Sweeney et al. tested the postprandial serum FA response to multiple dosages of FA in fortified bread and found

TABLE 3 Stratified analyses by participant characteristics on the effect of folic acid dosage on unmetabolized folic acid (UMFA)[a].

Subgroup	FA dosage: ≤ 0.8 mg/day (0, 0.4, 0.6, 0.8 mg)				FA dosage: >0.8 mg/day (1.2, 1.6, 2.0, 2.4 mg)			
	N	UMFA, ng/ml Mean ± SD	β (95% CI)	*P* for interaction	*N*	UMFA, ng/ml Mean ± SD	β (95% CI)	*P* for interaction
Center				<0.001				0.144
Anqing	155	4.5 ± 7.7	3.31 (2.39, 4.23)		148	45.2 ± 36.5	15.07 (10.25, 19.89)	
Lianyungang	278	2.6 ± 5.9	1.67 (1.08, 2.25)		232	23.0 ± 31.4	8.78 (5.17, 12.4)	
Wuyuan	387	4.8 ± 6.9	3.69 (3.2, 4.17)		367	43.0 ± 40.4	11.24 (7.66, 14.83)	
Sex				0.187				0.694
Male	388	4.0 ± 6.3	3.19 (2.74, 3.65)		359	36.8 ± 32.9	11.78 (9.04, 14.51)	
Female	432	4.2 ± 7.1	2.74 (2.21, 3.27)		388	36.8 ± 42.6	10.56 (7.07, 14.06)	
Age, year				0.089				0.264
<65.4 (median)	409	3.6 ± 6.6	2.64 (2.12, 3.16)		383	33.3 ± 33.8	9.91 (7, 12.82)	
≥65.4	411	4.4 ± 6.9	3.26 (2.78, 3.75)		364	41.0 ± 41.9	12.31 (8.84, 15.77)	
BMI, kg/m^2				<0.001				0.979
<24.5 (median)	406	4.8 ± 7.6	3.59 (3.04, 4.13)		390	41.9 ± 37.1	11.34 (8.26, 14.43)	
≥24.5	414	3.5 ± 5.9	2.33 (1.88, 2.77)		357	32.6 ± 38.9	10.65 (7.31, 13.99)	
Smoking				0.019				0.621
Never	530	4.0 ± 6.7	2.66 (2.21, 3.12)		475	39.1 ± 41.4	11.52 (8.48, 14.57)	
Former	105	3.2 ± 4.9	2.5 (1.80, 3.19)		106	35.8 ± 35.7	11.53 (5.57, 17.5)	
Current	185	5.0 ± 7.7	3.74 (2.94, 4.53)		166	33.8 ± 28.9	9.75 (6.14, 13.35)	
Drinking				0.562				0.619
Never	524	4.3 ± 7.1	2.8 (2.34, 3.27)		502	37.4 ± 40.2	10.55 (7.65, 13.45)	
Former	96	3.7 ± 5.7	3.16 (2.29, 4.03)		84	37.6 ± 35.9	13.09 (6.24, 19.94)	
Current	199	3.8 ± 6.4	3.12 (2.46, 3.78)		161	36.4 ± 32.9	11.19 (7.01, 15.37)	
MTHFR C677T				0.175				0.352
CC	250	4.1 ± 7.0	3.23 (2.56, 3.9)		233	38.6 ± 42.3	9.5 (5.02, 13.99)	
CT	389	4.2 ± 7.0	3.05 (2.52, 3.58)		331	36.3 ± 36.0	13.03 (9.81, 16.26)	
TT	181	4.0 ± 5.9	2.26 (1.6, 2.93)		183	37.9 ± 36.7	9.61 (5.12, 14.1)	
rs70991108				0.346				0.922
-/-	250	3.7 ± 6.2	2.61 (2.09, 3.12)		178	43.5 ± 41.0	13.07 (7.16, 18.98)	
±	351	4.2±7.1	3.11 (2.53, 3.69)		281	39.1±42.7	11 (6.71, 15.3)	

(Continued)

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TABLE 3 (Continued)

Subgroup	FA dosage: ≤ 0.8 mg/day (0, 0.4, 0.6, 0.8 mg)				FA dosage: >0.8 mg/day (1.2, 1.6, 2.0, 2.4 mg)			
	N	UMFA, ng/ml Mean ± SD	β (95% CI)	*P* for interaction	*N*	UMFA, ng/ml Mean ± SD	β (95% CI)	*P* for interaction
+ /+	70	4.0 ± 7.8	3.59 (1.99, 5.19)		45	31.5 ± 36.2	9.62 (−5.46, 24.69)	
eGFR, mL/min per 1.73 m^2				0.085				0.875
<96.5 (median)	411	4.7 ± 7.4	3.17 (2.63, 3.72)		379	41.1 ± 41.2	10.96 (7.41, 14.51)	
≥96.5	407	3.6 ± 6.1	2.59 (2.14, 3.03)		368	33.7 ± 34.5	11.39 (8.54, 14.23)	
GLU, mmol/L				0.058				0.647
<5.8 (median)	416	4.3 ± 6.9	3.29 (2.8, 3.78)		372	37.4 ± 35.7	11.94 (9, 14.89)	
≥5.8	402	4.0 ± 6.7	2.62 (2.11, 3.13)		375	37.4 ± 40.6	10.74 (7.25, 14.23)	
HDL-C, mmol/L				0.368				0.425
<1.7 (median)	421	3.8 ± 6.6	2.77 (2.26, 3.28)		398	34.4 ± 34.7	10.38 (7.58, 13.18)	
≥1.7	397	4.5 ± 6.9	3.08 (2.58, 3.58)		349	40.4 ± 41.6	11.96 (8.31, 15.62)	
TC, mmol/L				0.796				0.982
<5.3 (median)	406	4.0 ± 6.5	3.03 (2.56, 3.5)		362	36.9 ± 40.5	11.28 (7.79, 14.76)	
≥5.3	412	4.3 ± 7.0	2.93 (2.4, 3.46)		385	37.9 ± 36.0	11.18 (8.24, 14.12)	
TG, mmol/L				0.845				0.665
<1.4 (median)	397	4.1 ± 6.7	2.94 (2.45, 3.42)		367	39.3 ± 41.0	11.49 (8.07, 14.91)	
≥1.4	421	4.2 ± 6.9	2.9 (2.37, 3.42)		380	35.6 ± 35.2	10.35 (7.42, 13.28)	
DBP, mmHg				0.154				0.884
<90.0 (median)	409	4.4 ± 6.8	3.21 (2.72, 3.71)		367	39.3 ± 41.4	11.01 (7.54, 14.47)	
≥90.0	411	3.8 ± 6.7	2.69 (2.18, 3.2)		380	35.6 ± 34.7	11.39 (8.54, 14.24)	
SBP, mmHg				0.101				0.401
<151.0 (median)	407	3.8 ± 6.8	2.64 (2.1, 3.19)		356	39.6 ± 41.4	10.19 (6.51, 13.87)	
≥151.0	413	4.5 ± 6.7	3.24 (2.78, 3.69)		391	35.5 ± 35.0	12.13 (9.36, 14.91)	

[a] Adjusted for center, sex, age, BMI, smoking and drinking status, C677T, baseline eGFR, baseline GLU, baseline HD-CL, baseline TC, baseline TG, SBP, and DBP.

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the appearance of UMFA in the serum of all participants at all test dosages, showing apparent accumulation effects (22). However, these results only proved that higher intake of FA leads to higher occurrence of UMFA in the serum, without identifying which dosage of FA is the optimum, and offered no practical guiding significance for clinical application.

An understanding of the absorption and metabolism of FA in humans can reveal the reasons for the occurrence of UMFA in the serum. Previous studies have shown that FA is mainly absorbed in the proximal jejunum in a prototype form after oral administration, and oral doses of FA in excess of about 260–280 μg (589–634 nmol) leads to the direct appearance of UMFA in the systemic circulation (6). Absorbed folate, which may undergo biotransformation in the absorptive mucosa, is subsequently transferred via the mesenteric veins to the hepatic portal vein and carried to the liver where an extensive amount (liver "first-pass") is removed (23). While the liver has a high affinity for the removal of FA, it has a low affinity for the removal of 5-MTHF (24). This may have important implications for FA use as a supplement or fortification since the human liver has a low capacity for reduction and may eventually give rise to saturation, resulting in significant (and potentially deleterious) UMFA entering systemic circulation (25). Our study investigated the saturation point of oral FA transformation through two indicators, namely, folate and 5-MTHF, as well as the saturation point of FA on lowering Hcy levels. Our study also identified that when the FA dosage is equal to 0.8 mg/day, the biotransformation capacity of FA into 5-MTHF in humans is saturated, and the effect of FA on reducing Hcy is also basically saturated.

This study also revealed individual characteristics that may modify the FA supplementation and UMFA association. There was a significant interaction between FA supplementation dosage and age on UMFA levels (**Supplementary Table 3**). Compared with participants aged ≥65.4 years, significantly lower UMFA levels (mean: 17.9 vs. 21.6, $p < 0.001$) were found among those aged <65.4 years. It is likely that aging may slow down the absorption and metabolism of FA: as we age the older the age, the weaker the FA absorption declines, and metabolism weakens and the higher the UMFA levels increase. M Wolters et al. considered that atrophic gastritis could result in declining gastric acid and pepsinogen secretion, and hence decreasing the intestinal digestion and absorption of both B vitamins (i.e., vitamin B12 and FA), wherein atrophic gastritis occurred with a frequency of approximately 20–50% in the elderly subjects (26). There was also a significant interaction effect between FA supplementation and BMI on UMFA levels. Compared with participants with BMI ≥ 24.4, significantly higher UMFA levels were found among those with BMI < 24.4 (Mean: 22.8 vs. 16.7, $p < 0.001$). This indicates that people of different BMI have different FA requirements, which is consistent with the results reported in the previous literature (27). One explanation for this observation is that, as body size increases, the distribution of folate changes, resulting in changes of freely available plasma/serum folate and folate in the cells (28, 29).

Overall, our study provides a significant contribution to the literature on FA supplementation and UMFA levels in hypertensive adults. The research findings have several practical implications for clinicians, public health professionals, and policymakers for developing more effective interventions and strategies to reduce the risk of UMFA accumulation and its potential adverse health outcomes.

The research highlights the importance of regularly monitoring FA supplementation in patients with hypertension. However, attention should be paid to the limitations of the present study. We did not compare the correlation between FA intake and circulating UMFA among participants from different racial groups or ethnicities or for individuals under 45 years of age. It is important for future research to explore the optimal dosage of FA supplementation in other populations with different characteristics to investigate the effects of long-term, high-dosage FA intake on UMFA levels and related health outcomes.

Conclusion

This study, utilizing data from a large, randomized nutrition trial, showed a positive, non-linear, dosage-response relationship between FA supplementation ranging from 0 mg to 2.4 mg and circulating UMFA levels in Chinese adults with H-type hypertension. Our findings indicate that, on average, supplementation with 0.8 mg/day FA appears to be an optimal dosage in balancing efficacy vs. UMFA levels.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the Ethics Committee of The Second Affiliated Hospital of Nanchang University. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

PC, JJ, SL, XQ, and XX designed the research. PC, YS, NZ, YW, ZZ, QH, BW, LL, XH, XC, GT, YD, and HZ conducted the research. PC, XQ, SS, and ZZ collected and analyzed the data. PC, LT, ZZ, and QH drafted the manuscript. All authors read and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2023.1191610/full#supplementary-material

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EDITED BY
Iain Brownlee,
Northumbria University, United Kingdom

REVIEWED BY
Leila Itani,
Beirut Arab University, Lebanon
Susmita Sinha,
Khulna City Medical College and Hospital, Bangladesh

*CORRESPONDENCE
Sohyun Park
✉ sopark@hallym.ac.kr

†These authors have contributed equally to this work and share first authorship

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Higher consumption of ultra-processed food is associated with cardiovascular risk in Korean adults: KNHANES 2016–2018

Sukyoung Jung[1†], Eunjin Jang[2,3†], Hyeongyeong Lee[2,3], Jee Young Kim[4] and Sohyun Park[2,3*]

[1]Chungnam National University Hospital Biomedical Research Institute, Daejeon, Republic of Korea, [2]Department of Food Science and Nutrition, Hallym University, Chuncheon, Republic of Korea, [3]The Korean Institute of Nutrition, Hallym University, Chuncheon, Republic of Korea, [4]National Food Safety Information Service, Seoul, Republic of Korea

Background: Excessive consumption of ultra-processed foods (UPFs) has been linked to an increased risk of cardiovascular disease. We aimed to investigate the association between the percentage of energy intake from UPFs and the American Heart Association's cardiovascular health (CVH) metrics in Korean adults.

Methods: This study analyzed adults aged 40years and older using data from the Korean National Health and Nutrition Examination Survey 2016–2018 (*n*=9,351). All foods or beverages reported in a 24-h dietary recall were categorized using the NOVA system, and the percentage of energy from UPFs was calculated. Each CVH metric was scored 0–2 (poor, intermediate, ideal). The sum of six component scores was classified as inadequate, average, or optimum. Multinomial logistic regression models were used to estimate the covariate-adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for inadequate and average CVH versus optimum CVH.

Results: The mean percentage of energy from UPFs was 24.2%. After adjusting for covariates, participants in the highest UPF quartile had 26% higher odds of having inadequate CVH than those in the lowest quartile (OR 1.26, 95% CI 0.94–1.69, *P*-trend = 0.03). The percentage of energy from UPFs was positively associated with current smoking, physical inactivity, body mass index, and total cholesterol and was inversely associated with blood pressure and fasting glucose.

Conclusion: The percentage of energy from UPFs accounted for one-fourth of total calorie intake in Korean adults aged 40 years and older. Higher UPF consumption was associated with poorer CVH, underscoring the potential of limiting UPF consumption as a preventative measure for cardiovascular diseases.

KEYWORDS

ultra-processed foods, cardiovascular health, Korea National Health and Nutrition Examination Survey, Korea, odds ratio

Introduction

Cardiovascular diseases (CVDs) are the leading cause of death globally, responsible for 32% of all deaths in 2019 (1). In Korea, heart disease is the second leading cause of death in 2019, accounting for 59.6 and 61.3 deaths per 100,000 population for males and females (2). To monitor and improve CVD rates, the American Heart Association (AHA) has developed seven

cardiovascular health (CVH) metrics consisting of smoking status, physical activity, healthy diet score, body mass index, total cholesterol, blood pressure, and fasting glucose (3). These metrics align with the leading modifiable global CVD risk factors, according to the Global Burden of Disease Study (4). Research indicates that having more ideal CVH metrics is associated with a considerably lower risk of CVD incidence and mortality (5, 6).

Among the behavioral risk factors for CVD, dietary factors contribute the most to CVD mortality (4). Ultra-processed foods (UPFs) have drawn attention due to their harmful impact on health and increasing consumption (7). UPFs, as defined by NOVA, are often energy-dense, high in sugar, unhealthy fat, and salt, and low in fiber, protein, vitamins, and minerals (8). Examples include sweetened beverages, energy drinks, packaged snacks, processed cheese, instant sauces, nuggets, sausages, hot dogs, and ready-to-eat foods (8). Although UPFs are convenient to eat, tasty, and inexpensive (8), a growing body of evidence indicates their negative effects on health. According to previous studies, the consumption of UPFs is associated with lower nutritional quality of diets (9) and higher risks of chronic disease incidence including type 2 diabetes (10), cancer (11), cardiovascular disease (12), as well as mortality (13), and metabolic conditions including overweight and obesity (14), dyslipidemia (15), and hypertension (16).

Few studies have examined the relationship between UPF intake and CVH metrics, which assess cardiovascular risk comprehensively. In the United States, two studies have found an inverse association between UPF consumption and CVH metrics in both adults and adolescents (17, 18). Given an increasing trend in UPF consumption (19) and the burden of CVDs in Korea (2), it is necessary to examine the association between UPF consumption and CVH. Therefore, this study aimed to investigate the association between the percentage of energy intake (%E) from UPFs and the AHA's CVH metrics (excluding diet) in Korean adults aged 40 years and older, using data from the Korea National Health and Nutrition Examination Survey (KNHANES) 2016–2018. We hypothesized that higher UPF consumption would be associated with poorer CVH.

Methods

Study population

The KNHANES, administered by the Korea Disease Control and Prevention Agency, is an ongoing, cross-sectional, and nationally representative survey to monitor the health and nutritional status of the noninstitutionalized civilian population in Korea (20). To ensure the representativeness of the noninstitutionalized Korean population, KNHANES used a complex and multistage probability sampling design (20). KNHANES data collection includes health interviews, health examinations, and nutrition surveys. More information on the rationale, design, and methods of the KNHANES is detailed elsewhere (20). For the 7th KNHANES (2016–2018), 31,689 persons were screened, and 24,269 participants completed at least one or more surveys of health interviews, health examinations, and nutrition surveys (response rate: 76.6%) (21).

Among 13,959 adults aged 40 years and older, we excluded participants if they had the following conditions: missing information on dietary data or implausible energy intakes (<500 kcal or > 5,000 kcal) ($n = 2,430$); pregnant or lactating ($n = 4$); self-reported severe diseases ($n = 1,290$); missing information on CVH metrics ($n = 884$). The final analytic sample included 9,351 adults (Supplementary Figure 1). The study protocol was approved by the Institutional Review Board of Hallym University (HIRB-2021-087-R-CR).

Assessment of ultra-processed food consumption

The nutrition survey was administered 1 week after the health interviews and examinations. Trained dieticians collected dietary information (description, quantity, and time and place of eating) on all foods and beverages consumed using a 24-h dietary recall. The respondents reported the quantity of consumed foods and beverages in units of volume with the assistance of standard measuring tools and/or guides. The multiple-pass method was used to obtain a complete food recall while minimizing respondent burden. Daily energy and nutrient intakes were estimated from the Ninth Edition of the Korean Food Composition Table of the Rural Development Administration (22).

A NOVA classification system was used to classify all reported foods or underlying ingredients of mixed dishes into one of four food categories based on the extent and purpose of food processing. In NOVA, the first group indicates unprocessed or minimally processed foods; the second group indicates processed culinary ingredients; the third group indicates processed foods; and the fourth group indicates UPFs (23). A Korean NOVA system, based on the matrix maintenance of natural foods and traditional eating experiences, was used to account for the uniqueness of Korean cuisine (dish-based with multiple ingredients) (24). For example, Korean fermented sauces (e.g., soybean paste) can be classified as UPFs in the original NOVA system, while they could be classified as either ultra-processed or processed foods in the Korean NOVA system, depending on whether they are produced through mass production or traditionally. Detailed examples are available elsewhere (24). During the 24-h dietary recall interview, participants reported consuming 3,894 items in 2016–2018. Unprocessed or minimally processed foods included raw vegetables, fruits, meats, and grains (966 items). Processed culinary ingredients comprised condiments and oils (247 items). Processed foods include soups, stews, kimchi, and grilled or marinated vegetables and meat (504 items). Ultra-processed foods included mass-produced bread, snacks, soft drinks, and noodles (2,177 items).

Two investigators (S.J. and JY.K.) classified all foods and ingredients of mixed dishes into one of the four food groups in NOVA, and the entire classification was thoroughly cross-checked against one another. For dishes with multiple ingredients, we first sorted out the main ingredient in the mixed dishes using a standard recipe for Korean dishes and the ingredient database. The main ingredient was identified as the ingredient with the largest proportion of the total amount of dishes. When disagreement occurred, we then checked the following: (1) the product name and manufacturer information to identify the raw ingredients; and (2) the amount of sodium or sugar in such items based on the food code in the nutrient database. This is due to the likelihood that more processed foods tend to have more sodium and/or sugar content. All food items and ingredients were mutually exclusively classified into one of the four NOVA groups. Our focus was on the fourth group of the NOVA classification that is UPFs.

Calculation of cardiovascular health metrics

The CVH metrics were based on the Life's Simple 7 set of risk factors proposed by the AHA (3). Originally, there were seven health components, including smoking status, physical activity, healthy diet score, body mass index, total cholesterol, blood pressure, and fasting plasma glucose (3). In this study, the main exposure of interest was UPF consumption, and thus the diet component was omitted from the final CVH metrics calculation. We used the definitions of optimum, average, and inadequate CVH as described in Supplementary Table 1.

Smoking status

Current smokers were defined as those who are currently smoking cigarettes every day or some days. Former smokers were defined as those who had smoked at least 100 cigarettes in their lifetime but had quit for less than 12 months. Never smokers were defined as those who had smoked no more than 100 cigarettes in their lifetime or those who had smoked at least 100 cigarettes in their lifetime but had quit for more than 12 months. The status of never smokers, former smokers, and current smokers was defined as ideal, intermediate, and poor, respectively.

Physical activity

Participants reported the frequency and duration of any physical activity they engaged in for transportation, work, leisure, or exercise in a typical week. In KNHANES 2016–2018, there are five modes of activities, including vigorous work-related activity, moderate work-related activity, walking or bicycling, vigorous leisure-time activity, and moderate leisure-time activity. Physical activity (minutes per week) was quantified for each mode of activity by multiplying the frequency and duration. The physical activity component calculation used the following definitions: ideal was defined as "≥75 min of vigorous activity" or "≥150 min of moderate activity" or "≥150 min of combined moderate and vigorous physical activity"; intermediate was defined as more than 0 min of physical activity but less than recommendations; and poor was defined as 0 min of physical activity per week.

Body mass index

Anthropometric measurements were collected throughout the health examination using standardized examination procedures and calibrated equipment (20). Standing height (cm) was measured on a stadiometer, and body weight (kg) was measured with a metric weight scale, with sample participants in light clothing. Body mass index (BMI) was computed using the ratio of measured weight (kg) to standing height squared (m^2). The Korean Society for the Study of Obesity defined 18–22.9 of BMI as normal and ≥ 25 of BMI as obesity (25). Thus, the BMI component calculation used the following definitions: ideal was defined as <23; intermediate was defined as 23–24.9; and poor was defined as ≥25.

Total cholesterol

Ideal was defined as less than 200 mg/dL of untreated total cholesterol level; intermediate was defined as 200–239 mg/dL of untreated total cholesterol level or taking cholesterol-lowering medication and being treated to goal (<240 mg/dL); and poor was defined as ≥240 mg/dL of untreated total cholesterol level or taking cholesterol-lowering medication but not being treated to goal.

Blood pressure

Ideal was defined as untreated systolic blood pressure (SBP) <120 mmHg and untreated diastolic blood pressure (DBP) <80 mmHg; intermediate was defined as SBP 120–139 mmHg or DBP 80–89 mmHg or taking antihypertensive medication and being treated to goal (SBP <140 mmHg and DBP <90 mmHg); and poor was defined as SBP ≥140 mmHg or DBP ≥90 mmHg or taking antihypertensive medication but not being treated to goal.

Fasting plasma glucose

Ideal was defined as less than 100 mg/dL of untreated fasting plasma glucose level; intermediate was defined as 100–125 mg/dL of untreated fasting plasma glucose level or taking insulin or medication to lower blood glucose and being treated to goal (<126 mg/dL); and poor was defined as ≥126 mg/dL of untreated fasting plasma glucose level or taking medication for diabetes but not being treated to goal.

Scoring

Each of the CVH metric components received a score of 2 if categorized as ideal, 1 if categorized as intermediate, and 0 if categorized as poor. A total score was calculated by summing the scores of six components (range: 0–12). For the analysis, the total score was classified into three groups: inadequate (0–4), average (5–8), or optimum (9–12) (17).

Assessment of covariates

Potential covariates included age (40–49, 50–59, or ≥ 60 years), sex (male or female), residential area (urban or rural), education level (less than high school graduate, high school graduate or higher), monthly household income (quartiles of equivalized household income), and marital status (married or not).

Statistical analysis

In this study, UPF consumption was presented as %E from UPFs. To describe the general characteristics of the study participants, we presented the weighted means and their standard errors (SEs) for continuous variables and the weighted prevalence and their SEs for

categorical variables by CVH metrics categories (inadequate, average, or optimum). The significance of differences between CVH metrics categories was assessed by a student *t*-test for continuous variables and a chi-square test for categorical variables.

The restricted cubic spline model was fitted with 3 knots determined at the 5th, 50th, and 95th percentiles to test deviation from a linear association between %E from UPFs and CVH scores (26); no evidence of a nonlinear association was observed ($p = 0.58$ for nonlinearity). We also presented the adjusted differences in CVH scores by using the median of the lowest UPF consumption quartile (5.2% of calories from UPFs) as a reference (Supplementary Figure 2).

Multinomial logistic regression models were used to estimate the covariate-adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for inadequate and average CVH versus optimum CVH, comparing quartiles 2, 3, and 4 with quartile 1 of %E from UPFs. We also examined the association between %E from UPFs and individual components of CVH metrics. We presented the covariate-adjusted ORs and 95% CIs for poor and intermediate individual CVH components versus ideal, comparing quartiles 2, 3, and 4 with quartile 1 of %E from UPFs. To assess potential linear trends, the median %E from UPFs in each quartile was treated as a continuous variable in multinomial logistic regression models. We presented two adjusted models: (1) an age and sex-adjusted model; and (2) a multivariable-adjusted model including age, sex, residential area, high school graduate, monthly household income quartiles, and marital status. When analyzing individual CVH metrics separately, the multivariable-adjusted model additionally included other individual CVH components except for itself.

Potential interaction effects of %E from UPFs and selected sociodemographic covariates were tested by including the cross-product term of UPF consumption and each covariate. The only significant interaction found was between education and %E from UPFs ($p = 0.04$); consequently, estimates are presented overall and by education level (less than high school graduate vs. high school graduate or above).

For all analyses, sample weights accounting for the complex sampling design of the KNHANES were incorporated. SAS software (version 9.4, SAS Institute Inc., Cary, NC, United States) was used to analyze the data. All tests were two-sided, and the level of significance was set at 0.05.

Results

Participant characteristics

General characteristics of the sample by CVH metrics categories are shown in Table 1. Of the 9,351 participants, the mean age was 56.3 years (≥65 years, 24.3%), 51.5% were females, 84.8% were urban residents, 67.8% were at least high school graduates, 32.7% had the highest quartile of monthly household income, and 80.3% were married. The weighted prevalence of inadequate, average, and optimum CVH was 6.4, 55.0, and 38.7%, respectively. Participants with lower CVH scores were more likely to be male, reside in rural areas, have lower levels of education and monthly household income, and be unmarried.

Associations between UPF consumption and CVH

Table 2 shows the covariate-adjusted association between %E from UPFs and CVH. The mean %E from UPFs was 24.2% (with a median of 5.2% in quartile 1 and 45.6% in quartile 4). In the multivariable-adjusted model, participants in the highest UPF quartile had 26% higher odds of inadequate CVH than those in the lowest quartile (OR 1.26, 95% CI 0.94–1.69, *P*-trend = 0.03). After adjusting for confounders, the highest UPF consumption (quartile 4) was associated with 14% higher odds of average CVH compared to quartile 1, but was not statistically significant (OR 1.14, 95% CI 0.97–1.33, *P*-trend = 0.08). The age- and sex-adjusted results were not statistically significant.

Figure 1 shows the covariate-adjusted association between %E from UPFs and each individual CVH metric. The percentage of energy from UPFs was positively associated with poor CVH, including current smoking, physical inactivity, higher BMI, and higher total cholesterol, and was inversely associated with blood pressure and fasting glucose. The percentage of energy from UPFs was only positively associated with an intermediate CVH for BMI.

Subgroup analysis

Education-level stratified analysis shows that the positive association between %E from UPFs and inadequate CVH was greater for participants with a lower education level than those with a higher education level (p-interaction = 0.04) (Table 3). Participants with a lower education level in the highest quartile of %E from UPFs had 1.79 times higher odds of inadequate CVH than those in the lowest quartile (OR 1.79, 95% CI 1.11–2.89, p-trend = 0.02). Participants with a higher education level in the highest quartile of %E from UPFs had 1.28 times higher odds of inadequate CVH than those in the lowest quartile (OR 1.28, 95% CI 1.06–1.55, *P*-trend = 0.84).

Discussion

In this cross-sectional study of Korean adults, we observed a positive association between %E from UPFs and inadequate CVH after adjusting for sociodemographic characteristics. A higher %E from UPFs was associated with poorer individual CVH metrics, specifically current smoking, physical inactivity, higher BMI, and higher total cholesterol. Unexpectedly, there was an inverse association between UPF consumption and blood pressure and fasting plasma glucose. When stratified by education level, a stronger positive association between UPF consumption and inadequate CVH was observed in participants with a lower education level than in those with a higher education level.

A previous cross-sectional study reported that a higher %E from UPFs is linearly associated with 1.4–2.6 times higher odds of inadequate CVH in US adults (17). In our study, comparing quartiles 2, 3, and 4 with quartile 1 of %E from UPFs, the multivariable-adjusted ORs for inadequate CVH (compared with optimum) were 0.8, 0.8, and 1.3, respectively. This discrepancy may be explained by the

TABLE 1 General characteristics by cardiovascular health metric categories among Korean adults aged 40 years and older, KNHANES 2016–2018[a].

	Overall (*n* = 9,351)	CVH score 0–4 (*n* = 548)	CVH score 5–8 (*n* = 5,197)	CVH score 9–12 (*n* = 3,606)	*p* value[b]
Demographic					
Age, y	56.3 ± 0.2	54.3 ± 0.5	57.7 ± 0.2	54.7 ± 0.3	<0.0001
Age group, ≥65 years	24.3 (0.7)	16.4 (1.6)	28.1 (0.8)	20.2 (0.9)	<0.0001
Sex, females	51.5 (0.5)	24.5 (2.0)	45.4 (0.8)	64.6 (0.9)	<0.0001
Residency					
Urban	84.8 (1.4)	80.8 (2.5)	82.4 (1.6)	89.0 (1.2)	<0.0001
Rural	15.2 (1.4)	19.2 (2.5)	17.6 (1.6)	11.0 (1.2)	
Socioeconomic					
Education level					
Elementary school	20.6 (0.6)	20.1 (2.0)	24.5 (0.8)	15.1 (0.7)	<0.0001
Middle school	11.7 (0.4)	14.7 (1.8)	12.4 (0.6)	10.2 (0.6)	
High school	33.1 (0.7)	33.2 (2.4)	33.0 (0.9)	33.1 (1.1)	
College and higher	34.7 (1.0)	32.1 (2.5)	30.1 (1.0)	41.6 (1.3)	
Household income					
Q1	17.4 (0.7)	19.1 (1.8)	19.8 (0.8)	13.8 (0.8)	<0.0001
Q2	22.5 (0.7)	17.7 (1.8)	24.0 (0.8)	21.1 (0.9)	
Q3	27.4 (0.7)	34.8 (2.5)	26.8 (0.8)	27.1 (0.9)	
Q4	32.7 (1.0)	28.4 (2.6)	29.5 (1.0)	37.9 (1.4)	
Married[c]	80.3 (0.6)	79.0 (2.2)	78.1 (0.8)	83.7 (0.8)	<0.0001

CVH, cardiovascular health (excluding diet component); KNHANES, Korea National Health and Nutrition Examination Survey.[a]All results are weighted and presented as mean and standard error (SE) for continuous variables and percentage and SE for categorical variables.
[b]*p* values were determined by *t*-test for continuous variables and chi-square test for categorical variables.
[c]Married included participants who were married and cohabiting.

TABLE 2 Weighted odds ratios (95% confidence intervals) for cardiovascular health metrics across quartiles of ultra-processed food consumption among adults aged 40 years and older, KNHANES 2016–2018[a].

	Quartiles of percentages of calories from UPFs				
	Q1	Q2	Q3	Q4	*P* trend[b]
N	2,337	2,338	2,338	2,338	
Median of percentage of calories from UPFs (%)	5.2	19.9	26.6	45.6	
No. of cases (inadequate CVH) (%)	141 (6.0)	125 (5.4)	133 (5.7)	149 (6.4)	
No. of cases (average CVH) (%)	1,374 (58.9)	1,311 (56.1)	1,253 (53.6)	1,259 (53.9)	
Age and sex-adjusted					
Inadequate CVH vs. optimum	1.00 (reference)	0.72 (0.53–0.99)	0.76 (0.56–1.03)	1.11 (0.83–1.48)	0.17
Average CVH vs. optimum	1.00 (reference)	0.99 (0.85–1.15)	0.96 (0.82–1.12)	1.07 (0.92–1.24)	0.36
Multivariable-adjusted[c]					
Inadequate CVH vs. optimum	1.00 (reference)	0.77 (0.55–1.06)	0.84 (0.62–1.15)	1.26 (0.94–1.69)	0.03
Average CVH vs. optimum	1.00 (reference)	1.02 (0.87–1.19)	1.02 (0.87–1.19)	1.14 (0.97–1.33)	0.08

KNHANES, Korea National Health and Nutrition Examination Survey; UPF, ultra-processed food; Q, quartile; CVH, cardiovascular health (excluding diet component). [a]Optimum CVH: CVH metrics scores 9–12; average CVH: CVH metrics scores 5–8; inadequate CVH: CVH metrics scores 0–4.
[b]*p* for trends were determined by treating the median value of percentage of energy intake from UPFs as a continuous variable using multinomial logistic regression models.
[c]Multivariable-adjusted model was adjusted for age (40s, 50s, and ≥60 y), sex (males, females), residential area (urban or rural), high school graduate (yes, no), monthly household income quartiles, and marital status (yes, no).

considerable differences in the amount of UPF consumption between US and Korean adults. The midpoint of %E from UPFs ranged from 40.4 to 70.5% in US adults (17), while it ranged from 5.2 to 45.6% in Korean adults. Considerably lower levels of UPF consumption among Korean adults may not be enough to detect significant associations with CVH.

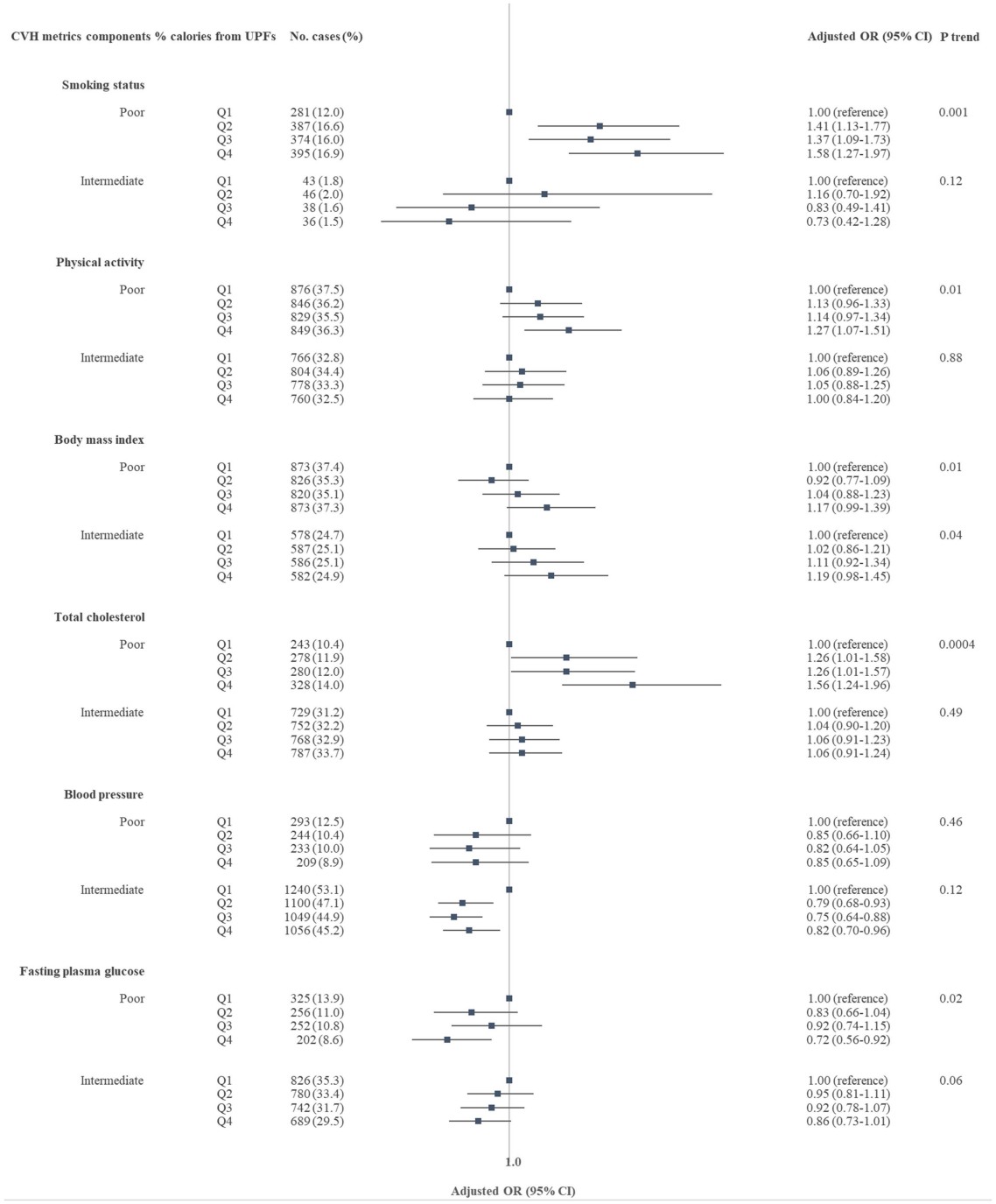

FIGURE 1
Adjusted odds ratios (95% confidence intervals) for poor or intermediate cardiovascular health metric (CVH) of each individual CVH metric associated with percentage of energy intake from ultra-processed foods, Korean adults aged 40 years and older, KNHANES 2016–2018. KNHANES, Korea National Health and Nutrition Examination Survey; UPFs, ultra-processed foods; Q, quartile; CVH, cardiovascular health (excluding diet component). Multinomial logistic regression models were used to estimate odds ratios and corresponding 95% CIs. All estimated were weighted and adjusted for age (40s, 50s, and ≥ 60 y), sex (males, females), residential area (urban or rural), high school graduate (yes, no), monthly household income quartiles, marital status (yes, no), and other individual CVH components except itself. The median value of percentages of energy intake from UPFs were 5.2% for quartile 1, 19.9% for quartile 2, 26.6% for quartile 3, and 45.6% for quartile 4, respectively.

Regarding individual metabolic CVH metrics, collective evidence suggests a positive association between UPF consumption and the risk of obesity, type 2 diabetes, and hypertension (10, 14, 16). A cohort study in older Spanish adults showed that higher UPF consumption is associated with a higher risk of dyslipidemia incidence (15). In Korea, high UPF consumption is positively associated with obesity only in women and an increased prevalence of elevated blood pressure in adults (27, 28). In our sample, there were positive associations between %E from UPFs and BMI and total cholesterol. As well supported both in the literature (8, 9) and our study, UPFs are high in energy density, trans and saturated fats, sodium, and sugar, but low in dietary fiber and several vitamins and minerals. Biological plausibility

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TABLE 3 Weighted odds ratios (95% confidence intervals) for cardiovascular health metrics across quartiles of ultra-processed food consumption and education level, Korean adults aged 40 years and older, KNHANES 2016–2018[a].

Subgroup	Percentages of energy intake from UPFs quartiles					
	Q1	Q2	Q3	Q4	*P* trend[b]	*p* interaction[c]
Education level						0.04
Less than high school						
N	1,279	967	806	699		
No. of cases (inadequate CVH) (%)	69 (5.4)	55 (5.7)	53 (6.6)	49 (7.0)		
No. of cases (average CVH) (%)	820 (64.1)	635 (65.7)	519 (64.4)	443 (63.4)		
Multivariable-adjusted[c]						
Inadequate CVH vs. optimum	1.00 (reference)	1.30 (0.79–2.14)	1.24 (0.77–2.01)	1.79 (1.11–2.89)	0.02	
Average CVH vs. optimum	1.00 (reference)	1.24 (0.98–1.56)	1.31 (1.04–1.65)	1.10 (0.87–1.40)	0.39	
High school graduate or above						
N	1,048	1,366	1,532	1,635		
No. of cases (inadequate CVH) (%)	70 (6.7)	70 (5.1)	80 (5.2)	100 (6.1)		
No. of cases (average CVH) (%)	549 (52.4)	673 (49.3)	734 (47.9)	813 (49.7)		
Multivariable-adjusted[d]						
Inadequate CVH vs. optimum	1.00 (reference)	0.87 (0.71–1.06)	0.86 (0.70–1.04)	1.28 (1.06–1.55)	0.84	
Average CVH vs. optimum	1.00 (reference)	0.88 (0.74–1.04)	0.76 (0.64–0.90)	1.02 (0.86–1.22)	0.58	

KNHANES, Korea National Health and Nutrition Examination Survey; UPF, ultra-processed food; Q, quartile; CVH, cardiovascular health (excluding diet component). [a]Optimum CVH: CVH metrics scores 9–12; average CVH: CVH metrics scores 5–8; inadequate CVH: CVH metrics scores 0–4.
[b]*p* for trends were determined by treating the median value of percentage of energy intake from UPFs as a continuous variable using multinomial logistic regression models.
[c]*p* value for interaction was determined by including the cross-product term of UPF consumption and education level.
[d]Multivariable-adjusted model was adjusted for age (40s, 50s, and ≥ 60 y), sex (males, females), residential area (urban or rural), monthly household income quartiles, and marital status (yes, no).

between unfavorable profiles of these nutrients in UPFs and metabolic risk factors for CVD includes increased oxidative stress and inflammation, enhancing visceral adipocyte hypertrophy, and glucose intolerance (29–31). Furthermore, high-intensity flavorings and low fiber content may disrupt digestion and satiety, which facilitate overeating and inhibit the glycemic response (32, 33). Some UPFs also contain harmful materials added during processing (e.g., food additives) and chemicals added while packaging (e.g., bisphenol A), which may be associated with negative health outcomes (34, 35).

In contrast to our hypothesis, we observed an inverse association between UPF consumption and blood pressure and fasting blood glucose. One possible explanation for this finding is that UPFs may include some dairy products (e.g., yogurt), which may play a beneficial role in diabetes or high blood pressure (36–38). In our sample, participants in the highest UPF consumption quartile group are likely to consume more dairy products than those in the lowest quartile group (Q1 vs. Q4, 53.1 g/day vs. 88.5 g/day) (Supplementary Table 2). Alternatively, it is possible that individuals with diabetes or hypertension may change their diets to be healthier and reduce UPF consumption, leading to potential reverse causation and biasing our findings. Further studies, using a cohort study design, are warranted to address this issue.

We found that the positive association between UPF consumption and inadequate CVH was more prominent in participants with lower education levels compared to those with higher education levels. Although participants with higher education levels consumed a higher %E from UPFs, it is possible that they consume more "premium" UPFs that tend to have healthier ingredients and functional attributes, such as granola with probiotics, than traditional UPFs. Premium UPFs can be expensive, and individuals with lower sociodemographic status may not have easy access to or cannot afford these products (39, 40). Further research is necessary to explore this matter and better understand the role of specific ingredients in the UPFs consumed, particularly in populations with different socioeconomic backgrounds.

This study has strengths. To our knowledge, this study is the first to evaluate the association between UPF consumption and CVH metrics in a nationally representative sample of Korean adults aged 40 years and older. A Korean NOVA system used in this study, based on the matrix maintenance of natural foods and traditional eating experiences, allowed us to consider the characteristics of Korean cuisine, which is dish-based with the combination of many different specific ingredients, and thus classify UPFs more accurately (24). There were several limitations. First, our findings were based on a

cross-sectional survey, which precludes making causal inferences. Second, despite adjusting for several covariates, the results might still have been impacted by unidentified or unmeasured variables. Third, the use of only one 24-h dietary recall may not accurately reflect an individual's usual intake due to day-to-day variation (a source of within-person error). Fourth, there are inevitable measurement errors due to the use of several self-reported variables (e.g., smoking status). Fifth, the simplistic definition, one of the unresolved issues of the NOVA classification system (41), may make it challenging to differentiate premium UPFs from conventional ones.

In conclusion, a higher %E from UPFs may be associated with poorer CVH in a nationally representative sample of Korean adults. The positive association between UPF consumption and CVH was more evident among those with a lower education level. Although our study is cross-sectional and cannot establish causality, our results could be used as evidence to recommend limiting UPF consumption for CVH improvement. Further studies with a prospective study design are required to establish a causal relationship, and investigating the underlying mechanisms of the association between UPF consumption and CVH can provide more definite evidence.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the Institutional Review Board of Hallym University. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

SJ: methodology, data curation, formal analysis, visualization, writing – original draft preparation, and writing – reviewing and editing. EJ and HL: writing – original draft preparation. JK: data curation and methodology. SP: conceptualization, writing – reviewing and editing, and supervision. All gave final approval and agreed to be accountable for all aspects of ensuring integrity and accuracy. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2023.1219216/full#supplementary-material

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EDITED BY
Mirko Marino,
University of Milan, Italy

REVIEWED BY
Ziwei Wang,
Stanford University, United States
Annalisa Giosuè,
Federico II University Hospital, Italy

*CORRESPONDENCE
Gholamreza Askari
✉ askari@mui.ac.ir

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Dietary inflammatory index in relation to severe coronary artery disease in Iranian adults

Zahra Dadaei[1,2], Mohammad Bagherniya[1], Omid Sadeghi[1], Alireza Khosravi[3], Shahin Shirani[4] and Gholamreza Askari[1]*

[1]Nutrition and Food Security Research Center, Department of Community Nutrition, School of Nutrition and Food Science, Isfahan University of Medical Sciences, Isfahan, Iran, [2]Student Research Committee, Isfahan University of Medical Sciences, Isfahan, Iran, [3]Department of Community of Cardiology, Isfahan Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran, [4]Hypertension Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran

Background: Limited findings are available on the relationship between dietary inflammation index (DII) and severe coronary artery disease (CAD). Considering the high prevalence of CAD and its complications, we examined the relationship between DII and CAD.

Methods: This cross-sectional study was conducted on 275 adults who underwent elective angiography. Severe coronary artery disease was measured by the gensini scoring system. DII was measured by a valid semi-quantitative 168-item food frequency questionnaire (FFQ). Blood samples were collected after 12 h of fasting to measure serum lipid profile and quantitative C-reactive protein (q-CRP) levels. Binary logistic regression was used to calculate the odds (OR) and 95% confidence interval (CI).

Results: People in the last tertile of the DII had a higher chance of suffering from severe coronary artery disease (OR: 3.71; 95% CI: 1.97–6.98), hypercholesterolemia (OR: 2.73; 95% CI: 5.03–1.48), reduced HDL-cholesterol levels (OR: 3.77; 95% CI: 9.34–1.52), and hypertension (OR: 1.93; 95% CI: 3.49–1.06) compared to people in the first tertile. After adjusting for confounding factors, the relationship remained significant. A direct and significant relationship was observed between the DII and increased q-CRP levels, which disappeared after adjusting for confounding factors in the adjusted model (OR: 2.02; 95% CI: 0.86–4.73).

Conclusion: This cross-sectional study showed a direct and linear relationship between following an anti-inflammatory diet and decreasing the chance of severe CAD. Therefore, it seems necessary to implement community-based educational programs to promote healthy nutrition in order to prevent CADs.

KEYWORDS

the financial support for conception, design, data analysis, dietary inflammation index, severe CAD, gensini scoring system

Introduction

Heart diseases and cardiovascular diseases (CVDs) are the most important cause of death in industrialized and developing countries (1). The prevalence of CVDs is increasing leading to mortality and reduced quality of life from childhood to old age (2). The World Health Organization reported that about 17.3 million deaths in 2008 were due to CVDs (30% of all deaths) and it is estimated that by 2030, there will be about 23.6 million deaths due to heart

diseases, especially stroke (3). Coronary artery disease (CAD) is the main cause of death and disability in the population of Iran and accounts for approximately 50% of deaths each year (4).

CAD is characterized by atherosclerosis in epicardial coronary arteries (5). The angiographic severity is important in the progression and prognosis of CAD, and gensini scoring is more reliable compared to other methods of grading its severity. In addition, gensini scoring provides a quantitative variable compared to other systems, which is more valid in statistical analyses (6, 7). Age, gender, and family history are unchangeable risk factors, and tobacco use, diabetes, lack of physical activity, unhealthy diet, and stress are modifiable CAD risk factors (5). Diet plays an important role in regulating chronic inflammation, lipid, and blood pressure dysregulation, and increasing the risk of CVDs (8–13). The dietary inflammatory index (DII) is a dietary index designed by South Carolina University researchers to measure the inflammatory potential of diet (14). In previous studies, the DII score obtained from the food frequency questionnaire (FFQ) was significantly related to inflammatory biomarkers so that higher DII scores (indicating a diet causing more inflammation) showed a direct relationship with interleukin-6 (IL-6), tumor necrosis factor receptor 2 alpha (TNFα-R2), and C-reactive protein (CRP) levels (15).

Eating healthy diets reduces the risk of developing CAD (16, 17). Also, lowest adherence to an anti-inflammatory diet and the risk of CVDs are associate (18, 19). However, it has not been confirmed in some studies and different findings have been reported in men and women (20, 21). No study has investigated the relationship between DII and severe CAD using the gensini score in IRAN; therefore, considering the high prevalence of CVD and related costs imposed on societies, it is of considerable importance to provide new strategies to prevent the disease and find effective treatments with fewer complications. The purpose of this study was to investigate the relationship between DII and severe CAD in adults. Accordingly, by understanding the dietary patterns of these patients, we can provide practical recommendations and take a step toward the health of society by promoting the correct dietary pattern.

Materials and methods

Study design and participants

The current cross-sectional observational study was conducted on adults of both sexes as the target population in 2021. The sample size was calculated to be 217 people based on the formula for confidence interval of 95%, precision (d) of 10 and 63.8% prevalence of sever CAD based on similar articles (17), Since covid-19 pandemic was very prevalent during our data collection and the possibility of drop-out was high, we invited a total of 275 individuals, rather than 217 subjects, to participate in the study.

The subjects were selected from the patients admitted to the Elective Angiography Department of Shahid Chamran and Asgaria Hospital in Isfahan, one of the big central cities of Iran, aged 25 to 75 years and underwent diagnostic coronary angiography and were willing and able to participate in the study.

However, those following the exclusion criteria were excluded: (1) using supplements and anti-inflammatory drugs, (2) smoking and alcohol use, (3) following a special diet, a history of cancer, heart failure, heart attack, percutaneous coronary intervention (PCI), and coronary artery bypass grafting (CABG), stage 3 or higher chronic kidney disease, specific liver disease or receiving medication for liver disorders, immune system impairment, and AIDS, and (4) those with restrictions on receiving food by mouth for any reason. Written informed consent was obtained from all participants. Process and timeline of the study design is shown in Figure 1. The study protocol was approved by the Ethics Committee of Isfahan University of Medical Sciences (IR.MUI.RESEARCH.REC.1399.376).

Assessment of dietary intakes

Food intakes were evaluated using a semi-quantitative 168-item food questionnaire (FFQ) specifically designed and validated for Iranian adults (22). According to a previous study on its validity, the dietary intake of 132 middle-aged adults using FFQ was assessed in comparison to a 24-h dietary recall (24HR). The correlation coefficients between food intake obtained from FFQ and 24HR were 0.59 for fat, 0.55 for total energy intake, 0.65 for proteins, 0.65 for magnesium, and 0.67 for fiber. The reliability of the FFQ was also evaluated by comparing the consumption of nutrients obtained from the FFQ at two time points with an interval of 1 year. In general, this FFQ has reported a valid and reliable tool for evaluating the common dietary intakes in Iranian adults (22). The FFQ was completed by a senior nutritionist with a face-to-face interview and the frequency and amount of food consumed by the participants in the last year were reported. Then, using household criteria, the amount of consumed foods was converted into grams per day (23). Finally, all the food items were

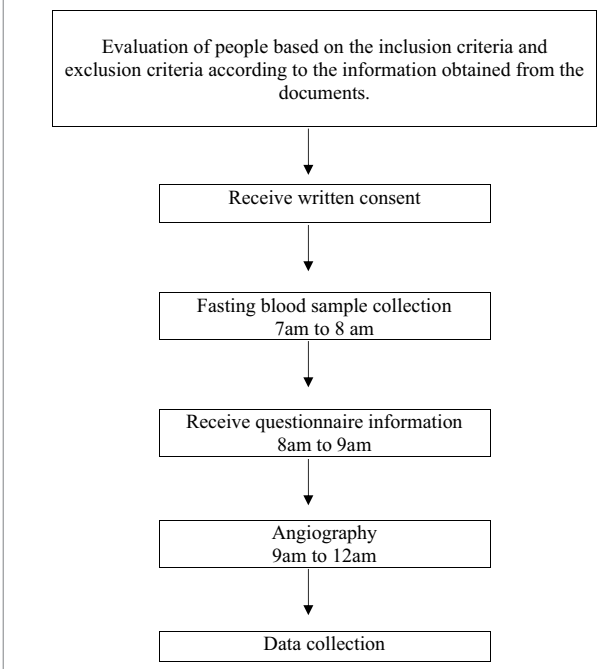

FIGURE 1
Process and timeline of the study design.

transferred to the Nutritionist IV (N4) software, and the daily consumption of energy and all the nutrients were calculated.

Evaluation of dietary inflammation index

The amounts of micronutrients to calculate the DII score were initially obtained as the mean and standard deviation of each food item. The z-score was obtained by subtracting the international standard average from the value derived from the FFQ and dividing it by the standard deviation. The z-score was then converted to a centered percentile score. The centered percentile score of each food item for each person was multiplied by the corresponding effect score of the food items (inflammatory potential for each food item) to obtain the DII score, and then by summing the score of food items for each person, the overall DII score was calculated (8). The nutritional items included energy, protein, total fat, Monounsaturated fatty acids (MUFA), polyunsaturated fatty acids(PUFAs), saturated fatty acids (SFAs), omega-6 fatty acids containing multiple double bonds, omega-3 fatty acids with multiple double bonds, trans fatty acid, cholesterol, carbohydrate, fiber, caffeine, vitamin A, beta-carotene, thiamine, riboflavin, niacin, vitamin B6, folate, vitamin B12, vitamin C, vitamin D, vitamin E, iron, magnesium, selenium, zinc, tea, garlic, onion, saffron, turmeric, ginger, pepper, thyme, rosemary, flavones, flavone 3l, flavonols, isoflavones, flavanones, anthocyanins, alcohol, and eugenol. A higher score reflects a diet with a higher degree of inflammation and vice versa (8). According to the items of the questionnaires and software used in this study, the DII with 32 items out of 45 reference items (except trans fatty acid, rosemary, saffron, ginger, thyme, flavones, flavone 3l, flavonols, isoflavones, flavanones, anthocyanins, alcohol, and eugenol) was calculated.

Evaluation of gensini score

Gensini score was calculated as mentioned earlier (24, 25). Those with a gensini score of 20 or more were considered to have severe coronary artery disease, which is roughly equivalent to a 70% or more blockage of the left anterior descending (LAD) artery (26, 27).

Assessment of biochemical markers

To evaluate the levels of blood lipids and q-CRP, 5 cc of fasting blood samples (12 h) were taken from the subjects. The blood samples were centrifuged for 10 min at 3000 rpm and the resulting serum was stored in a freezer at −20°C. Triglyceride (TG) and high-density lipoprotein cholesterol (HDL-C) concentrations were measured by enzymatic colorimetric method and total cholesterol concentration was also measured by a photometric method using French Cobus autoanalyzer (Pars Azmoun kit, Tehran, Iran). The concentration of LDL-C was also calculated using the Friedewald formula [LDL = TC − HDL − 1.5 (TG)] (28). The optimum value for total cholesterol was <200 mg/dl, for HDL was >40 mg/dl in men and > 50 mg/dl in women, and for LDL-C was <100 mg/dl and for TG < 150 mg/dl (29).

The serum level of q-CRP was measured quantitatively by the immunoturbidimetric method using the laboratory kit (Byrex Fox, Fars, Iran) with a cutoff point of 10 mg/L (30).

Assessment of other variables

Blood pressure (BP) was measured using a digital sphygmomanometer (OMRON, M3, HEM-7154-E, Japan) with an accuracy of 0.5 mmHg, twice for each participant after 5 min of resting time in a sitting position and their average was recorded (31). High blood pressure is considered as the average systolic blood pressure ≥ 130 mm Hg or the average diastolic blood pressure ≥ 80 mm Hg (31).

Anthropometric indicators, including weight (with light clothes and without shoes using a body composition analyzer (Tanita MC-780MA, Tokyo, Japan), with an accuracy of 0.1 kg) and height (without shoes using a non-elastic meter mounted on the wall) were measured. Body mass index (BMI/kg/m^2) was also calculated by dividing weight (kg) by the square of height (in meters).

Physical activity was evaluated using the International Valid Physical Activity Questionnaire (IPAQ) (32), which its validity and reliability have been measured in Iran (33). Demographic, socioeconomic characteristics, confounding and contextual variables, such as age, gender, education level, medical history, drug intake, and supplement use, were obtained using a general information questionnaire.

Statistical methods

The normal distribution of the variables was investigated using the Kolmogorov–Smirnov test. The values of quantitative and qualitative variables were presented as mean (± standard deviation) and percentage, respectively. First, subjects were ranked based on DII (energy-adjusted) tertiles. The chi-square test was used to compare qualitative variables and one-way analysis of variance (ANOVA) was used to compare quantitative variables in DII tertiles. Also, energy-adjusted dietary intakes of participants across tertiles of DII were evaluated by one-way analysis of variance (ANOVA). Binary logistic regression was used to report the odds ratio (OR) and 95% confidence interval (CI) for severe CAD, lipid profile, BP, and q-CRP in different DII tertiles in crude and adjusted models. In the adjusted model, age, sex, BMI, physical activity, medication use, medical history, number of family members, and education were adjusted. The first quartile of DII was considered the reference group in the crude and adjusted model. DII tertiles were considered as continuous variables to determine the P trend in binary logistic regression models. In addition, the raw and adjusted values (energy intake, age, sex, BMI, physical activity, taking medication, medical history, number of family members, and education) average gensini score, lipid profile values, q-CRP levels, and BP in DII tertiles was reported using ANCOVA. Statistical analyses were performed using SPSS 26 (SPSS Inc., version 0.21, Chicago, IL). *p*-values less than 0.05 were considered statistically significant.

Results

In this cross-sectional study, 275 Iranian adults referring to Chamran and Asgaria hospitals (a government hospital and a private hospital) for angiography were studied, of whom 59.3% were men. The average age, weight, and BMI of the participants were

59.10 ± 8.57 years, 77.63 ± 11.17 kg, and 28.5 ± 4.06 kg/m^2, respectively. Also, 59.6% of people had severe CAD and the average DII was −0.50 ± 4.49. The general characteristics of the participants regarding DII tertiles are presented in Table 1. Those in the upper tertiles of the DII were older and more anticoagulant drug consumption, had higher average weight and higher economic status, and were found with less fatty liver and diabetes compared to the lower tertiles. There was no significant difference in the distribution of other variables among the tertiles of the DII. The food intake of the participants in the study is presented in Table 2. Those in the upper tertile of the dietary inflammatory index had less intake of nuts, whole grains, carbohydrates, thiamin, vitamin D, pepper and tea than the lower tertiles. Also, those in the upper tertile of the DII were found with higher intakes of energy, protein, fat, SFA, monounsaturated fatty acid (MUFA), polyunsaturated fatty acid (PUFA), cholesterol, omega-3, omega-6, iron, zinc, vitamin B2, vitamin B6, vitamin B9, vitamin B12, vitamin C, vitamin E, vitamin A, beta carotene, onions, legumes, refined grains, red and processed meat, and vegetables compared to than the lower tertiles. No other significant difference in dietary intakes was observed among the tertiles of the dietary inflammatory index.

The raw and adjusted average severe CAD, lipid profile, and BP among the tertiles of DII are shown in Table 3. A significant difference was observed between the three levels of the DII in terms of the gensini score and the mean serum concentrations of q-CRP and total cholesterol, and this difference was also significant in the adjusted models. According to proximity tests, low adherence to the anti-inflammatory diet caused an increase in the gensini score ($p < 0.001$) and the mean concentrations of serum q-CRP ($p < 0.001$) and total cholesterol ($p < 0.001$). Also, those in higher tertiles of DII had higher mean systolic blood pressure than those in lower tertiles of DII ($p = 0.04$), which was not significant in the adjusted model. The crude and adjusted OR and 95% CI for severe CAD, high levels of lipid profile, high levels of q-CRP, and hypertension among the tertiles of DII are presented in Table 4. A direct and significant relationship was observed between the DII and severe CAD. People with the lowest

TABLE 1 General characteristics of study participants across tertile of DII (energy-adjusted).[1]

	T1 (n = 91)	T2 (n = 92)	T3 (n = 92)	p-value[2]
Demographic variables				
Sex, (Male) (%)	56 (61.5)	54 (58.7)	53 (57.6)	0.85
Age (year)	57.26 ± 7.28	59.29 ± 9.45	60.69 ± 8.09[a]	0.02
Weight (kg)	73.54 ± 11.59	78.85 ± 10.25	80.44 ± 10.55[a]	<0.001
BMI[3] (kg/m^2)	27.25 ± 4.59	29.00 ± 3.65	29.16 ± 3.63[a]	0.001
Physical activity (MET. min/wk)	1311.97 ± 360.40	1250.32 ± 387.28	1253.07 ± 369	0.45
Education[3] (University graduated) (%)	76 (83.5)	68 (73.9)	63 (68.5)	0.06
Number of people in the family[4] (less than 4) (%)	57 (32.4)	62 (35.2)	63 (68.5)	0.7
Marital status (single) (%)	13 (14.3)	8 (8.7)	14 (15.2)	0.36
High economic status[5] (%)	4 (4.4)	13 (14.1)	19 (20.7)[a]	0.005
Clinical history				
Disease history[6] (%)	76 (83.5)	68 (73.9)	63 (68.5)	0.06
Diabetes (%)	50 (49.9)	37 (40.2)	23 (25)[a,b]	<0.001
Fatty liver (%)	26 (28.6)	16 (17.4)	12 (13)[a]	0.02
Taking medication[7] (%)	79 (86.8)	85 (92.4)	80 (87)	0.39
Anti-inflammatory drug[8] (%)	56 (61.5)	49 (53.3)	51 (55.4)	0.5
Nitroglycerin (%)	0	3 (3.3)	0	0.05
Fat reducing drug[9] (%)	69 (75.8)	77 (83.7)	69 (75)	0.28
Anticoagulant[10] (%)	23 (25.3)	36 (39.1)	13 (14.1)	0.001

BMI, body mass index and MET, metabolic equivalent of task.
[1]Continuous variables are reported as mean ± SD. Categorical variables are reported as percentage.
[2]p-values obtained from ANOVA and $\chi 2$ test for continuous and categorical variables, respectively.
[3]Based on having university and non-university education.
[4]Number of family members based on more than 4 people and less than 4 people.
[5]Economic status based on foreign travel.
[6]Including diabetes, fatty liver.
[7]Including anti-inflammatory drug, nitroglycerin, fat-reducing drug, anticoagulant drug.
[8]Including corticosteroid and non-steroidal.
[9]Including statins, fibrates, ezetimibe, and niacin.
[10]Including clopidogrel, dipyridamole, ticlopidine, warfarin, enoxaparin, rivaroxaban.
[a]Is significant compared to the first tertile.
[b]Is significant compared to the second tertile.

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TABLE 2 Dietary intakes of study participants across tertile of DII (energy-adjusted).[1]

	T1 (n = 91)	T2 (n = 92)	T3 (n = 92)	p-value[2]
Food groups				
Whole grains (g/d)	167.30 ± 15.72	110.49 ± 11.73	129.09 ± 11.56[a]	<0.001
Refined grains (g/d)	192.68 ± 61.22	225.53 ± 59.52	398.92 ± 60.59[a]	0.04
Fruit (g/d)	571.30 ± 44.51	684.29 ± 38.92	687.93 ± 49.30	0.13
Vegetables (g/d)	285.38 ± 17.37	351.24 ± 22.36	386.92 ± 27.35[a]	0.02
Red and processed meat (g/d)	88.93 ± 6.45	92.81 ± 6.27	113.38 ± 6.36[a]	0.02
Dairy (g/d)	415.16 ± 30.93	346.60 ± 23.71	417.90 ± 29.48	0.15
Nuts (g/d)	12.16 ± 1.24	8.65 ± 1.21	7.38 ± 1.22[a]	0.02
Legumes (g/d)	34.82 ± 4.10	43.15 ± 3.99	56.45 ± 4.05[a]	0.001
Nutrients				
Energy intake (kcal/d)	1930 ± 420.45	2293.55 ± 485.20	2459 ± 455.25[a]	<0.001
Carbohydrates (% energy)	161.06 ± 24.61	152.86 ± 16.94	131.05 ± 17.28[a,b]	<0.001
Protein (% energy)	33.27 ± 5.06	36.71 ± 5.21	40.07 ± 6.00[a,b]	<0.001
Fat (% energy)	28.55 ± 9.75	31.12 ± 6.06	39.16 ± 7.03[a,b]	<0.001
SFA (g/d)	10.64 ± 0.39	11.40 ± 0.39	14.13 ± 0.39[a,b]	<0.001
PUFA (g/d)	5.04 ± 0.19	5.23 ± 0.196	6.91 ± 0.19[a,b]	<0.001
MUFA (g/d)	9.30 ± 0.33	10.49 ± 0.33	13.64 ± 0.32[a,b]	<0.001
Cholesterol (g/d)	88.59 ± 11.30	116.68 ± 11.23	225.38 ± 11.23[a,b]	<0.001
Omega 3 (g/d)	0.34 ± 0.02	0.37 ± 0.02	0.51 ± 0.02[a,b]	<0.001
Omega 6 (g/d)	0.02 ± 0.01	0.04 ± 0.01	0.05 ± 0.01[a]	0.001
Iron (mg/d)	11.55 ± 0.87	13.89 ± 0.87	19.98 ± 0.87[a,b]	<0.001
Magnesium (mg/d)	184.85 ± 3.62	191.82 ± 3.61	193.59 ± 3.61	0.19
Zinc (mg/d)	5.20 ± 0.11	5.80 ± 0.11	6.31 ± 0.11[a,b]	<0.001
Selenium (μg/d)	49.11 ± 1.47	44.77 ± 1.46	46.94 ± 1.46	0.11
Vitamin B1 (μg/d)	0.81 ± 0.02	0.72 ± 0.02	0.74 ± 0.02[a]	0.001
Vitamin B2 (mg/d)	0.75 ± 0.02	0.91 ± 0.02	1.05 ± 0.02[a,b]	<0.001
Vitamin B3 (mg/d)	9.48 ± 0.19	9.70 ± 0.19	9.68 ± 0.19	0.67
Vitamin B6 (mg/d)	0.88 ± 0.02	0.97 ± 0.02	1.04 ± 0.02[a,b]	<0.001
Vitamin B9 (μg/d)	209.23 ± 4.28	217.53 ± 4.25	226.76 ± 4.25[a]	0.02
Vitamin B12 (μg/d)	1.48 ± 0.11	2.10 ± 0.11	3.02 ± 0.11[a,b]	0.001
Vitamin C (mg/d)	61.06 ± 4.52	102.85 ± 4.50	94.37 ± 4.50[a]	<0.001
Vitamin D (μg/d)	0.55 ± 0.30	0.44 ± 0.29	0.42 ± 0.27[a]	0.04
Vitamin E (mg/d)	4.48 ± 0.16	4.96 ± 0.16	6.42 ± 0.16[a,b]	<0.001
Vitamin A (μg/d)	262.32 ± 15.90	421.27 ± 15.81	428.23 ± 15.81[a]	<0.001
Caffeine (g/d)	2.80 ± 0.23	2.75 ± 0.23	2.60 ± 0.23	0.83
Beta-carotene (μg/d)	2086.11 ± 187.27	3700.61 ± 186.28	3421.35 ± 186.25[a]	<0.001
Garlic (g/d)	0.81 ± 0.71	0.63 ± 0.70	0.62 ± 0.53[a,b]	0.11
Onion (g/d)	15.28 ± 10.92	19.30 ± 12.63	21.65 ± 12.87[a]	0.003
Pepper (g/d)	0.32 ± 0.07	0.16 ± 0.52	0.10 ± 0.24[a]	0.002
Tea (g/d)	0.77 ± 0.46	0.71 ± 0.39	0.60 ± 0.40[a]	0.02
DII	−5.55 ± 0.18	−0.592 ± 0.18	4.571 ± 0.18	<0.001

SFA, saturated fatty acids; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids.

[1]Values are mean ± SD. Intakes of food groups and nutrients were adjusted for energy intake.

[2]p-values obtained from ANOVA.

[a]Is significant compared to the first tertile.

[b]Is significant compared to the second tertile.

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TABLE 3 Adjusted average values of gensini score, lipid profile, and BP among the tertiles of DII (energy-adjusted).[1]

	T1 (n = 91)	T2 (n = 92)	T3 (n = 92)	p-value[2]
Gensini score				
Crude model	36.40 ± 5.45	41.88 ± 5.42	47.62 ± 5.42[a,b]	0.002
Adjusted model	34.45 ± 5.29	52.55 ± 5.05	63.72 ± 5.18[a,b]	<0.001
Quantitative c-reactive protein (mg/L)				
Crude model	5.59 ± 0.37	4.58 ± 0.36	7.61 ± 0.37[a,b]	<0.001
Adjusted model	5.65 ± 0.37	4.56 ± 0.36	7.57 ± 0.36[a,b]	<0.001
Triglycerides (mg/dl)				
Crude model	175.87 ± 5.29	173.92 ± 5.26	190.67 ± 5.26	0.05
Adjusted model	175.98 ± 5.54	173.74 ± 5.29	190.74 ± 5.43	0.06
Total cholesterol (mg/dl)				
Crude model	188.27 ± 6.37	193.63 ± 6.33	229.41 ± 6.33[a,b]	<0.001
Adjusted model	190.71 ± 6.17	192.19 ± 6.17	228.42 ± 6.33[a,b]	<0.001
HDL-cholesterol (mg/dl)				
Crude model	59.53 ± 1.34	50.56 ± 1.33	56.27 ± 1.33	0.16
Adjusted model	59.78 ± 1.37	56.37 ± 1.31	56.15 ± 1.34	0.13
LDL-cholesterol (mg/dl)				
Crude model	143.19 ± 7.30	128.68 ± 7.26	148.28 ± 7.26	0.14
Adjusted model	142.9 ± 7.66	129.42 ± 7.32	147.82 ± 7.50	0.19
Systolic blood pressure (mmHg)				
Crude model	132.20 ± 1.45	131.7 ± 1.45	136.46 ± 1.45[b]	0.04
Adjusted model	132.73 ± 1.54	131.68 ± 1.47	136.05 ± 1.51	0.11
Diastolic blood pressure (mmHg)				
Crude model	79.67 ± 0.97	81.72 ± 0.97	82.96 ± 0.97	0.06
Adjusted model	79.79 ± 0.96	81.58 ± 0.92	82.99 ± 0.94	0.07

Adjusted model: Adjusted for energy, age, gender, body mass index, physical activity, Taking medication, medical history, number of family members, education.

[1]Values are mean ± SE.

[2]p-values obtained from ANCOVA.

[a]Is significant compared to the first tertile.

[b]Is significant compared to the second tertile.

TABLE 4 Adjusted odds ratio (OR) and 95% confidence interval (CI) for severe CAD, high levels of lipid profile, high levels of q-CRP, and hypertension among the tertiles of DII (energy-adjusted).[1]

	T1 (n = 91)	T2 (n = 92)	T3 (n = 92)	p-trend[2]
Severe coronary artery disease (gensini score>20)				
Crude model	1.00 (Ref)	1.52 (0.85–2.71)	3.71 (1.97–6.98)	0.16
Adjusted model	1.00 (Ref)	2.11 (1.05–4.25)	6.09 (2.75–13.47)	<0.001
Quantitative c-reactive protein (>10mg/L)				
Crude model	1.00 (Ref)	0.83 (0.37–1.87)	2.11 (1.03–4.29)	0.03
Adjusted model	1.00 (Ref)	0.91 (0.37–2.25)	2.02 (0.86–4.73)	0.07
Triglycerides (>150mg/dl)				
Crude model	1.00 (Ref)	1.68 (0.87–3.27)	1.58 (0.82–3.05)	0.16
Adjusted model	1.00 (Ref)	1.85 (0.92–3.73)	1.69 (0.82–3.51)	0.15
Total cholesterol (>200mg/dl)				
Crude model	1.00 (Ref)	1.47 (0.78–2.72)	2.73 (1.48–5.03)	0.001
Adjusted model	1.00 (Ref)	1.33 (0.68–2.60)	2.81 (1.41–5.61)	0.003
HDL-cholesterol (<40mg/dl for men and <50 for women)				
Crude model	1.00 (Ref)	1.63 (0.60–4.4)	3.77 (1.52–9.34)	0.002
Adjusted model	1.00 (Ref)	2.03 (0.62–6.69)	6.68 (2.11–22.26)	0.001
LDL-cholesterol (>100mg/dl)				
Crude model	1.00 (Ref)	0.71 (0.39–1.29)	1.28 (0.71–2.28)	0.40
Adjusted model	1.00 (Ref)	0.69 (0.36–1.32)	1.21 (0.63–2.31)	0.56
Hypertension (systolic blood pressure>130 and diastolic blood pressure>80)				
Crude model	1.00 (Ref)	0.89 (0.50–1.60)	1.93 (1.06–3.49)	0.033
Adjusted model	1.00 (Ref)	0.71 (0.36–1.42)	2.34 (1.08–5.06)	0.034

Adjusted model: Adjusted for energy, age, gender, body mass index, physical activity, Taking medication, medical history, number of family members, education.

[1]All values are odds ratios and 95% confidence intervals obtained from Binary Logistic Regression.

[2]p-trend was obtained by the use of DII tertiles as a continuous rather than categorical variable.

adherence to anti-inflammatory diet had a 3.71 times higher chance of suffering from severe CAD than those with the highest adherence to anti-inflammatory (OR: 3.71; 95% CI: 1.97–6.98). This significance was also seen in the adjusted model, so that after adjusting the confounding variables, people with the lowest adherence to anti-inflammatory diet had a 6.09 times higher chance of suffering from severe CAD than those with the highest adherence to anti-inflammatory diet (OR: 6.09; 95% CI: 13.47–2.75). A direct and significant relationship was observed between the DII and increased q-CRP levels so that lower adherence to an anti-inflammatory diet

increased the odds of q-CRP positivity by 2.11 times. However, this association disappeared after adjusting for confounding factors in the adjusted model (OR: 2.02; 95% CI: 0.86–4.73). There was a direct and significant relationship was found between lower adherence to an anti-inflammatory diet and hypercholesterolemia (OR of the third tertile compared to the first tertile: 2.73; 95% CI: 1.48–5.03), decreased HDL-cholesterol levels (OR of the tertile third compared to the first tertile: 3.77; 95% CI: 1.52–9.34) and hypertension (OR of the third tertile compared to the first tertile: 1.93; 95% CI: 3.49–1/06) in the raw model. After adjustment for the confounding factors, the relationship remained direct and significant. In the crude model, regarding the lower adherence to the anti-inflammatory diet, the chance of developing hypertriglyceridemia (OR: 2.02; 95% CI: 0.86–4-73) and LDL-C (OR: 2.02; 95% CI: 0.86–4.73) increased; however, this relationship was not statistically significant, and after adjusting for confounding factors, no significance was observed.

Discussion

In the present study, a linear and direct relationship was observed between the DII and severe CAD. We also observed a significant difference between the DII tertiles in terms of gensini score. We found that a significant percentage of the participants were suffering from severe CAD (59.6%). Atherosclerosis is still the main cause of death with an increasing prevalence globally (34); thus, following anti-inflammatory regimens can positively affect the reduction of complications caused by blood clots.

Consistent with our study, other studies in the United States (35, 36), Australia (37), and Europe (38) showed that DII scores are positively associated with CAD risk. In a case–control study published in Jordan in 2019, a significant relationship was found between DII and the risk of CAD (18). In a prospective cohort study in Australia, the risk of CAD in men with a pro-inflammatory diet increased two times during the study (39). A randomized trial, PREDIMED, in Span showed that the risk of CAD in the fourth DII quartile increased by 73% compared to the first quartile (11). Also, in a case–control study conducted in northern Sweden, the risk of myocardial infarction in men with higher adherence to an inflammatory diet increased by 57% compared to people with low adherence (40). A meta-analysis, using data related to 14 eligible studies, examined the relationship between DII and the risk of CAD and its related mortality and it was found that the risk of CAD increased by 36% in people with higher adherence to the inflammatory diet (41). Another systematic review and meta-analysis conducted by Namazi et al. showed a positive and significant relationship between DII and the risk of CAD (42). In a cross-sectional study conducted in Iran, some components, such as nuts, showed an inverse and significant relationship with a decrease in the risk of the disease (21). However, our results are not consistent with some studies.

The contradictory results may be due to different food patterns, populations, sample sizes, and genetics. In the cross-sectional study conducted in Iran, no significant relationship was observed between red meat consumption and CAD. Patients with CAD reported more consumption of nuts and the use of fresh and cooked vegetables, dried fruits, animal oil cakes, fried potatoes, and some dairy products was correlated with CAD (20). Although several studies have been done on DII and its relationship with CAD, according to the researcher's knowledge, no study has evaluated the relationship between DII and CAD severity using the gensini score in IRAN.

Several mechanisms have been proposed to explain the association between DII and vascular occlusion. Several theories have shown the consistent relationship between DII and the risk of developing CAD and its mortality; for example, the pro-inflammatory association of diet on increasing the level of cytokines, such as IL-1 and TNF-α, which causes the attraction and movement of inflammatory cells to the surface of the vascular endothelium (43) and induces the expression of cell adhesion molecules mediating leukocyte adhesion to the vascular endothelium (44).They also induce "messenger" cytokines, which increase the production of acute phase reactants, including CRP and serum amyloid A (SAA) through releasing into the systemic circulation (45). Inflammation in all stages of atherothrombosis is the main cause of about 80% of sudden cardiac deaths (SCD) (46). In previous studies, the DII score obtained from the FFQ was significantly associated with inflammatory biomarkers. Thus, higher DII scores (indicating a more inflammatory diet) have been directly related to IL-6, TNFα-R2, and CRP (15). IL-6 is the main pro-coagulant cytokine and can increase the concentration of fibrinogen, plasminogen activator inhibitor type 1 (47), and CRP, leading to an increase in pro-inflammatory and pro-coagulant responses (48). The basis of the relationship between CRP and atherosclerosis is the CRP's potential to directly modulate the production of endothelium-derived vasoactive factors. Nitric oxide(NO) is the key factor in maintaining vascular tone and the central controller of cardiovascular homeostasis, which is derived from vascular endothelium (49). The reduced production or effect of NO through increased vascular contraction, leukocyte adhesion, platelet activation, oxidation, thrombosis, coagulation disorders, and vascular inflammation plays an essential role in the pathogenesis of the vascular atherosclerotic disease (50). Anti-inflammatory diet exert their effects on arterial blockage by reducing IL-6, TNFα-R2, and CRP levels (15). A number of studies have been shown that anti-inflammatory diet can modulate endothelium dependent vasodilation responses, endothelium-leukocyte interactions as well as balance between pro-and antithrombotic properties (51).

We also showed that lower adherence of an anti-inflammatory diet is related to an incremented risk of high blood pressure. The findings of the present study are confirmed by other studies indicating a positive relationship between the inflammatory potential of diet and hypertension (52, 53). Also, several prospective trials have associated increased inflammation with higher risks of hypertension (54). Inflammatory cytokines can strongly induce high blood pressure, which plays a role in regulating blood pressure due to the disruption of the renin-angiotensin system, vascular inflammation, and the reduction of NO production (55). The inflammation as well as the production of inflammatory cytokines activate the immune system and increase the expression of the angiotensinogen gene and angiotensin-converting enzyme (52), which ultimately causes the production of angiotensin 2, a strong constrictor, and increases blood pressure. On the other hand, inflammation and vascular damage can reduce the production of NO as a vasodilator, leading to high blood pressure (56).

Also, less following an anti-inflammatory diet was related to an increased risk of hypercholesterolemia and reduced HDL-C. A low-quality diet including excessive consumption of inflammatory food items increases lipogenesis (57, 58). A recently published prospective population-based study showed that a pro-inflammatory diet was associated with an increased risk of dyslipidemia (59). In a meta-analysis, higher levels of DII were associated with higher levels of TG and LDL-C in apparently healthy populations (60). The relationship between DII and increased TG and decreased HDL-C has also been reported (61). Therefore, the contradictory results may be due to different food patterns, populations, sample sizes, and genetics.

The present study had strengths and weaknesses. The severity of coronary artery disease was determined based on gensini's score, and its validity has been confirmed. Nutritional intake was evaluated using valid questionnaires. In addition, the effects of several potential confounding factors were controlled in data analyses. However, some limitations should be considered in interpreting the findings. Due to the cross-sectional design of the study, we could not infer a causal relationship between the DII and CAD. More prospective studies should be conducted to confirm the causality of the associations. Although a validated FFQ was used to assess dietary intakes, recall bias may have influenced the findings. In addition, we did not have information about family history of CAD and 12 dietary items to calculate the DII score, which could affect the results.

This cross-sectional study showed a direct and linear relationship between the DII and the occurrence of severe CAD. Also, a significant difference was found between the DII tertiles in terms of gensini score. It is recommended people that in order to reduce the inflammatory potential of the diet, people should minimize the consumption of foods such as fast food, bread and pasta made with white flour, deep fried items such as french fries, fried chicken and donuts.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Ethics Committee of Isfahan University of Medical Sciences. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

ZD, MB, OS, AK, SS, and GA contributed in design, conception, data interpretation, data collection, approval of the final version of the manuscript, manuscript drafting, and agreed for all aspects of the work. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Glossary

DII	Dietary inflammation index
FFQ	Food frequency questionnaire
OR	Odds ratios
95% CI	95% Confidence interval
BMI	Body mass index
MUFA	Mono unsaturated fatty acid
PUFA	Poly unsaturated fatty acid
SFA	Saturated fatty acid
ANOVA	Analysis of variance
ANCOVA	Analysis of covariance
SPSS	Statistical package for the social sciences
SD	Standard deviation
CAD	Coronary artery disease
LDL-c	Low-density lipoprotein cholesterol
CVDs	Cardiovascular diseases
TG	Triglyceride
HDL-c	High-density lipoprotein cholesterol
BP	Blood pressure
IL-6	Interleukin-6
IL-1b	Interleukin-1 beta
TNFα-R2	Tumor necrosis factor receptor 2 alpha
SES	Socioeconomic status
IPAQ	International Physical Activity Questionnaire
Q-CRP	Quantitative C-reactive protein
N4	Nutritionist IV
AHEI	Alternative healthy eating index
SCD	Sudden cardiac deaths
Enos	Endothelial nitric oxide synthase
ET-1	Endothelin-1
ICAM-1	Intracellular adhesion molecule type 1
NO	Nitric oxide
MET	Metabolic Equivalent of Task

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Balamurugan Ramadass,
All India Institute of Medical Sciences Bhubaneswar, India

REVIEWED BY
Piotr Konopelski,
Medical University of Warsaw, Poland
Patrick Devos,
Centre Hospitalier Regional et Universitaire de Lille, France

*CORRESPONDENCE
Qianfeng Jiang
✉ jiangqianfeng@zmu.edu.cn

†These authors have contributed equally to this work and share first authorship

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Gut microbiota and hypertension: a bibliometric analysis of recent research (2014–2023)

Yang Jiao[1†], Wenxing Li[1,2†], Qianyi Zhang[1,2] and Qianfeng Jiang[3*]

[1]Department of Cardiology, Zunyi First People's Hospital, The Third Affiliated Hospital of Zunyi Medical University, Zunyi, Guizhou, China, [2]Zunyi Medical University, Zunyi, Guizhou, China, [3]Department of Cardiology, Guizhou Aerospace Hospital, Zunyi, Guizhou, China

Background: Cardiovascular diseases persist as the primary cause of mortality in the global population. Hypertension (HTN) is widely recognized as one of the most crucial risk factors contributing to severe cardiovascular conditions. In recent years, a growing body of research has highlighted the therapeutic potential of gut microbiota (GM) in addressing cardiovascular diseases, particularly HTN. Consequently, unraveling and synthesizing the connections between GM and HTN, key research domains, and the underlying interaction mechanisms have grown increasingly vital.

Methods: We retrieved articles related to GM and HTN from 2014 to 2023 using Web of Science. Bibliometric tools employed in this analysis include CiteSpace and VOSviewer.

Result: From 2014 to 2023, we identified 1,730 related articles. These articles involved 88 countries (regions) and 9,573 authors. The articles were published in 593 journals, with 1000 references exhibiting co-occurrence more than 10 times. The number of studies in this field has been increasing, indicating that it remains a research hotspot. We expect this field to continue gaining attention in the future. China leads in the number of published articles, while the United States boasts the most extensive international collaborations, signifying its continued prominence as a research hub in this domain. Tain You-Lin, Hsu Chien-Ning, Raizada Mohan K, and Yang Tao are among the authors with the highest publication volume. Publications in this field are frequently found in nutrition, cardiovascular, and molecular biology journals. The most frequently occurring keywords include metabolic syndrome, cardiovascular disease, inflammation, short-chain fatty acids, trimethylamine N-oxide, chronic kidney disease, heart failure, and high-salt diet.

Conclusion: The relationship between GM and HTN is presently one of the most active research areas. By employing bibliometric tools, we analyzed critical and innovative articles in this field to provide an objective summary of the primary research directions, such as the relationship between GM and HTN, GM metabolites, high-salt diet, the developmental origins of health and disease, obstructive sleep apnea-Induced hypertension and antihypertensive peptide. Our analysis aims to offer researchers insights into hotspots and emerging trends in the field of GM and HTN for future research reference.

KEYWORDS

gut microbiota, hypertension, short-chain fatty acids, salt-sensitive hypertension, bibliometrics

1. Introduction

Cardiovascular disease poses a significant global health challenge and remains a leading cause of death. The prevalence of cardiovascular disease continues to rise, and hypertension (HTN) is among the primary risk factors for severe cardiovascular conditions (1, 2). Consequently, finding novel approaches to manage blood pressure is essential. The human body houses approximately 100 trillion microorganisms, with the majority residing in the intestines, forming the human gut microbiota (GM). This GM plays a role in regulating multiple bodily systems, including the cardiovascular, respiratory, and digestive systems. Recent studies have demonstrated that cardiovascular diseases, such as HTN, heart failure, myocardial infarction, and atrial fibrillation, are closely associated with the GM. Among the research exploring the connections between cardiovascular diseases and the GM, HTN has been an early and prominent concern. In 2015, Yang et al. established a correlation between GM and HTN (3). In 2017, Li et al. induced HTN in normal rats by transplanting GM from hypertensive patients (4). GM can metabolize dietary fiber into short-chain fatty acids (SCFAs). Francine et al.'s team provided hypertensive rats with dietary fiber or SCFAs, achieving a reduction in systolic and diastolic blood pressure (5). Presently, nutritionists advocate for increased dietary fiber consumption to lower the risk of cardiovascular disease (6). Consequently, conducting in-depth investigations into the association between GM and HTN bears significant implications for the treatment and prevention of cardiovascular diseases.

Bibliometrics, unlike traditional review articles, employ mathematical and statistical techniques to analyze texts and identify current trends and pressing issues in a specific research field (7). In recent times, researchers have carried out bibliometric analyses on GM in relation to atherosclerosis, heart failure, and other aspects (8, 9). However,as HTN poses one of the most substantial threats to cardiovascular health, it has yet to be explored through a corresponding bibliometric analysis. Therefore, there is an immediate demand for a bibliometric study to uncover the latest viewpoints and trending developments concerning the role of GM in HTN.

2. Materials and methods

2.1. Data sources and search strategy

A broad range of scholars concur that the Web of Science (WOS) is a reliable database ideally suited for bibliometric research. We extracted articles related to GM and HTN from the WOS database. To minimize search bias caused by database updates, we employed the following search query: TS = [(Microbiome∗ OR Microflora∗ OR Microbiota∗ OR Flora OR "Microbial Community" OR Bacteria) AND (Gastrointestinal OR Gut OR Gastric* OR Intestinal)] AND TS = (Hypertension OR "High Blood Pressure∗"). The search period spanned from January 1, 2014, to February 28, 2023, to further reduce bias. We limited our search to articles and reviews in English, with Figure 1 illustrating the specific flow chart.

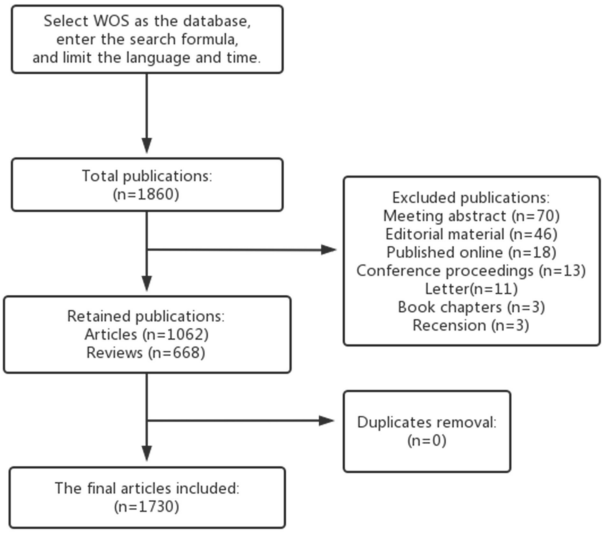

FIGURE 1
Flowchart for including and excluding publications.

2.2. Data analysis

We use VOSviewer and CiteSpace as bibliometric analysis tools to conduct a quantitative analysis of the countries, authors, journals, keywords, and references associated with GM and HTN research. VOSviewer is utilized to create visual network representations of countries, authors, and journals, as it effectively displays extensive bibliometric maps in more comprehensible images (10). Simultaneously, we use CiteSpace to analyze keywords and references in this domain, as the timelines, burst, and clustering analyses generated by CiteSpace enable a more in-depth analysis of the hotspots and frontiers in GM and HTN research, offering valuable insights for future studies.

3. Results

3.1. Analysis of growth trends of annual publications

An annual publication trend graph offers insight into the evolution and growth of a particular research field. In our study, we collated a total of 1,730 pertinent articles, comprising 1,062 research articles and 668 review articles. Out of these, 1,250 (72%) were open access, facilitating free knowledge dissemination, thereby promoting scientific progress in this field. As depicted in Figure 2, the research interest in this field has shown a consistent and rapid upward trajectory. Between 2014 and 2016, less than 100 articles were published annually. However, the publication rate markedly increased from 2017 to 2022, starting with 110 articles in 2017 and exhibiting an approximate annual addition of 80 articles thereafter. The year 2022 saw the publication of over 400 articles. Moreover, the proportion of GM+HTN research in relation to the broader field of hypertension-related research rose from 4% in 2014 to 43% in 2022. These trends suggest a continued and growing interest

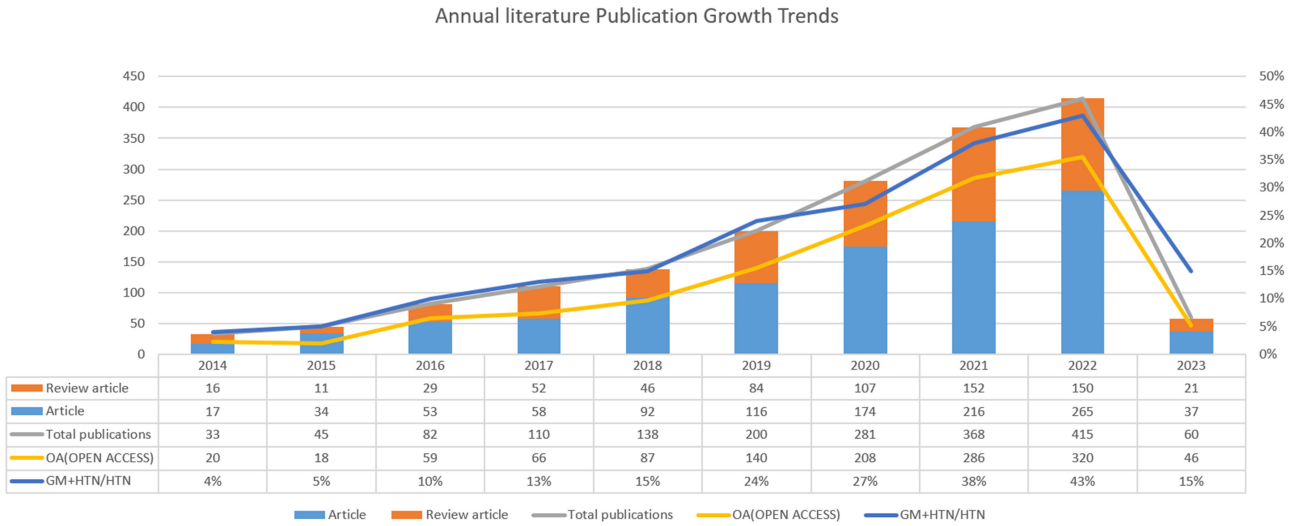

FIGURE 2
Annual literature publication growth trends.

TABLE 1 Top 10 countries/regions with the highest number of published articles.

Rank	Country	Documents	Citations	Average number of citations	Centrality	Year (Start of Research)
1	Peoples R China	500	10953	21.9	0.06	2014
2	USA	487	20308	41.7	0.47	2014
3	Spain	118	5050	42.8	0.09	2014
4	Italy	108	4632	42.9	0.14	2014
5	Australia	85	3080	36.2	0.17	2015
6	Germany	78	4084	52.4	0.25	2014
7	England	75	3598	48.0	0.10	2014
8	Canada	69	2458	35.6	0.03	2014
9	Japan	63	2002	31.8	0	2016
10	Brazil	58	1880	32.4	0.01	2014

in the intersection of GM and HTN, indicating that this area will remain a focal point for future research.

3.2. Analysis of countries (regions)

Among 88 nations, China stands as the leading contributor in terms of article publication, boasting 500 articles and a total citation count of 10,953 (Table 1). However, China's relatively low Centrality and average citation numbers suggest a need for more original research. The United States follows closely with 487 published articles and a substantial 20,308 citations. Among the top ten publishing countries, Germany holds the record for the highest average number of citations, at 52.4. Figure 3A showcases the yearly publication volumes across countries, where China and the United States outshine others in terms of output. Prior to 2020, the United States consistently led in publication volume. However, in 2021, China experienced a significant surge in output, surpassing the United States. The publication volumes of other countries have shown a relatively steady trend over the past decade. To further explore the interconnections between different countries, we utilized VOSviewer for a visual analysis of collaboration relationships and timelines. Figure 3B elucidates the collaborative ties between countries. Notably, the United States has forged the most extensive collaborative relationships, positioning itself at the heart of this research field. It shares its highest level of collaboration with China. Figure 3C reveals the average research initiation time in this field for different countries. Nations like Canada, France, Sweden, and Switzerland embarked on research in this area before 2019. The United States, Germany, Italy, and others began their involvement around mid-2019. Meanwhile, China, India, the Netherlands, and others initiated their research endeavors in this field around 2020.

3.3. Analysis of authors

To identify leading contributors in the field, we performed a visual analysis of authors (Table 2). We used Price's law, a

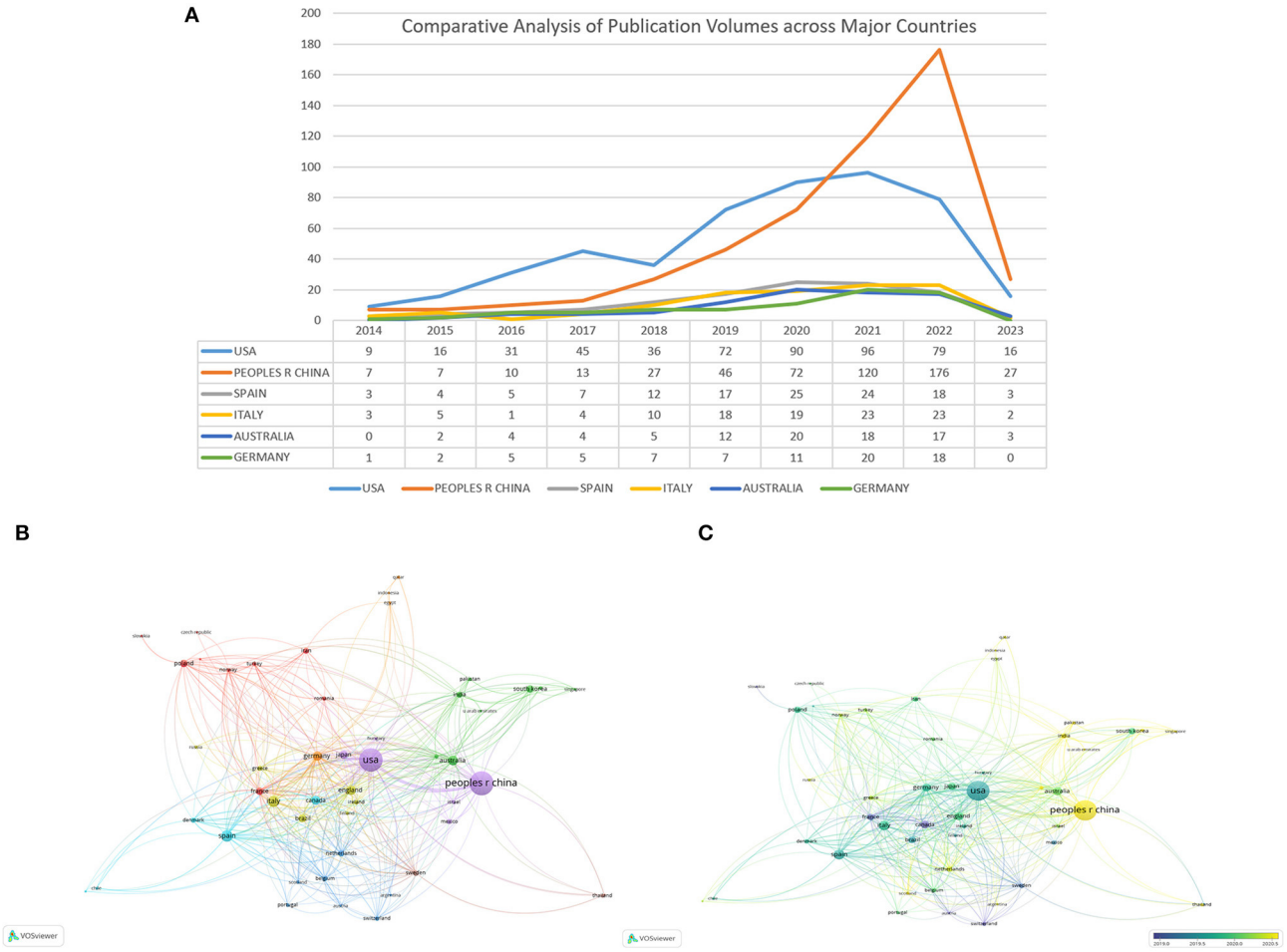

FIGURE 3
(A) Comparative analysis of publication volumes across major countries. **(B)** Collaboration network map among countries/regions using VOSviewer. **(C)** Timeline graphs displaying interactions among 88 countries/districts using VOSviewer the node size signifies the quantity of articles. Node color depicts the research topic, while lines connecting nodes indicate cooperative relationships between countries. A wider line between two nodes represents greater collaboration between the countries involved. Additionally, a node connected to numerous other nodes demonstrates its recognition and influence across multiple countries.

rule of thumb which suggests that half of the publications in a specific field are made by the square root of all contributors, to designate core authors as those who have published more than 19 articles. Among these, Tain You-Lin and Hsu Chien-Ning lead the pack with the highest publication counts of 51 and 42 articles, respectively. Yang Tao, Raizada Mohan K, and Hou Chih-yao have outstanding citation percentages of 98, 90.38, and 100%, respectively, with their work falling within the 85th, 71st, and 76th citation percentiles. We then employed VOSviewer for a visual representation of author clusters, focusing on authors who have published more than 5 articles. Authors publishing on similar research topics were grouped into same-color clusters (Figure 4A). Within the red cluster, Raizada Mohan K and Yang Tao show extensive collaborations with other authors and stand out as some of the most influential contributors. In the blue cluster, Robles-vera, Inaki, and Romero, Miguel are also recognized as influential authors. To examine the recent publication patterns of these authors, we analyzed the publication volumes of the top 20 authors over the past decade (Figure 4B). All these authors have published articles within the last 5 years, with the peak of publication volume appearing between 2018 and 2021.

3.4. Analysis of journals

Analyzing various journals can aid researchers in identifying suitable journals for submitting their articles. Table 3 displays the top fifteen journals based on publication volume. These journals, categorized as Q1 and Q2 (referring to the top 25 and 25–50% of journals in a specific field, respectively, based on their Impact Factor rankings), primarily concentrate on nutrition, cardiovascular, and molecular biology. Researchers in these areas may prioritize these journals for their submissions. Journals centered on nutrition feature the highest number of articles in this field. Among those related to cardiovascular studies, Circulation Research stands out with the highest Journal Impact Factor of 20.1. Notably, we observed that the majority of the top 15 Q1 journals

TABLE 2 Top 10 Authors with the highest number of published articles.

Rank	Author	Documents	Citations	CICN (2018–2022)	H-Index	% Documents cited (2018–2022)	Citation percentile
1	Tain, You-lin	51	963	1.06	41	87.27%	65th
2	Hsu, Chien-ning	42	747	0.98	32	77.14%	68th
3	Yang, Tao	34	2335	3.81	25	95.00%	85th
4	Raizada, Mohan K.	33	2775	5.63	72	90.38%	71th
5	Hou, Chih-yao	31	601	1.58	23	100%	76th
6	Duarte, Juan	23	925	1.77	51	79.55%	77th
7	Joe, Bina	23	746	1.8	32	58.33%	52th
8	Pepine, Carl J.	23	2450	2.41	69	82.04%	71th
9	Richards, Elaine M.	22	1165	5.32	22	91.89%	72th
10	Li, Jing	21	998	1.37	21	78.26%	55th

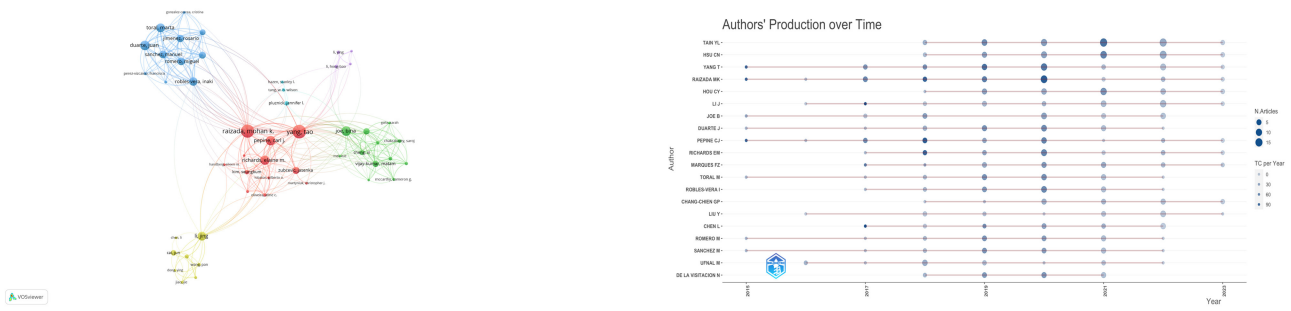

FIGURE 4
(A) Collaboration network map among authors using VOSviewer. **(B)** Authors' production over time.

are not open access (OA), a factor that could potentially impede scientific advancement in this field. Figure 5A presents a density plot depicting the number of articles indexed by journals, where brighter colors signify a higher count of indexed articles. Figure 5B offers a dual overlay of journals, illustrating the interconnectedness between various disciplines. For instance, clinical medicine is connected to molecular biology and nursing via green lines, signifying a close relationship among them.

3.5. Keyword analysis

Keyword analysis provides insights into the trending topics and emerging research directions in the study of GM and HTN (Table 4). Figure 6A showcases the top 15 keywords for both articles and review articles. To further understand these trends, we used CiteSpace and VOSviewer to perform a visual analysis of the keywords in this field. Figure 6A illustrates a CiteSpace timeline visualization of the keywords, demonstrating the temporal emergence of different keywords in the field. Prior to 2014, research related to GM was in progress but not deemed as a hot topic. In 2014, the field saw the emergence of keywords like hypertension, chronic kidney disease, bioactive peptides (fermented milk), and portal hypertension. The field gained substantial popularity from 2016 onwards, attracting a significant number of researchers. Around this time, prominent keywords included trimethylamine-N-oxide (TMAO), SCFAs, renin-angiotensin system, high-salt diet, and T cells. By 2019, new research hotspots surfaced with keywords such as fatty liver, tumors, gut-liver axis, myocardial infarction, and diabetes. In 2021 and 2022, this field became a major research hotspot. Alongside the aforementioned focus areas, there was a marked rise in articles related to sleep apnea-related hypertension, pulmonary arterial hypertension, gender differences, developmental origins of health and disease (DOHaD), GM and other cardiovascular diseases, and GM and other systemic diseases. Figure 6B presents the VOSviewer clustering results of the keywords, with GM and HTN serving as the central themes. Different-colored clusters represent different research directions in

TABLE 3 Top 15 journals with the highest number of publications.

Rank	Source	Documents	JIF (2022)	JCI (2022)	JIF QUARTILE	Open access (OA)
1	Nutrients	105	5.9	1.04	Q1	97.09%
2	International Journal of Molecular Sciences	47	5.6	0.71	Q1	97.88%
3	Hypertension	38	8.3	1.64	Q1	6.47%
4	Plos One	30	3.7	0.91	Q2	93.67%
5	Frontiers in Nutrition	27	5.0	0.90	Q2	94.44%
6	Frontiers in Microbiology	26	5.2	0.96	Q2	94.87%
7	Scientific Reports	26	4.6	1.06	Q2	95.03%
8	Current Hypertension Reports	23	5.6	0.71	Q2	17.59%
9	Frontiers in Physiology	23	4.0	1.00	Q2	92.48%
10	Food & Function	22	6.1	1.16	Q1	6.83%
11	Current Opinion in Nephrology and Hypertension	19	3.2	0.59	Q2	6.07%
12	Pharmacological Research	18	9.3	1.91	Q1	11.98%
13	Circulation Research	17	20.1	3.93	Q1	3.97%
14	Frontiers in Cellular and Infection Microbiology	17	5.7	0.83	Q1(Microbiology)	93.90%
15	Molecular Nutrition & Food Research	17	5.2	1.12	Q1	19.79%

the field. In the red cluster, keywords such as metabolic syndrome, obesity, insulin resistance, anthocyanins, and Lactobacillus are closely linked. In the light blue cluster, HTN is closely associated with DOHaD, renin-angiotensin system, chronic kidney disease, and nitric oxide. In the dark blue cluster, short-chain fatty acids, TMAO, pulmonary arterial hypertension, central nervous system inflammation, and novel coronavirus are interconnected. The yellow cluster focuses on important research topics in the field of GM and HTN, such as SCFAs, gut-liver axis, portal hypertension, non-alcoholic fatty liver, and others. Figure 6C depicts the average time of different research directions in the field, with most research directions indicated by light green, suggesting that a majority of studies were conducted around 2020. This finding aligns with the increased publication volume of core authors previously discussed. Figure 6D displays the keyword burst analysis, using CiteSpace to identify keywords that have seen sudden growth within a certain period, indicative of emerging hotspots in the field. Glucagon-like peptide-1 is the keyword with the highest surge in frequency, while spontaneous bacterial peritonitis and obesity are the keywords with the longest burst duration. High salt, bioactive peptides, tumors, and other keywords are the newly emerging burst keywords in the field of GM and HTN.

3.6. Analysis of references

Analyzing references, which serve as a reservoir of knowledge, can provide insights into the foundational research within a specific field. Table 5 comprises the top 20 co-occurring references with a Category Normalized Citation Impact (CNCI) greater than four. Moreover, we examined the 30 most frequently cited references and identified distinctive research directions. Among these 30 articles, the bulk of them explored the influence of GM and its metabolites on HTN, thereby establishing a strong foundation for further investigations into the mechanisms of gut microbiota's role in HTN. Works by authors such as Yang Tao and Li Jing have garnered considerable attention. The remaining articles primarily delved into the mechanisms of action of GM and its metabolites, focusing on the roles of receptors like Olfr78 and Gpr41 in the function of short-chain fatty acids, and the interplay between GM and immune regulation influencing the cardiovascular system. We also conducted a clustering analysis (Figure 7A) on the references to facilitate the identification of the theoretical basis for various research directions. For instance, in the 2nd cluster, articles by Yang T (https://doi.org/10.1161/HYPERTENSIONAHA.115.05315), Adnan S (https://doi.org/10.1152/physiolgenomics.00081.2016), and Sun S (https://doi.org/10.1161/HYPERTENSIONAHA.118.12109) demonstrated that dysbiosis of gut microbiota can lead to increased blood pressure. This provides a foundation for the DOHaD study on how interventions on maternal GM can impact blood pressure in offspring rats. In the 11th cluster, articles by Kim S (https://doi.org/10.1161/HYPERTENSIONAHA.119.14294), Sharma RK (https://doi.org/10.1161/CIRCRESAHA.118.313882), and Yang T (https://doi.org/10.3389/fphys.2017.00845) discussed the role of the immune system in HTN, the unique gut microbiota in pulmonary arterial hypertension, and so on, laying the groundwork for exploring the mechanisms of gut microbiota in the onset and progression of pulmonary arterial

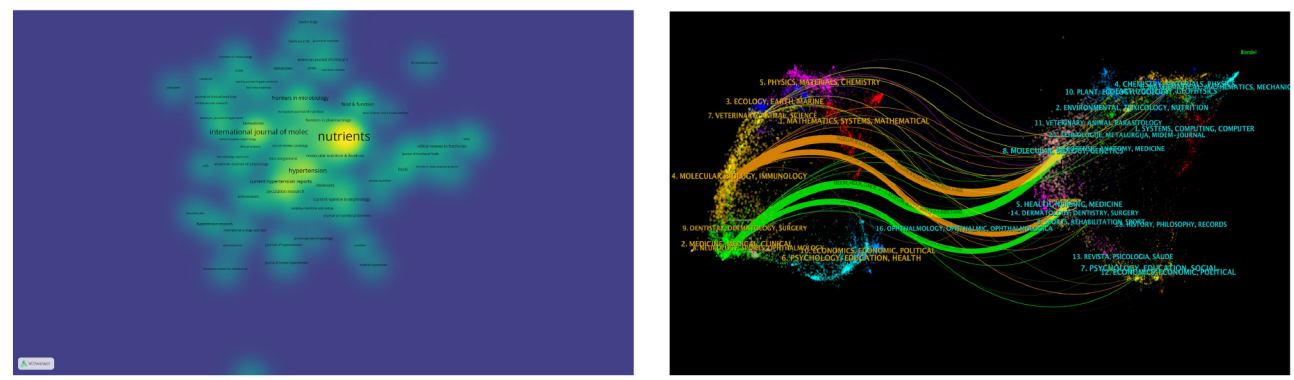

FIGURE 5
(A) Density map of journal article distribution using VOSviewer. **(B)** Dual-map overlay of journals in CiteSpace: citing journals are on the left, cited journals are on the right, colored paths indicate citation relationships.

TABLE 4 **Top 15 keywords associated with the highest number of publications.**

Rank	Keywords (article)	Count	Centrality	Rank	Keywords (review article)	Count	Centrality
1	Gut microbiota	717	0.12	1	Gut microbiota	438	0.06
2	Blood pressure	294	0.05	2	Blood pressure	240	0.15
3	Hypertension	171	0.05	3	Short-chain fatty acids	123	0.02
4	Metabolic syndrome	164	0.12	4	Cardiovascular disease	114	0.08
5	Obesity	131	0.02	5	Metabolic syndrome	103	0.02
6	Inflammation	108	0.02	6	Trimethylamine n-oxide	99	0.03
7	Short-chain fatty acids	100	0.07	7	Oxidative stress	90	0.02
8	Oxidative stress	88	0.21	8	Insulin resistance	76	0.02
9	Insulin resistance	79	0.06	9	Chronic kidney disease	60	0.06
10	Cardiovascular disease	68	0.04	10	Inflammation	60	0.03
11	Trimethylamine n-oxide	49	0.03	11	Hypertension	56	0.08
12	Chronic kidney disease	45	0.18	12	Heart failure	53	0.14
13	Nitric oxide	44	0.02	13	Bile acids	38	0.07
14	Endothelial dysfunction	39	0.05	14	Endothelial dysfunction	36	0.03
15	Probiotics	34	0.01	15	Cardiovascular diseases	34	0.02

hypertension. Finally, we performed a burst analysis (Figure 7B) on the references from 2019 to 2023 to identify the articles that suddenly gained popularity in this field. As depicted in the figure, the most cited references in the past five years were primarily from 2015 to 2017. Furthermore, the field received significant attention from 2019 to 2021. The article by Yang Tao presented the highest burst intensity of 42.66. In 2021, four highly regarded review articles (the last four articles) predominantly discussed the metabolism of microbiota metabolites and the interaction mechanisms between microbiota and cardiovascular diseases.

4. Discussion

4.1. General information

The field of GM and HTN has seen contributions from a total of 88 countries/regions and 9,573 authors, resulting in 1,730 articles. These articles were spread across 593 journals, with 1,000 references co-occurring more than 10 times. The volume of relevant studies in the area of GM and HTN has been on an upward trajectory in recent years, marking it as a burgeoning research hotspot. We anticipate that this field will continue to

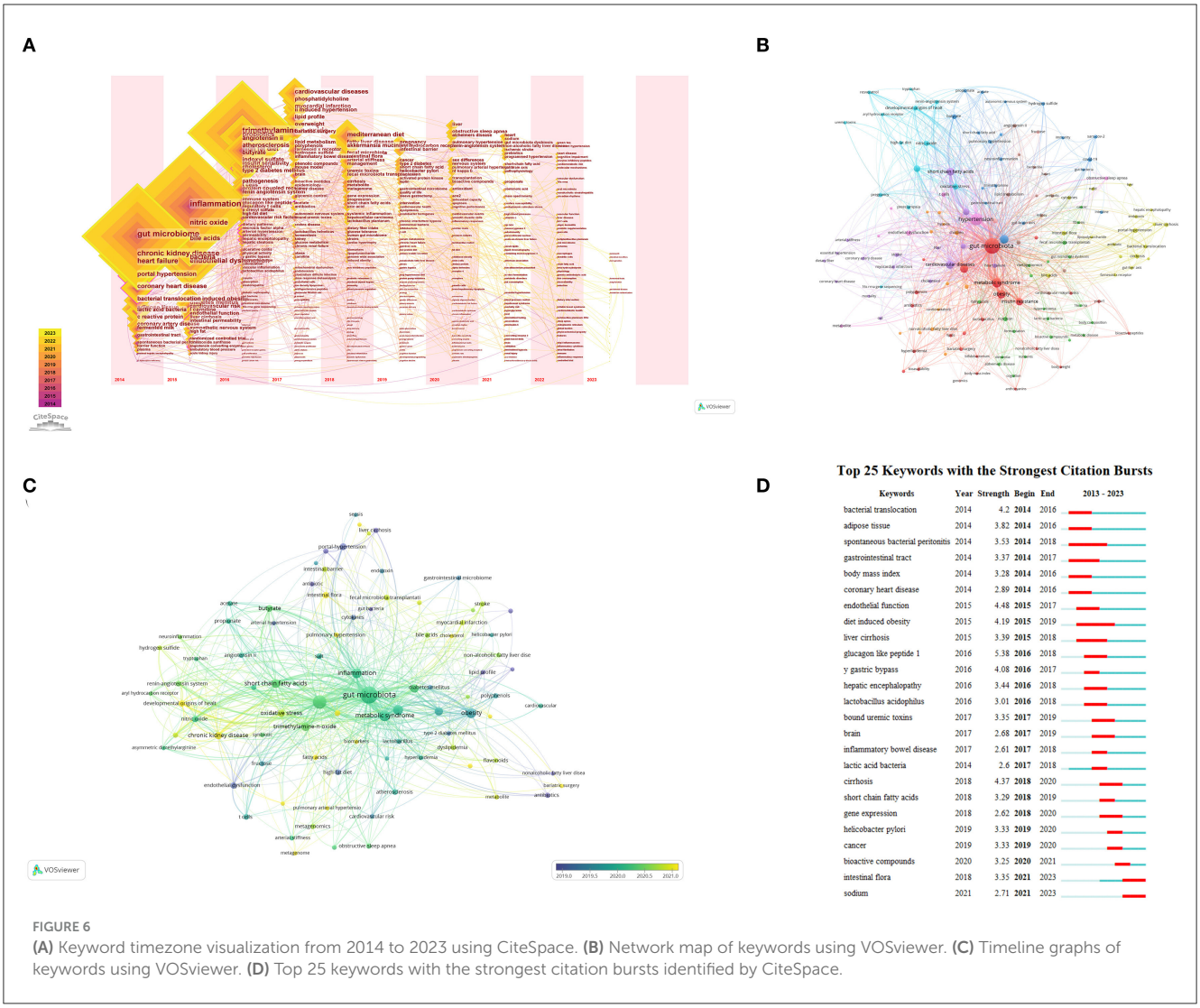

FIGURE 6
(A) Keyword timezone visualization from 2014 to 2023 using CiteSpace. **(B)** Network map of keywords using VOSviewer. **(C)** Timeline graphs of keywords using VOSviewer. **(D)** Top 25 keywords with the strongest citation bursts identified by CiteSpace.

garner increased attention moving forward. While China leads in the number of publications, the average citation per article is relatively low. The United States, although second in terms of publication volume, holds a central position in the research field, indicated by its extensive collaborations with other countries. Its most frequent collaborator is China. Our analysis of authors extends beyond merely considering the number of publications and H-index. It's evident that researchers from European and American countries have a longer history of studying this field, while Chinese researchers entered the field more recently. Furthermore, stable research communities have formed within the field, with individuals like Tain You-Lin, Hsu Chien-Ning, and Chih-Yao Hou holding pivotal roles in the field of developmental origins of health and disease. Journals in the domains of nutrition, cardiovascular research, and molecular biology have published the greatest number of articles in this field. Researchers looking to make manuscript submissions in this area should prioritize these journals.

4.2. Hot-spots and frontiers

Bibliometrics serve a crucial role in organizing key trends and advancing frontiers within a field. In our study, we employed tools such as CiteSpace and VOSviewer to analyze author keywords and references in this field. The objective was to identify seminal and innovative articles, and to objectively encapsulate different research directions. The interplay between GM and HTN has remained a solid research focal point from 2015 to 2022, with a large contingent of scholars participating actively, particularly between 2018 and 2021. This period saw considerable contributions that enriched the exploration within this area. The correlation between GM and heart failure has recently come into focus, surfacing around 2017, and gaining momentum with 14 publications in 2021 and rising to 28 in 2022. Investigations into the relationship between GM and coronary heart disease commenced around 2015, and those concerning GM and myocardial infarction started around 2017, with an average of 7–8 publications per annum.

TABLE 5 Top 20 References with the highest number of citations.

Rank	Cited references	Count	Centrality	CNCI
1	Li J, 2017, MICROBIOME, V5, PO, DOI 10.1186/s40168-016-0222-x	326	0.02	13.83
2	Yang T, 2015, HYPERTENSION, V65, Pl331, DOI 10.1161/HYPERTENSIONAHA.115.05315	218	0.05	14.09
3	Marques FZ, 2017, CIRCULATION, V135, P964, DOI 10.1161/CIRCULATIONAHA.116.024545	206	0.00	8.57
4	Santisteban MM, 2017, CIRC RES, V120, P312, DOI 10.1161/CIRCRESAHA.116.309006	171	0.04	4.94
5	Wilck N, 2017, NATURE, V551, P585, DOI 10.1038/nature24628	153	0.01	10.99
6	Kim S, 2018, CLIN SCI, V132, P701, DOI 10.1042/CS20180087	140	0.03	7.17
7	Mell B, 2015, PHYSIOL GENOMICS, V47, P187, DOI 10.1152/physiolgenomics.00136.2014	115	0.09	4.26
8	Marques FZ, 2018, NAT REV CARDIOL, V15, P20, DOI 10.1038/nrcardio.2017.120	109	0.08	5.99
9	Bartolomaeus H, 2019, CIRCULATION, V139, P1407, DOI 10.1161/CIRCULATIONAHA.118.036652	106	0.18	8.36
10	Tang WHW, 2017, CIRC RES, V120, P1183, DOI 10.1161/CIRCRESAHA.117.309715	105	0.00	15.12
11	Natarajan N, 2016, PHYSIOL GENOMICS, V48, P826, DOI 10.1152/physiolgenomics.00089.2016	91	0.00	4.41
12	Yang T, 2018, NAT REV NEPHROL, V14, P442, DOI 10.1038/s41581-018-0018-2	80	0.00	9.00
13	Jie ZY, 2017, NAT COMMUN, V8, P0, DOI 10.1038/s41467-017-00900-1	80	0.02	13.44
14	Zhu WF, 2016, CELL, V165, P111, DOI 10.1016/j.cell.2016.02.011	71	0.05	20.46
15	Khalesi S, 2014, HYPERTENSION, V64, P897, DOI 10.1161/HYPERTENSIONAHA.114.03469	58	0.05	6.38
16	Tang WHW, 2015, CIRC RES, V116, P448, DOI 10.1161/CIRCRESAHA.116.305360	55	0.25	11.74
17	Koh A, 2016, CELL, V165, P1332, DOI 10.1016/j.cell.2016.05.041	43	0.00	25.00
18	Wang ZN, 2015, CELL, V163, P1585, DOI 10.1016/j.cell.2015.11.055	41	0.03	12.85
19	Schiattarella GG, 2017, EUR HEART J, V38, P2948, DOI 10.1093/eurheartj/ehx342	35	0.04	5.70
20	Chen ML, 2016, MBIO, V7, P0, DOI 10.1128/mBio.02210-15	34	0.02	8.66

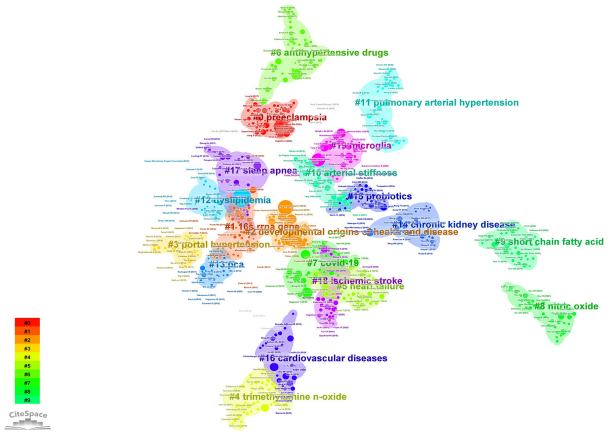

FIGURE 7
(A) The analysis of keyword clusters using citeSpace. **(B)** Top 25 references with the strongest citation bursts identified by citeSpace (2019–2023).

However, the linkage between GM and other cardiovascular diseases, such as hypertrophic cardiomyopathy, endocarditis, and arteritis, is less represented in the literature. This suggests that these diseases could become new research hotspots in the future. The association of GM with maladies such as metabolic syndrome, chronic kidney disease, pulmonary arterial hypertension, portal hypertension, and liver cirrhosis has also been a strong research hotspot, with a wealth of articles available on these subjects. The research is complex given GM's involvement in the progression of a multitude of diseases. Consequently, our analysis concentrated primarily on the significant clusters directly related to HTN.

4.2.1. GM and their mechanisms of action

Prior to 2014, research on the connection between GM and HTN was scant. A handful of clinical trials hinted that dietary modifications could improve weight, insulin sensitivity, blood lipids, and blood pressure in obese patients, coinciding with shifts in GM (11). Yet, a direct causal link between GM and HTN remained unproven, prompting some researchers to suggest GM as a potential therapeutic avenue for HTN. In 2015, a breakthrough came when Yang et al. (3) team conducted a gut genomic analysis on a select group of hypertensive patients and various hypertensive rat models. The findings illustrated comparable disruptions in gut bacteria proportions and SCFAs in both hypertensive humans and rats, signifying a strong correlation between GM dysbiosis and high blood pressure (3). Fast forward to 2017, Li et al. analyzed the metagenomic composition of fecal samples from healthy individuals, prehypertensive subjects, and primary hypertensive patients (4). They discovered that the microbial species in prehypertensive and hypertensive individuals closely resembled each other and significantly differed from those in healthy individuals, further reinforcing the link between microbiota dysbiosis and HTN. Moreover, the team transplanted fecal samples from hypertensive patients into germ-free mice with normal blood pressure. This transplantation led to an increase in the mice's blood pressure, furnishing direct evidence of GM dysbiosis's role in HTN (4). In 2020, Joonatan Palmu and his team conducted a genomic analysis of GM in 6,953 Finnish individuals, unearthing significant species variations such as lactobacilli, which displayed a negative correlation with HTN (12). Another study involving 4,672 participants from six different ethnic backgrounds underscored not only a connection between GM composition and blood pressure but also notable differences in microbiota composition among diverse ethnic groups (13). These investigations robustly endorse GM dysbiosis as a contributing factor in HTN, paving the way for further explorations into the link between GM and cardiovascular diseases. Works from researchers such as Yang Tao and Li Jing continue to garner considerable attention within the scientific community, ranking within the top 1% in the field of clinical medicine based on their high citation thresholds relative to their respective field and year of publication.

Once the link between GM and HTN was established, the mechanisms by which GM influences HTN piqued the interest of a multitude of researchers, making this a hotbed of scientific exploration. In 2017, more than 110 papers were published in this field, reflecting an annual growth of approximately 80 papers. A central focus of recent research is the influence of abnormal GM metabolites on blood pressure. The interest is particularly piqued by metabolites such as SCFAs, trimethylamine N-oxide (TMAO), and secondary bile acids. SCFAs are generally perceived as beneficial to human health. Research has revealed that hypertensive patients exhibit decreased levels of SCFAs (acetate and butyrate) in their blood, correlating with elevated blood pressure (3, 14). Supplementation with acetate (dietary fiber) in hypertensive rats resulted in significant reductions in systolic and diastolic blood pressures and mitigated fibrosis in the heart and kidneys (5). Moreover, supplementing SCFAs to high-fat diet-fed pregnant mice led to markedly lower blood pressure in their male offspring (15). SCFAs exert their antihypertensive effects primarily through immune regulation or receptor binding. They are known to modulate T cells and exhibit anti-inflammatory properties (16, 17), with their anti-inflammatory mechanism mediated by regulating the NLRP3 inflammasome (18). Two known receptors for SCFAs, Olfr78, and G-protein-coupled receptor 41 (Gpr41), are implicated in blood pressure reduction when bound to SCFAs (19). In particular, Gpr41 can regulate blood pressure by reducing arterial vascular tone (20). Recently, additional short-chain fatty acid receptors were discovered, including Gpr43, Gpr109A, and Olfr558 (14, 21). In contrast, TMAO is generally regarded as harmful to the body. A cohort study involving 4,007 participants found an association between increased plasma levels of TMAO and the incidence of cardiovascular events (22). TMAO is known to elevate the risk of cardiovascular disease via mechanisms such as Ang-II activation of the MAPK pathway, increased platelet reactivity, and inflammation promotion (23–25). Hence, TMAO inhibition can enhance cardiovascular disease prognosis (26–28). Notably, TMAO has become a prognostic indicator for various cardiovascular diseases, including atherosclerosis, heart failure, and pulmonary arterial hypertension (29–32). However, some studies have indicated that excessive SCFAs can induce Th1 and Th17 cell proliferation, which promotes inflammation (33), while some TMAO precursors have been found to exert protective effects on the cardiovascular system (34). Research has also shown that hypertensive rats exhibit impaired intestinal barrier function, increased inflammation, and enhanced sympathetic nerve impulses in the gut. However, supplementation with SCFAs lowers blood pressure in rats and improves intestinal barrier function (35, 36). Despite these findings, a causal relationship between the intestinal barrier, GM, and HTN has not been definitively established.Lastly, the influence of GM on the metabolism of antihypertensive drugs, which consequently affects the efficacy of HTN treatment, has also been a focal point of research.

Beyond the mechanisms through which GM impacts HTN, the association between GM and other diseases such as coronary heart disease, myocardial infarction, heart failure, and endothelial dysfunction (represented by the purple cluster in Figure 6B) is gradually emerging as a key research area for numerous scholars.

4.2.2. Salt-sensitive hypertension

Salt-sensitive hypertension (SSH) has emerged as a significant area in the field of GM and HTN research. As depicted in Figure 6C, the average research period for SSH in this field is around 2020, closely tied to keywords such as inflammation, renin-angiotensin system, SCFAs, and metabolic syndrome. In 2015, Blair Mell and colleagues built upon prior research, discovering that Dahl rats on a high-salt diet displayed increased blood pressure and altered GM. Notably, there was an increase in the S24-7 family of the Bacteroidetes phylum and the Veillonellaceae family of the Firmicutes phylum (37). Despite these findings, the mechanisms through which GM influences SSH remained unclear until around 2017 when explorations into the relevant mechanisms began. In 2018, a study by Bier, A et al. examined the SCFAs in the feces of Dahl rats on a high-salt diet and observed a significant decrease in acetate compared to the control

group (38). This finding suggests that high salt intake might influence salt-sensitive blood pressure through its effect on SCFAs. Concurrently, a cohort study of 145 individuals found that lowering sodium intake in hypertensive patients led to increased circulating SCFAs and decreased blood pressure (16). High salt intake has been shown to raise blood pressure by triggering inflammation (39–41). Several studies have highlighted the role of GM in inflammation induced by high salt intake: (1) Rats on a long-term high-salt diet showed elevated levels of TMAO in the systemic circulation and brain. TMAO is known to increase blood pressure by influencing central cardiovascular regulatory centers, promoting neural inflammation, and inducing oxidative stress (42). (2) Another critical study showed that a high-salt diet not only elevated inflammation-associated Th17 cells but also resulted in a decrease in gut lactate sensing (43). These studies set the stage for further research into the potential modulation of GM to alleviate inflammatory cell infiltrations and reduce blood pressure. Over the past three years, recent research has indicated that a high-salt diet can also affect HTN by altering the metabolism of amino acids by the GM (44, 45). For instance, a high-salt diet can modify GABA and glutamate/glutamine metabolism as well as glycolysis-related amino acid metabolism, thereby exacerbating HTN.

4.2.3. Developmental origins of health and disease

The developmental origins of health and disease (DOHaD) concept pertains to the long-lasting effects of certain environmental influences on the structure or function of organisms during early life (15). For instance, an improper diet during pregnancy can lead to various pathological alterations in male offspring, including HTN. However, timely intervention during pregnancy can mitigate high blood pressure in these offspring. In Figure 6B, DOHaD is depicted by a light blue cluster and closely connected with keywords such as SCFAs, TMAO, oxidative stress, chronic kidney disease, and the renin-angiotensin system with an average research year of 2021 (Figure 6C). Before 2014, a handful of studies had noted changes in the GM of pregnant women under the influence of external factors (46). In 2015, Tain et al. made the discovery that high salt intake can induce HTN in the offspring of mice fed a high-fructose diet under the DOHaD concept (47). Around 2017, researchers such as Tain, You-Lin, Hsu, Chien-Ning, and Chih-Yao Hou from the Kaohsiung Chang Gung Memorial Hospital established a strong link between DOHaD and GM. By delving into the underlying mechanisms, they published over 40 articles within this field, solidifying their positions as leading figures. For instance, they found that high-fat, high-fructose, and tryptophan-free diets in pregnant mice led to increased blood pressure in male offspring. However, when the diets of these pregnant mice were supplemented with SCFAs, antibiotics, and butyrate, a significant decrease in the blood pressure of their male offspring was observed, compared to the control group (15, 48, 49). By 2020, mechanisms explored in this field included the renin-angiotensin system, nitric oxide, hydrogen sulfide, oxidative stress, and microbial metabolites. Furthermore, chronic kidney disease has also emerged as a significant research direction within the intersection of DOHaD and GM.

4.2.4. Obstructive sleep apnea-induced hypertension

Obstructive sleep apnea (OSA) is a sleep-related respiratory disorder defined by symptoms such as snoring, respiratory pauses, and excessive daytime sleepiness. The research linking OSA and GM has predominantly revolved around keywords like T cells, HTN, and SCFAs, particularly around May 2020 (Figure 6B, pink cluster). Over the last two decades, multiple clinical trials have established a causal link between OSA and HTN (50). In 2016, a study led by Durgan et al. utilized rats to model OSA, feeding them either a high-fat diet or a regular diet (51). Their findings revealed that rats on the high-fat diet exhibited increased blood pressure and significant alterations in GM, while the rats on the regular diet maintained normal blood pressure. Interestingly, when GM from rats on the high-fat diet was transplanted into rats with normal blood pressure, the recipient rats experienced an increase in blood pressure (51). This experiment signified a causal link between GM and HTN in OSA, offering valuable direction for future research in this area. In 2018, researchers Ganesh and Durgan implemented an intervention using SCFAs in OSA rats. They found that suitable increases in cecal SCFAs concentration could prevent OSA-induced intestinal inflammation and HTN (52). More recently, a clinical study has indicated that OSA patients not only display an imbalance in GM but also an altered Th17/Treg cell ratio (53).

4.2.5. Antihypertensive peptides

Antihypertensive Peptides (ACEIPs) are bioactive peptides generated through fermentation by specific GM, exhibiting antioxidant, anti-inflammatory, and blood pressure-lowering properties (54). ACEIPs achieve their antihypertensive effects through the inhibition of the angiotensin-converting enzyme and the stimulation of angiotensin-converting enzyme 2 pathways (55, 56). As shown in Figure 6B, ACEIP, depicted by the red cluster, is closely tied to keywords like HTN, metabolic syndrome, and insulin resistance. Around 2014, comprehensive research on ACEIP revealed its beneficial effects on metabolic syndrome, including blood pressure reduction and improved insulin resistance. These benefits, derived from ACEIP extracted from animal sources, fermented milk, and other sources, have been confirmed through clinical trials. Presently, researchers are primarily interested in investigating the roles of various types of ACEIP in reducing blood pressure. For instance, numerous ACEIP with impacts on cardiovascular disease have been extracted from plants such as Rumex vesicarius, navy bean, and hidakakombu (57–59). Additionally, ACEIP extracted from human breast milk, cow milk, camel milk, and other animal sources have been examined (60–62), with over 100 ACEIP extracted from dairy products alone (63). Due to the incorporation of both animal and plant studies, some articles within this field have found their place in agriculture-related journals.

5. Conclusion

The study of GM and HTN has become an increasingly prominent research area, drawing the attention of a rising

number of researchers. Numerous experiments have established a causal relationship between GM and HTN. However, the interaction mechanisms between GM and HTN still hold many uncertainties, necessitating further investigation. Concurrently, GM may indirectly influence the development of HTN by affecting the progression of specific diseases. Additionally, the impact of GM on other cardiovascular diseases is progressively garnering interest among researchers. To summarize, we employed bibliometric tools to analyze all articles within this field over the past decade, highlighting important and innovative works across various research directions, uncovering hotspots and emerging trends, and offering valuable insights for future research endeavors.

Author contributions

QJ: Supervision, Writing—review and editing. YJ: Conceptualization, Methodology, Writing—original draft, Writing—review and editing. WL: Data curation, Methodology, Software, Visualization, Writing—original draft. QZ: Data curation, Software, Visualization, Writing—review and editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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EDITED BY
Iain Brownlee,
Northumbria University, United Kingdom

REVIEWED BY
Akira Takamata,
Nara Women's University, Japan
Aamer Sandoo,
Bangor University, United Kingdom

*CORRESPONDENCE
Catarina Rendeiro
✉ c.rendeiro@bham.ac.uk
Jet J. C. S. Veldhuijzen van Zanten
✉ j.j.veldhuijzenvanzant@bham.ac.uk

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Fat intake impairs the recovery of endothelial function following mental stress in young healthy adults

Rosalind Baynham[1], Samuel R. C. Weaver[1,2], Catarina Rendeiro[1,2]* and Jet J. C. S. Veldhuijzen van Zanten[1]*

[1]School of Sport, Exercise and Rehabilitation Sciences, University of Birmingham, Birmingham, United Kingdom, [2]Centre for Human Brain Health, University of Birmingham, Birmingham, United Kingdom

Introduction: Mental stress has been identified as a trigger of cardiovascular events. A single episode of stress can induce acute impairments in endothelial function in healthy adults. Importantly, during stressful periods, individuals often resort to unhealthy behaviors, such as increased consumption of high-fat foods, which is also known to negatively impact endothelial function. Therefore, this study examined whether consumption of a high-fat meal would further exacerbate the negative effect of mental stress on vascular function.

Methods: In a randomized, counterbalanced, cross- over, postprandial intervention study, 21 healthy males and females ingested a high-fat (56.5 g fat) or a low-fat (11.4 g fat) meal 1.5 h before an 8-min mental stress task (Paced-Auditory-Serial-Addition-Task, PASAT). Plasma triglyceride (TAG) concentration was assessed pre- and post-meal. Forearm blood flow (FBF), blood pressure (BP), and cardiovascular activity were assessed pre-meal at rest and post-meal at rest and during stress. Endothelial function, measured by brachial flow-mediated dilatation (FMD) was assessed pre-meal and 30 and 90 min following mental stress.

Results: Plasma TAG concentration was significantly increased following the high-fat meal compared to the low-fat condition. Mental stress induced similar increases in peripheral vasodilation, BP, and cardiovascular activity, and impaired FMD 30 min post-stress, in both conditions. FMD remained significantly impaired 90 min following stress in the high-fat condition only, suggesting that consumption of fat attenuates the recovery of endothelial function following mental stress.

Discussion: Given the prevalence of fat consumption during stressful periods among young adults, these findings have important implications for dietary choices to protect the vasculature during periods of stress.

KEYWORDS

high-fat, mental stress, vascular, endothelial function, flow-mediated dilatation

1. Introduction

Stress is extremely prevalent in today's society, with 74% of the population stating having felt so stressed they are unable to cope (1). Stress has also been linked with both poor physiological and psychological health (2). For example, epidemiological studies have shown that when a population is hit by stressful events such as earthquakes, war, and even losing key football matches, there is an increased incidence of myocardial infarction (3–5). Laboratory studies have shown that mental stress can induce myocardial ischemia (6), and that laboratory-based stress-induced myocardial ischemia is related to ambulatory ischemia (7). Although, the

underlying mechanisms are not yet fully understood, impairments in vascular function have been implicated as a possible mechanism. For example, those who experience mental stress-induced myocardial ischemia also have an attenuated peripheral vasodilatory response during stress (8), as well as increased vascular resistance (9, 10).

It has been well established that mental stress evokes increases in heart rate and blood pressure, driven by activation of the sympathetic nervous system and withdrawal of the parasympathetic nervous system (11). Mental stress also impacts the vasculature, and this sympathetic and parasympathetic activation is associated with a nitric oxide (NO)-mediated increase in peripheral vasodilation during mental stress (as measured by forearm blood flow; FBF) (12, 13). Importantly, stress-induced vasodilation is attenuated in populations at risk of cardiovascular disease (CVD), such as obesity (14). Furthermore, mental stress can trigger a transient, but clinically significant, decline in endothelial function (as measured by brachial flow-mediated dilatation; FMD) from 15 to 90 min following stress in young healthy adults (15, 16). Potential mechanisms have been suggested to involve stress-induced increases in cortico-releasing hormone (CRH), cortisol, and pro-inflammatory cytokines (15), as well as up-regulation of oxidative stress (17); all of which can attenuate NO-production and result in endothelial dysfunction (18).

Stress can also influence physical health indirectly through changes in behavior (19) and adoption of maladaptive coping mechanisms (2). Importantly, stress can impact eating patterns, with studies reporting 42% of individuals to consume more, and more often unhealthy foods (i.e., high-fat and sugar) during stressful periods (20–22). For instance, young adults are more likely to choose foods with higher levels of fat following stress compared to a no stress condition (23). Crucially, fat intake can negatively impact the vasculature: brachial FMD is reported to be impaired for 8 h following consumption of a high-fat meal in healthy and clinical populations (24–26). Hypertriglyceridemia and hyperglycemia following fat consumption (27, 28) have been shown to stimulate the vasoconstrictor endothelin-1 (ET-1), reactive oxygen species (ROS) and inflammatory markers (27, 29), which subsequently reduce endothelium-derived NO (30). Reduced NO production is implicated as a major mechanism driving fat-induced endothelial dysfunction. Furthermore, impaired resting endothelial function has been associated with poorer vascular responses to stress (31). As such, it is likely that increased fat intake during stress further aggravates the effect of stress on the vasculature. Given the high prevalence of fat consumption during stressful periods it is important to determine the full impact of such interactions on human vascular health.

To our knowledge, only one study has previously attempted to address this question using a model of repeated stress, but possibly due to a relatively low number of participants ($N = 10$) and timing of FMD measurements, did not show effects of stress and fat separately on FMD or an interaction between stress and fat (32). The current study aimed to investigate the effect of a high-fat meal on peripheral (FBF) blood flow as well as endothelial function (FMD) in healthy adults in the context of a mental stress challenge. We hypothesized that a high-fat meal will impair peripheral blood flow during stress and exacerbate mental stress-induced endothelial dysfunction, compared to a low-fat meal.

2. Materials and methods

2.1. Participants

Twenty-one participants (11 male, 10 female) were recruited via email and poster advertisements. Females were tested during the same phase of the menstrual cycle (early follicular, days 1–5 of menstruation) to control for the influence of menstrual hormones. Participants were between 18 and 45 years old. Exclusion criteria were: (i) smokers, (ii) consumption of >21 units alcohol per week, (iii) acute illness/infection, (iv) history of cardiovascular, respiratory, metabolic, liver, inflammatory diseases, or blood-clotting disorders, (v) allergies or food intolerances, (vi) weight reducing dietary regiment or dietary supplements, and (vii) long-term medication or antibiotics in the previous 3 months. Participants were awarded course credit marks when applicable. Ethical approval was obtained from the University of Birmingham Science, Technology, Engineering and Mathematics ethics committee (ERN17_1755D), and all participants gave written informed consent prior to participation in the study.

2.2. Habitual dietary intake

Habitual dietary intake was assessed using the validated European Prospective Investigation into Diet and Cancer (EPIC) Norfolk Food Frequency Questionnaire (FFQ) (33). Participants recalled their usual dietary intake over the previous 12 months, with 131 different food items, on a 9-point scale (never or less than once per month, 1–3 per month, once a week, 2–4 per week, 5–6 per week, once a day, 2–3 per day, 4–5 per day, and 6+ per day). The FFQ EPIC Tool for Analysis (FETA) was used to calculate nutrient data (34). The following nutrients are reported in this study: energy (kcal), fat (g), saturated fat (g), carbohydrate (g), sugars (g), fiber (g), protein (g) and portions of fruit and vegetables (calculated as 1 portion corresponding to 80 g), to give a general view of habitual dietary intake.

2.3. Study design

The study design was a randomized, counterbalanced, cross-over, postprandial intervention study (Figure 1). Participants visited the laboratory twice, at least a week apart for males and approximately 1 month apart for females. Participants were asked to refrain from food for 12 h and from alcohol, vigorous exercise, and caffeine 24 h before each testing session. Each session commenced at approximately 8 AM, and firstly, compliance with pre-visit requirements were checked. Participants were then instrumented with equipment to measure cardiovascular activity. Following this, participants rested in a supine position for 20 min before pre-intervention (Baseline) measurements were taken: (i) brachial FMD, (ii) FBF, (iii) cardiovascular activity (beat-to-beat blood pressure [BP], heart rate [HR], heart rate variability [HRV] and pre-ejection period [PEP]); (iv) blood sample (to measure plasma triglycerides [TAG] concentration). Following these assessments, participants consumed either a high-fat meal (HFM) or a low-fat meal (LFM). Participants then rested for 1.5 h during which they completed lifestyle questionnaires (only habitual dietary data reported, session 1) and had the option to complete

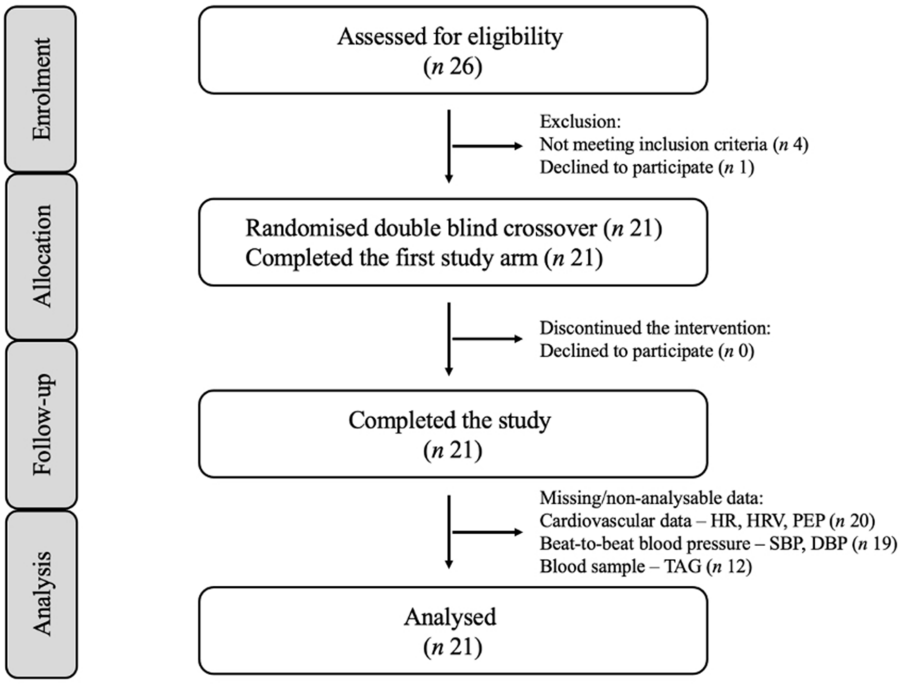

FIGURE 1
Consolidated standards of reporting trials (CONSORT) flow diagram for postprandial intervention study.

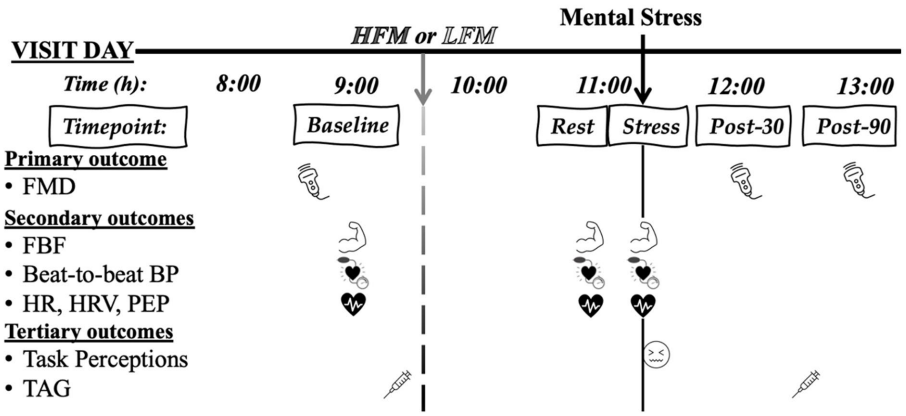

FIGURE 2
Experimental study design.

their own work or watch a nature documentary. Subsequently, FBF and cardiovascular activity were measured during an 8-min rest (Rest) and during an 8-min mental stress – Paced-Auditory-Serial-Addition-Task (PASAT) (Stress). During each 8-min assessment, FBF was measured during minutes 2, 4, 6, and 8. BP, HR, PEP and HRV were analysed for these minutes. Brachial FMD was measured 30 and 90 min following stress. A second blood sample to measure TAG concentration was taken 45 min following stress. A trained researcher carried out all measurements and analyses. Both sessions lasted 5 h and participants were debriefed following completion of both visits (Figure 2).

2.4. High- and low-fat interventions

The HFM and LFM were prepared just before consumption, and all fresh ingredients were bought within 24 h of each testing session. The meals were calorie matched, with the HFM containing 56.5 g fat and the LFM containing 11.4 g fat (24) (Table 1). All other nutrients were as closely matched as possible, except for carbohydrate as a higher level of carbohydrate in the LFM was necessary to match caloric intake. Participants were asked to consume the meal within 20 min. Seven participants were not able to finish the low-fat meal and 2 participants were not able to finish the high-fat meal, but no adverse side effects were reported. Whilst it was impossible to blind

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TABLE 1 Nutrient composition of the high-fat and low-fat meals.

Meal type	High-fat meal[1]	Low-fat meal[2]
Nutrient composition:		
Energy (Kcal)	891.0	886.0
Fat (g)	**56.5**	**11.4**
Saturated fat (g)	**35.1**	**5.6**
Carbohydrate (g)	65.0	160.1
Sugars (g)	20.2	19.4
Fiber (g)	2.4	5.9
Protein (g)	29.9	33.3
Salt (g)	2.0	2.5

[1]This meal consists of 2 butter croissants with 10 g salted butter, 1.5 slices of cheese and 250 ml whole milk. [2]This meal consists of 4 slices of white bread with 30 g Philadelphia light spread, 90 g so-organic cornflakes and 250 ml semi-skimmed milk.

experimenters and volunteers to the interventions during the visits, these were blinded during all data analyses.

2.5. Blood sampling and plasma triglycerides analysis

Blood samples were collected to assess fasting and post-meal plasma TAG concentration. Blood samples were collected in EDTA-coated 10 ml tubes by a trained phlebotomist, from the antecubital vein of the arm. The samples were immediately centrifuged at 5000 rpm for 10 min at 4°C to separate the plasma. 1,000 µl of plasma was pipetted into 1 aliquot for TAG analysis, and stored at −80°C for future assessment. Plasma was later analyzed using commercially available kits for TAG concentration (Triglyceride Kit, Randox, London, United Kingdom), using an automated photometric clinical chemistry analyzer RC Daytona+ (Randox). Samples were analyzed in duplicates, with a coefficient of variation (CV) of 0.44%.

2.6. Mental stress task

The mental stress task used was the 8-min PASAT, shown to have good test–retest reliability and to induce a physiological response (12, 35, 36). The PASAT requires participants to add two sequentially presented single-digit numbers (1–9), adding the number presented to the previous number they heard. The delivery of the numbers became quicker, with time intervals reducing every 2 min; from a 2.8 s interval to 2.4 s, 2.0 s, and finally 1.6 s. Participants were filmed and asked to watch themselves on the screen, which they were told would be evaluated by 2 independent body language assessors. An experimenter marked the participants' responses, whilst sounding a loud aversive buzzer-noise at standard intervals once every 10 answers: either following an incorrect response or at the end of the 10-number block. The participants were told they were in direct competition with other participants and lost points for each incorrect answer. These elements of social evaluation, punishment, and competition have been used previously (37) and have been shown to enhance the provocativeness of the task (38). Immediately following the PASAT, an experimenter asked the participant to verbally rate how difficult, stressful, competitive, and enjoyable they found the task, and to what extent they were trying to perform well, scored on a 7-point scale ranging from 0 'not at all' to 6 'extremely'. Following completion of both visits, participants were informed about the deception of the task.

2.7. Cardiovascular activity

2.7.1. Impedance cardiography

The Ambulatory Monitoring System, VU-AMS5s (TD-FPP, Vrije Universiteit, Amsterdam, Netherlands) was used to continuously record an electrocardiogram (ECG) and impedance cardiogram (ICG) to measure heart rate (HR, bpm), heart rate variability (HRV, ms – a measure of parasympathetic activity) and pre-ejection period (PEP, ms – a measure of sympathetic activity) in line with published guidelines (39, 40). The VuAMS5fs was connected to 7 Ag/AgCl spot electrodes (Invisatrace, ConMed Corpo- ration; Largo, FL, USA). ECG electrodes were placed below the right clavicle, between the lower 2 ribs on the right side, and at the apex of the heart on the left lateral margin of the chest. ICG electrodes were placed at the top end of the sternum at the suprasternal notch and at the bottom of the sternum at the xiphoid process, and on the spine, 3 cm above and 3 cm below the upper and lower electrodes, respectively. Analyses were undertaken offline using VU-DAMS software with manual inspection and correction of ECG and averaged ICG data, used to derive HR, HRV, and PEP, averaged for each minute of assessment. HRV was calculated from beat-to-beat ECG data as the square root of the mean of the sum of the squared successive differences in cardiac inter-beat intervals. PEP was defined as the time between Q-wave onset and commencement of systole (39, 40).

2.7.2. Beat-to-beat blood pressure

Beat-to-beat arterial BP was measured using a Finometer (Finapres Medical Systems; Amsterdam, Netherlands), with a cuff around the intermediate phalanx of the middle finger. Continuous data was recorded via a Power1401 (CED, Cambridge, UK) connected to a computer programmed in Spike2. Data was analyzed for the same minutes as FBF was recorded and averaged for each minute of assessment. Analyses were undertaken offline whereby each file was visually inspected, and systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP) were obtained.

2.8. Forearm blood flow

Forearm blood flow was measured using venous occlusion plethysmography. A mercury-in-silastic strain gauge was connected to a plethysmograph (ECG, Hokanson; Jacksonville, WA, USA), producing an output voltage with frequency 0–25 Hz. The plethysmograph signal was digitized at 100 Hz with 16-bit resolution, via a Power1401 (CED) connected to a computer programmed in Spike2, as previously described by Paine et al. (12). One congestion cuff was placed around the wrist (TMC7, Hokanson), and inflated for 1 min to supra-systolic blood pressure (>220 mmHg). Another congestion cuff was placed around the brachial region of the upper arm (SC12, Hokanson), and inflated for 5 s to above venous pressure (40 mmHg), every 15 s providing 3 blood flow measurements each minute. Blood flow analysis and calibration were undertaken offline using Spike2 (CED). Each increase in limb circumference is identified as a slope, which were averaged to yield a mean blood flow per minute

(12). Forearm vascular conductance (FVC) was calculated by dividing FBF by MAP per minute of assessment.

2.9. Flow-mediated dilatation

Flow-mediated dilatation was used to assess endothelial function of the brachial artery. A 15–4 Mhz (15L4 Smart MarK™; Terason, MA, USA) transducer was attached to a Terason Duplex Doppler System (Usmart 3,300 NexGen Ultrasound; Terason). This has a wall-tracking and automatic edge-detection software (Cardiovascular Suite, Quipu; Pisa, Italy), which allows for continuous measurement of diameter and blood velocity throughout the FMD assessment. Following 20 min of supine rest, the brachial artery was imaged longitudinally, 5–10 cm proximal to the antecubital fossa. A brachial cuff was placed around the forearm and, following a 1-min baseline, this was inflated to 220 mmHg for 5 min, to cause ischemia. Subsequently, the rapid cuff deflation caused reactive hyperemia, and the image was recorded continuously for 5 min post-pressure release. This is in accordance with established guidelines (41). All measurements were undertaken by the same trained researcher, who demonstrates sufficient reproducibility in brachial FMD measurements (coefficient of variation: intra-day 5.49%, inter-day 10.87%). All file images were analyzed by the same trained researcher, blinded to condition and measurement details. Peak diameter was defined as the largest diameter obtained after occlusion is released. The FMD response was calculated as the relative diastolic diameter change between baseline and peak diameter. Resting arterial diameter was also estimated based on a time-average across the first minute of recording.

2.10. Statistical analysis

All statistical analyses were conducted using IBM SPSS software (version 25). The cardiovascular and FBF measurements during pre-intervention baseline, rest, and stress were averaged separately to provide a mean pre-intervention baseline, rest, and stress value for each outcome. Pre-intervention baseline measures (FMD, FBF, HR, SBP, DBP, TAG), task perceptions and PASAT scores were compared using a 2 condition (HFM, LFM) repeated measures analysis of variance (ANOVA). Plasma TAG concentration was analyzed using a 2 condition (HFM, LFM) by 2 time (baseline, 2 h post-meal) repeated measures ANOVA. Subsequently, a series of 2 condition (HFM, LFM) by 3 time (baseline, rest, stress) repeated measures ANOVAs were conducted to analyze the cardiovascular and FBF variables. FMD (including resting arterial diameter) was analyzed using a 2 condition (HFM, LFM) by 3 time (baseline, post-30, post-90) repeated measures ANOVA. Where appropriate, pairwise comparisons using Bonferroni correction were conducted to investigate significant effects in more detail. All analyses were also conducted with sex as a between-subject variable. All values reported in text, tables, and graphs are mean ± SD. Occasional missing data are reflected in the reported '*n*' values, and include n-1 due to VU-AMS malfunction, n-2 due to Finapres malfunction and n-9 due to participants not willing to have a blood sample or missed sample time-points. Seven participants did not finish the meal. All statistical tests were repeated excluding these 7 participants. The results were broadly similar to the analyses with the full sample; therefore, it was decided to include all participants to maximize power. For all analyses, significance was set at $\alpha < 0.05$.

3. Results

3.1. Participant characteristics

Participant characteristics are presented in Table 2. Participants were aged 20–30 years old, with a healthy body mass index (BMI) and identified as white European ethnicity ($n = 19$) or Asian ethnicity ($n = 2$). Pre-intervention baseline FMD, FBF, HR, BP, and TAG concentration were similar in both conditions ($n = 21$, Table 2).

3.2. Habitual dietary intake

Table 3 displays participant's estimated daily intake of key nutrients and the percentage of participants exceeding or not meeting daily recommendations, as suggested by the National Health Service (NHS). The average daily intake of fat was 59.42 ± 18.85 g (23.8% of participants exceeding the recommended daily intake) and saturated fat was 21.30 ± 6.53 g (19.0% of participants exceeding the

TABLE 2 Mean ± SD participant pre-intervention baseline characteristics in the high-fat meal and low-fat meal condition.

Participant characteristics	High-fat meal	Low-fat meal	*p*-value
N	21 (M:11, F:10)		/
Age (years)	22.1 ± 2.7		/
BMI (kg/m^2)	23.62 ± 3.1		/
FMD (%)	5.62 ± 1.33	5.50 ± 1.32	0.474
FBF (mm/100 ml/min)	2.47 ± 0.98	2.21 ± 0.60	0.240
HR (bpm)	59.11 ± 8.70	59.26 ± 7.71	0.736
SBP (mmHg)	123.11 ± 22.23	118.82 ± 15.68	0.487
DBP (mmHg)	56.03 ± 12.49	52.05 ± 9.02	0.234
TAG (mmol/l)	0.78 ± 0.30	0.79 ± 0.28	0.956

N, number, BMI: body mass index; FMD, flow-mediated dilatation; FBF, forearm blood flow; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; TAG, triglycerides.

TABLE 3 Mean ± SD estimated daily intake of key nutrients.

Nutrients	Sample average	% of participants over/under recommended daily intake
Energy (Kcal)	1576.48 ± 418.93	N/A
Fat (g)	59.42 ± 18.85	23.8% over
Saturated fat (g)	21.30 ± 6.53	19.0% over
Carbohydrate (g)	185.50 ± 57.45	N/A
Sugars (g)	87.27 ± 42.51	100% over
Fiber (g)	14.09 ± 5.72	100% under
Protein (g)	74.34 ± 25.07	N/A
Portions of fruit and vegetables*	5.71 ± 3.32	38.1% under

Recommendations – fat: <70 g/day, saturated fat: <30 g/day (male)/<20 g/day (female), sugar: <30 g/day, fiber: >30 g/day, fruit and vegetables: >5 portions/day. *1 portion = 80 g (NHS guidelines).

recommended daily intake). Fat and saturated fat consumption was similar between males and females. The average intake of fruit and vegetables was 5.71 ± 3.32 portions per day, with females consuming almost 1 extra portion per day. However, 38.1% of participants did not meet the daily recommendations of 5 portions of fruit and vegetables per day. 100% of participants did not meet the suggested recommendations for fiber intake and exceeded the recommendations for sugar intake (Table 3).

3.3. Plasma TAG

A 2 condition (HFM, LFM) × 2 time (baseline, 2 h post-meal) ANOVA revealed an overall time effect ($n = 12$, $p < 0.001$), condition effect ($n = 12$, $p < 0.001$) and a condition × time interaction effect ($n = 12$, $p < 0.001$) for TAG concentration (Figure 3). *Post hoc* analyses revealed that TAG concentration was significantly higher after the high-fat meal compared to the low-fat meal ($p < 0.001$), and significantly higher 2 h post-meal compared to pre-intervention baseline ($p < 0.001$). Further exploration of the interaction effect revealed that there was no significant difference in TAG concentration between conditions at pre-intervention baseline ($p = 0.956$), but TAG concentration was significantly higher following the high-fat meal compared to the low-fat meal at 2 h post-meal ($p < 0.001$).

3.4. Mental stress task ratings

Separate two condition (HFM, LFM) ANOVAs revealed no significant difference in task performance (PASAT score) or task perceptions between high-fat and low-fat conditions ($n = 21$). Participants perceived the task as similarly difficult, stressful, competitive, enjoyable, and tried to perform well to the same extent after both high-fat and low-fat meals ($n = 21$, Table 4).

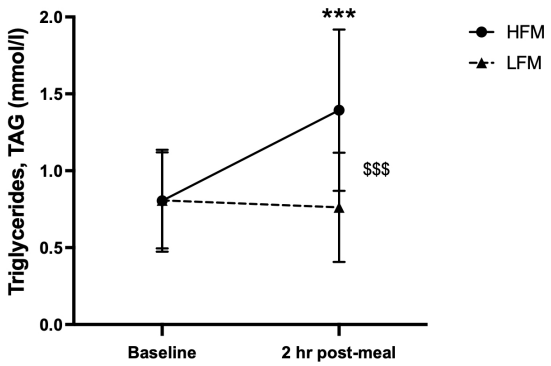

FIGURE 3
Time course of TAG concentration at baseline and 2 h post-meal. $n = 12$. Data are presented as Mean ± SD. * Significantly different compared to baseline in high-fat meal condition, $^{\$}$ significantly different between conditions, ***/$^{\$\$\$}p < 0.001$. HFM, high-fat meal; LFM, low-fat meal.

TABLE 4 Mean ± SD task performance (PASAT) and ratings ($n = 21$).

Task ratings	High-fat meal	Low-fat meal	*p*-value
PASAT score	141 ± 34	138 ± 35	0.544
Perceived difficulty	4.81 ± 0.60	4.71 ± 0.72	0.576
Perceived stressfulness	4.90 ± 0.94	4.66 ± 0.73	0.204
Perceived competitiveness	4.33 ± 1.20	3.86 ± 1.35	0.135
Perceived enjoyment	1.95 ± 1.16	1.48 ± 1.08	0.125
Perception of trying to perform well	5.00 ± 0.89	5.14 ± 0.96	0.419

Maximum score for PASAT is 228, task ratings are scored from 0 to 6. PASAT, paced-auditory-serial-addition-task.

3.5. Cardiovascular activity

Separate 2 condition (HFM, LFM) × 3 time (baseline, rest, stress) ANOVAs revealed an overall time effect for HR ($n = 20$, $p < 0.001$), PEP ($n = 20$, $p < 0.001$), HRV ($n = 20$, $p < 0.001$), SBP ($n = 19$, $p < 0.001$) and DBP ($n = 19$, $p < 0.001$) (Figure 4). *Post hoc* analyses revealed that HR was significantly higher during rest compared to baseline ($p < 0.001$) and increased further during stress ($p < 0.001$). HRV was significantly lower during stress compared to baseline and rest (p's < 0.001). Compared to baseline, PEP was significantly lower during rest (p < 0.001), with a further decrease during stress ($p < 0.001$). Both SBP and DBP were significantly higher during stress compared to both baseline (SBP: $p < 0.001$, DBP: $p = 0.002$) and rest (p's < 0.001) and no significant differences were found between pre-intervention baseline and rest (SBP: $p = 0.492$, DBP: $p = 0.152$). There were no significant condition or condition × time interaction effects for HR (condition: $p = 0.301$, interaction: $p = 0.562$), HRV (condition: $p = 0.773$, interaction: $p = 0.913$), PEP (condition: $p = 0.854$, interaction: $p = 0.608$), SBP (condition: $p = 0.463$, interaction $p = 0.882$) or DBP (condition: $p = 0.269$, interaction: $p = 0.620$).

3.6. Forearm blood flow during acute mental stress

A 2 condition × 3 time ANOVA revealed an overall time effect for FBF ($n = 21$, $p < 0.001$) and FVC ($n = 19$, $p = 0.007$) (Figure 5). *Post hoc* analyses revealed that FBF was significantly higher during stress compared to both baseline ($p < 0.001$) and rest ($p < 0.001$). Similarly, FVC was significantly higher during stress compared to baseline ($p = 0.023$) but not rest ($p = 0.062$). There were no condition nor condition × time interaction effects for FBF (condition: $p = 0.357$, interaction: $p = 0.136$) or FVC (condition: $p = 0.432$, interaction: $p = 0.188$).

3.7. Flow-mediated dilatation following mental stress

Brachial FMD following mental stress is reported in Figure 6 ($n = 21$). A 2 condition × 3 time ANOVA revealed a significant time effect for brachial FMD ($p < 0.001$). Post-hoc analyses showed that FMD at 30 min post-stress was significantly lower compared to both baseline ($p < 0.001$) and 90 min post-stress ($p = 0.001$), and FMD at 90 min post-stress was lower compared to baseline

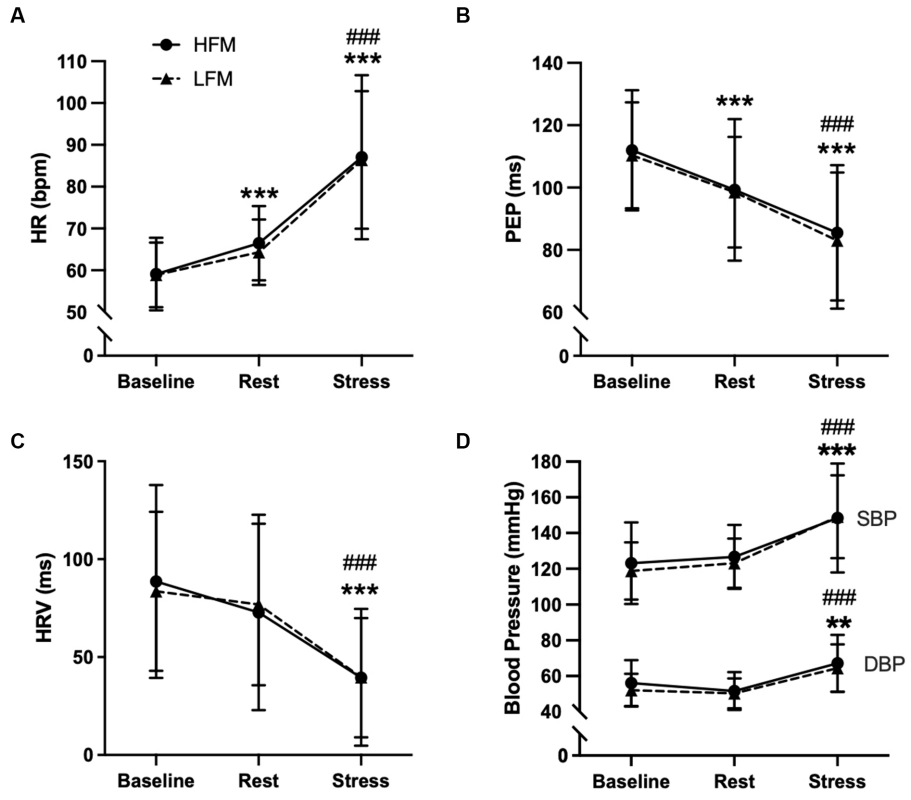

FIGURE 4
Time course of cardiovascular activity [HR **(A)**, PEP **(B)**, HRV **(C)**, BP **(D)** during baseline, rest and stress following either a high-fat or low-fat meal]. n=20 **(A–C)**/n = 19 **(D)**. Data are presented as Mean ± SD. * Significantly different from baseline, $^{\#}$ significantly different from rest, ***/$^{\#\#\#}p < 0.001$, **$p < 0.01$. HR, heart rate; HRV, heart rate variability; PEP, pre-ejection period; SBP, systolic blood pressure; DBP, diastolic blood pressure; HFM, high-fat meal; LFM, low-fat meal.

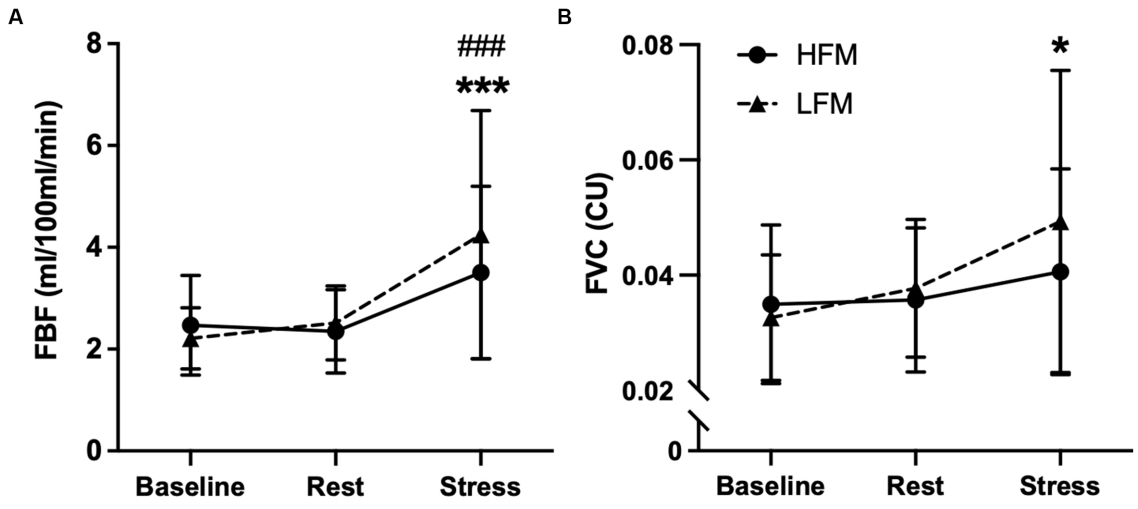

FIGURE 5
Time course of forearm blood flow [FBF **(A)** & FVC **(B)**] during baseline, rest and stress following either a high-fat or low-fat meal. n = 21**(A)**/19**(B)**. Data are presented as Mean ± SD. * Significantly different from baseline, $^{\#}$ significantly different from rest. ***/$^{\#\#\#}p < 0.001$, *p <0.05. FBF, forearm blood flow; FVC, forearm vascular conductance; HFM, high-fat meal; LFM, low-fat meal.

($p = 0.048$). Furthermore, there was a significant condition × time interaction effect for brachial FMD ($p = 0.008$) (Figure 6). Further exploration of this interaction effect revealed that FMD was significantly lower 90 min post-stress in the high-fat condition compared to the low-fat condition ($p = 0.018$). Examination of the time effects in both conditions separately, showed that in the

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high-fat condition, there was no significant difference in FMD between 30 min and 90 min post-stress ($p = 0.134$), but both were different from baseline ($p < 0.001$, $p = 0.003$, respectively). In the low-fat condition, FMD was significantly lower at 30 min post-stress compared to both baseline ($p = 0.008$) and 90 min post-stress ($p < 0.001$), but there was no difference between baseline and 90 min post-stress ($p = 1.000$). In other words, in the high-fat condition, FMD remained significantly lower up to 90 min post-stress, whereas in the low-fat condition, FMD was no longer significantly different from baseline 90 min post-stress. There was no significant condition effect for brachial FMD ($p = 0.085$).

Brachial arterial diameter ($n = 21$), positive blood flow ($n = 21$), and negative blood flow ($n = 19$) are reported in Table 5. There was no significant effect of condition ($p = 0.123$), time ($p = 0.316$) or condition × time interaction ($p = 0.219$) for arterial diameter, suggesting satisfactory sonography. There was no significant time ($p = 0.749$) or condition × time interaction ($p = 0.107$) effect for positive blood flow, yet a significant condition effect ($p = 0.002$), with a greater blood flow in the high-fat compared to the low-fat condition. There was no significant condition ($p = 0.421$) or condition × time interaction ($p = 0.723$) effect for negative blood flow, but a significant time effect ($p < 0.001$) with a significantly greater negative blood flow 30 min post-stress compared to baseline and 90 min post-stress.

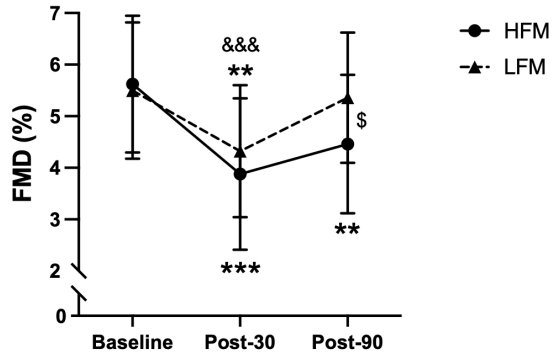

FIGURE 6
Time course of brachial artery FMD (%) during baseline, post-30 and post-90 following either a high-fat or low-fat meal. $n = 21$. Data are presented as Mean ± SD. $^{\$}$ Significantly different between conditions, * significantly different compared to baseline, $^{\&}$ significantly different compared to post-90. ***/$^{\&\&\&}p < 0.001$, **$p < 0.01$, $^{\$}p < 0.05$. FMD, Flow-mediated dilatation; HFM, high-fat meal; LFM, low-fat meal.

3.8. Sex differences

All analyses were also carried out with sex as a between-subject variable. There were no significant condition × sex interaction effects for FBF ($p = 0.380$), FVC ($p = 0.952$), HR ($p = 0.665$), HRV ($p = 0.947$), PEP ($p = 0.856$), SBP ($p = 0.746$), DBP ($p = 0.826$), FMD ($p = 0.710$) or TAG ($p = 0.404$). There were no significant time × sex interaction effects for FBF ($p = 0.207$), FVC ($p = 0.444$), HR ($p = 0.612$), HRV ($p = 0.193$), PEP ($p = 0.846$), DBP ($p = 0.065$), FMD ($p = 0.893$) or TAG ($p = 0.799$). However, there was a significant time × sex interaction for SBP ($p = 0.008$), whereby males have a significantly lower SBP compared to females at pre-intervention baseline ($p = 0.015$), and SBP significantly increases from pre-intervention baseline to rest for males ($p = 0.035$) but not for females ($p = 1.000$). Finally, there was no significant condition × time × sex interaction for FBF ($p = 0.665$), FVC ($p = 0.930$), HR ($p = 0.180$), HRV ($p = 0.444$), PEP ($p = 0.186$), SBP ($p = 0.397$), DBP ($p = 0.170$), FMD ($p = 0.908$) or TAG ($p = 0.357$).

4. Discussion

The current study investigated the effects of fat consumption and stress on the vasculature in young healthy adults. As expected, and shown previously, we observed peripheral vasodilation and cardiovascular perturbations during mental stress and a decline in brachial FMD 30 min following mental stress. To our knowledge, this is the first study to show that consumption of a high-fat meal prevents the recovery of endothelial function 90 min following mental stress. Fat consumption did not influence peripheral vasodilation or cardiovascular (HR, PEP, HRV, BP) responses during stress.

As previously shown, mental stress induced an acute increase in FBF (12, 37). Similarly, we observed a decline in brachial FMD 30 min following mental stress (1.74 and 1.18% decline following high and low-fat meals, respectively), in line with our (37) and other previous studies in healthy adults (42–46). NO has been implicated in both the peripheral vasodilation during mental stress and the decline in FMD following mental stress. Sympathetic activation and parasympathetic withdrawal are responsible for increased cardiovascular reactivity during stress (47), and this autonomic activity also contributes to NO-mediated vasodilation during stress (48, 49). Following stress, elevated levels of cortisol and inflammatory markers (42, 50) have been suggested to contribute to post-stress endothelial dysfunction (51) through a reduction in NO bioavailability (52, 53).

No change in resting or stress-induced FBF was reported following the high-fat meal in comparison to the low-fat meal control condition. Only a few studies have investigated the effect of a high-fat meal on resting FBF, with mixed findings reporting attenuated (54), improved (55) and no change (56) in peripheral vasodilation. However, differences in fat content, i.e., 30 g fat (54) vs. 60 g fat (56), calorie

TABLE 5 Mean ± SD brachial arterial diameter following mental stress ($n = 21$).

Timepoint	High-fat meal			Low-fat meal		
	Baseline	Post-30	Post-90	Baseline	Post-30	Post-90
Diameter (mm)	3.77 ± 0.63	3.83 ± 0.67	3.84 ± 0.67	3.76 ± 0.67	3.76 ± 0.69	3.75 ± 0.70
Positive blood flow (ml•min^{-1})	98.80 ± 54.98	107.14 ± 61.39	105.30 ± 69.20	86.27 ± 58.49	70.82 ± 40.66	81.86 ± 51.18
Negative blood flow (ml•min^{-1})	−7.84 ± 10.42	−17.04 ± 18.98	−11.51 ± 15.43	−10.90 ± 10.35	−17.74 ± 14.65	−13.10 ± 14.78

count, as well as other nutrients taken together with fat (55, 57) make a direct comparison between the studies challenging. Furthermore, the timing of the FBF assessment may also influence these results. For example, the present study measured resting FBF 1 h 15 min post-fat consumption, whilst Shimabukuro et al. (2007) measured FBF 2 h following a high-fat meal, and other studies' assessments have been at least 3 h post-fat intake, which is more in line with the fat-induced peak in TAG (58–60). Therefore, future studies should investigate resting FBF for longer periods following fat consumption, to provide evidence of the mechanisms involved in peripheral vasodilation following fat consumption.

Stress-induced FBF after a high-fat meal was only investigated by one other study, which reported attenuated FBF responses to stress post-fat intake, in contrast with our results (even though we used a comparable intervention) (56). There are, however, other notable methodological differences between the studies, such as provocativeness of the task, order of meal conditions, and control condition (fasted versus low-fat in the current study). The task used in the current study induced similar and substantial HR responses in both conditions (27 bpm increase in low-fat condition, 28 bpm increase in high-fat condition) in line with previous studies that have used this protocol (12, 35, 36). The shorter task applied by Gowdak and colleagues (56) induced a lower HR response, which was significantly lower after the high-fat meal (6 bpm increase) compared to the fasted condition (10 bpm increase). In the present study, the order of conditions was counterbalanced between participants and the conditions were completed on separate days. In contrast, in the previous study, all participants completed the fasted condition prior to the high-fat condition, and both conditions were completed on the same day (56). Finally, the previous study compared a high-fat condition with a fasted condition, whereas the control condition in the current study was a low-fat meal, meaning both conditions were similar and postprandial with the exception being a difference in fat content. Therefore, it is difficult to determine if the reduced FBF reported by Gowdak and colleagues (56) following a high-fat meal is due to an order effect of testing, or just a postprandial effect, or fat intake itself.

Fat consumption did not influence the observed decline in FMD 30 min post-stress yet did impact the recovery of FMD 90 min post-stress. Some studies have shown a < 1% decrease in FMD following fat consumption (24, 61) and a more consistent 1–3% decline in FMD following stress (15), yet these findings suggest there is no additive (or interaction) effect of fat and stress on FMD 30 min post-stress. However, in the present study, fat consumption did impair the recovery of FMD at 90 min following stress, suggesting that consuming fat during stressful periods can prolong impairments in endothelial function in healthy young adults. On the other hand, Poitras et al. (32) reported no effect of fat consumption on FMD 10 min following stress, which is in agreement with our results, as earlier time points (30 min post-stress) do not seem to result in worsened endothelial function. However, direct comparisons between the two studies must be taken with caution as there are significant methodological differences. Poitras and colleagues (32), subjected participants to four consecutive provocative stress tasks (50 min apart, inducing 20 bpm increases in HR) and no effects on FMD were detected 10 min post stress, in both low and high-fat conditions, indicating no impact of stress alone on endothelial function. Indeed, the literature presents more consistent FMD impairments 30 to 90 min post-stress (which we targeted in the current study) (15), with one study showing no FMD impairment 15 min post-stress (62). Furthermore, it is well-established that the autonomic nervous system is stimulated during mental stress (47), and it is possible that sympathetic activation remains elevated at 10 min post-stress, making the FMD assessments less reliable. Importantly, the design of the present study allowed us to determine the impact of fat consumption on FMD recovery following stress without the confounder of an activated sympathetic nervous system, which has not been possible with previous study designs. Overall, our data suggests that reduced post-stress endothelial function after fat consumption is only apparent at least 90 min post stress, whilst at earlier time points (30 min) no fat-stress interaction is detected.

The mechanisms by which fat consumption delays the recovery of FMD following mental stress are not known. TAG and C-reactive protein (CRP) have been evidenced to be increased in circulation 2–4 h post-fat consumption (58–60), as supported in the present study. This is reflected in our FMD assessments and may explain why intake of fat slows down endothelial function's recovery 90 min post-stress, but not 30 min post-stress (2 h post-fat intake). The mechanisms driving hypertriglyceridemia-induced endothelial dysfunction are not clear. However, there is evidence that triglyceride-rich lipoprotein particles may cause direct injury to the vascular wall (63). Alternatively, fat consumption may induce endothelial dysfunction indirectly by increasing oxidative stress, as hypertriglyceridemia has been evidenced to upregulate superoxide anion, a precursor of ROS (27). Finally, elevations in triglycerides and CRP following fat consumption have been shown to stimulate vasoconstrictor ET-1 and inflammatory markers (29). All of these mechanisms can subsequently reduce endothelium-derived NO (30), thus impairing endothelial function, and should be measured in future work. Whilst insulin and TAG start to increase in circulation 30 min following fat ingestion (58), they are unlikely to have reached their peak during our stress task and FBF assessment (1 h 15 min post-fat consumption), which may explain our null results for FBF. Furthermore, even though postprandial increases in TAG and insulin are likely to modulate FBF, the direction of this response is not well-established (55, 57). As FMD was our primary outcome, this informed the choice of timing post-fat consumption and, ensures that we are simultaneously targeting the timeframes in which circulatory TAGs rise and NO declines post-stress. Future studies should be designed to target the FBF response timeframe, allowing the direct assessment of the impact of fat on vascular responses during stress.

In line with previous research, the current study showed no influence of fat consumption on resting cardiovascular parameters (64, 65). Whilst fat consumption could influence sympathetic activation, there is evidence that other nutrients and consumption of food in general have a predominant role (66, 67). This is supported by the observed postprandial increase in HR at rest, following consumption of both high and low-fat meals. As expected, mental stress induced an immediate change in HR, BP, and measures of sympathetic and parasympathetic activity, which was not impacted by fat consumption. Perhaps this is unsurprising, as fat consumption does not impact resting cardiovascular parameters, so it is also unlikely to modify cardiovascular responses during stress. There is little evidence of the impact of fat on cardiovascular responses during stress, with vast methodological differences (56), and hence, future research is required in order to make a firm conclusion. Furthermore, while fat consumption does not seem to influence cardiovascular and vasodilatory responses during stress, fat intake may influence resting cardiovascular function following stress. Therefore, future research should similarly assess cardiovascular and vascular changes alongside FMD measurements following stress.

5. Limitations

One of the limitations in the present study is that the high-fat and low-fat meals were not tailored to individual metabolic rate. This is likely to translate into a higher variability in responses to fat-intake between participants, which can be considered more ecologically valid and further highlights the significance of our results. Furthermore, Jackson et al. (2007)'s review (25) suggests that approximately 50 g fat is sufficient to impact endothelial function, which is comparable to the 56.5 g dose of fat in the present study, previously shown to impair endothelial function (24).

The sample used for this study was moderate, yet a robust crossover design was employed, and as effect sizes for non-significant findings are small (interaction effect sizes for FBF, HR, HRV, PEP, and BP were 0.11, 0.08, 0.04, 0.04, and 0.02, respectively), a lack of power was not likely to drive these results. Furthermore, post-hoc power analyses revealed that a sample of 21 participants, power at 90% and alpha set at 0.05, allowed the detection of a medium size interaction effect (0.33) for our primary outcome measure, brachial FMD (68).

The present study population is estimated to have a relatively healthier habitual diet compared to the UK population. For example, 62% of participants consumed at least 5 portions of fruit and vegetables (average 5.7 portions/day), compared to 28% of UK adults (average 3.7 portions/day) (69). Similarly, only 19% of participants exceeded the recommended saturated fat value compared to 75% of UK adults (70). Therefore, the present study sample may represent a healthier population, which highlights additional significance of our observations. It is highly likely that such fat-induced impairments in endothelial function may be further aggravated in a general population with a poorer habitual diet, and particularly in individuals at risk of CVD, such as obese or hypertensive, known to have disturbed vascular responses to stress (14). Therefore, future research should target these populations. Furthermore, it would be interesting to understand how aspects of baseline characteristics, such as diet, fitness level, blood pressure and TAG concentration might influence responses to stress following a high-fat meal, yet a larger sample is required to address this. Therefore, future research should explore what characteristics may put people at higher risk from consuming fat during stress.

6. Conclusion

This study demonstrates the detrimental impact of a high-fat meal and stress on endothelial function. Whilst fat had no effect on vascular and cardiovascular responses during stress, the prolonged impairment in endothelial function following stress is significant. Given that a 1% impairment in FMD has been correlated with a 13% increase in CVD risk (16), future work should investigate how long such fat and stress-induced impairments in endothelial function last. This might be particularly critical if the combination of stress and fat ingestion becomes chronic, preventing the endothelium's chance to fully recover. Given the documented trend towards consumption of high-fat foods during periods of heightened stress, our data can have important implications for future dietary recommendations to protect the vascular system during periods of enhanced vulnerability (such as those rendered by stress).

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by University of Birmingham Science, Technology, Engineering and Mathematics ethics committee. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

RB: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Writing – original draft. SW: Data curation, Formal analysis, Investigation, Writing – review & editing. CR: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Writing – review & editing. JV: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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EDITED BY
Galya Bigman,
United States Department of Veterans Affairs, United States

REVIEWED BY
Andrew Carley,
The Ohio State University, United States
Yuying Li,
Chinese Academy of Agricultural Sciences, China

*CORRESPONDENCE
Lei Hou
✉ Dr_houlei@163.com

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Branched chain amino acids metabolism in heart failure

Chenshan Gao[1] and Lei Hou[1,2]*

[1]Collaborative Innovation Centre of Regenerative Medicine and Medical BioResource Development and Application Co-Constructed by the Province and Ministry, Guangxi Medical University, Nanning, China, [2]Department of Cardiology, Shanghai Songjiang District Central Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China

As a terminal stage of various cardiovascular diseases, heart failure is of great concern due to its high mortality rate and limited treatment options. Researchers are currently focusing their efforts on investigating the metabolism of carbohydrates, fatty acids, and amino acids to enhance the prognosis of cardiovascular diseases. Simultaneously, branched-chain amino acids (BCAAs), including leucine, isoleucine, and valine, play significant roles in blood glucose regulation, protein synthesis, and insulin sensitivity. However, disrupted BCAAs metabolism has been associated with conditions such as hypertension, obesity, and atherosclerosis. This article explores intricate metabolic pathways, unveiling the connection between disrupted BCAAs metabolism and the progression of heart failure. Furthermore, the article discusses therapeutic strategies, assesses the impact of BCAAs on cardiac dysfunction, and examines the potential of modulating BCAAs metabolism as a treatment for heart failure. BCAAs and their metabolites are also considered as biomarkers for evaluating cardiac metabolic risk. In conclusion, this article elucidates the multifaceted roles of BCAAs in heart failure and cardiovascular health, providing guidance for future research and intervention measures.

KEYWORDS

branched-chain amino acids, heart failure, metabolic dysregulation, HFrEF – heart failure with reduced ejection fraction, HFpEF – heart failure with preserved ejection fraction

Introduction

Leucine (Leu), isoleucine (Ile), and valine (Val) constitute essential branched-chain amino acids (BCAAs), acquired solely through dietary consumption (1–5). Serving as both signaling molecules and regulators, BCAAs play a pivotal role in diverse physiological processes. These processes encompass the maintenance of blood glucose balance, facilitation of protein synthesis, modulation of insulin resistance, and regulation of pathways associated with nutrient sensitivity (2–9). These roles highlight BCAAs' multifaceted impact on various physiological functions. As advancements in amino acid research shed light on BCAAs' roles, some studies propose that beyond being dietary nutrients, BCAAs may also contribute to regulating specific diseases. Notably, several studies have revealed a significant association between BCAAs and heart failure (HF), encompassing aspects of its progression, severity, and prognosis. However, further investigation is necessary to precisely determine the functional role of BCAAs in HF. This paper aims to fill this gap by providing a concise overview of the current research progress on the physiological and pathophysiological processes related to BCAAs in HF. Additionally, this paper explores the potential application, feasibility, and significance of harnessing BCAAs and their metabolism in the treatment of HF. Through this comprehensive exploration, we aim to

contribute to a deeper understanding of BCAAs' therapeutic potential in the context of heart failure.

Metabolic pathways and regulation of branched-chain amino acids

Tracer studies in mice have demonstrated that the oxidation of BCAAs primarily occurs in skeletal muscles, brown adipose tissue, liver, kidneys, and heart. Notably, the liver, pancreas, skeletal muscles, kidneys, and brown adipose tissue also play essential roles in BCAA protein synthesis (10). The initial metabolism of BCAAs takes place in extrahepatic tissues through enzymatic reactions involving isoleucine, leucine, and valine, with these metabolic pathways being conserved among eukaryotes (11).

The initiation of branched-chain amino acids (BCAAs) metabolism involves a reversible transamination process catalyzed by the enzyme BCAT2 within the mitochondria, resulting in the formation of branched-chain α-keto acids (BCαKAs). These BCαKAs subsequently undergo an irreversible decarboxylation process mediated by the enzyme complex BCKDH. The activity of the BCKDH complex is tightly regulated through mechanisms of phosphorylation and dephosphorylation, as demonstrated by various studies (5, 7, 9–12). Branched-chain α-keto acid dehydrogenase kinase (BCKDK) phosphorylates and inhibits branched-chain α-keto acid dehydrogenase, while its activation is facilitated by dephosphorylation mediated by the phosphatase PPM1K, also known as PP2Cm (13). Notably, exposure to BCαKAs, particularly α-KIC, suppresses BCKDK, promoting the kinase's oxidative metabolism and resulting in elevated BCαKAs levels. The subsequent reactions involving these BCαKAs contribute to the synthesis of end metabolites such as acetyl-CoA and succinyl-CoA, which actively participate in the oxidative steps of the tricarboxylic acid (TCA) cycle (3–5, 11).

Under normal physiological conditions, the intricate balance between the synthesis and consumption of amino acids directly influences protein synthesis. This balance extends to the dynamic interplay between branched-chain amino acids (BCAAs) and branched-chain α-keto acids (BCαKAs), primarily governed by the activity of the pivotal enzyme, BCαKAs dehydrogenase, within the oxidative metabolism pathway of BCAAs (3, 5). Therefore, the precise regulation of BCαKAs dehydrogenase expression and activity emerges as a critical determinant for preserving the delicate equilibrium of BCAAs within the body's cycling pool (14, 15).

The oxidative metabolism of BCAAs can lead to two outcomes: termination in the tricarboxylic acid cycle or the generation of intermediates with paracrine signaling activity, such as 3-hydroxyisobutyric acid (3-HIB). This process also produces monomethyl-branched chain fatty acids (mmBCFAs) (16, 17). Turning our focus to leucine, an essential BCAA, it activates mTOR in the heart, blocking ULK1 and inhibiting autophagy. Additionally, leucine promotes insulin resistance by phosphorylating IRS-1 via S6K and stimulates protein synthesis through the phosphorylation of 4E-BP1 (18). Furthermore, branched-chain α-keto acids (BCαKAs) enhance 4E-BP1 phosphorylation and activate the MEK–ERK protein kinase pathway, thus promoting protein synthesis (7). Notably, exposure to BCAAs negatively impacts cardiac mitochondrial complex activity, leading to the generation of reactive oxygen species and oxidative stress (3).

Impact of BCAAs on heart failure

Heart failure (HF) represents the clinical consequence of diverse cardiovascular diseases (CVDs), characterized by compromised heart structure or function that disrupts the coordinated ventricular contraction and filling processes. This disruption manifests as a complex array of intricate symptoms and signs. Categorically, HF is delineated by left ventricular ejection fraction (LVEF), wherein LVEF ≤40% defines HF with reduced ejection fraction (HFrEF), while LVEF ≥50% signifies HF with preserved ejection fraction (HFpEF). A compelling cross-sectional study conducted by Ruiz-Canela et al. substantiated the nexus between branched-chain amino acids (BCAAs) and escalated CVD risk (19). Remarkably, valine and leucine emerged as autonomous biomarkers, signifying augmented cardiovascular and metabolic jeopardy, independently of body mass index (BMI). Previous studies reporting on the association between BCAAs and HF have been conducted in several cohorts (Table 1).

Heart failure with reduced ejection fraction

A slew of investigations has concretely established the correlation between augmented circulating plasma BCAAs and subsequent adversities in HF patients (3, 20, 21). This propensity for elevated plasma BCAAs levels has been mirrored in animal models of HF, including myocardial infarction-induced HF in rats, positing an intricate connection between BCAAs and cardiac malaise (27). Studies have revealed that elevated levels of BCAAs impede glucose metabolism and increase the vulnerability of the heart to ischemic injury in a mouse model with impaired BCAAs metabolism (19). Advanced scrutiny has divulged the deranged BCAAs metabolism intrinsic to cardiac tissues, marked by dwindling BCAAs breakdown enzymes and an accrual of BCAAs within the cardiac milieu (28). Intriguingly, a study involving pressure-induced HF in mice spotlighted heightened levels of BCαKAs, enzymes pivotal in BCAAs degradation, corroborating the conjecture of distorted BCAAs metabolism in cardiac dysfunction (29).

A groundbreaking murine HF model, induced via oxidative stress, laid bare that compromised expression of BCAAs catabolic enzymes instigates elevated BCAAs levels intrinsically within the cardiac framework, while their circulatory counterparts remain unperturbed (30). These findings accentuate that impeded BCAAs metabolism and heightened intracardiac BCAAs levels typify prevailing hallmarks of cardiac dysfunction in HF. Moreover, HF patients are characterized by escalated circulating BCAAs levels. This is coupled with the downregulation of genes governing BCAAs breakdown in HF, which prompts the accumulation of BCAAs and their metabolic derivatives, BCαKAs, within cardiac tissues. Another murine model, simulating pressure overload-induced HF, unmasked malfunctions in BCAAs degradation, oxidative stress, and metabolic derangement. This chronic BCAAs buildup in metabolically compromised mice potently retards glucose metabolism and amplifies vulnerability to ischemia–reperfusion injury. Notably, patients afflicted with dilated

TABLE 1 Human epidemiological studies showing associations between BCAAs and heart failure.

Endpoint	Population	Findings	Refs.
Heart failure with reduced ejection fraction	HF patients	Elevated plasma BCAAs levels in HF patients	(3, 20, 21)
	DCM patients	Cardiac BCAA levels were dramatically elevated in left ventricular samples of patients with DCM	(11, 18)
Heart failure with preserved ejection fraction	T2DM patients	BCAAs in the fasting serum of type 2 diabetes mellitus (T2DM) patients have autonomously correlated with the emergence of incident HF, higher BCAA levels in people with and prior to development of type 2 diabetes	(22, 23)
	Obesity	The very fabric of obesity and insulin resistance orchestrates the repression of genes integral to BCAAs degradation, elevations in circulating BCAAs have gained attention as potential contributors to the development of insulin resistance and diabetes	(24)
	High cardiovascular risk population	Higher concentrations of baseline BCAAs were associated with increased risk of CVD, especially in a high cardiovascular risk population	(19)
	The Japanese population without diabetes mellitus.	In both sexes, the levels of individual BCAAs and the total BCAA levels correlated positively with triglyceride levels and negatively with high-density lipoprotein cholesterol levels	(25)
	HF patients	Elevated plasma BCAA levels have been distinctly discerned in HF patients with impaired systolic function when juxtaposed with those exhibiting sustained diastolic function and individuals devoid of HF	(26)

cardiomyopathy (DCM)-associated HF evinced escalated cardiac BCAAs levels, underscoring the pivotal role of impaired BCAAs breakdown in failing cardiac structures (11).

The inhibition of BCAAs breakdown in HF is intimately associated with the activation of the TAK1/P38MAPK signaling cascade, triggering a surge in cardiac BCAAs levels (18). Profound research has unequivocally established the efficacy of circulating BCAAs levels in distinguishing chronic HF model rats from sham-operated counterparts, thereby delineating the impaired BCAAs metabolic pathways characteristic of deteriorating cardiac function (27). This inhibition is concurrently accompanied by a diminution in PP2Cm expression (13). Elevated BCαKAs levels directly impede mitochondrial respiration, thereby fomenting oxidative stress and precipitating HF under oxidative duress and mechanical overloads, as illustrated in PP2Cm-knockout murine models (29).

Heart failure with preserved ejection fraction

Remarkably, BCAAs in the fasting serum of type 2 diabetes mellitus (T2DM) patients have autonomously correlated with the emergence of incident HF (22). Elevated plasma BCAA levels have been distinctly discerned in HF patients with impaired systolic function when juxtaposed with those exhibiting sustained diastolic function and individuals devoid of HF (26). Surprisingly, studies have unveiled augmented BCAAs oxidation within the heart during HF, defying expectations, and the abatement of plasma and cardiac BCAAs levels did not confer appreciable protective outcomes (11). Conversely, the emergence of evidence hints at the potential of activating BCAAs catabolism in mitigating blood pressure, thereby hinting at a potential modality for cardiac safeguarding. Mendelian randomization studies have further underscored the profound impact of regulating BCAAs catabolism on human blood pressure dynamics (11). As such, targeting BCAAs α-keto dehydrogenase kinase emerges as a prospective therapeutic strategy for HF amelioration.

Metabolomic profiling studies have unequivocally unveiled the promise of BCAAs and their associated metabolites as potent biomarkers for refined cardiac metabolic risk assessment. In the context of insulin resistance, plasma BCAAs levels exhibit a proclivity for elevation, thereby magnifying the nexus between BCAAs and metabolic aberrations (31–33). An intriguing amalgamation known as the diabetes risk index (DRI), which interweaves BCAAs and LP-IR, has duly emerged as a robust biomarker predictive of type 2 diabetes mellitus (T2DM) and newly diagnosed hypertension, irrespective of traditional clinical risk factors (34, 35). The tapestry of epidemiological and experimental evidence further bolsters the observed correlation between BCAAs levels and insulin resistance (23). Moreover, elevated plasma BCAAs levels have been discerned in metabolically infirm obese individuals, when juxtaposed with their metabolically resilient obese counterparts and individuals boasting normal BMI. The very fabric of obesity and insulin resistance orchestrates the repression of genes integral to BCAAs degradation (24). The synergy between escalated BCAAs levels and dyslipidemia and metabolic maladies poignantly underscores the pivotal role of BCAAs metabolism in orchestrating metabolic equilibrium (25). Lifestyle determinants such as elevated BMI, sedentary habits, and alcohol consumption have also found their cadence in the elevation of BCAAs levels (36). Paradoxically, dietary BCAAs intake seems to cast a shadow of insignificance on the primacy of elevated plasma levels (36).

The distorted BCAAs metabolism and resulting accumulation of BCAAs and their metabolites are recurring themes in HF, surpassing ejection fraction limits. Understanding their mechanisms and implications can unveil potential HF treatment targets. Revealing BCAAs' role in HF and metabolic changes can lead to valuable insights, fostering potent interventions. Exploring BCAAs α-ketodehydrogenase kinase and regulating catabolism offers innovative HF treatments. Leveraging BCAAs and associated metabolites as key factors in cardiac risk assessment enhances diagnostic precision and prognosis. A comprehensive grasp of BCAAs metabolism and its implications in HF and metabolic discord forms the foundation for innovative interventions and management.

Targeting BCAAs metabolism as a potential therapeutic approach for HF

Approximately 20% of HF patients experience muscle wasting and cachexia. Research indicates that supplementation with BCAAs can improve various aspects of the condition, including the 6 min walk test distance, muscle mass, and overall quality of life (37). Furthermore, an investigation by Uchino et al. found that BCAAs supplementation in hospitalized HF patients with hypoalbuminemia resulted in a reduction in the cardiothoracic ratio and an increase in serum albumin levels, as compared to the control group (38). However, it is crucial to consider that excessive BCAAs supplementation may impose additional strain on the already compromised heart, potentially exacerbating the clinical course of the disease. Therefore, a delicate balance in BCAAs supplementation is essential for optimizing therapeutic outcomes. Different strategies have been investigated to improve cardiac BCAAs oxidation and decrease plasma levels of BCAAs in preclinical models of heart HF due impaired cardiac BCAAs oxidation on cardiac energy metabolism, function, and structure (2, 18). For instance, a study involving pressure-overloaded HF mice demonstrated that the inhibition of amino acid dehydrogenase kinase using BT2, an amino acid dehydrogenase kinase inhibitor, enhanced BCAAs metabolism, facilitated the utilization of fatty acids by the heart, and ultimately improved systolic and diastolic functions (39). These findings highlight the potential of precisely targeting the BCAAs metabolic pathway as a promising treatment approach for HF within the cardiovascular field.

BCAAs play a critical role in protein synthesis, and their metabolism is intricately linked to overall health and disease. The PI3K-AKT-mTOR pathway serves as a pivotal signaling pathway connecting these physiological states. As BCAAs and their metabolites emerge as potential biomarkers and contributors to HF, an in-depth understanding of their regulatory roles can unveil new avenues for therapeutic interventions. Efficient modulation of BCAAs metabolism can potentially alleviate HF by restoring cardiac energy balance and function. Moreover, evidence suggests that BCAAs and their derivatives also hold promise as biomarkers for assessing cardiovascular risk, including coronary artery disease and HF. However, further research is warranted to elucidate the effectiveness of plasma detection of BCAAs and their metabolites in predicting a broader spectrum of cardiovascular diseases, such as atherosclerosis, hypertension, and arrhythmias. In conclusion, targeting the BCAAs metabolic pathway presents a promising therapeutic approach for HF within the cardiovascular field. A comprehensive understanding of the roles played by BCAAs and their metabolites in the context of HF can inform the development of effective treatment strategies and the identification of novel biomarkers for a range of cardiovascular diseases. By bridging the gap between metabolic dysregulation and cardiovascular health, this research paves the way for innovative interventions and improved patient outcomes.

Conclusion

Branched-chain amino acids (BCAAs) – leucine, isoleucine, and valine – are crucial dietary nutrients with diverse roles in physiology. They regulate blood glucose, promote protein synthesis, and affect insulin resistance. Recent research highlights their connection to heart failure (HF), with elevated BCAAs levels influencing disease progression. In HF, impaired BCAAs metabolism, characterized by reduced breakdown and cardiac tissue accumulation, plays a key role. Understanding the role of enzymes like BCKDH and BCAAs dehydrogenase kinase in BCAAs metabolism holds promise for innovative HF therapies. Careful BCAAs supplementation is vital to avoid exacerbating the condition.

BCAAs and their metabolites are also emerging as potential biomarkers for assessing cardiovascular risk, offering insights into disease prediction and prognosis. Further research is needed to explore their effectiveness in predicting a wider range of cardiovascular diseases, such as atherosclerosis, hypertension, and arrhythmias.

Author contributions

CG: Writing – original draft, Writing – review & editing. LH: Conceptualization, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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EDITED BY
Galya Bigman,
Baltimore VA Medical Center, United States

REVIEWED BY
Zanzhe Yu,
Shanghai Jiao Tong University, China
Xiaofei Hu,
Army Medical University, China

*CORRESPONDENCE
Xiaoping Chen
✉ xiaopingchen13@sina.com

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Association of dietary live microbe intake with abdominal aortic calcification in US adults: a cross-sectional study of NHANES 2013–2014

Xingwei Huo[1], Shanshan Jia[1], Xin Zhang[1], Lirong Sun[1,2], Xueting Liu[1], Lu Liu[1], Xianghao Zuo[1] and Xiaoping Chen[1]*

[1]Department of Cardiology, West China Hospital, Sichuan University, Chengdu, Sichuan, China, [2]Second Department of Internal Medicine, Affiliated Hospital of Tibet University for Nationalities, Xianyang, Shaanxi, China

Object: To explore the potential association between dietary live microbe intake and abdominal aortic calcification (AAC).

Methods: We conducted a cross-section study based on the National Health and Nutrition Examination Survey (NHANES). We categorized the participants into three groups (low, medium, and high dietary intake of live microbes) according to Sanders's dietary live microbe classification system and participants' 24-h dietary recall data. AAC was quantified by using dual-energy X-ray absorptiometry (DXA) and diagnosed by using the Kauppila AAC-24 score system. The analyses utilized weighted logistic regression and weighted linear regression.

Results: A total of 2,586 participants were included. After the full adjustment for covariates, compared to participants with a low dietary live microbe intake, participants with a high dietary live microbe intake had a significantly lower risk of severe AAC (OR: 0.39, 95% CI: 0.22, 0.68, $p = 0.003$), and the AAC score was also significantly decreased (β:−0.53, 95% CI: −0.83, −0.23, $p = 0.002$).

Conclusion: In this study, more dietary live microbial intake was associated with lower AAC scores and a lower risk of severe AAC. However, more research is needed to verify this.

KEYWORDS

dietary live microbes, abdominal aortic calcification, food-gut-health axis, NHANES, cross-sectional study

1 Introduction

Vascular calcification (VC) is the abnormal deposition of calcium and phosphorus in the walls of blood vessels (1). Although studies on VC have primarily focused on coronary artery calcification (CAC), the multi-ethnic study of atherosclerosis (MESA) study suggests that abdominal aortic calcification (AAC) occurs earlier and is a more effective prognostic marker than CAC, independent of CAC scores (2, 3). Current studies have established a strong correlation between AAC and cardiovascular events as well as mortality (3–5), but another study still believed AAC is an underestimated cardiovascular

disease risk factor (6). As the AAC severity increases, the risk of fatal cardiovascular events and mortality also increases significantly (7, 8).

Since the progression of VC is difficult to reverse, prevention and treatment are extremely important (9). Although VC is often considered the advanced stage of atherosclerosis (AS) (3), current medications targeting AS have shown limited efficacy in treating VC (10). Several drugs, such as bisphosphonates, calcium channel blockers, vitamin K, and dietary magnesium, may have therapeutic potential, but there is still a lack of robust clinical evidence (3, 11, 12). To date, there are no approved treatment strategies for preventing or managing AAC (13).

Adopting healthy diets is widely recognized as an effective approach to preventing cardiovascular diseases (CVD) (14). Healthy diets such as anti-inflammatory diets (15), Mediterranean diets (14), and DASH diets (16), decreased the risk of having AAC. These studies mainly focused on the role of food ingredients but ignored the impact of dietary live microbes. Studies have found that diets can influence gut flora composition and metabolites (17) and impact disease susceptibility (18, 19). Therefore, there is growing interest in the health effects of live microbes in diets. Recently, Sanders et al. (20) used the National Health and Nutrition Examination Survey (NHANES) database to assess the number of live mircrobes in various foods. They also discovered live microbe-rich diets improved health outcomes, including lower BMI, blood pressure, lipids, glucose, insulin, and inflammation level (21). These benefits from dietary live microbes may prevent diseases. Based on NHANES data and Sanders' dietary live microbe classification system, we explored the association between dietary live microbes and AAC.

2 Materials and methods

2.1 Data source and participants

The NHANES survey design follows a complex, multistage probability sampling method to obtain nationally representative samples of the non-institutionalized US civilian population. The data collected includes demographics, physical examinations, laboratory tests, dietary information, and other questionnaires. The National Center for Health Statistics (NCHS) Institutional Review Board has approved the NHANES protocol, and participants provided informed consent before the collection of personal information, blood, and urine samples. The 2013–2014 cycle was chosen because it was the only cycle that dual X-ray absorptiometry (DXA) scans for AAC were performed. All data in this study is publicly available on the NHANES website.[1] For the 2013–2014 cycle, the total population was 10,175. However, only participants over 40 years old received the DXA examination to obtain AAC score data. After excluding those with missing AAC data ($n = 7035$), missing dietary data ($n = 243$), and missing covariate data ($n = 311$), the final analysis consisted of 2586 participants, as depicted in **Figure 1**.

1 wwwn.cdc.gov/nchs/nhanes/Default.aspx

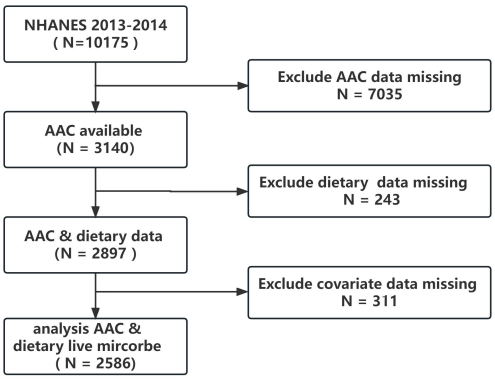

FIGURE 1
Participant flowchart.

2.2 Dietary live microbe intake category

The dietary live microbe intake was estimated by using 24-h dietary recall data from NHANES. The food codes in the NHANES database were linked to the United States Department of Agriculture (USDA) to obtain the food composition and energy content data. A team of four experts, relying on values reported in the primary literature, estimated the levels of live microbes (CFU/g) for 9,388 food codes across 48 subgroups in the NHANES database. The experts categorized microbial levels as low ($< 10^4$ CFU/g), medium (10^4–10^7 CFU/g), or high ($> 10^7$ CFU/g) based on the quantity of live microorganisms per gram of food. Any uncertain or conflicting data was resolved through external consultation. In short, the low class is mainly pasteurized foods, the medium class is mainly fresh fruits and vegetables that have not been peeled and the high class is fermented foods and probiotic supplements that have not been pasteurized. Although this classification method is useful for estimating liver microbes in foods, it may not be suitable for estimating entire diet live microbe intake. Following the approach of Sanders et al. (20), participants were grouped into three categories according to their overall live microbe intake from all foods: (1) low diet microbe intake group (only low level foods), (2) medium diet microbe intake group (medium level but not high level foods), and (3) high diet microbe intake group (any high level foods). This previously validated method allowed for the classification of participants' diets based on estimated live microbe content (22, 23).

2.3 Outcome

The outcome variable in this analysis was AAC. The NHANES Mobile Examination Center (MEC) conducted lateral DXA scans of the thoracic and lumbar spine in 2013–2014. Exclusion criteria included age under 40 years, pregnancy, weight over 450 pounds, or recent barium contrast use in the past 7 days. The Kauppila score system (24) was utilized to evaluate AAC from the DXA scans. This involved dividing the anterior and posterior aortic walls corresponding to vertebral levels L1–L4 into 8 segments. Each segment was scored from 0 to 3 according to the extent of calcific deposits visualized. The sum of the 8 segment scores produced the

total AAC score, ranging from 0 to 24. We defined AAC presence as a score above 0 and severe AAC as a score above 6. In addition, we performed sensitivity analysis using the AAC-8 score (Schousboe score), with a total score ranging from 0 to 8 (25). A score of 3 or more is defined as severe AAC (26).

2.4 Covariates

To avoid the influence of confounding factors, covariates were included in the analysis based on known or potential relationships with AAC. Demographic factors consisted of age, gender, race, education, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), smoking, and alcohol use. Medical conditions included hypertension, diabetes, and congestive heart failure. Laboratory measurements collected were serum calcium, phosphorus, total 25-hydroxyvitamin D, potassium, HbA1c, uric acid, creatinine, total cholesterol, white blood cells (WBC), and estimated glomerular filtration rate (eGFR). Use of antidiabetic, antihyperlipidemic, and antihypertensive medications was recorded. Dietary energy was also considered a covariate. Smoking was defined as having smoked $\geq$ 100 cigarettes over their lifetime. The diagnostic criteria for diabetes included self-reported diabetes, HbA1c $\geq$ 6.5%, fasting serum glucose $\geq$ 126 mg/dL, random serum glucose $>$ 11.1 mmol, or 2-h postprandial glucose $\geq$ 200 mg/dL, or any self-reported insulin and antidiabetic medication use. Hypertension was defined as having a history of hypertension, an average SBP $\geq$ 140 mmHg, or DBP $\geq$ 90 mmHg based on at least three standard consecutive seated measurements or self-reported use of any hypertension-related medications. The eGFR was calculated by using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation (27).

2.5 Statistical analyses

All analyses accounted for the complex, multistage probability sampling design of NHANES by incorporating appropriate sampling weight. The R (Core Team, Vienna, Austria, version 4.1.2) and the survey package were utilized for complex sampling analysis. Continuous variables were reported as weighted means with standard errors (SE) while categorical variables were reported as weighted proportions. Baseline clinical characteristics were compared among groups using weighted *t*-tests and Rao-Scott chi-square tests. The association between dietary live microbe intake and AAC score was analyzed using weighted linear regression. Weighted logistic regression examined the association between dietary live microbe intake and severe AAC. Three regression models were constructed: model 1, adjusted for non-covariates; model 2, adjusted for age, gender, race, and education; and model 3, further adjusted for BMI, smoking, alcohol use, SBP, DBP, uric acid, creatinine, eGFR, HbA1c, total cholesterol, potassium, WBC, dietary energy, medical conditions (diabetes, hypertension, and congestive heart failure), medication use (antihypertensive, antihyperlipidemic, and antidiabetic), and bone metabolism markers (serum calcium, phosphorus, and total 25-hydroxyvitamin D). To avoid bias caused by deleting samples with missing covariates, we performed multiple imputations as a sensitivity analysis. In addition, we tested the robustness of the association using the AAC-8 score system. Subgroup analyses were conducted to examine potential effect modification by stratifying weighted multivariate regression models for age, gender, education, BMI, hypertension, diabetes, eGFR, smoking, and alcohol use. Trend tests to detect potential dose-response effects. A two-sided *P*-value < 0.05 was considered statistically significant.

3 Results

3.1 Clinical characteristics of participants

Table 1 presented the clinical characteristics of 2,586 individuals categorized by different dietary live microbe groups. The average age of the study population was 57.71 $\pm$ 0.29 years with a gender distribution of 51.75% females and 48.25% males. The average AAC scores for the overall population were 1.42 $\pm$ 0.10. Notably, there was a significant difference in the mean AAC scores among the three groups, with the high dietary live microbe intake group scoring the lowest, followed by the medium intake group. Furthermore, there were notable distinctions in several demographic and clinical parameters including age, gender, race, education, BMI, DBP, smoking, creatinine, HbA1c, total 25-hydroxyvitamin D, energy intake, and the prevalence of hypertension and diabetes among three groups (all $P < 0.05$). However, there were no statistically significant differences observed for SBP, alcohol use, uric acid, total cholesterol, WBC, eGFR, phosphorus, calcium, potassium, drug use, and the prevalence of congestive heart failure among the three groups.

3.2 Association between dietary live microbes and AAC

The relationship between dietary live microbes and AAC was evaluated by employing weighted multivariate linear regression and weighted multivariate logistic regression. Three models were constructed and the results are presented in Table 2. Compared to individuals with low dietary live microbe intake group, those in high dietary live microbe intake group exhibited significantly lower AAC scores (model 1: $\beta = -0.52$, 95% CI: -0.90, -0.15, $p = 0.009$; model 2: $\beta = -0.68$, 95% CI: -1.05, -0.31, $p = 0.004$; model 3: $\beta = -0.53$, 95% CI: -0.83, -0.23, $p = 0.002$). Furthermore, after accounting for covariates, the medium dietary live microbe intake group also demonstrated lower AAC scores than the low intake group (model 1: $\beta = -0.07$, 95% CI: -0.34, 0.19, $p = 0.557$; model 2: $\beta = -0.30$, 95% CI: -0.49, -0.12, $p = 0.007$; model 3: $\beta = -0.29$, 95% CI: -0.50, -0.08, $p = 0.011$).

Additionally, for severe AAC, the results were similar. Compared to individuals in low dietary live microbe intake group, those in high dietary live microbe intake group exhibited lower risk of severe AAC (model 1, OR = 0.50, 95% CI: 0.29, 0.88, $p = 0.020$; model 2, OR = 0.38, 95% CI: 0.21, 0.68, $p = 0.007$; model 3, OR = 0.39, 95% CI: 0.22, 0.68, $p = 0.003$). Similarly, the medium dietary live microbe intake group also showed diminished risk (model 1: OR = 0.90, 95% CI: 0.69, 1.16, $p = 0.372$; model

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TABLE 1 Clinical characteristics of participants by dietary live microbe groups.

Variables	Total	Low	Medium	High	*P*-value
Age (years)	57.71 (0.29)	56.40 (0.49)	58.59 (0.65)	58.00 (0.41)	0.007
Gender (%)					0.004
Female	51.75 (0.03)	45.45 (2.04)	54.35 (1.52)	55.12 (2.13)	
Male	48.25 (0.03)	54.55 (2.04)	45.65 (1.52)	44.88 (2.13)	
Race (%)					< 0.001
Black	9.62 (0.01)	14.48 (2.48)	9.02 (1.27)	5.35 (0.94)	
Mexican	6.84 (0.02)	5.97 (1.35)	9.48 (2.46)	4.60 (1.33)	
Other	12.10 (0.01)	10.85 (1.74)	16.38 (1.46)	8.32 (1.57)	
White	71.45 (0.07)	68.70 (4.04)	65.13 (3.60)	81.74 (2.87)	
Education level (%)					< 0.001
Less than high school	14.45 (0.02)	21.25 (3.14)	13.76 (1.69)	8.32 (1.45)	
High school or GED	21.71 (0.02)	26.59 (2.25)	20.96 (2.47)	17.60 (1.85)	
Above high school	63.83 (0.05)	52.16 (3.94)	65.28 (3.43)	74.08 (2.20)	
BMI (kg/m^2)	28.48 (0.18)	29.23 (0.41)	28.23 (0.26)	28.00 (0.22)	0.035
SBP (mmHg)	125.36 (0.65)	126.03 (1.29)	126.14 (0.65)	123.76 (1.01)	0.085
DBP (mmHg)	71.19 (0.37)	72.09 (0.58)	70.32 (0.48)	71.31 (0.70)	0.047
Smoking (%)	45.90 (0.04)	53.86 (2.69)	44.48 (2.29)	39.42 (2.63)	< 0.001
Alcohol use (%)	89.51 (0.06)	90.62 (0.81)	88.12 (1.85)	90.03 (2.38)	0.381
Hypertension (%)	51.27 (0.03)	54.53 (1.83)	53.51 (1.81)	45.27 (3.40)	0.039
Diabetes (%)	18.10 (0.01)	20.31 (1.58)	19.13 (1.86)	14.62 (1.04)	0.031
Congestive heart failure (%)	2.70 (0.00)	3.10 (0.55)	2.86 (0.64)	2.09 (0.61)	0.531
Antidiabetic (%)	11.39 (0.01)	14.26 (1.64)	10.58 (1.00)	9.40 (1.29)	0.069
Antihypertensive (%)	39.15 (0.02)	41.04 (2.68)	40.20 (2.01)	35.98 (2.26)	0.310
Antihyperlipidemic (%)	30.34 (0.02)	29.44 (1.85)	30.51 (1.86)	31.06 (3.04)	0.845
Serum uric acid (μmol/L)	321.10 (1.73)	330.53 (5.27)	319.01 (3.55)	313.92 (2.53)	0.097
HbA1c (%)	5.76 (0.03)	5.82 (0.05)	5.77 (0.04)	5.67 (0.04)	0.019
Total cholesterol (mmol/L)	5.07 (0.02)	5.02 (0.04)	5.04 (0.04)	5.14 (0.05)	0.237
WBC, (1,000 cells/uL)	7.19 (0.06)	7.36 (0.08)	7.19 (0.09)	7.00 (0.12)	0.101
eGFR ml· $(min \times 1.73\ m^2)^{-1}$	84.09 (0.43)	84.87 (0.56)	83.70 (0.89)	83.77 (0.99)	0.337
Serum creatinine (mmol/l)	81.46 (0.79)	82.89 (0.77)	81.84 (1.31)	79.53 (1.00)	0.006
Total 25-hydroxyvitamin D (nmol/L)	75.61 (1.47)	69.56 (1.61)	77.25 (1.77)	79.86 (1.63)	< 0.001
Serum calcium (mmol/l)	2.37 (0.00)	2.36 (0.01)	2.37 (0.00)	2.37 (0.01)	0.423
Serum phosphorus (mmol/l)	1.23 (0.01)	1.22 (0.01)	1.24 (0.01)	1.24 (0.01)	0.077
Serum potassium (mmol/l)	4.03 (0.02)	4.02 (0.02)	4.03 (0.02)	4.04 (0.03)	0.649
Energy (kcal)	2,052.11 (24.98)	2,025.40 (37.13)	1,987.05 (28.71)	2,156.42 (55.11)	0.031
AAC24 score	1.42 (0.10)	1.61 (0.11)	1.54 (0.16)	1.09 (0.13)	0.030
Sever AAC (%)					0.037
No	92.36 (0.06)	90.65 (0.73)	91.54 (1.24)	95.07 (1.12)	
Yes	7.64 (0.01)	9.35 (0.73)	8.46 (1.24)	4.93 (1.12)	

GED, general educational development; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; WBC, white blood cells; AAC, abdominal aortic calcification.

2: OR = 0.61, 95% CI: 0.46, 0.80, $p = 0.004$; model 3: OR = 0.58, 95% CI: 0.43, 0.77, $p = 0.001$). In summary, more dietary live microbe intake was associated with lower AAC scores and lower risk of severe AAC.

3.3 Subgroup analysis

To examine the stability of the association between AAC and dietary live microbes, we conducted subgroup analyses, interaction

TABLE 2 Association between dietary live microbes and AAC.

	β [a]/OR[b] (95% CI[c]), *p*-value			
	Low	Medium	High	*p* for trend
AAC[d] score				
Model 1[e]	Reference	−0.07 (−0.34, 0.19) 0.557	−0.52 (−0.90, −0.15) 0.009	0.009
Model 2[f]	Reference	−0.30 (−0.49, −0.12) 0.007	−0.68 (−1.05, −0.31) 0.004	0.003
Model 3[g]	Reference	−0.29 (−0.50, −0.08) 0.011	−0.53 (−0.83, −0.23) 0.002	0.002
severe AAC[d]				
Model 1[e]	Reference	0.90 (0.69, 1.16) 0.372	0.50 (0.29, 0.88) 0.020	0.008
Model 2[f]	Reference	0.61 (0.46, 0.80) 0.004	0.38 (0.21, 0.68) 0.007	0.003
Model 3[g]	Reference	0.58 (0.43, 0.77) 0.001	0.39 (0.22, 0.68) 0.003	0.002

[a]β, effect sizes.
[b]OR, odds ratio.
[c]95% CI, 95% confidence interval.
[d]AAC, abdominal aortic calcification.
[e]Model 1: adjusted for non-covariates.
[f]Model 2: adjusted for age, gender, race, education.
[g]Model 3: further adjusted for body mass index, systolic blood pressure, diastolic blood pressure, smoking, alcohol use, hypertension, diabetes, congestive heart failure, HbA1c, total cholesterol, uric acid, estimated glomerular filtration rate, creatine, potassium, calcium, phosphorus, total 25-hydroxyvitamin D, white blood cells, antidiabetic, antihypertensive, antihyperlipidemic and dietary energy.

tests, and trend tests between dietary live microbes and AAC across age, gender, education, hypertension, diabetes, eGFR, BMI, smoking, and alcohol use. Compared to those with low dietary live microbe intake, those who were older than 60 years, with hypertension, diabetes, eGFR $\geq$60ml · (min × 1.73 m^2)$^{-1}$, BMI greater than 25, smoking, or drinking were more likely to benefit from more dietary intake of live microbes. Only the interaction test for hypertension and BMI were meaningful. Interestingly, males benefited from medium live microbe diets, while females benefited from high live microbe diets. All subgroup analysis results are shown in Table 3.

3.4 Sensitivity analysis

To prevent bias caused by excluding samples with missing covariates, we also performed multiple imputations. The results showed that this correlation remained robust. In addition, we used the AAC8 scoring system to define patients with AAC8 scores greater than or equal to 3 as severe AAC. The results of the correlation analysis also remained stable. All sensitivity analysis data are in the Supplementary material.

4 Discussion

To our knowledge, this is the first study examining the association between dietary live microbe intake, assessed through NHANES 24-h recall data, and AAC within a nationally representative sample of US adults. Our findings indicated that compared to the low intake group, the high dietary live microbe intake group was associated with lower AAC scores and lower risk of severe AAC. The observed relationship persisted even after adjustment for relevant confounders, including demographics, bone metabolism markers, kidney function, other laboratory tests, comorbidities, drug use, and energy intake. In the subgroup analysis, the benefit of increased live microbe intake was particularly pronounced among age above 60 years, eGFR $\geq$ 60 ml· (min × 1.73 m^2) $^{-1}$ and those with cardiovascular risk factors like hypertension, smoking, alcohol use, overweight, and diabetes. These findings underscored the potential therapeutic role of dietary live microbes, especially for individuals facing heightened cardiovascular risks, and these deserved further exploration and validation in future research.

Our findings are consistent with previous research, reinforcing the potential benefits of dietary interventions. A dietary intervention randomized controlled trial (RCT) included 90 patients with CVD risk factors who received probiotic alone, lactofermented Annurca apple puree (lfAAP), or unfermented Annurca apple puree (AAP) for 8 weeks according to a 1:1:1 allocation. At the end of the intervention, compared with other groups, the treatment effect of the lfAAP group was most obvious; HDLC increased by 61.8% compared with before intervention, while trimethylamine N-oxide (TMAO) decreased by 63% (28). Moreover, it enhanced the bioavailability of dietary polyphenols in the gut to exert antioxidant and anti-inflammatory cardiovascular benefits (28–30). A recent study found that participants who consumed medium or high levels of dietary live microbes showed better cognitive function compared to those with low intake, particularly for those with certain medical conditions like CVD, diabetes, and hypertension (23). Taking into consideration recent research, the potential health advantages associated with augmenting dietary live microbe intake, spanning improvements in blood pressure, glucose and lipid metabolism, cognitive function, intestinal nutrient absorption, and its influence on the intestinal flora, may indeed form a fundamental strategy for mitigating the risk of severe AAC (21, 23).

Previous studies have observed changes in the gut flora of VC patients. An observational study investigated differences in gut flora composition among chronic disease patients with varying degrees of aortic arch calcification (AoAC) (31). Individuals with the highest AoAC scores displayed a significant decrease

TABLE 3 Subgroup analysis.

Subgroup	Low	Medium	High	P for trend	P for interaction
Age					0.071
<60	Reference	0.48 (0.22, 1.04) 0.062	0.02 (0.00, 0.23) 0.004	<0.001	
≥60	Reference	0.65 (0.43, 0.98) 0.041	0.49 (0.27, 0.87) 0.019	0.016	
Gender					0.710
Female	Reference	0.59 (0.33, 1.05) 0.069	0.33 (0.16, 0.68) 0.005	0.004	
Male	Reference	0.52 (0.29, 0.93) 0.030	0.44 (0.13, 1.48) 0.170	0.162	
Education					0.790
Less than high school	Reference	0.52 (0.26, 1.05) 0.067	0.32 (0.05, 2.07) 0.216	0.084	
High school or GED	Reference	0.57 (0.16, 2.06) 0.366	0.23 (0.04, 1.16) 0.072	0.074	
Above high school	Reference	0.66 (0.35, 1.24) 0.184	0.51 (0.27, 0.97) 0.042	0.048	
Hypertension					0.016
No	Reference	0.75 (0.22, 2.55) 0.623	0.09 (0.01, 0.68) 0.023	0.015	
Yes	Reference	0.53 (0.36, 0.78) 0.003	0.55 (0.32, 0.95) 0.034	0.034	
Diabetes					0.891
No	Reference	0.58 (0.33, 1.02) 0.056	0.40 (0.18, 0.87) 0.024	0.024	
Yes	Reference	0.53 (0.29, 0.97) 0.040	0.33 (0.15, 0.71) 0.008	0.004	
eGFR					0.408
<60	Reference	0.61 (0.25, 1.53) 0.271	0.59 (0.22, 1.62) 0.284	0.271	
≥60	Reference	0.58 (0.39, 0.87) 0.012	0.33 (0.16, 0.67) 0.004	0.003	
BMI					0.040
<25	Reference	1.53 (0.60, 3.88) 0.345	0.65 (0.21, 1.99) 0.429	0.306	
≥25	Reference	0.47 (0.35, 0.65) < 0.001	0.36 (0.19, 0.66) 0.003	0.002	
Smoking					0.307
No	Reference	0.79 (0.41, 1.51) 0.443	0.55 (0.25, 1.22) 0.131	0.128	
Yes	Reference	0.45 (0.27, 0.77) 0.006	0.30 (0.13, 0.69) 0.008	0.006	
Alcohol use					0.166
No	Reference	0.35 (0.07, 1.67) 0.173	1.03 (0.25, 4.18) 0.970	0.917	
Yes	Reference	0.57 (0.40, 0.80) 0.003	0.34 (0.20, 0.59) < 0.001	<0.001	

The results of subgroup analysis were adjusted for all covariates except the effect modifier.

in α-diversity along with a heightened prevalence of *Clostridia* species; those with lower AoAC scores exhibited a more favorable microbial profile, characterized by a higher abundance of beneficial bacteria such as *Agathobacter* (31). In another study involving 73 hemodialysis patients, notable distinctions in gut flora were discerned across various VC groups (32). *Escherichia coli* exhibited a positive correlation with VC and emerged as the primary contributor to VC progression; conversely, *Ruminococcus*, the bacterium recognized for producing short-chain fatty acids (SCFAs), displayed a negative correlation with VC and had the second most significant impact on VC (32). These SCFAs can promote tissue repair, regulate immunity, and are closely related to VC (33). In the rat vascular calcification model induced by vitamin D3 and nicotine, it was found that *Akkermansia* supplementation can enhance intestinal flora diversity, promote SCFA production, reduce inflammation, and ultimately alleviate VC (9). Consequently, these findings suggest a potential role for the gut flora in the development and progression of AAC.

One plausible explanatory mechanism for the observed association involves the food-gut-health axis (34). Diet can exert selective pressure on the gut flora, determining which microorganisms can colonize, persist, or become extinct in the gastrointestinal tract (35). It therefore plays a key role in shaping the composition and diversity of the gut microbiota (35, 36). Fermented Foods, fresh fruits and vegetables are an important source of probiotics, including *Lactobacillus*, *Bifidobacterium*, and *Escherichia coli* (37, 38). Probiotics exert anti-vascular calcification effects by acting on the intestines and throughout the body (39). First, probiotics play a pivotal role in restoring microbial equilibrium by upholding the integrity of the intestinal epithelial barrier and facilitating rebalancing (40). This maintenance protects

the intestinal barrier, reduces the overpopulation of harmful bacteria, and prevents the production and leakage of harmful bacterial by-products into the circulation (41). It can regulate the expression of specific microRNAs and inhibit synthetases to reduce the production of TMAO metabolites (42, 43). Furthermore, the beneficial effects of probiotics extend to regulating the absorptive function of the intestines (44). They aid in the conversion of inorganic zinc into its organic form, thereby promoting its absorption—an action that contributes to the fight against AS and VC (44). Moreover, probiotics can promote the absorption of nutrients such as polyphenols, magnesium, vitamin D, vitamin C, and vitamin E (29, 45, 46). Not only that, it can inhibit the absorption of heavy metals and cholesterol in the intestine, and the heavy metals are thought to promote AS and calcification (47). Additionally, probiotics contribute to the production of substances associated with the prevention of VC, including vitamin K, and SCFAs (33, 48). These findings underscore the diverse and impactful role of probiotics in promoting gut-health and their potential implications for broader systemic wellbeing.

Our focus on habitual dietary microbe intake, rather than probiotic supplements, enhances the translational potential of these findings. A sustained, stable, and long-term dietary regimen significantly influences the composition and functional dynamics of the gut microbiota (49), and the impact of probiotics tends to be relatively transient (50, 51). However, we cannot directly recommend that the general population increase their intake of dietary live micorbes. Because its long-term effects are unknown, and its safety needs to be considered, especially for certain special groups including those with multiple severe infections, immune deficiencies, or gastrointestinal inflammation (52). In addition, the effects of dietary interventions enriched with dietary live microbes may vary by strain. Therefore, it may be important to emphasize tailoring the approach to individual health status and goals. Nonetheless, current evidence suggests that increasing the intake of microbe-rich foods may be a valuable strategy for improving cardiovascular health. It may have practical implications for public health and dietary guidelines. But longitudinal studies and RCTs are necessary.

There are several limitations in this study. First, in this cross-sectional study we observed the association, but causation cannot be established. Second, 24-h dietary recall data may be inaccurate due to recall bias and dietary live microbes can be affected by transportation, storage, and cooking. Third, Sanders' dietary live microbe classification system may have lower accuracy than direct measurement. However, direct measurement requires a long time and huge expenditure, which limits its application. Fourth, the rough grouping of microbial diets may introduce estimation errors in assessing microbial intake. Fifth, our study is based on the US population, and the generalizability of the results to other populations worldwide may be limited. Sixth, although NHANES covers most of the US population through complex sampling, it does not include the hospitalized population. This results in under-assessment of critically ill patients. Seventh, despite adjusting for confounding factors, there may still be unknown confounders that have not been accounted for. Therefore, our research results should be treated with caution and can not directly guide the diet of the population. Nonetheless, our study provides new evidence for the health benefits of a diet rich in live microbes, and we call on more researchers to conduct further studies on dietary live microbes.

5 Conclusion

Our study demonstrated that more intake of dietary live microbes was associated with a reduced AAC score and the risk of severe AAC among United States adults. However, more studies are still needed to validate our findings.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: https://www.cdc.gov/nchs/nhanes/index.htm.

Ethics statement

The studies involving humans were approved by the National Center for Health Statistics Ethics Review Board. The studies were conducted in accordance with the local legislation and institutional requirements. Participants provided written informed consent for participation in NHANES. The data were de-identified and all participant data were obtained from publicly available NHANES. Therefore, this study did not require further approval and followed ethical guidelines.

Author contributions

XH: Conceptualization, Data curation, Formal analysis, Investigation, Writing – original draft, Writing – review and editing. SJ: Writing – original draft, Writing – review and editing, Conceptualization. XZh: Investigation, Writing – review and editing. LS Investigation, Writing – review and editing. XL: Investigation, Writing – review and editing. LL: Investigation, Writing – review and editing. XZu: Investigation, Writing – review and editing. XC: Funding acquisition, Investigation, Supervision, Writing – review and editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2023.1267607/full#supplementary-material

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EDITED BY
Iain Brownlee,
Northumbria University, United Kingdom

REVIEWED BY
Longlong Hu,
Second Affiliated Hospital of Nanchang University, China
Yu Min,
Sichuan University, China

*CORRESPONDENCE
Meihua Bao
✉ mhbao78@163.com
Sen Li
✉ senli@connect.hku.hk

†These authors have contributed equally to this work and share first authorship

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Sodium intake and the risk of various types of cardiovascular diseases: a Mendelian randomization study

Qingming Fu[1†], Rumeng Chen[2†], Yining Ding[3†], Shuling Xu[4], Chunxia Huang[1], Binsheng He[5], Ting Jiang[1], Bin Zeng[1], Meihua Bao[5,6*] and Sen Li[3*]

[1]School of Stomatology, Changsha Medical University, Changsha, China, [2]Hospital of Chengdu University of Traditional Chinese Medicine, Chengdu, China, [3]School of Life Sciences, Beijing University of Chinese Medicine, Beijing, China, [4]The Second Affiliated Hospital of Anhui Medical University, Heifei, China, [5]The Hunan Provincial Key Laboratory of the TCM Agricultural Biogenomics, Changsha Medical University, Changsha, China, [6]Hunan Key Laboratory of the Research and Development of Novel Pharmaceutical Preparations, School of Pharmaceutical Science, Changsha Medical University, Changsha, China

Background: The existing literature on the link between sodium intake and cardiovascular disease (CVD) largely consists of observational studies that have yielded inconsistent conclusions. In this study, our objective is to assess the causal relationship between sodium intake and 50 CVDs using two-sample Mendelian randomization (MR) analysis.

Methods: MR analyses were performed to investigate the associations between urinary sodium/creatinine ratio (U_{Na}/U_{Cr}), an indicator of sodium intake, and 50 CVDs. The genome-wide association study (GWAS) for U_{Na}/U_{Cr} was from the UK Biobank (UKBB), and the GWASs for CVDs were from FinnGen. A false discovery rate (FDR) threshold of 5% was applied for multiple comparison correction.

Results: The inverse-variance weighted method indicated that the genetically predicted U_{Na}/U_{Cr} was significantly associated with 7 of 50 CVDs, including "Coronary atherosclerosis" (OR = 2.01; 95% CI: 1.37, 2.95), "Diseases of arteries, arterioles and capillaries" (OR = 1.88; 95% CI: 1.20, 2.94), "Hard cardiovascular diseases" (OR = 1.71; 95% CI: 1.24, 2.35), "Ischemic heart diseases" (OR = 2.06; 95% CI: 1.46, 2.93), "Major coronary heart disease event" (OR = 1.99; 95% CI: 1.36, 2.91), "Myocardial infarction" (OR = 2.03; 95% CI: 1.29, 3.19), and "Peripheral artery disease" (OR = 2.50; 95% CI: 1.35, 4.63). Similar results were obtained with the MR-Egger and weighted median methods. No significant heterogeneity or horizontal pleiotropy was found in this analysis.

Conclusion: Our study has uncovered a significant positive causal relationship between U_{Na}/U_{Cr} and various CVDs. These results offer a new theoretical foundation for advocating the restriction of sodium intake as a preventive measure against CVD.

KEYWORDS

sodium intake, cardiovascular disease, Mendelian randomization, UK Biobank, FinnGen

Introduction

Cardiovascular disease (CVD) ranks as the primary global cause of mortality (1–3), accounting for approximately 32% of all mortality cases (4). Since 1990, the number of individuals affected by CVD has doubled, and as of 2019, it is estimated that approximately 523 million individuals have suffered from CVD worldwide (5). Furthermore, CVD is associated with a high global disability rate, placing a significant burden on both patients and their families (6, 7).

The observational studies have indeed shown that both excessive and insufficient salt intake can elevate the risk of cardiovascular disease and mortality (8–10). Accurate assessment of sodium intake is crucial, but direct measurement of sodium intake levels in clinical settings is challenging. Several studies have shown that the urinary sodium/creatinine ratio (U_{Na}/U_{Cr}) is a reliable indicator and is a simpler, more accessible approach for sodium intake assessment (11–13). However, previous observational research on the association between U_{Na}/U_{Cr} and the risk of CVD has yielded inconsistent results. A cross-sectional study carried out in South Korea found a correlation between U_{Na}/U_{Cr} and hypertension (14), whereas two other studies in Chinese populations did not find any association between U_{Na}/U_{Cr} and hypertension (15, 16). Observational studies are limited in their ability to establish causal relationships, and causal studies are needed to investigate the relationship between U_{Na}/U_{Cr} and CVDs.

Mendelian randomization (MR) analysis is an epidemiological approach that employs genetic variation closely linked to the exposure of interest as an instrumental variable (IV). The methodologies used in MR analysis are based on Mendel's second law, which states that alleles follow a principle of random allocation. This property assists in mitigating biases arising from confounding factors and reverses causation. In order to investigate if high levels of U_{Na}/U_{Cr} can result in numerous cardiovascular diseases (including 50 types of CVDs), this study will apply MR analyses.

Methods

Study design

Single-nucleotide polymorphisms (SNPs) are the most common genetic variations used as IVs in MR, which are employed to calculate the causal associations of traits with diseases. In this study, we performed MR analyses employing data from GWAS datasets for both exposure (U_{Na}/U_{Cr}) and outcome (50 CVDs).

Abbreviations: CVD, cardiovascular disease; MR, Mendelian randomization; U_{Na}/U_{Cr}, urinary sodium/creatinine ratio; GWAS, genome-wide association study; UKBB, UK Biobank; IVW, inverse-variance weighted; WM, weighted median; FDR, false discovery rate; OR, odds ratio; CI, confidence interval; RCTs, randomized controlled trials; SNP, single-nucleotide polymorphism; IV, instrumental variable; LD, linkage disequilibrium; MAF, minor allele frequency; IHD, ischemic heart disease; CHD, coronary heart disease; MMPs, matrix metalloproteinases; TGF-β1, transforming growth factor-beta 1; HF, heart failure.

Data sources

In the MR analysis, we used a variety of publicly available GWAS summary data (Supplementary Table 1). To fulfill the requirements of the two-sample MR design, the exposure and outcome were obtained from two different European populations, as described previously (17).

Previous studies have shown that estimates obtained from spotted urine samples are effective in assessing 24-h urinary sodium excretion. This effectiveness can be achieved by establishing equations that take into account the U_{Na}/U_{Cr}. Because sodium intake and excretion are correlated, U_{Na}/U_{Cr} was used as a measure of sodium intake. This approach corrected for variations in urinary concentration due to differences in fluid intake levels, making it a more precise indicator of sodium intake. The GWAS for U_{Na}/U_{Cr} (sample size = 327,616) was obtained from the UK Biobank (UKBB) (18). The UKBB enlisted half a million individuals, aged 40–69, from various regions of the country to participate in this initiative between 2006 and 2010. These participants have undergone assessments, submitted samples of blood, urine, and saliva for future analysis, provided comprehensive personal information, and consented to continuous health monitoring.

We selected the GWASs for CVDs from the FinnGen datasets, a large-scale biomedical research project based in Finland (19). The FinnGen dataset consisted of genomic data collected from 500,000 individuals of Finnish ancestry. This dataset was then merged with data obtained from the National Healthcare Register of Finland. During the selection process, we excluded a series of phenotypes, such as (1) phenotypes that are not related to the circulation system; (2) similar phenotypes but with a smaller sample size or particular population; (3) broad-defined phenotypes that cannot be specifically categorized as a certain disease; and (4) phenotypes that involved interventions such as operations and medications. As a result, we retained 50 CVDs as outcomes for this study. The corresponding sample sizes for each CVD are provided in Supplementary Table 1.

Statistical method

In the MR analysis, IVs were selected according to a set of criteria, including: (1) IVs and exposure were significantly associated at the genomic level ($P < 5.00E-08$); (2) independent IVs identified by clumping within a 10 Mb window and linkage disequilibrium (LD) of $R^2 < 0.001$; and (3) the minor allele frequency (MAF) > 0.01. Additionally, we excluded palindromic SNPs with an intermediate allele frequency, as previously reported (20). The F-statistics were calculated for the strength of IVs, and a value over 10 indicates a lower risk of weak IV bias (Supplementary Table 2) (21).

The primary strategy utilized in the MR analysis was the inverse-variance weighted (IVW) method. Additionally, we used the weighted median (WM) and MR-Egger methods in sensitivity analyses. The WM method remains unbiased under the condition that no more than 50% of the weight comes from invalid instruments. The pleiotropy-corrected data from MR-PRESSO were used to eliminate probable outliers. The Cochrane Q-value

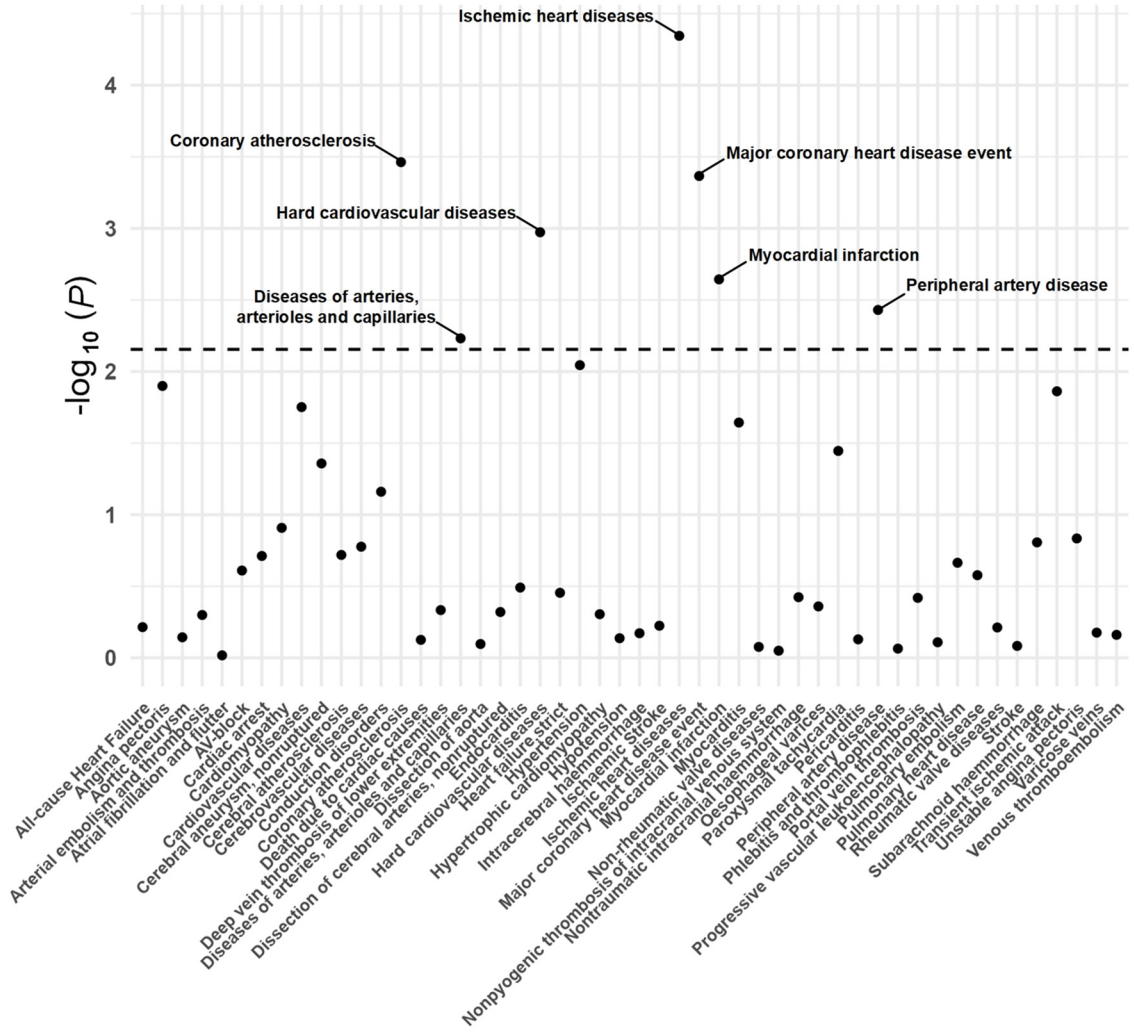

FIGURE 1
P-value distribution of associations between urinary sodium/creatinine ratio (U_{Na}/U_{Cr}) and 50 CVDs in the Mendelian randomization analysis. The dashed line represents the significance threshold adjusted by the false discovery rate.

was employed to assess heterogeneity. With the leave-one-out strategy, which examined how each included IV affected the causal associations, the robustness of the results was assessed. Causal estimations were presented as odds ratios (ORs) and 95% confidence intervals (CIs). To address multiple comparisons, a false discovery rate (FDR) threshold of 5% was applied for correction. The two-sample MR package was used to perform all the MR analyses in R.

Results

A total of 20 distinct SNPs were used as the genetic IVs for U_{Na}/U_{Cr}, and the F-statistics for the IVs ranged from 30.53 to 125.48, suggesting good instrument strength (Supplementary Table 2). FDR correction for multiple testing was used to guide the interpretation of the findings. The genetically predicted U_{Na}/U_{Cr} was found to be strongly linked with 7 of 50 CVDs, according to the IVW approach in MR, including "Coronary atherosclerosis" (OR = 2.01; 95% CI: 1.37, 2.95), "Diseases of arteries, arterioles and capillaries" (OR = 1.88; 95% CI: 1.20, 2.94), "Hard cardiovascular diseases" (OR = 1.71; 95% CI: 1.24, 2.35), "Ischemic heart diseases" (OR = 2.06; 95% CI: 1.46, 2.93), "Major coronary heart disease event" (OR = 1.99; 95% CI: 1.36, 2.91), "Myocardial infarction" (OR = 2.03; 95% CI: 1.29, 3.19), and "Peripheral artery disease" (OR = 2.50; 95% CI: 1.35, 4.63) (Figures 1, 2; Supplementary Table 3). Using the MR-Egger and WM approaches, the relationships between U_{Na}/U_{Cr} and seven CVDs had the same direction (Figure 2; Supplementary Table 3). The scatter plot visually showed causal associations between U_{Na}/U_{Cr} and seven diseases of the circulation system (Figure 3). This analysis revealed no discernible heterogeneity (Figure 4; Supplementary Table 4). According to the intercept term of the MR-Egger technique (Supplementary Table 5), horizontal

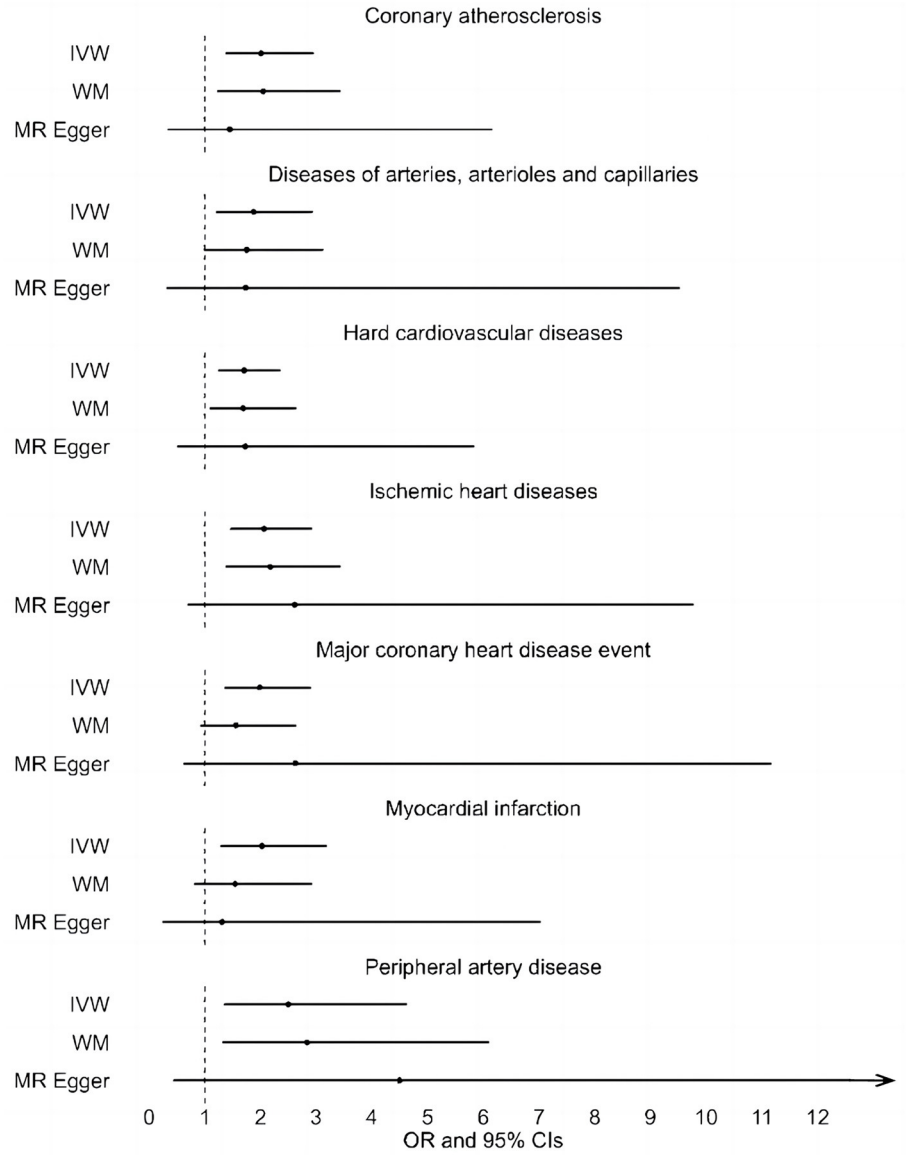

FIGURE 2
Associations between genetically predicted U_{Na}/U_{Cr} and seven CVDs examined by three MR methods. MR, Mendelian randomization; U_{Na}/U_{Cr}, urinary sodium/creatinine ratio; IVW, inverse-variance weighted; WM, weighted median; OR, odds ratio; CI, confidence interval.

pleiotropy was not significant in the causality analysis, which is similar to the findings of MR-PRESSO, where no outlier IV was found. The leave-one-out analysis revealed that the exclusion of one SNP could not significantly change the observed outcomes (Figure 5).

Discussion

This study employed a two-sample MR analysis to evaluate the causal association between sodium intake and a wide range of 50 CVDs, leveraging data from public databases and comprehensive GWAS. The results showed a positive causal relationship between U_{Na}/U_{Cr} and seven types of CVDs. To account for the overlap among some of the seven CVDs, we have categorized and discussed them separately into the following two categories.

The site of disease onset is primarily in the heart

Ischemic heart disease (IHD) is an umbrella term used to describe various heart problems resulting from reduced blood flow to the heart. IHD is the predominant manifestation of coronary heart diseases (CHDs). It arises due to arterial stenosis, or the narrowing of the blood vessels responsible for supplying

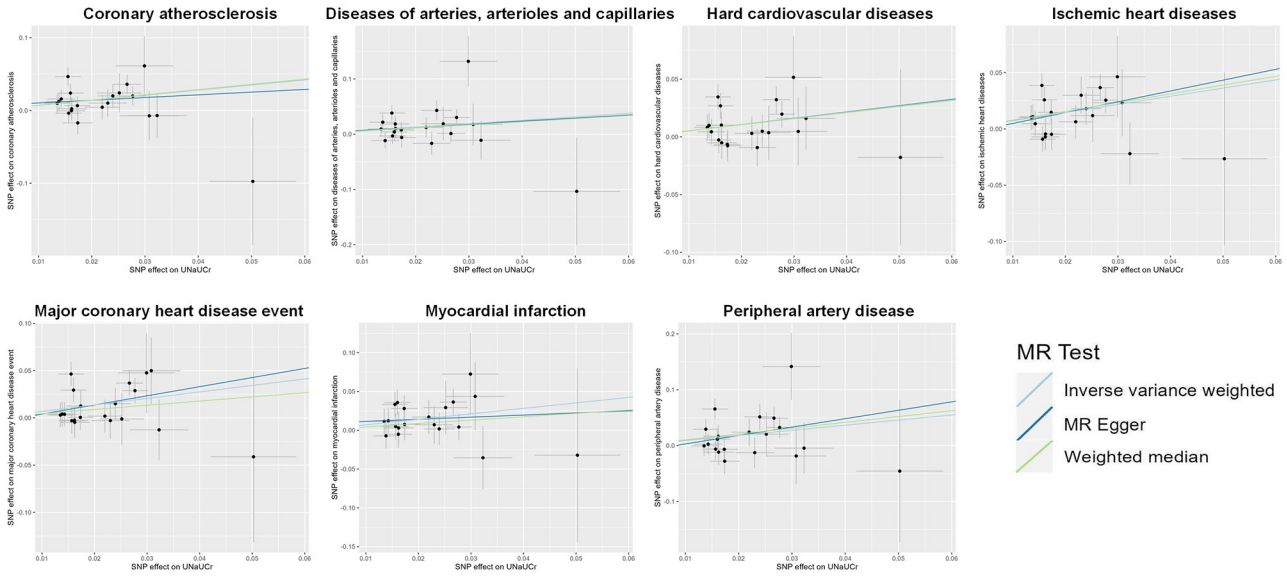

FIGURE 3
Scatter plot showing the causal effects of U_{Na}/U_{Cr} on seven CVDs. SNP, single-nucleotide polymorphism; U_{Na}/U_{Cr}, urinary sodium/creatinine ratio.

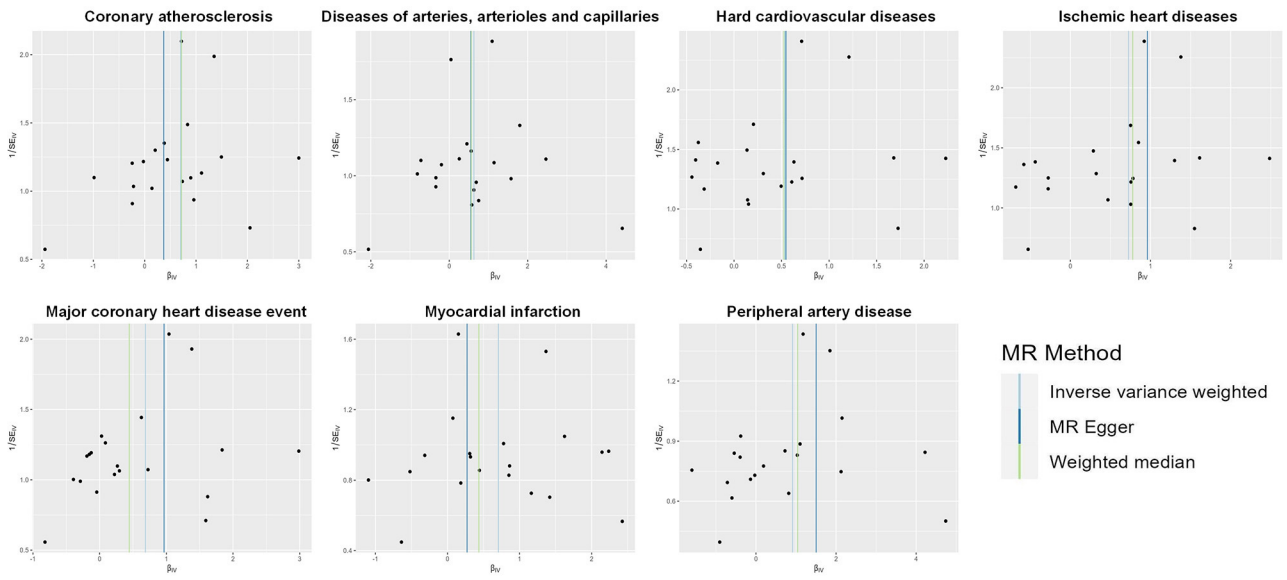

FIGURE 4
Funnel plot indicating the causal associations of U_{Na}/U_{Cr} on seven CVDs. SNP, single-nucleotide polymorphism; U_{Na}/U_{Cr}, urinary sodium/creatinine ratio; IV, instrumental variable; SE, standard error.

oxygenated blood to the myocardium, also known as the heart muscle (22). A model study conducted in China demonstrated that reducing salt intake by 1 gram per day could potentially lower the risk of IHD by approximately 4% (23). The findings of our study are consistent with prior research. IHD is most commonly caused by atherosclerosis (24, 25). A Swedish cohort study found a correlation between a higher estimated 24-h sodium excretion and coronary atherosclerosis (26). This finding provides additional support for the conclusions drawn in our study. Major coronary heart disease (CHD) events consist of both fatal and non-fatal events, with the former defined as death resulting from CHD and the latter indicating myocardial infarction or heart attack (27). Several observational studies have found that high urinary sodium excretion is linked to an increased risk of myocardial infarction. For example, a study carried out in China revealed a significant correlation between

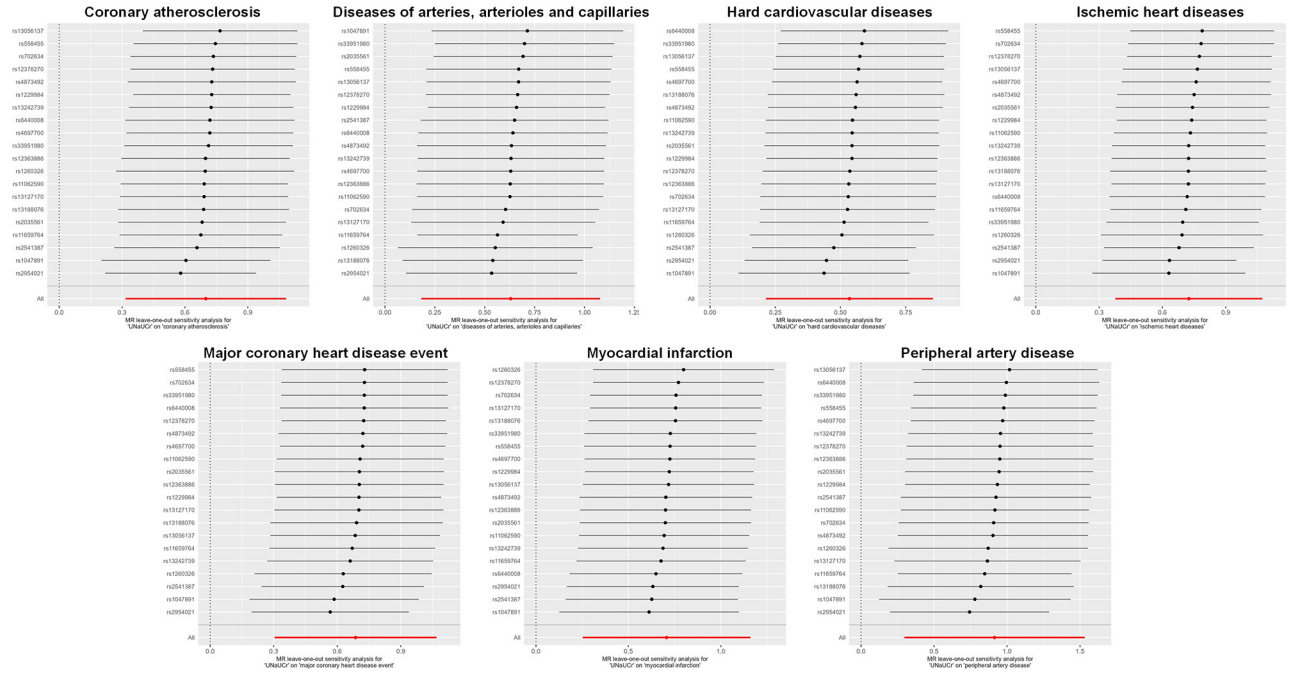

FIGURE 5
Leave-one-out sensitivity analysis examining the causal estimates of U_{Na}/U_{Cr} on seven CVDs by the IVW method after excluding a specific SNP from the analysis. MR, Mendelian randomization; SNP, single-nucleotide polymorphism; U_{Na}/U_{Cr}, urinary sodium/creatinine ratio; IVW, inverse-variance weighted.

excessive excretion of urinary sodium and increased susceptibility to cardiovascular diseases. This connection was noticed concerning instances of non-fatal heart attacks and fatalities attributed to coronary heart disease (28). Additionally, a meta-analysis indicated that elevated sodium levels, detected through multiple 24-h urine collections, were associated with a heightened risk of cardiovascular events. These occurrences encompass both lethal and non-lethal instances of heart attack, stroke, or the requirement for coronary revascularization (29).

Arterial stiffness is a well-known contributor to CVD. Studies have found that excessive sodium intake in the diet can induce changes in the extracellular matrix of the arterial wall, thereby facilitating the process of arteriosclerosis (30). Arterial stiffness is characterized by an imbalance between elastin and collagen fibers, which are key components of arterial elasticity. This process is regulated by matrix metalloproteinases (MMPs) (31). It has been discovered that a high sodium intake leads to the activation of extracellular matrix metalloproteinases, specifically MMP-2 and MMP-9, which subsequently stimulate the production of transforming growth factor-beta 1 (TGF-β1) (31, 32). TGF-β1 is a fibrotic growth factor that, when overexpressed, can cause thickening of the arterial intima, thinning and fracturing of elastin fibers, and a reduction in the ratio of elastin to collagen. These changes ultimately contribute to the development of arterial stiffness (33).

Furthermore, an MR study investigating the impact of urinary sodium on cardiovascular risk factors, ischemic stroke, and heart failure (HF) demonstrated that higher levels of urinary sodium were associated with an elevated risk of both HF and global ischemic stroke (34). Consistent with our own findings, a cohort study conducted in Taiwan revealed a significant association between increased urine sodium excretion and a higher risk of CVD, particularly stroke (35). However, a Finnish cohort study reported contrasting results, finding no significant correlation between urinary sodium levels and major adverse coronary events in men with HF (36). This discrepancy may be attributed to the population selection in the study, which excluded female patients with chronic HF and included only male patients.

The onset site is not within the heart

This study has shown a positive causal association between U_{Na}/U_{Cr} and peripheral arterial disease, as well as diseases affecting arteries, arterioles, and capillaries. These findings are in line with our study and support the conclusions of previous investigations. Two cross-sectional studies conducted in China demonstrated a robust positive association between urine sodium excretion and the presence of carotid atherosclerosis (37, 38). In a Korean cohort study, it was found that dietary sodium intake in adults aged 40 years and older may be positively associated with subsequent levels of carotid intima-media thickness (39). However, another cross-sectional study and systematic evaluation reported a limited correlation between small vessel disease and current salt intake, or U_{Na}/U_{Cr} (40).

The underlying biological mechanism may be due to oxidative stress and endothelial dysfunction. The endothelium serves as

a dynamic monolayer that critically regulates vascular tone and inflammation in the blood vessel wall (41, 42). Endothelial cells synthesize nitric oxide (NO), which acts as a protective molecule crucial for maintaining optimal vascular function (43, 44). Several enzymatic systems, such as NADPH oxidase and xanthine oxidase, are responsible for deactivating NO while simultaneously increasing levels of superoxide anions ($O_2^{\bullet -}$) (45), contributing to the development of endothelial dysfunction. Previous studies have demonstrated that salt loading impairs vascular endothelial function (46, 47). In a study on middle-aged hypertensive individuals, restricted sodium intake was found to reverse microvascular endothelial dysfunction through a reduction in oxidative stress (48). Additionally, administration of the antioxidant ascorbic acid improved microvascular function after another sodium-induced impairment, further supporting the role of oxidative stress in this process (49).

Strengths and limitations

This study has several noteworthy advantages. First, a two-sample MR strategy was used in the study to reduce the influence of confounding factors and reverse causality on the outcomes. Second, this study is the largest investigation to date on the causal relationship between U_{Na}/U_{Cr} and a broad type of CVD. Finally, we achieved relatively robust results by using GWAS summary statistics and conducting various sensitivity analyses to minimize the possibility of horizontal pleiotropy.

Our study also has limitations. First, our study only included individuals from Europe, which limits the generalizability of our findings to other ethnic groups because there may be variations in the association between U_{Na}/U_{Cr} and CVD across different ethnicities. Further research should encompass large-scale GWAS across diverse geographical regions. Second, selection bias may have affected our results, as individuals who died due to outcome competing risk might have been missed in GWAS. Third, stratification is necessary when populations demonstrate different disease rates, trait distributions, and allele frequencies. However, we encountered limitations in conducting population stratification based on additional factors such as age and gender due to using GWAS summary data instead of individual-level data in our study. Finally, previous observational studies have shown a U-shaped or J-shaped relationship between sodium intake and diverse cardiovascular diseases (50, 51), and this study neglects assessing possible non-linear connections between sodium consumption and outcomes. Future research utilizing extensive biobanks may provide further insight into the potential existence of such a relationship.

Conclusion

Our research has identified a significant and positive causal relationship between U_{Na}/U_{Cr} and seven CVDs. This provides evidence that elevated levels of sodium intake may play a contributing role in the onset or advancement of these CVDs. Therefore, it underscores the importance of closely monitoring and effectively managing sodium intake to mitigate the risk of developing CVD.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent from the patients/participants or patients/participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

SL designed the manuscript. QF, RC, YD, SX, CH, BH, TJ, and BZ performed the statistical analyses and drafted the manuscript. MB critically reviewed the manuscript. All authors read and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2023.1250509/full#supplementary-material

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EDITED BY
Iain Brownlee,
Northumbria University, United Kingdom

REVIEWED BY
Marzieh Taheri,
Isfahan University of Medical Sciences, Iran
Omid Toupchian,
North Khorasan University of Medical Sciences, Iran

*CORRESPONDENCE
Marjan Ajami
✉ marjan.ajami80@gmail.com
Saeid Doaei
✉ sdoaee@yahoo.com

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Association between ischemic heart disease and dietary intake of lycopene: a case–control study

Arezoo Amjadi[1], Farkhondeh Alami[2], Mohammad Keshavarz Mohammadian[3], Seyed Reza Mirshafaei[4], Fatemeh Azaryan[5], Anahita Houshiar-Rad[6], Mina Esmaeili[7], Soheila Shekari[3], Morteza Abdollahi[8], Sara Khoshdooz[9], Marjan Ajami[10]*, Saeid Doaei[11]* and Maryam Gholamalizadeh[12]

[1]Department of Nutrition, School of Nutritional Sciences and Food Technology, Kermanshah University of Medical Sciences, Kermanshah, Iran, [2]Student Research Committee, Department of Nutrition, Faculty of Medicine, Urmia University of Medical Sciences, Urmia, Iran, [3]Department of Nutrition, Science and Research Branch, Islamic Azad University, Tehran, Iran, [4]Department of Applied Mathematics, Faculty of Mathematical Sciences, Roudsar and Amlash Branch, Islamic Azad University, Roudsar, Iran, [5]Department of Physiology, School of Medicine, Zahedan University of Medical Sciences, Zahedan, Iran, [6]Department of Nutrition Research, Faculty of Nutrition Sciences and Food Technology, National Nutrition and Food Technology Research Institute, Shahid Beheshti University of Medical Sciences, Tehran, Iran, [7]Department of Nutrition Research, National Nutrition and Food Technology Research Institute, School of Nutrition Sciences and Food Technology, Shahid Beheshti University of Medical Sciences, Tehran, Iran, [8]Department of Nutrition Research, National Nutrition and Food Technology Research Institute; and Faculty of Nutrition Sciences and Food Technology, Shahid Beheshti University of Medical Sciences, Tehran, Iran, [9]Faculty of Medicine, Guilan University of Medical Sciences, Rasht, Iran, [10]Department of Food and Nutrition Policy and Planning, National Nutrition and Food Technology Research Institute, School of Nutrition Sciences and Food Technology, Shahid Beheshti University of Medical Sciences, Tehran, Iran, [11]Department of Community Nutrition, School of Nutrition and Food Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran, [12]Cancer Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Aim: The effect of dietary lycopene on ischemic heart disease (IHD) is not clear. Hence, this study aimed to determine the association between dietary lycopene and IHD.

Methods: This case–control study was conducted on 443 patients with physician confirmed diagnosis of IHD as the case group and 443 healthy individuals as the control group. Data on demographic, medical history, anthropometric, and physical activity of the participants were collected. Food intake was evaluated using a 237-item semi-quantitative food frequency questionnaire (FFQ). The dietary intake of lycopene was assessed using Nutritionist IV software.

Results: A negative association was found between IHD and lycopene (OR: 0.98, CI 95%: 0.963–0.996, $p = 0.02$). The results remained significant after adjustment for age and sex, additional adjustment for dietary intake of calorie and fat, further adjustments for BMI, and additional adjustment for smoking, drinking alcohol, and physical activity. The risk of IHD in people with the highest quartile of dietary intake of lycopene was significantly lower than those with the lowest quartile (OR = 0.67, CI 95%: 0.46–0.97, $p = 0.036$).

Conclusion: There was a significant inverse relationship between intake of lycopene and IHD. Further prospective studies in different populations are required to elucidate the roles of lycopene against IHD.

KEYWORDS

ischemic heart disease, lycopene, dietary intake, coronary heart disease, IHD

Introduction

Ischemic heart disease (IHD) is a pathological condition characterized by decreased cardiac blood flow that causes a non-accordance between myocardial oxygen supply and demand (1). The number of patients diagnosed with IHD increased in recent years and the prevalence of IHD was reported to be around 126 million individuals (1,655 per 100,000), approximately 1.72% of the world's population (2). The most common complications of IHD include acute mitral regurgitation (MR) secondary to papillary muscle rupture (PMR), ventricular septal defect (VSD), pseudoaneurysm, and free wall rupture (FWR). Each of these complications are related to increased risk of morbidity, mortality, and length of hospitalization (3, 4).

IHD has several risk factors such as genetic, socioeconomic factors, industrialization, urbanization, increased life expectancy, inadequate physical activity, and alternation of dietary patterns (5, 6). Numerous nutrients in fruits, vegetables, legumes, nuts, and seeds could be protective against IHD including potassium, dietary fibers, carotenoids, and subtypes of polyphenols (i.e., phenolic acids, flavonoids, stilbenes and lignans) (7–13). Lycopene is a member of the carotenoid family, a class of compounds found in fruits and vegetables (14–16). Growing evidence has indicated that lycopene's antioxidant properties protect against cardiovascular disease, diabetes, and inflammatory diseases (17). Some studies suggested that lycopene's antioxidant capabilities cause its cardioprotective effects. Also, Lycopene blocks angiotensin-converting enzyme (ACE) and may acts in reducing oxidative stress caused by angiotensin II and indirectly increasing NO synthesis in the endothelium (18).

Furthermore, Lycopene suppresses reactive oxygen species production, potentially preventing endothelial dysfunction through direct antioxidative actions (19). A recent meta-analysis found an inverse association between fruits and vegetables with risk of IHD (20). Furthermore, randomized controlled trials have shown that increased consumption of fruits and vegetables combinedly reduces blood pressure (21–23). In addition, Numerous studies have shown that higher intakes or blood concentrations of carotenoids have been linked to a reduced risk of CVD (13). A population-based study has shown that a lower risk for acute coronary events or stroke was associated with higher serum lycopene concentration (13). In agreement with the previous reports, the results of one nested case–control study demonstrated that higher plasma lycopene concentrations had been related to a lower risk of CVD in middle-aged and elderly women (24).

There are few studies on the association between lycopene and IHD (25–28). Moreover, the results of these studies have been inconsistent (29). Lycopene's role has been ascribed to its potent antioxidant properties and other functions of lycopene such as gene expression regulation not yet completely understood. Many aspects regarding the roles of lycopene against IHD independent from other environmental and dietary factors are still unknown (13). The aim of the present case–control study was to evaluate the association between lycopene and the risk of of IHD after adjusting a broad range of confounders.

Methods

The present case–control study was conducted on 443 patients with physician-confirmed IHD as the cases and 443 individuals without IHD as the controls. The sample size was obtained using Open EPI online software (30) and the odds ratio obtained in similar previous studies (28). A consecutive method was applied for selection of the case group among newly diagnosed subjects who were visited the Shahid Rajaei Hospital and Tehran Heart Center in Tehran, Iran. They all had IHD. Then, an oral explanation was given about the aim, the study's implementation, and the information's confidentiality. The control group was selected among individuals who visited the hospital for general check-up or were from the hospital staff without diagnosed heart disease. All demographic information, medical history, anthropometric measurements, physical activity levels, and food intake information were collected by a trained interviewer. The inclusion criteria for the case group were adults aged 40–80, suffering from IHD, diagnosed in the last three month before the baseline, and consent to participate. The inclusion criteria for the control group were adults aged 40–80, without IHD with the physician's approval, and consent to participate. The exclusion criteria of the case and control groups were a history of mental disorders, cancer, malignant diseases, using lycopene supplements, and failure in gathering the required data.

The participant's body weight was measured with clothing and without shoes and recorded to the nearest 0.1 kg using a digital scale. Their height was measured in a standing position without shoes and with a tapeline with an accuracy of 1 cm. Socio-demographic, medical, and dietary data were collected using a self-administered questionnaire consisted of three parts: first, general information such as age, gender, height, weight, and place of residence. Afterward, medical and lifestyle information including the use of medicine or supplements, smoking and physical was collected. Also, food intake was evaluated using a 237-item semi-quantitative food frequency questionnaire (FFQ) with standard portion sizes commonly consumed by Iranian people. The validity and reliability of FFQ was already confirmed in Iran for the evaluation of nutrients' intake (31). Data on food intake during the last year in the control group and related to food intake in the last year before cancer diagnosis in the case group were collected through a face-to-face interviews by a trained dietitian. All reported consumptions were converted to grams per day by using household measures. Then, the intake of dietary lycopene was analyzed using Nutritionist IV software (version 7.0; N-Squared Computing, Salem, OR, USA). Data on biochemical and hematologic indices including red blood cells (RBC), white blood cells (RBC), fasting blood sugar (FBS), SBP (systolic blood pressure), right DBP (diastolic blood pressure), hemoglobin (HGB), hematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), the mean corpuscular hemoglobin concentration (MCHC), high-density lipoprotein cholesterol (HDLC), low-density lipoprotein cholesterol (LDLC), and triglycerides (TG) were extracted from participants' file.

Statistical analysis

An independent sample T-test (shown as mean ± sd), and chi-squared test [shown as frequency(percent)] were used for

quantitative and qualitative data, respectively. Normal distribution of continuous data was confirmed using the Kolmogorov–Smirnov test. Logistic regression method [shown as OR and 95% Confidence Interval (CI)] was used for the association between IHD and dietary intake of lycopene and the confounding variables including age at interview, gender, total fat and energy intake, BMI, smoking, using alcohol, and physical activity were adjusted in different models. Data was performed using SPSS software version 21 (IBM Corp., Armonk, NY, USA) and $p < 0.05$ was considered significant in all analyses.

Ethical considerations

The informed written consent was obtained from all participants. This study has been approved by Local ethics review boards at Shahid Beheshti University, Tehran, Iran (Code: IR.SBMU.NNFTRI.REC.1400.030).

Results

Characteristics of the participants are presented in Table 1. No significant difference was found regarding age, sex, physical activity, height, weight, BMI, smoking, and drink alcohol between the groups. Table 2 presents the biochemical measurements of the participants. The cases had lower RBC (4.86 ± 1.66 vs. 4.96 ± 1.52, $p < 0.01$) and higher WBC (6.67 ± 0.53 vs. 6.32 ± 0.56, $p < 0.01$) and FBS (121.11 ± 37.36 vs. 107.96 ± 43.20, $p < 0.01$) than the controls. There was no significant difference in BMI, smoking, drink alcohol, right SBP, right DBP, HGB, HCT, MCV, MCH, MCHC, HDLC, LDLC, TG, and cholesterol.

A comparison of dietary intake among the case and control groups is presented in Table 3. The case group had a lower intake of lycopene (12.99 + 8.42 vs. 14.234 + 7.28 mg/d, $p = 0.01$) than the control group. No significant difference was found in dietary intake of protein, total fat, carbohydrate, energy, saturated fatty acids, and other micronutrients between the groups.

The association of IHD and dietary intake of lycopene is presented in Table 4. A negative association was found between IHD and lycopene (OR: 0.98, CI 95%: 0.963–0.99, $p = 0.021$) (Model 1). The results remained significant after adjustment for age and sex (OR: 0.980, CI 95%: 0.96–0.99, $p = 0.024$) (Model 2), after additional adjustment for dietary calorie and total fat (OR: 0.98, CI 95%: 0.96–0.99, $p = 0.024$) (Model 3), after further adjustments for BMI (OR: 0.97, CI 95%: 0.96–0.99, $p = 0.016$) (Model 4), and after further adjustments for smoking, drink alcohol, and and physical activity (OR: 0.97, CI 95%: 0.95–0.99, $p = 0.015$) (Model 5). The IHD relationship with the categorical values of the lycopene was also evaluated. The risk of IHD in people with the highest quartile of dietary intake of lycopene was significantly lower than those with the lowest quartile (OR = 0.67, CI 95%: 0.46–0.97, $p = 0.036$). This association remained significant after adjusting the confounders (Table 4).

Discussion

According to this case–control study, the patients with IHD had a lower lycopene intake than the control group. The present study discovered an inverse association between lycopene intake and the risk of IHD. The associations remained significant after age and sex, after additional adjustments for dietary calorie and total fat, after additional adjustments for BMI, and after further adjustments for smoking and physical activity (Figure 1). In line with the present findings, a population-based study has shown that a lower risk for acute coronary events or stroke was associated with higher serum lycopene concentration (13). Data from previous studies suggests that consuming more lycopene-containing foods leads to higher levels of lycopene in the bloodstream (32). Moreover, high serum levels of lycopene were significantly related to low hazard ratios for CVD mortality in a Japanese population-based study (33). In addition, Rissanen et al. demonstrated that a low plasma concentration of lycopene was associated with a 17.8% increase in the carotid intima-media thickness (CIMT) in men compared to subjects with higher plasma concentrations of lycopene after adjustments for cardiovascular risk factors and nutrients intake (34). In addition, a cross-sectional study on 1,028 middle-aged men confirmed that low serum lycopene concentrations were associated with higher CIMT in middle-aged men (35). On the other hand, another study by Bruneck et al. found no association between lycopene plasma levels and atherosclerosis (36). Moreover, a nested case–control study utilizing the PHS database did not find any association between increasing concentrations of plasma lycopene and the risk of CVD (37). It is important to note that the conflicting results on the potential cardioprotective effects of

TABLE 1 General characteristics of the participants.

	Cases (n = 443)	Controls (n = 443)	p value*
Age (y)	55.59 ± 14.43	54.67 ± 11.13	0.106
MET (kcal/kg*h)	37.53 ± 7.72	38.01 ± 8.38	0.391
Height (Cm)	161.48 ± 34.16	161.03 ± 27.61	0.461
Weight (Kg)	74.38 ± 17.31	72.64 ± 15.54	0.057
BMI (Kg/m^2)	28.54 ± 6.3	28.06 ± 6.01	0.135
Smoking (n, %)	108 (24.83)	87 (19.21)	0.064
Male (n, %)	208 (47.92)	204 (45.03)	0.402
Drink Alcohol (n, %)	38 (8.74)	45 (9.94)	0.479

*Independent sample T-test (shown as mean ± sd) and chi-squared test [shown as frequency(percent)]. MET: metabolic equivalent of task, BMI: body mass index.

TABLE 2 Biochemical measurements of the participants.

	Cases (n = 443)	Controls (n = 443)	p value*
Right SBP (mmHg)	114.47 ± 16.63	114.51 ± 17.37	0.871
Right DBP (mmHg)	71.950 ± 10.40	71.96 ± 10.64	0.842
WBC (K/μL)	6.67 ± 0.53	6.32 ± 0.56	0.001
RBC (M/μL)	4.86 ± 1.66	4.96 ± 1.52	0.003
Hb (gr/dl)	13.99 ± 1.53	14.08 ± 1.55	0.428
HCT (%)	41.04 ± 4.14	41.36 ± 4.29	0.173
MCV (fL)	84.87 ± 5.81	85.002 ± 5.72	0.804
MCH (pg)	28.95 ± 2.59	28.97 ± 2.54	0.852
MCHC (gr)	34.08 ± 1.43	34.05 ± 1.41	0.164
PLT (K/μL)	283.75 ± 67.55	276.68 ± 68.09	0.204
FBS (mg/dl)	121.11 ± 37.36	107.96 ± 43.20	0.001
BUN (mg/dl)	13.58 ± 3.75	13.89 ± 3.82	0.094
Creatinine (mg/ml)	1.08 ± 0.27	1.10 ± 0.216	0.683
TG (mg/dl)	148.33 ± 109.08	144.51 ± 95.82	0.282
Cholesterol (mg/dl)	192.03 ± 40.39	191.26 ± 40.12	0.831
SGOT (IU/L)	19.97 ± 7.39	20.40 ± 10.05	0.091
SGPT (IU/L)	21.95 ± 13.52	22.29 ± 16.61	0.093
ALP (IU/L)	222.07 ± 68.79	222.21 ± 67.23	0.673
HDLC (mg/dl)	52.42 ± 10.54	52.35 ± 10.69	0.876
LDLC (mg/dl)	110.16 ± 34.06	110.40 ± 33.43	0.812

*Independent sample t-test. SBP: systolic blood pressure, DBP: diastolic blood pressure, WBC: white blood cell, RBC: red blood cell, FBS: fasting blood sugar, TG: triglyceride, HDL-c: high density lipoprotein cholesterol, LDL-c: low-density lipoprotein cholesterol.

TABLE 3 Dietary nutrient intake among the Cases and the controls.

	Cases (n = 443)	Controls (n = 443)	p value*
Protein (g/day)	78.37 ± 25.76	78.97 ± 26.36	0.452
Fat (g/day)	64.39 ± 24.79	64.59 ± 25.71	0.228
Carbohydrate (g/day)	409.62 ± 135.34	415.49 ± 140.59	0.193
Calorie (Kcal/day)	2482.58 ± 768.69	2511.78 ± 799.43	0.254
Lycopene (mg/day)	12.99 ± 8.42	14.234 ± 7.28	0.011
Galactose (mg/day)	0.192 ± 0.188	0.21 ± 0.216	0.069
Fiber (g/day)	27.11 ± 10.37	28.01 ± 10.12	0.224
Calcium (mg/day)	912.24 ± 328.5	918.67 ± 329.5	0.814
Iron (mg/day)	13.38 ± 4.73	344.82 ± 110.76	0.801
Magnesium (mg/day)	344.8 ± 110.76	343.98 ± 110.69	0.835
Phosphorus (mg/day)	1198.2 ± 389.77	1199.44 ± 398.51	0.417
Potassium (mg/day)	3674.27 ± 1278.79	3642.93 ± 1257.57	0.744
Sodium (mg/day)	4554.7 ± 2054.61	4633.84 ± 2088.36	0.788
Zinc (mg/day)	10.08 ± 3.35	10.08 ± 3.42	0.438
Copper (mg/day)	1.83 ± 0.71	1.83 ± 0.66	0.662
Fluoride (mg/day)	3573.2 ± 2394.6	3576.44 ± 2342.34	0.231
Manganese (mg/day)	5.65 ± 1.95	5.66 ± 1.93	0.916
Selenium (μg/day)	55.78 ± 29.63	54.66 ± 28.13	0.658
Vitamin A (IU/d)	8692.01 ± 5640.81	8720.66 ± 5552.12	0.621
Retinol (IU/d)	338.25 ± 394.44	333.88 ± 281.89	0.553

(Continued)

TABLE 3 (Continued)

	Cases (n = 443)	Controls (n = 443)	p value*
Vitamin A (mg/day)	715.08 ± 508.06	713.19 ± 425.37	0.964
Beta Carotene (μg/day)	4019.38 ± 2739.06	4044.64 ± 2746.80	0.411
Alpha Carotene (μg/day)	665.44 ± 838.02	685.43 ± 856.74	0.206
Alpha tocopherol (mg/day)	7.24 ± 3.28	7.14 ± 3.22	0.654
Vitamin D (IU)	42.91 ± 27.26	42.96 ± 27.10	0.291
Vitamin D2, D3 (mg/day)	1.21 ± 0.703	1.21 ± 0.69	0.239
Vitamin C (mg/day)	143.73 ± 83.78	139.96 ± 78.97	0.448
Vitamin B1 (mg/day)	1.62 ± 0.59	1.64 ± 0.60	0.821
Vitamin B2 (mg/day)	1.76 ± 0.66	1.74 ± 0.626	0.544
Vitamin B3 (mg/day)	18.16 ± 6.53	18.17 ± 6.51	0.682
Vitamin B5 (mg/day)	5.93 ± 1.90	5.90 ± 1.92	0.452
Vitamin B6 (mg/day)	9.77 ± 5.91	10.04 ± 4.91	0.511
Folate (μg/day)	381.07 ± 138.89	377.18 ± 130.77	0.358
Vitamin B12 (μg/day)	6.07 ± 6.43	5.87 ± 4.50	0.257
Vitamin K (mg/day)	164.5 ± 102.65	165.39 ± 100.9	0.542

*Independent sample t-test.

TABLE 4 Odds ratio and CI95% of the association between ischemic heart disease (IHD) and dietary intake of lycopene.

	Trend	Quartile 1 (<7.91 mg/d)	Quartile 2 (7.91–11.64 mg/d)	Quartile 3 (11.64–16.47 mg/d/)	Quartile 4 (16.47 < mg/d)
Model 1	**0.98 (0.96–0.99)**	**1**	**0.79 (0.54–1.15)**	**1.14 (0.78–1.66)**	**0.67 (0.46–0.97)**
Model 2	0.98 (0.96–0.99)	1	0.79 (0.54–1.16)	1.13 (0.77–1.65)	0.67 (0.46–0.99)
Model 3	0.98 (0.96–0.99)	1	0.78 (0.53–1.15)	1.11 (0.75–1.64)	0.65 (0.42–0.99)
Model 4	0.97 (0.96–0.99)	1	0.77 (0.52–1.13)	1.09 (0.73–1.61)	0.63 (0.41–0.97)
Model 5	0.97 (0.95–0.99)	1	0.78 (0.53–1.15)	1.07 (0.72–1.59)	0.64 (0.41–0.99)

* Binominal Logistic regression, Model 1: crude, Model 2: adjusted for Age at interview and gender, Model 3: Additionally adjusted for total fat and energy, Model 4: Additionally adjusted for BMI, Model 5: Further adjusting for smoking, drink alcohol, and physical activity.

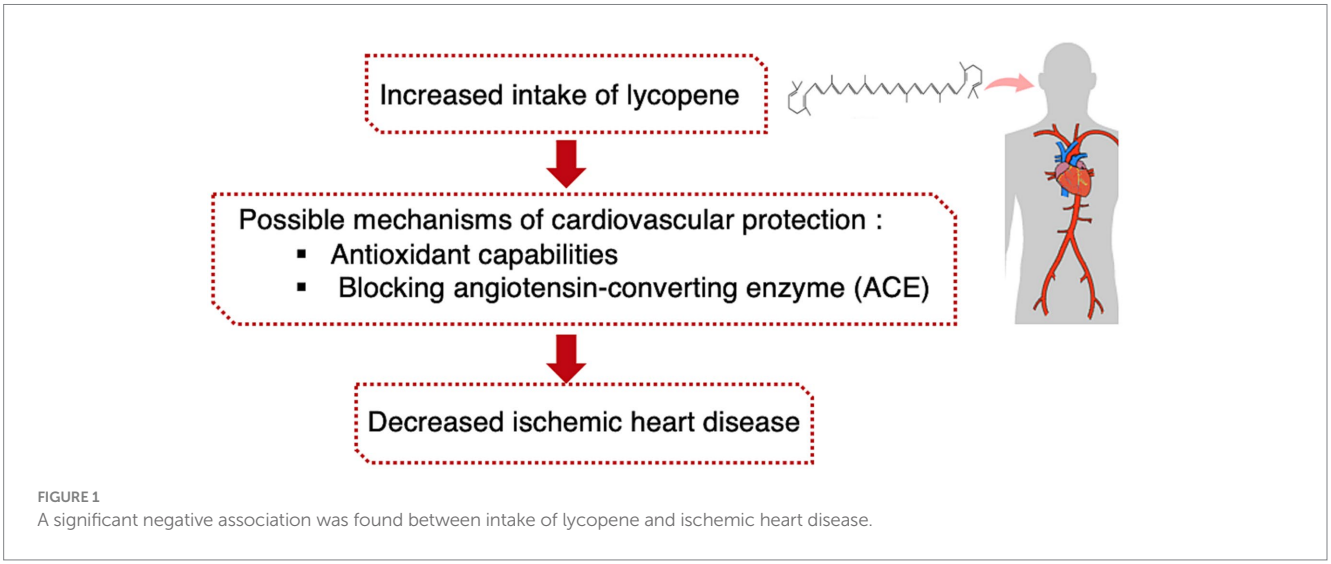

FIGURE 1
A significant negative association was found between intake of lycopene and ischemic heart disease.

lycopene may be caused by the wide variety of experimental protocols used to discover the association between lycopene consumption and cardiovascular disease (38). Pre-existing levels of lycopene, the dietary source of lycopene, and the characteristics of the target populations are essential factors that can affect any association between lycopene consumption and cardiovascular disease (38).

Possible explanations for the effect of lycopene on IHD might be the antithrombotic and antiplatelet effects of lycopene (39, 40), potent antioxidant properties of lycopene (41, 42), induction of detoxifying enzymes (43, 44) and reduction of cell surface adhesion and intima-media thickness (45). Oxidative stress can lead to the production of proinflammatory mediators, including vascular cell adhesion molecules, intracellular adhesion molecules, and chemoattractant proteins, which contribute to the development of early atherosclerosis (46, 47). On the other hand, lycopene is a powerful antioxidant that can effectively reduce levels of reactive oxygen species and eliminate singlet oxygen (48, 49). Thus, lycopene may suppress oxidative stress and acts against IHD. The strength of the present study is the adjustment for a broad range of potential confounding factors. However, this study had some limitations. First, the study design was case–control and did not allow to discover the cause and effect relationship. Second, the FFQ was used to assess food intake in the study, which may lead to over-reporting or under-reporting of dietary intake. Third, the way of cooking food was not investigated in the present study, which can affect the bioavailability of food lycopene.

Conclusion

A significant negative association was found between intake of lycopene and IHD. If this result is confirmed in future studies, high dietary intake of lycopene and lycopene supplementation can be considered complementary strategies against IHD. Further prospective studies in different populations are required to elucidate the roles of lycopene against IHD.

Data availabiulity statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The ethics committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran approved the study (Ethics Code: IR.SBMU.nnftri.Rec.1400.030). The study was conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

SD: Formal analysis, Writing – original draft. AA: Data curation, Writing – review & editing. FAl: Data curation, Writing – original draft. MM: Software, Writing – review & editing. RM: Software, Writing – review & editing. FAz: Software, Writing – review & editing. AR: Methodology, Writing – review & editing. ME: Formal analysis, Writing – review & editing. SS: Software, Writing – review & editing. MA: Data curation, Writing – review & editing. SK: Data curation, Writing – review & editing. MA: Data curation, Writing – review & editing. MG: Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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EDITED BY
Iain Brownlee,
Northumbria University, United Kingdom

REVIEWED BY
Niels Graudal,
University Hospital of Copenhagen, Denmark
Tommaso Filippini,
University of Modena and Reggio Emilia, Italy

*CORRESPONDENCE
Dengfeng Gao
✉ gaomedic@mail.xjtu.edu.cn
Ning Ning
✉ Hers0@163.com

†These authors have contributed equally this work and share first authorship

‡These authors have contributed equally to this work and share last authorship

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Sodium intake and the risk of heart failure and hypertension: epidemiological and Mendelian randomization analysis

Miao Yuan[1†], Dingyi Yan[2,3†], Yu Wang[1], Mengyao Qi[1], Kexin Li[1], Zhi Lv[1], Dengfeng Gao[1*‡] and Ning Ning[4*‡]

[1]Cardiology Diseases Department, The Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China, [2]Cardiology Diseases Department, Xi'an No. 3 Hospital, Xi'an, China, [3]Cardiology Diseases Department, The Affiliated Hospital of Northwest University, Xi'an, China, [4]Nuclear Medicine Department, Xi'an Jiaotong University Second Affiliated Hospital, Xi'an, China

Background: This study aimed to analysis the relationship between sodium intake and the risk of heart failure and hypertension through epidemiological studies and Mendelian randomization analysis.

Methods and result: We initially conducted an analysis using data from the National Health and Nutrition Examination Survey (NHANES) database to examine the relationship between sodium intake and heart failure, hypertension, systolic blood pressure, and diastolic blood pressure. After adjusting for confounding factors, we found a non-linear association between sodium intake and heart failure (p nonlinear = 0.0448). Subsequently, we utilized Mendelian randomization (MR) analysis by utilizing urinary sodium as a proxy for sodium intake to investigate the relationships between sodium and heart failure, hypertension, systolic blood pressure, and diastolic blood pressure. The results indicated that with increasing urinary sodium, there is an increase in systolic and diastolic blood pressure, as well as an elevated risk of heart failure and hypertension.

Conclusion: The evidence provided by this study suggests that higher sodium intake is associated with an increased risk of heart failure and hypertension. However, excessively low sodium intake may not necessarily be beneficial, as there may be maximum benefits at a sodium intake level of around 3,000 mg/d.

KEYWORDS

dietary salt, heart failure, hypertension, Mendelian randomization, NHANES

1 Introduction

Heart failure is a prevalent and severe cardiovascular disease that affects the quality of life and lifespan of millions of people globally (1, 2). Despite advances in medical management, heart failure remains a leading cause of incidence, hospitalization, and mortality (3, 4). One of the critical modifiable risk factors for heart failure is dietary sodium intake, and dietary sodium restriction has traditionally been a cornerstone of non-pharmacological therapy for heart failure (5–7). However, the relationship between dietary sodium intake and heart failure is complex and controversial, with many studies reporting conflicting finding (8, 9). While

some studies suggest benefits (10, 11), others indicate better outcomes with sodium liberalization (12, 13). To better understand the relationship between dietary sodium intake and heart failure, we analyzed data from the National Health and Nutrition Examination Survey (NHANES) and conducted a Mendelian randomization analysis to investigate the causal relationship between urinary sodium excretion and heart failure. Mendelian randomization (MR) is an emerging epidemiological method that uses genetic variants as instrumental variables for exposure to estimate the causal effect on a specific outcome. This approach is less susceptible to confounding and reverse causality biases than observational studies (14, 15).

The aim of this study was to examine the relationship between dietary sodium intake and incident heart failure in NHANES patients and to test the causal relationship between urinary sodium excretion and heart failure using the Mendelian randomization method. We also discussed the clinical implications of our findings for the prevention and management of heart failure.

2 Materials and methods

2.1 Observational epidemiological analysis

The data analyzed in this study was obtained from NHANES, which is a program of the National Center for Health Statistics (NCHS) consisting of a series of continuous cross-sectional surveys. The database contains nutritional and health information for adults and children, including interviews and physical examinations. As NHANES is a publicly available database and all patients provided informed consent at the time of participation, ethical approval for this study was waived. The detailed NHANES study design and data are publicly available at https://www.cdc.gov/nchs/nhanes/. We downloaded and analyzed the data according to the tutorials of NHANES[1] and survey content brochure.[2] We included data from 2008 to 2018 and excluded individuals: (1) People younger than 20 years old, (2) Missing the data of sodium intake, (3) Missing data on diastolic and systolic or the pulse is irregular; (4) Missing data on heart failure or hypertension, (5) Missing the data on alcohol intake or smoking, and (6) Missing the data on marital status.

In this study, we extracted data on sodium intake from the dietary data section. In cases where an individual reported sodium intake on both the first and second day of the dietary interview, the average of the 2 days was calculated and taken as their sodium intake. However, if only the first day's sodium intake data was available, it was used as their sodium intake value. We obtained the definitions of heart failure from the medical conditions mentioned in the questionnaire data, specifically MCQ160b (Ever told had congestive heart failure?). For hypertension, we relied on the response to question BPQ 120 (Ever told you had hypertension?) to determine its definition. A previous study demonstrated good correlation between self-reported cardiovascular disease and clinically confirmed (16, 17).

In this study, the SMQ120 (Smoked at least 100 cigarettes in life) was utilized to ascertain an individual's smoking status based on the questionnaire data. The criterion used to differentiate between smokers and non-smokers was based on a lifetime consumption of fewer or more than 100 cigarettes. Similarly, the ALQ110 (Had at least 12 alcohol drinks/lifetime?) was employed to establish drinking behavior. Specifically, consuming more than 12 alcoholic drinks within the past year was classified as drinking, while a consumption of fewer than 12 drinks was classified as non-drinking.

Continine is a metabolite of nicotine, thus we use the level of continine in blood as a covariate to adjust for the effect of smoking on the risk of developing heart failure. The estimated glomerular filtration rate (eGFR) was calculated from serum creatinine levels using the following formula: $eGFR = 175 \times \text{serum creatinine (mg/dl)}^{-1.154} \times \text{age}^{-0.203} \times 1.212$ (if black) $\times$ 0.742 (if female) (18). In addition to the above variables, we also incorporated age, sex, race, marital status, ratio of family income to poverty (PIR), body mass index (BMI), total cholesterol, serum sodium, education level as covariates in this analysis.

According to research, 90% of the world's population has a sodium intake between 115–215 mmol/d (2,622–4,830 mg/d) (19). Considering that the Institute of Medicine (IOM) set the upper sodium intake (UL) at 2600 mg / day (20), we categorized the study population into four groups based on their sodium intake: low sodium diet (<2,600 mg/d), normal low sodium diet (2600–3800 mg/d), normal high sodium diet (3800–4800 mg/d), and high sodium diet (>4,800 mg/d). The distribution of data was assessed using the Kolmogorov test. Continuous variables and categorical variables were displayed using means or medians (interquartile range) and counts (frequencies), respectively, depending on the normality of the variable's distribution. Baseline characteristics between groups were compared using analysis of variance (for normally distributed continuous data), chi-square test (for categorical variables), or Kruskal-Wallis H test (for non-normally distributed continuous data).

We used logistic regression to determine the relationship between sodium intake and outcome risk and adjusted for confounding factors. The 95% confidence interval (CI) of the odds ratio of the relationship between sodium intake and outcome was determined through multivariate adjustment. Three models were established: Model 1 was the crude model without confounder adjusted; Model 2 was adjusted for age, sex, and race; and Model 3 was further adjusted for age, sex, race, marital status, PIR, education level, alcohol intake, continine, total cholesterol, BMI, and eGFR. The low sodium diet group was used as the reference in all models. Finally, the restricted cubic spline (RCS) with four knots at the 5th, 35th, 65th, and 95th centiles was used to analyze the nonlinear relationship between sodium intake and heart failure (HF). We also used three models in RCS analysis to explore the nonlinear relationship between sodium intake and HF, hypertension, systolic blood pressure and diastolic blood pressure. In Model 1, no covariates were adjusted, in Model 2, sex, age, and race were adjusted, and in Model 3 age, sex, race, marital status, PIR, education level, alcohol intake, continine, total cholesterol, BMI, and eGFR were adjusted. Based on Model 3, we further constructed Model 4, 5 and 6 to adjust for systolic pressure, diastolic pressure, and hypertension respectively, as sodium intake may increase the risk of heart failure by affecting blood pressure. The likelihood ratio test was used to examine the nonlinearity.

Data analysis was performed using the Statistical Package for the Social Sciences (SPSS Statistics 26) and R (version 4.2.1). Statistical

1 https://wwwn.cdc.gov/nchs/nhanes/tutorials/default.aspx

2 https://wwwn.cdc.gov/nchs/data/nhanes/survey_contents.pdf

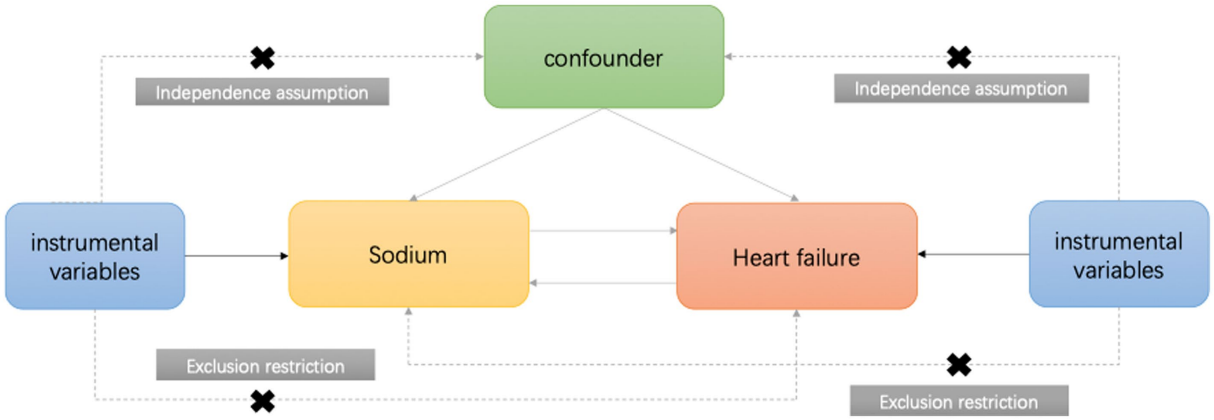


FIGURE 1
The key assumptions of MR analysis.

significance was determined by two-sided tests with a value of p threshold of less than 0.05.

2.2 MR analysis

The summary data from the Genome Wide Association Study (GWAS) used in the MR analysis are publicly available and do not require an additional ethical statement. While there are no GWAS studies specifically related to dietary sodium, the estimation of sodium intake through urinary sodium measurement is a commonly used method. In this study, we utilized urinary sodium data from the UK Biobank,[3] comprising 462,630 individuals predominantly of European ancestry, and employed two-sample Mendelian randomization (MR) to investigate the association between urinary sodium and HF, hypertension as well as blood pressure. We selected instructor variables (IVs) for MR analysis based on GWAS of the exposure data, and these IVs satisfied three key assumptions: (I) strong association with the exposure, (II) independence from potential environmental confounders, and (III) influence on the outcome risk only through the exposure variable (Figure 1). The outcome variable was derived from publicly available GWAS summary data, including heart failure, hypertension, systolic blood pressure, and diastolic blood pressure. Details of the dataset are provided in Supplementary Table S1.

We identified independent single nucleotide polymorphisms (SNPs) ($r^2 < 0.0001$) associated with urinary sodium ($p < 5\times10^{-8}$) by analyzing GWAS summary data of urinary sodium from spot urine samples in the UK Biobank database. For each SNP, we calculated the *F*-value to assess the risk of weak instrument bias. An F-value greater than 10 indicates a low risk of weak instrument bias. The F-value for the instrumental variable was obtained by summing the *F*-values for each SNP. The calculation of F was based on the formula: $F = r^2 * (n-2) / (1-r^2)$, where r^2 was calculated using the following equation: $r^2 = 2 *$ effect allele frequency * (1−effect allele frequency) × β^2 (n = sample size).

Given the potential for pleiotropy in genetic variation, we employed three methods to calculate MR for exposure and outcome after harmonizing effect alleles between exposure and outcome GWAS, including fixed-effects inverse-variance-weighted (IVW) method, MR-Egger, and weighted median. IVW provides a combined causal estimate for each SNP and is considered to have strong statistical power, so we used IVW as the primary analysis. IVW multiplicative random effects was used if there was heterogeneity between IVs and IVW fixed effects if there was no heterogeneity. MR-Egger allows for pleiotropy in all genetic variants, and the weighted median assumes that at least 50% of the information comes from valid instrumental variables. These two methods were used as supplements to IVW, as they can provide more robust estimates in a wider range of scenarios, albeit with lower efficiency (wider CI).

Horizontal pleiotropy occurs when genetic variants associated with the exposure of interest indirectly affect the outcome through pathways other than the assumed direct exposure. Therefore, sensitivity analysis was conducted. We used Cochran's Q test to assess heterogeneity among different IVs in sensitivity analysis. When the *p* value of the Cochran's Q test was less than 0.05, heterogeneity was detected. MR-Egger with a zero intercept ($p > 0.05$) was considered to have no pleiotropic bias. MR pleiotropy residual and MR-PRESSO methods were used to perform global heterogeneity tests and identify horizontal pleiotropy. Leave-one-out analysis was used to detect horizontal pleiotropy by sequentially removing SNP in the instrumental variable and calculating the impact of the remaining SNPs on the result. We also evaluated whether each SNP in the IVs had potential pleiotropy using the PhenoScanner website.[4] SNPs with potential pleiotropy were removed, and IVW analysis was conducted again to avoid potential effects of pleiotropy on causal relationships.

In the MR analysis, we used the Bonferroni correction for *p*-values. As we had five outcome variables, the significance threshold was 0.0125 (0.05/4). $p < 0.05$, but >0.0125, was considered a potential association.

3 https://www.ukbiobank.ac.uk

4 http://www.phenoscanner.medschl.cam.ac.uk

3 Results

3.1 Analysis of data from the NHANES database

We analyzed data from the NHANES database spanning from 2008 to 2018. Participants were selected based on predefined inclusion and exclusion criteria, as illustrated in Supplementary Figure S1, resulting in a total of 27,120 participants being included in the study. The median daily sodium intake was 3458.63 mg/d. Participants were divided into four groups based on their daily sodium intake, and the baseline characteristics of each group are presented in Table 1. The results demonstrate that individuals with lower sodium intake had a higher median age ($p < 0.001$) and a greater proportion of females ($p < 0.001$) compared to those with higher sodium intake. The group with higher sodium intake exhibited a higher percentage of individuals living alone ($p < 0.001$), and there were significant differences in sodium intake based on race ($p < 0.001$). Additionally, the group with lower sodium intake had significantly higher levels of continine and eGFR ($p < 0.001$), and there were differences in alcohol consumption and total cholesterol levels across the different sodium intake groups ($p < 0.001$). However, there were no significant differences in BMI or serum sodium levels across the groups ($p = 0.811$, $p = 0.057$).

Table 2 compares the risk of developing HF and hypertension across the different sodium intake groups while including various covariates. In Model 1 which did not adjust for any covariates, the risk of HF and hypertension was lower in the normal and high sodium intake groups compared to the low sodium intake group ($p < 0.001$). In Model 2, after adjusting for sex, race, and age, the risk of HF was lower in the normal sodium intake group (normal low sodium diet and normal high sodium diet) compared to the low sodium intake group ($p = 0.015$, $p = 0.003$), while there was no significant difference in the risk of heart failure between the high and low sodium intake groups ($p = 0.419$). Different sodium intakes were associated with the risk of hypertension ($p = 0.018$), but a normal sodium diet (normal low sodium diet and normal high sodium diet) did not increase the risk of hypertension compared to a low sodium diet ($p = 0.155$, $p = 0.373$). The high sodium intake group did not exhibit a higher risk of hypertension compared to the low sodium intake group, but the value of p was borderline at 0.05 ($p = 0.055$). Model 3 included age, sex, race, marital status, PIR, education level, alcohol intake, continine, total cholesterol, BMI, and eGFR as covariates. The results indicated that the risk of HF was lower in the normal sodium intake group (normal low sodium diet and normal high sodium diet) compared to the low sodium intake group ($p = 0.028$, $p = 0.002$), and there was no significant difference in the risk of heart failure between the high and low sodium intake groups ($p = 0.189$). Furthermore, the risk of hypertension was lower in the normal (normal low sodium diet and normal high sodium diet) and high sodium intake groups compared to the low sodium intake group ($p = 0.022$, $p = 0.985$, $p = 0.66$).

As shown in Figure 2, the RCS analysis revealed an 'L'-shaped non-linear relationship (p nonlinear = 0.0161) between HF and sodium intake without adjustment for covariates. In Model 2 and Model 3, a "U"-shaped relationship was observed (p nonlinear = 0.0465, p nonlinear = 0.0448). On the basis of Model 3, the Model4, Model5, Model6 adjusted for systolic pressure, diastolic pressure, and hypertension individually, the nonlinear relationship between sodium intake and the risk of heart failure remains (p nonlinear = 0.0420, p nonlinear = 0.0436, p nonlinear = 0.0343). As shown in Supplementary Figure S2 in Model 1 an 'L'-shaped relationship was observed between sodium intake and hypertension (p nonlinear = 0.0018), but there was no non-linear relationship between sodium intake and hypertension in Model 2 and Model 3 (p nonlinear = 0.2508, p nonlinear = 0.2457). In Model 1 and Model 2 sodium intake had a non-linear relationship with SBP and DBP (p nonlinear for SBP < 0.0001, p nonlinear for SBP = 0.0020, p nonlinear for DBP = 0.0044, p nonlinear for DBP = 0.0403). As shown in Model 3, after adjusted for all covariates the nonlinear relationship between sodium intake and SBP disappears (p nonlinear for SBP = 0.0513) (p nonlinear for DBP = 0.5789).

3.2 MR analysis

We used 29 SNPs associated with urinary sodium as instrumental variables and their characteristics are presented in Supplementary Table S2. The F value of each SNP was greater than 10. We employed these instrumental variables to investigate the associations of urinary sodium with heart failure, hypertension, systolic blood pressure, and diastolic blood pressure. We found no significant SNP-outcome associations when we searched for the roles of these SNPs on Phenoscanner.

Table 3 shows that the Cochrane Q test detected heterogeneity for heart failure, hypertension, systolic blood pressure, and diastolic blood pressure ($p < 0.05$). To address this issue, we applied multiple random effects in the IVW analysis for these outcomes. Moreover, the intercept p-value was greater than 0.05 for all outcomes, indicating no evidence of horizontal pleiotropy. Notably, the MR-PRESSO global test revealed a potential pleiotropy for heart failure, hypertension, and diastolic blood pressure ($p < 0.001$).

Furthermore, as shown in Figure 3, our multiplicative random effects IVW estimates suggest a potential correlation between urinary sodium and heart failure ($p = 0.030$, OR 1.417, OR 95% CI 1.035–1.940). A similar result with broader CI was obtained through the weighted median ($p = 0.262$, OR 1.44, OR 95% CI 0.772–2.684) and MR-Egger test ($p = 0.807$, OR 1.207, OR 95% CI 0.71–5.371). The present study reveals a significant association between urine sodium and hypertension in both the inverse-variance weighted (IVW) test and weighted median analysis (IVW $p = 0.036$, OR 1.584, OR 95% CI 1.03–2.436; weighted median $p = 0.012$, OR 1.606, OR 95% CI 1.109–2.326). Results from MR-Egger analysis also indicated a similar association, but with wider CI ($p = 0.898$, OR 1.144, OR 95% CI 0.149–8.80).

Moreover, the leave-one-out and single SNP analyzes illustrated that the overall effect was not driven by any individual SNP between urinary sodium and HF, hypertension, systolic blood pressure or diastolic blood pressure (Supplementary Figure S3).

Moreover, a positive correlation was observed between urinary sodium and systolic blood pressure (IVW $p = 0.00098$), and a potential correlation was suggested by the weighted median analysis ($p = 0.004$), with similar results obtained from MR-Egger ($p = 0.988$). However, no correlation was found between urinary sodium and diastolic blood pressure in the IVW analysis ($p = 0.586$) or MR-Egger analysis ($p = 0.235$), and a positive correlation was suggested by the weighted median analysis ($p < 0.001$).

TABLE 1 The baseline characteristics of different sodium intake group.

Total = 27,120	The group of sodium intake per day				*p* value
	<2,600 mg	2,600 ~ 3,800 mg	3,800 ~ 4,900 mg	>4,900 mg	
	N = 9,762	*N* = 8,074	*N* = 4,672	*N* = 4,612	
Characteristics					
Age (years)	54 (38–67)	52 (35–64)	47 (33–60)	42 (30–55)	<0.001
Sex					<0.001
Male	3,375 (34.6%)	3,748 (46.4%)	2,766 (59.2%)	3,395 (73.6%)	
Female	6,387 (65.4%)	4,326 (53.6%)	1906 (40.8%)	1,217 (26.4%)	
Race					<0.001
Mexican American	1,504 (15.4%)	1,181 (14.6%)	668 (14.3%)	759 (16.5%)	
Other Hispanic	1,158 (11.9%)	803 (9.9%)	450 (9.6%)	402 (8.7%)	
Non-Hispanic Blake	3,839 (39.3%)	3,513 (43.5%)	2069 (44.3%)	1922 (41.7%)	
Non-Hispanic White	2,308 (23.6%)	1,651 (20.4%)	957 (20.5%)	910(19.7%)	
Other Race	953 (9.8%)	926 (11.5%)	528 (11.3%)	619 (13.4%)	
Education level					
Less than 9th grade	1,257 (12.9%)	718 (8.9%)	351 (7.5%)	279(6.0%)	<0.001
9–11 grade	1,496 (15.3%)	1,046 (13.0%)	574 (12.3%)	637(13.8%)	
High school or equivalent	2,315 (23.7%)	1742 (21.5%)	1,082 (23.2%)	1,110 (24.1%)	
Some collage or AA degree	2,789 (28.6%)	2,468 (30.6%)	1,408 (30.1%)	1,476 (32.0%)	
Collage graduate or above	1905 (19.5%)	2,100 (26.0%)	1,257 (26.9%)	1,110 (24.1%)	
Marital status					<0.001
Living with partner	5,430 (55.6%)	4,861 (60.2%)	2,962 (63.4%)	2,834 (61.4%)	
Living alone	4,332 (44.4%)	3,213 (39.8%)	1710 (36.6%)	1778 (38.6%)	
Smoke					<0.001
Yes	4,132 (42.4%)	3,512 (43.5%)	2,143 (45.9%)	2,194 (47.6%)	
No	5,624 (57.6%)	4,562 (56.5%)	2,529 (54.1%)	2,418 (52.4%)	
Alcohol					<0.001
Yes	6,645 (68.1%)	6,043 (74.8%)	3,748 (80.2%)	3,838 (83.2%)	
No	3,117 (31.9%)	2031 (25.2%)	924 (19.8%)	774 (16.8%)	
BMI	28.12 (24.40–32.70)	28.2 (24.5–33.0)	28.20 (24.40–32.81)	28.33 (24.37–33.1)	0.057
Continine (ng/ml)	0.04 (0.011–15.325)	0.037 (0.011–8.103)	0.045 (0.011–30.68)	0.016 (0.066–65.38)	<0.001
Total cholesterol (mmol/L)	4.97 (4.27–5.72)	4.91 (4.24–5.66)	4.89 (4.19–5.64)	4.83 (4.16–5.56)	<0.001
Glucose (mmol/L)	5.22 (4.77–5.94)	5.16 (4.72–5.83)	5.16 (4.72–5.83)	5.16 (4.72–5.77)	<0.001
Serum sodium (mmol/L)	139.00 (138–141)	139 (138–141)	139 (138–141)	139 (138–141)	0.811
eGFR	93.01 (66.71–123.51)	98.70 (73.03–128.92)	105.91 (79.33–135.29)	115.64 (87.12–141.83)	<0.001
Systolic blood pressure (mmHg)	122.5 (111.5–136)	121 (111–133.5)	120.5 (111.5–131.5)	120.5 (112–130.5)	<0.001
Diastolic blood pressure (mmHg)	70 (62.5–77.5)	70.5 (63–78)	71.5 (64–78.5)	72 (64.5–79.5)	<0.001
Hypertension					<0.001
No	5,796 (59.4%)	5,210(64.5%)	3,099 (66.3%)	3,234 (70.1%)	
Yes	3,966 (40.6%)	2,864 (35.5%)	1,573 (33.7%)	1,378 (29.9%)	
Heart failure					<0.001
No	7,189 (96.1%)	12,453 (97.3%)	4,854 (97.7%)	1840 (98.1%)	
Yes	295 (3.9%)	340 (2.7%)	113 (2.3%)	36 (1.9%)	
Coronary heart disease					<0.001
No	7,143 (95.4%)	12,294 (96.1%)	4,807 (96.8%)	1833 (97.7%)	
Yes	341 (4.6%)	499 (3.9%)	160 (3.2%)	43 (2.3%)	

BMI, Body Mass Index; eGFR, estimated Glomerular Filtration Rate.

TABLE 2 Multivariable-adjusted logistic regression analysis of the risk of heart failure (HF) and hypertension across various levels of sodium intake.

Variable	Model I		Model II		Model III	
Heart failure	OR (95% CIs)	*p* value	OR (95% CIs)	*p* value	OR (95% CIs)	*p* value
Sodium intake						
<2,600 mg	1		1		1	
2,600 ~ 3,800 mg	0.711 (0.600–0.842)	<0.001	0.804 (0.675–0.958)	0.015	0.819(0.685–0.979)	0.047
3,800 ~ 4,900 mg	0.538 (0.429–0.675)	<0.001	0.703 (0.556–0.890)	0.003	0.683(0.537–0.868)	0.010
>4,900 mg	0.545 (0.435–0.684)	<0.001	0.905 (0.710–1.153)	0.419	0.847(0.661–1.085)	0.416
p trend		<0.001		0.01		0.049
Hypertension						
Sodium						
<2,600 mg	1		1		1	
2,600 ~ 3,800 mg	0.803 (0.756–0.854)	<0.001	0.951 (0.888–1.019)	0.155	0.920 (0.857–0.988)	0.049
3,800 ~ 4,900 mg	0.742 (0.690–0.798)	<0.001	1.039 (0.956–1.129)	0.373	0.999 (0.916–1.089)	0.711
>4,900 mg	0.623 (−0.578–0.671)	<0.001	1.089 (0.998–1.189)	0.055	1.021 (0.932–1.118)	0.552
p trend		<0.001		0.018		0.047

Corrected covariates.
Model I without covariant.
Model II adjusted gender, age, race.
Model III adjusted age, gender, race, marital status, PIR, education level, alcohol intake, continine, total cholesterol, BMI, and eGFR.
PIR, ratio of family income to poverty; BMI, body mass index; eGFR, estimated glomerular filtration rate.

4 Discussion

This study used epidemiological analysis and two-sample MR analysis to investigate the causal relationship between sodium intake and the risk of HF and hypertension. We found that high sodium intake is associated with an increased risk of heart failure and hypertension, and that the relationship between high sodium intake and heart failure risk is nonlinear. This suggests that lower sodium intake does not necessarily confer greater benefits, but maintaining sodium intake within an appropriate range may yield greater benefits.

Many studies have explored the relationship between sodium and cardiovascular disease. In patients with type 2 diabetes, reduced 24-h urinary sodium excretion is paradoxically associated with increased all-cause and cardiovascular mortality (21). Both low and high sodium intake were associated with all-cause mortality and the duration of cardiovascular disease (22, 23). In most national and international guidelines recommended minimizing sodium intake (24–26), however, increasing evidence suggests that very low sodium intake does not necessarily reduce the incidence of cardiovascular disease (27) or heart failure (28–30). The benefits of restricting sodium intake may have been overestimated.

Research on the relationship between sodium intake and blood pressure is extensive and far-reaching. The linear relationship between sodium intake and blood pressure has been confirmed in multiple studies (31, 32), and our study reached a similar conclusion: after adjusting for confounding factors, there is a linear relationship between sodium intake and diastolic blood pressure and systolic blood pressure. When analyzing the relationship between sodium intake and blood pressure, we found that even with an increase of 100 mmol in sodium intake, the increase in blood pressure is limited (approximately 4 mmHg for systolic blood pressure and 2 mmHg for diastolic blood pressure). This limited effect can explain why we did not find a correlation between high sodium intake and the incidence of hypertension after adjusting for all confounding factors. This contradicts previous research results, and we believe it may be due to the fact that the population's sodium intake is relatively concentrated. A smaller number of people have very high sodium intake, and the limited number of them having hypertension results in a wide 95% confidence interval for our odds ratio and non-significant results. Is sodium intake related to the risk of developing heart failure through its influence on blood pressure? We found that even after correcting for blood pressure, there still exists a non-linear relationship between sodium intake and the risk of heart failure. The impact of dietary sodium on the cardiovascular system may not solely be mediated by blood pressure. Previous studies have shown that high sodium intake can directly lead to ventricular remodeling (33, 34). We believe that sodium does not affect the pathogenesis of heart failure solely through its impact on blood pressure but rather through distinct mechanisms.

The relationship between sodium intake and heart failure is complex, as high salt intake exacerbates sodium and water retention, thereby aggravating heart failure symptoms and disease progression (35). Low salt intake is the main dietary strategy for treating heart failure. However, the benefit of very low sodium intake for heart failure is controversial. A study by Hummel et al. (36) of 443 heart

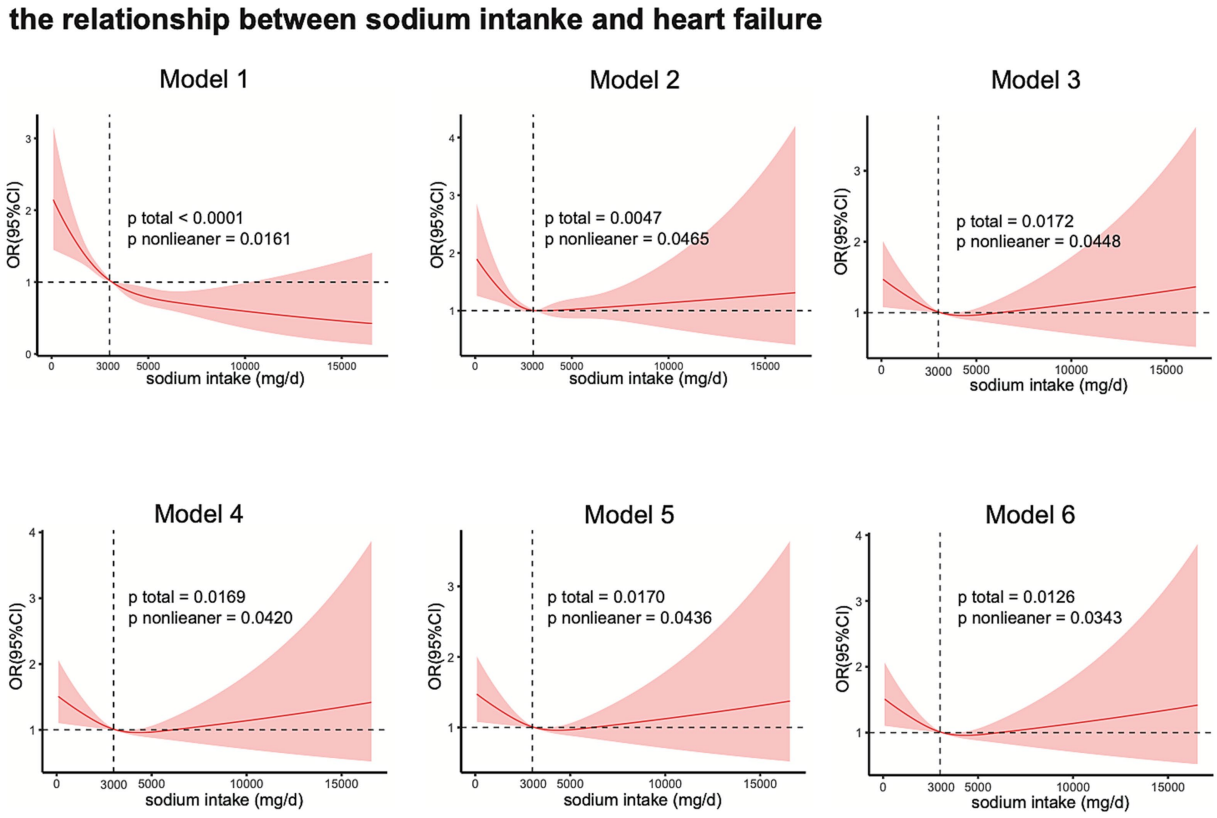


FIGURE 2
The relationship between sodium intake and the risk of heart failure.

TABLE 3 Results of potential pleiotropy and heterogeneity assessments.

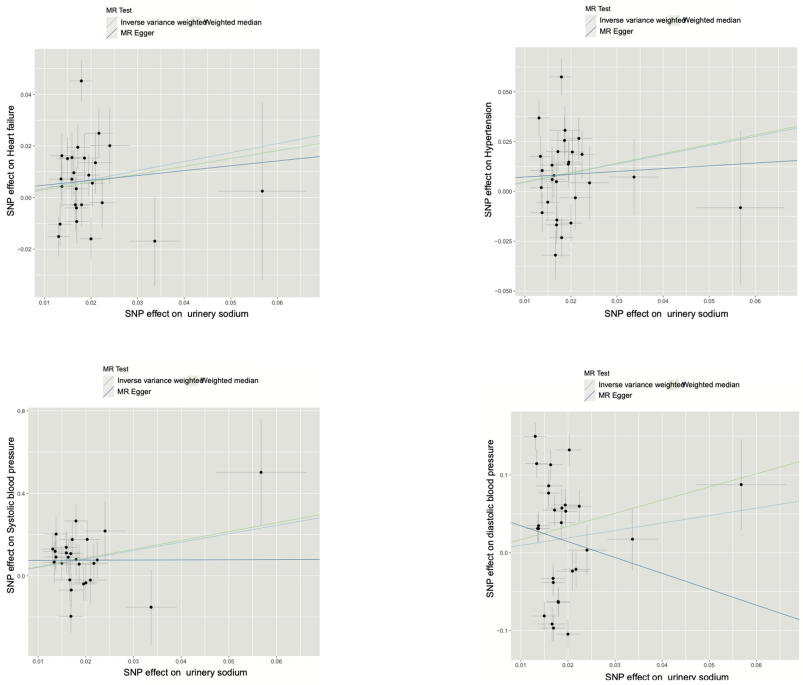
outcome	Cochran's Q statistic	*p*-value for Cochran's Q	*p*-value for intercept	MR-PRESSO global test
HF	63.377	3.525E-05	0.8312526	<0.001
Hypertension	100.18118	2.40E-10	0.7518133	<0.001
Systolic	38.82936	0.03831589	0.4537263	0.046
Diastolic	391.9251	2.20E-66	0.4084242	<0.001

HF, heart failure.

failure patients with preserved systolic function showed that recommendations for salt restriction were associated with lower readmission and mortality rates within 30 days of discharge. In contrast, a recent randomized trial by Paterna et al. (37) showed that lower salt intake has adverse effects on the kidneys and neurohormones. How much should the salt intake of heart failure patients be reduced? Unfortunately, there is no clear evidence to answer this question.

Our study results indicate that even after adjusting for confounding factors, there is still a positive correlation between high sodium intake and the risk of heart failure. Restricted cubic spline analysis revealed that a lower sodium intake did not necessarily result in a lower risk of heart failure. The non-linear relationship between sodium intake and heart failure. When the sodium intake is less than 3,000 mg/d, we can observe that there is a negative correlation between sodium intake and heart failure with a 95% confidence interval that does not include 1. While a positive correlation between sodium intake and heart failure can be seen when the sodium intake is above 3,000 mg/d, the 95% confidence interval for the odds ratio is wide and even crosses 1. Therefore, we believe that higher sodium intake below 3,000 mg/d can actually decrease the incidence of heart failure. Unlike hypertension, the relationship between sodium intake and heart failure follows a U-shaped curve. Our study results suggest that the lowest risk of heart failure occurs at a sodium intake level of around 3,000 mg/d. This happens to be the average sodium intake for most people's diets, so we believe that salt restriction may not necessarily lower the risk of heart failure.

To supplement and validate our cross-sectional investigation, we employed Mendelian randomization to yield congruent outcomes using diverse methodologies, thereby substantiating the reliability of our study findings. Mendelian randomization analysis confers several merits and carries profound implications for drawing deductions. One of the primary strengths lies in its capacity to furnish evidence for causal relationships. By employing genetic variants as instrumental



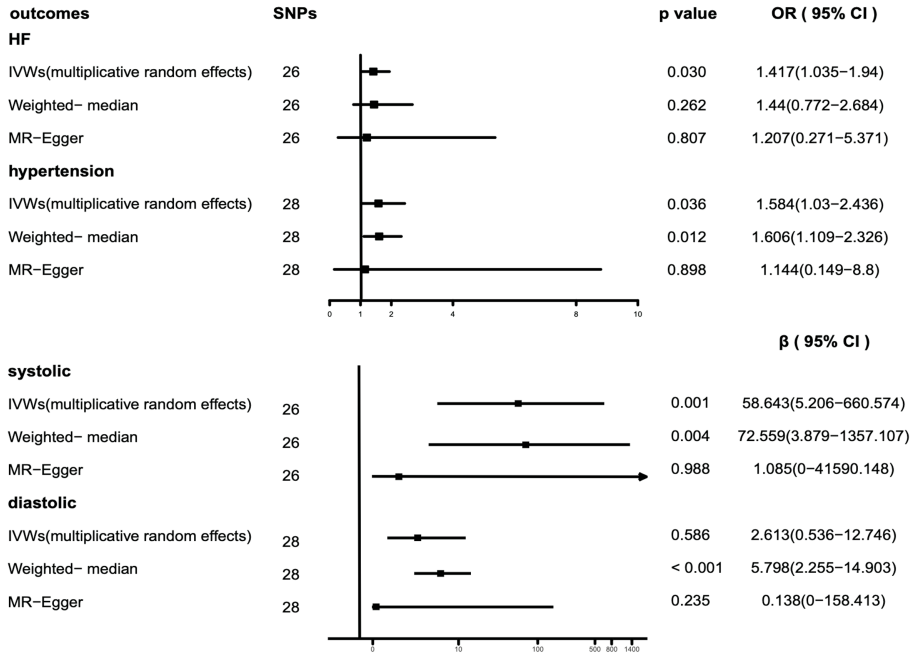


FIGURE 3
Impact of urinary sodium on heart failure risk and hypertension using Mendelian randomization.

variables, it surmounts confounding and reverse causality biases frequently encountered in observational studies. The utilization of genetic variants in Mendelian randomization introduces a facet of inherent randomization. As these variants are randomly assigned during meiosis, they remain unaffected by extraneous factors or confounding variables. This process emulates the random allocation of participants in a randomized controlled trial, fortifying Mendelian randomization studies against bias. This study benefits from the substantial sample size of GWAS data. Mendelian randomization analysis affirms that an escalation in urinary sodium corresponds to an elevation in both systolic and diastolic blood pressure. The higher urinary sodium engendering an augmented risk of hypertension and heart failure. These findings harmonize with the outcomes obtained from cross-sectional investigations.

Our study provides a new direction for the impact of sodium intake on cardiovascular disease. Lower sodium intake does not

necessarily reduce the risk of disease occurrence, and maintaining sodium intake within a normal range may have greater benefits. This value is approximately 3,000 mg per day. A very low sodium intake, which means far below the normal sodium intake, may not necessarily bring benefits. Our research is based on analyzing the estimated sodium intake in the diet, which cannot accurately reflect the intake of sodium during evaluation. Therefore, further research is needed to determine whether a lower sodium intake is harmful or not. There is still much debate about sodium intake, and all of this remains inconclusive, indicating that large-scale studies may be necessary to obtain more valuable conclusions.

There are some limitations to our research. Instead of 24 h urinary excretion of sodium, NHANES obtained information about dietary sodium intake through a questionnaire survey, which may differ from individual's actual daily sodium intake. In addition, Mendelian randomization was analyzed using urinary sodium, while cross-sectional studies were analyzed using dietary sodium. A recent study found that there may be differences in evaluating the relationship between sodium intake and disease through 24-h urine excretion, spot urine sodium (38). In addition, this study is a cross-sectional study, and there may be a causal reversal relationship. Although we attempted to avoid this limitation as much as possible through MR analysis, prospective randomized controlled studies are still necessary.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request. The National Health and Nutrition Examination Survey (NHANES) database used in this study is publicly available and can be accessed at https://www.cdc.gov/nchs/nhanes/index.htm. In addition, the GWAS data used in this study are available from the following sources: exposure data (urinary sodium) can be downloaded from the UK Biobank (https://www.ukbiobank.ac.uk/), outcome data for heart failure can be downloaded from the Hermès Consortium (https://www.hermesconsortium.org/), blood pressure data can be downloaded fromIEU (https://gwas.mrcieu.ac.uk/files/ieu-b-4817/ieu-b-4817.vcf.gz), and systolic blood pressure data can be downloaded from the Within-Family GWAS Consortium (https://www.withinfamilyconsortium.com/home/).

Author contributions

MY: Data curation, Formal analysis, Writing – original draft, Writing – review & editing. DY: Data curation, Formal analysis, Writing – original draft, Writing – review & editing. YW: Data curation, Formal analysis, Writing – review & editing. KL: Data curation, Writing – review & editing. ZL: Writing – review & editing, Data curation. DG: Funding acquisition, Project administration, Supervision, Writing – review & editing. NN: Project administration, Supervision, Writing – review & editing. MQ: Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

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Iain Brownlee,
Northumbria University, United Kingdom

REVIEWED BY
Bente Morseth,
UiT The Arctic University of Norway, Norway
Mehran Rahimlou,
Zanjan University of Medical Sciences, Iran

*CORRESPONDENCE
Zach Conrad
✉ zsconrad@wm.edu

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Restricted carbohydrate diets below 45% energy are not associated with risk of mortality in the National Health and Nutrition Examination Survey, 1999–2018

Austin Angelotti[1], Corina Kowalski[2], LuAnn K. Johnson[3], Martha A. Belury[4] and Zach Conrad[5,6]*

[1]Department of Physiology and Cell Biology, College of Medicine, The Ohio State University, Columbus, OH, United States, [2]College of Arts and Sciences, Williamsburg, VA, United States, [3]Independent Contractor, Warren, MN, United States, [4]Department of Food Science and Technology, The Ohio State University, Columbus, OH, United States, [5]Department of Kinesiology, Williamsburg, VA, United States, [6]Global Research Institute, Williamsburg, VA, United States

Introduction: Cardiometabolic diseases (CMD) are the leading causes of death for people living in the United States. Dietary strategies, such as restricting carbohydrate intake, are becoming popular strategies for improving health status. However, there is limited and often contradictory evidence on whether restricting carbohydrate intake is related to all-cause, CMD, or cardiovascular disease (CVD) mortality.

Methods: The objective of the present study was to evaluate the association between restricted carbohydrate diets (<45%en) and mortality from all-causes, CMD, and CVD, stratified by fat amount and class. Data were acquired using the National Health and Nutrition Examination Survey (1999–2018) linked with mortality follow-up until December 31, 2019 from the Public-use Linked Mortality Files. Multivariable survey-weighted Cox proportional hazards models estimated hazard ratios for 7,958 adults (≥20 y) that consumed <45%en from carbohydrates and 27,930 adults that consumed 45-65%en from carbohydrates.

Results: During the study period a total of 3,780 deaths occurred, including 1,048 from CMD and 1,007 from CVD, during a mean follow-up of 10.2 y. Compared to individuals that met carbohydrate recommendations (45-65%en), those that consumed carbohydrate restricted diets (<45%en) did not have significantly altered risk of mortality from all-causes (HR: 0.98; 95% CI: 0.87, 1.11), CMD (1.18; 0.95, 1.46), or CVD (1.20; 0.96, 1.49). These findings were maintained when the restricted carbohydrate diet group was stratified by intake of total fat, saturated fat (SFA), monounsaturated fat (MUFA), and polyunsaturated fat (PUFA).

Discussion: Carbohydrate restriction (<45%en) was not associated with mortality from all-causes, CVD, or CMD. Greater efforts are needed to characterize the risk of mortality associated with varied degrees of carbohydrate restriction, e.g., low (<26%en) and high (>65%en) carbohydrate diets separately.

KEYWORDS

NHANES, restricted carbohydrate, mortality, cardiometabolic disease, cardiovascular disease, saturated fat, monounsaturated fat, polyunsaturated fat

1 Introduction

Cardiometabolic diseases (CMD), which include heart disease, stroke, and diabetes, are the leading causes of death for men and women in the United States (1). While mortality from cardiovascular diseases (CVD) has declined over the past 20 years, mortality from endocrine and metabolic diseases has increased (2, 3). Modifiable lifestyle factors, including a healthy diet, can help mitigate the risk of mortality associated with CMD by over 60% (4).

The Acceptable Macronutrient Distribution Range (AMDR) for carbohydrates is 45–65% of total calories (5). Despite this recommendation, consumers report adopting restricted carbohydrate diets (<45%en from carbohydrates) because of their perceived health benefits (6). However, research remains inconsistent on whether restricted carbohydrate diets impact mortality risk (7–9). Some studies suggest that adopting a low carbohydrate diet elevates mortality risk due to decreased intake of fiber, fruits, and vegetables, or increased consumption of animal products and saturated fats (10, 11). Conversely, other studies suggest that a low carbohydrate diet reduces mortality risk by improving insulin sensitivity (potentially influenced by changes in hormones such as the insulin-sensitizing adipokine adiponectin) or by inhibiting the longevity-related protein, the mammalian target of rapamycin (mTOR) (12, 13).

One meta-analysis of cohort studies showed that participants that consumed lower carbohydrate diets had a 31% greater risk of all-cause mortality compared to those that consumed more carbohydrates, though no association with CVD-mortality was observed (14). A separate meta-analysis of 281 observational studies demonstrated that higher carbohydrate intake was associated with a 19% greater risk of all-cause mortality (15). Furthermore, while several nationally representative studies have observed both positive and negative associations of varied carbohydrate intake with mortality from all-causes (7, 8, 16–23) and CVD (17–21, 23, 24), none have evaluated CMD mortality. Without a clear consensus, there is a need for more high-quality studies to assess whether carbohydrate restriction is associated with reduced risk of mortality from all-causes, CMD, and CVD.

The proportion of energy derived from fat increases when carbohydrates are restricted in the diet. Dietary fat quality is known to modify the risk of all-cause and CVD mortality (25–27). Saturated fat (SFA) intake is often associated with an increased risk of all-cause and CVD mortality, while polyunsaturated fat (PUFA) is associated with a decreased risk of both (25, 27). Yet, few studies have considered dietary fat quality when studying associations between restricted carbohydrate diets and mortality.

To address these research gaps and to further inform dietary recommendations, the present study used 20 y of dietary data from the National Health and Nutrition Examination Survey (NHANES) to examine associations between restricted carbohydrate diets and risk of mortality from all-causes, CMD, and CVD. We further stratified participants consuming restricted carbohydrate diets by intake of total fat, SFA, monounsaturated fat (MUFA), and PUFA to explore whether fat quality alters the associations between carbohydrate restriction and mortality.

Abbreviations: AMDR, acceptable macronutrient distribution range; AMPM, automated multiple pass method; CMD, cardiometabolic disease; CVD, cardiovascular disease; HR, hazard ratio; MUFA, monounsaturated fat; NCI, national cancer institute; NCHS, national center for health statistics; NDI, national death index; NHANES, national health and nutrition examination survey; PUFA, polyunsaturated fat; SFA, saturated fat.

2 Methods

2.1 Data acquisition

Data on individual-level nutrient intake from foods and supplements, food intake, medication use, health behaviors, prevalent health conditions, family history of health conditions, and sociodemographics were acquired from NHANES, 1999–2018. NHANES collects data from approximately 5,000 non-institutionalized participants per year using a multi-stage sampling design (28). Data are collected by trained staff using in-person surveys, physical examinations, and laboratory tests. Some demographic groups are oversampled to increase reliability and precision (28). Data are collected continuously but released in two-year cycles. Dietary data are collected from participants by trained staff using an in-person 24-h dietary recall, and approximately 80% of the sample completes a second recall 3–10 days later by telephone. The computer-assisted Automated Multiple Pass Method (AMPM) is used to minimize respondent burden and increase reliability and validity (29, 30). The present study is a secondary analysis of publicly available and de-identified data and was deemed exempt from human studies ethical review by the Institutional Review Board at William & Mary. Pre-registration for this study can be found elsewhere (31).

2.2 Diet categorization

Usual food and nutrient intake was estimated using the National Cancer Institute's (NCI) usual intake methodology (32). This method estimates within-person variation of the entire sample using data from two 24-h recalls collected from most participants using the SAS macros MIXTRAN, DISTRIB, and INDIVINT provided by NCI (33–35). A nonlinear mixed effects model is fit to repeated 24-h recalls using MIXTRAN. These parameter estimates are passed to DISTRIB to estimate the usual intake distribution in the population, and to INDIVINT to estimate predicted intakes at the individual level. Participants were primarily categorized into one of two groups, restricted carbohydrate (<45%en) (36) and those that met the AMDR for carbohydrate intake (45–65%en) (37), which are consistent with the categorizations used by the Nutrition and Lifestyle Task Force of the National Lipid Association (36) and the Food and Nutrient Board of the Institute of Medicine, National Academy of Sciences (Dietary Reference Intakes) (37). To investigate the effects of fat amount and class, restricted carbohydrate intakes were further stratified by intake tertiles of total fat (<35.5%en, 35.5–38.3%en, >38.3%en), SFA (<11.3%en, 11.3–12.4%en, >12.4%en), MUFA (<12.7%en, 12.7–13.8%en, >13.8%en), and PUFA (<7.6%en, 7.6–8.7%en, >8.7%en).

2.3 Outcome ascertainment

Participants from NHANES were linked to the Public-use Linked Mortality Files (1999–2019) (38), which provide mortality follow-up through December 31, 2019, the latest date available.

Follow-up was defined as the time from NHANES data collection to death or December 31, 2019, whichever came first. Standardized procedures were used by the National Center for Health Statistics (NCHS) to adjudicate deaths. Staff at NCHS used probabilistic matching to link NHANES participants to records in the National Death Index (NDI) using identifying information such as social security number, name, date of birth, and state of residence (39). The NDI records all US deaths since 1979, and includes nearly all deaths (~97%) when social security numbers are available, such is the case for all eligible NHANES participants linked to the NDI (40, 41).

Mortality follow-up data for NHANES participants were collected for all causes, coronary heart disease (International Classification of Disease 10th revision codes I00–I09, I11, I13, I20–I51), stroke (I60–I69), and diabetes (E10–E14). Deaths from coronary heart disease and stroke were summed to represent deaths from CVD, and deaths from CVD and diabetes were summed to represent deaths from CMD. Deaths from heart disease, stroke, and diabetes were evaluated as part of CVD and CMD, but were not evaluated as separate outcomes due to insufficient sample sizes (829, 178, 41 cases, respectively).

2.4 Covariates

Data on self-reported age, sex, education, and race/ethnicity were acquired from the demographic questionnaire. NHANES staff used self-reported information on household income and household composition (number of persons including children) to calculate income-to-poverty ratio (ratio of household income compared to the federal poverty guideline). Data on physical activity were acquired from the physical activity questionnaire, and data from 1999–2006 and 2007–2018 were harmonized using the approach by Bailey et al. (42). Data on smoking status were acquired from the questionnaire on recent tobacco use. NHANES staff collected height and weight measurements and used this information to calculate Body Mass Index (BMI; kg/m2). NHANES staff measured systolic and diastolic blood pressure at the brachial artery after participants were seated and resting, and the average of ≥2 measurements were calculated for each participant, which is consistent with clinical standards (43). Hypertension was determined by systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 80 mmHg or self-report of current prescription drug treatment (43). Lipid panels were used to collect information on serum triglycerides and high-density lipoprotein cholesterol (HDL-C). Participants with triglyceride levels ≥150 mg/dL (≥1.695 mmol/L) or self-report of current prescription drug treatment were identified as having elevated triglycerides, and those with HDL-C < 50 mg/dL (<1.295 mmol/L) for women or < 40 mg/dL (<1.036 mmol/L) for men or self-report of current prescription drug treatment were identified as having low HDL-C (44). Participants with elevated triglycerides and low HDL-C were classified as having dyslipidemia (44). Baseline heart disease, stroke, and diabetes were evaluated using standard measures from the American Heart Association (45), which include self-report of physician diagnosis, prescription drug treatment, fasting plasma glucose, and the Rose questionnaire (undiagnosed angina), described elsewhere (46). Data on daily intake of energy, protein, and alcohol were acquired from the 24-h recall files. Data on daily intake of refined grains and added sugar were acquired from the Food Patterns Equivalents Database, which converts data on food intake from 24-h recalls into food group equivalents (47).

2.5 Statistical analyses

Multivariable Cox proportional hazards regression models assessed the association between diet patterns and mortality from all causes, CMD, and CVD. Base models were adjusted for demographic variables, health behaviors, and baseline health status including age (20–30 y, 31–50 y, 51–70 y, or ≥ 71 y), sex (male or female), education (<high school, high school or equivalent, some college, or college graduate), race-ethnicity (non-Hispanic white, non-Hispanic black, Mexican-American, or other), income-to-poverty ratio (<0.75, 0.75–1.30, 1.31–1.99, 2.00–3.99, or ≥ 4.00), physical activity (sedentary, moderate, or vigorous) (42), smoking status (<100 cigarettes in lifetime, ≥100 cigarettes in lifetime but not current smoker, ≥100 cigarettes in lifetime and currently smoke some days, or ≥ 100 cigarettes in lifetime and currently smoke everyday), BMI (<18.5, 18.5- < 25, 25- < 30, or ≥ 30), baseline hypertension (yes or no), baseline dyslipidemia (yes or no), family history of heart disease (yes or no), family history of diabetes (yes or no), and survey cycle (continuous). Missing values for each covariate were included as a dummy indicator to preserve sample size.

Fully adjusted models were adjusted for dietary factors including daily intake of energy (kcal, continuous), refined grains (oz. equivalents, continuous), added sugar (tspn. Equivalents, continuous), fiber (g, continuous), protein (%en, continuous), and alcohol (%en, continuous). Models stratified by total fat intake were also adjusted for unsaturated-to-saturated fat ratio, models stratified by SFA intake were additionally adjusted for MUFA (%en, continuous) and PUFA (%en, continuous), models stratified by MUFA intake were additionally adjusted for SFA (%en, continuous) and PUFA (%en, continuous), and models stratified by PUFA intake were additionally adjusted for SFA (%en, continuous) and MUFA (%en, continuous). Supplemental models adjusted for additional dietary factors that may have a neutral or beneficial effect on CMD (48). Models stratified by SFA intake were additionally adjusted for stearic acid, models stratified by MUFA intake were additionally adjusted for oleic acid, and models stratified by PUFA intake were additionally adjusted for linoleic acid, α-linolenic acid, eicosapentaenoic acid, and docosahexaenoic acid.

Statistical significance was set at $p < 0.05$ with Bonferroni adjustment for multiple comparisons. Standard errors were estimated with the balanced repeated replication method while accounting for the multistage probability sampling design of NHANES. Stata 16.1 (StataCorp; College Station, TX) (49) was used for data management and SAS 9.4 (SAS Institute; Cary, NC) (50) was used for all analyses.

3 Results

3.1 Participant characteristics

A total of 96,766 individuals provided dietary data from 1999–2018 (Supplementary Figure S1). Participants were excluded if they were < 20 y of age ($n = 44,368$); pregnant or breastfeeding ($n = 1,827$); had incomplete or unreliable dietary recalls as deemed by trained NHANES staff ($n = 3,570$); were unable to be linked to the National

Death Index due to incomplete identifying information ($n = 81$); died during the first year of follow up ($n = 468$); had heart disease, stroke, or diabetes at baseline ($n = 10,542$); or consumed >65%en from carbohydrates ($n = 22$). A total of 35,888 US participants were included in the analytic sample. During the study period a total of 3,780 deaths occurred, including 1,048 from cardiometabolic disease (CMD), and 1,007 from cardiovascular disease (CVD).

Table 1 describes participant characteristics for those consuming 45-65%en carbohydrate (recommended carbohydrate) and those consuming <45%en carbohydrate (restricted carbohydrate). Mean carbohydrate intake was 41%en for the restricted carbohydrate group and 50.4%en for the recommended carbohydrate group ($p < 0.001$). Accordingly, the restricted carbohydrate group had higher mean fat and protein intakes (37%en fat, 16%en protein) than the recommended carbohydrate group (34%en fat, 15%en protein; $p < 0.001$ for both comparisons). Mean alcohol intake was also higher among the restricted carbohydrate group (7%en) compared to the recommended carbohydrate group (4%en; $p < 0.001$).

The restricted carbohydrate group had a higher mean age (+0.6 years; $p = 0.036$), BMI (+0.7 kg/m2; $p < 0.001$), and income-to-poverty ratio (+0.4; $p < 0.001$) when compared to the recommended carbohydrate group. A greater proportion of participants in the restricted carbohydrate group were male (+9.1 percentage points; $p < 0.001$), non-Hispanic white (+7.8 percentage points; $p < 0.001$), college graduates (+6.7 percentage points; $p < 0.001$), participated in vigorous physical activity (+5.2 percentage points; $p < 0.001$), and smoked cigarettes every day (+2.9 percentage points; $p < 0.001$).

3.2 Restricted carbohydrate diet and mortality

In the multivariable base model, hazard ratios for participants that consumed restricted carbohydrate diets were 0.98 (95% CI: 0.87, 1.11) for all-cause mortality, 1.18 (0.95, 1.46) for CMD mortality, and 1.20 (0.96, 1.49) for CVD mortality, compared to participants that met carbohydrate recommendations (Figure 1). These findings did not change upon further adjustment for dietary factors (energy, refined grains, added sugars, fiber, protein, and alcohol) in the fully adjusted model ($p > 0.05$ for all comparisons).

Figure 2 presents the association between carbohydrate restriction and mortality stratified by total fat intake. The hazard ratios for all-cause mortality, from the highest to the lowest tertile of fat intake, were 0.91 (95% CI: 0.73, 1.15), 0.94 (0.75, 1.18), and 1.09 (0.90, 1.33; $p > 0.05$ for all comparisons). The hazard ratios for CMD mortality, from the highest to lowest tertile of fat intake, were 1.16 (0.76, 1.77), 1.42 (0.97, 2.07), and 0.93 (0.56, 1.55; $p > 0.05$ for all comparisons), which were similar to the hazard ratios for CVD mortality. Additional adjustments for energy intake, refined grains, added sugars, fiber, protein, alcohol, and unsaturated to saturated fat ratio in the fully adjusted models did not modify these findings.

3.3 Restricted carbohydrate diet and mortality, stratified by fat class

Figure 3 presents the association between carbohydrate restriction and mortality stratified by SFA intake. Hazard ratios for all-cause mortality, from highest to lowest tertile of SFA intake, were 1.02 (95% CI: 0.82, 1.27), 0.91 (0.71, 1.15), and 1.02 (0.78, 1.33; $p > 0.05$ for all comparisons). The hazard ratios for CMD mortality, from the highest to lowest tertile of SFA intake, were 1.38 (0.93, 2.05), 1.27 (0.82, 1.99), and 0.87 (0.50, 1.52; $p > 0.05$ for all comparisons), which mirrored the hazard ratios for CVD mortality. The additional adjustments in the fully adjusted models (energy, refined grains, added sugars, fiber, protein, and alcohol), along with the adjustment for steric acid intake (Supplementary Figure S2), did not meaningfully alter the results.

Figure 4 shows the associations between carbohydrate restricted diets and mortality, stratified by MUFA intake. Hazard ratios for all-cause mortality, from highest to lowest tertile of MUFA intake, were 0.88 (95% CI: 0.69, 1.12), 0.99 (0.82, 1.20), and 1.09 (0.88, 1.35; $p > 0.05$ for all comparisons). The hazard ratios for CMD mortality, from the highest to lowest tertile of MUFA intake, were 1.11 (0.72, 1.73), 1.42 (0.97, 2.08), and 0.96 (0.59, 1.57; $p > 0.05$ for all comparisons). For CVD mortality, participants with moderate intakes had elevated mortality risk (1.47, 1.00–2.15; $p = 0.049$) but this became non-statistically significant in the fully adjusted model (energy, refined grains, added sugars, fiber, protein, and alcohol; $p > 0.05$) and the supplemental model additionally adjusted for oleic acid intake ($p > 0.05$; Supplementary Figure S3). For participants in the highest and lowest tertiles, hazard ratios for CVD mortality were similar to mortality from CMD and all causes, and neither the adjustments made in the fully adjusted models (energy, refined grains, added sugars, fiber, protein, and alcohol) nor the additional adjustment for oleic acid intake (Supplementary Figure S3) changed the results.

Figure 5 presents the association between carbohydrate restriction and mortality stratified by PUFA intake. The multivariate base model hazard ratios, from the highest to lowest tertile of PUFA intake, were 0.93 (95% CI: 0.72, 1.21), 1.03 (0.83, 1.27), and 0.99 (0.79, 1.24; $p > 0.05$ for all comparisons). The hazard ratios for CMD mortality, from the highest to lowest tertile of PUFA intake, were 1.30 (0.84, 2.03), 1.15 (0.76, 1.73), and 1.08 (0.70, 1.67; $p > 0.05$ for all comparisons), which were similar to that hazard ratios for CVD mortality. Further adjustment for energy, refined grains, added sugars, fiber, protein, and alcohol in the fully adjusted model, as well as additional adjustment for intake of eicosapentaenoic acid and docosahexaenoic acid (Supplementary Figure S4), did not modify the main findings.

4 Discussion

In this nationally representative study of over 35,000 participants with a mean follow-up of 10.2 y, a restricted carbohydrate diet (<45%en carbohydrate) was not associated with risk of mortality from all-causes, CMD, or CVD in fully adjusted models compared to a diet that met carbohydrate recommendations (45–65%en). Stratification by fat amount and class did not alter these main findings.

To our knowledge, only two other nationally representative studies in the US have reported associations between carbohydrate intake and mortality risk, of which have conflicting results (10, 16). Mazidi et al. (10) reported that lower carbohydrate diets were associated with an elevated risk of mortality from all-causes, coronary heart disease, and stroke in a 1999–2010 sample of 24,825 NHANES participants with follow-up until 2011. A later study by Shan et al. (16) found no association between carbohydrate restriction and mortality from all causes in a 1999–2014 sample of 37,233 NHANES participants

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TABLE 1 Participant characteristics, National Health and Nutrition Examination Survey, 1999–2018 (n = 35,888).

	Recommended carbohydrate[a] (n = 27,930)	Restricted carbohydrate[a] (n = 7,958)	p-value[b]
Energy (kcal)	2,211 (2,203 to 2,221)	2,217 (2,200 to 2,234)	0.574
Macronutrient intake			
Carbohydrate intake (%en)	50.4 (50.4 to 50.5)	41.3 (41.2 to 41.4)	<0.001
Fat intake (%en)	33.5 (33.4 to 33.5)	36.6 (36.5 to 36.8)	<0.001
Protein intake (%en)	15.1 (15.1 to 15.1)	16.3 (16.2 to 16.3)	<0.001
Alcohol intake (%en)	3.5 (3.4 to 3.6)	7.1 (6.9 to 7.3)	<0.001
Age (mean years)	44.4 (44.0 to 44.7)	44.9 (44.4 to 45.5)	0.036
Income-to-poverty ratio (mean)	3.0 (2.9 to 3.0)	3.4 (3.3 to 3.5)	<0.001
BMI (mean kg/m2)	28.1 (27.9 to 28.2)	28.7 (28.5 to 29.0)	<0.001
Female (%)	53.6 (52.8 to 54.4)	44.5 (43.0 to 46.0)	<0.001
Race/ethnicity (%)			<0.001
Non-Hispanic white	66.9 (64.7 to 69.0)	74.7 (72.7 to 76.6)	
Non-Hispanic black	11.0 (9.9 to 12.1)	10.2 (9.1 to 11.3)	
Mexican American	9.0 (7.9 to 10.2)	6.2 (5.3 to 7.4)	
Other	13.2 (12.1 to 14.4)	8.9 (8.0 to 9.9)	
Education (%)			<0.001
Less than high school	16.4 (15.6 to 17.3)	11.8 (10.8 to 12.9)	
High school or equivalent	24.5 (23.5 to 25.5)	21.4 (20.2 to 22.7)	
Some college	31.5 (30.6 to 32.4)	32.5 (30.9 to 34.0)	
College graduate	27.5 (26.1 to 29.0)	34.2 (31.9 to 36.6)	
Physical activity (%)			<0.001
Sedentary	25.0 (24.1 to 26.0)	20.9 (19.6 to 22.2)	
Moderate	33.5 (32.5 to 34.4)	32.4 (30.9 to 33.9)	
Vigorous	41.5 (40.2 to 42.8)	46.7 (45.1 to 48.4)	
Smoking status (%)			<0.001
<100 lifetime cigarettes	57.5 (56.4 to 58.6)	47.8 (46.0 to 49.6)	
>100 lifetime cigarettes, current non-smoker	21.4 (20.6 to 22.2)	26.6 (25.2 to 28.0)	
>100 lifetime cigarettes, smokes some days	3.7 (3.4 to 4.1)	5.4 (4.7 to 4.1)	
>100 lifetime cigarettes, every day smoker	17.3 (19.0 to 21.6)	20.2 (16.4 to 18.2)	
Hypertension[a]			0.007
Yes	43.3 (42.4–44.2)	46.2 (44.7–47.7)	
No	56.7 (55.8–57.6)	53.8 (52.3–55.3)	
Dyslipidemia[b]			0.323
Yes	13.7 (13.0–14.4)	13.5 (12.4–14.6)	
No	35.5 (34.5–36.5)	36.8 (35.2–38.4)	
Missing	50.8 (50.0–51.9)	49.7 (48.0–51.6)	
Mortality cases			
All causes	3,060	720	
Cardiometabolic disease[c]	846	202	
Cardiovascular disease[d]	810	197	

Values in parentheses are 95% CI.

[a]Systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 80 mmHg or self-report of current prescription drug treatment (43).

[b]Elevated triglycerides (≥150 mg/dL or self-report of current prescription drug treatment) and low HDL-C (<50 mg/dL for women or < 40 mg/dL for men or self-report of current prescription drug treatment) (44).

[c]Heart disease, stroke, and diabetes.

[d]Heart disease and stroke.

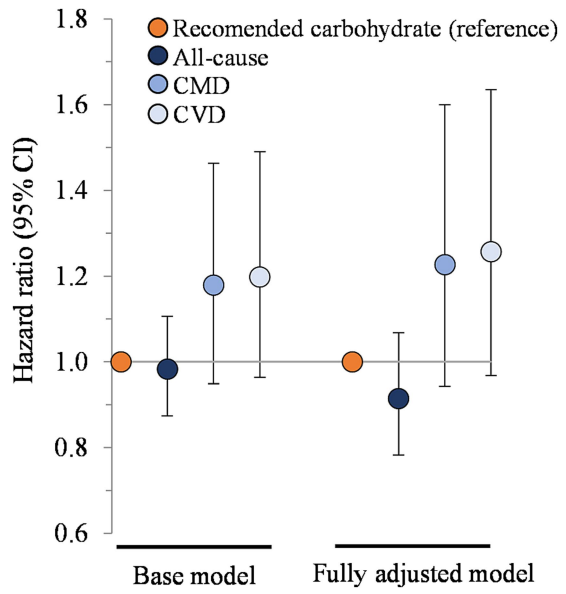

FIGURE 1
Association between carbohydrate restriction and risk of mortality from all causes, CMD, and CVD, 1999–2018 (*n*=35,888). Hazard ratios (with 95% confidence intervals) comparing risk of mortality between carbohydrate restricted diet patterns (<45%en) to recommended carbohydrate diet patterns (45–65%en), calculated using Cox proportional hazards models. Base model: adjusted for age (y), sex, race/ethnicity, education, smoking status, income-to-poverty ratio, physical activity (level), baseline hypertension, baseline dyslipidemia, family history of heart disease, family history of diabetes, body mass index (kg/m2), and NHANES survey wave. Fully adjusted model: base model + energy (kcal), refined grains (ounce-equivalents), added sugars (tsp equivalent), fiber (grams), protein (%en), and alcohol (%en). CMD, cardiometabolic disease; CVD, cardiovascular disease; NHANES, National Health and Nutrition Examination Survey.

with follow-up until 2015, which is consistent with the present study. This discrepancy between prior studies is likely due to differences in assessment of dietary intake and exclusion criteria. Mazidi et al. (10) used a single day of dietary recall to evaluate acute intake rather than usual intake, and was thus subject to within-person random error and overestimates the range of dietary intakes in the population (51) (mean carbohydrate intake of extreme quartiles was 39%en and 64%en). Rather, it is recommended that longitudinal studies employ multiple dietary recalls collected from most participants to reduce measurement bias, and analyze these data using usual intake methodologies such as the NCI method (51), as did Shan et al. (16) (mean carbohydrate intake of extreme quintiles was 46 and 58%). To further control for bias, Shan et al. excluded participants with a history of heart disease or cancer, as well as those that died during the first year of follow-up (16), whereas Mazidi et al. did not (10). The methodology and results of the present study (mean carbohydrate intake of 41% in the restricted carbohydrate group and 50% in the recommended carbohydrate group) are consistent with Shan et al. (16).

Several other studies have compared carbohydrate intake and the risk of all-cause mortality in prospective cohorts, with inconsistent findings (7, 11, 18–21, 23, 52–54). Of these studies, six reported either no association between carbohydrate intake and all-cause mortality (18, 23) or a "U"-shaped association with the lowest risk of all-cause mortality within the 45-65%en range for carbohydrate intake (7, 21, 52, 53). Two studies reported a modest increase in all-cause mortality risk (HR: 1.12; 95% CI: 1.01, 1.24 and 1.06; 1.00, 1.12 respectively) with lower carbohydrate diet score (11, 20), and two studies reported a decreased risk of all-cause mortality (HR: 0.74, 0.57–0.95; 1.28, 1.12–1.46 respectively) with lower carbohydrate intake (19, 54). Interestingly, the two studies that reported lower all-cause mortality risk included participants

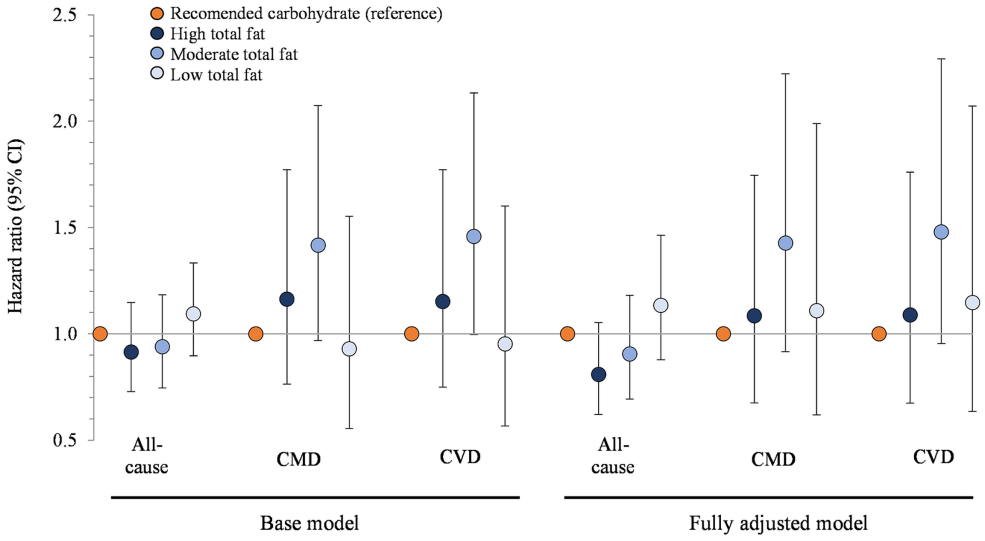

FIGURE 2
Associations between carbohydrate restriction, stratified by total fat intake, and risk of mortality from all causes, CMD, and CVD, 1999–2018 (*n* = 35,888). Hazard ratios (with 95% confidence intervals) comparing risk of mortality between carbohydrate restricted diet patterns (<45%en) to recommended carbohydrate diet patterns (45–65%en), calculated using Cox proportional hazards models. Base model: adjusted for age (y), sex, race/ethnicity, education, smoking status, income-to-poverty ratio, physical activity (level), baseline hypertension, baseline dyslipidemia, family history of heart disease, family history of diabetes, body mass index (kg/m2), and NHANES survey wave. Fully adjusted model: base model + energy (kcal), refined grains (ounce-equivalents), added sugars (tsp equivalent), fiber (grams), protein (%en), alcohol (%en), unsaturated to saturated fat ratio. CMD, cardiometabolic disease; CVD, cardiovascular disease; NHANES, National Health and Nutrition Examination Survey.

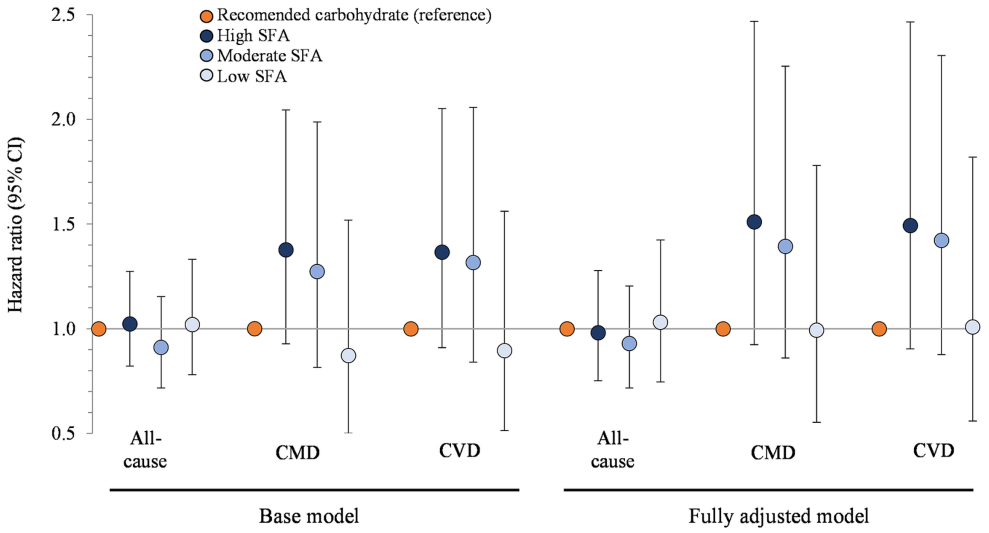

FIGURE 3
Associations between carbohydrate restriction, stratified by SFA intake, and risk of mortality from all causes, CMD, and CVD, 1999–2018 (n = 35,888). Hazard ratios (with 95% confidence intervals) comparing risk of mortality between carbohydrate restricted diet patterns (<45%en) to recommended carbohydrate diet patterns (45–65%en), calculated using Cox proportional hazards models. Base model: adjusted for age (y), sex, race/ethnicity, education, smoking status, income-to-poverty ratio, physical activity (level), baseline hypertension, baseline dyslipidemia, family history of heart disease, family history of diabetes, body mass index (kg/m2), and NHANES survey wave. Fully adjusted model: base model + energy (kcal), refined grains (ounce-equivalents), added sugars (tsp equivalent), fiber (grams), protein (%en), alcohol (%en), MUFA (%en), and PUFA (%en). CMD, cardiometabolic disease; CVD, cardiovascular disease; NHANES, National Health and Nutrition Examination Survey; SFA, saturated fat; MUFA, monounsaturated fat; PUFA, polyunsaturated fat.

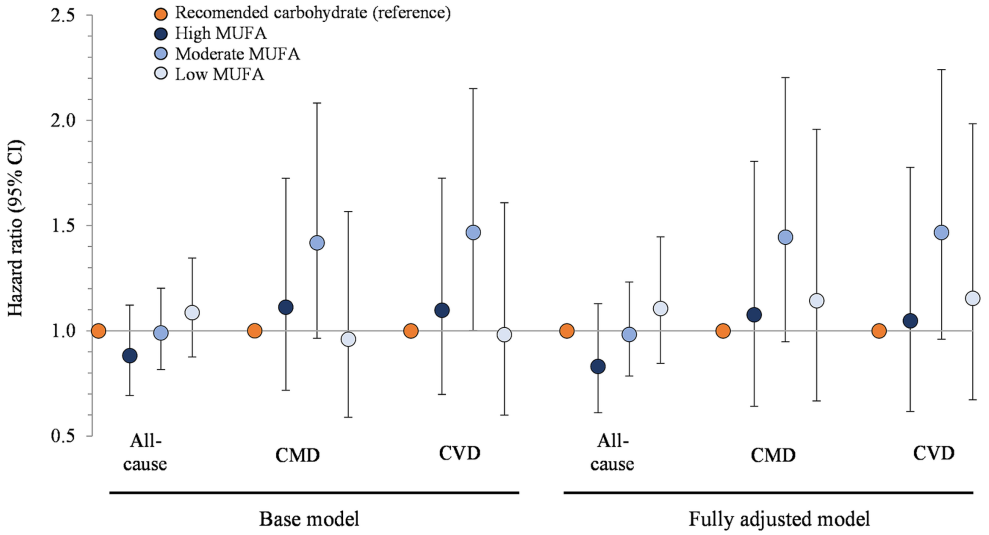

FIGURE 4
Associations between carbohydrate restriction, stratified by MUFA intake, and risk of mortality from all causes, CMD, and CVD, 1999–2018 (n = 35,888). Hazard ratios (with 95% confidence intervals) comparing risk of mortality between carbohydrate restricted diet patterns (<45%en) to recommended carbohydrate diet patterns (45–65%en), calculated using Cox proportional hazards models. Base model: adjusted for age (y), sex, race/ethnicity, education, smoking status, income-to-poverty ratio, physical activity (level), baseline hypertension, baseline dyslipidemia, family history of heart disease, family history of diabetes, body mass index (kg/m2), and NHANES survey wave. Fully adjusted model: base model + energy (kcal), refined grains (ounce-equivalents), added sugars (tsp equivalent), fiber (grams), protein (%en), alcohol (%en), SFA (%en), and PUFA (%en). CMD, cardiometabolic disease; CVD, cardiovascular disease; NHANES, National Health and Nutrition Examination Survey; MUFA, monounsaturated fat; SFA, saturated fat; PUFA, polyunsaturated fat.

with a large range of carbohydrate intake from 45%en to above 70%en (19, 54). This could explain the discrepancies between their results and the results reported in this study (which excluded participants that consumed above the recommended carbohydrate intake of 65%en). If individuals that consume >65%en from carbohydrates have a higher risk of all-cause mortality (as some studies suggest), study populations with higher carbohydrate intake would likely show a decreased risk of all-cause mortality with lower carbohydrate intake, while studies such as ours would not be able to detect.

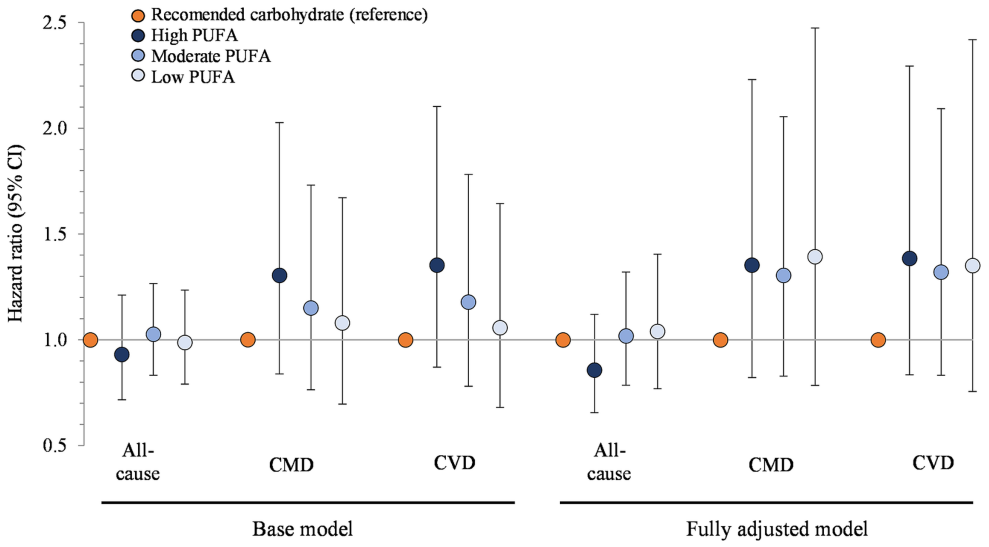

FIGURE 5
Associations between carbohydrate restriction, stratified by PUFA intake, and risk of mortality from all causes, CMD, and CVD, 1999–2018 (n = 35,888). Hazard ratios (with 95% confidence intervals) comparing risk of mortality between carbohydrate restricted diet patterns (<45%en) to recommended carbohydrate diet patterns (45–65%en), calculated using Cox proportional hazards models. Base model: adjusted for age (y), sex, race/ethnicity, education, smoking status, income-to-poverty ratio, physical activity (level), baseline hypertension, baseline dyslipidemia, family history of heart disease, family history of diabetes, body mass index (kg/m2), and NHANES survey wave. Fully adjusted model: base model + energy (kcal), refined grains (ounce-equivalents), added sugars (tsp equivalent), fiber (grams), protein (%en), alcohol (%en), SFA (%en), and MUFA (%en). CMD, cardiometabolic disease; CVD, cardiovascular disease; NHANES, National Health and Nutrition Examination Survey; PUFA, polyunsaturated fat; SFA, saturated fat; MUFA, monounsaturated fat.

Prior studies that evaluated the association between carbohydrate intake and CVD mortality have also shown mixed results (11, 19–21, 23, 24, 52, 54, 55). Several reported no association between low carbohydrate intake and CVD mortality (20, 23, 24, 54, 55). Alternatively, two prior studies reported a non-linear "U"-shaped association with CVD mortality with the lowest risk associated with 50-55%en from carbohydrates (21, 52), two studies reported a lower carbohydrate diet score resulted in an increased risk of CVD mortality in men (11, 52), and one study reported that a lower carbohydrate diet score resulted in a decreased risk of CVD mortality in women (19).

To our knowledge, no other study has evaluated the association between carbohydrate intake and CMD mortality, despite the rise of mortality from metabolic diseases over the last decade (2). In this study, the hazard ratios for CMD mortality mirrored the hazard ratios for CVD, likely because 96% of deaths from CMD were also categorized as CVD deaths. More research is needed to confirm the CMD mortality findings of the present study.

Additionally, no prior studies have evaluated the association between restricted carbohydrate diets and mortality when stratified by intake of dietary fat classes. The lack of association between fat-stratified diets in this study is surprising, given that prior evidence generally demonstrates a reduced risk of mortality (all-cause and CVD) associated with higher intake of unsaturated fats (21, 27, 56–59) and an elevated risk of mortality associated with higher intake of SFA (21, 27, 57). However, these previous studies focused on total intake of SFA, MUFA, and PUFA, while in this study only those consuming restricted carbohydrate diets (<45%en carbohydrates) were stratified by dietary fat class. It is possible that changes in dietary fat class have a greater impact on mortality at lower ranges of intake. For example, a difference in PUFA intake from 2%en to 4%en may impact mortality more than a difference from 10%en to 12%en. Because those consuming restricted carbohydrate diets had higher fat intake, changes in dietary fat class may be less impactful (or even non-existent) at these higher intakes.

Other studies have reported associations between carbohydrate intake and mortality after categorizing carbohydrate intake into "healthy" or "unhealthy" (8, 16), animal or plant-based (9), and carbohydrate type, such as starch or fiber (17, 21, 24, 55). Generally, these studies reported that consuming diets lower in "healthy" carbohydrates (8, 16), lower in vegetable-based carbohydrates (52), and lower in fiber (17, 55) increased mortality risk, while consuming diets lower in "unhealthy" carbohydrates (8, 16), lower in animal-based carbohydrates (9), and lower in starch and sugar (17, 55) decreased mortality risk. These findings suggest that carbohydrate quality impacts mortality risk more than carbohydrate quantity.

This study has several strengths. The large sample size, multistage sampling design, and survey weighting make these findings generalizable to the US population. Usual dietary intake was assessed from multiple 24-h recalls using the NCI method which reduces bias by accounting for within-person variation, measuring habitual and episodic intake of foods and nutrients, and correlating the amount consumed to the probability of intake. Modification by fat intake was assessed by evaluating fat classes independently (SFA, MUFA, and PUFA) as well as cumulatively (total fat). To further minimize bias, participants were excluded if they had died during the first year of follow up or if they had outcome measures at baseline (prevalent heart disease, stroke, or diabetes). Further, iterative models adjusted for sociodemographic factors and health behaviors (base); energy, food components, and fat classes (fully adjusted); and individual fatty acids (supplemental). This study also has limitations. NHANES samples

new participants during each survey cycle (2-year period) so long-term changes in individual-level dietary intake cannot be measured. The sample sizes for participants that consumed low (<26%en) and high (>65%en) carbohydrate diets were too small to produce reliable nationally representative estimates, so future studies are needed to evaluate diet-disease relationships for these groups. Mortality from coronary heart disease, stroke, and diabetes could not be evaluated separately due to small sample sizes for these outcomes (829, 178, and 41 cases, respectively) so these were included in aggregate analyses (all-cause, CMD, and CVD). Finally, the observational design of this study precludes determination of causality.

5 Conclusion

In this nationally representative sample of over 35,000 individuals followed for a mean of over 10 years, those that consumed restricted carbohydrate diets (<45%en) did not have significantly different risk of mortality (from all-causes, cardiometabolic disease, or cardiovascular disease) compared to those that met carbohydrate intake recommendations (45–65%en) These findings remained consistent after stratifying by fat amount and class (saturated fat, monounsaturated fat, and polyunsaturated fat). Due to the limited number of participants that consumed <26%en and > 65%en from carbohydrates, it was not feasible to measure the mortality risk associated with these extreme intakes, emphasizing the need for future research in this area.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: https://www.cdc.gov/nchs/nhanes/index.htm; https://www.cdc.gov/nchs/data-linkage/mortality-public.htm.

Ethics statement

The studies involving humans were approved by Institutional Review Board at William & Mary. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

ZC and MB: conceptualization, methodology, and funding acquisition. ZC and LJ: software, validation, formal analysis, investigation, and data curation. ZC: resources, supervision, and project administration. AA: writing—original draft preparation. AA, CK, LJ, MB, and ZC: writing—review and editing. AA and ZC: visualization. All authors contributed to the article and approved the submitted version.

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Conflict of interest

ZC has research awards from The Thomas F. and Kate Miller Jeffress Memorial Trust for a project unrelated to the present study; and received honoraria from MKYoung Food & Nutrition Strategies, National Geographic Society, The Ohio State University, Routledge, Princeton University Press, and Nutrition Today for professional activities unrelated to the present research. MB has a research award from the United Soybean Board that has no relevance to the present project.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2024.1225674/full#supplementary-material

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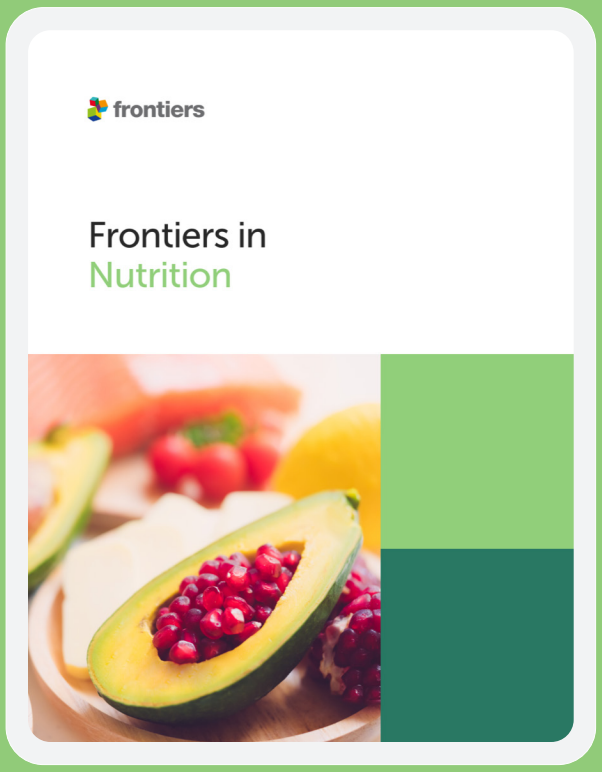

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