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Diet behavior and heart health

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Diet behavior and heart health

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Table of contents

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Editorial: Diet behavior and heart health

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Editorial on the Research Topic
Diet behavior and heart health

The association between diet and health has been identified, and a healthy diet can prevent various cardiovascular diseases (CVDs) (1). Dietary behaviors and patterns are changing, especially in developing countries with the ever-increasing amount of processed food and changing lifestyles, people eat more foods rich in energy, fat, free sugars, and salt, but not enough in fruits, vegetables, and other dietary fibers (2).

CVDs, including coronary heart disease, heart failure, stroke, and hypertension, are the leading cause of mortality worldwide. Poor dietary behaviors and patterns are risk factors for the continuing increase of CVDs incidence, accounting for more than 11 million deaths (3, 4). Although there are accumulating manuscripts investigating the relationship between dietary behaviors and patterns and CVDs, more high-quality evidence to support the improvement of cardiovascular health through dietary behavior is needed.

This Research Topic aims to investigate the relationship between diet behavior, including various dietary patterns, adverse dietary behaviors, and trace elements in food, and heart health. A total of 20 studies have been published on this Research Topic. The researchers focused on the effects of different eating patterns, several different food groups, and the eating behavior of different populations on heart health.

Poor diet quality is closely associated with CVD morbidity and mortality (5). The American Heart Association (AHA) and many other researchers have focused on the impact of dietary patterns on heart health, such as the DASH dietary pattern, the Mediterranean dietary pattern (MED), and the plant-based food dietary pattern (6–8). Notably, in a cross-sectional and longitudinal study, Dou et al. revealed for the first time the value of the Mediterranean-Dietary Approaches to Stop Hypertension for neurodegenerative delay (MIND) dietary pattern, a promising dietary pattern designed from most of the ingredients in the MED and DASH diets, in the primary and secondary prevention of hypertension, suggesting the MIND diet as a novel anti-hypertensive dietary pattern. In addition, in a prospective cohort study based on the 2007–2014 National Health and Nutrition Examination Survey, Zhang Y. et al. showed that adherence to higher intake of green vegetables and legumes, vegetables, total protein foods, seafood and plant protein, unsaturated fatty acids, and moderate intake of empty calories was associated with lower all-cause mortality from hypertension. Wang et al. show that diets low in whole grains, low in legumes and high in sodium are the three main dietary factors that increase the risk of

ischemic heart disease burden. These studies will promote dietary patterns that affect heart health-related research.

Five publications investigated the effects of foods and their various components on heart health. Yang X. et al. conducted a systematic review and dose-response meta-analysis showing that drinking more green tea can reduce the risk of coronary heart disease, but drinking more than 4–6 cups of black tea per day may increase the risk of coronary heart disease, which provides new insights into the relationship between tea consumption and its preventive effect on coronary heart disease. Chen et al. have shown that moderate caffeine intake can reduce all-cause mortality and cardiovascular mortality in elderly patients with hypertension. Huang Y. et al. conducted a retrospective cohort study showing that drinking very low-mineral water may increase homocysteine level and oxidative stress, worsen lipid profile, and threaten the cardiovascular system in children, while reducing 1,25, (OH)2D3, and disordering of calcium metabolism might play important roles. Huang J. et al. conducted a Mendelian randomized study showing that socioeconomic status, which was closely associated with other eating habits and lifestyle, may affect the association between vegetable intake and ischemic cardio-cerebral vascular diseases. Yang Y. et al. showed that decreasing the intake of edible oil n-6/n-3 ratio can improve blood lipids and quality of life.

In previous studies, few studies have been conducted on the effects of dietary behaviors on heart health in different populations. Notably, in this Research Topic, four publications have respectively studied adults, people in rural areas, people with sleep disorders, and only children, which will provide new ideas for the study of the effect of diet on heart health. Rikhtehgaran et al. conducted a prospective population cohort study showing that adults in the unhealthy diet group had twice the risk of developing CVD. Zhang J. et al. showed that in patients with sleep disorders, a higher intake of red and orange vegetables, starchy vegetables, and fermented dairy products in the morning, and a higher intake of milk and eggs in the evening, were associated with a lower risk of cardiovascular disease. Dang et al. show that single children with a poor lifestyle are significantly associated with the risk of developing cardio-metabolic risk factors, and that increasing family size (number of siblings) or establishing a good lifestyle may partially offset this risk. Hou et al. show that a healthy diet, such as high consumption of vegetables and seafood, as well as foods rich in selenium, may help prevent and control hypertension in Keshan endemic areas and other rural areas in China.

All in all, this Research Topic provides new ideas and insights into the influence of dietary behavior on heart health, especially for different populations and diversified eating patterns. Although a large number of studies have been carried out in this field, due to the diversity of food types, the complexity of food collocation, and the differences between different populations, the impact of dietary behavior on heart health needs more in-depth and extensive research. Future research should focus on the dietary behaviors of different regional cultures and different populations, the effects of processed foods, and diverse dietary patterns on heart health.

Author contributions

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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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The independent and combined effects of single-child status and ideal lifestyle on clustered cardio-metabolic risk factors among Chinese children and adolescents

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Background: Cardio-metabolic risk factors (CMRFs) represent the accumulation of metabolic abnormalities, significantly increasing the likelihood of cardiovascular diseases. Although studies assessed the independent association of single-child status and lifestyle risk factors with components of CMRFs or clustered CMRFs, little has been known about the combined effect of single-child status and lifestyles on clustered CMRFs as well as sex differences.

Materials and methods: Data was collected from a cross-sectional survey conducted in September 2013 in China. A total of 13,859 children and adolescents aged 7–18 years with blood samples were included. Anthropometric measurements and serum biochemical indexes were collected to assess clustered CMRFs, while questionnaires were used to obtain single-child status, lifestyle information, and characteristics of children and their parents. Mixed effect logistic regression was applied to analyze the independent and the combined effects of single-child status and ideal lifestyle category on clustered CMRFs.

Results: The prevalence of clustered CMRFs was 3.4%, with a higher prevalence in boys (4.0%) than girls (2.7%). Children and adolescents with clustered CMRFs had a higher proportion of single children (76.6 vs. 69.7%) and unfavorable lifestyles (62.1 vs. 29.2%) compared with their peers with non-clustered CMRFs. Both single children (OR = 1.67, 95% CI: 1.32–2.11) and unfavorable lifestyles (OR = 9.03, 95% CI: 6.26–13.02) were associated with an increased risk of clustered CMRFs. The risk of clustered CMRFs increased significantly (OR = 12.79, 95% CI: 6.67–24.52) when single children and an unfavorable lifestyle were combined, which was almost neutralized

(OR = 1.33, 95% CI: 0.63–2.82) when single children adhered to a favorable lifestyle. However, no sex differences were observed in this study.

Conclusion: Single children with unfavorable lifestyles were associated with an obvious risk of clustered CMRFs, which might be partially offset by expanding family size (the number of siblings) or establishing a favorable lifestyle. A birth-friendly social environment as well as a family environment with a favorable lifestyle are encouraged in China.

KEYWORDS

single-child, ideal lifestyle, clustered CMRFs, children, adolescents

Introduction

Cardiovascular diseases (CVDs) are the leading cause of death globally, accounting for 32% of all deaths (1), while in China this proportion has exceeded 40%, accompanied by an age-standardized mortality rate for males being 1.5 times higher than females (2). Cardio-metabolic risk factors (CMRFs) represent the accumulation of metabolic abnormalities, including hypertension, dyslipidemia, hyperglycemia, and abdominal obesity, while clustered CMRFs are defined as meeting at least three of these four abnormalities, significantly increasing the likelihood of CVDs (3). Although CMRFs are more common in adults, a substantial body of research indicated that pre-CMRFs and behavioral patterns were formed in childhood and adolescence (4–6), and that adverse levels of clustered CMRFs often coexisted in the same individual (7). Therefore, identifying modifiable factors for clustered CMRFs in children and adolescents is becoming to be recognized as a useful strategy to reduce the lifetime incidence of CVDs.

In the past few decades, China has undergone a remarkable shift in family structure under the implementation of the one-child policy since 1979, which resulted in the birth of more than 100 million families with single children (8). At the same time, the prevalence of cardiovascular and metabolic diseases skyrocketed (9). Based on this, many studies have noted the impact of different family structures on CMRFs, as well as sex differences. Recent studies provided evidence for the association of single children with components of CMRFs such as dyslipidemia (10), abdominal obesity (11), and hypertension (12) in children and adolescents, however, the findings were inconsistent in the direction of the association and sex differences. In addition, only one Iranian study explored the association between single children and all components of CMRFs, and this positive association was mainly manifested in abdominal obesity (13). These evidences suggested that single-child status might play an important role in CMRFs, with varied effects in different sexes. However, so far, studies have focused on the effects of single-child status on the single/multiple components of CMRFs rather than clustered CMRFs.

Furtherly, previous studies found that alcohol intake (14), sedentary behavior (15), insufficient sleep duration (16) and dairy intake (17) all played a significant role in clustered CMRFs. The high prevalence of these behavioral risk factors in childhood and adolescence has been a major concern because they are often maintained to adulthood (18, 19). However, the majority of CVDs can be avoided by addressing behavioral risk factors like tobacco and alcohol consumption, unhealthy diet, obesity, and lack of physical activity (1), which epidemiological studies has validated (20, 21), and so did expect to work for clustered CMRFs.

Although studies have shown that single children are more likely to establish an unfavorable lifestyle (22, 23), little has been known about the interaction of single-child status and lifestyles on clustered CMRFs as well as sex differences. In the real world, it is critical to comprehend the combined impact of disease risk factors, particularly those that coexist or cluster in the same individual, such as CMRFs. In this case, determining the combined impact of its risk factors enables a greater emphasis on controlling modifiable risks and, as a result, better prevention. Therefore, in this study, we hypothesized that there was a combined effect of single children and lifestyles on clustered CMRFs in children and adolescents, and this effect differed by sex. We aimed to investigate the independent and combined effects of two risk factors, single-child status and lifestyles, on clustered CMRFs among children and adolescents aged 7–18 years and the sex differences in these effects using data from a cross-sectional study in China in 2013.

Materials and methods

Study design and participants

Data was collected from a cross-sectional survey conducted in September 2013 with multi-stage cluster random sampling method, involving seven provinces (Liaoning, Ningxia, Tianjin, Shanghai, Hunan, Chongqing, and Guangdong) in China. The specific sampling and implementation

methods have been described previously (24). A total of 15,733 children and adolescents aged 7–18 years with blood samples were included. Participants with missing data about anthropometric measurements and failed imputation of missing variables were excluded. The remaining 13,859 children and adolescents were included in the final analysis (**Figure 1**).

Data collection and questionnaire survey

Anthropometric measurements

All anthropometric measurements were carried out by trained investigators using standardized instruments and procedures, which was described in detail in previous study (24). Briefly, children and adolescents needed to wear light clothing and no shoes when having their body height, weight and waist circumference (WC) measured. Height and WC were measured to the nearest 0.1 cm, and weight was measured to the nearest 0.1 kg. Prior to measuring systolic blood pressure (SBP) and diastolic blood pressure (DBP), participants were required to mediate for 5 mins. All indicators were measured twice, with the mean value being used as the final value.

Blood sample collection and detection

After 12 h of fasting, venipuncture was used to draw blood from the veins. Serum was then extracted after centrifugation at 3,000 rpm for 10 min and brought to the testing facility at low temperature (−80°C). A biomedical analysis company with Peking University certification carried out blood biochemical analysis (25). Finally, fasting blood glucose (FBG) and four lipid indicators, including total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C), were collected.

Questionnaire survey

A questionnaire for children and adolescents was used to collect sociodemographic characteristics (age, sex, residence, and school) and lifestyle information such as tobacco and alcohol consumption in the last 30 days, dietary consumption (meat, sugar-sweetened beverage, fruit, and vegetable), physical activity and screen time in the last 7 days, and daily sleep duration. The frequency (day) and amount (servings)/duration (h) were collected for the average daily consumption of each food, as well as daily physical activity and screen time using the following equation: (day × quantity for each day)/7.

A parental questionnaire was used to assess single-child status, which was divided into two categories: single children and non-single children. In addition, a family history of diseases (obesity, hypertension, diabetes, or cerebrovascular disease), parental education, parental tobacco, and alcohol consumption were also gathered.

Definition and categorization of indicators

Clustered cardio-metabolic risk factors

Cardio-metabolic risk factors were defined as hypertension, dyslipidemia, hyperglycemia, and abdominal obesity (26). Hypertension was considered as SBP and/or DBP $\geq$ the 95th percentile of blood pressure sex- and age-specific group (27). Dyslipidemia was considered as abnormal in any of the following four indicators (28): (I) TC $\geq$ 5.2 mmol/L; (II) In 0–9 age group, TG $\geq$ 1.1 mmol/L; In 10–18 age group, TG $\geq$ 1.5 mmol/L; (III) LDL-C $\geq$ 3.4 mmol/L; (IV) HDL-C $\leq$ 1.0 mmol/L. Hyperglycemia was considered as FBG $\geq$ 5.6 mmol/L (29). Abdominal obesity was considered as WC $\geq$ the 90th percentile of WC sex- and age-specific group (30). Clustered CMRFs was termed as meeting at least three of the above four items (31).

Ideal lifestyle category

Current smoking, current alcohol, dietary consumption, physical activity, sleep duration, screen time and healthy body mass index (BMI) were included to construct an ideal lifestyle score according to the definition of ideal cardiovascular health from the American Heart Association (32) and the Dietary Guidelines for School-age Children in China (33). Current smoking status was classified as smoking in the past 30 days (Yes/No), and current alcohol consumption was similar to smoking. The optimal dietary composition was defined as $\geq$3 servings of fruit per day (about 100 g per serving), $\geq$4 servings of vegetables (about 100 g per serving), 2–3 servings of meat products (about 50 g per serving), and <1 serving of sugar-sweetened beverage per week (about 250 mL per serving) according to the Dietary Guidelines for School-age Children in China (33). A healthy diet was described as the consumption of at least three or more foods in prescribed amounts. Adequate physical activity was characterized as 1 h or more of moderate to vigorous activity per day. The cut-off for sleep duration and screen time were 9 and 2 h, respectively. A healthy BMI was classified as lower than the 85th percentile of BMI for sex- and age-specific group (34). Children and adolescents who met each of the seven specified ideal lifestyles were given one point, and the total scores were 7. The ideal lifestyle scores were further divided into three groups as unfavorable lifestyles (0–3 points), intermediate lifestyles (4 points) and favorable lifestyles (5–7 points).

The combined subgroups

The single-child status was divided into single children and non-single children. Combining the single-child status and ideal lifestyle category, they can be further divided into six groups, namely the single children and favorable lifestyles, single children and intermediate lifestyles, single children and unfavorable lifestyles, non-single children and favorable

lifestyles, non-single children and intermediate lifestyles, and non-single children and unfavorable lifestyles.

Covariates

In this study, age, residence, family history of diseases, parental education, parental tobacco, and alcohol consumption were considered as context covariates. A family history of the disease was considered a history of obesity, hypertension, diabetes or cerebrovascular disease in either parent. Parental education level was recorded by the highest educational level of the parents and divided into primary or below, secondary or equivalent and junior college or above. Parental tobacco consumption (Yes/No) was defined as smoking by either parent and parental alcohol consumption (Yes/No) was similar.

Statistics analysis

Hot-deck Imputation method was used for missing variables (e.g., lifestyle information), and background variables were set as school, grade, urban and rural area, and sex. The quantitative variables were described by median (interquartile spacing), and group differences were tested by Mann-Whitney *U* test according to the normality of distribution. Qualitative variables were described by frequency (percentage) and group differences were tested by Chi-square test. Mixed effect logistic regression was applied to analyze the independent and the combined effects of single-child status and ideal lifestyle category on clustered CMRFs. Only the random effect of schools was adjusted for all crude models. The fixed effect of covariates and the random effect of schools were adjusted in all adjusted models. We also constructed sex interaction terms and conducted stratified analysis to explore sex differences between these association. All analyses were performed in SPSS 26.0 and GraphPad Prism 9. A two-tailed P value < 0.05 was considered statistically significant.

We also analyzed the independent and combined effects of single-child status and ideal lifestyle category on components of CMRFs, including hyperglycemia, hypertension, dyslipidemia, and abdominal obesity as a supplementary result.

Results

Characteristics of participants

The characteristics of participants and their parents were showed in **Table 1** and **Supplementary Table 1**. Overall, the prevalence of clustered CMRFs was 3.4%, with a higher prevalence in boys (4.0%) than girls (2.7%). Children and adolescents with clustered CMRFs had a higher proportion of single children (76.6 vs. 69.7%) and unfavorable lifestyles (62.1 vs. 29.2%) compared with their peers with non-clustered CMRFs. Children and adolescents with clustered CMRFs were more likely than those without clustered CMRFs to be male (61.1 vs. 50.8%), rural (50.2 vs. 41.1%), have a family history of diseases (18.9 vs. 12.5%), and have parents with lower proportion of high education level (24.9 vs. 30.3% for junior college or above).

Children who were included in the final sample (n = 13,859) were more likely than those in the primary sample (n = 15,733) to be rural (41.4 vs. 38.2%). There were no statistically significant differences in age group and sex between the primary sample and the final sample (**Supplementary Table 2**).

The independent effects of single-child status and lifestyle category on clustered cardio-metabolic risk factors

As presented in **Figure 2**, single children had a higher risk of CMRFs (adjusted model: OR = 1.67, 95% CI: 1.32–2.11) than non-single children in both crude and adjusted models. Although the sex interaction was not statistically significant, we stratified it by sex and found that this effect remained statistically significant for both boys (OR = 1.59, 95% CI: 1.16–2.20) and girls (OR = 1.48, 95% CI: 1.04–2.12). In the total population, participants engaged in intermediate (OR = 2.81, 95% CI: 1.92–4.12) and unfavorable lifestyles (OR = 9.03, 95% CI: 6.26–13.02) had a higher risk of clustered CMRFs compared to favorable lifestyles after adjusting for covariates (**Figure 3**). When stratified by sex, slightly higher OR values were observed in the unfavorable lifestyle group of boys (boys: OR = 9.42, 95% CI: 5.80–15.33 vs. girls: OR = 8.92, 95% CI: 5.08–15.67), although the difference was not statistically significant. The independent effects of single-child status and ideal lifestyle category on components of CMRFs have been shown in **Supplementary Tables 3**, **4**.

The combined effect of single-child status and lifestyle category on clustered cardio-metabolic risk factors

As shown in **Figure 4**, a stronger combined effect of single children and ideal lifestyle category was found in clustered CMRFs. Compared to children and adolescents in the non-single children and favorable lifestyle group, an extremely high risk of clustered CMRFs was observed among those in the non-single children and unfavorable lifestyle group (OR = 7.60, 95% CI: 3.85–14.96) and single children and unfavorable lifestyle group (OR = 12.79, 95% CI: 6.67–24.52). No statistical significance was found in the single children and favorable lifestyle group (OR = 1.33, 95% CI: 0.63–2.82). When stratified by sex, these relationships remained consistent with the total population but with no statistical difference between boys and

TABLE 1 Demographic characteristics of eligible children and adolescents and their parents, stratified by clustered cardio-metabolic risk factors (CMRFs).

Characteristic	Total (n = 13,859)	Clustered CMRFs		P-value
		Yes (n = 470)	No (n = 13,389)	
Age*	12.2 (5.7)	12.2 (5.7)	12.7 (5.5)	<0.001
Boys	7,091 (51.2)	287 (61.1)	6,804 (50.8)	<0.001
Urban	8,117 (58.6)	234 (49.8)	7,883 (58.9)	<0.001
CMRFs				
High SBP (%)	1,090 (7.9)	247 (52.6)	843 (6.3)	<0.001
High DBP (%)	1,882 (13.6)	373 (79.4)	1,509 (11.3)	<0.001
Hypertension (%)	2,327 (16.8)	448 (95.3)	1,879 (14.0)	<0.001
High TC (%)	725 (5.2)	67 (14.3)	658 (4.9)	<0.001
High TG (%)	2,700 (19.5)	335 (71.3)	2,365 (17.7)	<0.001
High LDL-C (%)	379 (2.7)	47 (10.0)	332 (2.5)	<0.001
Low HDL-C (%)	1,343 (9.7)	201 (42.8)	1,142 (8.5)	<0.001
Dyslipidemia (%)	3,948 (28.5)	452 (96.2)	3,496 (26.1)	<0.001
High FBG (%)	258 (1.9)	55 (11.7)	203 (1.5)	<0.001
Abdominal obesity (%)	3,101 (22.4)	466 (99.1)	2,635 (19.7)	<0.001
Single children	9,688 (69.9)	360 (76.6)	9,328 (69.7)	0.001
Number of ideal lifestyle factors				<0.001
0–3 (unfavorable lifestyle)	4,199 (30.3)	292 (62.1)	3,907 (29.2)	
4 (intermediate lifestyle)	5,996 (43.3)	144 (30.6)	5,852 (43.7)	
5–7 (favorable lifestyle)	3,664 (26.4)	34 (7.2)	3,630 (27.1)	
Family history of diseases[$]	1,761 (12.7)	89 (18.9)	1,672 (12.5)	<0.001
Parental education level				0.036
Primary or below	385 (2.8)	12 (2.6)	373 (2.8)	
Secondary or equivalent	9,300 (67.1)	341 (72.5)	8,959 (66.9)	
Junior college or above	4,174 (30.1)	117 (24.9)	4,057 (30.3)	
Parental current tobacco consumption	7,991 (57.7)	273 (58.1)	7,718 (57.6)	0.849
Parental current alcohol consumption	3,935 (28.4)	129 (27.4)	3,806 (28.4)	0.643

*Quantitative variables are shown as median (interquartile range). [$]Family history of diseases includes obesity, hypertension, diabetes mellitus and cerebrovascular disease. CMRFs, cardio-metabolic risk factors; SBP, systolic blood pressure; DBP, diastolic blood pressure; BP, blood pressure; TC, total cholesterol; TG, triglycerides; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; FBG, fasting blood glucose.

girls in the OR values of each subgroup. **Supplementary Table 5** shows the combined effect of single-child status and ideal lifestyle category on components of CMRFs. In addition to high FBG, the combined effect of single children and ideal lifestyle category was statistically significant for hypertension, dyslipidemia and abdominal obesity, with the largest OR for abdominal obesity.

Discussion

To the best of our knowledge, this study is the first to evaluate the combined effect of single children and lifestyle category on clustered CMRFs. According to the findings of this study, both single children and unfavorable lifestyles were associated with an increased risk of clustered CMRFs. The risk of clustered CMRFs increased significantly when single children and an unfavorable lifestyle were combined, which was almost neutralized when single children adhered to a favorable lifestyle. However, no sex difference was observed in this study.

The associations between the single children and an increased risk of elevated blood pressure (35), dyslipidemia (10), hypertension (13), abdominal obesity (11, 35), overweight and obesity (36, 37) were confirmed in China and European countries. However, one study found the opposite results that children with siblings were associated with a higher risk of hypertension (12), which the authors believed was likely attributed to adjustments for BMI or obesity status. The results of existing studies on lifestyles on CMRFs were more consistent, finding that an unfavorable lifestyle increased the risk of CMRFs or CVDs (38–40). Moreover, a meta-analysis showed that for each increase in ideal cardiovascular health as defined by the American Heart Association, cardiovascular mortality decreased by 19% (41). This present study added

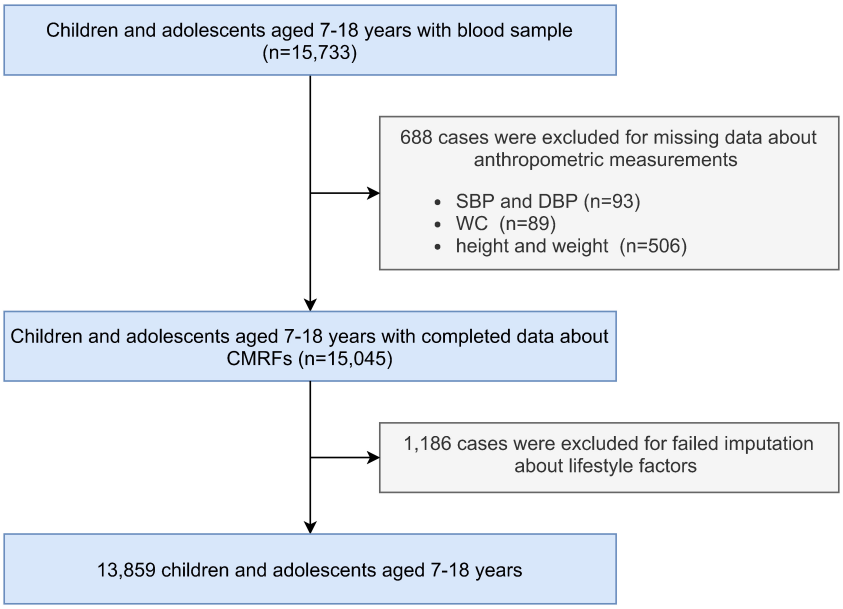

FIGURE 1
Flow chart of participants' inclusion. SBP, systolic blood pressure; DBP, diastolic blood pressure; WC, waist circumference; CMRFs, cardio-metabolic risk factors.

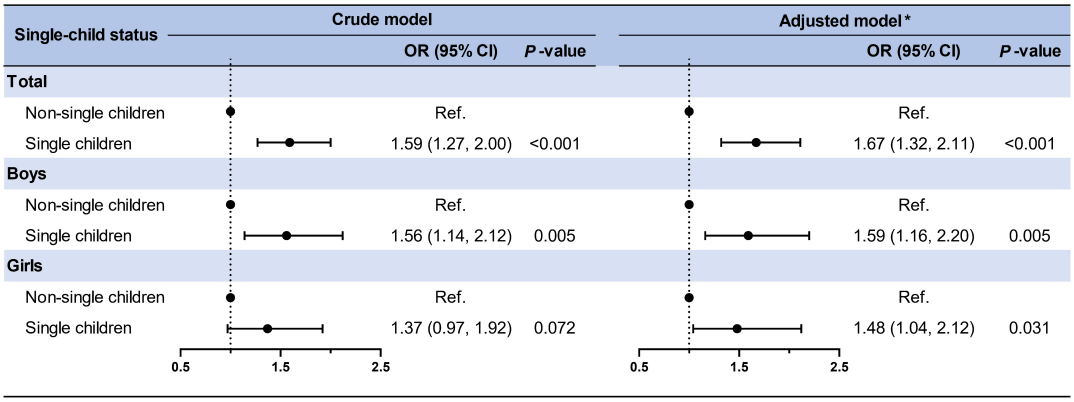

FIGURE 2
Association between single-child status and clustered CMRFs in children and adolescents. *Adjusted for age, residence, family history of diseases (obesity, hypertension, diabetes mellitus, and cerebrovascular disease), parental education level, parental tobacco, and alcohol consumption and the clustered effect of schools.

to the evidence that further emphasized the importance of adhering to a favorable lifestyle. No sex differences were found in this study, most likely due to the low prevalence of clustered CMRFs (3.4%) and, as a result, the relatively small number of children in each subgroup when stratified by sex, but indicated that intervention developed from single-child status or lifestyle perspectives or both would work for both sexes under such level of CMRFs.

Previous studies have identified an association between single-child families and components of CMRFs, however, the underlying mechanisms remain unknown. Even though the resource dilution theory (42, 43) contended that single children received more resources and care than children with siblings, the current nutritional and social environment may encourage the adoption of unhealthy lifestyles, which in turn resulted in metabolic abnormalities. Notably, this study discovered that when single children maintained a healthy lifestyle, the negative effect of single children on clustered CMRFs appeared to be offset, implying that the mechanism of health risks caused by single children was most likely due to their tendency to unfavorable lifestyles, such as fast food over intake (22), sugar excessive consumption (36), and physical

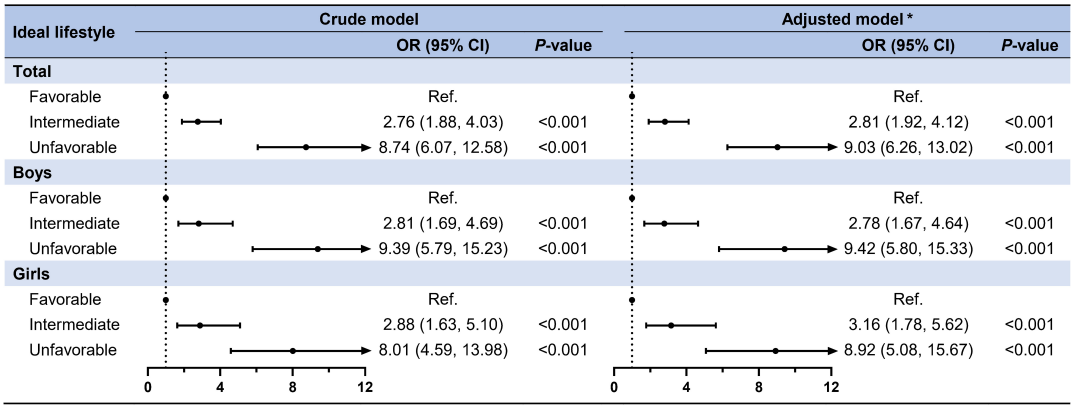

FIGURE 3
Association between ideal lifestyle factors and clustered CMRFs in children and adolescents. *Adjusted for age, residence, family history of diseases (obesity, hypertension, diabetes mellitus, and cerebrovascular disease), parental education level, parental tobacco, and alcohol consumption and the clustered effect of schools.

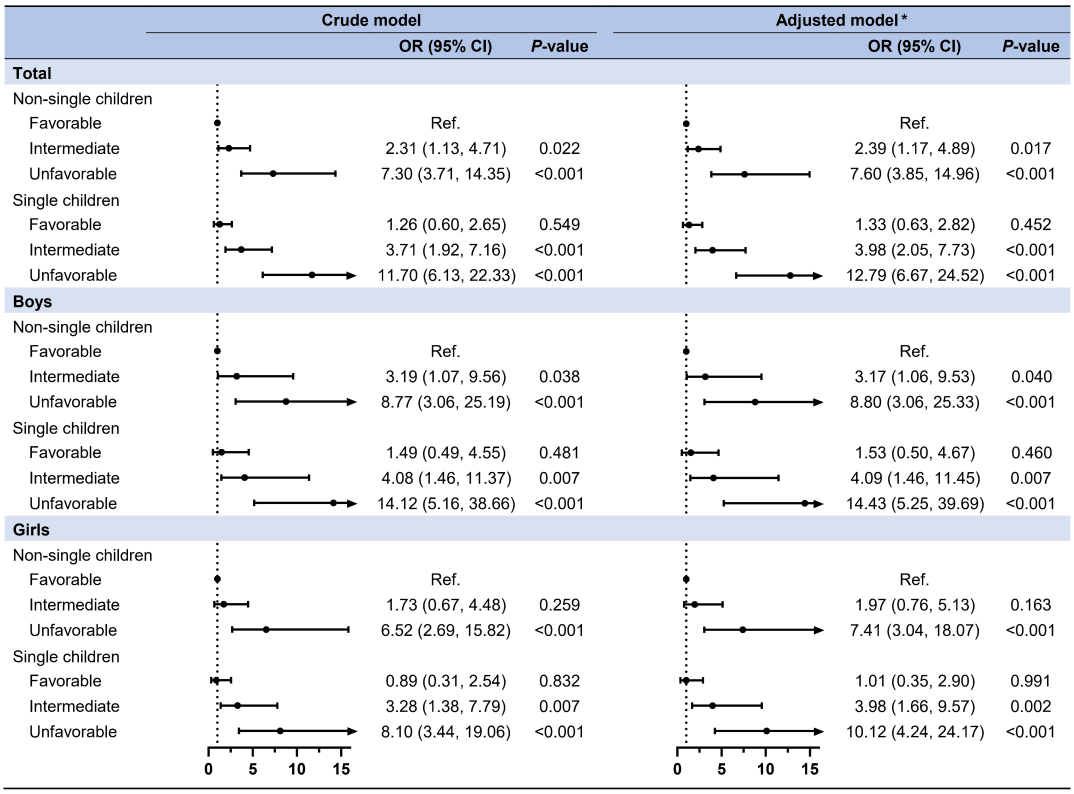

FIGURE 4
The combined effect of single-child status and ideal lifestyle on clustered CMRFs. *Adjusted for age, residence, family history of diseases (obesity, hypertension, diabetes mellitus, and cerebrovascular disease), parental education level, parental tobacco, and alcohol consumption and the clustered effect of schools.

inactivity (23). Based on the available evidence, the risks of being a single child might be mitigated by diluting the allocation of resources by expanding the family. On the other hand, children and adolescents should be encouraged to cultivate and maintain a healthy lifestyle, whether from single child or non-single child families.

To cope with the challenge of aging issue, the Chinese government ended one-child policy with the two-child

policy in Zeng and Hesketh (44), and opened up the three-child policy in Jing et al. (45). However, the increasingly open policy has not improved China's low fertility rate as expected (46, 47). According to the China Women's Federation, the intention rate of parents to have a second child was 20.5% in 2017 (48), significantly lower than the 61.25% recorded under the one-child policy (49). Single children made up a large proportion of all structural families in an international environment of high income and low fertility (50). The level of delaying childbearing has been increasing, especially with the emergence of the second demographic transition (51), which suggested that this proportion was likely to increase in the future, and the resulting health problems should not be ignored. This study highlighted the need for the government and society to increase support for the birth of second and third children, such as reducing the financial burden and relieving the pressure of childrearing, and increasing couples' free time. The findings of this study provided new evidence that single children with unfavorable lifestyles might be an important target group for future clustered CMRFs interventions, and it was necessary to strengthen the establishment of a friendly birth environment and health education at the family level to guide children toward a favorable lifestyle.

There were several limitations to the study. Firstly, this was a cross-sectional study with limited causal inference. Secondly, the lifestyle information of children and adolescents was entirely based on a questionnaire survey, which had a certain recall bias. Thirdly, although the method of imputation was used for missing variables, 12% of the samples were still excluded in this study, and thus there may be some selection bias in the final analyzed samples. However, when the background variables of the initial and final samples were compared, only urban and rural differences were discovered in this study. Fourthly, although some confounding factors were adjusted in this study, there was still residual confounding. Lastly, adding BMI as a scoring indicator in the definition of a healthy lifestyle may improve the correlation of lifestyle with clustered CMRFs, especially since abdominal obesity was included as a component of CMRFs in this study.

Conclusion

Single children with unfavorable lifestyles were associated with an obvious risk of clustered CMRFs, which might be partially offset by expanding family size (the number of siblings) or establishing a favorable lifestyle. A birth-friendly social environment as well as a family environment with a favorable lifestyle are encouraged in China.

Data availability statement

The data supporting the conclusions of this article can be made available from the corresponding author upon request.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of Peking University (NO.IRB0000105213034). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

YD, ZZ, YM, YS, and JM conducted data collection and data management. JD and YS conducted manuscript design. JD, NM, and YL conducted statistical analysis. JD, NM, YL, PZ, DS, SC, YD, ZZ, and YM wrote and finalized the manuscript. YS and JM reviewed and revised the 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.

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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.2022.987334/full#supplementary-material

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Associations between the timing of different foods' consumption with cardiovascular disease and all-cause mortality among adults with sleep disorders

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Introduction: People with sleep disorders are under disrupted biological rhythms. Whether changing the timing of specific food consumption contributes to decreasing cardiovascular and all-cause risk is unknown.

Methods: A total of 8,005 participants with sleep disorders were selected from the U.S. National Health and Nutrition Examination Survey (NHANES) from 2005 to 2014. Cox proportional hazards regression models were used to analyze the relationship between the consumption time of foods and cardiovascular disease (CVD) and all-cause death. Moreover, equivalent food substitution models were carried out to evaluate the alterations in the risk of CVD mortality for the changed food intake time.

Results: After adjusting for multiple confounders, participants who consume red and orange vegetables, starchy vegetables, and fermented dairy in the morning (hazard ratio (HR)$_{red\ and\ orange\ vegetables}$ = 0.45, 95% CI: 0.26–0.81; $HR_{starchy\ vegetables}$ = 0.47, 95% CI: 0.25–0.88; $HR_{fermented\ dairy}$ = 0.57, 95% CI: 0.36–0.89) and milk and eggs in the evening contribute to reducing the likelihood of death from CVD (HR_{milk} = 0.65, 95% CI: 0.43–0.96; HR_{eggs} = 0.72, 95% CI: 0.53–0.98). Iso-calorically switching 0.1 serving of starchy vegetable and fermented dairy and milk intake from one period to another does significantly reduce the mortality risk of CVD.

Conclusion: Higher intake of red and orange vegetables, starchy vegetables, and fermented dairy in the morning and milk and eggs in the evening confers a lower risk of CVD among individuals with sleep disorders.

KEYWORDS

sleep disorder, chrono-nutrition, cardiovascular diseases, mortality, NHANES

Introduction

Sleep disorders have become a new public health burden worldwide. Epidemiological surveys show that people with insufficient sleep alone account for one-third of the total adults in the USA (1, 2). Sleep disorder has been shown to be associated with multiple chronic diseases (3, 4), among which cardiovascular disease (CVD), as the leading cause of death worldwide, accounts for about one-third of global deaths (5, 6). The mechanism between sleep disorders and CVD could be explained by the relationships between sleep, circadian disruption, and metabolic physiology (7), which means that the disordered circadian rhythm of inflammation, oxidative stress, and sympathetic activity induced by sleep disorders further contribute to endothelial dysfunction and metabolic disturbances (8, 9). However, the circadian rhythm disorder caused by sleep disorders could be improved by accepted modifiable behaviors, among which adjusting the dietary factor is the most economical and convenient way (10–13).

However, most studies related to dietary interventions focus on the quantity or quality of dietary factors (14, 15). As an emerging field of nutritional research, chrono-nutrition aims to emphasize the importance of dietary intake time for health (16). It is well known that circadian rhythms could regulate a variety of physiological activities, such as food intake, which in turn feedback regulates nutrient absorption, distribution, metabolism, and excretion by driving peripheral circadian clocks (16). In short, the concept of "chrono-nutrition" is mainly derived from the abovementioned coordination between food intake time and the circadian body rhythm, which is broadly covers in three parts: (1) the distribution of energy intake in a day; (2) the frequency of food intake per day; and (3) the timing of food intake (17). Several studies published recently successively demonstrated the close association between the fields of chrono-nutrition and health (18–21). Circadian rhythms have a strong association between sleep and food intake time, but few studies investigated whether and how the timing of food consumption affects CVD in people with sleep disturbances. Therefore, our study was conducted to examine the association between the intake time of different foods and the mortality of all-cause and CVD among individuals with sleep disorders, aiming to provide practical intervention strategies for the prevention and treatment of CVD.

Materials and methods

Study population

The National Health and Nutrition Examination Survey (NHANES) is a stratified, multistage study conducted by the U.S. National Center for Health Statistics (NCHS). The researcher used professional interviews and examinations to collect nationally representative data of American civilians. Adults with a sleep duration of less than 6 h, self-reporting sleep trouble, or diagnosed with a sleep disorder by a doctor-were classified as having a sleep disorder (22, 23). After excluding the participants who had missed dietary intake and/or mortality variables, a total of 8,005 participants with sleep disorders (3,636 men and 4,370 women) were selected. The NHANES data obtained the approval of the NCHS Institutional Review Board and the informed consent of the participants and could be available through https://wwwn.cdc.gov/nchs/nhanes/Default.aspx.

Dietary and sleep duration assessment

The dietary food intake of each participant was assessed over 2 non-consecutive days through 24-h diet recalls. Dietary foods and energy intake were estimated based on the guidelines of the U.S. Department of Agriculture's Dietary Research Food and Nutrition Database. According to the user guide of the MPED2.0 of the U.S. Department of Agriculture Survey Foods, 15 different food groups were selected and used for further analysis. A sleep questionnaire was used to assess the sleep status of each participant. Based on the time point of food intake, these meals are classified as breakfast, lunch, dinner, and snacks.

Main exposure

The food groups included in this study were mainly whole grains, refined grains, dark green vegetables, red and orange vegetables, starchy vegetables, total fruit, milk, fermented dairy, eggs, red meat, poultry, cured meat, seafood, soybean products, and legumes. The exposure variables were set as food intakes in the morning, afternoon, and evening.

Main outcome

The main outcome variable was the mortality of CVD and all causes, which was determined by the National Death Index (NDI). As a highly reliable resource, NDI is widely used for death identification. The International Classification of Diseases 10th Revision (ICD-10) is used to determine disease-specific death, among which ICD-10 codes, such as I00–I09, I11, I13, I20–I51, or I60–I69 are defined as CVD mortality. A total of 658 deaths, including 189 deaths due to CVD, were used for further analysis.

Confounding and effect modification measurements

Potential covariates are as follows: age (years), sex (men/women), race/ethnicity (non-Hispanic white/non-Hispanic black/Mexican American/other), annual household income level (less than $20,000, between $20,000 and $45,000, between $45,000 and $75,000, between $75,000 and $100,000, or over $100,000), educational level (below 9th grade, between 9th and 11th grade, finish high school, finish GED or equivalent, finish college or Associate in Arts degree, or finish college graduate or above), regular exercise (yes/no), cigarette and alcohol use (yes/no), body mass index (BMI) (kg/m^2), disease history of diabetes, hypertension, and dyslipidemia (yes/no), covered by health insurance (yes/no), total energy intake (kcal/day), total fat intake (g/day), total carbohydrate intake (g/day), total protein intake (g/day), whole grains (ounce equivalents), refined grains (ounce equivalents), dark green vegetables (cup equivalents), red and orange vegetables (cup equivalents), starchy vegetables (cup equivalents), fruit (cup equivalents), milk (cup equivalents), fermented dairy (cup equivalents), eggs (ounce equivalents), red meat (ounce equivalents), poultry (ounce equivalents), cured meat (ounce equivalents), seafood (ounce equivalents), soybean products (ounce equivalents), legumes (ounce equivalents), and the Alternative Healthy Eating Index (AHEI).

Statistical analysis

The intake of food groups in the morning, afternoon, and evening were divided into two (whether or not to eat) or three (base on the distribution) parts according to their distribution. For social demographics, lifestyle and eating behavior, and anthropometric indicators, categorical variables were represented by percentages, and continuous variables were represented by median (P25, P75). The baseline characteristics were compared by the Mann–Whitney *U*-test and the Chi-square test. R 4.0.2 was used to conduct all statistical analyses, and a two-sided p-value < 0.05 was considered to be statistically significant. The median was used to replace missing values for covariates with less than 5% missing values.

Cox proportional hazards models were established to evaluate the relationship between food intake across a day and CVD and all-cause mortality. Confounding factors were adjusted in all models, such as age, gender, race, BMI, drinking, smoking, exercise, income, education, total energy intake, total fat intake, total carbohydrate intake, total protein intake, AHEI, health insurance coverage, disease history of diabetes, hypertension, and dyslipidemia. In addition, the total intake of every food group in a 24-h period was adjusted in the model.

An equivalent food substitution model was carried out to evaluate the alterations in the risk of CVD mortality for the changed food intake time. A substitution analysis is mainly conducted by converting food intake time points and keeping the total energy and other food intake constant.

Sensitivity analysis

In set 1, sensitivity analyses were performed to assess the relationship between total red and orange vegetable, starchy vegetable, milk, fermented dairy, and egg intake in a whole day and CVD and all-cause mortality to check whether the intake time could provide more information. In set 2, sensitivity analyses were performed among individuals with sound sleep to evaluate the impact of sleep status on the results. In set 3, AHEI was additionally adjusted to evaluate the impact of dietary quality on the results. In set 4, a sensitivity analysis was conducted to evaluate whether sex, diabetes, hypertension, and dyslipidemia could affect the relationship between food intake time and CVD and all-cause risk.

Results

Baseline characteristics

The demographic and nutrition characteristics on the basis of the disease status of CVD mortality are presented in **Table 1**. Compared with other participants, the participants who died due to CVD were more likely to be men, less likely to be non-Hispanic white, had a higher age, the prevalence of dyslipidemia, hypertension, and diabetes, and a lower percentage of health insurance coverage, exercise, education, income, total energy, fat, protein, carbohydrate intake, and AHEI ($P < 0.05$).

Associations of foods intake time with all-cause and cardiovascular disease mortality

The association of red and orange vegetable, starchy vegetable, milk, fermented dairy, and egg intake consumed in the morning and evening with all-cause and CVD mortality is presented in **Table 2** among participants with sleep disorders. In addition, the association of other dietary foods consumed in the morning and evening with CVD and all-cause mortality is presented in **Supplementary Table 1**. The results indicated that participants who eat red and orange vegetables, starchy vegetables, and fermented dairy in the morning had lower CVD mortality, compared with participants who skip red and orange vegetables, starchy vegetables, and fermented

dairy in the morning, as indicated by hazard ratio (*HR*) and 95% CI ($HR_{\text{red and orange vegetables}}$ = 0.46, 95% CI: 0.26–0.82; $HR_{\text{starchy vegetables}}$ = 0.47, 95% CI: 0.25–0.88; and $HR_{\text{fermented dairy}}$ = 0.57, 95% CI: 0.36–0.90). Furthermore, compared with participants in the highest quintile of milk intake in the evening, those in the lowest quintile were more likely to die due to CVD, as indicated by *HR* and 95% CI (HR_{milk} = 0.65, 95% CI: 0.43–0.96). Similarly, the consumption of eggs in the evening also confers a lower risk of CVD (HR_{eggs} = 0.72, 95% CI: 0.53–0.98). Moreover, participants who consumed red and orange vegetables in the morning and fermented dairy in the evening had a lower association with all-cause mortality ($HR_{\text{red and orange vegetables}}$ = 0.75, 95% CI: 0.58–0.97; and $HR_{\text{fermented dairy}}$ = 0.77, 95% CI: 0.64–0.92).

Equivalent substitution analysis

Figure 1 shows that the mortality risk of CVD in the predicted equivalent substitution models through switching food intake from one period to another among participants with sleep disorders. Figure 1 shows that the *HR* of CVD mortality decreased by 3% (*HR* = 0.97, 95% CI: 0.94–0.99) in models with 0.1 serving of starchy vegetables in the evening being equivalently switched to morning. Similarly, the results

TABLE 1 The baseline characteristics of studying variables by disease status.

Variables	CVD mortality (*N* = 189)	Non-CVD mortality (*N* = 7,817)	*P*-value
Age (years)	73.00 (64.00, 80.00)	50.00 (37.00, 63.00)	<0.001
Men (%)	116 (61.37)	3,250 (45.03)	0.995
Non-Hispanic white (%)	16 (8.46)	873 (11.16)	0.002
Current smoking (%)	46 (24.33)	2,350 (30.06)	0.233
Current drinking (%)	129 (68.25)	5,677 (72.62)	0.184
Regular exercise (%)	12 (6.34)	1,255 (16.05)	0.001
College graduate or above (%)	20 (10.58)	1,570 (20.08)	<0.001
>$100,000 annual household income (%)	7 (3.70)	924 (11.82)	<0.001
BMI (kg/m^2)	28.75 (24.70, 33.02)	29.00 (24.94, 34.06)	0.295
Total energy intake (kcal/day)	1,610.50 (1,222.50, 2,005.00)	1,884.00 (1,431.50, 2,460.50)	<0.001
Total fat intake (g/day)	58.57 (39.64, 81.69)	70.00 (49.28, 96.69)	<0.001
Total protein intake (g/day)	64.01 (48.01, 86.38)	72.39 (53.95, 96.04)	<0.001
Total carbohydrate intake (g/day)	202.05 (155.91, 252.87)	229.23 (171.50, 301.96)	<0.001
AHEI	47.00 (37.00, 55.00)	52.00 (42.00, 62.00)	<0.001
Diabetes (%)	63 (33.33)	1,513 (19.36)	<0.001
Hypertension (%)	157 (83.07)	3,830 (49.00)	<0.001
Dyslipidemia (%)	98 (51.85)	3,059 (39.13)	<0.001
Covered by health insurance (%)	6,383 (81.7)	180 (95.2)	<0.001
Whole grain (ounce equivalents)	0.55 (0.00, 1.24)	0.42 (0.00, 1.18)	0.159
Refined grain (ounce equivalents)	4.01 (2.71, 5.91)	4.75 (3.09, 6.87)	0.001
Dark green vegetable (cup equivalents)	0.00 (0.00, 0.00)	0.00 (0.00, 0.11)	0.012
Red and orange vegetable (cup equivalents)	0.37 (0.06, 0.84)	0.51 (0.19, 1.02)	<0.001
Starchy vegetable (cup equivalents)	0.66 (0.00, 1.41)	0.55 (0.00, 1.27)	0.632
Fruit (cup equivalents)	0.89 (0.25, 1.43)	0.63 (0.05, 1.41)	0.005
Milk (cup equivalents)	0.62 (0.17, 1.20)	0.45 (0.12, 1.05)	0.010
Fermented dairy (cup equivalents)	0.47 (0.09, 1.00)	0.28 (0.00, 0.67)	<0.001
Eggs (ounce equivalents)	0.28 (0.03, 0.89)	0.22 (0.03, 0.88)	0.357
Red meat (ounce equivalents)	0.90 (0.00, 2.23)	1.00 (0.00, 2.38)	0.178
Poultry (ounce equivalents)	0.41 (0.00, 2.09)	0.83 (0.00, 2.26)	0.050
Cured meat (ounce equivalents)	4.97 (2.96, 7.65)	4.17 (2.66, 7.18)	0.039
Seafood (ounce equivalents)	0.00 (0.00, 0.28)	0.00 (0.00, 0.43)	0.454
Soybean products (ounce equivalents)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.018
Legumes (ounce equivalents)	0.00 (0.00, 0.00)	0.00 (0.00, 0.40)	0.021

Continuous variables are presented as median (P25, P75). Categorical variables are presented as percentages. Hypertension is defined by a self-reported diagnosis, systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg. Hyperlipidemia is defined as serum triglyceride ≥2.26 mmol/L, or serum cholesterol ≥6.22 mmol/L, or low-density lipoprotein ≥4.14 mmol/L. Diabetes is defined by a self-reported diagnosis, an HbA1c level ≥6.5%, or a fasting plasma glucose level ≥7.0 mmol/L. AHEI, Alternative Healthy Eating Index.

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TABLE 2 Multivariate adjusted hazard ratios (*HR*s) of the dietary red and orange vegetables, starchy vegetables, milk, fermented dairy, and eggs intake in the morning and the evening and CVD-mortality and all-cause mortality among participants with sleep disorders.

	CVD mortality		All-cause mortality	
	Case/*N*	HR (95% CI)	Case/*N*	HR (95% CI)
In the morning				
Red and orange vegetables (yes/no)				
No	176/6,838	1	588/6,838	1
Yes	13/1,168	0.46 (0.26, 0.82)	70/1,168	0.75 (0.58, 0.97)
P for trend		0.008		0.030
Starchy vegetables (yes/no)				
No	178/7,099	1	595/7,099	1
Yes	11/907	0.47 (0.25, 0.88)	63/907	0.82 (0.62, 1.07)
P for trend		0.017		0.143
Milk (tertiles)				
Q1	51/2,401	1	180/2,401	1
Q2	59/2,721	0.87 (0.59, 1.28)	218/2,721	0.92 (0.75, 1.13)
Q3	79/2,884	0.75 (0.48, 1.18)	260/2,884	0.79 (0.63, 1.01)
P for trend		0.279		0.063
Fermented dairy (yes/no)				
No	166/5,966	1	547/5,966	1
Yes	23/2,040	0.57 (0.36, 0.90)	111/2,040	0.82 (0.66, 1.02)
P for trend		0.015		0.074
Eggs (yes/no)				
No	97/4,338	1	346/4,338	1
Yes	92/3,668	0.93 (0.66, 1.31)	312/3,668	0.99 (0.82, 1.18)
P for trend		0.667		0.869
In the evening				
Red and orange vegetables (yes/no)				
No	68/5,131	1	225/2,079	1
Yes	121/3,999	0.83 (0.59, 1.17)	433/5,927	0.84 (0.70, 1.01)
P for trend		0.281		0.062
Starchy vegetables (yes/no)				
No	92/2,079	1	225/2,079	1
Yes	97/5,927	0.74 (0.51, 1.07)	433/5,927	0.93 (0.76, 1.14)
P for trend		0.109		0.483
Milk (tertiles)				
Q1	56/2,470	1	173/2,470	1
Q2	63/2,309	1.07 (0.74, 1.54)	179/2,309	1.01 (0.82, 1.25)
Q3	70/3,227	0.65 (0.43, 0.96)	306/3,227	1.03 (0.83, 1.27)
P for trend		0.006		0.835
Fermented dairy (yes/no)				
No	108/3,397	1	371/3,397	1
Yes	81/4,609	0.77 (0.55, 1.08)	287/4,609	0.77 (0.64, 0.92)
P for trend		0.131		0.004
Eggs (yes/no)				
No	83/3,296	1	266/3,296	1
Yes	106/4,710	0.72 (0.53, 0.98)	392/4,710	0.91 (0.77, 1.07)
P for trend		0.039		0.256

Adjustments included age, gender, race, body mass index (BMI), drinking, smoking, exercise, income, education, total energy intake, total fat intake, total carbohydrate intake, total protein intake, AHEI, covered by health insurance, disease history of diabetes, disease history of hypertension, disease history of dyslipidemia, and total intake of specific food group in the 24-h period. Case/*N*, number of case participants/total; Q, quarter; AHEI, Alternative Healthy Eating Index.

indicated that *HR*s for CVD decreased by 12 or 9% (*HR* = 0.90, 95% CI: 0.83–0.97; and *HR* = 0.92, 95% CI: 0.85–0.99) in models with 0.1 serving of fermented dairy in the afternoon or evening being equivalently switched to the morning. In addition, it can be concluded that *HR*s for CVD decreased by 4% (*HR* = 0.97, 95% CI: 0.94–0.99) in models with 0.1 serving of milk intake in the afternoon being equivalently switched to the evening.

Sensitivity analysis

The result of the first sensitivity analysis showed that the total intake of red and orange vegetables, starchy vegetables, milk, fermented dairy, and eggs was not associated with CVD and all-cause mortality, which suggested that the analysis of the dietary intake time could provide more information than the total daily food intake only (**Supplementary Table 2**). The second set of the sensitivity analysis demonstrated that the association between intake of fermented dairy in the morning and milk and eggs in the evening with CVD mortality disappeared among participants with normal sleep (**Supplementary Table 3**), which means that the intake time of the above foods may play a role in reducing CVD death by improving the adverse effects of sleep or sleep deprivation among participants with sleep disorders. The third set of the sensitivity analysis indicated that, after additionally adjusting dietary quality, the relationship between the consumption time of the above foods and CVD was still significant (**Supplementary Table 4**). The fourth set of the sensitivity analysis showed that sex, diabetes, hypertension, and dyslipidemia could not affect the relationship between the consumption time of the above food items and CVD (**Supplementary Tables 5–7**).

Discussion

Our study showed that people with sleep disorders who have red and orange vegetables, starchy vegetables, and fermented dairy consumption in the morning and milk and eggs in the evening seem to have decreased CVD mortality. In addition, while keeping food quality and quantity constant, switching 0.1 serving of milk intake from afternoon to morning, switching 0.1 serving of fermented dairy intake from afternoon or evening to morning, or switching 0.1 serving of starchy vegetables intake from evening to morning confer a lower risk of CVD.

Most studies focused on investigating the association between quantity and quality of different foods or dietary patterns and CVD (14, 15). However, as we all know, this was the first study to explore the association of the consumption time of dietary foods with CVD mortality among individuals with sleep disorders. Abundant studies illustrated that sleep disorders could activate inflammatory gene expression and the production of proinflammatory cytokines in the morning by increasing sympathetic nerve activity at midnight, which gradually decreases under normal circumstances, and exacerbate impairment on vascular reactivity in the morning (24–27). Based on the above evidence, attenuating the inflammatory response may be a way for reducing adverse effects caused by sleep disorders in the morning. As a type of food rich in anti-inflammatory phytochemicals, such as lycopene and carotenoids, red orange vegetables have been found to reduce oxidative stress and inflammation by influencing inflammatory markers and their downstream targets (28–30). This indicated that the benefits of a higher intake of red orange vegetables in the morning may be explained by the anti-inflammatory effects of phytochemicals, which suggests that we should pay more attention to increase its intake in the morning rather than other foods in the case of sleep disorder.

In addition to attenuating inflammatory effects, the interaction of sleep disorders and metabolic disorders is a basis of CVD (31, 32), which should be paid more attention. First, sleep disorders have been shown to increase the total amount and time of energy intake (33), which manifests as a decrease in energy intake at breakfast and an increase in energy intake at dinner, with fat and carbohydrate accounting for a large proportion of energy source at dinner (34, 35). However, evidence indicated that carbohydrate metabolism have an internal biological rhythm, which is highest in the morning and gradually decreases in the evening (36). It means that the right time of carbohydrates consumption should be in the morning rather than in the evening, which is the same as our result. In addition, another study demonstrated that higher energy intake at breakfast with lower intake at dinner have beneficial effects on metabolic control (37). Similarly, several random control trails showed that the carbohydrate-rich breakfast and fermented dairy could decrease food intake after lunch or later by increasing satiety and decreasing hunger rating (38–40), which supports the beneficial effect of high intakes of starchy vegetables and fermented dairy in the morning. The mechanism of the benefit of eating eggs in the evening in our results is still opaque. As a food source of high-quality protein, eggs have been shown to increase satiety and decrease food intake later (41). In addition, consuming eggs in the evening has been proven to improve glycometabolism, compared with other high-carbohydrate protein-matched sources (42). It demonstrated that eggs may be a suitable energy source in the evening and may help to improve metabolic disorders by reducing excessive energy intake in the evening.

Studies showed that most hormones regulate metabolism and energy balance through own circadian rhythms (43). Circadian rhythm disturbance caused by a sleep disorder has a great impact on the role of hormones. First of all, under normal circumstances, insulin sensitivity, and insulin secretion will decrease at night and increase in the morning (44).

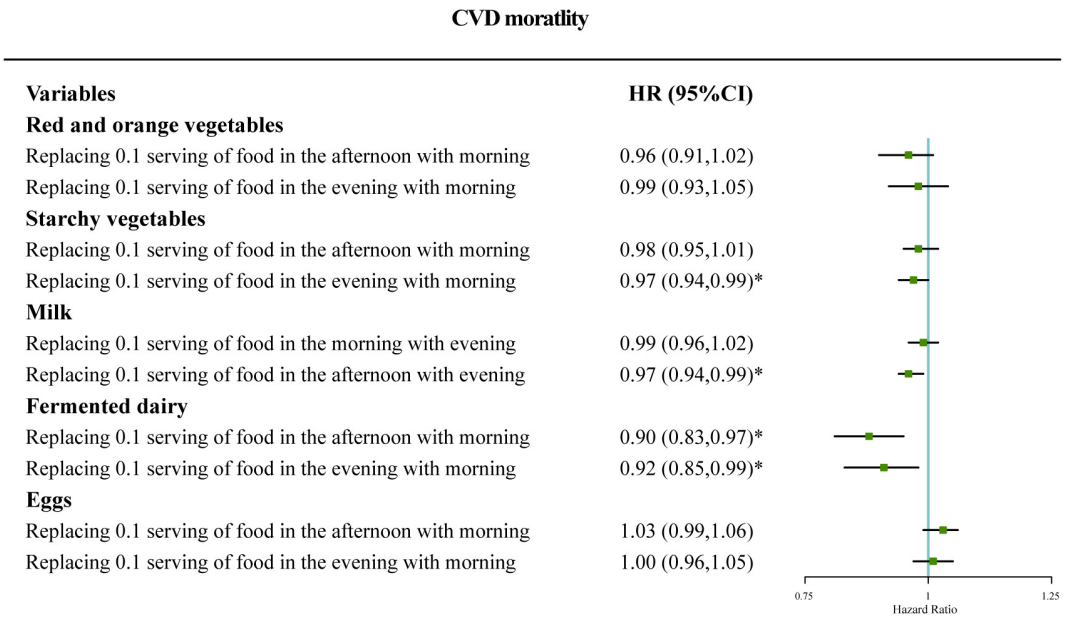

FIGURE 1
Adjusted hazard ratio (HR) for cardiovascular disease (CVD) mortality: iso-caloric substitution of red and orange vegetables, starchy vegetables, and fermented dairy consumed in the afternoon or the evening to morning and iso-caloric substitution of milk and eggs in the morning or the afternoon to the evening. Adjustments included age, gender, race, BMI, drinking, smoking, exercise, income, education, total energy intake, total fat intake, total carbohydrate intake, total protein intake, AHEI, health insurance coverage, disease history of diabetes, disease history of hypertension, disease history of dyslipidemia, and total intake of specific food group in the 24 h period. Case/*N*, number of case participants/total; Q, quarter; AHEI, Alternative Healthy Eating Index.

Therefore, people with insulin rhythm disturbances caused by sleep disorders should adapt to their normal rhythmic activity at an appropriate time, which is consistent with our result that starchy vegetables should be eaten in the morning (45). In addition, the nocturnal secretion of the appetite-related hormone leptin is reduced due to sleep disorders, which leads to an increase in total energy intake to energy imbalance (46). Consistent with the above statement, the energy imbalance is mainly manifested in the increased intake of high-carbohydrate and high-fat foods at night (35). However, as a decomposition hormone, cortisol itself has a low secretion level at night (44), and the dual effects of increased nighttime energy intake and decreased catabolism lead to increased susceptibility to metabolic disturbances. Therefore, it is recommended to consume some satiety foods, such as eggs at night to restrict energy intake. Melatonin, an important hormone that maintains the biological clock and regulates body rhythms (47), is also affected by sleep disorders, resulting in decreased secretion at night (44). Therefore, drinking milk rich in tryptophan at night helps to provide precursors for the synthesis of melatonin and improves sleep.

In addition to attenuating inflammatory effects and metabolic disorders, improving sleep may be another way to affect cardiovascular health. Our results found that the intake of milk and eggs in the evening helps to reduce CVD mortality. As the precursor of serotonin and melatonin, milk-rich tryptophan has been shown to play a major role in sleep/wake and cortical activity and contributes to promoting sleep (48–50). These studies provided the potential mechanism and evidence for the association of higher milk consumption in the evening and lower mortality of CVD in this study. Moreover, taking egg protein hydrolyzate before sleep also has been shown to improve sleep quality (51, 52), which may be another reason to reduce adverse effects of sleep disorder after eating eggs in the evening.

Moreover, the association between foods consumption time and CVD mortality was improved but not statistically protective after switching red and orange vegetable and egg intake time points, which may also be explained by lower energy intake in the morning caused by the excessive single red and orange vegetable intake and the high energy intake in the evening caused by excessive egg intake in the food substitution analysis. Therefore, it is suggested that we should consider the dietary quality, quantity, and time of food intake in all direction so as to avoid the nutritional imbalance caused by excessive attention to one part, which results in adverse consequences.

Based on our results above, we put forward the following suggestions for people with sleep disorders on the basis of keeping energy distribution balanced and reasonable in all three meals. Carbohydrates are best eaten in the forenoon, and in the selection of high-carbohydrate foods types, it is highly recommended to choose high-fiber-carbohydrate foods, such as starchy vegetables rather than high-energy carbohydrate-type

foods, such as refined grains. High fiber-carbohydrate foods combined with red and orange vegetables rich in lycopene and carotenoids for breakfast provide energy in a nutritionally balanced manner and are more beneficial to combat the increased levels of oxidative stress and inflammation caused by sleep disorders. Fermented dairy products should be selected for forenoon snacks, which not only have higher nutritional value but also have a satiety effect to reduce subsequent energy intake. For dinner, a moderate amount of high-quality protein meals, such as eggs, should be used to replenish energy and increase satiety after meals. While reducing the adverse effects of excessive energy intake on sleep, a moderate intake of tryptophan-rich milk can also help improve sleep.

The advantages and limitations of our study are presented in the following. First, it is the first time to explore the relationship between the consumption time of foods and CVD mortality among individuals with sleep disorders. Then, consistent results were observed after adjusting lots of important confounding factors and conducting multiple sensitivity analyses in the process of research. Besides, the NHANES provides the nationally representative data in the USA, such as dietary intake and lifestyle factors. In addition, our research has certain limitations. First, the dietary data were only obtained through the 24-h diet recall on 2 days within 2 weeks, which cannot reflect long-term exposure. Second, the status of sleep condition was assessed by a single sleep disorder questionnaire, which is highly subjective and less accurate, compared with a real-time sleep monitoring equipment. In addition, other factors related to sleep disorders that might not be aware of or measured can also bring about bias.

Conclusion

There are some important implications in our findings. People with sleep disorders are under a disrupted biological rhythm, which indicates that ill-rested people should pay more attention to eating habits due to their worse health condition. Accumulating evidence has suggested that food consumption time is no less important than quantity and quality for maintaining health. Based on the above results, we believe that the specific food consumption time play an important role in changing the risk of CVD death among individuals with sleep disorders. Therefore, adjusting the intake time of different food groups is of importance in the prevention and treatment of CVD and should be integrated into the nutritional recommendation.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: https://wwwn.cdc.gov/nchs/nhanes/Default.aspx.

Ethics statement

The studies involving human participants were reviewed and approved by the NCHS Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

Authors contributions

YL, TH, and WW designed the research and had primary responsibility for final manuscript. JZ and YZ performed all statistical analyses and wrote the manuscript. LL, XW, and XX conducted the data review. All authors contributed to conduct literature research and providing corresponding suggestion, and 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.2022.967996/full#supplementary-material

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Association between dietary intake of one-carbon metabolism nutrients and hyperglycemia in coal-burning fluorosis areas of Guizhou, China

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Background and aims: There are limited studies describing the association between dietary intake of one-carbon metabolism nutrients and hyperglycemia. The present study aimed to investigate the association of habitual dietary intake of one-carbon metabolism nutrients with hyperglycemia in a fluorosis area in China, and explored the interaction between these nutrients and fluorosis related to hyperglycemia.

Method: In a cross-sectional study, we recruited 901 villagers, ages ranging from 18–75, in Guizhou Province. Dietary data and other covariate data were obtained through an interviewer-administered questionnaire. We collected venous blood samples from participants who had fasted for one night to obtain fasting blood glucose levels and we categorized dietary intake of betaine, total choline, methionine, folate, vitamins B_6 and B_{12}, and choline subclasses into quartiles (Q1–Q4). The lowest quartile (Q1) served as the reference group. An unconditional logistic regression model was used to evaluate the protective effects of a dietary intake of one-carbon nutrients against hyperglycemia. We calculated Odds Ratios (ORs) with 95% confidence intervals (CIs). A presence or absence of fluorosis subgroup analysis was performed to determine the potential effect of fluorosis on hyperglycemia.

Result: After adjusting for potential confounding factors, we found that a greater intake of dietary vitamin B_6, total choline and methyl-donor index was inversely associated with the occurrence of hyperglycemia (P-trend <0.05). However, there were no significant associations between hyperglycemia and the dietary intake of folate, vitamin B_{12}, methionine, and betaine. As for the choline subgroups, it showed that the dietary intake of free choline, phosphatidylcholine, and glycerol phosphatidylcholine was negatively correlated with the occurrence of hyperglycemia ($P < 0.05$). In contrast, there was no statistical association between dietary phosphatidylcholine and sphingomyelin and hyperglycemia (all $P > 0.05$). The results of subgroup

analysis showed that dietary intake of folate, vitamin B_6, total choline, free choline, glycerol phosphorylcholine, and phosphocholine had a protective effect against the occurrence of hyperglycemia in the non-fluorosis subgroup, although no effects were observed in the fluorosis subgroup. There were significant interactions between these nutrients and fluorosis (P = 0.010–0.048).

Conclusion: The study demonstrated that higher dietary intake of vitamin B_6, total choline, methyl-donor index, free choline, glycerol phosphorylcholine, and phosphocholine in choline compounds were associated with a lower incidence of hyperglycemia. Moreover, the associations were modified by the presence or absence of fluorosis. Further investigation is needed to test the association in large-scale follow-up studies.

KEYWORDS

one-carbon metabolism, hyperglycemia, betaine, choline, methionine, folate, vitamin B_6, vitamin B_{12}

Introduction

Hyperglycemia is an asymptomatic disease involving the development of cardiovascular problems and diabetes. According to the 2017 Global Burden of Disease study, about 1.02 million died from diabetes worldwide; 15.09 million died of cardiovascular and cerebrovascular diseases, among which about 3.54 million died of hyperglycemia (1). The global prevalence of diabetes is estimated at 9.3% (463 million) in 2017 and is predicted to increase to 10.2% (578.8 million) by 2030 (2). Therefore, hyperglycemia is a notably high risk chronic disease (3, 4). Hyperglycemia is preventable through healthy eating, maintaining a normal weight, and physical activity. An intervention study has shown that nutritional supplementation with folic acid, vitamin B_{12}, vitamin B_6, choline, and protein altered the cardiometabolic risk profiles of older adults (5). Therefore, this has aroused considerable interest in identifying the association between one-carbon metabolism nutrients and hyperglycemia.

One-carbon metabolites are a series of interconnected metabolic pathways, including the folate and methionine cycles, which provide methyl groups for the synthesis of DNA (6, 7). DNA methylation plays a key role in cardiovascular disease (CVD) and diabetes. The function of one-carbon metabolites and the availability of adequate methyl groups depend on essential nutrients, such as folate, methionine, choline, betaine, vitamin B_6, and vitamin B_{12} (8, 9). Many studies have explored the effect of one-carbon metabolism nutrients on diabetes and CVDs (10, 11). However, most studies have drawn inconsistent conclusions whether hyperglycemia, a risk factor for diabetes and CVDs, is affected by one-carbon metabolism nutrients (12–16). Moreover, evidence from choline and betaine is limited. Studies reported hyperglycemia was associated with choline and betaine in Norway (17) and Newfoundland population (18). However, these associations have not been established in Canadian women (19) and American (20). These studies suggested that the results were inconsistent across countries because of dietary habits. Therefore, it needs to be clarified the association between one-carbon metabolism nutrients and hyperglycemia among Chinese. However, no studies have explored the association of habitual dietary intake of choline and betaine and with risk of hyperglycemia in China.

Previous studies observed a positive effect of fluoride on the incidence and prevalence of diabetes in the USA and Canada (21, 22). It was reported that a higher intake of one-carbon metabolism nutrients was associated with a lower occurrence of fluorosis (23). The interaction between one-carbon metabolism nutrients and fluorosis related to glucose levels needs to be clarified.

The present study aims to comprehensively investigate the associations between dietary intake of six one-carbon metabolism nutrients (betaine, choline, methionine, folate, vitamin B_6 and vitamin B_{12}) and hyperglycemia among a Chinese population in areas known for coal-burning fluorosis. The study also explores whether the associations between one-carbon metabolism nutrient intake and hyperglycemia are modified by the presence or absence of fluorosis.

Methods

Study population

We used a cross-sectional study design conducted in Zhijin County, Guizhou province, China. A two-stage cluster sampling method was used in this study. The three towns of Chadian, Chengguang, and Puweng were selected by simple random

sampling approach from 10 towns in Zhijin County. From each of these towns, we selected four villages at random. The 12 villages were Dazai, Ganhe, Gaofeng, Guihua, Guohua, Hehua, Hualuo, Jiangyan, Shangzai, Yutang, Xianfeng, and Moda. Participants were recruited through village doctors and the Center for Disease Control and Prevention from each selected village. Participants diagnosed with either dental fluorosis or skeletal fluorosis were identified as fluorosis patients. The diagnoses of dental fluorosis (WS/T208-2011, China) and skeletal fluorosis (GB 16396–1996) were performed by a specialist from the CDC. A detailed description of the method is described in our previous studies (24, 25). We used the following participant inclusion criteria: (1) participants must have lived in Zhijin County for at least 10 years; and (2) be between 18 and 75 years old. We used the following exclusion criteria: (1) Participants had a prior history of cancer, coronary heart disease, stroke, gout, or kidney disease; (2) Participants' whose eating habits had changed significantly over the past 5 years; (3) Participants who currently had a chronic medical condition that may affect their eating habits, such as cancer, gout or hypertension; (4) Participants with incomplete questionnaire information. The final analyses involved 901 subjects. We obtained post-fasting blood data from all the 901 participants who attended the interview. All of the subjects in this study were provided written informed consent before the interview. This study protocol was approved by the Ethics Committee of Zunyi Medical University.

Data collection pertaining to diet and lifestyle

The data that related to sociodemographic characteristics (age, sex, marital status, education level, average yearly household income, ethnicity, smoking status, and alcohol consumption) and disease history (cancer, endemic fluorosis, coronary heart disease, stroke, gout, and kidney disease) were collected by questionnaires. Smokers were defined as those who smoke cigarettes $\geq$1/day for at least 1 year. Alcohol drinkers were defined as those who drink $\geq$50 g alcohol/day for at least 1 year.

Dietary nutrient intake information was collected through a valid and reliable food-frequency questionnaire (FFQ). The participants gave frequency of consumption information (never, daily, weekly, monthly, yearly) for each food item over the previous year. The 75-item FFQ involved seven categories including fruits, animal products, cereals, beans, vegetables, algae and nuts, beverage drinks and soups. Pictures of food portion sizes were offered to help participants to estimate the quantity of food consumption. Then portion size of each food was converted to grams. Daily dietary intakes of one-carbon metabolism nutrients were estimated by multiplying the consumption frequency and portion size of each food by the nutrient content based on the Chinese Food Composition Database. We used the Chinese food composition database to calculate the estimated intake of vitamin B_6, B_{12}, folate, and methionine (26). In addition, the USDA choline content database was used to calculate the estimated intake of betaine, choline, and choline subclasses, including free choline, glycerol phosphorylcholine, phosphocholine, phosphatidylcholine, and sphingomyelin (27). Total choline intake was calculated as the sum of choline intake from glycerophosphocholine, phosphocholine, phosphatidylcholine, sphingomyelin and free choline. Previous studies have shown high correlations between USDA and Chinese database estimates for common nutrient intakes. For example, $r > 0.90$ for B vitamins and methionine indicates the validity of using the USDA database in the Chinese population to evaluate the intake of choline and betaine (28).

Measurement and detection

Waist Circumference (WC), weight, and body height were measured following a standardized protocol, and body mass index (BMI) was calculated as weight divided by height^2 (kg/m^2). Weight was measured to the nearest 0.1 kg, and height and WC were measured to the nearest 0.1 cm. Venous blood samples were collected from 7 to 9 am following an overnight fast of at least 8 h. A drop of venous blood was used for bedside measurement of blood glucose, using the Accu-Chek Active glucometer (Roche Diagnostics GmbH, Germany). According to the World Health Organization (WHO) (29), patients with fasting glucose $\geq$6.1 mmol/L were diagnosed hyperglycemia.

Statistical analysis

All statistical analyses were performed using SPSS software (version 17.0). All *P*-values were two-sided, and the level of significance was set at 0.05. Continuous variables were reported as means and standard deviations or median values, while categorical variables were expressed as numbers and percentages. Analyses of two independent sample *t*-tests were used to analyze the normally distributed mean differences between the participants' characteristics. The *Mann-Whitney* test was used to compare the median consumption levels, which did not have a normal distribution. Chi square ($\chi 2$) tests were used to compare the among dietary frequency categories between hyperglycemic and normal blood glucose level participants. A logistic regression model was applied to estimate the association between dietary intake of one-carbon metabolism nutrients and hyperglycemia. Odds Ratios (ORs) with 95% confidence intervals (95% CIs) were reported for each quartile of one-carbon metabolism nutrient intake. The first quartile was considered as a reference. The multivariable models were adjusted for age, BMI, sex, marital status, family income, education level, smoking status, alcohol consumption, total energy intake, and dietary fiber intake. Moreover, all six

nutrients were placed in a single model, with adjustment of the risk factors listed above. Because one-carbon metabolism–related nutrients are thought to influence disease risk by donating methyl groups for methylation reactions (30, 31), we also calculated a "methyl-donor index" as a composite measure of dietary methyl intake by standardizing the nutrient intake levels on the log-scale ([nutrient value – mean] / standard deviation) then summed across all six nutrients, as described previously (32). The methyl-donor index also was adjusted for total calorie intake using the residual method then categorized into quartile. Trend tests were performed by using the sequential values of the quartiles of dietary one-carbon metabolism nutrients as a continuous variable. Moreover, we evaluated if associations were modified by the presence or absence of fluorosis. The multivariable models were adjusted for age, BMI, and gender. Trend tests were conducted by entering the ordinal values of the quartile of dietary one-carbon metabolism nutrients as continuous variables in the models.

Results

In this cross-sectional study, we collected blood glucose level data from 901 subjects including 417 males (46.28%) and 484 females (53.27%). According to blood glucose levels, they were divided into a hyperglycemic group (n = 184, 20.42%) and a normal group (n = 717, 79.58%). The general information and measurement indicators are shown in Table 1. The average age of the participant was 49 years old, and the average age of the hyperglycemic group (52.99 ± 12.76) was higher than the normal glucose level group (48.59 ± 13.01). There was a significant difference in age, BMI, and waist circumference between the two groups ($P < 0.001$–$P = 0.005$), although the differences in gender, education level, ethnicity, per capita annual income, marital status, smoking, alcohol consumption, height, weight and fluorosis between the two groups were not observed ($P > 0.05$).

Intake of folate, vitamin B_6, total choline and methyl-donor index in the hyperglycemia group was lower than that in the normal blood glucose level group ($P = 0.035$, $P = 0.011$, $P = 0.006$, $P = 0.002$, respectively). As for the choline subclass, the intake of free choline, glycerol phosphorylcholine, phosphatidylcholine, and phosphocholine had significant differences between the two groups (all $P < 0.05$). Dietary choline intake of the hyperglycemic group was lower than the normal glucose level group. However, no differences in energy intake, vitamin B_{12}, methionine, betaine and sphingomyelin intake between the two groups were observed ($P = 0.074$–0.384). The overall intake of one-carbon metabolism nutrients was generally lower in the hyperglycemic group (Table 2).

The ORs (95% CI) for the occurrence of hyperglycemia according to quartiles of one-carbon metabolism nutrient intake and methyl-donor index are presented in Table 3. After adjusting for age, sex, marital status, education level, average yearly household income, ethnicity, smoking status, and alcohol consumption, we found a greater intake of dietary vitamin B_6 and total choline were inversely associated with the occurrence of hyperglycemia. The adjusted OR (95% CI) in the highest quartile compared with the lowest was 0.599 (0.365, 0.984) for total choline and 0.579 (0.349, 0.961) for vitamin B_6. The inverse associations remained after further adjustments for total energy and dietary fiber. There also was a suggestion that methyl-donor index was inversely associated with the occurrence of hyperglycemia, with adjustment for potential confounding factors ($P = 0.011$). However, there were no significant associations between the intake of folate, vitamin B_{12}, methionine, betaine and hyperglycemia after adjusting for non-dietary and dietary factors.

The OR (95% CI) for the occurrence of hyperglycemia according to quartiles of five choline intakes subclasses is presented in Table 4. In the unadjusted model, compared with the lowest quartile, the ORs (95% CIs) of hyperglycemia for the highest quartile intakes of free choline, glycerol phosphatidylcholine, and phosphocholine were 0.414 (0.259, 0.661), 0.490 (0.306, 0.783), and 0.420 (0.260, 0.678), respectively. The observed inverse associations remained after further adjustment for potential confounding factors. In contrast, no statistical association between dietary intake of phosphatidylcholine and sphingomyelin and hyperglycemia was observed ($P > 0.05$).

We further assessed the associations between one-carbon metabolism nutrients and hyperglycemia across subgroups stratified by the presence or absence of fluorosis, shown in Tables 5, 6. We observed that the nutrients folate, vitamin B_6, total choline, free choline, glycerol phosphorylcholine, and phosphocholine had a protective effect against the occurrence of hyperglycemia in the non-fluorosis subgroup. There were inverse associations of the above nutrients with hyperglycemia in the non-fluorosis subgroup ($P < 0.05$), but not in the fluorosis subgroup ($P > 0.05$). There were significant interactive effects for the above nutrient intakes with fluorosis (*P-interaction* = 0.010 P=0.048). There was no significant interactive effect for the other nutrients betaine, methionine, vitamin B_{12}, phosphatidylcholine, sphingomyelin, and methyl-donor index with fluorosis (*P-interaction* = 0.077 to 0.527).

Discussion

In the present study, we found the intake of vitamin B_6, total choline, methyl-donor index, free choline, glycerol phosphorylcholine, and phosphocholine were inversely associated with the occurrence of hyperglycemia in Guizhou province, China. Additionally, we also observed that there were interactions between one carbon

TABLE 1 The general information of participants.

Characteristics	Total population NO.(%)/Median	Hyperglycemia ($n = 184$)	Normal blood glucose ($n = 717$)	$t/X^2/Z$	*P*-value
**Age, year	49.49	52.99 ± 12.76	48.59 ± 13.01	−4.109	<0.001
Gender, (%)				2.147	0.143
Men	417 (46.28)	94 (51.10)	325 (45.00)		
Women	484 (53.27)	90 (48.90)	394 (55.00)		
Marital status, (%)				4.355	0.113
Married or cohabiting	756 (84.09)	152 (82.60)	604 (84.20)		
Divorced or separated	96 (10.67)	26 (14.10)	70 (9.70)		
Unmarried	47 (5.22)	6 (3.30)	41 (5.70)		
Education, (%)				−1.539	0.124
Illiteracy	425 (47.27)	94 (51.10)	331 (46.20)		
Primary school	300 (33.37)	63 (34.20)	237 (33.10)		
Secondary school	131 (14.57)	19 (19.30)	112 (15.60)		
High school or above	43 (4.78)	8 (4.30)	35 (4.80)		
Ethnicity, (%)				0.733	0.693
Han	510 (56.70)	101 (54.90)	409 (57.20)		
Buyei	80 (8.90)	15 (8.20)	65 (9.10)		
Other ethnicity	309 (34.40)	68 (37.00)	241 (33.70)		
Income, (yuan/capita/year), (%)				−0.175	0.861
≤1,000	177 (19.68)	41 (22.30)	136 (19.00)		
1,001–2,000	257 (28.58)	48 (26.00)	209 (29.20)		
2,001–4,000	242 (26.91)	47 (25.50)	195 (27.20)		
4,001–6,000	116 (12.90)	25 (13.60)	91 (12.70)		
>6,000	107 (11.90)	23 (12.50)	84 (11.70)		
Smoker[a], (%)	365 (40.60)	82 (44.60)	283 (39.60)	1.508	0.219
Alcohol drinker[b], (%)	278 (30.82)	53 (28.80)	225 (31.40)	0.502	0.479
**Height, cm	155.72	155.35 ± 8.26	155.81 ± 8.07	0.696	0.486
*Weight, kg	55.00	56.05 (48.30, 65.37)	54.50 (49.50, 61.10)	−1.709	0.087
*Body mass index, kg/m^2	22.53	23.66 (20.57,27.16)	22.46 (20.26,25.10)	−2.837	0.005
*Waist circumference, cm	77.00	79.75 (72.00, 88.75)	77.00 (70.00, 84.00)	−3.197	0.001
Fluorosis	657 (72.91)	131 (71.20)	526 (73.40)	0.348	0.555

**Continuous normal data were expressed as Mean ± SD, *Skewness data were represented by Median (25th, 75th). [a]Smokers were defined as smoking cigarettes ≥1/day on average for at least 1 year. [b]Alcohol drinkers were defined as having drunk ≥50 g/day for one consecutive year or more. SD, Standard Deviation.

metabolic nutrients and fluorosis, such as vitamin B_6, total choline, free choline, glycerol phosphorylcholine, and phosphocholine.

Association between choline and betaine intake and hyperglycemia

Hyperglycemia is an important risk factor for diabetes and CVDs. Limited studies evaluated the association of choline and betaine with hyperglycemia and suggested that the results may be inconsistent due to participants from different countries had different dietary habits (17–20). Previous studies reported there was a positive effect of fluoride on the incidence and prevalence of diabetes (21, 22). It is well known that the interaction between nutrition and environment plays an important role in disease. However, whether there is a different relationship between one-carbon metabolism nutrients and hyperglycemia in coal-burning fluorosis areas and how does fluorosis modify the association needs to be evaluated. Therefore, we conducted this study in fluorosis area. To our knowledge we first found protective associations of total choline, free choline, glycerol phosphorylcholine, and phosphocholine with the occurrence of hyperglycemia in Chinese population. Furthermore, these associations were modified by fluorosis. Studies on the association between dietary intake of choline and betaine

TABLE 2 Comparison of energy, one-carbon metabolism nutrients intake between hyperglycemia and normal blood.

Items	Hyperglycemia ($n = 184$)	Normal blood glucose ($n = 717$)	Z/t	P-value
	Median (25th, 75th)	Median (25th, 75th)		
*Energy (kcal/d)	2,718.20 (2,107.35, 3,446.64)	2,521.18 (1,966.43, 3,355.63)	−1.786	0.074
*Folate (ug/d)	403.39 (316.08, 521.25)	439.50 (336.62, 561.97)	−2.104	0.035
*Vitamin B_6 (mg/d)	1.44 (1.07, 1.86)	1.57 (1.19, 1.99)	−2.534	0.011
*Vitamin B_{12} (ug/d)	1.98 (0.90, 3.04)	2.00 (1.11, 3.18)	−1.145	0.252
*Methionine (mg/d)	2,040.94 (1,495.73, 2,586.20)	2,088.86 (1631.59, 2596.95)	−1.080	0.280
*Betaine (mg/d)	92.21 (56.97, 148.1)	96.98 (59.34, 167.19)	−0.871	0.384
*Total choline (mg/d)	168.49 (118.91, 253.48)	194.03 (134.49, 285.12)	−2.759	0.006
*Free choline (mg/d)	43.53 (32.25, 61.95)	50.62 (37.32, 72.62)	−3.795	<0.001
*glycerol *phosphorylcholine (mg/d)	16.69 (12.50, 22.71)	19.60 (15.27, 26.28)	−4.275	<0.001
*Phosphocholine (mg/d)	7.66 (5.02, 11.41)	9.54 (6.33, 14.06)	−3.964	<0.001
*Phosphatidylcholine (mg/d)	91.80 (54.58, 153.29)	103.99 (63.18, 162.28)	−2.010	0.044
*Sphingomyelin (mg/d)	4.09 (1.93, 7.51)	4.78 (2.46, 8.27)	−1.718	0.086
**methyl-donor index[a]	−1.70 ± 9.39	0.55 ± 8.56	3.118	0.002

The intakes of one-carbon metabolism nutrition and choline subclass were adjusted by the residual method. P25 and P75 represent the 25th and 75th percentiles respectively. SD, Standard Deviation. d, day. *Mann-Whitney test was used to compare median intake levels in the hyperglycemic and the normal group. **Two independent sample t-tests were used to analyze mean intake levels in the hyperglycemic and the normal group. Total choline intake is the sum of phosphocholine, free choline, glycerol phosphorylcholine, phosphatidylcholine, and sphingomyelin. [a]Sum over the six nutrients of z scores of log of nutrient intake.

and hyperglycemia are limited. Some studies explored the relationship of dietary or blood serum choline and betaine with glucose and type 2 diabetes. A cross-sectional study involving 2,394 subjects reported dietary choline intake was negatively associated with fasting blood glucose levels in Newfoundland (18). A cohort study involving 2,332 men (33) found the highest choline and phosphatidylcholine intake was associated with a 25 and a 41% reduction, respectively, in the risk of type 2 diabetes, compared with the lowest quartile in Finland. Moreover, a randomized clinical trial, reported that compared with placebo, betaine tended to reduce fasting glucose levels but had no effect on glycemia and insulin sensitivity (34). It was indicated that betaine may prevent hyperglycemia, even be a potential therapy for the progression of diabetes-induced hyperglycemia. However, choline can be transformed into betaine and phosphatidylcholine through various chemical reactions in the body, which jointly participate in one-carbon metabolism and affect blood glucose levels. More studies are needed to confirm the association between choline, betaine and blood glucose levels.

Association between vitamin B_6 and vitamin B_{12} intake and hyperglycemia

Vitamin B_6 and B_{12} are important co-factors in the one-carbon metabolic pathway. Jin et al. (35) reported that vitamin B_6 and B_{12} intake was inversely associated with the risk of diabetes in the National Health and Nutrition Examination Survey (NHANES) of 2007–2016. Compared with the lowest quartile, the ORs (95% CIs) of diabetes for the highest quartile intake of vitamin B_6 was 0.61 (0.42–0.89), the OR (95% CI) of diabetes for the third quartile of dietary vitamin B_{12} was 0.76 (0.60–0.97). A linear inverse relationship was found between vitamin B_{12} and diabetes, and a nonlinear inverse relationship was found between dietary vitamin B_6 and diabetes. Several small studies explored the association between vitamin B_6 and diabetes complications and observed B_6 may play a protective role against various diabetes complications (36, 37). Consistent with these results, we also found that dietary intake of vitamin B_6 was a protective factor against the occurrence of hyperglycemia. Unlike vitamin B_6, very few studies have investigated the independent role of vitamin B_{12} in glucose metabolism. China Stroke Primary Prevention Trial longitudinal analyses showed no association between baseline levels of vitamin B_{12} and a new-onset of diabetes or changes in fasting blood glucose levels (38). Zhu et al. (13) observed no association between the intake of vitamin B_{12} and diabetes incidence. Our results on the effect of vitamin B_{12} on hyperglycemia are consistent with these observations. However, a follow-up south Indian study involving 1,500 individuals (12) reported that the levels of vitamin B_{12} decreased with increasing severity of glucose tolerance. Similar results have been reported in another study (39). The inconsistent results could be attributed to the patients countries. Additionally, baseline serums reflect short-term intake levels, whereas FFQ-based surveys on behavior long-term intake levels. More studies combining dietary intake and blood serum levels are needed to investigate the association between vitamin B_6/B_{12} and blood glucose.

TABLE 3 Odds Ratios (*ORs*) and 95% confidence intervals (95%*CIs*) of hyperglycemia according to quartiles of one-carbon metabolism intake.

Items	Quartiles of one-carbon metabolism nutrients intake				*P*-value
	Q1	Q2	Q3	Q4	
Folate (ug/d)	268.23	381.82	486.97	669.68	
OR (95% CI)	1	0.927 (0.597, 1.440)	0.763 (0.485, 1.199)	0.659 (0.414, 1.050)	0.056
OR (95% CI)[1]	1	0.991 (0.624, 1.575)	0.790 (0.491, 1.272)	0.707 (0.428, 1.168)	0.118
OR (95% CI)[2]	1	0.988 (0.621, 1.572)	0.777 (0.482, 1.253)	0.710 (0.429, 1.174)	0.121
Vitamin B_6 (mg/d)	0.95	1.36	1.76	2.35	
OR (95% CI)	1	0.861 (0.555, 1.335)	0.790 (0.507, 1.232)	0.550 (0.342, 0.885)*	0.012
OR (95% CI)[1]	1	0.852 (0.538, 1.349)	0.774 (0.484, 1.240)	0.579 (0.349, 0.961)*	0.037
OR (95% CI)[2]	1	0.841 (0.531, 1.333)	0.780 (0.487, 1.250)	0.575 (0.346, 0.956)*	0.038
Vitamin B_{12} (ug/d)	0.66	1.54	2.52	4.16	
OR (95%CI)	1	0.628 (0.395, 0.998)*	0.834 (0.537, 1.295)	0.730 (0.465, 1.146)	0.507
OR (95%CI)[1]	1	0.653 (0.403, 1.057)	0.873 (0.547, 1.393)	0.774 (0.478, 1.254)	0.681
OR (95%CI)[2]	1	0.653 (0.402, 1.059)	0.877 (0.549, 1.400)	0.777 (0.479, 1.261)	0.695
Methionine (mg/d)	1,297.23	1,837.71	2„309.96	3,042.96	
OR (95%CI)	1	0.723 (0.458, 1.143)	0.785 (0.500, 1.231)	0.834 (0.533, 1.304)	0.294
OR (95%CI)[1]	1	0.775 (0.481, 1.251)	0.847 (0.526, 1.364)	0.917 (0.562, 1.497)	0.421
OR (95%CI)[2]	1	0.783 (0.485, 1.264)	0.847 (0.525, 1.366)	0.942 (0.576, 1.540)	0.467
Betaine (mg/d)	29.03	76.53	122.34	262.66	
OR (95%CI)	1	1.054 (0.673, 1.649)	0.968 (0.616, 1.523)	0.773 (0.483, 1.237)	0.189
OR (95%CI)[1]	1	1.057 (0.662, 1.688)	0.931 (0.576, 1.507)	0.790 (0.480, 1.302)	0.223
OR (95%CI)[2]	1	1.078 (0.674, 1.724)	0.944 (0.583, 1.530)	0.810 (0.491, 1.337)	0.220
Total choline (mg/d)	100.21	159.50	225.35	376.13	
OR (95%CI)	1	0.720 (0.462, 1.121)	0.696 (0.446, 1.086)	0.567 (0.457, 0.899)*	0.015
OR (95%CI)[1]	1	0.718 (0.452, 1.139)	0.693 (0.434, 1.105)	0.599 (0.365, 0.984)*	0.032
OR(95%CI)[2]	1	0.723 (0.455, 1.148)	0.695 (0.435, 1.109)	0.601 (0.365, 0.988)*	0.032
Methyl-donor index[a]	−9.7251	−2.2502	3.2221	9.8571	
OR (95%CI)	1	0.818 (0.530, 1.233)	0.508 (0.311, 0.832)**	0.666 (0.406,1.094)	0.002
OR (95%CI)[1]	1	0.783 (0.498, 1.352)	0.659 (0.410, 1.059)	0.809 (0.497, 1.317)	0.010
OR(95%CI)[2]	1	0.779 (0.495, 1.227)	0.505 (0.308, 0.827) **	0.671 (0.407, 1.104)	0.011

Q1 was used as the reference, and OR (95%) was unadjusted.OR (95%); [1]adjusted for age, gender, BMI, marital status, family income, smoking status, and alcohol consumption. OR (95%); [2]further adjusted for total energy intake and dietary fiber. *$P < 0.05$. [a]Sum over the six nutrients of z-scores of log of nutrient intake.

Association between folate and methionine intake and hyperglycemia

A number of studies have examined the role of folate on glucose and type 2 diabetes, though the results have been inconsistent. In a meta-analysis of 29 randomized controlled trials (RCTs), Lind et al. (14) found that folate supplementation have no overall effect on fasting glucose levels. Recently, Akbari et al. (40) conducted a meta-analysis on RCTs and also observed no significant changes in fasting blood glucose and HbA1c levels among participants with metabolic diseases after folate supplementation, although folate supplementation resulted in decreased plasma insulin levels and insulin resistance. The present study was consistent with the result of RCTs. However, there are two studies that found an inverse association between dietary folate and diabetes risk in Korean (41) and Japanese (42) adults. The Korean study observed that higher dietary folate intake was associated with a lower risk of developing type 2 diabetes for women but not men (41). However, the present study showed no significant association between folate intake and hyperglycemia and no gender difference (Supplementary Tables 1, 2). The reasons for the different results may relate to the adjustment of confounding factors and the use of folate supplements. Additionally, we found that methionine intake was not associated with the occurrence of hyperglycemia. There are few studies methionine and blood glucose. More epidemiological studies are needed to clarify the association between methionine and hyperglycemia.

TABLE 4 Odds Ratios (*ORs*) and 95% confidence intervals (95%*CIs*) of hyperglycemic according to quartiles of five choline-containing compounds intake.

Items	Quartiles of five choline-containing compounds intake				*P*-value
	Q1	Q2	Q3	Q4	
Free choline (mg/d)	29.14	42.57	57.45	91.27	
OR (95%CI)	1	0.602 (0.390, 0.930)*	0.518 (0.332, 0.930)**	0.414 (0.259, 0.661)**	0.001
OR (95%CI)[a]	1	0.625 (0.397, 0.984)*	0.474 (0.294, 0.762)**	0.419 (0.255, 0.690)**	0.002
OR (95%CI)[b]	1	0.635 (0.403, 1.002)	0.477 (0.296, 0.768)**	0.425 (0.258, 0.700)**	0.002
Glycerophosphoryl choline (mg/d)	11.30	16.79	21.88	31.42	
OR (95%CI)	1	0.955 (0.627, 1.454)	0.454 (0.282, 0.731)*	0.490 (0.306, 0.783)**	<0.001
OR (95%CI)[a]	1	0.941 (0.605, 1.462)	0.409 (0.247, 0.677)**	0.485 (0.294, 0.801)**	0.001
OR (95%CI)[b]	1	0.941 (0.604, 1.464)	0.407 (0.245, 0.675)**	0.496 (0.300, 0.821)**	0.002
Phosphocholine (mg/d)	4.28	7.52	10.87	17.91	
OR (95%CI)	1	0.771 (0.502, 1.182)	0.565 (0.361, 0.886)*	0.420 (0.260, 0.678)**	<0.001
OR (95%CI)[a]	1	0.721 (0.459, 1.132)	0.506 (0.313, 0.818)**	0.443 (0.266, 0.736)**	0.001
OR (95%CI)[b]	1	0.725 (0.461, 1.139)	0.508 (0.314, 0.823)**	0.447 (0.268, 0.743)**	0.001
Phosphatidylcholine (mg/d)	44.41	82.11	124.60	223.56	
OR (95%CI)	1	0.792 (0.506, 1.239)	0.766 (0.488, 1.200)	0.706 (0.447, 1.114)	0.116
OR (95%CI)[a]	1	0.792 (0.497, 1.262)	0.750 (0.468, 1.204)	0.773 (0.474, 1.261)	0.177
OR (95%CI)[b]	1	0.794 (0.498, 1.265)	0.752 (0.468, 1.207)	0.765 (0.469, 1.253)	0.175
Sphingomyelin (mg/d)	1.28	3.53	6.37	11.83	
OR (95%CI)	1	0.880 (0.565, 1.371)	0.763 (0.485, 1.199)	0.702 (0.443, 1.112)	0.470
OR (95%CI)[a]	1	0.986 (0.619, 1.572)	0.814 (0.506, 1.308)	0.767 (0.470, 1.253)	0.594
OR (95%CI)[b]	1	0.989 (0.620, 1.577)	0.818 (0.508, 1.317)	0.775 (0.474, 1.267)	0.617

Q1 was used as the reference, and OR (95%) was unadjusted.OR (95%); [a]Adjusted for age, gender, BMI, marital status, family income, smoking status, and alcohol consumption. OR (95%); [b]Further adjusted for total energy intake and dietary fiber. *$P < 0.05$, **$P < 0.01$.

Underlining mechanisms

The effect of one-carbon metabolism nutrients on hyperglycemia may be partly related to DNA methylation in epigenetics. DNA methylation during glucose metabolism was implicated in the pathogenesis of type 2 diabetes (43–45). Deficiency or excess of nutrients can affect one-carbon metabolism, which changes the availability of S-adenosyl methionine (SAM) in the methionine cycle and interferes with DNA and histone methylation patterns (46). holine supplementation (1 mM) increased global DNA methylation and DNA methyltransferase expression in both low-glucose (5 mM) and high-glucose (35 mM) conditions. Choline supplementation increased the expression of peroxisomal acyl-coenzyme A oxidase 1 (ACOX1), which mediates fatty acid β-oxidation, especially in high-glucose conditions. High-glucose exposure increased the transcription of the gluconeogenic gene phosphoenolpyruvate carboxykinase (PEPCK), while choline supplementation mitigated increase. Compared to HepG2 cells, the placenta-derived BeWo cells were relatively unresponsive to either high-glucose or high-choline treatment (47). In a word, choline and glucose interacted to affect macronutrient metabolic genes, yet there was no indication that choline may worsen glycemic control in these *in vitro* human cell culture models. Another mechanism may be related to oxidative stress. Oxidative stress leads to impaired glucose uptake in muscle and fat cells and decreases insulin secretion from beta cells (48, 49). Mitochondrial respiration is the major cellular source of reactive oxygen species (ROS), and this production is balanced by through antioxidant systems superoxide dismutase (SOD). In hyperglycemic states, such as prediabetes and diabetes, ROS can accumulate and lead to non-specific oxidative damage to DNA (50). One-carbon metabolism nutrients can directly scavenge reactive oxygen species and can act as an antioxidant *in vivo* (51). In a word, insufficient intake of dietary one-carbon metabolism nutrients may affect the methylation and of ROS, which may prevent the occurrence of hyperglycemia.

Subgroup analysis

We evaluated the associations whether or not be modified by fluorosis due to this cross-sectional study was conducted in fluorosis area. In the present study, we first observed the interactions between vitamin B_6, total choline, etc and fluorosis. The result showed that the nutrients folate, vitamin

TABLE 5 Odds Ratios (OR) and 95% confidence intervals (95%CIs) of hyperglycemia according to quartiles of one-carbon metabolism nutrients by fluorosis.

	Intake of one-carbon metabolism nutrients					
	Q1	Q2	Q3	Q4	P^a	P^b
Folate (ug/d)						0.041
Fluorosis	1	0.949 (0.561, 1.606)	0.833 (0.478, 1.451)	0.859 (0.486, 1.520)	0.747	
Non-fluorosis	1	1.073 (0.414, 2.777)	0.609 (0.241, 1.540)	0.367 (0.137, 0.984)*	0.012	
Betaine (mg/d)						0.114
Fluorosis	1	1.027 (0.597, 1.764)	1.007 (0.578, 1.754)	1.033 (0.589, 1.813)	0.973	
Non-fluorosis	1	1.126 (0.461, 2.752)	0.957 (0.396, 2.313)	0.398 (0.151, 1.049)	0.085	
Methionine (mg/d)						0.425
Fluorosis	1	0.696 (0.405, 1.195)	0.797 (0.463, 1.372)	0.894 (0.505, 1.582)	0.741	
Non-fluorosis	1	1.137 (0.425, 3.044)	0.892 (0.351, 2.269)	0.882 (0.359, 2.165)	0.281	
Vitamin B_6 (mg/d)						0.039
Fluorosis	1	0.908 (0.542, 1.519)	0.732 (0.419, 1.279)	0.760 (0.430, 1.342)	0.461	
Non-fluorosis	1	0.727 (0.279, 1.892)	0.772 (0.317, 1.880)	0.266 (0.096, 0.733)*	0.005	
Vitamin B_{12}(ug/d)						0.224
Fluorosis	1	0.724 (0.420, 1.250)	0.997 (0.586, 1.696)	0.689 (0.389, 1.220)	0.303	
Non-fluorosis	1	0.439 (0.165, 1.171)	0.572 (0.232, 1.408)	0.922 (0.395, 2.150)	0.396	
Total choline (mg/d)						0.048
Fluorosis	1	0.811 (0.479, 1.373)	0.639 (0.370, 1.105)	0.820 (0.471, 1.429)	0.376	
Non-fluorosis	1	0.534 (0.215, 1.328)	0.674 (0.274, 1.656)	0.236 (0.087, 0.639) *	0.007	
Methyl-donor index [c]						0.077
Fluorosis	1	0.871 (0.522, 1.456)	0.474 (0.261, 0.859)*	0.904 (0.522, 1.567)	0.983	
Non-fluorosis	1	0.603 (0.236, 1.544)	0.436 (0.176, 1.079)	0.241 (0.089, 0.655)**	0.994	

OR (95%), adjusted for age, gender and BMI. [a]P-value for linear trend; [b]P-value for interaction; [c]Methyl-donor index: Sum over the six nutrients of z scores of log of nutrient intake. *$P < 0.05$, **$P < 0.01$.

B_6, total choline, free choline, glycerol phosphorylcholine, and phosphocholine had a protective effect on the occurrence of hyperglycemia in the non-fluorosis subgroup, but not in the fluorosis subgroup. Two studies found that fluoride was significantly and positively associated with increases in both the incidence and prevalence of diabetes (21, 22). Previous animal studies have shown that exposure to high levels of fluoride would decrease insulin mRNA and its secretion from beta-cells, and affect the OGTT (52). Thus, the protective effect hyperglycemia disappeared due to the toxicity of fluorosis. Fluorosis decreased superoxide dismutase (SOD) activity, accompanied by an increase in the generation of superoxide anion and decreased mitochondrial membrane potential in fluoride exposed cells (52). However, one-carbon metabolism nutrients may influence fluorosis by means of their antioxidant properties, as they are well documented antioxidant compounds that reduce the risk of diseases (53, 54). Furthermore, DNA methylation plays an important role in fluorosis (55), one-carbon metabolism nutrients as methyl donors may prevent the change of DNA methylation induced by fluoride. Further studies are warranted to elucidate the competing pathophysiological mechanisms.

Limitations

The present study has several limitations. First, it did not clearly identify the causal relationship between one-carbon metabolism-related nutrients and hyperglycemia. This was in part because of a cross-sectional study design, even though we minimized the potential reverse causation by excluding participants with other diseases. Second, we could not avoid memory recall bias, although we emphasized unbiased investigative techniques and objective data, discrepancies could exist between what answer was given in the questionnaire and real life behaviors. Thirdly, we cannot exclude the influence of fluorosis, but the subgroup analysis showed that the protective effect was observed in non-fluorosis subgroup against the occurrence of hyperglycemia was consistent with our participant group as a whole. Additionally, our findings generalized to brick-tea or drinking water fluorosis affected areas should be with caution due to this study was conducted in coal-burning fluorosis areas. Fourthly, serum levels of the one-carbon metabolism nutrients were not detected because of traumatic, low-cooperative and expensive, but we investigated dietary intake in a non-invasive and low-cost manner using an FFQ.

TABLE 6 Odds Ratios (OR) and 95% confidence intervals (95%CIs) of hyperglycemia according to quartiles of five choline-containing compounds by fluorosis.

Items (mg/d)	Five choline-containing compounds intakes				P_1[a]	P_2[b]
	Q1	Q2	Q3	Q4		
Free choline						0.010
Fluorosis	1	0.613 (0.361, 1.041)	0.581 (0.339, 0.997)*	0.663 (0.382, 1.152)	0.201	
Non-fluorosis	1	0.627 (0.255, 1.542)	0.283 (0.111, 0.725)**	0.115 (0.040, 0.328)**	<0.001	
glycerol phosphorylcholine						0.047
Fluorosis	1	0.942 (0.567, 1.565)	0.438 (0.244, 0.787)**	0.617 (0.353, 1.081)	0.072	
Non-fluorosis	1	0.902 (0.382, 2.127)	0.369 (0.143, 0.955)*	0.262 (0.096, 0.716)**	0.002	
Phosphocholine						0.038
Fluorosis	1	0.761 (0.458, 1.264)	0.585 (0.336, 1.091)	0.630 (0.359, 1.103)	0.114	
Non-fluorosis	1	0.629 (0.243, 1.625)	0.371 (0.146, 0.945)*	0.162 (0.055, 0.473)**	0.001	
Phosphatidylcholine						0.147
Fluorosis	1	0.842 (0.493, 1.438)	0.791 (00.461, 1.357)	0.892 (0.510, 1.558)	0.621	
Non-fluorosis	1	0.631 (0.257, 1.549)	0.574 (0.230, 1.430)	0.440 (0.176, 1.100)	0.062	
Sphingomyelin						0.527
Fluorosis	1	1.017 (0.595, 1.736)	0.906 (0.528, 1.555)	0.727 (0.412, 1.284)	0.418	
Non-fluorosis	1	0.929 (0.387, 2.229)	0.636 (0.255, 1.584)	0.796 (0.327, 1.938)	0.782	

OR (95%): adjusted for age, gender and BMI. [a]P^1-value for linear trend; [b]P^2-value for interaction. *$P < 0.05$. **$P < 0.01$.

Finally, we only collected sedentary frequency without detailed physical activity level, so only sedentary frequency was adjusted to control for the effect of activity level. Furthermore, although we adjusted for many factors during statistical analysis, residual confounding factors were still unavoidable.

Conclusions

In conclusion, higher dietary intakes of vitamin B_6, total choline, free choline, glycerol phosphorylcholine, and phosphocholine in choline subgroups are associated with a lower incidence of hyperglycemia. This protective effect was modified by the presence or absence of fluorosis. This finding provides a nutritional basis for the prevention of hyperglycemia in patients with fluorosis.

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/s.

Ethics statement

The studies involving human participants were reviewed and approved by Zunyi Medical University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

LD was responsible for analysis and wrote the first draft of the manuscript. QY responsible for data management and revised manuscript. ZS, LL, and ZM assisted in conducting research and data collection. NT carried out the survey and determination. XZ was responsible for organization and survey. JL designed and conducted the study and revised the 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.

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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.2022.1002044/full#supplementary-material

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Provision of non-invasive coronary and carotid vascular imaging results on changes in diet and physical activity in asymptomatic adults: A scoping review

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Background: Although a healthy diet and physical activity have been shown to prevent or delay cardiovascular disease (CVD) hospitalizations and deaths, most adults do not meet current guidelines. Provision of coronary artery calcification (CAC) and carotid ultrasound (CUS) imaging results may motivate beneficial lifestyle changes. We scoped the existing literature for studies providing non-invasive vascular imaging results and reporting diet, physical activity, and/or anthropometric measures to identify knowledge gaps and opportunities for further research.

Methods: A systematic search was performed across three electronic databases, in line with PRISMA ScR guidelines and Arksey and O'Malley's scoping review framework.

Results: Twenty studies (thirteen observational and seven randomized controlled trials) examining the impact of provision of CAC/CUS imaging results on diet and/or physical activity behaviors were included. Nearly half the studies did not clearly state whether participants received dietary and physical activity advice along with vascular imaging results, and these were secondary outcomes in most studies, with data assessment and reporting being inconsistent.

Conclusion: Well-designed clinical trials with consistent and clear messaging based on detailed subjective and objective measures of diet and physical activity are needed to determine whether this approach may stimulate long-term dietary and physical activity change.

KEYWORDS

coronary artery calcification (CAC), carotid ultrasound (CUS), vascular imagining, cardiovascular disease (CVD), diet and physical activity change

Introduction

Cardiovascular disease (CVD) accounts for almost 1 in 3 deaths globally, with the majority (85%) attributable to either ischemic heart disease or cerebrovascular disease (1). Most survivors have substantially impaired quality of life due to ongoing functional deficits (2, 3). Suboptimal lifestyle behaviors are the leading causes of CVD globally (4), and most CVD-related events could be prevented or substantially delayed by improving diet, increasing physical activity, and ceasing smoking (1). Even modest sustained lifestyle changes can reduce CVD risk (5). Despite evidence showing that high consumption of fruit and vegetables (FV) can lead to an estimated 20% lower risk of CVD, compared to low FV intake (a 5% lower risk for each additional serving) (6), only 51 and 8% of Australians meet the minimum recommended 2 serves of fruit (≥300 g/d) and 5 serves of vegetables (≥375 g/d) daily (7, 8), respectively. Moreover, only 15% of adults age 18–64 years meet the recommended amount of physical activity (9) each week. Clearly, currently policies and strategies to increase FV intake to recommended amounts have not been successful. New strategies are warranted to further encourage a healthier diet and lifestyle, aiming at improving heart health, and provision of vascular health may further encourage these changes. High quality evidence from large randomized controlled trials (RCTs) and meta-analyses has shown that provision of vascular imaging can increase behavior change resulting in improved medication adherence in the long term (10–12), highlighting its potential utility as a promising approach to elicit diet and physical activity change. This is because people are more likely to make healthy changes if they perceive they are at risk of developing a disease and that the condition can lead to serious consequences (13).

Vascular health is commonly assessed in the coronary arteries (coronary artery calcification [CAC]) or in the carotid arteries (carotid ultrasound [CUS]). CAC testing has been increasingly used in clinical practice to screen asymptomatic patients for advanced atherosclerosis (14, 15) and to identify asymptomatic individuals at higher risk of future cardiovascular events (16). CUS is used to assess common carotid artery intimal medial thickness (cIMT) and focal carotid atherosclerotic plaques, as measures of carotid atherosclerosis (17). Detection of CAC using computed tomography (CT) and ultrasound, has been shown to strongly predict future cardiovascular events (16) among asymptomatic individuals. It has been proposed that such imaging techniques could provide superior insight as a marker of CVD risk, beyond conventional risk factors (18).

Although the impact of provision of vascular health imaging on medication adherence is well-known, the effects on diet and physical activity behaviors are less certain due to the lack of well-designed clinical trials with a focus on those outcomes. A systematic review and meta-analysis including six studies with a total of 11,256 participants on the impact of provision of CAC results on medication initiation and continuation, as well as on preventive lifestyle changes, observed improvements in the use of aspirin (OR [95%CI]: 2.6 [1.8–3.8], lipid-lowering medication: 2.9 [1.9–4.4], hypertension medication: 1.9 [1.6–2.3] and continuation of lipid-lowering medication: 2.3 [1.6–3.3]) (19). In addition, participants with abnormal CAC scans significantly improved their diet and exercise (OR [95%CI]: 1.9 [1.5–2.5] and 1.8 [1.4–2.4], respectively), compared to those with absence of CAC (19). However, no studies have mapped the literature to understand key features of these studies and highlight the areas of focus for improving diet and physical activity as part of provision of vascular health imaging.

The aim of this scoping review was to map the literature to understand the evidence to date and identify opportunities to implement diet and physical activity interventions to support changes in these areas. We sought to summarize the literature to identify the nature of study participants, understand how messages were conveyed to participants and which recommendations were provided, as well as to highlight which tools were used to measure the outcomes of interest, and the duration of follow-up period. The outcomes of this study may allow us to identify gaps in the literature to guide the design of high-quality RCTs.

Methods

Our study was guided by Arksey and O'Malley (20) scoping review framework and included five stages: (1) the research question was identified; (2) relevant studies were flagged; (3)

suitable studies were selected; (4) data was charted and; (5) relevant information was collated, summarized and described. The PRISMA Extension for Scoping Reviews (PRISMA-ScR) checklist was also used to guide this review (21).

Research questions

A scoping review question was established with the view of broadly scoping the evidence in the literature that suggests provision of non-invasive carotid or coronary vascular imaging can promote healthy diet and physical activity change, with best practices being not clear:

> *By scoping the literature to identify studies in asymptomatic adults that provided non-invasive carotid or coronary vascular imaging and measured diet and/or physical activity, can we determine which approaches may lead to healthy long-term changes in diet and physical activity, in whom and why?*

Eligibility criteria

The search for studies focused on the effects of knowledge of vascular health across the adult lifespan on changes in diet and physical activity, and anthropometric measures (as a result of changes in diet and physical activity). Full text original articles available in English with no restriction on year of publication were included. The inclusion criteria for studies were: (1) adult men and women without prior diagnosis of CVD; (2) carotid or coronary vascular imagining results provided to participants; (3) studies with information on changes in diet and/or physical activity and/or anthropometric measures after provision of vascular imaging results. We used these inclusion criteria to reflect an approach to primary prevention using vascular imaging results.

Search strategy and study selection

A comprehensive online literature search of scientific papers listed on Medline, Embase, and CINAHL was undertaken from database inception until January 24th, 2022. A hand search of references and gray literature sources were also performed (e.g., Google Scholar), to ensure that all relevant articles were included. Table 1 shows the search terms included in this review. Although the term "behavior change" is broad and may include behaviors not related to diet and physical activity (psychological behavior changes, for example), this was included in our search to identify any publications that may have included any of our outcomes of interest and avoid missing relevant studies. To ensure that variations of all keywords were retrieved, keywords and combinations of keywords were used, as well as the wildcard symbol (*). No limits or filters were used for year of publication. Only articles published in English and including adults (age ≥18 years) were considered. Only data related to pre-established outcomes of interest were extracted.

TABLE 1 Study search terms.

Exposures
'vascular calci*' OR 'coronary calci*' OR 'coronary artery disease' OR 'carotid stenosis' OR 'carotid arter*' OR 'atherosclerotic plaque*' OR 'arter* plaque'
AND (assessments)
'comp* tomography' OR angiography OR 'X-ray computed' OR ultraso* OR CT
AND (broad key words)
'life style change' OR 'lifestyle change' OR 'lifestyle behav*' OR 'behav* change' OR 'behav* modification' OR 'health behav*' OR 'motivation to change' OR 'risk factor* change' OR 'risk factor* modification'

Search terms using individual and combinations of keywords, as well as the wildcard symbol (*), with no limits or filters for year of publication. Only articles published in English and including adults (age ≥18 years) were considered.

A total of 821 publications were retrieved using the search terms, and 4 other articles were retrieved by hand search. Figure 1 shows the PRISMA flow diagram. All references were imported into EndNote software and screened for duplicates (n = 188). Screening of the remaining 637 studies was conducted in the following order: (i) article title; (ii) abstract; and (iii) full text. Two authors (SRB and AKG) screened all articles for specific outcomes of interest. The following words were used to identify the outcomes of interest for this review: diet, exercise, physical activity, exercise, nutrition, weight, BMI, body mass index, body mass, body composition, waist circumference. Discrepancies between the screening authors were resolved through discussions with a senior author (JRL) until consensus was reached. A total of 20 studies were eligible and therefore included in this scoping review (Figure 1).

Data charting and reporting

Data from each of the selected records were presented in a narrative format and sorted into tables in chronological order (oldest to newest publications). Pertinent data were retrieved from eligible articles including authorship, publication year, and country; population details (sample size, age, sex); methods and intervention details; outcomes of interest (for RCTs); follow-up period; and significant findings for the outcomes of interest, for both observational (Table 2) and RCT (Table 3) studies. The outcomes of interest found in the records included: overall diet composition, vegetable intake, fiber intake, fat intake, salt intake, consumption of processed

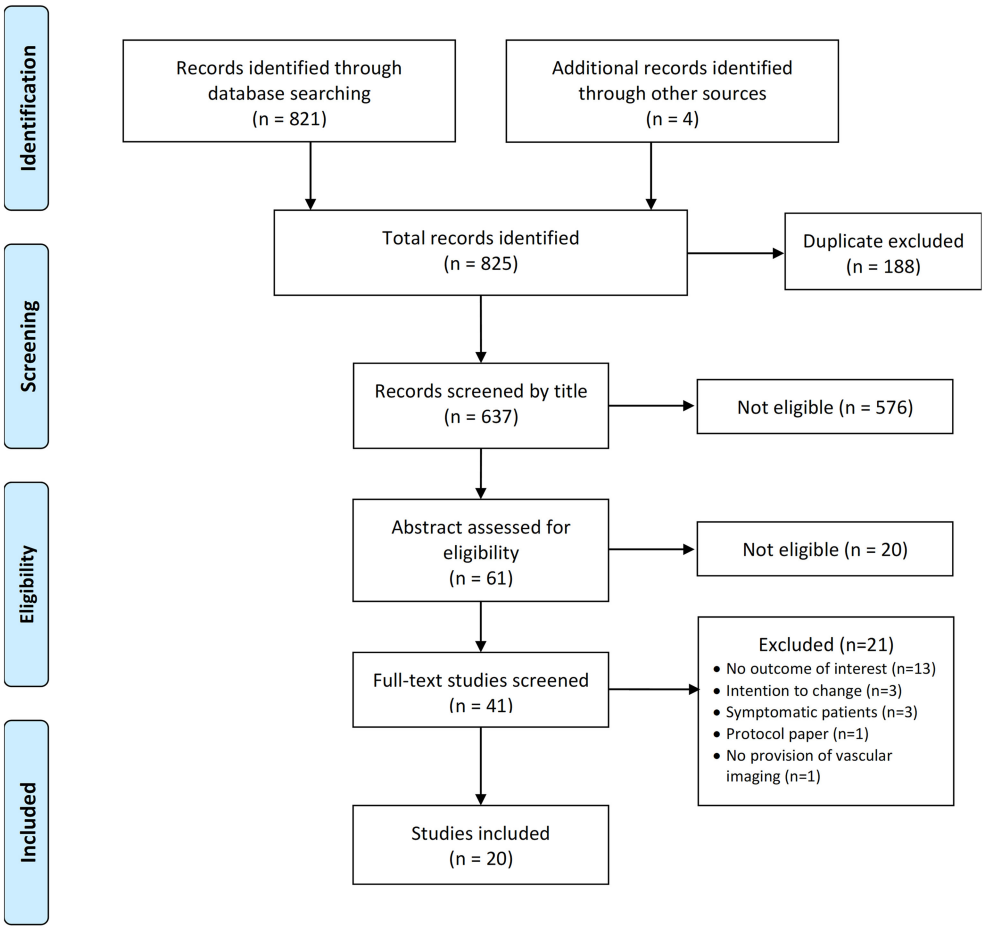

FIGURE 1
Flow diagram for the scoping review process.

foods, exercise/physical activity and anthropometric measures which included body weight and/or body mass index (BMI), and waist circumference.

Results

Synthesis of results

Twenty studies (10, 12, 22–34, 36–40) met the inclusion criteria by providing vascular images to motivate changes toward improving diet, physical activity or anthropometric measures. Of these, thirteen were observational studies (22–34) and 7 were RCTs (10, 12, 36–40). Nineteen articles were published within 2006 to 2021, while one study was published in 1996 (Tables 2, 3).

The outcomes of interest found in the eligible studies comprised: overall diet composition (23, 25–27, 29, 31, 34), vegetable intake (34), fiber intake (32, 37), fat and cholesterol intake (22, 24, 36, 37), salt intake (24, 32), consumption of processed foods (34), and amount of physical activity or exercise (10, 22, 23, 25–27, 30–32, 34, 36, 39). These components were chosen due to their role as critical modifiable lifestyle factors to prevent and/or delay the development of CVD. Studies which examined weight and/or BMI (10, 12, 22, 24, 28–30, 32, 33, 36–38, 40) and waist circumference (10, 12, 33, 40) were also included, as those measures are likely to change primarily as a result of changes in diet and/or physical activity. Results regarding the positive and neutral changes on diet, physical activity, and anthropometric measures, due to provision of vascular imaging, for the observational studies and RCTs can be found in Table 4.

The mean age of participants across studies ranged from 45 to 69 years, and the sample sizes varied from 30 to 2,608. The changes in diet, physical activity or anthropometric measures were investigated over a period of 1 month to 6 years following provision of results. For clarity, the characteristics and findings of the studies are presented separately for observational studies

and RCTs, due to the particular characteristics of each type of study.

Observational studies

Participant details and enrolment methods

In the observational studies, participants were asymptomatic (Table 2) and included healthy individuals (22–26, 28, 29), smokers (30), adults with at least one CVD risk factor (27, 31, 32), individuals with hypertension (33) and individuals with type 2 diabetes (34). Participants were recruited by contacting the study investigators directly (22, 30), or referred by physicians (23, 25, 31), or a combination of the above (26–28), and were enrolled at routine clinic visits (29, 32, 33), or at hospitals (34). In one study, investigators recruited a subsample of most residents (82%) from a southern California community (24) (Table 2).

Provision of results and diet and lifestyle recommendations

In the observational studies, CAC and CUS results were provided to participants either as images only (23, 25, 28, 32), a combination of images/graphs and/or scores/text (24, 26), pictures followed by an educational tutorial (30), or via a phone call followed by mailed written information (27). Five studies did not report or specify this information (22, 29, 31, 33, 34). The results were provided to participants by physicians (25, 26, 28), a primary care provider (27, 32), mailed to participants (24) or were not reported / not specified (22–24, 29–31, 33, 34). Two observational studies (26, 28) clearly stated that participants were provided with diet and physical activity recommendations, with all other studies mentioning general lifestyle modifications or not reporting on providing any information. Only 38% ($n = 5$) of the studies provided participants with specific recommendations for lifestyle change (25, 26, 28, 30, 32), with one proving specific lifestyle advice to a subgroup with abnormal lipid or glucose levels (30).

Duration of follow-up methods

In the observational studies, diet and physical activity changes made by participants were followed up via mail (22, 24, 26, 27, 32), electronically (29) and face-to-face during clinic visits (28, 30, 34). In two studies, follow-up data were obtained via surveys/interviews (25, 31), but the authors did not specify whether surveys were mailed to participants, or whether interviews took place face-to-face or via phone.

Qualitative and quantitative outcomes

Results relating to the impact of provision of vascular imaging results on diet, physical activity and anthropometric measures were charted (Table 2). Observational studies exploring the associations between provision of coronary artery and carotid calcification and changes in diet yielded mixed results. Five studies (out of seven studies) observed a positive change in overall diet measures (23, 25–27, 29). Improvements in dietary fiber (32), fat (22, 24) and salt (24, 32) were observed. However, no changes were observed for consumption of vegetables (34) or processed foods (34). Positive changes in weight and/or BMI were observed in three studies (out of seven studies) (22, 28, 29). However, waist circumference remained similar (33). Three studies (25–27) reported an increase in physical activity levels after provision of vascular imaging results (Table 2).

Randomized controlled trials

Participant details and enrolment methods

In the RCTs (Table 3), participant were either smokers (39), post-menopausal women (37), adults with CVD risk factors (10, 38, 40), and otherwise healthy individuals (12, 36). Sample sizes varied from 56 to 3,532 and the mean/median age of participants ranged from 42 to 65 years. The duration of interventions in the RCTs ranged from 6 months to 4 years. Across RCTs, participants were recruited from previous trials (12, 38, 40), a medical center (10), self-referral (39), both self-referral or referral from physicians (37), or a mandatory periodic physical examination (36) (Table 3).

Provision of results and diet and lifestyle recommendations

In the RCTs, CAC and CUS results were mainly provided as images (36), or a combination of images with written information (12, 37, 40), including scores (10), as well as a video (39). In one of the studies this information was not reported (38). Except for two RCTs that reported that the results were delivered to participants by a research nurse (10, 36) and via mail (12), this information in all others studies was not specifically stated (37–40). Only two RCTs (36, 37) clearly specified that counseling on diet and physical activity was provided to participants. All other RCTs ($n = 5$) provided counseling with focus on risk factor management and lifestyle without explicitly mentioning diet and physical activity (10, 12, 38–40). Further details have been reported in Table 3.

Follow-up methods

RCT study participants were followed-up at clinic visits after 6 months to 4 years following provision of results (10, 12, 36–40).

TABLE 2 Summary of observational studies on provision of CAC and CUS results and changes in diet, physical activity and anthropometric measures.

Author, year, country	Sample details (size, age, sex, type)	Methods	CAC or CUS classification	Findings based on the outcomes of interest	Follow-up period
Coronary artery calcification (CAC)					
Wong et al. (22) US	Seven hundred and three asymptomatic adults with no CVD, 59% men; 53.7 ± 9.9 y, self-referred, who had CAC scans performed at Harbor-UCLA Medical Center (1992–1994)	Provision of CAC results were not reported. Follow-up questionnaire mailed ∼1–2 y after the initial CAC scan, assessing health behaviors and medication use, as well as information on hospitalization and whether a physician had been consulted. Information on counseling not reported	CAC assessed by EBT, with scores determined according to Agatston	Presence of calcium was associated with losing weight and decreasing dietary fat ($p < 0.05$). Exercise levels remained the same ($p > 0.05$)	1–2 years
Kalia et al. (23), US	Five hundred and five asymptomatic adults with no CVD, 82% men, 61 ± 10 y, referred by physician	CAC scan images shown to participants, with CAC seen as bright white spots in their coronary arteries. Atherosclerosis was classified as none, mild, moderate or severe. CAC was described as identifying underlying coronary atherosclerosis and a heart disease predictor. Information on diet and lifestyle (D&L) counseling not reported	CAC assessed by EBT, with scores determined according to Agatston as: none, mild, moderate or severe	Participants were divided into quartiles (Q) according to baseline CAC score (Q1: 0–30, Q2: 31–149, Q3: 151–526 and; Q4: ≥527). Those in Q1 were least likely to make changes to their diet and cardiovascular exercise. Dietary change increased from 41 to 64% across quartiles ($p = 0.001$)	3 ± 2 years
Sandwell et al. (24), US	Three hundred and sixty four asymptomatic adults with no CVD, 53.7% men, 68.7 y, 82% of all adult residents of Rancho Bernardo, a southern California community, invited to take part in a study of heart disease risk factors (1972–1974)	Written CAC scan results and a graph were mailed to all participants within a week. Those with scores >1,000 received a phone call. All participants were asked to share their results with their physician. Information on D&L counseling not reported	CAC assessed by EBT, with scores determined according to Agatston as: 0–10 = low risk, 11–400 = moderate >400 = high risk for CAD	Among participants with suboptimal lifestyle before the scan, those with higher risk were more likely to make dietary changes, particularly on intake of fat ($p = 0.007$), cholesterol ($p = 0.030$), and salt ($p = 0.059$) compared with those with lower risk. Body weight did not change	6 months
Orakzai et al. (25), US	Nine hundred and eighty asymptomatic adults, 78% men, 60 ± 8 y, referred by physician	Participants were allocated to 4 groups based on their CAC scores. Physicians or technologists discussed the CAC scans with participants. CAC was seen as bright white spots and defined as identifying underlying coronary atherosclerosis and a risk factor for heart disease. Atherosclerosis was classified as none, mild, moderate or severe. Those with presence of CAC received recommendations to change lifestyle	CAC assessed by EBT, with scores determined according to Agatston: CAC = 0, CAC = 1–99, CAC = 100–399, and CAC≥400	Participants with CAC = 0 had the least changes in diet and exercise (33% and 44%, respectively), with a gradual increase observed with higher CAC scores (diet: 1–99, 40%; 100–399, 58%; >400, 56%; exercise 1–99, 62%; 100–399, 63%; >400, 67%;); all $p < 0.001$	3 ± 2 years

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10.3389/fnut.2022.946378

TABLE 2 (Continued)

Author, year, country	Sample details (size, age, sex, type)	Methods	CAC or CUS classification	Findings based on the outcomes of interest	Follow-up period
Schwartz et al. (26), US	Five hundred and ten asymptomatic adults, 42.8% men, 64 ± 9.69 y, physician or self-referred as a supplement to their preventive health care	CAC images and scores provided to participants by a physician, and counseled for lifestyle and risk factor modification, including diet and exercise advice, and smoking cessation, based on their CAC scores. Participants were informed that CAC was an underlying coronary atherosclerosis and associated with heart disease	CAC assessed by EBT, with scores determined according to Agatston	Participants with greater CAC scores were more likely to report increasing exercise (OR = 1.34, $P = 0.02$), improving diet (OR = 1.40, $P < 0.01$), and reducing alcohol intake (OR = 1.46, $p = 0.05$)	6 ± 1 years
Johnson et al. (27), US	One hundred and seventy four high-risk adults (≥3 major risk factors), 62% men, 58 ± 7.5 y, referred by physicians or self-referral to a private radiology center	CAC results provided by a nurse via a phone call ∼2–3 days after patients' scan. Results were mailed to participants, and they were encouraged to follow up with their physician. Information on D&L counseling not reported	CAC determined according to Agatston score: 0 = no risk/normal, 1–10 = very low risk, 11–100 = mild risk, 101–400 = moderate risk, and >400 = high risk for a stenotic lesion	The study observed improvements in self-reported diet and exercise (data not shown)	3 months
Kalia et al. (28), US	Two thousand six hundred and eight asymptomatic adults, 72% men, 58 ± 8 y, referred by physicians or self-referral to University-Affiliated Disease Prevention Center in California	CAC scan images shown to participants, and presence and severity of atherosclerosis discussed. A physician discussed the risk factors associated with CAC and provided recommendations on nutrition, exercise, and smoking cessation for risk reduction, based on CAC scores	CAC scores were determined according to Agatston	Participants with CAC = 0 had the least weight loss (19.8%), with a gradual increase in weight loss observed with higher CAC scores (1–99, 23.4%; 100–399, 30.8%; ≥400, 33.6%; $p < 0.001$ for trend)	4.1 ± 3.2 years
Schurink et al. (29), The Netherlands	Three hundred and eighteen asymptomatic sportsmen aged ≥45 years attending routine sports medical examination who underwent additional cardiac CT imaging	At least two (sports) cardiologists and one radiologist reviewed the abnormal findings on the scans.[#] Provision of CAC results to participants not reported. Those with CAC scores 100–400 were provided with lifestyle recommendations and advised on statin treatment	CAC scores were determined according to Agatston	Approximately 23% of sportsmen improved their lifestyle, with the majority reporting changes to a healthier diet (46.8%) and weight loss (35.9%)	7–30 months
Carotid ultrasound (CUS)					
Rodondi N et al. (30), Switzerland	Thirty smokers (at least 30 cigarettes/d), 56.7% men, 51.8 ± 9.4 y, self-referred	CUS performed in all smokers, plus smoking cessation counseling and therapy, and an educational tutorial on atherosclerosis, provided by a trained physician. Smokers with plaques received two images of their plaques and a 6-min educational tutorial on their ultrasound results. Smokers without plaques received a similar 6-min tutorial modified accordingly and were informed that their cardiovascular risk depended on other CVD risk factors and smoking, despite the absence of plaques. Those with suboptimal lipid or glucose levels received advice for lifestyle modification	Carotid atherosclerosis assessed by CUS, and defined as a focal widening of more than 50% relative to adjacent segment	PA did not increase from BL to 2 months in the group with presence of plaques (BL median ([IQR]: 1,517 [914–2,255] vs. 2 months: 3,437 [2,306–5,505] MET. Min/w [$p = 0.02$]), whereas PA increased in the group without plaques (BL: 1,517 [914–2,255] vs. 2 months: 3,437 [2,306–5,505] MET x Min/w [$p = 0.02$]). Body weight remained unchanged in both groups	1 week, 2 weeks and 2 months

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10.3389/fnut.2022.946378

TABLE 2 (Continued)

Author, year, country	Sample details (size, age, sex, type)	Methods	CAC or CUS classification	Findings based on the outcomes of interest	Follow-up period
Johnson et al. (31), US*	Five hundred and twenty nine adults with ≥1 risk factors and no CVD, 56.7% men, 54 ± 7 y, referred by physicians to the University of Wisconsin Vascular Health Screening Program	CUS was performed to assess cIMT and to identify carotid plaques. Information on D&L counseling not reported	cIMT in the highest >75th percentile for age, sex, and race, or carotid plaque presence	Advanced atherosclerosis did not predict changes in diet, exercise frequency, or long-term health-related behavior change	1 year
Johnson et al. (32), US	Three hundred and fifty five asymptomatic adults with ≥1 risk factors, 42% men, 53.6 ± 7.9y from 5 community, non-academic, primary care medical practices, screened during routine office visits	Participants with abnormal CUS were shown images of their arteries and received standardized education about the relationship of abnormal CUS with CVD. A primary care professional provided lifestyle recommendations for CVD risk-reduction and if indicated, medication use was recommended	Carotid atherosclerosis defined as cIMT >75th percentile or carotid plaque presence	Although an increase in exercise frequency and weight loss was reported by participants (34 and 37%, respectively), these changes were not predicted by CUS results. Abnormal CUS discreetly predicted reduced intake of dietary sodium (OR = 1.45, $p = 0.002$) and increased intake of fiber (OR = 1.55, $p = 0.022$)	1 month
Hong et al. (33), Korea	Three hundred and forty seven asymptomatic hypertensive adults, 54.5% men, 61 ± 8 y, from 22 hospitals in Korea, screened during routine office visits	CUS performed to assess cIMT and to identify carotid plaques. Results were informed to participants and recommendations provided by a physician. Participants were informed about the association of CAD with CVD and that presence of plaque or increased cIMT indicated increased risk for heart attack, stroke, and death. Information on D&L counseling not reported	Carotid atherosclerosis defined as carotid plaque or cIMT ≥0.9 mm	BMI decreased at 6 months only in the negative CUS group (*delta* = −0.1±0.4 kg/m2, $p = 0.006$). Waist circumference remained unchanged at 6 months for both groups	6 months
Jeong et al. (34), Korea	Seven hundred and ninety seven adults with T2D, 49.6% men, 60 ± 9.5 y, recruited from 24 hospitals in Korea	CUS was performed to assess cIMT and to identify carotid plaques. Information on D&L counseling not reported	Carotid atherosclerosis defined as carotid plaque or cIMT ≥1 mm	PA remained unchanged, as well as consumption of vegetables, processed foods, and soy sauce intake. Soup intake reduced significantly at 6 months (authors suggested patients tried to reduce their salt intake)	6 months

BL, baseline; BMI, Body Mass Index; cIMT, carotid Intima-Media Thickness; CT, Computed Tomography; CAC, Coronary Artery Calcification; CHD, Coronary Heart Disease; CAD, Coronary Artery Disease; CUS, Carotid Ultrasound; CVD, Cardiovascular Disease; EBT, Electron Beam Tomography; ICM, Intensive Case Management; PA, Physical Activity; RCT, Randomized Control Trial; *Research letter; #Methods have been previously described (35).

10.3389/fnut.2022.946378

TABLE 3 Summary of RCTs on provision of CAC and CUS results and changes in diet, physical activity and anthropometric measures.

Author, year, country	Sample details (size, age, sex, type)	Methods and intervention	CAC classification	Outcomes	Findings based on the outcomes of interest	Follow-up period
Coronary artery calcification (CAC)						
O'Malley et al. (36), US	Four hundred and fifty active-duty US Army personnel, 79% men, 42 ± 1.9 y, booked for a periodic Army mandated physical examination	Participants were randomly allocated to 1 of 4 interventions: EBT plus either ICM or usual care; EBT not provided plus either ICM or usual care; EBT results included an illustrative picture of the coronary artery with focus on any abnormalities and the CAC score and were provided by the research nurse. Counseling involved risk factor identification and advice in those with CAC, including risk factor management (hypertension, hypercholesterolemia, obesity, high-fat diet, sedentary lifestyle, smoking and glucose intolerance). Participants with risk factors were referred to their physician/dietitian	CAC assessed by EBT, with scores determined according to Agatston	Primary outcome was change in FRS. Secondary outcomes included dietary fat intake, PA and BMI	EBT information, with or without ICM, was not associated with changes in BMI, PA, and dietary fat consumption	12 months
Lederman et al. (37), US	Fifty six post-menopausal women, 64.7 ± 6.9 y, self-referred from press advertisements or were referred by their physician	Participants were randomly allocated to conventional screening or conventional screening plus DHCT. CAC group received images of their CAC and an interpretation from a radiologist. A physician provided a tailored counseling session on nutrition, supplement use, PA, weight control, smoking cessation, and use of HRT and medication for CHD risk reduction to all participants	CAC assessed by DHCT, with scores determined according to Agatston: <10 = very low risk, ≥10-<100 = low risk; ≥100-< 400 = medium risk, and ≥400 = high risk for CAD	Primary outcomes included BMI. Other measures included change in dietary fat, fiber, and PA	There was no change in BMI, fat and fiber intake in both the conventional screening group and CT imaging group	6 and 12 months
Rozanski et al. (10), US	Two thousand and one hundred and thirty seven adults with CVD risk factors, 52.5% men, 58.5 ± 8.4 y, from Cedars-Sinai Medical Center	Participants were randomly allocated to no CAC scan or CAC scan. CAC images, score and percentile scores were discussed with those in the CAC group. Nurses provided risk factor counseling session to participants. This comprised provision of a printed customized risk factor management pack with information from the American Heart Association guidelines on cardiac risk factors, results for each risk factor and information on how to improve their risk factors	CAC assessed by EBT, with scores determined according to Agatston	Primary outcome was change in CAD risk factors and FRS. Other measures included weight, WC and PA	WC was significantly lower in those with increased abdominal girth in the scan group, compared with the no-scan group. Weight remained unchanged. Those with higher CAC reported increased exercise (non-exercisers at BL)	4 years
Venkataraman et al. (38)*	Four hundred and fifty five adults, 43% men; 59 ± 8 y, with CVD risk and family history of premature CAD from the CAUGHT-CAD trial	Participants underwent standard risk factor management. The CAC-guided arm started on statins	CAC assessed by EBT, with scores determined according to Agatston	Primary outcome was change in anthropometric parameters (weight)	Weight remained the same in both within and between CAC groups	12 months

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10.3389/fnut.2022.946378

TABLE 3 (Continued)

Author, year, country	Sample details (size, age, sex, type)	Methods and intervention	CAC classification	Outcomes	Findings based on the outcomes of interest	Follow-up period
Carotid ultrasound (CUS)						
Rodondi et al. (39), Switzerland	Five hundred and thirty six smokers (≥10 cigarettes/d), 55% men, 51.1 ± 7.3 y, from the general population in the French speaking part of Switzerland self-referred from press advertisements	Participants were randomly allocated to screening or no screening of carotid plaque. Smokers with plaque received 2 images of their plaques and a 7-min tutorial about atherosclerotic plaques. Smokers without plaques and the control group were provided with a 7-min tutorial on the smoking related-risks. All participants underwent a smoking cessation program for 1 year. Information on D&L not reported	Carotid plaques were defined as a focal widening of at least 50% relative to an adjacent segment	Primary outcome was smoking cessation. Other measures included PA	PA did not change in both groups	12 months
Näslund et al. (40), Sweden	Three thousand and five hundred and thirty two adults with ≥1 risk factor, 47% men, 40–60 y, from the Västerbotten Intervention Programme (VIP)	Participants were randomly allocated to receive illustration of CUS plus a nurse phone call or not informed group. Presence of plaque was shown as a traffic light for each carotid artery, with a red circle for a plaque or a green circle for no plaque, and image was included. Written material was provided and contained information about atherosclerosis being a process that is modifiable by a healthy lifestyle and medication. Nurses and physicians provided interpretation of the results and advice on prevention of CVD	Carotid plaque assessed by CUS with cIMT measured in the left and right common carotid arteries	Primary outcomes were FRS and SCORE. Secondary outcomes included weight and WC	There was a slight non-significant decrease in weight in the intervention group. WC remained unchanged	12 months
Bengtsson et al. (12), Sweden	Three thousand and five hundred and thirty two healthy adults aged 40–60 y from the Västerbotten Intervention Programme (VIP)	Participants were randomly allocated to receive CUS pictorial information plus additional information or no pictorial information. CUS results were mailed to the intervention group in a pictorial format. Presence of plaque was illustrated with a red circle while no plaque was a green circle, with cIMT illustrated with a color gage indicating vascular age and ranging from green to yellow, orange and red. Written information on atherosclerosis was provided, with participants receiving healthy lifestyle changes advice to prevent atherosclerosis progression	Carotid plaque assessed by CUS	Primary outcomes were FRS and SCORE. Secondary outcomes included weight and WC	WC was significantly lower in the intervention group. Weight remained unchanged	3 years

BL, baseline; BMI, Body Mass Index; CAC, Coronary Artery Calcification; CAD, Coronary Artery Disease; CHD, Coronary Heart Disease; cIMT, carotid Intima-Media Thickness; CT, Computed Tomography; CUS, Carotid Ultrasound; CVD, Cardiovascular Disease; DHCT, Double-Helical Computed Tomography; EBT, Electron Beam Tomography; FRS, Framingham Risk Score; HRT, Hormone Replacement Therapy; ICM, Intensive Case Management; NRT, Nicotine Replacement Therapy; PA, Physical Activity; RCT, Randomized Control Trial; WC, Waist Circumference; SCORE, Systematic COronary Risk Evaluation; *Poster.

10.3389/fnut.2022.946378

TABLE 4 Changes in diet, physical activity and anthropometric measures in observational studies and RCTs.

Outcomes of interest	Observational CAC	Observational CUS	RCT CAC	RCT CUS
Overall diet	✓✓✓✓✓ (23, 25–27, 29)	xx (31, 34)		
Vegetable intake		x (34)		
Intake of processed foods		x (34)		
Fiber intake		✓(32)	x (37)	
Fat and cholesterol intake	✓✓ (22, 24)		xx (36, 37)	
Salt intake	✓ (24)	✓(32)		
Physical activity/exercise	✓✓✓ (25–27); xx (22, 23)	xxxx (30–32, 34)	x (36);✓(10)	x (39)
Weight/BMI	✓✓✓ (22, 28, 29); x (24)	xxx (30, 32, 33)	xxxx (10, 36–38)	xx (12, 40)
Waist circumference		x (33)	✓ (10)	x (40);✓(12)

BMI, Body Mass Index; CAC, Coronary Artery Calcification; CUS, Carotid Ultrasound; RCT, Randomized Control trial. ✓, significant beneficial change; x, no significant change.

Qualitative and quantitative outcomes

The RCTs focused on changing Framingham Risk Score (FRS) (10, 12, 36, 40), Systematic Coronary Risk Evaluation (SCORE) (12, 40), smoking cessation (39), and improving risk factors such as blood pressure and lipids, rather than diet, physical activity and anthropometric measures. Therefore, these trials were not specifically designed to examine whether provision of CAC and CUS could lead to healthy changes in diet, physical activity and anthropometric measures. Only two RCTs (37, 38) included BMI and body weight within their primary outcomes. In all other RCTs, diet, physical activity and anthropometric measures were considered secondary or non-specified outcomes (Table 3).

CAC/CUS scan vs. no scan

Findings from seven RCTs included in this scoping review (Table 5) showed that provision of scan results did not lead to changes in the intake of dietary fiber and fat a year later, compared to the no scan group (37). Similarly, BMI remained unchanged in both the scan and no scan groups (37). In the EISNER (Early Identification of Subclinical Atherosclerosis by non-invasive Imaging Research) study (10), when comparing the CAC scan group with the non-CAC scan group, investigators observed a significant decrease in waist circumference at 4 years in a subgroup with increased waist circumference (M>40, W>35) at baseline (Table 5), whereas body weight remained unchanged (10). Provision of vascular imaging did not lead to changes in physical activity levels in the scan group, compared to no scan group over 1 year (39) and 4 years (10).

CAC/CUS scan informed vs. not informed

Compared to participants who were not informed of their scan results, provision of vascular imaging did not lead to reductions in body weight (12, 38, 40) or BMI (36). Waist circumference did not change after 1 year in one study (40), but provision of CUS led to significant reductions in another study (12) after 3 years of provision of results, compared to the group not informed (Table 5). No changes in physical activity were observed in participants after a year of being informed of their vascular results, compared to those who were not informed (36).

Evidence vs. no evidence of CAC/CUS (zero/low to higher scores)

When examining the changes within groups according to CAC/CUS scores in the EISNER study (10), participants who were overweight and had a CAC score >100 had a greater weight loss after 4 years (Table 5). However, no significant changes in body weight were observed within groups in the Venkataraman trial (38). Participants with higher CAC scores in the EISNER study (10), who were non-exercisers at baseline, reported an increase in exercise levels after 4 years.

Clinical assessments and reporting in both observational and RCT studies

A range of instruments were used to assess diet and physical activity in the eligible studies, with many being self-reported or single-item questions (Supplementary Tables S1, S2, for observational and RCT studies, respectively). The results were also reported in several different ways (i.e., mean ± SE, mean (SE), median and interquartile range, mean and 95% confidence interval) and given in dissimilar unit measures (i.e., MET, min/week, percentages), which makes comparability of results difficult.

Discussion

In this scoping review, we identified many gaps and opportunities to inform the design of future high quality RCTs providing vascular imagining results to elicit positive

TABLE 5 Changes in diet, physical activity and anthropometric measures according to CAC and CUS scores in RCTs.

Randomized controlled trials - CAC groups		Change	*P*-value
O'Malley et al. (36), US		**12 months**	
Change in BMI, kg/m2, mean (SE)	CAC informed vs. CAC not informed	0.38 (0.12)	0.84
Change in exercise[a], sports index, mean (SE)	CAC informed vs. CAC not informed	0.02 (0.05)	0.23
Lederman et al. (37), US		**12 months**	
Change in BMI, kg/m2, mean (SD)	CAC plus Counseling vs. Counseling alone (no CAC scan)	0.10 (1.33)	>0.05
Change in fiber intake, *n* (%)	CAC plus Counseling vs. Counseling alone (no CAC scan)	3 (13.0%)	>0.05
Change in fat intake, *n* (%)	CAC plus Counseling vs. Counseling alone (no CAC scan)	7 (29.2%)	>0.05
Rozanski Al et al. (10), US		**4 years**	
Change in weight, kg, median (IQR)	CAC scan vs. no CAC scan (BM I≥25 kg/m2 at baseline)	0 (−2.72, 3.17)	0.07
Change in WC, cm, median (IQR)	CAC scan vs. no CAC scan (increased WC [M>40, W>35] at baseline)	0 (−7.62, 5.08)	**0.01**
Change in exercise, ≥3 times/week, *n* (%)	CAC scan vs. no CAC scan (no exercise at baseline)	214/582 (37%)	0.77
Change in weight, kg, median (IQR)	Highest vs. lowest CAC scores (BMI ≥25 kg/m2 at baseline)	−3 (−10, 3)	**<0.001**
Change in WC, cm, median (IQR)	Highest vs. lowest CAC scores (increased WC [M>40, W>35] at baseline)	−1 (3.3, 0.5)	0.56
Change in exercise, ≥3 times/week, *n* (%)	Highest vs. lowest CAC scores (no exercise at baseline)	17/36 (47%)	**0.03**
Venkataraman et al. AU (38)		**12 months**	
Change in weight, kg, mean	CAC informed vs. CAC not informed	3.92	0.30
Change in weight, kg, mean	Highest vs. lowest CAC scores	−0.12	0.11
Randomized controlled trials - CUS groups			
Rodondi et al. (39), Switzerland		**12 months**	
Change in exercise, MET min/wk, mean (SE)	CUS scan vs. no CUS scan	−784 (205)	0.98
Näslund et al. (40), Sweden		**12 months**	
Change in weight, Kg, mean (95%CI)	CUS informed plus a nurse phone call vs. CUS not informed	1.62 (−0.06, 3.30)	>0.05
Change in WC, cm, mean (95%CI)	CUS informed plus a nurse phone call vs. CUS not informed	1.3 (−0.01, 2.60)	>0.05
Bengtsson et al. (12), Sweden		**3 years**	
Change in weight, Kg, mean (95%CI)	CUS informed vs. CUS not informed	0.8227 (−0.2186, 1.864)	>0.05
Change in WC, cm, mean (95%CI)	CUS informed vs. CUS not informed	0.8681 (0.0072, 1.729)	**0.032**

BMI, Body Mass Index; CAC, Coronary Artery Calcification; CUS, Carotid Ultrasound, WC, Waist Circumference. [a]Baecke Physical activity questionnaire – sports index ranges from 0 to 5. *P*-values marked in bold indicate statistically significant results.

changes to diet and physical activity. We revealed three key messages. First, the results of observational studies gathered in this scoping review suggest that providing CAC and CUS imaging could lead to healthy changes to diet, physical activity, and anthropometric measures (weight, BMI and waist circumference). However, well-designed clinical trials with particular focus on improving diet and physical activity and reducing anthropometric measures (rather than focused on CVD risk factor management) are needed to strengthen quality of evidence regarding the impact of CAC and CUS imaging results on these particular lifestyle behaviors. Secondly, the outcomes of interest in the present review were mainly secondary or non-specified outcomes for the studies included. These studies were largely designed to answer a broader question, focusing mainly on estimated cardiovascular risk or smoking cessation. Finally, the methodologies used varied significantly. For instance, few studies included counseling sessions or other well-recognized behavior change techniques, such as methods for self-monitoring (41). Studies using provision of vascular health imagining eliciting changes on CVD risk have demonstrated mixed results. There is need for interventions to be tested in large clinical trials before implementing in clinical practice (15).

Overall results

Twenty studies examining the impact of provision of CAC/CUS imaging results on diet and/or physical activity were reviewed. Of these, twelve studies focused on CAC (four RCTs and eight observational) and eight studies focused on CUS (three RCTs and five observational). Half of the participants were free of CVD and the other half were at high risk for CVD (at least 1 CVD risk factor, i.e., smokers, hypertensive). Most studies reported providing written/verbal/imaging results but only some studies clearly stated they provided dietary and physical activity advice when providing vascular imaging results. None of the RCTs had dietary or physical activity as a primary outcomes and assessment and reporting of the outcomes were suboptimal and inconsistent among studies. The

considerations discussed below can potentially help with the design of future studies where participants receive appropriate guidance and support after provision of vascular imaging, which can be translated into significant changes to their diet and physical activity.

Diet and physical activity as non-primary outcomes

We observed that the primary outcomes of most of the studies included in this scoping review focused on managing blood pressure and smoking cessation, rather than changing diet, physical activity and anthropometric measures. Hence, the recommendations for behavior changes were focused on medication and other therapies specific to manage those outcomes. Although some RCTs provided information on risk factor management (10, 36, 38, 39), specific recommendations to promote a healthy diet and lifestyle, beyond risk factor management, was a missed opportunity. Evidence shows that providing this information grounded in theory can produce change, helping people to make healthier choices. Such changes have the potential to translate to a more successful change in diet, physical activity and body weight as well as risk factor management.

Inconsistent methodologies among studies

In general, the methodologies of the studies included in this review varied greatly, making it difficult to determine which study design would have been potentially more promising at leading to positive changes in diet and physical activity. These included: disparities in randomization methods (i.e., CAC informed group vs. not informed, or CAC performed vs. not performed), instruments used to assess diet and physical activity (e.g., no reference to questionnaires being validated), how the messages were conveyed (including a lack of clarity in how this was performed), which recommendations for lifestyle change were provided (i.e., recommendations from national/international guidelines), and by whom (i.e., clinician, counselor, researcher, etc.). Some observational studies reported physicians had delivered the results to participants, although in most of the observational studies, this was not specified. Only one RCT clearly stated that a physician provided the participants with their results; in all others, this information was not reported or not specified. Previous studies have shown that interventions are more likely to be unsuccessful if not delivered by a clinician (36). In addition, individuals are unlikely to make changes to their diet and lifestyle if no guidance is provided on how to achieve specific goals to improve risk factors (36).

Overall, behavior change has been shown to be possible but needs to be deliberately included and designed, taking advantage of the "teachable moment" (42). These are brief moments during life when people are more receptive to behavior change messages, and these moments can be used to encourage individuals to change unhealthy behaviors (43). The findings of this study indicate that future well-designed interventions should not only focus on providing recommendations on diet and physical activity change, but equally important, follow up, motivate, and support individuals, to enhance the likelihood of achieving significant beneficial changes.

The use of behavior change techniques (BCTs) appears to positively impact the effectiveness of behavior change interventions. A meta-analysis investigating e-health interventions to increase fruit and vegetable intake observed that interventions using 7–8 BCTs ($n = 4$) were more successful compared with interventions using six or less BCTs (44). The following 5 BCTs identified as more commonly used in studies appeared to equally positively influence the study interventions (44): i. *Provide directions on how to change behavior; ii. Provide feedback on performance; iii. Identification of barriers; iv. Goal Setting* and v. *Inform on consequences of behaviors* (44). This suggests that adding BCT may improve effectiveness of interventions, by providing further support to individuals to achieve and maintain a healthy lifestyle (37).

Evidence shows that presence of CAC, rather than simply having a scan performed, leads to a greater motivation toward improving CVD risk factors (19). Moreover, participants with presence of calcification, and more importantly those with higher risk factors for CVD (14) seem to be more motivated to change their behavior (37), with interventions being more successful (14) among those with higher risk. Conversely, having a normal vascular image (no calcification) has been suggested to discourage behavior change toward risk factors (37), but the evidence for this remains limited. This highlights the importance of clarifying to individuals that changes in diet and physical activity, do not only slow the progression of CVD, but can also prevent the onset of vascular-related conditions, particularly in those with CVD risk factors.

Furthermore, vascular imaging has been shown to improve CVD management without leading to great increase in medical costs to participants (10). The need for larger clinical trials has been suggested to confirm whether these findings can be extended to more diverse populations, as well as to investigate whether provision of vascular imaging and the subsequent improvement in CVD risk factors lead to a lower rate of cardiovascular events (10).

A systematic review and meta-analysis including 21 RCTs published in 2022 (45) reported the potential of provision of medical images to encourage risk-reducing behaviors and reduce risk factors. However, they indicated the need for further satisfactorily powered trials well-controlled for risk of bias (45). The review also suggested that building further

evidence for some key behavioral outcomes is warranted, as most trials focused on medication use and adherence, smoking cessation, and increase physical activity (45). A study protocol investigating whether provision of vascular imagining to individuals could significantly lead to beneficial behavior change, including diet and physical activity among other behavior change outcomes has been previously published (46) with the RCT underway. Results of this study may contribute to further understanding and potentially strengthening the current evidence that provision of imagining can encourage health behavior modification.

Overall, the data summarized in this review contributes to the literature on the topic and can serve as a reference for future clinical trials and as a guide for future research. We have identified numerous opportunities to improve interventions aiming to promote changes to diet and physical activity via the provision of vascular imaging.

Limitations

A limitation was the lack of studies specifically designed to answer the question on whether visualization of non-invasive vascular imaging results could lead to beneficial changes in diet and physical activity, and as such it is difficult to evaluate specific knowledge gaps or beneficial approaches. Most of the existing studies focused on smoking cessation and improving estimated cardiovascular risks, with changes in diet and physical activity being mainly secondary outcomes. In addition, the outcomes of interest were assessed using several different instruments. Noteworthy, physical activity/exercise levels were estimated using different and non-comparable instruments (i.e., questions to estimate physical activity [yes/no questions], and the disparities in reporting the results [i.e., MET min/week, mean ± SE]) made comparison difficult. Furthermore, the terms exercise and physical activity were used interchangeably in many studies (i.e., self-reported physical activity was referred as exercise – structured exercise such as going to the gym). As physical activity and dietary intake data was mostly self-reported, these data should be interpreted with caution.

Conclusion

The results of this scoping review suggest the need for well-structured interventions with the objective of motivating individuals to make positive changes to their diet and physical activity. Although there is consistent evidence that provision of non-invasive vascular imaging results can encourage individuals to make positive behavior changes in relation to medication adherence and other CVD risk factors, evidence for its impact on diet and physical activity remains very weak. However, this is largely due to the lack of studies designed to address this question. Well-designed clinical trials are warranted to further clarify and strengthen the beneficial results mainly seen in observational studies. Future clinical trials should consider a consistent and clear message on how to achieve positive diet, physical activity and other lifestyle changes, preferably be delivered by a trained counselor, and include a follow up session to reinforce advice, ensure understanding, and to provide further encouragement to support positive diet and physical activity changes.

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/s.

Author contributions

SR-B searched the literature and retrieved the articles. SR-B and AKG screened the papers for eligibility. SR-B, MAK, and JRL participated in the writing of the manuscript. SR-B, AKG, MAK, MS, LCB, CPB, BJ, JD, MPS, JMH, and JRL contributed to the work's conception and design, data interpretation, critical revision of the manuscript, and approved the version of the manuscript being submitted. 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

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Association between tea consumption and prevention of coronary artery disease: A systematic review and dose-response meta-analysis

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Background: Evidence from previous studies reporting on the relationship between tea consumption and its preventive effect on coronary artery disease (CAD) has conflicting outcomes. With the accumulation of new clinical evidence, we conducted this meta-analysis to assess tea consumption and CAD risk.

Methods: We searched PubMed, EMBASE, Cochrane Library, and Medline databases for published observational studies from their inception to May 2022. A random-effects model was used to calculate risk ratios with 95% confidence intervals. We also conducted linear and non-linear dose-response meta-analyses to analyze the association. We regarded that one cup equals 237 mL. Subgroup analyses and univariate meta-regression were conducted to explore the source of heterogeneity.

Results: A total of 35 studies, including 24 on green tea and 11 on black tea consumption, were included in this meta-analysis. An inverse association for the risk of CAD was observed for black tea (RR: 0.85; 95% CI: 0.76, 0.96) and green tea (RR: 0.93; 95% CI: 0.88, 0.99). The dose-response meta-analysis showed that drinking less than four cups of black tea daily may effectively prevent CAD, while more than 4–6 cups/d will promote disease risk. Furthermore, the dose-response relationship between green tea consumption and the prevention of CAD showed that the risk of CAD gradually decreased as green tea consumption increased. We also demonstrated that the more cups of green tea consumed, the lower the risk of CAD. In the subgroup analysis by continent, a significant negative correlation between CAD risk and green tea consumption was observed in the Asian population (RR: 0.92; 95% CI: 0.85, 0.99) but not in the western population [North America (RR: 0.97; 95% CI: 0.92, 1.03), Europe/Oceana (RR: 0.91; 95% CI: 0.78, 1.07)].

Conclusions: Higher green tea consumption was associated with reduced CAD risk, but drinking more than 4–6 cups of black tea per day may

increase the risk. This study offers new insight into the relationship between tea consumption and its preventive effect on CAD. However, further large prospective cohort studies are needed to validate these findings.

Systematic review registration: The protocol of this systematic review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) system (CRD42022348069).

KEYWORDS

tea, coronary artery disease, cardiovascular disease, dose-response, meta-analysis

Introduction

Despite significant advances in prevention and treatment, coronary artery disease (CAD) arising from atherosclerosis is a leading cause of morbidity, mortality, and disability worldwide (1, 2). With around 11.39 million CAD patients, the prevalence of CAD is increasing in China (3). The detrimental effect of CAD has become one of the key issues in terms of the economic burden on people in both developed and developing countries (4). Therefore, the primary prevention of CAD has become one of the major focuses of public health and preventive medicine.

As one of the most popular beverages in the world, tea consumption (black or green) has been regarded as health-promoting for millennia, and the polyphenols, particularly flavonoids in tea, are recognized as natural antioxidants and play an essential role in preventing cardiovascular disease, mainly due to their antiatherogenic and antithrombotic properties (5–7). Generally, tea may be classified into six types depending on its processing and fermentation: green tea, black tea, white tea, yellow tea, oolong tea, and dark tea (8, 9). Tea drinking and its preventative impact on CAD have previously been studied (10–17). The findings of these studies, however, are inconsistent and conflicting. Previous studies have shown that drinking tea may lower the risk of morbidity and mortality from cardiovascular disease (10–12). However, some studies have shown that drinking tea has minimal effect on cardiovascular disease (13, 15, 17). Wang et al. (18) conducted a meta-analysis that examined the relationship between black tea intake, green tea consumption, and the risk of CAD using published data from 18 studies. They revealed that black tea drinking was not associated with a lower risk of CAD, whereas green tea consumption reduced the risk of CAD. This meta-analysis, however, did not examine the dose-response association between tea drinking and the risk of CAD in detail. Furthermore, the studies in their meta-analysis varied greatly due to the types of tea, the differences in the surveyed population, gender, age, and other confounding factors.

To date, the association between tea consumption and the risk of CAD has not yet been fully elucidated. In this study, we performed a meta-analysis to provide comprehensive and updated evidence on the relationship between tea consumption and its preventive effect on CAD. Additionally, we conducted a dose-response meta-analysis to determine the optimal tea consumption for preventing CAD.

Methods

The protocol of this systematic review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) system (CRD42022348069). For this systematic review and meta-analysis, we followed the preferred reporting items for systematic reviews and meta-analyses (PRISMA) Guidelines (19). For the meta-analysis, the population, intervention, comparison, and outcome (PICO) format was used, i.e., P: people without coronary heart disease; I: green tea OR black tea; C: don't drink tea; O: the mortality or incidence of coronary heart disease.

Search strategy

We conducted a comprehensive search on the PubMed, Embase, Medline, and Cochrane library databases from their inception to May 2022 for prospective cohort studies published in journals that described the association between drinking different types of tea and the risk of CAD. The MeSH and search terms were: "tea" OR "black tea" OR "green tea" OR "flavonoid" OR "catechin" OR "cyanidanol" OR "theaflavin" combined with "coronary Disease" OR "Myocardial Ischemia" OR "myocard* infarct*" OR "coronary disease*" OR "ischemic heart" OR "atherosclerosis" OR "atherosclero*" OR "angina*" The search was restricted to human research, and the language of the publication was limited to English. We also reviewed the references of the retrieved articles to identify additional studies. One investigator (XY) screened the titles and abstracts of all identified articles; two researchers (XY and HD) read the full text to assess the eligible studies.

Eligibility criteria for study inclusion

This meta-analysis included studies that met the following criteria: (a) Study type: a cohort study or case-control study; (b) the exposure of interest: tea consumption; (c) the outcome: the prevalence or mortality of CAD (including myocardial infarction, CAD, non-stroke cardiovascular disease and other coronary events), (d) Studies that reported the 95% confidence interval odds ratio (OR) or relative risk (RR) of the relationship between black tea or green tea and CAD or provided other corresponding data to calculate the variance. If duplicate publications from the same study were found, we used the results of the study with the largest number of cases. The following were the exclusion criteria: meta-analyses, reviews, duplicate studies, and studies lacking adequate data.

Data extraction

The two researchers (XY and ZZ) independently extracted data using a standardized electronic format. The following data were extracted for each eligible study: the first author's name, year of publication, study site, sample size, sex, age range or average age, follow-up time, number of cases, exposure assessment methods, outcome measurements, odds ratio (OR) or relative risk (RR) between black and green tea and CAD and corresponding 95%CI. For dose-response analysis, we standardized all data as cup/day when the study reported daily, weekly, or monthly doses or times. When the tea consumption metric is expressed in grams (g) or milliliters (ml), we regarded 125 g/month as 2 cups/day and 237 ml as 1 cup (20). The discrepancies in data extraction among the three researchers were solved by a discussion with the third researcher (HD).

Quality assessment

The methodological quality was evaluated by the Newcastle-Ottawa scale (NOS) (21). NOS is a comprehensive tool that has been validated to assess the quality of observational research in the meta-analysis, and it is based on the following three subscales: selection (4 items), comparability (1 item), and results (3 items). The NOS star system was used to assess the quality of the included studies (range, 0–9 stars). Studies with scores >6 were regarded as high-quality, while those below four were excluded. The quality evaluation was carried out by two authors (ZZ and YQ) independently, and the information was reviewed and verified by another author (XY).

Statistical analysis

The random effect model was used to calculate the aggregate RR and corresponding 95% CI of the highest and lowest levels of black and green tea consumption and dose-response analysis. Analysis was performed using the Mantel-Haenszel random effects model (22). For studies that include data from multiple queues, we regard the analysis of each queue as an independent report. Seven studies reported estimates of black and green tea consumption and CAD risk by sex (male and female). One article may be divided into two separate reports. In any study that separately expressed lethal CAD and non-lethal MI, the analysis of each gender or subtype of CAD was also considered an independent report. In addition, we also carried out subgroup analyses, such as gender, age, race, etc., to analyze the differences in the role of tea drinking in different populations. For dose-response analysis, we used the methods described by Greenland and Longnecker to calculate trends from the correlation estimates of the relative risk of black and green tea consumption (23). According to this method, tea consumption, the number of cases, RRs, and 95% CI were extracted. We evaluated heterogeneity by estimating the variance between studies using Q and I^2 statistics. In order to adjust the type I and type II errors, we set the significance level to the traditional 0.05. When statistical heterogeneity was detected, the source of heterogeneity was explored, and subgroup analysis and regression were performed. A funnel chart and Egger's test were used to evaluate potential publication bias (24, 25). The trim and fill method was used to examine the possible effect of publication bias on the results (26). All analyses were conducted with STATA 17 software (STATA Corp, College Station, TX). *P*-values were two-tailed, and $p < 0.05$ were considered statistically significant.

Results

Search results

The flowchart of the literature search and study selection process is presented in Figure 1. We identified 7,551 studies from a database search and ten additional records through other sources, from which 1,839 duplicate studies were excluded. After duplicates were removed, the titles and abstracts of 5,722 records were assessed. A total of 279 full texts were assessed, and after a further detailed evaluation of the full text, 35 prospective observational studies were included in this meta-analysis. Details of reasons for exclusion are reported in Figure 1.

Study characteristics

The characteristics of the included studies are shown in Table 1 (black tea) and Table 2 (green tea). These studies were published between 1972 and 2020, with follow-up periods ranging from 1 to 34 years. There were 11 studies on black tea (10, 27–36) and 24 studies (13–16, 37–56) on green tea. There were 13 studies from the United States, seven from Europe, and 15 from Asia (China and Japan).

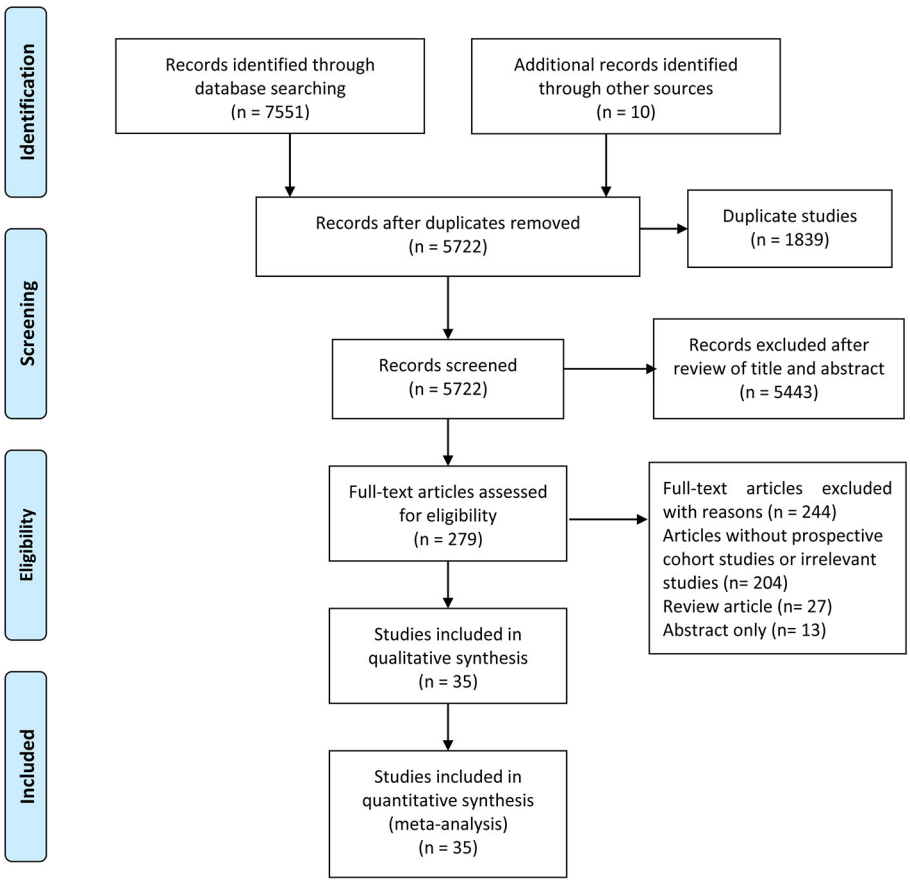

FIGURE 1
Flow diagram of literature search and study selection.

Quality of included studies

The overall NOS score of each included study is presented in Supplementary Table 1. Overall, 21 studies were evaluated as having high methodological quality, while the remaining 14 were considered low methodological quality (Figure 2).

Black tea

Eleven studies investigated the relationship between the highest vs. the lowest categories of black tea consumption and the risk of CAD. Figure 3 depicts the RRs of CAD for the highest vs. lowest total black tea consumption categories, demonstrating an association between the highest black tea consumption and CAD risk (summary RR: 0.85; 95% CI: 0.76, 0.96) with a high degree of heterogeneity ($I^2 = 73.2\%$; $P < 0.001$). We performed subgroup and regression analyses to investigate the sources of heterogeneity. Subgroup analyses were performed according to continent, nationality, study design, and gender (Figures 4, 5). Although no source of heterogeneity was found in the subgroup analysis, we found that studies in the United States, Norway, and the Netherlands supported that black tea drinking could reduce the risk of CAD. Notably, sub-group analysis by nationality revealed that black tea might reduce the incidence of CAD by 50% in Norway (RR: 0.46 95% CI:0.29, 0.75) and the Netherlands (RR: 0.54 95% CI: 0.35, 0.82) (Figure 4).

In addition, we performed a meta-regression analysis on the publication year and follow-up time to check whether the heterogeneity was caused by this (tau = 0.01662), a decrease of 0.00208 compared with the prior (tau 0.0187), indicating that this was attributable to study year differences. The difference in follow-up time could explain 11.12% of the heterogeneity. We created a funnel plot to evaluate the publication bias (Figure 6). We also used Egger's test to assess publication bias quantitatively (Figure 6). Egger's test revealed no evidence of publication bias ($P = 0.519$, 95% CI = −2.20, 1.18).

Our dose-response analysis did not show a linear-dose-response relationship (chi2 (1) = 16.59 Prob>chi2 = 0.0000). Therefore, we established a regression model using the

TABLE 1 Epidemiological studies on black tea consumption in association with coronary artery disease (CAD) risk.

Study (year)	Country	Design	Study period	Follow–up	Gender	Outcome	Simple size[2]	Tea consumption	RR/OR (95% CI)	Continent
Stensvold et al. (27)	Norway	Cohort	1976–1988	13 Y	M	CD	141/9,863	<1 cup/d	1	Northern
								≥1 cup/d	0.49 (0.30–0.81)	Europe
					F	CD	18/10,224	<1 cup/d	1	Northern
								≥1 cup/d	0.29 (0.07–1.28)	Europe
De Koning Gans et al. (10)	USA	Cohort	1998–2010	13 Y	both	CHD	1,387/37,514	<1 cup/d	1	North America
								1–2 cups/d	0.93 (0.81–1.06)	
								2.1–3 cups/d	0.74 (0.72–1.06)	
								3.1–4 cups/d	0.88 (0.72–1.06)	
								4.1–6 cups/d	0.91 (0.74–1.11)	
								>6 cups/d	0.64 (0.46–0.90)	
Geleijnset al. (28)	USA	Cohort	1990–2001	12 y	Both	MI	146/4,661	0	1	North America
								1–375 ml/d	0.72 (0.49–1.13)	
								>375 ml/d	0.51 (0.30–0.84)	
Hertog et al. (29)	Netherland	Cohort	1960–1993	34 y	M	CHD death	43/762	≤1 cup/d	1	Europe
								1–2 cups/d	0.48 (0.22–1.01)	
								≥3 cup/d	0.55 (0.27 1.13)	
Hertog et al. (30)	USA	Cohort	1983–1996	13 y	M	IHD death	131/1,769	0–300 ml/d	1	North America
								450–750 ml/d	1.6 (0.80–3.00)	
								900–1,200 ml/d	2.1 (1.10–4.10)	
								>1,200 ml/d	2.2 (1.00–4.70)	
Keli et al. (31)	Netherlands	Cohort	1970–1996	27 y	M	stroke	42/510	<330 ml/d	1	Europe
								330–586.6 ml/d	0.6 (0.31–1.18)	
								≥586.7 ml/d	0.38 (0.15–0.99)	
Sesso et al. (32)	USA	Case control	1984–1999	16 y	Both	MI	341/680	0	1	North America
								1–3 cup/month	0.86 (0.70–1.04)	
								1–6 cup/week	0.86 (0.70–1.06)	
								≥1 cup/d	0.75 (0.61 0.92)	

(Continued)

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TABLE 1 (Continued)

Study (year)	Country	Design	Study period	Follow–up	Gender	Outcome	Simple size[2]	Tea consumption	RR/OR (95% CI)	Continent
Woodward et al. (33)	UK	Cause control	1984–1993	7.7 y	F	IHD	47/6,703	0 cup/day	1	Europe
								1–2 cups/day	0.74 (0.25–2.15)	
								3–4 cups/day	0.76 (0.25–2.25)	
								5 cups/day	1.41 (0.54–3.69)	
					M	IHD	159/5,724	0 cup/day	1	Europe
								1–2 cups/day	1.17 (0.6–2.29)	
								3–4 cups/day	1.34 (0.71–2.53)	
								5 cups/day	1.96 (1.07–3.57)	
Rosenberg et al. (34)	USA	Cause control	1976–1979	3 y	F	MI	472/1,423	0 cup/day	1	North America
								1–2 cups/day	0.81 (0.69–0.97)	
								3–4 cups/day	0.94 (0.71–1.25)	
								5 cups/day		
Klatsky et al. (35)	USA	Cause control	1978–1985	7 y	both	MI	4208/125356	0 cup/day	1	North America
								<1 cup/day	0.77 (0.72–0.83)	
								1–3 cups/day	0.92 (0.85–1)	
								>=4 cups/day	1.08 (0.91–1.29)	
Sesso et al. (36)	USA	Cohort	1977–1988	11 y	both	CHD	1,613/1,7228	0 cup/day	1	North America
								<1 cup/d	0.97 (0.85–1.11)	
								1cup/d	0.98 (0.89–1.09)	
								2 cups/d	0.93 (0.83–1.04)	
								3 cups/d	0.85 (0.69–1.06)	
								≥4 cups/d	0.98 (0.82–1.18)	

CD, coronary death; CHD, coronary heart disease; MI, myocardial infarction; CAD, coronary artery disease; d, day; RR, relative risk; OR, odd ratio; CI, confidence interval.
[2]Cases/controls or cohort size.

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TABLE 2 Epidemiological studies on green tea consumption in association with coronary artery disease (CAD) risk.

Study (year)	Country	Design	Study period	Follow–up	Gender	Outcome	Simple size[2]	Tea consumption	RR/OR, (95% CI)	Continent
Tavani et al. (37)	Italy	Case control	1995–1999	4 y	Both	MI	507/985	<1 cup/d	1	Europe
								≥1 cup/d	1 (0.7–1.3)	
Thrift et al. (38)	Australia	Case control	1990–1992	3 y	Both	Stroke	331/662	<1 cup/day	1	Europe
								≥1 cup/day	1.35 (0.93–1.96)	
Tian et al. (39)	China	Cohort	2008–2013	5 y	M	CHD	968/8,585	<1 cup/day	1	Asia
								≥1 cup/day	0.84 (0.74–0.95)	
					F	CHD	1,097/9,789	<1 cup/day	1	Asia
								≥1 cup/day	0.83 (0.72–0.96)	
Wang et al. (40)	China	Case control	2008–2009	1 y	M	CAD	246/379	0 g/month	1	Asia
								<125 g/month	1 (0.59–1.72)	
								125–249 g/month	0.45 (0.24–0.82)	
								>250 g/month	0.42 (0.22–0.81)	
					F	CAD	89/151	<1 cup/day	1	Asia
								≥1 cup/day	0.65 (0.27–1.57)	
Hirvonen et al. (41)	USA	Cohort	1986–1993	6 y	F	CD	815/27,122	<1 cup/day	1	North America
								≥1 cup/day	1.09 (0.92–1.30)	
Wen et al. (42)	China	Case control	2002–2006	4 y	M	MI	518/2,590	<1 cup/day	1	Asia
								≥1 cup/day	0.89 (0.72–1.09)	
Sato et al. (15)	Japan	Cohort	1984–1988	4 y	F	Stroke	174/9,511	<5 cups/day	1	Asia
								≥5 cups/day	0.35 (0.24–0.51)	
Hirano et al. (43)	USA	Cohort	1986–1993	6 y	F	CD	815/24,304	<1 cup/day	m 1	North America
								≥1 cup/day	1.09 (0.91–1.30)	
Gramenzi et al. (14)	Italy	Case control	1983–1989	5 y	F	MI	287/936	<1 cup/day	1	Europe
								1 cup/day	0.66 (0.47–0.91)	
								>1 cups/day	0.88 (0.57–1.37)	
Klatsky et al. (44)	USA	Cohort	1978–1986	5 y	both	MI	740/11,900	0 cup/day	1	North America
								<1 cup/day	0.82 (0.7–0.98)	
								1–3 cups/day	1.01 (0.83–1.22)	
								4–6 cups/day	0.79 (0.44–1.42)	
								>6 cups/day	1.49 (0.77–2.89)	
Boston study et al. (45)	USA	Case control			both	MI	276/1,380	0 cup/day	1	North America
								1–5 cups/day	0.9 (0.72–1.11)	
								≥6 cups/day	0.71 (0.4–1.25)	

(Continued)

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TABLE 2 (Continued)

Study (year)	Country	Design	Study period	Follow–up	Gender	Outcome	Simple size[2]	Tea consumption	RR/OR, (95% CI)	Continent
Hao et al. (46)	China	Case cohort	1999–2003	4 y	both	MI	3,039/6,146	0 cup/day	1	Asia
								1 cup/day	1.1 (1.02–1.18)	
								2 cups/day	1.03 (0.96–1.12)	
								3 cups/day	1.13 (1.05–1.22)	
								≥4 cups/day	1.15(1.06–1.24)	
Sano et al. (47)	Japan	Case control	1997–2003	6 y	both	CAD	109/203	0–3 cups/day	1	Asia
								4–7 cups/day	0.79 (0.61–1.03)	
								8–11 cups/day	0.26 (0.11–0.58)	
								12–15 cups/day	0.75 (0.33–1.68)	
								16–19 cups/day	1.12 (0.5–2.53)	
								20–23 cups/day	0.25 (0.02–3.14)	
								24–27 cups/day	0.37 (0.03–4.14)	
Miller et al. (48)	USA	Cohort	2000–2013	11.1 y	both	MI	3,115/6,187	0 cup/day	1	North America
								<1 cup/day	1.07 (0.89–1.28)	
								1 cup/day	1.04 (0.88–1.22)	
Li et al. (49)	China	Cohort	2004–2013	7.2y	both	IHD	6,377/1,28280	0	1	Asia
								0–1cup/day	0.97 (0.94–1)	
								1–1.5 cup/day	0.94 (0.9–0.99)	
								1.5–2.5 cups/day	0.93 (0.87–1)	
								>2.5 cups/day	0.96 (0.9–1.02)	
Kishimoto et al. (50)	Japan	Case control	2008–2017	9 y	both	MI	388/612	<1 cup/day	1	Asia
								1–3 cups/day	0.9 (0.79–1.04)	
								>3 cups/day	0.82 (0.68–0.98)	
Kokubo et al. (51)	USA	Cohort	1995–2007	13 y	both	CHD	910/82,369	None	1	North America
								1–2 cup/week	0.8 (0.61–1.04)	
								3–6 cup/week	0.99 (0.76–1.29)	
								1 cup/d	0.91 (0.7–1.18)	
								2–3 cups/d	0.82 (0.67–1.02)	
								>=4 cups/d	0.99 (0.83–1.2)	

(Continued)

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TABLE 2 (Continued)

Study (year)	Country	Design	Study period	Follow–up	Gender	Outcome	Simple size[2]	Tea consumption	RR/OR, (95% CI)	Continent
Pang et al. (52)	China	Case control	2012–2014	3 y	both	CHD	370/628	0	1	Asia
								1–2 cups/d	0.95 (0.83–1.09)	
								3 cups/d	0.7 (0.57–0.86)	
Yan et al. (53)	USA	Cohort	1971–2017	47y	both	cardiovascular disease	250/11,808	0 cup/week	1	North America
								1–7 cup/week	1.17 (0.865–1.577)	
								8–14 cup/week	1.26 (0.88–1.80)	
								>14 cup/week	0.94 (0.58–1.53)	
Liu et al. (54)	China	Cohort	1990–2016	27 y	M	cardiovascular disease	11,839/1,62,681	0	1	Asia
								≤5 cup/d	0.93 (0.85–1.01)	
								5–10 cup/d	0.91 (0.85–0.98)	
								>10 cup/d	0.86 (0.79–0.93)	
Xiang et al. (55)	China	Case control	2013–2014	1 y	M	CHD	172/277	0	1	Asia
								1–2 cups/d	1.11 (0.78–1.56)	
								3–5 cups/day	1.29 (1.02–1.64)	
								>5 cups/d	1.19 (0.93–1.53)	
					F	CHD	94/251	0	1	Asia
								1–2 cups/d	1.51 (0.96–2.38)	
								3–5 cups/day	0.64 (0.39–1.06)	
								>5 cups/d	0.79 (0.4–1.58)	
Mineharu et al. (13)	Japan	Cohort	1988–2003	13.1 y	Both	CHD	729/74,789	None	1	Asia
								0–1 cup/d	0.34 (0.06–1.75)	
								1–2 cups/day	0.28 (0.07–1.11)	
								3–5 cups/day	0.39 (0.18–0.85)	
								>6 cups/day	0.42 (0.15–0.92)	
Kuriyama et al. (16)	China	Cohort	1994–2006	13 y	M	CHD	129/19,060	1 cups/d	1	Asia
								1–2 cups/d	1.03 (0.62–1.71)	
								3–4 cups/d	0.96 (0.57–1.62)	
								>5 cups/d	0.91 (0.56–1.48)	

(Continued)

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TABLE 2 (Continued)

Study (year)	Country	Design	Study period	Follow–up	Gender	Outcome	Simple size[2]	Tea consumption	RR/OR, (95% CI)	Continent
					F	CHD	80/21,470	1 cups/d	1	Asia
								1–2 cups/d	1.04 (0.54–2.01)	
								3–4 cups/d	0.79 (0.4–1.56)	
								>5 cups/d	0.77 (0.42–1.44)	
Chen et al. (56)	China	Cohort	2013–2014	2 y	F	CHD	157/256	0	1	Asia
								1–2 cups/d	1.867 (1.018–3.426)	
								>3 cups/d	1.834 (0.947–3.551)	
					M	CHD	91/212	0	1	Asia
								1–2 cups/d	0.323 (0.173–0.601)	
								>3 cups/d	1.497 (0.436–2.439)	

CD, coronary death; CHD, Coronary Heart Disease; MI, myocardial infarction; CAD, coronary atherosclerotic heart disease; d, day; RR, relative risk; OR, odd ratio; CI, confidence interval.
[2]Cases/controls or cohort size.

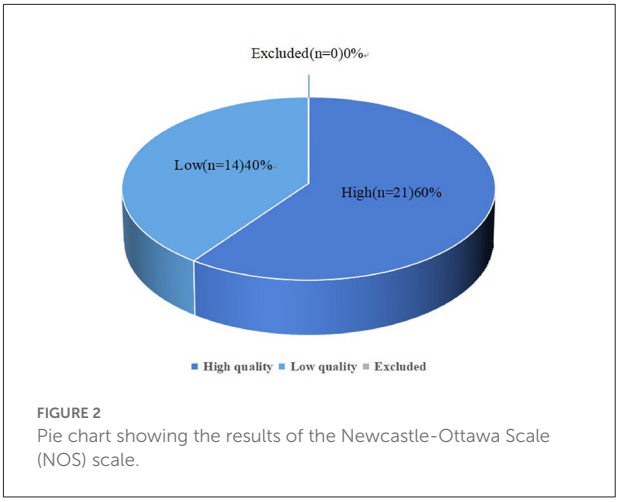


FIGURE 2
Pie chart showing the results of the Newcastle-Ottawa Scale (NOS) scale.

regression coefficients of the nonlinear regression equation and plotted the non-linear dose-response meta-analysis graph. As shown in Figure 7, drinking <3 cups of black tea daily may effectively prevent CAD, while more than 4–6 cups/d will promote the risk of disease.

Green tea

Twenty-four studies investigated the relationship between the highest vs. the lowest categories of green tea consumption and CAD risk. The pooled results showed the association between highest green tea consumption and CAD risk (summary RR: 0.93; 95% CI: 0.88, 0.99), with a high heterogeneity (I^2 = 79.3%; P < 0.001) (Figure 8). We used subgroup and regression analyses to account for the heterogeneity. We also did subgroup analysis according to gender, continent, nationality, study design, and gender (Figures 9, 10). The findings revealed that heterogeneity was associated with nationality: the Japanese group (I^2 = 80.8%, p < 0.001), the Italian group (I^2 = 78.4%, p = 0.032), and the Chinese group (I^2 = 83.5%, p < 0.001). Further assessment of a meta-analysis for the dimensions of published time and study location showed the heterogeneity of this study (tau^2 = 0.2892) was higher than the previous (tau^2 = 0.0134), which indicated that the heterogeneity could not be explained by different years and regional dimensions of the study.

A funnel plot (Figure 11) and Egger's test (Figure 11) were used to assess publication bias, with the result of Egger's test indicating that bias may exist. To determine the impact of this bias on the conclusion, we used the trim and fill method (diff = 0) and found that the final number of missing literature was k = 0, which indicated that despite the publication bias, our findings were robust.

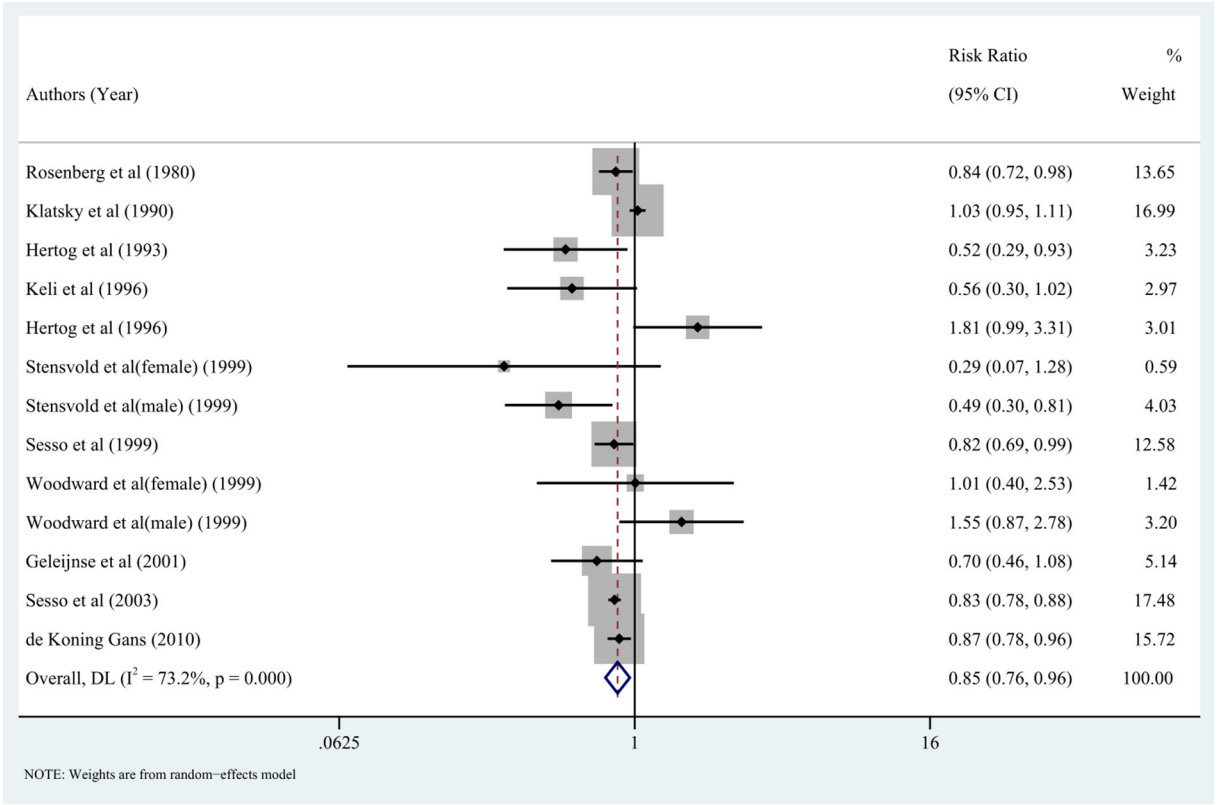


FIGURE 3
Forest plot: Summary relative risks (RRs) of coronary artery disease (CAD) for comparing the highest black tea consumption with the lowest black tea consumption. The squares indicate study-specific risk estimates (the size of the square reflects the study's statistical weight), the horizontal lines indicate the 95% confidence intervals (CIs), and the diamond shows the summary RR estimate with its corresponding 95% CI.

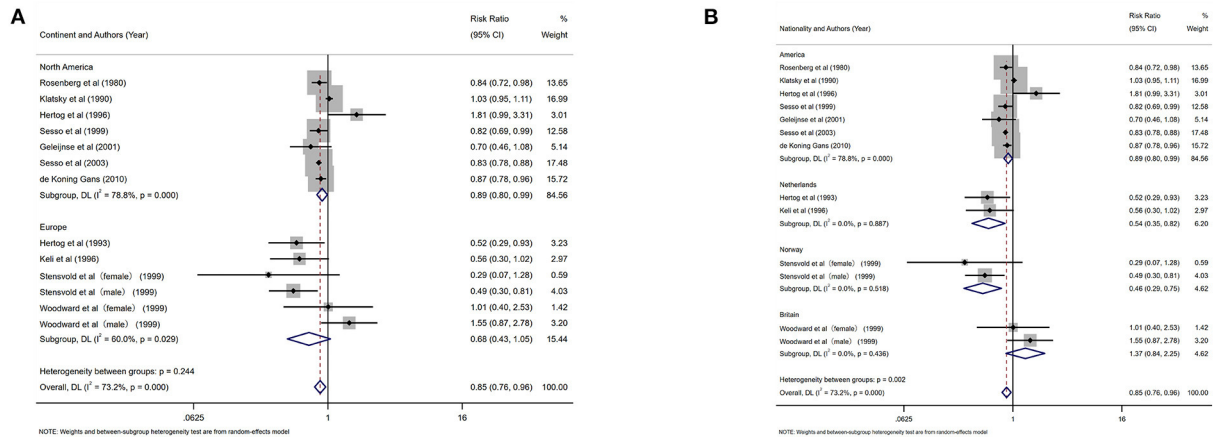


FIGURE 4
Forest plot: results of subgroup analysis of black tea consumption and coronary artery disease (CAD) risk. **(A)** Forest plot of black tea consumption and CAD risk after subgroup analysis stratified by continent. **(B)** Forest plot of black tea consumption and CAD risk after subgroup analysis stratified by country.

The dose-response analysis showed that the increase in green tea consumption by 1 cup per day did not result in a statistically significant reduction in the risk of CAD (summary RR = 0.98; 95% CI = 0.95, 1.02). However, the non-linear test result (I^2 = 0.47%, P = 0.49) was statistically significant; thus, we fitted both non-linear and linear models (Figure 12). Our findings revealed

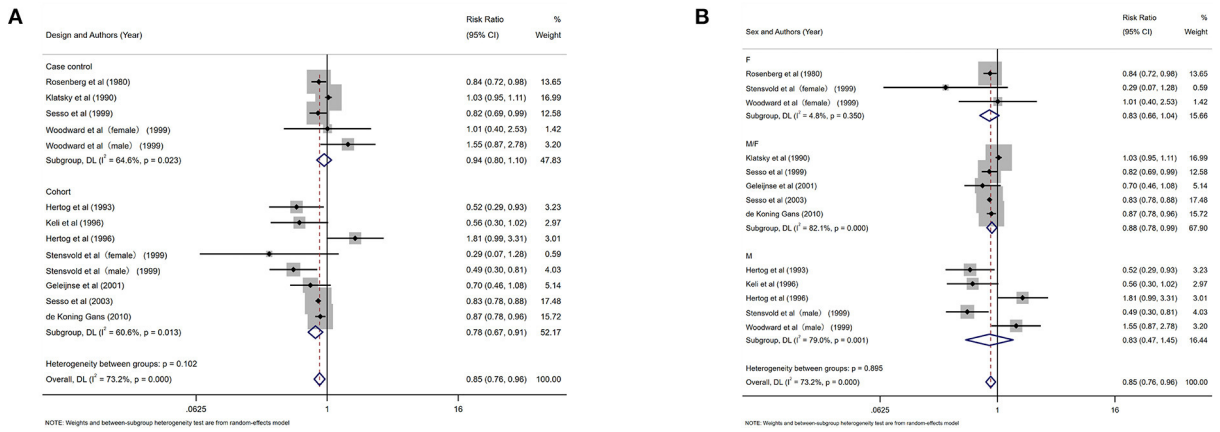


FIGURE 5
Subgroup analysis of black tea intake and coronary artery disease (CAD) risk. **(A)** Forest plot of subgroup analysis stratified by the study design. **(B)** Forest plot of subgroup analysis stratified by gender.

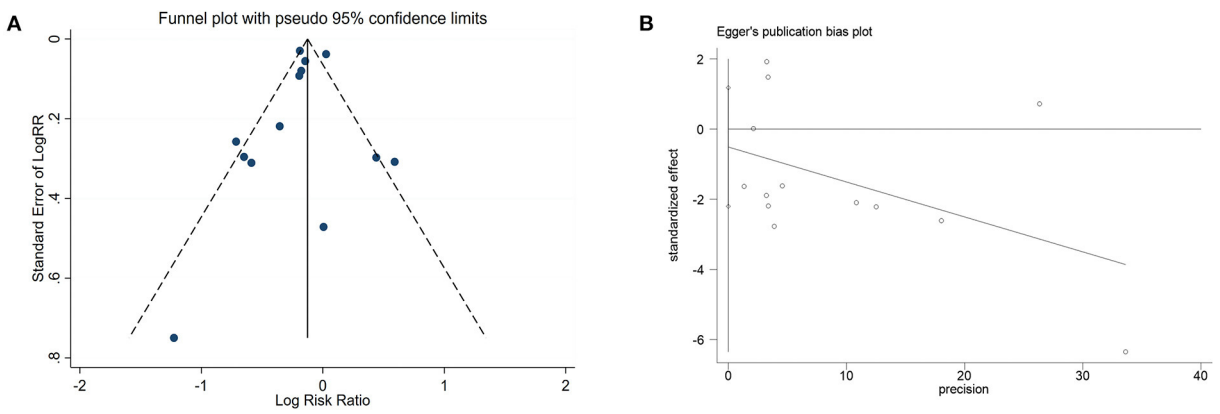


FIGURE 6
Funnel plot and Egger's test analyses to detect publication bias of studies on black tea consumption and coronary artery disease (CAD) risk. **(A)** Funnel plot: used to detect the publication bias studies. **(B)** Egger chart: used to detect the publication bias of studies.

that the RR of these two models decreased as the number of green tea cups consumed per day increased.

Discussion

Tea is a traditional and popular beverage worldwide; regular tea consumption as part of a healthy habitual dietary pattern may substantially impact public health. To our knowledge, this is by far the largest meta-analysis assessing the association between tea consumption and its preventive effect on CAD. In this systematic review and meta-analysis of 35 observational studies, the pooled analysis showed that both black and green tea consumption might significantly reduce the risk of CAD. In dose-response analysis, a moderate amount of black tea drinking (<4 cups per day) has been shown to be beneficial; however, a large amount (more than 4–6 cups per day) has been shown to increase the risk of CAD. The dose-response relationship between green tea consumption and prevention of CAD based on linear and non-linear models revealed that the risk of CAD gradually decreased as green tea consumption increased.

The concept that tea intake may help prevent coronary artery disease has received much interest among medical professionals and the general public. The meta-analysis by Wang et al. (18) revealed that an increase in green tea consumption by one cup/d was associated with a 10% decreased risk of CAD. Consistent with findings from a meta-analysis by Wang et al. (18), we observed that green tea drinking could prevent CAD in this study. Concerning the biological mechanisms involved in the prevention of CAD, studies have shown that

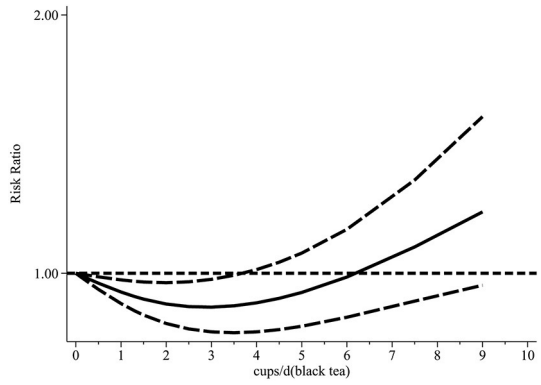


FIGURE 7
Dose-response relationship between black tea cup number (cups/d) and coronary artery disease (non-linear model).

tea is high in antioxidant polyphenols (catechins, flavonols, theaflavins, and thearubigins) that protect the cardiovascular system (6, 57, 58). Catechins are flavan-3-ols that account for 30%–42% of the dry weight of tea (59). Studies have shown that catechin may promote nitric oxide production and enhance endothelial function (60, 61). Moreover, green tea contains more catechin polyphenols than black tea, and catechins have been shown to have vascular protective benefits through various pathways, including antioxidative, antihypertensive, anti-inflammatory, anti-proliferative, anti-thrombogenic, and lipid-lowering properties (62). Moderate tea consumption enhances endothelium-dependent vasodilation and significantly decreases blood pressure, which is beneficial for the cardiovascular system (63). Furthermore, tea drinking may reduce low-density lipoprotein cholesterol (LDL-c) and delay the formation of atherosclerosis (64). Tea's antioxidant

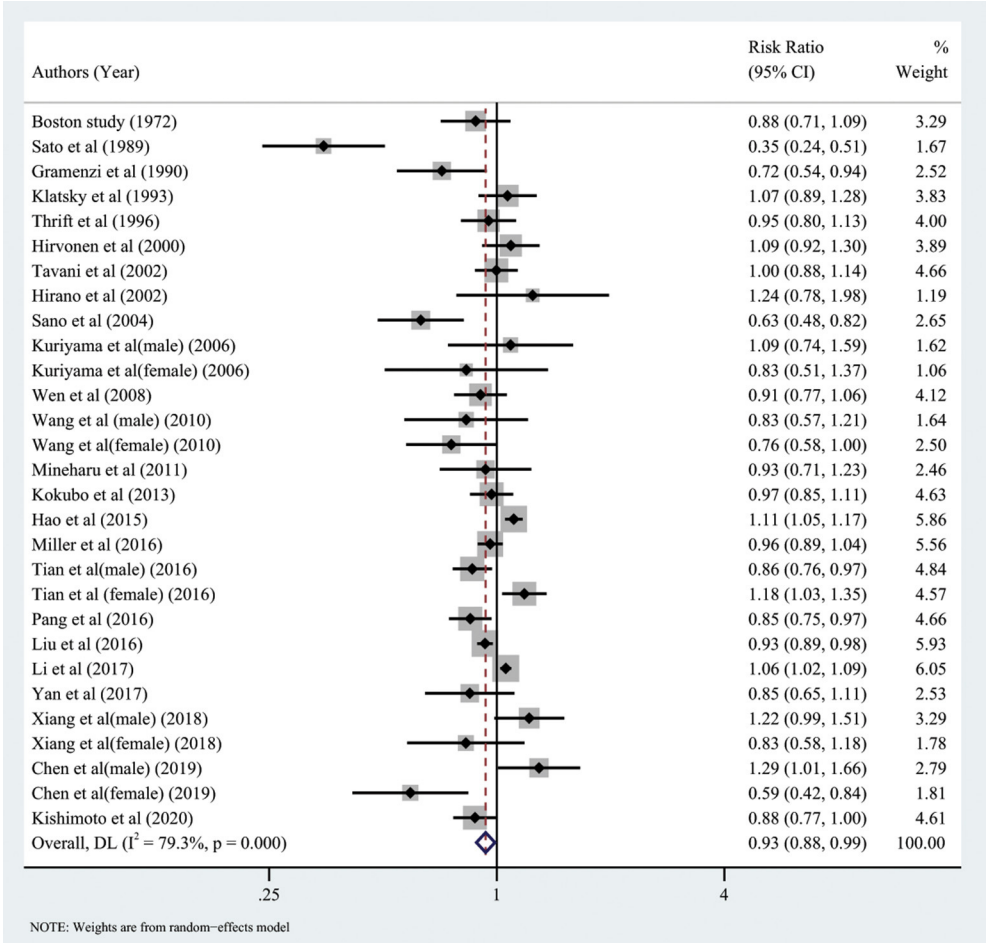
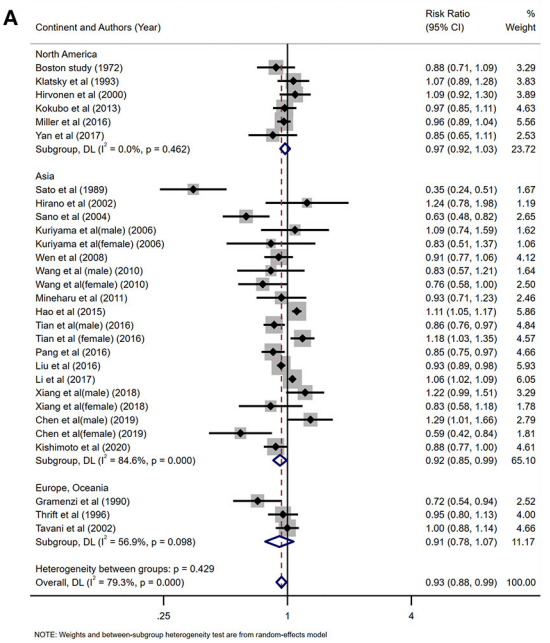


FIGURE 8
Forest plot: Summary relative risks (RRs) of coronary artery disease for comparing the highest green tea consumption with the lowest green tea consumption. The squares indicate study-specific risk estimates (the size of the square reflects the study's statistical weight), the horizontal lines indicate the 95% confidence intervals (CIs), and the diamond shows the summary RR estimate with its corresponding 95% CI.



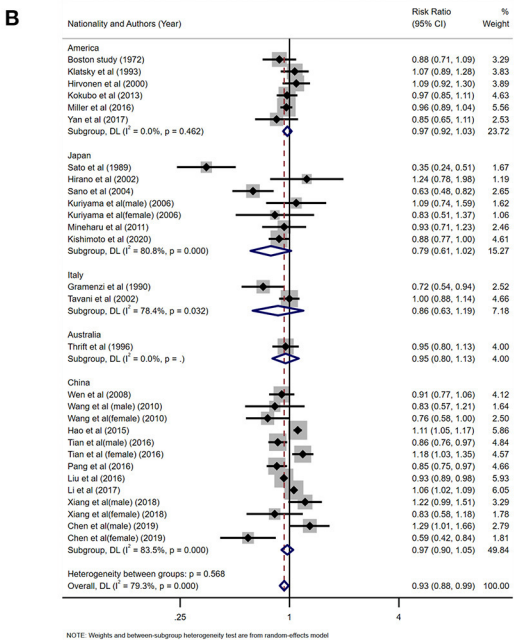
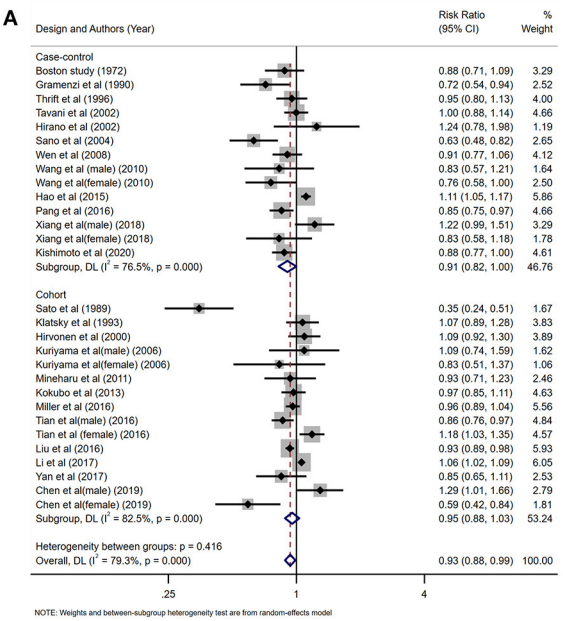


FIGURE 9
Forest plot: results of subgroup analysis of green tea consumption and coronary artery disease (CAD) risk. **(A)** Forest plot depicting green tea consumption and CAD risk after subgroup analysis stratified by continent. **(B)** Forest plot showing green tea consumption and CAD risk after subgroup analysis stratified based on country.



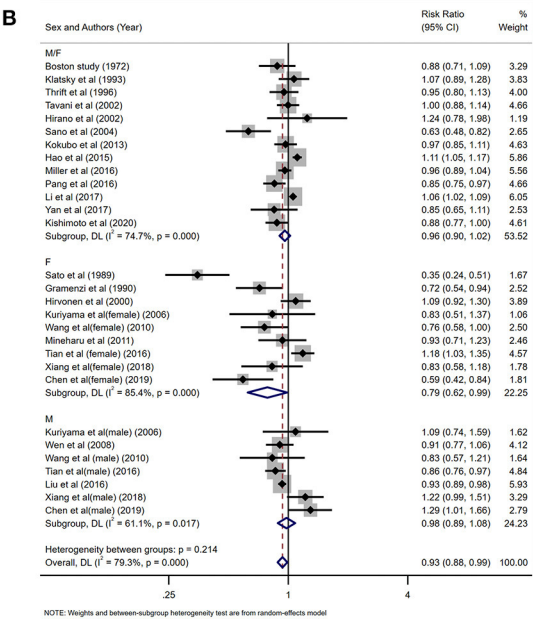


FIGURE 10
Forest plot depicting the subgroup analysis of green tea intake and coronary artery disease (CAD) risk. **(A)** Subgroup analysis forest plot stratified by the study design. **(B)** Forest plot of subgroup analysis based on gender.

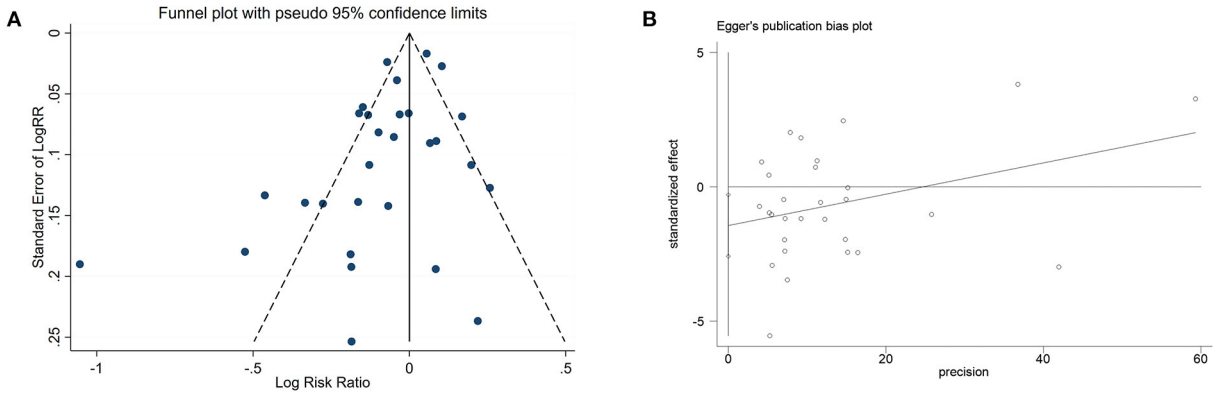


FIGURE 11
Funnel plot and Egger's test analyses to detect publication bias of studies on green tea consumption and coronary artery disease (CAD) risk. **(A)** Funnel plot: used to detect studies on green tea consumption and CAD risk publication bias. **(B)** Egger chart: used to detect studies evaluating green tea consumption and CAD risk publication bias.

and antithrombotic properties are significant in preventing CAD (62).

In line with our findings, a dose-response meta-analysis of 22 prospective observational studies (65) examining the relationship between tea consumption and major cardiovascular outcomes found that increasing tea consumption by three cups per day was associated with a lower risk of coronary heart disease, cardiac death, stroke, and cerebral infarction. However, the main limitation of the meta-analysis by Zhang et al. (65) was the use of diverse methodologies for evaluating tea intake and varied cup sizes. Another systematic review and meta-analysis (66) evaluating the link between tea consumption and CVD risks found that an increase in daily tea intake by one cup (236.6 mL) was associated with lower risks of CVD mortality by 4%. Nonetheless, in the present study increasing green tea intake by one cup per day did not result in a statistically significant decrease in the risk of CAD.

In contrast with the findings of a previous meta-analysis (18), we found that a moderate amount of black tea drinking (<4 cups/d) was associated with a reduction of CAD risk, while daily consumption exceeding 4–6 cups would increase the risk. To the best of our knowledge, the present study is the first to report these findings. As previously mentioned, catechins present in both green and black tea have cardioprotective qualities (60, 62). The catechin concentration of partly fermented black tea is about half that of green tea (67), which may explain the discrepancy in the dose-response relationship between black tea and green tea. Furthermore, a recent double-blind, randomized, placebo-controlled cross-over study (68) found that black tea may significantly raise central systolic blood pressure compared to green tea and placebo. Because black tea contains more caffeine than green tea, this effect could be attributed to caffeine. Therefore, we speculate that caffeine has a more significant

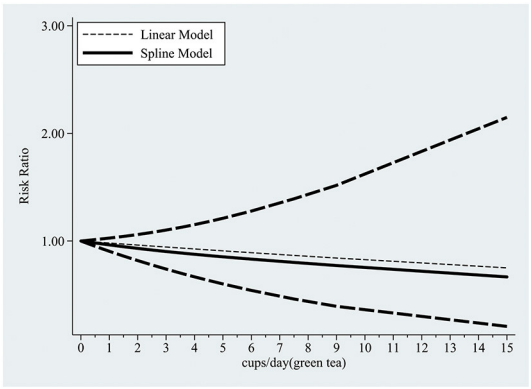


FIGURE 12
The dose-response relationship between green tea cup number (cups/d) and coronary artery disease (linear and non-linear models).

impact on raising blood pressure and increases the risk of CAD when the dosage of black tea exceeds 4–6 cups. In subgroup analysis, we found a noteworthy and significant finding that there was a substantial inverse correlation between green tea drinking and the incidence of CAD in Asian populations but not in Western ones. Due to a lack of relevant gene sequencing data, we could not explain this variance from an ethnic or genetic viewpoint, although the influence of varied cooking techniques may play a role. Orientals prefer to boil tea with only hot water; however, in the west, high-lipid components such as milk are added to tea, which may elevate blood cholesterol and reduce the decrease the benefit of catechins (69, 70). In addition, Orientals treat tea drinking as a self-cultivation practice, and this emotional recognition may also affect blood pressure (68, 69).

Strengths and limitations of this study

This study has the following strengths. Firstly, this systematic review and meta-analysis assessing the association between tea consumption and the risk of CAD are the largest to date, with more than two times the number of studies included in the previous meta-analysis. Secondly, we demonstrated a novel finding of a significant inverse association between green tea consumption and CAD risk in Asian populations but not in Western populations. Thirdly, we performed a dose-response analysis to investigate the linear and non-linear relationships, which may help quantify these possible associations' linkages. In addition, the majority of the studies included in this analysis are prospective studies, which would reduce the recall bias to a certain extent.

There are several limitations of this meta-analysis. Firstly, the quantity of antioxidant components such as flavonoids in tea varies depending on tea variety and region of origin, and the size of cups was not stated in detail in some research; therefore, we tried our best to avoid potential confounding bias from cup size. Secondly, this meta-analysis is based on observational studies, which are prone to bias. We cannot rule out uncontrolled confounders, such as fruit and vegetable consumption, socioeconomic status, and education level, as a possible explanations for the observed link between tea consumption and CAD risk. Thirdly, measurement mistakes in food and nutrient consumption estimations are unavoidable, and measurement errors may result in underestimating the relationship between tea consumption and CAD risk. Finally, all the articles included are in English, which may indirectly restrict the range of countries where the studies originated, so the findings may not be generalized to other areas of the world.

Conclusions

In conclusion, the data presented in this study demonstrated that black tea and green tea had preventive effects on CAD. Green tea drinking could effectively reduce the risk of CAD in the Asian population (Chinese and Japanese), but not in Europeans and Americans. More than 4–6 cups of black tea consumption may promote CAD. The dose-response relationship of green tea showed that the risk of CAD gradually decreased with increased green tea consumption. Notably, the consumption of green tea in the Asian population is more popular than in western countries. Extrapolation of these results to the global population should be done with caution since the majority of studies included in the meta-analysis are from Asian nations, and few studies from other countries have been published. Therefore, further multi-center prospective studies should be conducted to examine the impact of tea drinking on the risk of CAD.

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/s.

Author contributions

XY, HD, RD, MG, and JS: conception and design of the study. XY, ZZ, RD, and YQ: acquisition and analysis of the data. XY, HD, RD, and JS: interpreted the results. XY, HD, and ZZ: drafted the manuscript. XY, HD, RD, ZZ, MG, YQ, and JS: review and editing. 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.

The handling editor declared a shared parent affiliation with the authors at the time of review.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2022.1021405/full#supplementary-material

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Secular trends of the prevalence of emaciation, overweight, and obesity among school-aged children in Yunnan province, 1985–2019: A serial cross-sectional surveillance study in China

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Objective: To understand the trends of nutrition in children and adolescents, which may further help to prevent and control chronic diseases in younger ages.

Methods: The Chinese National Surveys on Students' Constitution and Health (CNSSCH) in Yunnan is a survey of growth conditions, physical fitness, and health status of students in Yunnan and uses a series of complex multistage stratified sampling of seven prefectures consisting of 16 counties. Sampling schools were held constant over 35 years. The participants were randomly selected among 7–18 aged students. We used data from 1985, 1991, 2000, 2005, 2010, 2014, and 2019 CNSSCH of Yunnan. According to body mass index (BMI) criteria of National Working Group for Obesity in China (WGOC-BMI criteria), a participant's nutrition (emaciation, overweight or obesity) was defined. This study is based on survey data from 129,520 participants in 1985 (n = 14,683), 1991 (n = 4,894), 1995 (n = 6,673), 2000 (n = 9,751), 2005 (n = 23,461), 2010 (n = 22,889), 2014 (n = 23,003) and 2019 (24,166).

Results: Since 1985, the trends of emaciation over 35 years were decreasing. Regardless of gender, area, and age, the prevalence of obesity and overweight were increased. The average annual growth rate of overweight and obesity was quicker in rural areas and boys than in urban areas and girls. In Yunnan, emaciation, overweight, and obesity disparity in children were common phenomena, with differences in areas and gender.

Conclusion: Children in Yunnan faced the triple burden of malnutrition (emaciation, overweight, and obesity). We should take comprehensive policies and effective intervention measures to decrease the rate of nutrition deficiencies in school-aged children.

KEYWORDS

nutrition, overweight and obesity, children, adolescent, epidemic, prevalence, trend

Introduction

Nutrition is associated not only with the growth and physical development of children and adolescents but also with their health throughout their life. A few studies have confirmed that the effects of nutrition on the development of children and adolescents extend to cardiorespiratory fitness, musculoskeletal growth, neurodevelopment, and the immune system, as well as any potential general health of children (1) and increase the risk of noncommunicable diseases in later life (2).

With unprecedented changes in the food environment and lifestyle, the problem of malnutrition is not prominent. Nonetheless, overweight and obesity in childhood and adolescence are the most important global public health challenges and influence all countries in the world (3, 4). The mean age-standardized body mass index (BMI) of children and adolescents has increased globally in most regions from 1975 to 2016. In school-aged children and adolescents, the number of people with obesity has increased by more than 10-fold over the last 40 years, from 11 to 124 million (2016 estimates). This global increase was observed in virtually identical age-standardized mean BMIs from 17.2 kg/m^2 in 1975 to 18.6 kg/m^2 for girls in 2016 and from 16.8 to 18.5 kg/m^2 for boys (5). China is no exception. With rapid economic growth and the urbanization of China, the prevalence of obesity has risen dramatically among children and adolescents in recent decades (4, 6, 7). Some cities (e.g., Beijing, Shanghai, Tianjin, Shijiazhuang, Shenyang, Dalian, Jinan, Qingdao, and Nanjing) had a prevalence of obesity very similar to developed countries (8, 9). Overweight and obesity in childhood not only affect their later growth, physical fitness, and mental health, but also cause obesity in adults, even leading to the early onset of chronic disorders such as hypertension, diabetes, asthma, fatty liver disease, cardiovascular and cerebrovascular diseases, or some advanced tumors (10–15). Obesity in childhood can be a serious threat to adult health (16), which increases the risk of morbidity and mortality in adults (14).

Abbreviations: WHO, World Health Organization; BMI, body mass index; CNSSCH, Chinese National Survey on Students' Constitution and Health; WGOC, Working Group for Obesity in China; OV, Overweight; OB, Obesity.

Yunnan province, located in southwest China, is one of the underdeveloped plateau regions with multi-ethnics in China. Few studies have estimated the epidemic situation of nutrition among children and adolescents in Yunnan. This information could guide interventions and strategies that not only prevent children and adolescents from experiencing malnutrition (emaciation, overweight and obesity), but also mitigate its consequences. Since 1985, we have conducted surveys on students' health among school children and adolescents every 5 years in Yunnan. This study aimed to explore the prevalence of nutrition (emaciation, overweight, and obesity) among school-aged children in Yunnan, to estimate the epidemic level and trends of child nutrition in Yunnan province over 35 years. We also provide baseline data for developing child nutrition prevention interventions in Yunnan.

Materials and methods

Survey sites

This study was conducted in seven prefectures consisting of 16 counties in Yunnan province, which accounted for 12.4% of the regions in the province, and sampling in schools was maintained over a 35-year period. In total, 62 schools were enrolled in our study with an average of 16,190 (129,520/8) students included annually.

Data collection

Data were obtained from the Chinese National Surveys on Students' Constitution and Health (CNSSCH) in Yunnan from 1985 to 2019. These surveys were implemented in 1985, 1991, 1995, 2000, 2005, 2010, 2014, and 2019. CNSSCH was a series of surveys with data being collected every 5 years. The sampling method was a complex multistage, cross-sectional, nationwide survey that used a standardized methodology (9).

In brief, at first, the study participants were randomly sampled from the seven surveillance prefectures (namely, Kunming, Honghe, Dali, Lijiang, Lincang, Nujiang, and Xishuangbanna) in Yunnan. In all prefectures, to achieve a better representation within seven prefectures, participants were

classified by gender and region (urban or rural) and each of the four groups consisted of equal numbers of individuals from three socioeconomic classes (upper, middle, and lower). In 1985, the five indicators used to define these socioeconomic classes were made prefecture-specific: the regional gross domestic product, total annual income per capita, average food consumption, and regional social welfare index (8, 17, 18). And, the surveillance regions remained constant from 1985 to 2019. Secondly, three urban areas and three rural areas were randomly selected from each prefecture. Then, we randomly selected several schools as surveillance schools in each area (including both junior and senior schools). These schools were randomly selected from a list compiled by the local education committee. And, surveillance schools remained constant from 1985 to 2019. Finally, a list of students from grades 1 to 12 was compiled, and a random selection of two or three classes (depending on their size) was made from each grade. Participants who have diseases in the heart, liver, kidney, and other major organs were excluded. Those who were not willing to sign informed consent were also excluded. Participants aged 7–18 years were randomly selected from surveillance primary and secondary schools in seven prefectures. And, all participants and/or their parents/guardians provided written informed consent. Data were collected through field interviews in all surveys. All surveys used the same sampling methods, surveillance areas, and surveillance schools.

Our study is based on the survey data from 129,520 participants in 1985 (n = 14,683), 1991 (n = 4,894), 1995 (n = 6,673), 2000 (n = 9,751), 2005 (n = 23,461), 2010 (n = 22,889), 2014 (n = 23,003), and 2019 (n = 24,166). The total number of participants comprises 1.32% of the total number of students in Yunnan.

Measurements and definitions

The surveys have included a standardized physical examination, which has been conducted by well-trained health workers who followed a reference protocol recommended by the WHO.

Physical examinations included the measurement of individuals' height and weight. Height was measured to the nearest 0.1 cm with a metal column height and sitting height measuring instrument when participants were without shoes. Weight was measured to the nearest 0.10 kg with a balance-beam scale when participants wore lightweight clothing. Both scales and stadiometers were calibrated before use (8, 9, 17, 18). BMI was calculated as weight in kilograms divided by height in meters squared. With reference to WHO Standards, emaciation was defined as BMI <(Means-2SD) (19). Sex- and age-specific BMI cutoff points, recommended by the Working Group for Obesity in China (WGOC-BMI criteria), were used to define overweight and obesity (19). A new BMI classification reference recommended by the WGOC in 2004 is considered to be the most appropriate, shows its superiority in both prospectiveness and authenticity, and is consistent with the Eastern Asia Ethnic characteristics of body fatness growth (20). For both boys and girls aged 7–17 years, overweight was defined as BMI ≥85th percentile but <95th percentile, stratified by gender and age, whereas obesity was defined as BMI ≥95th percentile. For both boys and girls aged 18 years, BMIs of 24.0 and 28.0 kg/m^2 are set as the cutoffs for overweight and obesity, respectively (19). This study adopted the WGOC-BMI criteria to define overweight and obesity.

Statistical analysis

The primary data analysis was conducted in 2022. Differences in the mean BMI by age, gender, and area (urban and rural) were compared using ANOVA test. The estimates of the prevalence of emaciation, overweight, and obesity in different survey years were stratified by age, gender, and area. The physical division of different areas was based on the Chinese Administrative Division.

For comparability, the age-standardized and gender-standardized prevalence of the population was calculated using the 2010 China Census as a standard population. Linear by linear association trend and chi-squared analyses were conducted to assess the trends and differences in the prevalence of emaciation, overweight, and obesity for subgroups. All data were analyzed using SPSS 21.0 software. Statistical significance was defined as $p < 0.05$.

Results

The demographic characteristics of participants

As shown in Table 1, the study samples were recruited from primary, middle, and high schools in Yunnan, China. A total of 129,520 students were included from 1985, 1991, 1995, 2000, 2005, 2010, 2014, and 2019 surveys, with 64,696 boys and 64,824 girls. The average age was 12.49 ± 3.45 years. In different years, there were no significant differences in the distribution of numbers by gender and age subgroups. These data could be compared ($p > 0.05$). There were 31,463 urban and 98,057 rural participants. There was a significant difference in the distribution of numbers by the area group from 1985 to 2019.

Secular changes in BMI

From 1985 to 2019, the mean BMI of boys increased from 16.82 to 18.54 kg/m^2, while it increased from 17.14 to 18.52 kg/m^2 for girls (Table 2). Compared with girls, the mean BMI for boys increased slightly faster. As shown in Figure 1, similar slight decreasing and then increasing trends were seen across

TABLE 1 The distribution of sociodemographic factors in survey children from 1985 to 2019.

Index	1985	1991	1995	2000	2005	2010	2014	2019	χ^2	P
All	14,683	4,894	6,673	9,751	23,461	22,889	23,003	24,116		
Gender									0.16	1.00
Boy	7,342	2,447	3,336	4,879	11,715	11,436	11,494	12,047		
Girl	7,341	2,447	3,337	4,872	11,746	11,453	11,509	12,119		
Age									3.73	1.00
7–9	3,672	1,223	1,664	2,447	5,909	5,742	5,749	6,018		
10–12	3,670	1,224	1,659	2,457	5,846	5,754	5,755	6,051		
13–15	3,669	1,224	1,671	2,464	5,824	5,750	5,747	6,062		
16–18	3,672	1,223	1,679	2,383	5,882	5,643	5,752	6,035		
Area									15149.70	0.00
Urban	7,341	2,447	4,032	2,521	3,909	3,595	3,600	4,018		
Rural	7,342	2,447	2,641	7,230	19,552	19,294	19,403	20,148		

TABLE 2 The mean BMI of survey children from 1985 to 2019.

Index	1985	1991	1995	2000	2005	2010	2014	2019	*F*	P
All	16.98 ± 2.62	17.09 ± 2.75	16.96 ± 2.76	17.26 ± 2.86	17.47 ± 2.87	17.74 ± 3.02	18.08 ± 3.23	18.53 ± 3.51	550.98	0.00
Gender									53.95	0.00
Boy	16.82 ± 2.34	17.04 ± 2.60	16.92 ± 2.61	17.19 ± 2.78	17.38 ± 2.75	17.64 ± 2.96	18.06 ± 3.26	18.54 ± 3.56		
girl	17.14 ± 2.85	17.14 ± 2.90	17.00 ± 2.90	17.33 ± 2.95	17.55 ± 2.98	17.84 ± 3.06	18.09 ± 3.19	18.52 ± 3.45		
Age									25365.79	0.00
7–9	14.55 ± 1.19	14.64 ± 1.50	14.45 ± 1.53	14.89 ± 1.80	15.06 ± 1.78	15.27 ± 1.95	15.54 ± 2.31	15.80 ± 2.39		
10–12	15.65 ± 1.58	15.92 ± 2.07	15.90 ± 2.17	16.06 ± 2.13	16.42 ± 2.33	16.76 ± 2.55	17.35 ± 3.02	17.71 ± 3.23		
13–15	18.06 ± 2.00	18.14 ± 2.13	18.03 ± 2.20	18.29 ± 2.34	18.55 ± 2.45	18.86 ± 2.57	19.11 ± 2.69	19.77 ± 3.07		
16–18	19.67 ± 1.85	19.66 ± 2.02	19.43 ± 1.98	19.87 ± 2.18	19.85 ± 2.15	20.11 ± 2.38	20.30 ± 2.64	20.81 ± 2.97		
Area									0.26	0.61
urban	16.80 ± 2.58	17.11 ± 2.79	17.03 ± 2.82	17.92 ± 3.18	17.97 ± 3.27	18.21 ± 3.44	18.56 ± 3.67	18.77 ± 3.75		
rural	17.17 ± 2.64	17.06 ± 2.71	16.86 ± 2.67	17.03 ± 2.71	17.37 ± 2.77	17.65 ± 2.92	17.98 ± 3.13	18.48 ± 3.46		

all age subgroups and in different genders ($p < 0.01$), with an average annual growth ranging from 0.09% to 0.33% (Table 2). BMI distribution curves for boys shifted upwards between 1985 and 2019, and their upper tails were somewhat elevated. In girls, BMI distribution curves were somewhat volatile.

In some places, there were no statistical differences in mean BMI between urban and rural areas from 1985 to 2019 ($p > 0.05$). However, from 1985 to 2019, the mean BMI in urban areas increased from 16.80 to 18.77 kg/m^2, while it increased from 17.17 to 18.48 kg/m^2 in rural areas (Table 2). The mean BMI has a faster rising speed in urban than in rural areas. Differences in the mean BMI between the urban and rural areas increased from 0.37 in 1985 to 0.29 in 2019.

Secular trends in the prevalence of emaciation

The total age-standardized prevalence of emaciation was 13.53%. As shown in Figure 2, in the past 35 years, the trends in age-standardized prevalence of emaciation increased from 1985 to 1995 and decreased significantly year by year after reaching its peak in 1995. The total age-standardized prevalence of emaciation decreased from 20.44 to 9.41% ($p < 0.05$). For boys, the age-standardized prevalence of emaciation decreased from 22.64 to 11.49%. For girls, it decreased from 13.12 to 5.59%. Average annual decreasing rates were 1.39 and 0.94% for boys and girls, respectively. The emaciation rate of boys was still higher than that of girls.

As age increased, the prevalence of emaciation decreased (Figure 3). This decline was evident in children aged 7–12 years.

In some places, school-aged children in urban areas had a higher prevalence of emaciation than those in rural areas during the same year. Regardless of urban or rural, the prevalence of emaciation decreased over years. In urban areas, the prevalence of emaciation decreased from 23.31% (940/4,032) to 11.27% (453/4,018). Meanwhile, in rural areas, it decreased from 23.48% (620/2,641) to 9.99% (2,012/20,148), with average annual decrease rates of 6.46 and 7.18% in urban and rural, respectively ($p < 0.01$).

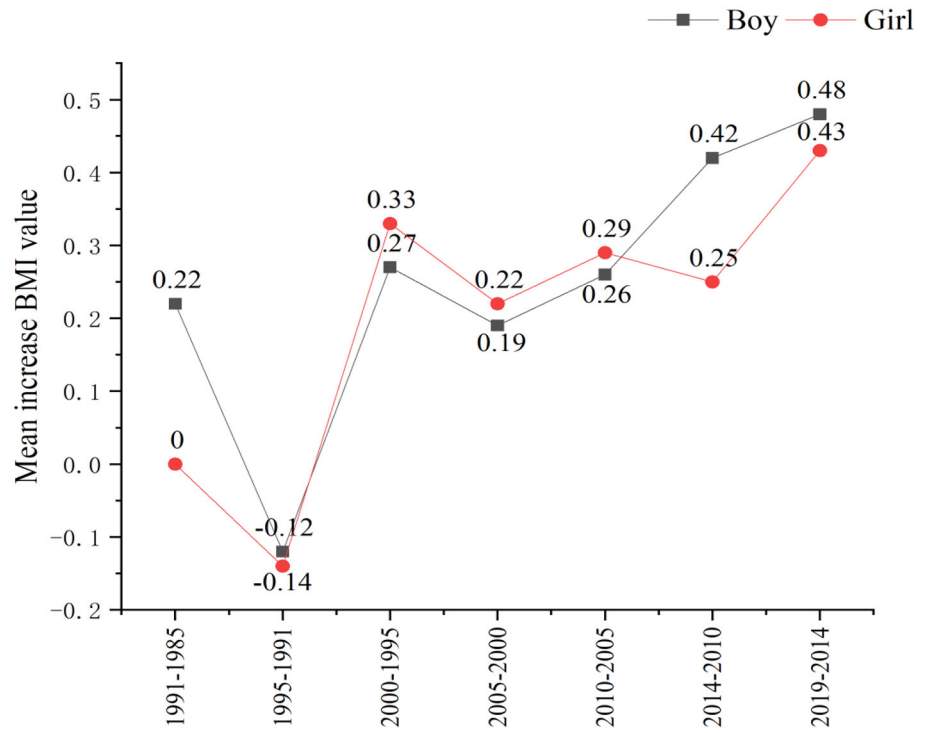

FIGURE 1
The increase in the mean body mass index (BMI) value of different genders in Yunnan school-aged children from 1985 to 2019.

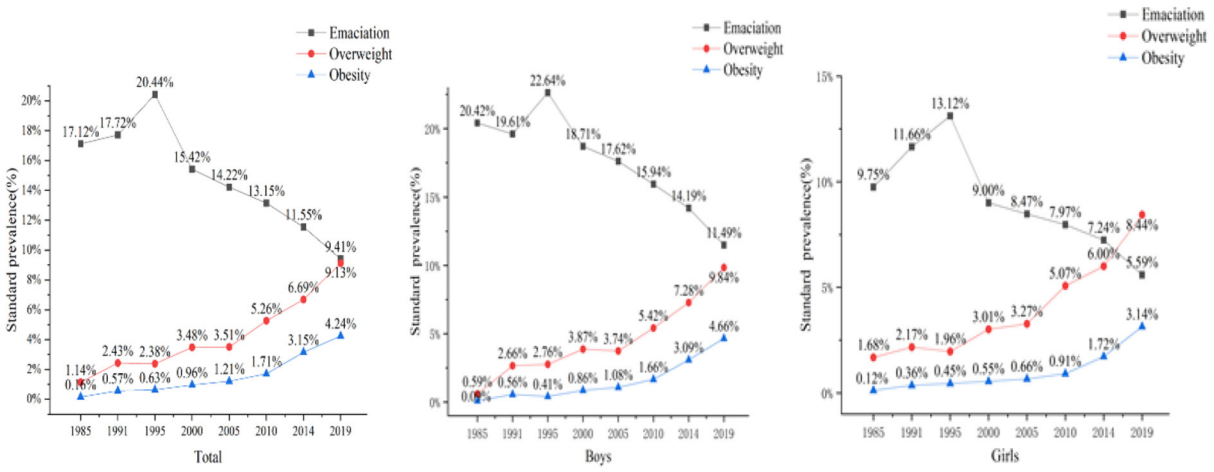

FIGURE 2
Age-standardized prevalence of emaciation, overweight, and obesity among school-aged children in total and different genders from 1985 to 2019.

Secular trends in the prevalence of overweight

The total age-standardized prevalence of overweight was 5.17%. Over 35 years, there was a significant increase in the prevalence of overweight among children and adolescents in Yunnan. As shown in Table 3, the total age-standardized prevalence of overweight increased from 1.14 to 9.13% ($p < 0.05$). Age-standardized prevalence of overweight increased from 0.59 to 9.84% and 1.68 to 8.44%, with average annual growth rates of 44.79 and 11.50% for boys and girls, respectively. Trends are shown in Figure 2, and an increase was

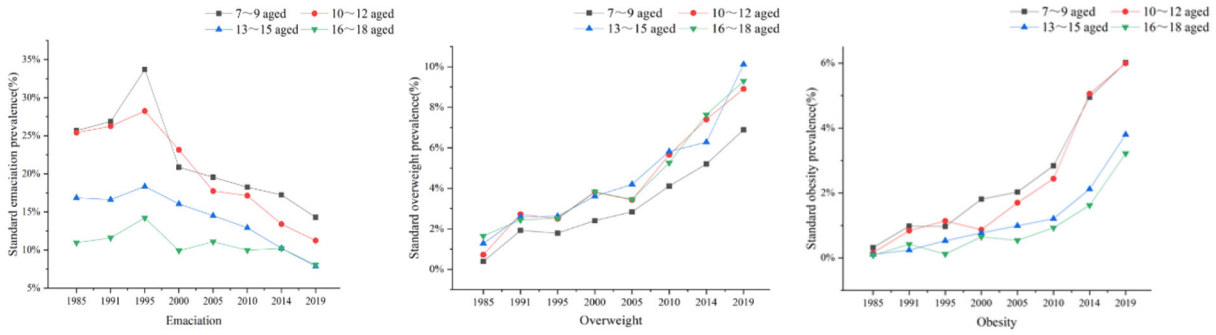

FIGURE 3
Gender-standardized prevalence of emaciation, overweight, and obesity among school-aged children of different ages from 1985 to 2019.

TABLE 3 The prevalence of overweight and obesity for urban and rural in Yunnan: 1985–2019.

Survey year	Urban				Rural			
	N	Emaciation (%)	OV (%)	OB (%)	N	Emaciation (%)	OV (%)	OB (%)
1985	7341	1729 (23.55)	63 (0.86)	19 (0.26)	7342	1121 (15.27)	91 (1.24)	6 (0.08)
1991	2447	521 (21.29)	85 (3.47)	20 (0.82)	2447	465 (19.00)	32 (1.31)	10 (0.41)
1995	4032	940 (23.31)	115 (2.85)	34 (0.84)	2641	620 (23.48)	40 (1.51)	12 (0.45)
2000	2521	343 (13.61)	197 (7.81)	62 (2.46)	7230	1342 (18.56)	132 (1.83)	36 (0.50)
2005	3909	575 (14.71)	282 (7.21)	120 (3.07)	19552	3066 (15.68)	531 (2.72)	186 (0.95)
2010	3595	515 (14.33)	350 (9.74)	126 (3.50)	19294	2769 (14.35)	842 (4.36)	294 (1.52)
2014	3600	487 (13.53)	391 (10.86)	213 (5.92)	19403	2402 (12.38)	1121 (5.78)	562 (2.90)
2019	4018	453 (11.27)	443 (11.03)	263 (6.55)	20148	2012 (9.99)	1672 (8.30)	872 (4.33)
All	27445	5563 (20.27)	1483 (5.40)	594 (2.16)	77909	13797 (17.71)	2789 (3.58)	1106 (1.42)

shown across all age subgroups and in both genders. Obviously, the prevalence of overweight in boys was much higher than that of the same age group in girls, and it increased more quickly in boys.

Regardless of the survey year, as age increased, the prevalence of overweight also increased (Figure 3). Children aged 13–15 years increased most obviously.

In some areas, school-aged children in urban areas had a higher prevalence of overweight than those in rural areas during the same year. Regardless of urban or rural, the prevalence of overweight increased. In urban areas, the prevalence of overweight increased from 0.86 to 11.03%. Meanwhile, in rural areas, it rose from 1.24 to 8.30%. Average annual growth rates in urban and rural areas were 33.79% and 16.27%, respectively ($p < 0.01$, Table 3).

Secular trends in the prevalence of obesity

As shown in Table 3, the total age-standardized prevalence of obesity was 1.91%. The prevalence of obesity also increased significantly over a 35-year period. The total age-standardized prevalence of obesity increased from 0.16 to 4.24% ($p < 0.05$). Age-standardized prevalence of obesity in boys increased from 0.14 to 5.03%, with average annual growth rates of 99.80%. And, for girls, it increased from 0.18 to 3.45%, with average annual growth rates of 51.90%. Disparities between different genders were obvious. In Figure 2, noticeable increases are shown across all age subgroups and in both genders. Obviously, the prevalence of overweight in boys was higher than that of the same age group in girls, and it increased more quickly in boys.

Regardless of the survey year, as age increased, the prevalence rate of obesity also further increased (Figure 3), especially in children aged 10–12 years.

In some regions, school-aged children in urban areas had a higher prevalence of obesity than those in rural areas during the same year. Regardless of urban or rural, the prevalence of obesity increased. For urban areas, the prevalence of obesity increased from 0.26 to 6.55%. For rural areas, it increased from 0.08 to 4.33%, and the average annual growth rates for urban and rural areas were 69.12 and 151.79%, respectively ($p < 0.01$, Table 3).

Discussion

The age-standardized prevalences of emaciation, overweight, and obesity in the total number of participants were 13.53, 5.17, and 1.91% respectively, among 7–18 school-aged children and adolescents in Yunnan. The main findings of this study were given as follows.

Firstly, the trends in the prevalence of emaciation decreased, while the trends of overweight and obesity increased across gender, age, or areas. The total age-standardized prevalence of overweight increased from 1.14 to 9.13% ($p < 0.05$; the total age-standardized prevalence of obesity increased from 0.16 to 4.24% ($p < 0.05$). The increase in the prevalence of overweight and obesity was more rapid in the most recent decade of 2005–2019 in Yunnan, which is consistent with the findings of a recent Taiwan, Australian, and US study (3, 17, 20–22). This study revealed that the epidemic of emaciation, overweight, and obesity in Yunnan children over 35 years was characterized by the triple burden of nutrition health in Yunnan children, which included the other provinces of China (23). In other words, emaciation was still severe [the rate of emaciation was higher in Yunnan than in China (10.2%)] (23), and secular trends of overweight and obesity among school-aged children and adolescents in Yunnan showed a continuous and fast increase (24–29). This problem may be caused by fast economic development, rising family income (19, 30), and changes in people's lifestyles. The increasing prevalence of overweight and obesity in children and adolescents is bound to increase the risk of chronic diseases, which seriously affects the health status and life quality of children and adolescents in the future.

Secondly, gender disparities in emaciation, overweight, and obesity in children were common phenomena in China (31–35). Yunnan is also no exception. It is mainly manifested in three aspects: first, the mean BMI increased significantly across all age-sex-area-specific subgroups in Yunnan school-aged children since 1985, especially for boys (36–39); second, the age-standardized prevalence of emaciation, overweight, and obesity was higher in boys than in girls; third, the acceleration in the prevalence of overweight and obesity with the average annual growth rate was quicker in boys than in girls (the average annual growth rate of age-standardized prevalence of overweight was 44.79 and 11.50% for boys and girls, respectively; the average annual growth rate of age-standardized prevalence of obesity was 99.80 and 51.90% for boys and girls, respectively). This phenomenon may be related to androgens, which can increase blood pressure by activating the renin-angiotensin system (40). Therefore, boys should be a priority population for the prevention and control of nutrition (including emaciation, overweight, and obesity).

Thirdly, regional differences in the trends and levels of emaciation, overweight, and obesity were evident (32–36, 41–44). This may be due to regional development and differences in individual composition, local economies, and lifestyles. This finding is alarming as the epidemic situation of nutrition among 7–18 school-aged children and adolescents in Yunnan urban areas is accelerating (20, 35, 41–43). Therefore, urban areas should be considered priority areas for the prevention of nutrition.

Fourthly, emaciation among children aged 7–12 years, overweight among children aged 13–15 years, and obesity among children aged 10–12 years all increased significantly. This may be explained by the fact that different populations have different growth patterns. Adolescence is one of the stages of great changes in growth and development. Thus, adolescents should be the priority population for the prevention and control of nutrition.

Based on the results of previous studies, prevention is recognized as the only feasible option to curb the epidemic (36). In the Yunnan survey of CNSSCH in 2014, a multivariate logistic analysis showed that the local average annual temperature and daily physical exercise were the protective factors for protecting children and adolescents from overweight and obesity [odds ratio (OR) values are 0.32 and 0.93, respectively]. Abdominal obesity (OR = 9.53), boys (OR = 1.74), and Han minority (OR = 0.50), living in high latitudes (OR = 2.92) and with a better economic development level (OR = 1.11), playing on the computer or electronic devices every day (OR = 1.14), lack of sleep (OR =1.12) and the heavy burden of conscious work (OR = 1.47) were independent risk factors for overweight and obesity (35, 36, 44, 45). In addition, other studies indicated that different dietary habits (46), different cultures (47), socioeconomic and family economic factors (48), perceptions of body image ideals (49), etc. were factors associated with overweight and obesity. This indicated that we should enhance health education in the prevention and control of nutrition-related health problems, especially taking comprehensive measures to change unhealthy dietary habits, increase the frequency and strength of physical exercise, decrease daily static time of playing on the computer or electronic devices, and getting enough of sleep and relieving the heavy burden of conscious work (50, 51).

Limitations

This study has some limitations. Firstly, the prevalence of emaciation, overweight, and obesity in 7–18-year-old students may be underestimated. However, this study explored relative changes in its prevalence because, no matter the measures used, the trends were evident. Secondly, this study used data from 35 cross-sectional surveys, with each survey being conducted on different people in field research. It is possible that unintentional errors occurred when estimating the prevalence of emaciation, overweight, and obesity. Lastly, this study did not consider the influence of environmental elements.

Recommendations

On one hand, in our future research, we should pay more attention to the impact of environmental factors, ethnic culture, and life and behavioral factors. On the other hand, according to a previous study, it was important to develop child-friendly health education materials in the next research. And, we need to concentrate on developing a series of educational electronic animations and pamphlets for children.

Conclusion

In summary, this study was the first investigation conducted in Yunnan, which used long-term follow-up data and large-scale school-aged children to analyze the trends in emaciation, overweight, and obesity in children and evaluate the epidemic development of nutrition health in children and adolescents in Yunnan. The prevalence of emaciation among 7–18 school-aged children and adolescents in Yunnan decreased from 1985 to 2019. However, the prevalence of emaciation was relatively high in China. The prevalence of overweight and obesity continued to rise in Yunnan. Urban children and adolescents, especially boys, had a higher prevalence of overweight and obesity than other groups. The prevalence of overweight and obesity in school-aged children and adolescents has increased more quickly in the last 5 years than it did in the years before. Thus, nutritional deficiencies, mainly overweight and obesity, have been a major public threat to children and adolescents in Yunnan. Effective comprehensive policies and intervention measures are required to reduce the prevalence of overweight and obesity among school-aged children.

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 survey of Medical Research Ethics Committee of Yunnan Preventive Medical Institute. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

YY conceived the study and its design and wrote the manuscript. YY, JD, SH, and TL performed data analysis and altogether drafted the article. ZS, SZha, CM, LC, and SZhan co-ordinated the research sites. YY, HL, DW, FY, LD, and MT performed the survey. XZ and YL performed data analysis and picture drawing. JK tutored and modified the 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.

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Association of caffeine intake with all-cause and cardiovascular mortality in elderly patients with hypertension

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Background: Caffeine is widely consumed not only in coffee but also in soft drinks and tea. However, the long-term health effects of caffeine are still controversial, especially in people with high cardiovascular risk such as elderly patients with hypertension.

Methods: This study analyzed data from the National Health and Nutrition Examination Survey 2003–2018. Caffeine intake was calculated by two 24-h dietary recall interviews. Complex sampling-weighted multivariable Cox proportional hazards models were used to compare the hazard ratios (HRs) of all-cause and cardiovascular mortality in elderly hypertensive patients with different caffeine intake (<10, 10 to <100, 100 to <200, 200 to <300, and ≥300 mg/day).

Results: This study included 6,076 elderly hypertensive patients. The mean ± standard error follow-up duration was 6.86 ± 0.12 years. During this period, a total of 2,200 all-cause deaths occurred, of which 765 were cardiovascular deaths. Taking patients with caffeine intake < 10 mg/day as a reference, patients with moderate caffeine intake (200 to <300 mg/day) had a lower risk of all-cause (HR, 0.70 [95% CI, 0.56–0.87]) and cardiovascular (HR, 0.55 [95% CI, 0.39–0.77]) mortality. The benefit of reducing all-cause mortality risk was significant in female patients (HR, 0.65 [95% CI, 0.50–0.85]) or patients with well-controlled blood pressure (HR, 0.63 [95% CI, 0.46–0.87]), but not in male patients or patients with poorly controlled blood pressure. In addition, non-linear relationship analysis also showed that moderate caffeine intake

had the lowest HRs of all-cause (Non-linear p = 0.022) and cardiovascular mortality (Non-linear p = 0.032) in the present study.

Conclusion: Moderate caffeine intake is associated with reduced risk of all-cause and cardiovascular mortality in elderly hypertensive patients.

KEYWORDS

caffeine intake, mortality, cardiovascular risk, hypertension, elderly patients

Introduction

Coffee is one of the most widely consumed beverages in the world. Numerous observational studies have shown that moderate coffee consumption has beneficial effects on the circulatory system, central nervous system, respiratory system, immune system, etc. (1–6). And present research found an inverse relationship between moderate coffee consumption with all-cause and cause-specific mortality (7–10).

Caffeine is consumed not only in coffee but also in soft drinks and tea. And because coffee also contains many other ingredients, caffeine and coffee cannot be considered the same. The relationship between caffeine intake and cardiovascular disease risk remains controversial. Excessive intake of caffeine can lead to increases in sympathetic nerve activity and circulating catecholamine concentrations, mediated by stimulation of the central nervous system (11, 12). Caffeine is thought to acutely increase blood pressure in caffeine-sensitive individuals, which may temporarily increase the risk of cardiovascular events (1, 6, 13). This acute effect limits the recommendation of coffee and caffeine in the hypertensive population, although there is no evidence that long-term habitual caffeine intake is associated with hypertension and cardiovascular risk. Currently, studies investigating the association between caffeine intake and mortality remain sparse, especially in hypertensive patients. Elderly hypertensive patients are at high risk of cardiovascular death and may be more susceptible to caffeine intake (14–17). Therefore, this study aimed to assess the association of caffeine intake with all-cause and cardiovascular mortality in elderly hypertensive patients.

Materials and methods

Study participants

All information on participants in this retrospective cohort study was obtained from the National Health and Nutrition Examination Survey (NHANES) (18). The NHANES is a program of studies designed to assess the health and nutritional status of the population in the US. This survey is unique in that it combines interviews and physical examinations (18). The US National Center for Health Statistics (NCHS) has the responsibility for producing vital health statistics, using a stratified, multi-stage probability sampling design that enables participants to be representative of the civilian deinstitutionalized population of the US.

This study obtained data on 80,312 participants between 2003 and 2018 from the NHANES database. We focused on participants aged ≥65 years with hypertension (n = 8,521). Hypertension was defined as measured systolic blood pressure (SBP) ≥140 mmHg or/and diastolic blood pressure (DBP) ≥90 mmHg, or/and previous diagnosis of hypertension, or/and taking antihypertensive prescription. Of these, we excluded patients with missing information on caffeine intake (n = 1,780). Then, patients with missing blood pressure data were also excluded (n = 180). Additionally, participants lacking follow-up data were excluded (n = 8). Finally, we excluded those patients with missing information on potential confounding variables (n = 477). A total of 6,076 participants were included for analysis in this study (**Figure 1**). The follow-up period is from the date of participation in the survey until December 31, 2019 (19). The NCHS Research Ethics Review Board approved the NHANES protocol (20). The NHANES has obtained written informed consent from each participant.

Caffeine intake assessment

Since 2003, all NHANES participants are eligible for two 24-h dietary recall interviews. The first dietary recall interview is collected in person in the Mobile Examination Center and the second interview is collected by telephone 3–10 days later (21). The dietary intake data are used to estimate the types and amounts of foods and beverages (including all types of water) consumed during the 24-h period prior to the interview (midnight to midnight). Then, The NHANES used the US Department of Agriculture Food and Nutrient Database for Dietary Studies (FNDDS) (22) to identify those foods and beverages as intakes of various nutrients and food ingredients. The FNDDS contained data on the nutritional content of all foods and beverages consumed by participants, including more

Abbreviations: HR, hazard ratio; CI, confidence interval; NHANES, National Health and Nutrition Examination Survey; NCHS, National Center for Health Statistics; SBP, systolic blood pressure; DBP, diastolic blood pressure; ICD-10, International Classification of Diseases, 10th revision; BMI, body mass index; eGFR, estimated glomerular filtration rate; SE, standard error; Ref, reference.

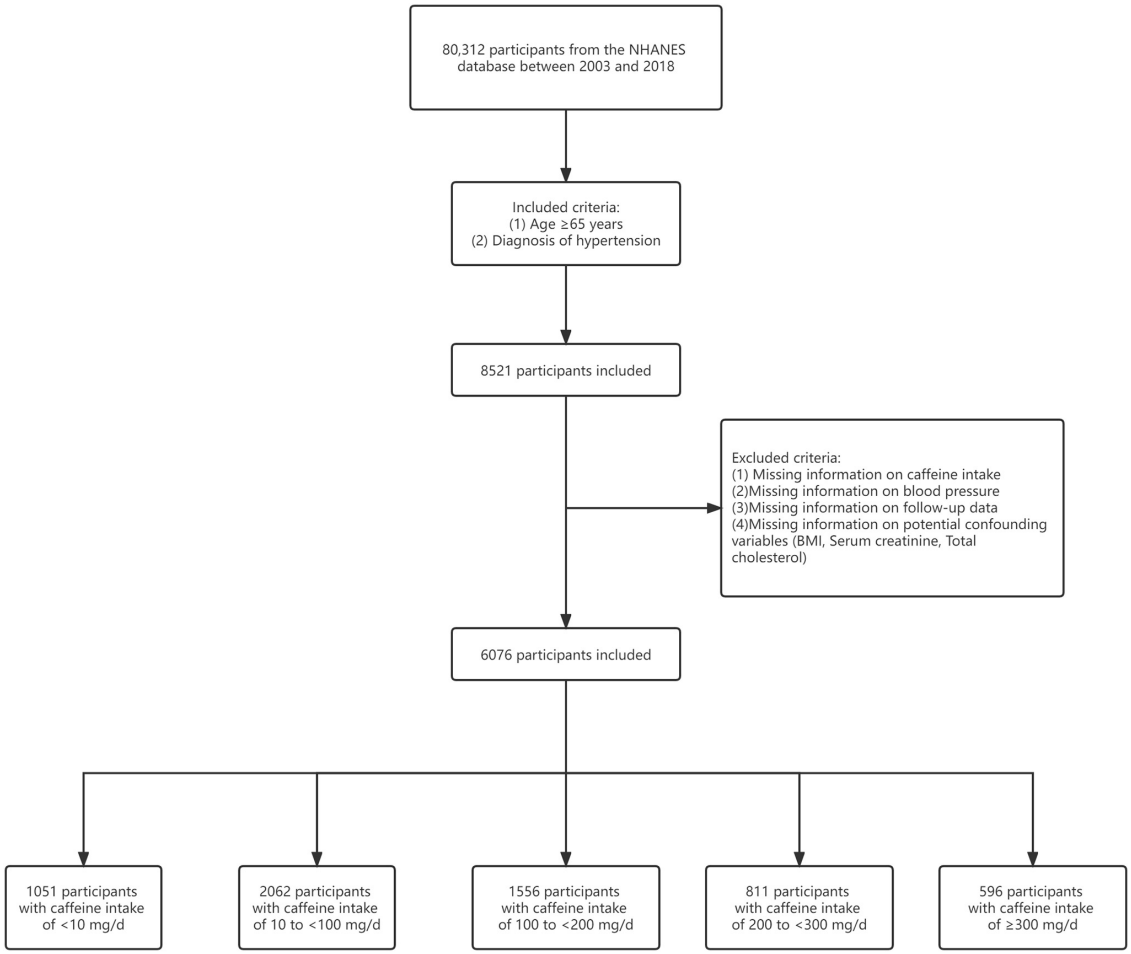

FIGURE 1
Flowchart of patient selection.

than 7,000 individual foods and beverages. The exact caffeine content of various foods and drinks was also available on the FNDDS (23). Sources of caffeine include coffee, tea, soda, energy drinks, milk, other beverages and foods, and versions with or without caffeine were considered (24). The study divided participants into five groups based on their 2-day average caffeine intake (<10, 10 to <100, 100 to <200, 200 to <300, and ≥300 mg/day).

Outcome ascertainment

The outcomes of this study were all-cause and cardiovascular death. All-cause death was defined as death from any cause. According to the International Classification of Diseases, 10th revision (ICD-10), cardiovascular death was defined as death due to I00-I09, I11, I13, I20-I51, and I60-I69. The NHANES linked mortality data have been updated with mortality follow-up data through December 31, 2019 (19).

Covariate assessment

The following variables were obtained through the interview questionnaire: age, sex, race/ethnicity, educational level, smoking status (current, former, and never), medical conditions (including hypertension, diabetes, asthma, heart failure, coronary heart disease, stroke, emphysema, thyroid problem, chronic bronchitis, liver condition, and cancer), and antihypertensive medication use. Total daily energy, protein, carbohydrate, sugar, dietary fiber, fat, alcohol, and sodium intakes were obtained in the same way as the caffeine intake assessment above. The following variables were measured according to standard protocols: body mass index (BMI; calculated as weight in kilograms divided by height in meters squared), blood pressure, total cholesterol, triglycerides, high density lipoprotein, serum creatinine, and uric acid. The estimated glomerular filtration rate (eGFR) was calculated by the Chronic Kidney Disease Epidemiology Collaboration equation (25). Hyperuricemia was defined as serum uric acid

level >420 mcmol/L for male patients and >360 mcmol/L for female patients. Obese was defined as BMI ≥ 30 kg/m^2. Well-controlled blood pressure was defined as SBP < 140 mmHg and DBP < 90 mmHg.

Statistical analysis

The NHANES samples are not simple random samples, and complex survey designs need to be considered. Following the recommendations of the US Centers for Disease Control and Prevention for the analysis of NHANES data (26), we used appropriate weights for each analysis based on the selected variables. Weights are provided by NCHS. Continuous variables were expressed as mean ± standard error (mean ± SE), the normality of each continuous variable was evaluated using Kolmogorov Smirnov test, the comparison between groups of continuous variables with normal distribution using analysis of variance, and the comparison between groups of continuous variables with non-normal distribution using Kruskal–Wallis test. Categorical variables were expressed as percentages, and comparisons between groups were made by the chi-square test. For the analysis of mortality outcomes, multivariable Cox proportional hazards regression was performed to calculate hazard ratios (HR) and 95% confidence intervals (CI) with reference to participants with caffeine intake <10 mg/day. Model 1 adjusted for age, sex, race/ethnicity, educational level, smoking status, and BMI. Adjustments for model 2 included adjustments for model 1 plus non-cardiovascular disease conditions (diabetes, asthma, emphysema, thyroid problem, chronic bronchitis, liver condition, and cancer), eGFR, uric acid, total daily energy, protein, carbohydrate, sugar, dietary fiber, fat, alcohol, and sodium intakes. Adjustments for model 3 included adjustments for model 2 plus cardiovascular disease conditions (heart failure, coronary heart disease, and stroke), SBP, DBP, total cholesterol, triglycerides, and high-density lipoprotein. The HRs for the most adequately adjusted model 3 were analyzed separately by sex, blood pressure control, hyperuricemia, obese, or eGFR. Restricted cubic spline (RCS) regression with three knots at the 10th, 50th, and 90th centiles was used to explore the non-linear relationship between caffeine intake and mortality. All statistical analyses were performed using R version 4.1.2 (R Project for Statistical Computing). $P < 0.05$ was regarded as statistically significant for all tests.

Results

Baseline characteristics

Table 1 summarizes the weighted baseline information for 6,076 elderly hypertensive patients. Among total patients, the mean ± SE age was 73.39 ± 0.12 years, 43% were male, 81.2% were self-identified as non-Hispanic white, and the mean ± SE caffeine intake was 146.16 ± 2.98 mg/day. Compared with patients with lower caffeine intake, patients with higher caffeine intake were younger, more likely to be male, non-Hispanic white, and smoker, had higher education level and intake of various nutrients, higher eGFR level, lower systolic blood pressure, lower high density lipoprotein, and lower prevalence of asthma. Notably, although not statistically significant, patients with higher caffeine intake may be predisposed to coronary heart disease. And compared with other groups, the 200 to <300 group may have a higher prevalence of heart failure and cancer, and a lower prevalence of stroke.

Association of caffeine intake with all-cause and cardiovascular mortality

During the follow-up of 6,076 participants, a total of 2,200 all-cause deaths occurred, of which 765 were cardiovascular deaths. The mean ± SE follow-up duration was 6.86 ± 0.12 years. The results of Cox regression analysis were shown in Table 2.

The most adequately adjusted model 3 results show that moderate caffeine intake can reduce all-cause and cardiovascular mortality in elderly hypertensive patients. Taking caffeine intake <10 mg/day as reference, the risk of all-cause mortality was significantly reduced in all groups. Patients with caffeine intake of 200 to <300 mg/day had the lowest HR of all-cause mortality (HR, 0.70 [95% CI, 0.56–0.87]). For cardiovascular mortality, we observed similar results. Taking caffeine intake <10 mg/day as a reference, the full-adjusted HR for cardiovascular mortality in patients with caffeine intake of 200 to <300 mg/day was 0.55 [95% CI, 0.39–0.77].

The results of parameter estimation in cox models were listed in Supplementary materials. In addition to caffeine intake, age, diabetes, emphysema, systolic and diastolic blood pressure, heart failure, and stroke were all associated with all-cause and cardiovascular mortality.

Subgroup analysis

The results of subgroup analysis according to the most adequately adjusted Cox regression model 3 are presented in Table 3. Except for the male subgroup and poorly controlled blood pressure subgroup, caffeine intake was beneficial in reducing all-cause and cardiovascular mortality of elderly hypertensive patients in all subgroups. And no significant interaction was observed between each subgroup (Sex, Blood pressure control, Hyperuricemia, Obese, and eGFR) and caffeine intake groups (Supplementary Table 1). For all-cause mortality (Figure 2), caffeine intake showed a significant benefit in the female subgroup (10 to <100 mg/day: HR, 0.76 [95% CI,

TABLE 1 Participants' baseline demographic and clinical characteristics.

Characteristic	Total	Caffeine intake (mg/day)					*P*-value
		<10	10 to <100	100 to <200	200 to <300	≥300	
Unweighted sample (*n*)	6,076	1,051	2,062	1,556	811	596	
Age (years)	73.39 ± 0.12	73.76 ± 0.29	74.16 ± 0.18	73.41 ± 0.23	72.79 ± 0.28	71.77 ± 0.24	<0.001
Sex (%)							<0.001
Male	43	37.9	36.2	39.2	53.1	61.2	
Female	57	62.1	63.8	60.8	46.9	38.8	
Race (%)							<0.001
Mexican American	3.7	3.2	5	3.6	2.9	2.3	
Other Hispanic	2.8	2.8	3.9	2.9	1.6	1.1	
Non-Hispanic white	81.2	74.3	73.3	83.8	90.8	90.9	
Non-Hispanic black	8.3	15.4	12.1	6.2	3	1.4	
Other race	4	4.3	5.7	3.5	1.8	4.3	
Education level (%)							<0.001
Less than high school	21.7	24.4	25.8	20.6	15.7	19	
At least high school	78.3	75.6	74.2	79.4	84.3	81	
Smoking status (%)							<0.001
Current	7.4	4.5	5.4	6.5	7.8	18.2	
Former	43.5	40.1	38.9	40.2	54.3	52.5	
Never	49	55.4	55.7	53.3	38	29.3	
Body mass index (kg/m^2)	29.31 ± 0.11	29.23 ± 0.28	29.06 ± 0.19	29.13 ± 0.25	29.95 ± 0.34	29.53 ± 0.30	0.109
Body mass index (%)							0.067
<30	60.6	60.1	62.5	63.1	57.4	55.1	
≥30	39.4	39.9	37.5	36.9	42.6	44.9	
Systolic blood pressure (mmHg)	138.81 ± 0.41	138.40 ± 0.96	141.15 ± 0.73	137.91 ± 0.82	137.75 ± 0.96	137.24 ± 1.28	0.011
Diastolic blood pressure (mmHg)	66.10 ± 0.30	65.99 ± 0.77	65.52 ± 0.46	66.03 ± 0.56	66.44 ± 0.72	67.33 ± 0.94	0.396
Total cholesterol (mmol/L)	4.97 ± 0.03	5.01 ± 0.07	5.00 ± 0.04	4.95 ± 0.04	4.93 ± 0.05	4.93 ± 0.08	0.629
Triglycerides (mmol/L)	1.77 ± 0.02	1.65 ± 0.05	1.81 ± 0.04	1.79 ± 0.05	1.76 ± 0.04	1.78 ± 0.07	0.110
High density lipoprotein (mmol/L)	1.44 ± 0.01	1.48 ± 0.03	1.42 ± 0.01	1.48 ± 0.02	1.40 ± 0.02	1.37 ± 0.02	0.001
Uric acid (mcmol/L)	344.69 ± 1.69	339.90 ± 5.11	343.94 ± 2.88	341.49 ± 3.21	354.99 ± 4.90	346.08 ± 4.79	0.158
Hyperuricemia (%)	28.5	28.3	30.3	26.6	30.1	26.5	0.514
eGFR ($ml/min/1.73\ m^2$)	67.89 ± 0.35	68.49 ± 0.89	66.11 ± 0.54	67.68 ± 0.62	68.51 ± 0.90	71.14 ± 0.89	<0.001
eGFR (%)							0.019

(Continued)

TABLE 1 (Continued)

Characteristic	Total	Caffeine intake (mg/day)					*P*-value
		<10	10 to <100	100 to <200	200 to <300	≥300	
<60	32.5	32.6	35.2	34.6	30.7	22.9	
≥60	67.5	67.2	64.7	66.6	68.5	75.5	
Energy (kcal)	1,780.59 ± 13.58	1,645.53 ± 29.90	1,673.13 ± 19.30	1,747.23 ± 21.53	1,959.58 ± 30.06	2,056.60 ± 40.00	<0.001
Protein (gm)	69.73 ± 0.58	66.46 ± 1.56	65.80 ± 0.83	67.16 ± 0.90	76.07 ± 1.18	81.04 ± 0.80	<0.001
Carbohydrate (gm)	215.51 ± 1.58	203.63 ± 3.85	207.65 ± 2.33	213.88 ± 2.86	228.89 ± 3.91	236.11 ± 6.11	<0.001
Total sugar (gm)	94.30 ± 0.87	88.94 ± 2.15	93.32 ± 1.33	93.72 ± 1.76	98.93 ± 2.43	98.86 ± 3.12	0.044
Dietary fiber (gm)	16.33 ± 0.16	16.31 ± 0.37	15.73 ± 0.26	16.10 ± 0.27	16.93 ± 0.29	17.58 ± 0.50	0.001
Total fat (gm)	69.89 ± 0.66	62.42 ± 1.42	64.45 ± 1.01	68.10 ± 1.05	79.33 ± 1.57	84.47 ± 2.02	<0.001
Alcohol (gm)	5.69 ± 0.30	4.74 ± 0.74	4.15 ± 0.37	5.57 ± 0.51	7.79 ± 0.89	8.10 ± 1.01	<0.001
Sodium (mg)	2,957.24 ± 26.53	2,732.39 ± 59.52	2,752.45 ± 37.87	2,878.13 ± 42.53	3,290.50 ± 60.08	3,486.76 ± 82.34	<0.001
Diabetes (%)	23.1	20.5	23	23.1	25	23.6	0.678
Asthma (%)	12.8	17.6	14	12	10	8.9	0.005
Heart failure (%)	8.6	9	9.7	6.6	11.2	6.5	0.015
Coronary heart disease (%)	13.4	13.4	12.4	12.1	14.4	17.9	0.105
Stroke (%)	9.7	9.8	12	8.5	7.4	9.6	0.043
Emphysema (%)	4.7	3.9	4.7	3.8	4.8	7.8	0.038
Thyroid problem (%)	22.2	23.7	22.1	24.4	21.2	16.6	0.118
Chronic bronchitis (%)	8.7	9.7	8	6.9	11.1	10.2	0.077
Liver condition (%)	4.4	3.1	5.2	4	5.2	4	0.459
Cancer (%)	28.2	30.1	24.6	28.8	32.7	26.4	0.05

eGFR, estimated glomerular filtration rate. Continuous variables are expressed as means and standard error and categorical variables as percentages. Means and percentages are weighted.

0.61–0.94]; 100 to <200 mg/day: HR, 0.79 [95% CI, 0.64–0.98]; and 200 to <300 mg/day: HR, 0.65 [95% CI, 0.50–0.85] compared with female participants with caffeine intake of <10 mg/day) and well-controlled blood pressure subgroup (10 to <100 mg/day: HR, 0.70 [95% CI, 0.57–0.85]; 100 to <200 mg/day: HR, 0.73 [95% CI, 0.57–0.93]; and 200 to <300 mg/day: HR, 0.63 [95% CI, 0.46–0.87] compared with well-controlled blood pressure participants with caffeine intake of <10 mg/day), but not in the male subgroup and poorly controlled blood pressure subgroup. In addition, the hyperuricemia subgroup had lower HRs for all-cause mortality than the non-hyperuricemia subgroup. Interestingly, caffeine intake with the lowest HR of all-cause mortality is different in obese subgroup (≥300 mg/day: HR, 0.66 [95% CI, 0.47–0.94]) and non-obese subgroup (200 to <300 mg/day: HR, 0.63 [95% CI, 0.49–0.81]). For cardiovascular mortality (Figure 3), moderate caffeine intake (200 to <300 mg/day) showed a significant benefit in all subgroups, except for the obese subgroup. In the obese subgroup, caffeine intake with the lowest HR of cardiovascular mortality was ≥300 mg/day (HR, 0.51 [95% CI, 0.26–0.96]), which was similar to the results of all-cause mortality. We also observed that caffeine intake of 10 to <100 mg/day significantly reduced cardiovascular mortality risk in the female subgroup (HR, 0.60 [95% CI, 0.39–0.93]).

Non-linear relationship analysis

The most adequately adjusted RCS regression results are shown in Figure 4. There was a significant non-linear relationship between caffeine intake and all-cause mortality in elderly hypertensive patients (Non-linear $p = 0.022$), and caffeine intake with the lowest HR was 254 mg/day. There was also a significant non-linear relationship between caffeine intake and cardiovascular mortality in elderly hypertensive patients (Non-linear $p = 0.032$), and caffeine intake with the lowest HR was 204 mg/day. Non-linear relationship analysis also showed that moderate caffeine intake can reduce all-cause and cardiovascular mortality in elderly hypertensive patients.

TABLE 2 Hazard ratios for all-cause and cardiovascular mortality of all participants, stratified by caffeine intake.

Outcomes	Caffeine intake (mg/day)				
	<10	10 to <100	100 to <200	200 to <300	≥300
All-cause mortality					
Unadjusted HR	1 [Ref]	**0.84 (0.72–0.99)**	0.86 (0.72–1.02)	**0.76 (0.61–0.95)**	**0.75 (0.59–0.96)**
P		**0.035**	0.081	**0.014**	**0.024**
Model 1 HR	1 [Ref]	0.87 (0.74–1.01)	0.89 (0.75–1.06)	**0.79 (0.63–0.99)**	0.83 (0.64–1.07)
P		0.076	0.189	**0.040**	0.147
Model 2 HR	1 [Ref]	**0.80 (0.69–0.93)**	**0.83 (0.70–0.98)**	**0.73 (0.58–0.91)**	**0.77 (0.60–1.00)**
P		**0.004**	**0.027**	**0.005**	**0.047**
Model 3 HR	1 [Ref]	**0.77 (0.66–0.90)**	**0.83 (0.70–0.98)**	**0.70 (0.56–0.87)**	**0.74 (0.57–0.96)**
P		**<0.001**	**0.026**	**0.001**	**0.023**
Cardiovascular mortality					
Unadjusted HR	1 [Ref]	0.82 (0.61–1.11)	0.89 (0.67–1.17)	**0.63 (0.45–0.89)**	0.75 (0.51–1.09)
P		0.206	0.402	**0.008**	0.134
Model 1 HR	1 [Ref]	0.85 (0.63–1.16)	0.93 (0.70–1.24)	**0.68 (0.48–0.97)**	0.90 (0.60–1.36)
P		0.315	0.607	**0.035**	0.624
Model 2 HR	1 [Ref]	0.76 (0.57–1.01)	0.84 (0.63–1.10)	**0.61 (0.43–0.88)**	0.85 (0.57–1.26)
P		0.056	0.203	**0.008**	0.408
Model 3 HR	1 [Ref]	**0.69 (0.52–0.91)**	0.80 (0.61–1.06)	**0.55 (0.39–0.77)**	0.76 (0.51–1.14)
P		**0.009**	0.12	**<0.001**	0.184

HR, Hazard ratio; Ref, reference; BMI, body mass index; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; DBP, diastolic blood pressure. Model 1: adjusted for age, sex, race/ethnicity, educational level, smoking status, and BMI. Model 2: adjustments for model 1 plus non-cardiovascular disease conditions (diabetes, asthma, emphysema, thyroid problem, chronic bronchitis, liver condition, and cancer), eGFR, uric acid, total daily energy, protein, carbohydrate, sugar, dietary fiber, fat, alcohol, and sodium intakes. Model 3: adjustments for model 2 plus cardiovascular disease conditions (heart failure, coronary heart disease, and stroke), SBP, DBP, total cholesterol, triglycerides, and high-density lipoprotein. Statistically significant HR and *p*-values were shown in bold.

Sensitivity analysis

Sensitivity analyses were performed to test the robustness of the results, including removing participants with extreme energy intake (energy intake <1,000 kcal or energy intake >3,000 kcal) or with baseline history of cardiovascular diseases and cancer or with missing low density lipoprotein data (low density lipoprotein included in the model). The results of three sensitivity analyses based on model 3 were basically consistent with the above results (**Table 4**). Participants with moderate caffeine intake (200 to <300 mg/day) had significantly lower HRs for all-cause and cardiovascular mortality compared with participants with caffeine intake of <10 mg/day.

Discussion

In this study, we observed that moderate caffeine intake was associated with decreased risk of all-cause and cardiovascular mortality in elderly hypertensive patients. The HRs for all-cause and cardiovascular mortality were lowest in participants with caffeine intake of 200 to <300 mg/day (one cup of coffee contains approximately 100 mg of caffeine). Although no significant interaction was observed, elderly hypertensive female patients or patients with well-controlled blood pressure may be more likely to benefit from caffeine intake, further studies are warranted to elucidate differences in the effects of caffeine intake among various populations.

Many studies have demonstrated a beneficial effect of moderate coffee consumption on the risk of all-cause and cardiovascular mortality (1, 8, 27–29). But the effects of caffeine and coffee cannot be viewed on the same level. Caffeine, as a most important ingredient in coffee, has received extensive attention. Several studies in recent years have also observed that caffeine reduces the risk of all-cause mortality (9, 10, 30). However, the relationship between caffeine and cardiovascular mortality is still controversial. Feng et al. (30) suggested that higher caffeine intake was associated with lower cardiovascular mortality. A study on an elderly population also supports this view (14). But several studies have shown no association between caffeine intake and cardiovascular mortality (9, 10). In addition, a study suggests that caffeine consumption in patients with cardiovascular disease may increase the risk of cardiovascular death (7). In this regard, the effect of caffeine

TABLE 3 Multivariable model 3 hazard ratios for all-cause and cardiovascular mortality of subgroups (Sex, Blood pressure control, Hyperuricemia, Obese, and eGFR), stratified by caffeine intake.

Outcomes	Death/n	Caffeine intake (mg/day)				
		<10	10 to <100	100 to <200	200 to <300	≥300
All-cause mortality						
Sex						
Male	1,162/2,910	1 [Ref]	0.82 (0.65–1.03)	0.88 (0.67–1.14)	0.76 (0.53–1.08)	0.75 (0.55–1.03)
P			0.085	0.333	0.127	0.074
Female	1,038/3,166	1 [Ref]	**0.76 (0.61–0.94)**	**0.79 (0.64–0.98)**	**0.65 (0.50–0.85)**	0.70 (0.47–1.05)
P			**0.012**	**0.033**	**0.002**	0.082
Blood pressure control						
Yes	1,074/3,133	1 [Ref]	**0.70 (0.57–0.85)**	**0.73 (0.57–0.93)**	**0.63 (0.46–0.87)**	0.75 (0.55–1.02)
P			**<0.001**	**0.011**	**0.004**	0.063
No	1,126/2,943	1 [Ref]	0.92 (0.71–1.19)	0.98 (0.78–1.24)	0.79 (0.59–1.06)	0.74 (0.48–1.13)
P			0.511	0.891	0.121	0.161
Hyperuricemia						
Yes	723/1,750	1 [Ref]	0.74 (0.55–1.01)	**0.75 (0.56–1.00)**	**0.62 (0.46–0.85)**	**0.57 (0.33–1.00)**
P			0.057	**0.049**	**0.003**	**0.049**
No	1,477/4,326	1 [Ref]	**0.81 (0.68–0.96)**	0.89 (0.71–1.10)	0.75 (0.56–1.01)	0.81 (0.61–1.08)
P			**0.016**	0.285	0.054	0.157
Obese						
Yes	1,445/3,743	1 [Ref]	0.80 (0.61–1.04)	0.79 (0.63–1.01)	0.88 (0.61–1.26)	**0.66 (0.47–0.94)**
P			0.094	0.057	0.492	**0.022**
No	755/2,333	1 [Ref]	**0.78 (0.64–0.97)**	0.87 (0.70–1.08)	**0.63 (0.49–0.81)**	0.83 (0.61–1.12)
P			**0.022**	0.198	**<0.001**	0.22
eGFR						
<60	1,011/2,020	1 [Ref]	**0.78 (0.63–0.97)**	0.85 (0.68–1.06)	0.76 (0.51–1.14)	0.76 (0.52–1.11)
P			**0.028**	0.146	0.19	0.155
≥60	1,189/4,056	1 [Ref]	**0.77 (0.62–0.94)**	0.83 (0.64–1.08)	**0.69 (0.52–0.92)**	0.78 (0.57–1.06)
P			**0.013**	0.16	**0.011**	0.111
Cardiovascular mortality						
Sex						
Male	409/2,910	1 [Ref]	0.88 (0.58–1.35)	0.92 (0.58–1.46)	**0.54 (0.32–0.90)**	0.62 (0.35–1.12)
P			0.556	0.729	**0.018**	0.113
Female	356/3,166	1 [Ref]	**0.60 (0.39–0.93)**	0.79 (0.54–1.14)	**0.64 (0.42–0.98)**	1.07 (0.54–2.12)
P			**0.022**	0.203	**0.039**	0.838
Blood pressure control						
Yes	366/3,133	1 [Ref]	0.65 (0.41–1.04)	0.75 (0.48–1.16)	**0.56 (0.32–0.99)**	0.79 (0.43–1.45)
P			0.072	0.196	**0.046**	0.442
No	399/2,943	1 [Ref]	0.86 (0.59–1.26)	0.95 (0.67–1.34)	**0.60 (0.38–0.96)**	0.92 (0.52–1.60)
P			0.437	0.77	**0.035**	0.756
Hyperuricemia						
Yes	266/1,750	1 [Ref]	0.74 (0.43–1.27)	0.72 (0.45–1.16)	**0.54 (0.31–0.96)**	0.78 (0.39–1.59)
P			0.276	0.175	**0.037**	0.499

(Continued)

TABLE 3 (Continued)

Outcomes	Death/n	Caffeine intake (mg/day)				
		<10	10 to <100	100 to <200	200 to <300	≥300
No	499/4,326	1 [Ref]	**0.68 (0.48–0.97)**	0.88 (0.61–1.28)	**0.56 (0.36–0.88)**	0.78 (0.47–1.29)
P			**0.035**	0.502	**0.011**	0.332
Obese						
Yes	484/3,743	1 [Ref]	0.75 (0.47–1.21)	**0.68 (0.47–0.99)**	0.72 (0.45–1.15)	**0.51 (0.26–0.96)**
P			0.242	**0.042**	0.163	**0.039**
No	281/2,333	1 [Ref]	0.72 (0.50–1.04)	0.94 (0.63–1.40)	**0.51 (0.31–0.86)**	1.12 (0.67–1.88)
P			0.08	0.765	**0.011**	0.664
eGFR						
<60	378/2,020	1 [Ref]	**0.65 (0.46–0.93)**	0.78 (0.53–1.15)	**0.53 (0.34–0.85)**	0.82 (0.47–1.45)
P			**0.019**	0.203	**0.008**	0.499
≥60	387/4,056	1 [Ref]	0.70 (0.46–1.05)	0.81 (0.53–1.24)	**0.57 (0.36–0.92)**	0.73 (0.43–1.26)
P			0.085	0.332	**0.02**	0.265

HR, Hazard ratio; Ref, reference; BMI, body mass index; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; DBP, diastolic blood pressure. Model 3: adjustments for age, sex, race/ethnicity, educational level, smoking status, BMI, non-cardiovascular disease conditions (diabetes, asthma, emphysema, thyroid problem, chronic bronchitis, liver condition, and cancer), eGFR, uric acid, energy intake, protein intake, carbohydrate intake, sugar intake, dietary fiber intake, fat intake, alcohol intake, sodium intake, cardiovascular disease conditions (heart failure, coronary heart disease, and stroke), SBP, DBP, total cholesterol, triglycerides, and high-density lipoprotein. Statistically significant HR and *p*-values were shown in bold.

on blood pressure may limit its reduction in the risk of cardiovascular death. Past studies have found that caffeine induces an acute vasopressor effect that increases blood pressure (6, 14). Coffee consumption was associated with uncontrolled blood pressure in a hypertensive elderly population (15). At present, research on the long-term effects of caffeine in hypertensive patients is still limited, especially in the elderly population with high cardiovascular risk.

As early as 1988, Martin et al. (31) proposed that increased levels of caffeine consumption were not associated with increased all-cause or cardiovascular mortality in hypertensive patients aged 30–69 years over the subsequent 4 years. However, follow-up time was insufficient, and covariates were not fully adjusted in their study. In addition, with the dramatic changes in dietary caffeine, results from decades ago are no longer appropriate for the current situation. Recently, Palatini et al. (32) found that coffee is a dietary risk factor for adverse cardiovascular outcomes in hypertensive patients. But they mainly focused on coffee consumption without specifically assessing caffeine intake. Besides, their study was limited to Caucasian stage 1 hypertensive patients aged from 18 to 45 years and the proportion of outcome events was too small. Based on NHANES data from 1999 to 2010, Tsujimoto et al. (10) found that moderate caffeine intake can reduce the risk of all-cause mortality in hypertensive patients. However, Tsujimoto et al. (10) did not further assess the effect of caffeine intake on the risk of cardiovascular death in hypertensive patients.

Our study used 2003–2018 NHANES data and applied complex sampling weighted multivariable Cox proportional hazards models to assess the association of caffeine intake with cardiovascular and all-cause mortality in elderly patients with hypertension in detail. Furthermore, we performed subgroup analysis and performed RCS analysis to evaluate the specific non-linear relationship. Therefore, our study is novel and reliable. The present study suggests that appropriate caffeine intake is beneficial in reducing the risk of all-cause and cardiovascular mortality in elderly hypertensive patients. This extends the recommendation of moderate caffeine intake for elderly people with hypertension based on previous research, which is conducive to the long-term health management of elderly hypertensive patients.

Caffeine, as one of the most commonly consumed substances, can widely act on various systems of the human body, such as the circulatory system, central nervous system, respiratory system, immune system, etc. (17). The health benefits of caffeine may be due to its antioxidant and anti-inflammatory properties. About the circulatory system, it has been suggested that caffeine has a positive inotropic effect, possibly related to an increase in intracellular calcium concentration, release of norepinephrine, and sensitization of dopamine receptors (33). In general, acute caffeine intake stimulates a modest increase in blood pressure. However, long-term chronic caffeine intake did not show a blood pressure-raising effect (6). Interestingly, it has been suggested that caffeine metabolites may reduce the incidence of hypertension (34). Even considering the potential blood pressure-raising effect of caffeine, we believe that the benefits of caffeine in elderly hypertensive patients with well-controlled blood pressure are worthy of recognition.

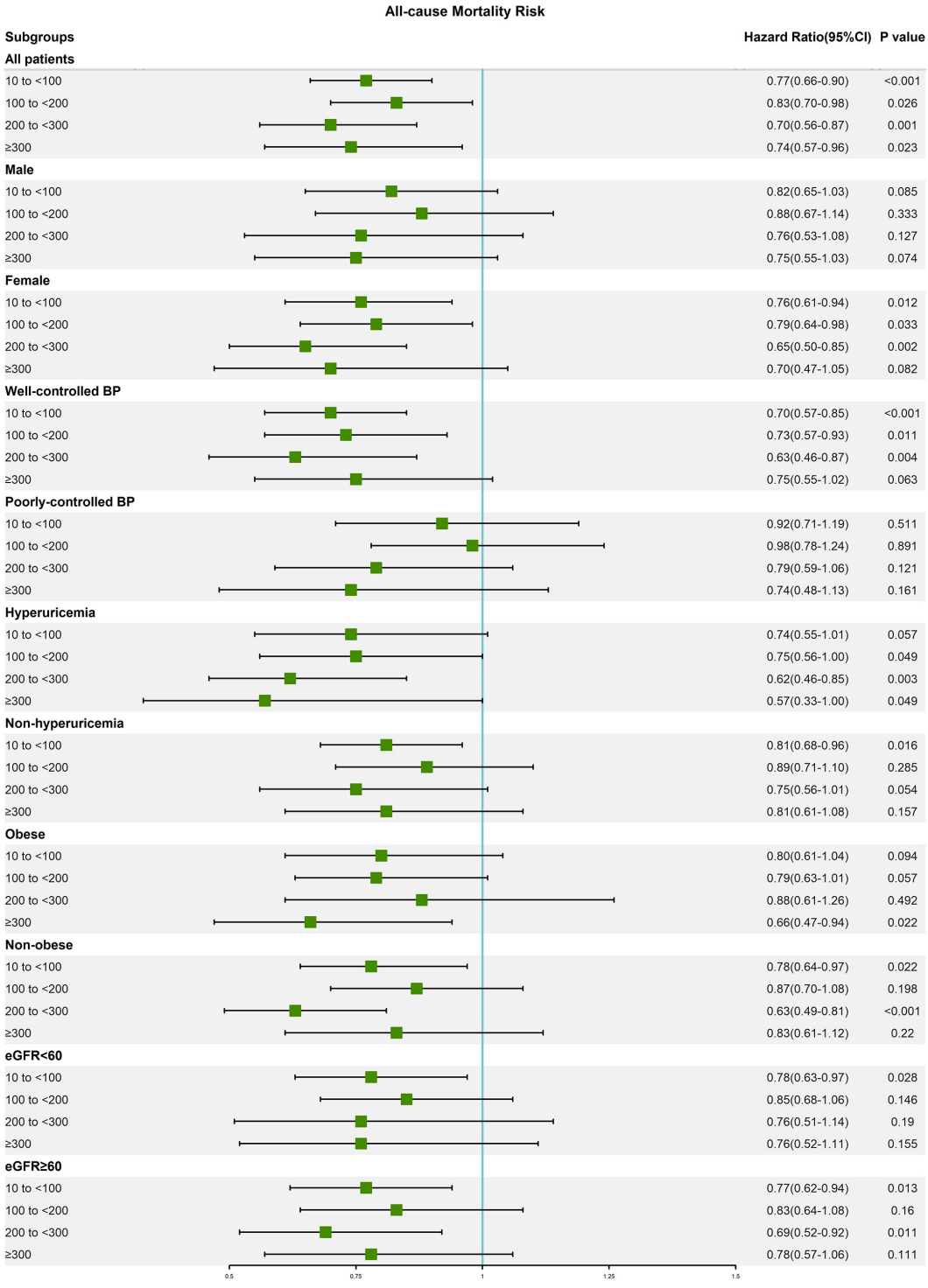

FIGURE 2
Forest plot of multivariable model 3 hazard ratios for all-cause mortality in subgroup analysis.

This study found that the HRs of mortality in women were lower than that in men, especially all-cause mortality. the effect of caffeine intake on mortality may be potentially gender-differentiated, and several previous studies have reported similar results (10, 35). This may be related to genes, hormone levels, sensitivity to caffeine, etc. (36–38). Further studies are necessary to explore the underlying specific mechanisms. We also found that obesity may have affected the beneficial

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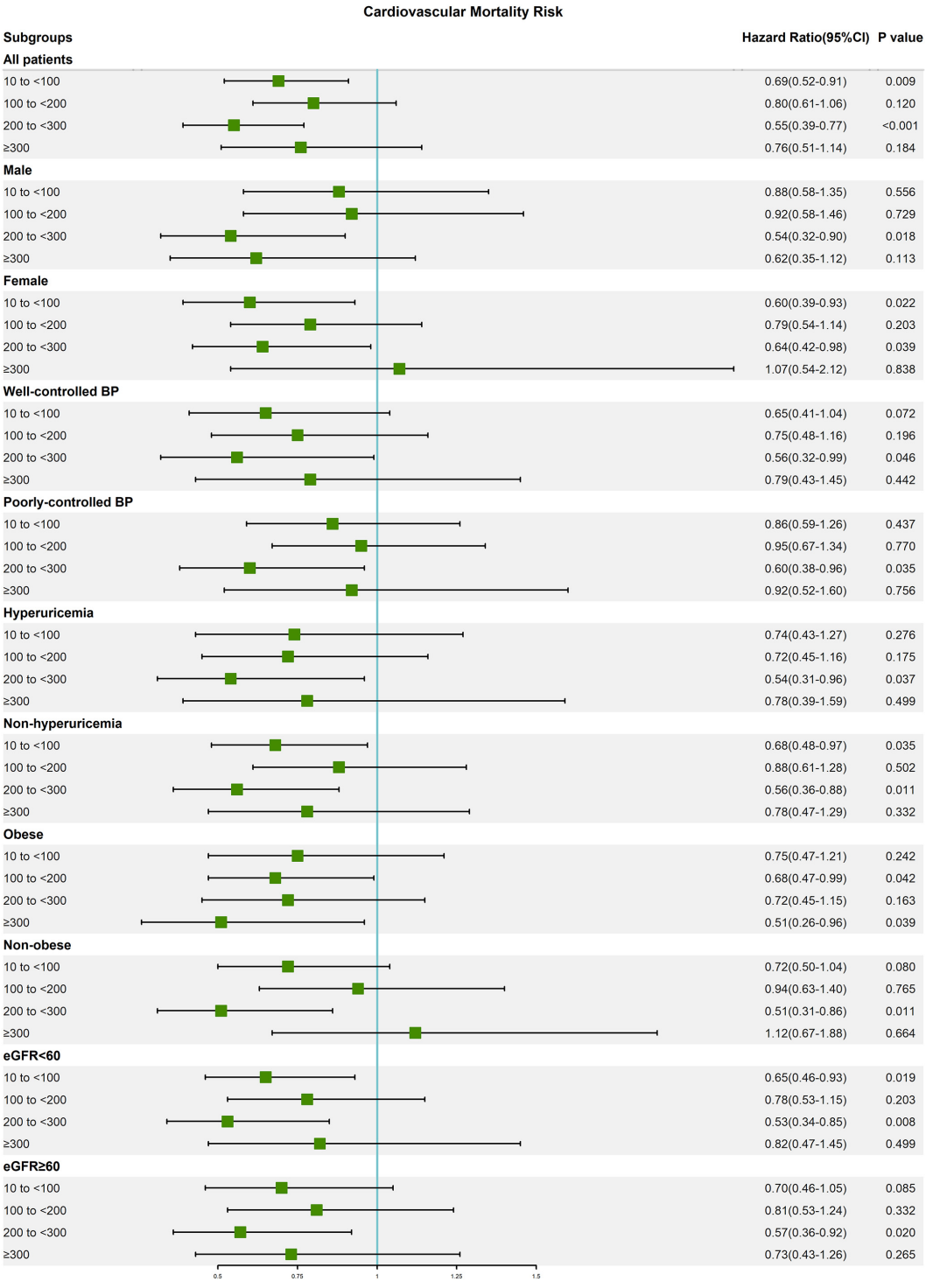

FIGURE 3
Forest plot of multivariable model 3 hazard ratios for cardiovascular mortality in subgroup analysis.

effects of caffeine intake, which is consistent with previous studies (9, 10, 30). This may be related to the tendency of obese patients to consume more caffeine-containing diets, which suggests that obese patients may be able to adapt to higher caffeine intake. More studies are needed to clarify the appropriate caffeine intake for people with different weight statuses. In addition, hyperuricemia is a risk factor for kidney disease and cardiovascular disease (16, 39–41). Some studies

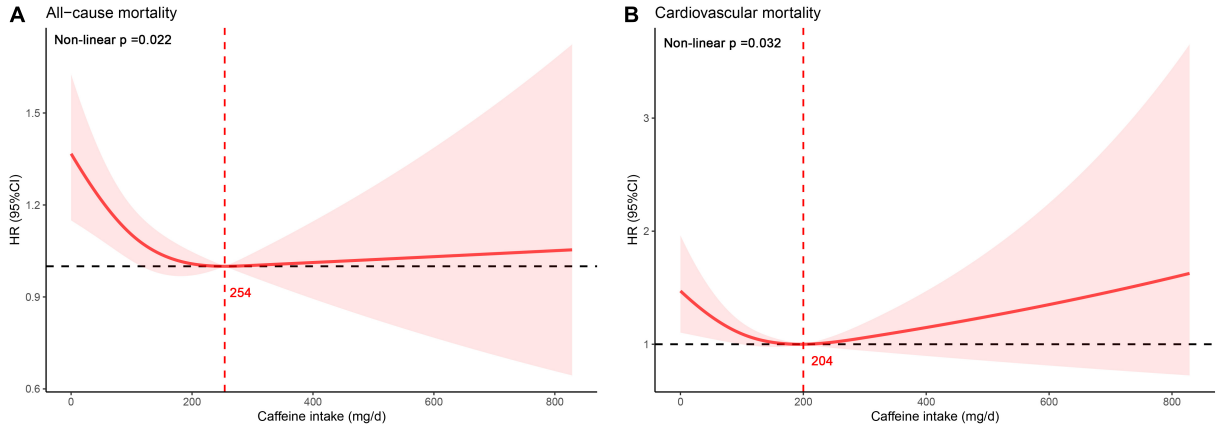

FIGURE 4
Non-linear relationship between caffeine intake and mortality. **(A)** All-cause mortality. **(B)** Cardiovascular mortality.

TABLE 4 Sensitivity analysis between caffeine intake with mortality based on multivariable model 3.

Outcomes	Death/n	Caffeine intake (mg/day)				
		<10	10 to <100	100 to <200	200 to <300	≥300
All-cause mortality						
Remove participants with extreme energy intake	1,901/5,236	1 [Ref]	**0.77 (0.66–0.90)**	**0.81 (0.67–0.99)**	**0.71 (0.57–0.88)**	0.80 (0.61–1.04)
P			**<0.001**	**0.035**	**0.002**	0.099
Remove participants with baseline history of CVD and cancer	967/3,280	1 [Ref]	0.80 (0.63–1.01)	0.87 (0.69–1.12)	**0.63 (0.47–0.85)**	0.82 (0.56–1.21)
P			0.06	0.283	**0.003**	0.318
Low density lipoprotein included	1,049/2,876	1 [Ref]	**0.75 (0.59–0.94)**	**0.75 (0.60–0.92)**	**0.55 (0.44–0.70)**	**0.64 (0.44–0.92)**
P			**0.014**	**0.007**	**<0.001**	**0.016**
Cardiovascular mortality						
Remove participants with extreme energy intake	649/5,236	1 [Ref]	**0.68 (0.52–0.90)**	0.74 (0.52–1.04)	**0.54 (0.37–0.79)**	0.75 (0.48–1.18)
P			**0.007**	0.084	**0.002**	0.217
Remove participants with baseline history of CVD and cancer	313/3,280	1 [Ref]	0.67 (0.43–1.04)	0.82 (0.57–1.18)	**0.46 (0.29–0.73)**	0.68 (0.40–1.15)
P			0.076	0.289	**0.001**	0.146
Low density lipoprotein included	376/2,876	1 [Ref]	0.76 (0.51–1.12)	0.79 (0.55–1.14)	**0.41 (0.23–0.72)**	0.93 (0.53–1.63)
P			0.167	0.213	**0.002**	0.805

HR, Hazard ratio; Ref, reference; BMI, body mass index; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; CVD, Cardiovascular diseases. Model 3: adjustments for age, sex, race/ethnicity, educational level, smoking status, BMI, non-cardiovascular disease conditions (diabetes, asthma, emphysema, thyroid problem, chronic bronchitis, liver condition and cancer), eGFR, uric acid, energy intake, protein intake, carbohydrate intake, sugar intake, dietary fiber intake, fat intake, alcohol intake, sodium intake, cardiovascular disease conditions (heart failure, coronary heart disease and stroke), SBP, DBP, total cholesterol, triglycerides, and high-density lipoprotein. Extreme energy intake was defined as energy intake <1,000 kcal or energy intake >3,000 kcal. Cardiovascular diseases were defined as coronary heart disease, heart failure, stroke, angina, and heart attack. Model with low density lipoprotein included: adjustments for model 3 plus low density lipoprotein. Statistically significant HR and *p*-values were shown in bold.

have suggested that caffeine intake and coffee consumption are inversely associated with serum uric acid levels (42–44). Our study observed that elderly hypertensive patients with hyperuricemia had lower HRs for all-cause mortality than those without hyperuricemia. This suggests that elderly hypertensive patients with hyperuricemia may be more inclined to obtain the benefits of caffeine, and further research is warranted to clarify the differences in the effect of caffeine intake in people with different uric acid levels. We considered that the benefits of caffeine may vary among elderly hypertensive patients with different statuses. Appropriate caffeine intake according to the condition of elderly hypertensive patients is healthy.

This is the first study of caffeine on the risk of death in elderly hypertensive patients. The sample size and follow-up time included in this study were sufficient. And we took full account of various potential confounding factors, including demographic variables, dietary intakes, laboratory measurements, medical conditions, etc. However, the research still has several limitations. First, caffeine intake was estimated based on self-reported dietary information, and there was inevitable measurement error. Second, 2-day average caffeine intake may not accurately reflect long-term caffeine intake. Last but not least, this study is a retrospective cohort study. Even after adjusting for many confounding variables, there is still a substantial risk of confounding bias.

Conclusion

Moderate caffeine intake is associated with reduced risk of all-cause and cardiovascular mortality in elderly hypertensive patients. Although no significant interaction was observed, the benefits of caffeine may be more pronounced in elderly hypertensive female patients or patients with well-controlled blood pressure, and further studies are warranted to elucidate differences in the effects of caffeine intake among various populations.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: NHANES Questionnaires, Datasets, and Related Documentation (https://wwwn.cdc.gov/nchs/nhanes/Default.aspx).

Ethics statement

The studies involving human participants were reviewed and approved by National Center for Health Statistics Research Ethics Review Board approved the NHANES protocol (https://www.cdc.gov/nchs/nhanes/irba98.htm). The patients/participants provided their written informed consent to participate in this study.

Author contributions

WZ and SC conceived and designed the research. JL, MG, DL, RS, and JS processed data and performed the statistical analysis. SC, JL, and MG wrote the initial manuscript. WZ, TW, GF, LL, and XS reviewed and corrected 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.2022.1023345/full#supplementary-material

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Naturally cultured high resistant starch rice improved postprandial glucose levels in patients with type 2 diabetes: A randomized, double-blinded, controlled trial

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Objective: To assess the effect of a novel naturally cultured rice with high resistant starch (RS) on postprandial glycemia in patients with type 2 diabetes compared to ordinary rice.

Design: This study is a randomized, double-blinded controlled trial.

Methods: Patients with type 2 diabetes were recruited, and postprandial glucose levels were measured at 5-time points after the ingestion of one of two types of cooked rice in random order. Paired *t*-tests were used to compare postprandial blood glucose changes and increment areas under the blood glucose curve between high-RS rice and ordinary rice.

Results: The increments of the postprandial blood glucose levels for high-RS rice were significantly lower than that for ordinary rice, i.e., 2.80 ± 1.38 mmol/L vs. 3.04 ± 1.50 mmol/L ($P = 0.043$) and 3.94 ± 2.25 mmol/L vs. 4.25 ± 2.29 mmol/L ($P = 0.036$) at 30 min and 60 min, respectively. The incremental areas under the blood glucose curve for high-RS rice were also significantly lower than that for ordinary rice, i.e., 42.04 ± 20.65 [mmol/(L·min)] vs. 45.53 ± 22.45 [mmol/(L·min)] ($P = 0.043$), 143.54 ±69.63 [mmol/(L·min)] vs. 155.15 ± 73.53 [mmol/(L·min)] ($P = 0.026$), and 354.61 ± 191.96 [mmol/(L·min)] vs. 379.78 ± 195.30 [mmol/(L·min)] ($P = 0.042$) at 30, 60, and 120 min, respectively. Repeated-measures ANOVA showed that postprandial glucose levels were not affected by the test order.

Conclusion: The novel high-RS rice as a staple food when substituting for widely consumed ordinary rice may provide potential health benefits by lowering blood glucose in patients with type 2 diabetes.

KEYWORDS

resistant starch (RS), rice, diabetes, postprandial glucose level, randomized controlled trial (RCT)

Introduction

Diabetes is one of the most common chronic non-communicable diseases in China and worldwide and has become a great public concern. According to the data released by the International Diabetes Federation in 2019, the global prevalence of diabetes was 9.3% (1). While the number of people with diabetes in China has exceeded 100 million, it is ranking first in the world (2). Most cases of diabetes worldwide are type 2 diabetes (3). The epidemic of type 2 diabetes affects patients' health to varying degrees and may even threaten their lives in serious cases (4). In addition, the high cost of treatment imposes a huge economic burden on individuals and countries (2). Currently, lifestyle interventions are the major preventive and basic therapeutic measures for patients with diabetes (5, 6). The main strategy for reducing the risk of complications and improving the quality of life of patients with diabetes is intensive glycemic control (7, 8). Therefore, dietary interventions as a part of lifestyle change play an important role in controlling blood glucose levels (9).

Starch is one of the main forms of carbohydrates in the diet and is classified into three categories according to its digestibility: rapidly digestible starch (RDS), slowly digestible starch (SDS), and resistant starch (RS) (10). RS cannot be digested and absorbed in the small intestine but can be fermented by the microflora in the colon and subsequently exerts beneficial physiological effects. Therefore, RS is regarded as one type of dietary fiber (11). RS can be found in cereal products, seeds, beans, bananas, and potatoes, and in a commercially purified form as an additive to foods (12). The initial development of RS products was mainly based on corn with a high amylose (AM) content, more RS based on cassava, wheat, potato, and barley has also been made with great success (13). RS is classified into five forms, from RS1- to RS5, according to its origin and digestibility, i.e., physically inaccessible starch (RS1), high starch (RS2), modified starch (RS3), chemically modified starch (RS4), and starch-lipid complexes (RS5) (14). The unique properties of RS, such as its natural origin, mild flavor, white color, and low water retention, have made it a prominent topic for research on a variety of functional foods (15).

Based on accumulating evidence, RS is beneficial for human health. Animal studies have shown that RS intake ameliorates intestinal dysbiosis and chronic inflammation (11). Similar results have been obtained from population trials: wheat high in RS modulated fecal metabolites and microorganisms which are associated with gastrointestinal health in healthy adults (16). A meta-analysis showed that RS improved total cholesterol, low-density lipoprotein (LDL) cholesterol, and tumor necrosis factor-α (TNF-α) levels (17). The most well-studied function of RS might be the ability to improve glucose homeostasis. RS intervention has consistently been shown to help control postprandial glucose levels (18, 19). However, most of the published studies used RS as supplement in processed products [such as bagels (20) and cereal bars (21)] which are often consumed as snacks. Rice, on the contrary, as a main staple food for more than half of the global population (22) would be an ideal carrier for RS. Since refined ordinary rice usually has low fiber and high glycemic index (GI), it is not recommended as a daily staple food for patients with diabetes. So, cultivating high-RS rice with hypoglycemic properties may be a good option for diabetes control (23, 24). Although evidence for RS in reducing postprandial glycemic response is well-documented, most studies on diabetes used RS as supplement. Therefore, this study is about to confirm the effect of newly cultured high-RS rice on postprandial blood glucose levels in patients with type 2 diabetes, which may provide scientific evidence for the promotion of high-RS rice consumption to improve the health of diabetes.

Materials and methods

Study design

This study was a randomized, double-blinded controlled trial. The study was approved by the Research Ethics Committee of Chongqing Medical University (2021089). Subjects signed informed consent to take part in.

The trial site was in the Health Management Center of the Second Hospital of Chongqing Medical University, Chongqing, China.

Subjects

Subjects were recruited through the advertisement posted on the official social media (WeChat) account of the Health Management Center of the Second Hospital of Chongqing Medical University between November 2021 and February 2022. People who were interested in this study contacted the researcher for details. Inclusion criteria included: (1) age is between 40–70 years old; (2) diagnosed type 2 diabetes has medical records; (3) the patient's condition is stable without acute complications; (4) having the ability to do social communication. Exclusion criteria included patients with serious diseases or conditions, such as malignant tumors, severe heart disease, stroke, liver and kidney insufficiency, acute respiratory infections, fever, and those who have limited mobility. Subjects were interviewed at the first time of testing for basic information. A total of 106 patients with diagnosed type 2 diabetes finally were recruited.

Random grouping

Subjects were randomly assigned into two groups according to the order of testing. Group A: RS rice then ordinary rice; Group B: ordinary rice then RS rice.

Cards labeled with group assignments (Group A; Group B) were placed into sealed envelopes. The first time when subjects arrived at the test site, they were given an envelope randomly to decide the test order of the two rices. The rices of testing were blinded (cooked rices were indistinguishable by texture and taste in our pretest) to study subjects and the blood glucose sample testers.

Preparing testing meals

The Chongqing Academy of Agricultural Sciences cultured and provided both types of refined rice, i.e., high-RS rice and ordinary rice. High-RS rice has 8.44% of resistant starch, while it is only 0.46% in ordinary rice. The nutrition facts were shown in Table 1.

Rice was weighed, washed once with water, and cooked by using an electric rice cooker. The final rice-to-water ratio for cooking was 1:1.8 (decided by the taste and texture of cooked rice in pretest). The cooked rice/raw rice ratio was 2.39 and 2.46 for high-RS rice and ordinary rice, respectively (measured in pretest).

Three sizes of cooked rice (large portion: 200 g cooked rice; medium portion: 150 g cooked rice; small portion: 100 g cooked rice) were provided for subjects to choose according to their appetite.

To simulate the real diet, side dishes were also added, including a portion of boiled bok choy (100 g raw vegetable, 5 ml of soy sauce, and 5 ml of sesame oil), one cup (200 ml) of soup (5 grams nori and 1 stirred egg boiled in 2 liters of water), 1 boiled egg, and a small pinch of pickled vegetable.

Meals were freshly prepared on the testing day morning by the cafeteria staff in the hospital.

Test procedure

One week before testing day, subjects were required to maintain their usual lifestyle. On the day before the testing, subjects were told to avoid foods high in dietary fiber and sugar at dinner, to fast after 10:00 pm, and to keep fasting until the testing in the next morning. Subjects were also required to bring any medications they were prescribed to take in the morning, including hypoglycemic drugs.

Before taking the testing meal, 1 ml of fasting venous blood was collected to measure the fasting glucose. At their first bite of the meal, it was defined as the zero-time of trial. The whole meal was eaten up in 10 min. After the meal, subjects were reminded to take their medicine if prescribed.

Each time at 30, 60, 120, and 180 min after the meal, 1 ml of venous blood was drawn. Blood samples were collected from the subjects by nurses and sent to the hospital laboratory to do blood glucose tests.

After a 7-days washout period, the second round trial was conducted with the other rice according to the test order assigned at the first trial. In the second round, all except the rice type remained the same as in the first round for each subject, including meal size and medications.

TABLE 1 Nutrition facts of test rices* (per 100 g refined rice).

Item	Unit	High-RS rice	Ordinary rice
Energy	KJ	1,485	1,462
Protein	G	7.7	6.6
Fat	G	0.9	0.6
Carbohydrates	G	77.1	77.7
Sodium	Mg	0	0
Dietary fiber	G	1.2	0.8
Resistant starch content	G	8.44	0.46

*Data were reported by an independent qualified laboratory in Beijing, China.

Outcome indicators

Outcome indicators included the change of postprandial glucose level [ΔCt (mmol/L)] and the incremental area under the glucose curve (IAUC [mmol/ (L·min)]).

ΔCt is blood glucose level at a time point minus fasting blood glucose level.

IAUC is calculated using the trapezoidal rule, with the fasting blood glucose level as the baseline and ignoring the area below the baseline.

Statistical analysis

All continuous values were expressed as the mean ± standard deviation (SD). To control the confounding factors, studends *t*-tests and chi-square tests were used to analyze the baseline situation of the two AB groups. Paired *t*-test was used to compare the difference between groups at each time point. Repeated-measures ANOVA was used to detect the effect of test order (25). Statistical analysis was performed using SPSS 25.0 software. $P < 0.05$ was considered statistically significant.

Results

Overview of subjects

Eighty one out of 107 recruited patients with type 2 diabetes eventually were eligible for this study. During testing, 1 subject who failed two rounds of trial and 7 subjects who failed to fully follow the instructions were excluded from the data analysis.

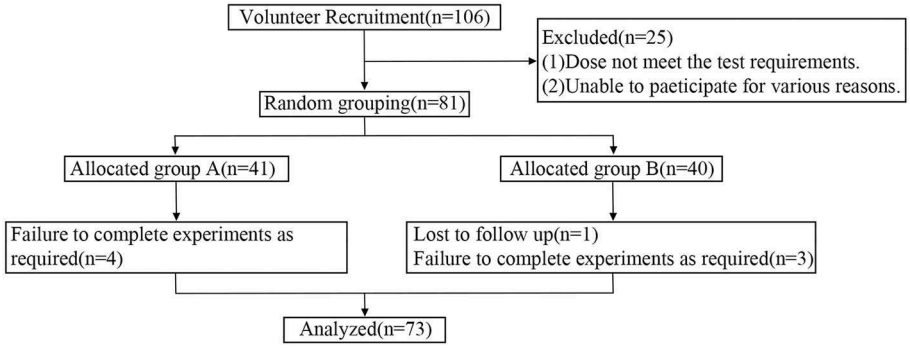

FIGURE 1
Flow diagram of participant recruitment and included.

TABLE 2 General condition of the subjects ($n = 73$).

Item	Total ($n = 73$)	Group A ($n = 37$)	Group B ($n = 36$)	*P*
Age (years)	59.74 ± 8.89	58.14 ± 8.60	61.39 ± 8.99	0.118
Sex (male/female)	46 / 27	25 / 12	21 / 15	0.414
Height (cm)	163.42 ± 7.77	163.35 ± 8.81	163.50 ± 6.65	0.936
Body weight (kg)	62.04 ± 8.27	62.60 ± 8.71	61.46 ± 7.87	0.559
BMI (kg/m^2)	23.22 ± 2.66	23.45 ± 2.63	22.99 ± 2.71	0.462
Hypertension (with/without)	19 / 54	10 / 27	9 / 27	0.844
Duration of diabetes	9.49 ± 7.02	9.89 ± 6.67	9.08 ± 7.44	0.626
Anti-diabetic drugs (yes/no)	61 / 12	31 / 6	30 / 6	0.959
Other prescribed drug (yes/no)	9 / 64	5 / 32	4 / 32	0.755
Rice portion (small, medium, and large)	0 / 8 / 65	0 / 1 / 36	0 / 7 / 29	0.056

Each value is expressed as the mean ± SD. Group A, RS rice then ordinary rice; Group B, ordinary rice then RS rice.

Ultimately, 73 subjects were included in this study. The process of subject screening was shown in Figure 1.

For those who were included, the age was 59.74 ± 8.89 years, the body mass index (BMI) was 23.22 ± 2.66 kg/m^2, and the duration of diabetes was 9.49 ± 7.02 years. There were no significant differences between the two groups (two testing orders) in terms of baseline conditions such as mean age, sex, height, weight, and BMI ($P > 0.05$). The profile of the subjects was shown in Table 2.

The postprandial blood glucose level

The paired *t*-test showed that the subjects when taking the cooked high-RS rice had significantly lower changes in postprandial blood glucose than the time when taking cooked ordinary rice at 30 and 60 min ($P < 0.05$, Table 3).

Incremental area of the blood glucose curve

The incremental area under the blood glucose curve in patients with diabetes when taking cooked high-RS rice was smaller than that when taking cooked ordinary rice. The paired *t*-test revealed statistically significant differences between the two kinds of rice at 30, 60, and 120 min ($P < 0.05$, Table 4).

The impact of testing order

Repeated-measures ANOVA showed that the treatment factors (types of rice) but not the test order caused the differences in postprandial blood glucose in patients with diabetes at 30 and 60 min ($P < 0.05$, Table 5).

TABLE 3 Comparisons of postprandial blood glucose levels (mean ± SD) between high-RS rice meal and ordinary rice meal ($n = 73$).

Item	High-RS rice	Ordinary rice	t	P
ΔC_{30min} (mmol/L)	2.80 ± 1.38*	3.04 ± 1.50	−2.057	0.043
ΔC_{60min} (mmol/L)	3.94 ± 2.25*	4.25 ± 2.29	−2.131	0.036
ΔC_{120min} (mmol/L)	3.00 ± 2.56	3.14 ± 2.54	−0.698	0.488
ΔC_{180min} (mmol/L)	1.13 ± 2.58	1.16 ± 2.17	−0.158	0.875

ΔCt is the change between postprandial blood sugar and fasting blood glucose. *P <0.05 (paired t-test).

TABLE 4 Comparison of IAUC (mean ± SD) between high-RS rice meal and ordinary rice meal ($n = 73$).

Item	High-RS rice	Ordinary rice	t	P
$IAUC_{30min}$ [mmol/(L·min)]	42.04 ± 20.65*	45.53 ± 22.45	−2.057	0.043
$IAUC_{60min}$ [mmol/(L·min)]	143.54 ± 69.63*	155.15 ± 73.53	−2.277	0.026
$IAUC_{120min}$ [mmol/(L·min)]	354.61 ± 191.96*	379.78 ± 195.30	−2.066	0.042
$IAUC_{180min}$ [mmol/(L·min)]	493.33 ± 308.03	519.78 ± 304.21	−1.381	0.171

IAUC, incremental area under the postprandial glucose curve. *P < 0.05 (paired t-test).

Discussion

As a metabolic disease, diabetes will gradually progress with a variety of acute and chronic complications of varying severities, which is the main cause of disability and death of patients with diabetes (26). The development of diabetic complications is not only associated with persistent chronic hyperglycemia but also closely related to fluctuations in blood glucose levels (27, 28).

We have found in this study that patients with type 2 diabetes when consuming high-RS rice had smaller fluctuations in postprandial blood glucose levels than when consuming ordinary rice in the real world with antidiabetic drugs and simulated ordinary diet, and their glycemic changes were significantly lower at 30 min and 60 min after meals when consuming high-RS rice. Moreover, the incremental area under the blood glucose curve of patients with diabetes when consuming high-RS rice was also smaller than that of patients when consuming ordinary rice.

Other studies have also reported similar results. For example, Yuhi Saito (29) conducted two randomized, single-blinded, crossover trials to study the effects of a single intake of high-RS crackers and cooked high-RS rice on postprandial glycemic and insulin responses in healthy adults and compared them with rice crackers and cooked rice prepared from ordinary varieties, and the results indicated that both high-RS rice crackers and high-RS rice had lower postprandial glycemic and insulin responses. Takahashi (30) conducted a non-randomized crossover design trial in which five healthy men consumed two types of cooked rice, i.e. control (low-RS) and test (high-RS) rice, and found that high-RS rice improved postprandial hyperglycemia and hyperinsulinemia. But unlike our study, those studies investigated postprandial blood glucose in healthy people. The present study showed that naturally cultured high-RS rice has the same effects on postprandial blood glucose in type 2 diabetes. Although the benefits of resistant starch on diabetes have been reported in some studies, nearly all studies used RS supplements as intervention and postprandial blood glucose was not measured (31). Until now, the effects of naturally cultured high-RS rice on diabetes were rarely reported.

RS, as a special dietary carbohydrate, is considered one of the most important factors in the study of the relationship between carbohydrates and health (31). In our study, the refined high-RS rice has 8.44% of resistant starch, obviously high than ordinary refined rice which has <1% of RS. Not surprisingly, studies have shown that high-RS rice has a lower GI value than ordinary rice (32). Numerous studies have shown that the consumption of low-GI food has improved the drastic changes in postprandial blood glucose levels (33, 34). Moreover, a significant negative correlation was also observed between GI and RS (35). The novel high-RS rice in this study have a GI value of 65 when cooked, which is lower than 80 of ordinary cooked rice (result from our preliminary study, data have not been reported). The low GI value may explain the reduced postprandial glycemic response of high RS rice in diabetes compared with ordinary rice.

There are some strengths in this study. Firstly, randomized controlled trial (RCT) design was used in this study which can effectively control kinds of confounders. Secondly, a double-blinding method was used to avoid possible bias related to the researchers and subjects. Thirdly, postprandial glucose was measured at multiple time points, which provided an overall view of high-RS rice on postprandial glucose. Fourthly, this study tested high-RS rice in real-life conditions by simulating the real diet and allowing the medicine prescribed (31). Therefore, the results are reliable and can be generalized to the real world.

TABLE 5 Repeated ANOVA of postprandial glucose by test order.

Item	Group A ($n = 37$)	Group B ($n = 36$)	Repeated-measures ANOVA(*P*)	
			Treat	Test order
ΔC_{30min} (mmol/L)	2.86 ± 1.50	2.98 ± 1.38	0.045*	0.297
ΔC_{60min} (mmol/L)	3.97 ± 2.32	4.22 ± 2.22	0.036*	0.085
ΔC_{120min} (mmol/L)	3.04 ± 2.59	3.09 ± 2.50	0.493	0.797
ΔC_{180min} (mmol/L)	1.18 ± 2.33	1.10 ± 2.42	0.871	0.676

Group A, RS rice then ordinary rice; Group B, ordinary rice then RS rice. * $P < 0.05$.

Some limitations of our study also must be mentioned. Since this study only measured postprandial glucose, the long term effects of high-RS rice on blood sugar and other health effects are still undecided. Therefore, studies about high-RS rice on diabetes or other metabolic diseases in the long term with more biomarkers are warranted.

Conclusion

The novel high-RS rice as a staple food when substituting for widely consumed ordinary rice may provide potential health benefits by lowering blood glucose in patients with type 2 diabetes.

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 Ethics Committee of Chongqing Medical University. The patients/participants provided their written informed consent to participate in this study approval number: 2021089.

Author contributions

YZ and L-LT reviewed the literature and completed the protocol design. L-LT, YM, X-YQ, W-QD, and M-XC conducted the clinical trial and were responsible for data collection. L-LT performed the statistical analysis and data interpretation under the direction of YZ, wrote the manuscript, and revised 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

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Prevalence of hypertension in endemic and non-endemic areas of Keshan disease: A cross-sectional study in rural areas of China

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Background: Hypertension is a major public health concern that strongly influences the quality of life of people worldwide. Keshan disease (KD) is an endemic cardiomyopathy related to low selenium, threatening residents in rural areas of 16 provinces in China. Furthermore, the prevalence of hypertension in the KD-endemic areas has been increasing annually. However, hypertension research associated with KD has only focused on endemic regions, and no studies have compared hypertension prevalence between endemic and non-endemic areas. Therefore, this study investigated the prevalence of hypertension to provide a basis for preventing and controlling hypertension in the KD-endemic areas, even in rural areas.

Methods: We extracted blood pressure information from cardiomyopathy investigation data from a cross-sectional study of the KD-endemic and non-endemic areas. The hypertension prevalence between the two groups was compared using the Chi-square test or FisherŠs exact test. Additionally, Pearson's correlation coefficient was employed to evaluate the relationship between the per capita gross domestic product (GDP) and hypertension prevalence.

Results: There was a statistically significant increase of hypertension prevalence in the KD-endemic areas (22.79%, 95% confidence interval [CI]: 22.30–23.27%) over the non-endemic areas (21.55%, 95% CI: 21.09–22.02%). In the KD-endemic areas, more men had hypertension than women (23.90% vs. 21.65%, $P < 0.001$). Furthermore, the hypertension prevalence was higher in the north than in the south in the KD-endemic areas (27.52% vs. 18.76%, $P < 0.001$), non-endemic areas (24.86% vs. 18.66%, $P < 0.001$), and overall (26.17% vs. 18.68%, $P < 0.001$). Finally, the prevalence of hypertension positively correlated with per capita GDP at province level.

Conclusions: The increasing hypertension prevalence is a public health problem in the KD-endemic areas. Healthy diets, such as high consumption of vegetables and seafoods, and foods that are rich in selenium, might help prevent and control hypertension in the KD-endemic areas and other rural areas in China.

KEYWORDS

hypertension, Keshan disease, cross-sectional study, blood pressure, selenium, diet

1. Introduction

More than 200 million adults have hypertension in China, accounting for over one-fifth of China's adult population (1). Moreover, hypertension is a major public health concern worldwide and is a risk factor for abundant diseases, such as cardiovascular (2, 3) and kidney diseases (4). More than half of the global adult population have not been diagnosed with or treated for hypertension. Consequently, only approximately 20% of adult patients have experienced hypertension control through medical care (4). Moreover, residents of rural areas may be at higher risk than those in urban areas in low-and middle-income countries.

Keshan disease (KD) is an endemic cardiomyopathy characterized by degeneration, necrosis, and fibrosis of cardiomyocytes, and heart dilatation, threatening the residents of rural areas in 16 provinces of China (5). In addition, hair and serum samples from individuals from these populations and soil and grain samples from the KD-endemic areas indicated low selenium levels (6, 7). Moreover, Mihailović et al. (8) found that patients with arterial hypertension had significantly lower whole-blood and plasma selenium concentrations.

A 10-year follow-up study verified that hypertension is a risk factor for latent KD worsening into chronic KD (9). Recently, with economic development and changes in diet, the prevalence of hypertension in the KD-endemic areas has increased annually (10), exceeding the national average (11). Previous hypertension research associated with KD has focused on the endemic areas, whilst no studies have investigated hypertension disparities between the KD-endemic and non-endemic areas. Therefore, this study used the blood pressure data from a cardiomyopathy investigation of residents of the KD-endemic and non-endemic areas in 2011 to understand the prevalence of hypertension and provide a base for preventing and controlling hypertension in the KD-endemic areas, even in the rural areas in China.

2. Materials and methods

2.1. Multistage cluster sampling

We extracted data from a cross-sectional study comprising KD surveillance in KD-endemic counties and dilated cardiomyopathy surveyed in non-endemic counties in 13 provinces. The provinces included Heilongjiang, Nei Mongol, Jilin, Gansu, Shaanxi, Liaoning, Shanxi, Shandong, Henan, Hebei, Yunnan, Sichuan, and Chongqing. There are more endemic counties and higher KD prevalence in the 13 provinces among 16 provinces affected by KD in China. KD surveillance has been gradually conducted in those provinces since 1990. The other three provinces, Hubei, Guizhou and Tibet, were excluded due to only one KD county and few KD cases occurred. The KD-endemic areas were determined using the Delimitation and Classification of Keshan Disease Areas (GB17020-2010) (12). In this study, we used multistage cluster sampling. For each county, we performed the case search (6) to identify two townships with the most patients with KD or dilated cardiomyopathy. Then, we selected the village with the most patients in either of the two townships for the investigation. The included villages had populations greater than or equal to 500 people. The endemic and non-endemic counties were individually matched based on the geographical location and residents' lifestyles. Finally, hypertension data were collected from the 49 KD-endemic and 49 non-endemic counties.

2.2. Participants

All village residents underwent medical examinations, including blood pressure and electrocardiograms. After, patients with suspected KD or dilated cardiomyopathy were examined using echocardiography and chest radiography. We required a response rate of 80% or higher or at least 400 surveyed individuals. If the quantity did not meet these requirements, it would be supplemented by the neighboring village. All included participants had lived in the surveyed village for more than 6 consecutive months or had left for no more than 3 months in the past year. We examined 43,240 and 104,166 people in the KD-endemic and non-endemic areas, respectively. Then, we extracted blood pressure data for 58,994 participants aged 20 years or older for the analysis.

2.3. Blood pressure measurements

After sitting in a relaxed position comfortably and quietly for more than 5 min, blood pressure was measured using a mercury sphygmomanometer. The participants were informed that smoking, drinking, and other activities resulting in blood pressure instability were forbidden for at least 30 min before the measurement. During the measurement, the elbow and forearm were bent flush with the heart, and the cuff was placed on the right bare upper arm one inch above the bend of the elbow with appropriate tightness. The disk of the stethoscope was placed face down under the cuff, just to the inner side of the upper arm, where the brachial artery pulse could be felt. The cuff was rapidly inflated until the pulse voice disappeared and continued to be pressurized until it was slowly deflated after the gauge reading had risen by 20–30 mmHg. The first loud beat heard was the

Abbreviations: KD, keshan disease; GDP, gross domestic product; SBP, systolic blood pressure; DBP, diastolic blood pressure; CI, confidence interval.

systolic blood pressure (SBP), and the last beat before it disappeared was the diastolic blood pressure (DBP).

2.4. Economic and demographic data

Demographic data including age and sex and the per capita gross domestic product (GDP) were collected for each province in 2011 from the 2012 China Statistical Yearbook (13).

2.5. Ethics

All participants signed an informed statement to give permission and indicate that they had no direct interest in the study's results. This study conformed to the Declaration of Helsinki and has been authorized by the Medical Ethics Committee of Harbin Medical University.

2.6. Statistical analyses

The statistical analyses were executed with R Studio version 1.4.1717.[1] Hypertension was defined as either a SBP of 140 mmHg or greater or a DBP of 90 mmHg or greater or the presence of both based on the 2019 Annual Report on Cardiovascular Health and Diseases in China (14). Hypertension was classified into three categories: Grade 1 (140–159/90–99 mmHg), Grade 2 (160–179/100–109 mmHg), and Grade 3 (≥180/110 mmHg) (15). We excluded SBP, DBP, or pulse pressure data outside a 99.73% confidence interval (CI). We also screened for duplicated records and, if identified, randomly retained one of the duplicates. Repeat data were defined as consistent information, including province, county, township, age, sex, SBP, DBP, pinyin of name, and telephone number.

The distributions of the participant characteristics were described using the population pyramid. Bar charts were used to depict the prevalence of hypertension in the KD-endemic and non-endemic areas by age categories. Forest plots were employed to describe the hypertension prevalence rate at the province level, while error bars with 95% CIs were used to demonstrate hypertension differences between the sexes. The prevalence was standardized by age and sex based on the 2012 China Statistical Yearbook (13). The prevalence between the two groups was compared using the Chi-square test or Fisher's exact test, and the relationship between the per capita GDP and hypertension prevalence at province level was analyzed using Pearson's correlation coefficient. The statistical significance was delimited at $P < 0.05$.

3. Results

3.1. Total hypertension prevalence

We recruited 58,994 participants, including 28,738 participants from the KD-endemic areas and 30,256 from the non-endemic areas. Figure 1 presents the age and sex distributions of the respondents. The prevalence of hypertension was higher in the KD-endemic areas (22.79%, 95% CI: 22.30–23.27%) than in the non-endemic areas (21.55%, 95% CI: 21.09–22.02%, $P < 0.001$, Table 1).

3.2. Hypertension prevalence by age categories, sex, and grade

Hypertension prevalence increased with age; the highest prevalence was in the 75–79 and 80+ year age groups in the endemic and non-endemic areas, respectively. Furthermore, in four age groups (50–54, 55–59, 60–64, and 70–74 years), the prevalence of hypertension was lower in the non-endemic areas than in the KD-endemic areas ($P < 0.05$, Figure 2 and Supplementary Table 1).

The prevalence of hypertension among men in the KD-endemic areas exceeded that among men in the non-endemic areas and women in the KD-endemic areas ($P < 0.001$, Figure 3). The prevalence of Grade 1 and 2 hypertension was higher in the KD-endemic areas than in the non-endemic areas, whereas the prevalence of Grade 3 hypertension was the opposite ($P < 0.001$, Table 2).

3.3. Hypertension prevalence by region

The annual average temperature of the capital cities in the provinces included in this investigation was 11.7°C. Therefore, provinces with an annual average temperature above 11.7°C were classified as being in the south and included Shandong, Shaanxi, Henan, Hebei, Yunnan, Sichuan, and Chongqing. Conversely, provinces with an annual average temperature below 11.7°C were classified as being in the north and included Heilongjiang, Jilin, Liaoning, Nei Mongol, Shanxi, and Gansu.

In the north, the prevalence of hypertension was significantly higher in the KD-endemic areas than in the non-endemic areas ($P < 0.001$). Moreover, the prevalence of hypertension was significantly higher in the north than in the south, regardless of the endemic classification ($P < 0.001$, Table 3).

3.4. Hypertension prevalence by province

In the Shanxi, Henan, Heilongjiang, and Chongqing provinces, the prevalence of hypertension was significantly lower in the non-endemic areas than in the endemic areas ($P < 0.001$, Figure 4 and Supplementary Table 2). However, the opposite was observed in the Sichuan ($P < 0.001$), Shandong ($P < 0.001$), and Shaanxi ($P < 0.05$) provinces.

3.5. Hypertension prevalence and per capita GDP

Pearson's correlation coefficient was determined to be $r = 0.6672$ ($P = 0.0127$), suggesting that the prevalence of hypertension positively correlated with the per capita GDP by province (Figure 5, Supplementary Table 3 and Supplementary Figure 1).

1 https://www.rstudio.com/products

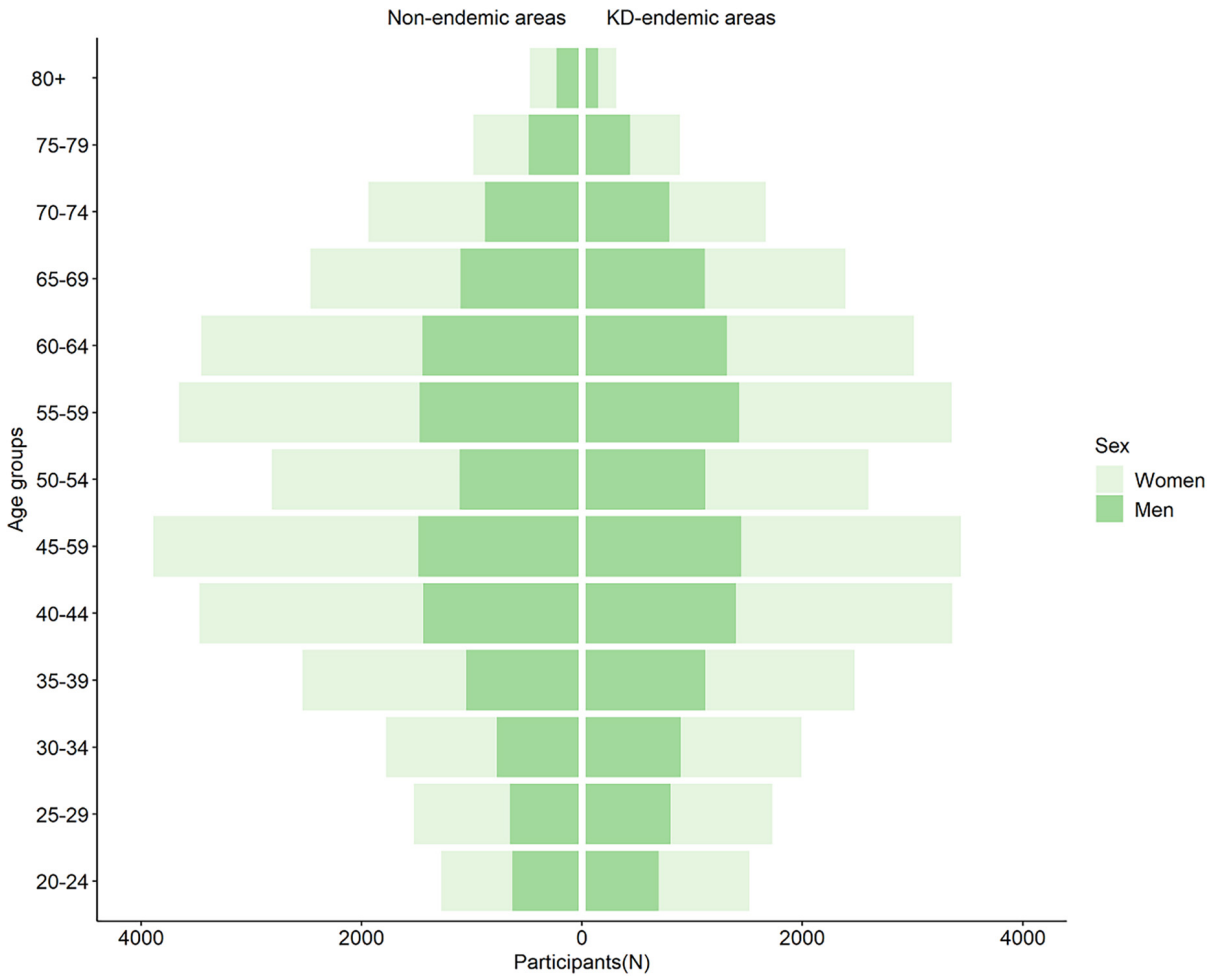

FIGURE 1
Population pyramid of participants in KD-endemic and non-endemic areas. KD, Keshan disease; N, number.

TABLE 1 Prevalence of hypertension in KD-endemic and non-endemic areas.

KD areas	Participants	Patients with hypertension	Prevalence (95% CI)	Age, sex-standardized prevalence (95% CI)
Endemic	28,738	8,172	28.44% (27.92–28.96%)	22.79% (22.30–23.27%)[a]
Non-endemic	30,256	8,364	27.64% (27.14–28.15%)	21.55% (21.09–22.02%)

CI, confidence interval; KD, Keshan disease.
[a] $P < 0.001$ compared with the non-endemic areas.

4. Discussion

We conducted a large-scale and representative study, reporting for the first time that the prevalence of hypertension is higher in the KD-endemic areas than in the non-endemic areas. This may be related to the suboptimal selenium intake of residents in the KD-endemic areas. The Western European longitudinal population study demonstrated that a 20 μg/L or higher blood selenium level at baseline reduced the risk of hypertension by 37% in men (16), and adults with low toenail selenium concentrations had an increased risk of hypertension (17). Furthermore, Xie et al. (18) reported a negative correlation between selenium intake and hypertension in participants in northern provinces but a positive correlation in participants in southern provinces in China. Lower urinary selenium concentrations were also associated with higher SBP and DBP values in Asian countries (19), similar to the associations identified between the serum selenium level and SBP and DBP in pregnant women (20). However, some studies have suggested a positive correlation between selenium levels and hypertension (21–23), which may be due to the presence of high levels of selenium in the areas investigated. About half of the Chinese population does not meet the recommended selenium intake defined by the Food and Agriculture Organization and the World Health Organization (24). Therefore, increasing the intake of selenium-rich foods might be beneficial for the residents of low-selenium areas, reducing the prevalence of hypertension.

Men are more prone to hypertension than women (25–27), which is consistent with our study's results (**Supplementary Figures 2, 3**). We found that the prevalence of hypertension was higher in men than in women in the KD-endemic areas. Everett and Zajacova (28) reported that among Americans aged 24–34 years, women were

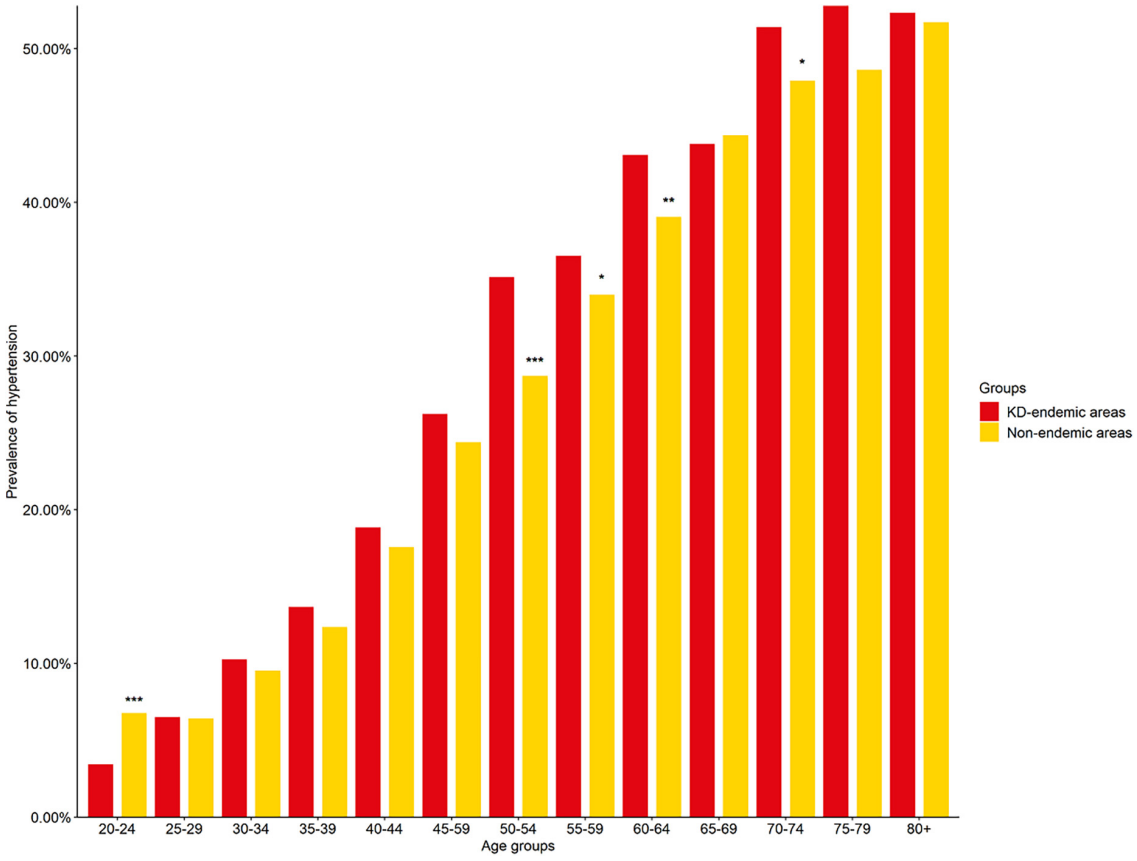

FIGURE 2
Hypertension prevalence in KD-endemic and non-endemic areas by age groups. The prevalence was standardized by age and sex based on the 2012 China Statistical Yearbook. KD. Keshan disease; *$P < 0.05$ compared with KD-endemic areas; **$P < 0.01$ compared with KD-endemic areas; ***$P < 0.001$ compared with KD-endemic areas.

far less likely to be hypertensive because they were more aware of hypertension than men. Women had more advanced hypertension awareness than men in China (1), the United States (29), and Romania (30). Meanwhile, men consumed alcohol in larger amounts and more frequently than women (31). After stratifying by sex, daily drinking increased the risk of hypertension in men but did not affect women in Southwest China (32). A J-shaped relationship between alcohol consumption and hypertension has been identified in women, while alcohol consumption was linearly correlated with the risk of hypertension in men (33, 34). These studies indicate that alcohol consumption could be the reason for a higher hypertension prevalence in men.

We found the hypertension prevalence was higher in the north than in the south, perhaps highlighting the role of temperature. A previous study reported that the prevalence of hypertension and the average SBP and DBP in northern tourists in Hainan, located in one of the most southern regions of China, were significantly higher than those of local residents and northern residents living in Hainan for more than 5 years (35). Moreover, Duranton et al. (36) collected data from 261 hemodialysis patients in different latitudes, discovering that the rising outdoor temperatures and prolonged sunshine hours were associated with decreased blood pressure before dialysis. When the temperature dropped by 1°C, the SBP and DBP for the total population rose by 0.55 and 0.26 mmHg, respectively (37). Moreover, residents in the north of China had 2.32 g more sodium daily than those in the south of China (38). One study reported that individuals with hypertension or normal blood pressure could lower their blood pressure by moderately reducing their salt intake for 4 weeks or more (39). Another study reported a reduction in SBP and DBP by 1.10 mmHg and 0.33 mmHg, respectively, for every 50 mmol of sodium excretion in 24 h (40). Thus, temperature and the amount of salt in the diet may explain the distinct hypertension prevalence in the northern and southern regions.

Income has been identified as a hypertension risk factor (41), and our study supports these findings. We identified a positive correlation between the prevalence of hypertension and per capita GDP by province. In Bengal, adults in richer household wealth quintiles had a significantly higher prevalence and odds of hypertension (42), and women in the highest wealth quantile were more prone to hypertension in Kenya (43). In developing countries, generally, hypertension is positively correlated with economic status, but the opposite is true in many developed countries, such as the United States and Canada (44). It was revealed that higher income, occupation, and the mother's education level were protective factors for hypertension among African Americans (45). Diet might also play a key role in influencing blood pressure by income. In developed countries, individuals with high socioeconomic status (based on occupation, education, and income) mainly consume foods abundant in fiber and protein and low in fat (46). In China, dietary consumption patterns are changing; the consumption of vegetable oil, animal foods, and sweeteners is increasing, and the consumption of coarse grains and beans is decreasing (47), especially

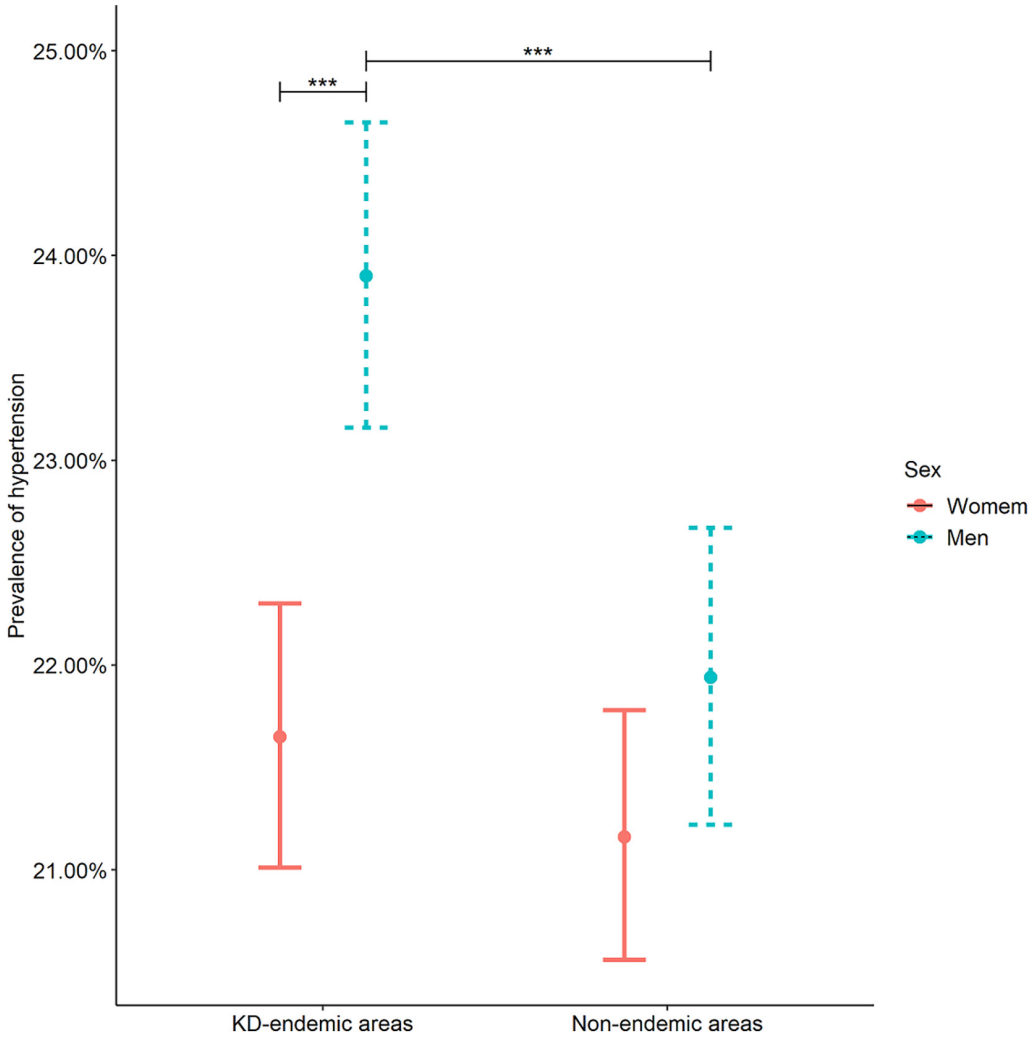

FIGURE 3
Hypertension prevalence in KD-endemic and non-endemic areas by sex. Error bars with 95% CIs were used to demonstrate hypertension differences between the sexes. The prevalence was standardized by age and sex based on the 2012 China Statistical Yearbook. KD, Keshan disease; ***$P < 0.001$ compared with women in the KD-endemic areas or men in the non-endemic areas.

TABLE 2 Prevalence of hypertension grades in KD-endemic and non-endemic areas.

Hypertension grade	KD areas	Participants	Patients with hypertension	Prevalence (95% CI)	Age, sex-standardized prevalence (95% CI)
Grade 1	Endemic	28,738	5,501	19.14% (18.69–19.60%)	15.79% (15.37–16.22%)[a]
	Non-endemic	30,256	5,455	18.03% (17.60–18.48%)	14.74% (14.34–15.15%)
Grade 2	Endemic	28,738	2,025	7.05% (6.75–7.35%)	5.36% (5.10–5.61%)[a]
	Non-endemic	30,256	2,011	6.65% (6.37–6.93%)	4.74% (4.50–4.99%)
Grade 3	Endemic	28,738	646	2.25% (2.08–2.46%)	1.65% (1.51–1.80%)[a]
	Non-endemic	30,256	898	2.97% (2.78–3.17%)	2.08% (1.92–2.25%)

Grade 1, 140–159/90–99 mmHg; Grade 2, 160–179/100–109 mmHg; Grade 3, ≥180/110 mmHg; CI, confidence interval; KD, Keshan disease.
[a]$P < 0.001$ compared with the non-endemic areas.

among wealthier individuals (48). Vegetables might help reduce blood pressure (49, 50), and vegans and vegetarians have been shown to have lower SBP and DBP values than omnivores (51). A national cross-sectional study among Chinese adolescents aged 13–17 years found that adolescents whose daily vegetable consumption was three or more servings (one serving is approximately one cup, approximately 200 g) had a lower hazard ratio for high blood pressure than those who consumed less than one serving daily (52). Another study reported that both raw (tomatoes, carrots, and shallots) and cooked (tomatoes, peas, and celery) vegetable intake significantly affected blood pressure (53). Conversely, a Korean study found that vegetable intake did not influence the risk of hypertension (54), which might be owing to the manner of cooking. The Dietary Approaches to Stop Hypertension Diet, comprising whole cereal, vegetables,

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TABLE 3 Prevalence of hypertension in KD-endemic and non-endemic areas in the southern and northern regions of China.

Region	KD areas	Participants	Patients with hypertension	Prevalence (95% CI)	Age, sex-standardized prevalence (95% CI)
South	Endemic	15,741	3,727	23.68% (23.01–24.35%)	18.76% (18.15–19.38%)
	Non-endemic	16,043	3,962	24.70% (24.03–25.37%)	18.66% (18.06–19.27%)
	Total	31,784	7,689	24.19% (23.72–24.67%)	18.68% (18.25–19.11%)
North	Endemic	12,997	4,445	34.20% (33.38–35.02%)	27.52% (26.76–28.30%)[a,b]
	Non-endemic	14,213	4,402	30.97% (30.21–31.74%)	24.86% (24.15–25.58%)[b]
	Total	27,210	8,847	32.51% (31.96–33.07%)	26.17% (25.65–26.70%)[b]

South, provinces with an annual average temperature higher than 11.7°C, including Shandong, Shaanxi, Henan, Hebei, Yunnan, Sichuan, and Chongqing; North, provinces with an annual average temperature lower than 11.7°C, including Heilongjiang, Jilin, Liaoning, Nei Mongol, Shanxi, and Gansu; CI, confidence interval; KD, Keshan disease.

[a] $P < 0.001$ compared with the non-endemic areas in the north.

[b] $P < 0.001$ compared with the south.

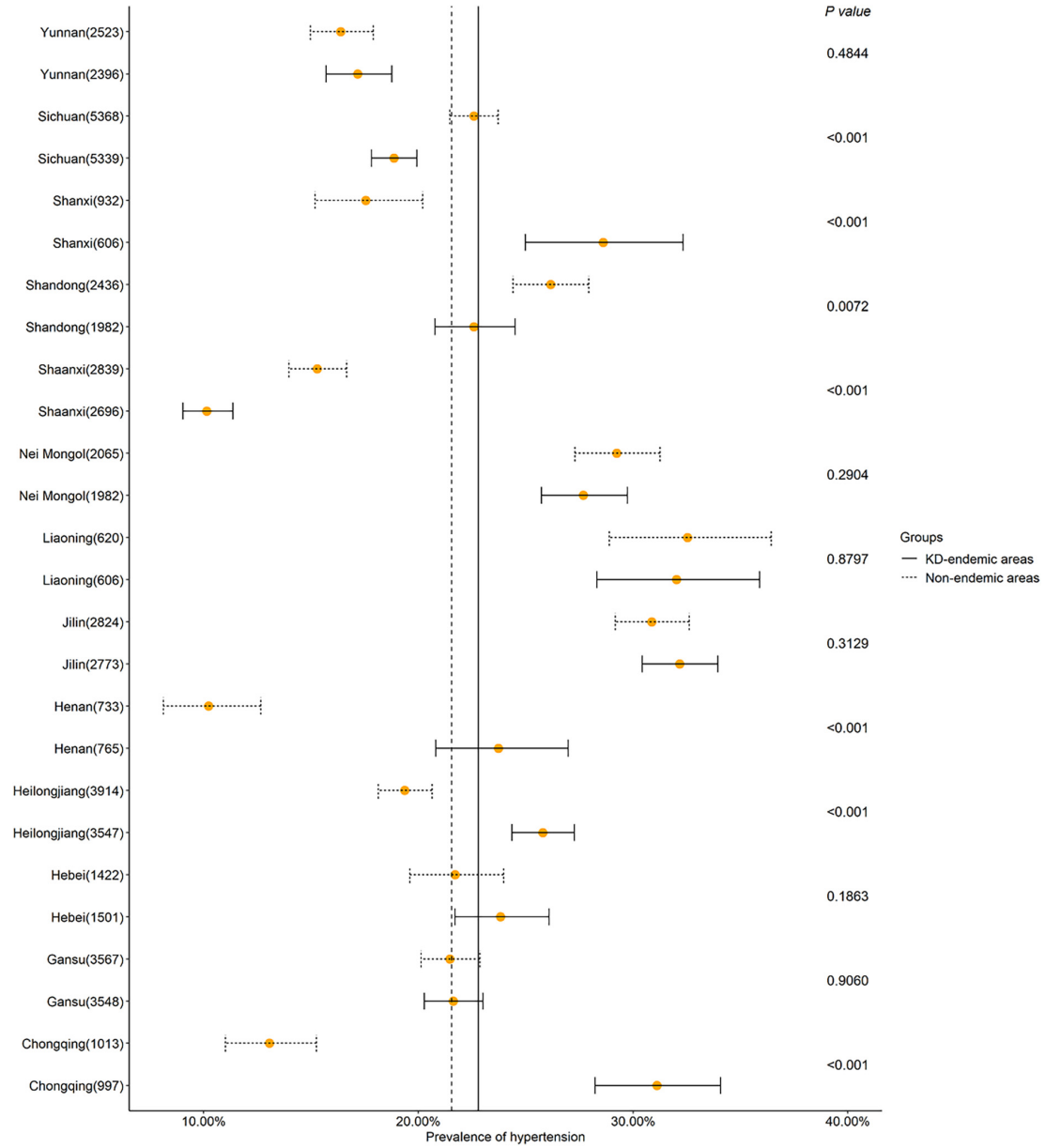

FIGURE 4
Hypertension prevalence in KD-endemic and non-endemic areas by province. Forest plots were employed to describe the hypertension prevalence rate at the province level. The prevalence was standardized by age and sex based on the 2012 China Statistical Yearbook. KD, Keshan disease; The number in the bracket represents the total number of participants in each province. The upright solid line indicates the hypertension prevalence in the KD-endemic areas in total. The upright dotted line indicates the hypertension prevalence in the non-endemic areas in total.

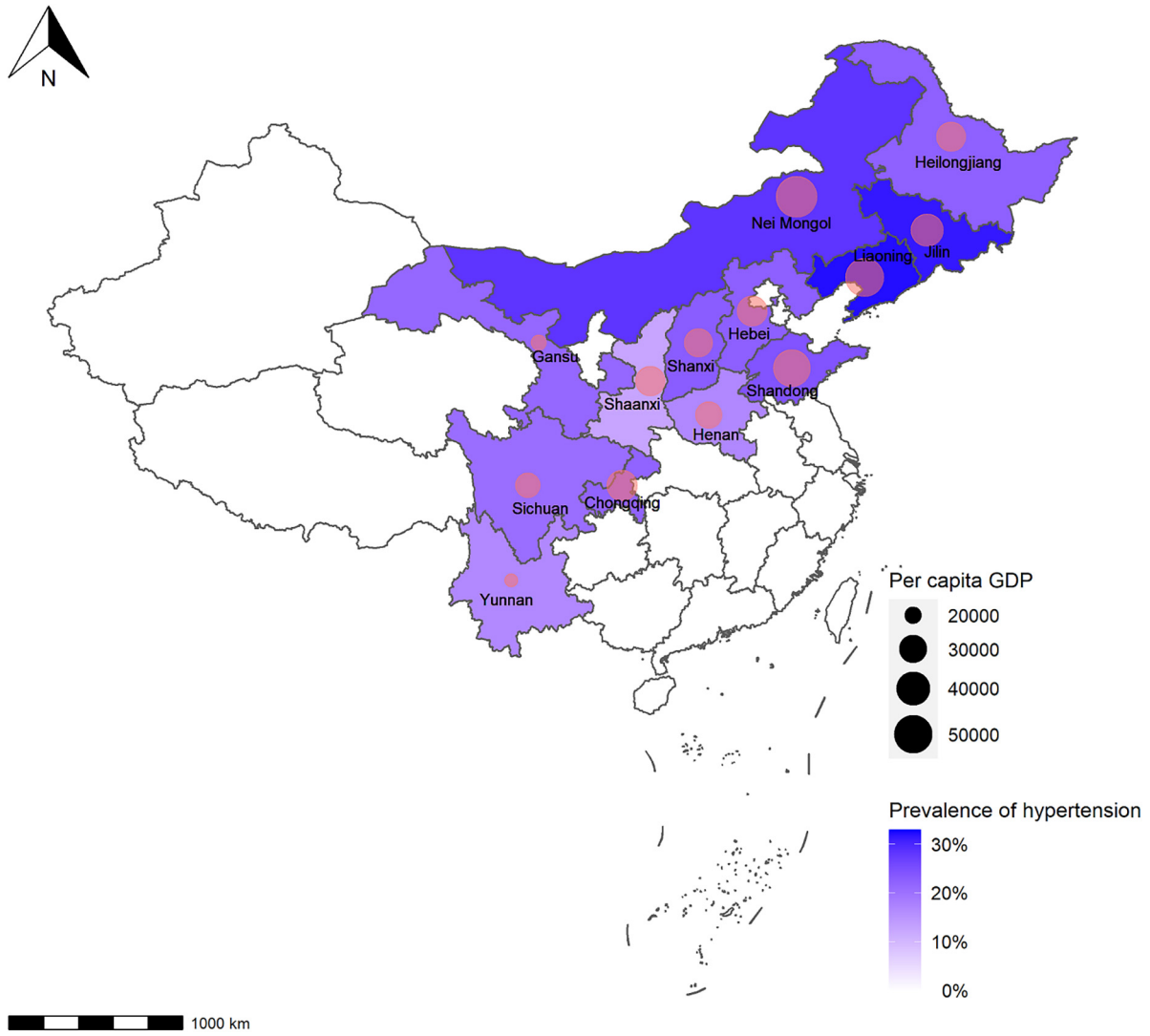

FIGURE 5
Hypertension prevalence and per capita GDP at province level. The relationship between the per capita GDP and hypertension prevalence at province level was analyzed using Pearson's correlation coefficient (r = 0.6672, P = 0.0127). The prevalence was standardized by age and sex based on the 2012 China Statistical Yearbook. GDP, gross domestic product.

fruits, and low-fat food, was as effective as some antihypertensive drugs and significantly reduced blood pressure (55). Not only vegetables but also seafoods lessened the risk of hypertension. The inverse relationship was identified between high seafood intake and childhood hypertension in Iranian students aged 7–12 years (56). Seafood is abundant in omega-3 polyunsaturated fatty acids, resulting in a small but significant decrease in blood pressure (57). Moreover, one study found that people in the highest quarter of the Omega-3 Index had an SBP and DBP 4 mmHg and 2 mmHg lower, respectively, than those in the lowest quarter (58). It was noteworthy that obtaining more omega-3 polyunsaturated fatty acids from the diet led to a clinically related decrease in DBP in a randomized controlled trial (59). Since the KD-endemic areas all lie within the agricultural hinterland, increasing the intake of seafood is widely advocated for preventing hypertension in the affected population and may be an important control strategy.

This study has some limitations. First, only those aged 20 or older were included owing to the 2012 China Statistical Yearbook age group classifications; adults aged 18 and 19 years were not included. Second, the survey included many participants from several rural areas of China. Thus, we did not collect information on the participants' hypertension drug use.

In conclusion, the prevalence of hypertension was higher in the KD-endemic areas than in the non-endemic areas. Therefore, healthy diets, such as high consumption of vegetables and seafoods, and foods that are rich in selenium, might help prevent and control hypertension in the KD-endemic areas. In addition, this study provides a better understanding of hypertension statuses in rural China, which may help with prevention.

Data availability statement

The datasets presented in this article are not readily available because the data supporting the results of this study were obtained from the Center for Endemic Disease Control, Chinese Center for Disease Control and Prevention. The data were licensed to be used in

the current study, but sharing of data was not allowed; therefore, the data resource is not publicly available. Nonetheless, the data can be available upon rational demand and with the approval of the Center for Endemic Disease Control. Requests to access the datasets should be directed to JH, houjie@ems.hrbmu.edu.cn.

Ethics statement

The studies involving human participants were reviewed and approved by the Medical Ethics Committee of Harbin Medical University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

JH and TW performed the design and concretization of the study. JH, LZ, and SJ performed the data analysis and participated in the writing of manuscript and revision and result interpretation. JH, JSL, ZX, YW, XYW, XG, AW, XHW, JML, JM, SZ, XZ, HZ, JW, HF, and SS contributed to the field investigation and data collection. TW contributed to the project funds. All authors read the final version and approved it.

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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.2023.1086507/full#supplementary-material

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Associations of the Healthy Eating Index-2010 with risk of all-cause and heart disease mortality among adults with hypertension: Results from the National Health and Nutrition Examination Survey 2007–2014

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Background: Studies regarding the impact of the Healthy Eating Index-2010 (HEI-2010) on the mortality of adults with hypertension are lacking.

Objectives: This study aimed to prospectively explore the relationships between HEI-2010 and mortality from heart disease and all causes in adults with hypertension based on the National Health and Nutrition Examination Survey (NHANES), 2007–2014.

Methods: This is a prospective cohort study including 6,690 adults with hypertension from NHANES (2007–2014). National Death Index data up to 31 December 2019 were used to determine the number of deaths due to heart disease and all other causes. We evaluated hazard ratios (HRs) and 95% confidence intervals (CIs) using the Cox proportional hazards model.

Results: A total of 1,259 deaths from all causes, including 338 due to heart disease, were documented over an average follow-up duration of 8.4 years. In comparison with the lowest quartile of HEI-2010 scores, multivariable-adjusted HRs (95% CIs) for all-cause mortality were 0.82 (0.70, 0.97), 0.78 (0.64, 0.95), and 0.68 (0.54, 0.85) for the second, third, and fourth quartiles of the HEI-2010 scores (P-trend < 0.001) and for heart disease mortality were 0.60 (0.44, 0.81), 0.59 (0.40, 0.89), and 0.53 (0.35, 0.80) (P-trend $= 0.010$). Each increment in natural-log-transformed HEI-2010 scores was linked to a 43% reduction in the risk of all-cause mortality ($P < 0.001$) and a 55% reduction in the risk of heart disease mortality ($P = 0.003$). Among the 12 components of HEI-2010, adherence to a higher intake of greens and beans, vegetables, total protein foods, seafood and plant proteins, and unsaturated fatty acids, as well as moderate consumption of empty calories, were related to a 21–29% lower risk of all-cause mortality.

Conclusion: In the current study, there was a statistically significant inverse relationship between HEI-2010 and mortality from heart disease and all causes among adults with hypertension. Based on the findings, it may help guide the dietary intake for adults with hypertension.

KEYWORDS

Healthy Eating Index, adults with hypertension, heart disease, mortality, NHANES

1. Introduction

Hypertension is becoming a global public health challenge. Among people aged 30–79 years, the prevalence of hypertension doubled from 1990 to 2019 (1). Elevated blood pressure (BP) has been recognized to be responsible for pathophysiological changes in the end organs of the brain (infarction and hemorrhage), the heart (myocardial ischemia and left ventricular hypertrophy, and heart failure), and the kidneys (renal sclerosis and proteinuria) (2). The presence of hypertension increases the risk of cardiovascular disease (CVD) and stroke, leading to an increase in CVD and all-cause mortality (3, 4). With the growing recognition of the major role diet plays in disease risk, identifying healthy dietary patterns that can prevent CVD and premature death in adults with hypertension is critical.

Dietary research is increasingly focusing on dietary patterns rather than single nutrients or food groups as dietary components are interrelated and consumed in combination. Healthy dietary patterns were characterized as diets low in saturated fat, added sugars, and sodium and high in vegetables, whole grains, fruits, lean protein, and low- and non-fat dairy (5). The HEI, as one of the healthy dietary patterns, is a comprehensive measurement of dietary quality in line with the Dietary Guidelines for Americans (DGA) and is the basis for US government nutrition policy. Based on the DGA recommendations, which included adding fruits, vegetables, low-fat dairy products, and whole grains, as well as limiting added sugars, saturated fats, and refined grains, the HEI generated scores for each component and a total score showing the diet quality over multiple dietary dimensions (6). Modeled on the 2010 DGA recommendations, the HEI-2010 included 12 components that were proven to be a reliable and valid measurement of dietary quality for Americans (7). In two studies, HEI-2010 has been shown to have a reverse relationship with serum C-reactive protein (CRP), apolipoprotein B, and systolic blood pressure (8, 9). In a cross-sectional research study involving 1036 women in Iran, the HEI-2010 was related to a lower metabolic syndrome risk (10). Meanwhile, two other prospective cohort studies suggested that HEI-2010 was inversely correlated with CVD and all-cause mortality in multiethnic populations (11) or older adults (12). Even with these advantages, among individuals with hypertension who often had unhealthy lifestyle factors (13), endothelial dysfunction, increased oxidative stress, vascular remodeling (14), pro-inflammatory release (15), and higher risk of developing heart disease and mortality, the health impacts of HEI-2010 on heart disease mortality remain unclear.

Therefore, the purposes of the present study were to explore the relationship of HEI-2010 and its components with mortality from heart disease and all causes in adults with hypertension based on NHANES.

2. Materials and methods

2.1. Study population

With a nationally representative sample, NHANES estimates the nutritional and health status of the US civilian population. The survey was performed by the National Center for Health Statistics, and it collected information through personal structured interviews at home, health screenings at a mobile examination center (MEC), and laboratory examinations. Detailed information can be obtained elsewhere (https://www.cdc.gov/nchs/nhanes/index.htm).

Based on NHANES 2007–2014 surveys, 7914 participants with hypertension aged 20 years and older were included when complete dietary intakes of the 2-day dietary interviews were provided. Hypertension was defined as systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg, physician-diagnosed hypertension, or consuming anti-hypertensive medicine. In the final analysis, 6,690 participants with hypertension were included after excluding those who reported pregnancy (n=20), cancer (n = 1,200) or those with no follow-up data (n = 4) (Supplementary Figure 1).

2.2. HEI-2010 scores

HEI-2010 was calculated to indicate diet quality from two 24-h dietary recollection data collected, one of which was a face-to-face survey conducted at the MEC by trained interviewers, followed by a telephone follow-up 3–10 days later to obtain a more complete picture of the usual dietary intake of the US population. Average dietary intake data were used for analysis only when participants completed two 24-h recalls. A total of 12 components make up HEI-2010, with nine adequacy components (total vegetables, whole fruits, total fruits, whole grains, greens and beans, total dairy, seafood and plant proteins, total protein foods, and fatty acid ratio) and three moderation components (sodium, empty calories, and refined grains). Supplementary Table 1 illustrates HEI-2010 components along with their point values and scoring criteria (6). The HEI 2010 scores consist of 12 dietary component scores, which add up to a total score of 100. For adequacy components, the highest score was awarded for intake at or above the criteria. As for the moderation components, the highest score was awarded for intake at or below the criteria. A proportional score is assigned to intakes between the lowest and highest criteria (6). For each of the 12 HEI-2010 components, participants were considered compliant if they obtained the highest component score; otherwise, they were classified as non-compliant. Thus, the compliant participants had the highest score of 5, 10, or 20, while non-compliant participants scored lower than this, with higher scores indicating closer adherence to the dietary guidelines.

2.3. Ascertainment of mortality

We assessed mortality over the follow-up period based on National Death Index records through 31 December 2019 (https://www.cdc.gov/nchs/data-linkage/mortality-public.htm). The codes of the *International Classification of Diseases, Tenth Revision* (*ICD-10*) were used to classify the causes of death. Death due to heart disease included rheumatic heart disease, hypertensive heart and renal disease, ischemic heart disease, and heart failure (ICD10 codes I00–I09, I11, I13, and I20–I51). Other causes of death included chronic lower respiratory diseases (J40–J47), malignant neoplasms (C00–C97), cerebrovascular diseases (I60–I69), influenza and

pneumonia (J09–J18), Alzheimer's disease (G30), diabetes mellitus (E10–E14), nephritis, nephrotic syndrome and nephrosis (N00–N07, N17–N19, N25–N27), accidents (unintentional injuries) (V01–X59, Y85–Y86), and all other causes (residual).

2.4. Assessment of covariates

Sociodemographic variables included age, sex (male and female), ethnicity (non-Hispanic white, non-Hispanic Black, Mexican American, and other races), and education (below high school, high school, and above high school), which were assessed during the interview. Corresponding questionnaires and MEC obtained data on body mass index (BMI), alcohol consumption, smoking, dietary intake, recreational activity, anti-hypertensive medicine use, blood pressure level, and presence of hyperlipidemia, diabetes, and CVD. Never smokers were defined as those who smoked <100 cigarettes in their lifetime. Those who smoked >100 cigarettes and no longer smoke were considered former smokers, and those who smoked >100 cigarettes in their lifetime and still smoke some days or every day were considered current smokers. Drinking status was grouped into nondrinker, low-to-moderate drinker (<3 drinks/day in men and <2 drinks/day in women), or heavy drinker (≥3 drinks/day in men and ≥2 drinks/day in women). The recreational activity was categorized into three groups: inactive (no recreational physical activity), moderately active (moderate recreational physical activity), or vigorously active (vigorous recreational physical activity). Based on the physical activity questionnaire, recreational activities leading to a slight increase in heart rate or breath such as bicycling, brisk walking, golf, or swimming for at least 10 continuous min were considered moderate activity, and recreational activities leading to great increases in heart rate or breath such as running or basketball for at least 10 continuous min were considered vigorous activity.

Diabetes is defined as fasting blood glucose ≥7.0 mmol/L, plasma glucose levels 2 h after meals ≥11.1 mmol/L, physician-diagnosed diabetes, use of hypoglycemic medications, or glycosylated hemoglobin (HbA1c) ≥6.5% (16). Participants with total cholesterol levels ≥240 mg/dL, fasting triglyceride ≥150 mg/dL, high-density lipoprotein (HDL) cholesterol<40 mg/dL, low-density lipoprotein (LDL) cholesterol ≥100 mg/dL, and a history of taking lipid-lowering medications were regarded as hyperlipidemia. Based on self-reported information, CVD (yes/no) and anti-hypertensive medicine use (yes/no) were defined. Three and sometimes four BP determinations (systolic and diastolic) are taken in the MEC and during home examinations on all eligible individuals using a mercury sphygmomanometer. SBP average and DBP average represent blood pressure results that were reported to the examinee. A detailed information can be obtained elsewhere (https://wwwn.cdc.gov/Nchs/Nhanes/2001-2002/BPX_B.htm#Quality_Assurance_&_Quality_Control). In our study, the SBP average and DBP average represent blood pressure results. We categorized participants into two groups based on their blood pressure levels: SBP/DBP < 160/100 mmHg (either SBP < 160 mmHg and/or DBP < 100 mmHg) and SBP/DBP ≥ 160/100 mmHg (either SBP ≥ 160 mmHg and/or DBP ≥ 100 mmHg). Furthermore, strict laboratory analyses, including measurement of estimated glomerular filtration rate (eGFR) and total cholesterol levels at baseline, were conducted.

2.5. Statistical analysis

All analyses were conducted using sample weights, strata, and primary sampling units to obtain accurate national estimates. Continuous variables were expressed as mean (SE) and categorical variables as numbers (percentages). HEI-2010 total scores were divided into quartiles, and the difference between the four groups was compared by one-way ANOVA tests (continuous variables with normal distribution) and χ^2 test (categorical variables). We estimated HRs and 95% CIs for heart disease and all-cause mortality based on quartiles of HEI-2010 scores using the Cox proportional hazards model. Person-time is referred to the period between the NHANES interview date and the date of death or the end of the follow-up (31 December 2019). We fitted three statistical models. Model 1 was adjusted for age (continuous), sex (male or female), and ethnicity (non-Hispanic white, non-Hispanic Black, Mexican American, and other race). Model 2 was adjusted for education (below high school, high school, and above high school), BMI (continuous), smoking status (never smoker, former smoker, and current smoker), drinking status (nondrinker, low-to-moderate drinker, and heavy drinker), recreational activity (inactive, moderately active, and vigorously active), and total energy intakes (in quartiles). Model 3 was further adjusted for blood pressure level (SBP/DBP ≥ 160/100 mmHg or SBP/DBP < 160/100 mmHg), anti-hypertensive medicine use (yes or no), hyperlipidemia (yes or no), diabetes (yes or no), and CVD (yes or no). To analyze the linear trend, each category was assigned a median value as a continuous variable. Multiple imputations were conducted to minimize the reduction in sample size resulting from missing covariates.

To investigate dose-response associations between HEI-2010 scores and mortality, we used a restricted cubic spline regression model with four knots at the 5th, 35th, 65th, and 95th percentiles of the HEI-2010 scores, excluding the most extreme 5% values to reduce the potential influence of outliers. The likelihood ratio test was used for testing non-linearity. Furthermore, stratified analyses were performed to assess whether the relationship of HEI-2010 scores with all-cause mortality differed by age (<60 and ≥60 years), sex (men and women), ethnicity (non-Hispanic white and others), BMI (<30 and ≥30), drinking status (non-drinker and drinker), smoking status (never smoker and former/current smoker), recreational activity (inactive group and active group), blood pressure level (SBP/DBP ≥ 160/100 mmHg or SBP/DBP < 160/100 mmHg), anti-hypertensive medicine use (yes or no), hyperlipidemia (yes or no), diabetes (yes or no), and CVD (yes or no). The *P*-value of the product term between continuous HEI-2010 scores and stratified variables was calculated to assess the significance of the interaction.

To determine whether statistically significant correlations were ascribed to specific components of the HEI-2010, we further assessed the correlation between the HEI-2010 components and all-cause mortality adjusted for all covariates. We classified the component scores by selecting appropriate cutoff points according to the overall sample score distribution or restricted cubic spline model. To better show the percentage contribution of the dietary components to the maximum possible score, we created radar plots.

We also conducted several sensitivity analyses to assess the robustness of our findings. First, we excluded participants who died within the first 2 years of follow-up (n = 199) to minimize the potential reverse causation bias. Second, we further adjusted for individual foods or nutrients, including intakes of fiber, total fat, cholesterol, vitamin A, vitamin C, and vitamin E (all in quartiles). Third, we further adjusted for other biomarkers, including total cholesterol levels and eGFR (all in quartiles). Finally, we also assessed the associations of HEI-2010 scores with cerebrovascular deaths and cancer deaths.

We performed all analyses with R version 4.2.0. A two-sided P-value of <0.05 was considered statistically significant.

3. Results

3.1. Participants characteristics

The baseline characteristics according to quartiles of HEI-2010 scores are summarized in Table 1. Out of 6,690 participants with hypertension (mean age, 55.91 years; 51.9% women), the median (interquartile range) HEI-2010 score was 53.9 (44.1, 64.1). Individuals with higher HEI-2010 scores were older, were more likely to be women, tended to have higher educational levels, engaged in more recreational activities, never smoked, and were less likely to be obese.

3.2. HEI-2010 scores and mortality

During an average follow-up of 8.4 years, 1259 deaths from all causes were documented, including 338 heart disease deaths. The relationship between HEI-2010 scores with heart disease and all-cause mortality is presented in Table 2. After multivariate adjustment, higher HEI-2010 scores were linked to lower heart disease and all-cause mortality. In comparison with the lowest quartile of HEI-2010 scores, multivariable-adjusted HRs (95% CIs) for all-cause mortality were 0.82 (0.70, 0.97), 0.78 (0.64, 0.95), and 0.68 (0.54, 0.85) for the second, third, and fourth quartiles of the HEI-2010 scores (P-trend < 0.001), as for heart disease mortality were 0.60 (0.44, 0.81), 0.59 (0.40, 0.89), and 0.53 (0.35, 0.80) (P-trend = 0.010). The curve associations of HEI-2010 scores (range: 32.2–78.6) with all-cause mortality (non-linear P = 0.899) and heart disease mortality (non-linear P = 0.455) were described based on the restricted cubic spline models (Figure 1). Each increment in natural-log-transformed HEI-2010 scores was linked to a 43% reduction in the risk of all-cause mortality (P < 0.001) and a 55% reduction in the risk of heart disease mortality (P = 0.003).

3.3. Subgroup analysis

Consistent findings were found between HEI-2010 scores and all-cause mortality when stratifying the analysis by age (≤60 and >60 y), sex (male and female), ethnicity (non-Hispanic white and others), education (below/high school and above high school), BMI (<30 and ≥30), drinking status (non-drinker and drinker), smoking status (never smoker and former/current smoker), recreational activity (inactive and active), hyperlipidemia (no or yes), diabetes (no or yes), CVD (no or yes), and blood pressure level (SBP/DBP ≥ 160/100 mmHg or SBP/DBP < 160/100 mmHg) (Table 3). Whereas, when the analysis was stratified by anti-hypertensive medicine use (yes or no), the subgroup dataset analyses were all statistically significant (P-trend < 0.05), but the direction was not consistent across subgroups (Table 3). No significant interactions were found between HEI-2010 scores and strata variables (all P for interaction > 0.05), except for smoking (P for interaction= 0.022). Stronger inverse relationship between HEI-2010 scores and all-cause mortality in the hypertension population was observed in adults who never smoked.

3.4. HEI-2010 component scores and mortality

There were significant differences in the weighted proportions of participants who obtained the maximum component score by the HEI-2010 component (Table 4), which we presented as a radar plot (Figure 2). The proportion of participants receiving the highest component score for each component was over 60% for total protein foods, 20–40% for total seafood and plant proteins, greens and beans, vegetables, refined grains, total fruits, and whole fruits; 10–20% for dairy, unsaturated fatty acids, and empty calories; and <10% for sodium and whole grains. When the components of HEI-2010 were evaluated (Table 4), higher component scores were linked to a lower all-cause mortality risk in all three multivariate models for six of the 12 components: seafood and plant protein, total protein foods, greens and beans, total vegetables, unsaturated fatty acids, and empty calories, reducing the risk of all-cause mortality by 21–29%. For instance, participants consuming at least 2.5 oz per 1,000 calories a day of total protein foods reduced their risk of death from all causes by 25% based on the results in Model 3. Other HEI-2010 components not shown to be linked to all-cause mortality were whole grains, refined grains, dairy, sodium, whole fruit, and total fruit.

3.5. Sensitivity analyses

In sensitivity analyses, the inverse relationship of HEI-2010 scores with heart disease and all-cause mortality remained largely unchanged after excluding the participants who died within the first 2 years of follow-up (n = 199) (Supplementary Table 2). After additional adjustments for dietary intakes of cholesterol, fiber, total fat, vitamin E, vitamin A, vitamin C, and biomarkers of serum total cholesterol, eGFR, the results remained largely unchanged (Supplementary Table 3). Finally, HEI-2010 scores were

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TABLE 1 Study characteristics of participants with hypertension in NHANES 2007–2014 according to HEI-2010 scores quartiles ($n = 6,690$)[a].

Characteristics	HEI-2010 scores					*P* value
	Total					
Range		14.0–44.1	44.1–53.9	53.9–64.1	64.1–98.8	
Patients, *n*	6,690	1,668	1,682	1,667	1,673	
Age, years	55.91 ± 0.25	50.61 ± 0.45	55.36 ± 0.52	57.89 ± 0.48	59.93 ± 0.42	<0.001
Sex, *n* (%)						<0.001
Women	3,471 (51.90)	751 (45.03)	851 (48.92)	881 (51.96)	988 (59.87)	
Men	3,219 (48.10)	917 (54.97)	831 (51.08)	786 (48.04)	685 (40.13)	
Ethnicity, *n* (%)						<0.001
Non-Hispanic white	2,922 (43.70)	762 (66.41)	769 (70.30)	690 (69.51)	701 (69.18)	
Non-Hispanic Black	1,862 (27.80)	535 (18.61)	474 (15.07)	449 (13.93)	404 (12.43)	
Mexican American	824 (12.30)	185 (6.53)	191 (5.59)	258 (7.30)	190 (5.10)	
Other race	1,082 (16.20)	186 (8.45)	248 (9.05)	270 (9.26)	378 (13.28)	
BMI, kg m^2	31.18 ± 0.13	32.08 ± 0.19	31.50 ± 0.27	31.12 ± 0.22	29.95 ± 0.19	<0.001
Education, n (%)						<0.001
Below high school	1,926 (28.80)	538 (23.75)	493 (20.63)	499 (20.29)	396 (15.28)	
High school	1,685 (25.20)	478 (30.00)	461 (27.72)	405 (24.08)	341 (19.96)	
Above high school	3,079 (46.00)	652 (46.25)	728 (51.65)	763 (55.63)	936 (64.76)	
Recreational activity, *n* (%)						<0.001
Inactive	4,060 (60.70)	1,142 (64.72)	1,077 (58.82)	997 (54.90)	844 (45.90)	
Moderately active	1,819 (27.20)	371 (25.68)	425 (28.68)	462 (30.26)	561 (34.10)	
Vigorously active	811 (12.10)	155 (9.60)	180 (12.50)	208 (14.84)	268 (20.00)	
Smoking status, *n* (%)						<0.001
Never smoker	3,452 (51.60)	708 (45.40)	825 (49.85)	909 (53.09)	1,010 (57.65)	
Former smoker	1,966 (29.40)	420 (23.30)	494 (29.50)	529 (33.43)	523 (33.87)	
Current smoker	1,272 (19.00)	540 (31.29)	363 (20.65)	229 (13.48)	140 (8.48)	
Drinking status, *n* (%)						<0.001
Non-drinker	2,671 (39.90)	650 (35.02)	639 (31.44)	686 (32.50)	696 (33.49)	
Low-to-moderate drinker	2,996 (44.80)	646 (41.91)	741 (49.40)	789 (54.82)	820 (57.53)	
Heavy drinker	1,023 (15.30)	372 (23.07)	302 (19.16)	192 (12.68)	157 (8.97)	
Total energy intakes, *n*						<0.001
Q1 (<2,702)	1,673 (25.00)	349 (15.45)	381 (17.67)	446 (21.24)	497 (24.43)	
Q2 (2,702–3,591)	1,671 (25.00)	332 (19.24)	421 (25.33)	449 (26.13)	469 (27.20)	
Q3 (3,591–4,644)	1,673 (25.00)	413 (26.67)	441 (26.06)	397 (26.23)	422 (28.66)	
Q4 (≥4,644)	1,673 (25.00)	574 (38.64)	439 (30.94)	375 (26.39)	285 (19.72)	
Blood pressure level, *n* (%)						0.630
SBP/DBP < 160/100 mmHg	5,976 (89.30)	1,493 (90.97)	1,511 (91.64)	1,469 (90.48)	1,503 (91.64)	
SBP/DBP ≥ 160/100 mmHg	714 (10.70)	175 (9.03)	171 (8.36)	198 (9.52)	170 (8.36)	
Anti-hypertensive medicine use, *n* (%)						0.100
No	5,579 (83.40)	1,428 (86.04)	1,402 (83.99)	1,374 (83.50)	1,375 (81.77)	
Yes	1,111 (16.60)	240 (13.96)	280 (16.01)	293 (16.50)	298 (18.23)	
CVD, *n* (%)	1,280 (19.10)	330 (15.68)	315 (15.95)	340 (17.69)	295 (15.82)	0.580
Diabetes, *n* (%)	2,079 (31.10)	441 (21.39)	503 (24.60)	589 (27.50)	546 (25.72)	0.010
Hyperlipidemia, *n* (%)	5,359 (80.10)	1,322 (81.09)	1,321 (78.73)	1,379 (83.82)	1,337 (80.62)	0.080

[a]Continuous variables are described as mean (SE). Categorical variables are presented as numbers (percentages). Complex survey designs were considered in all estimates. BMI, body mass index; CVD, cardiovascular disease; Q, quartile; NHANES, National Health and Nutrition Examination Surveys.

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TABLE 2 HR of all-cause and heart disease mortality according to quartiles of HEI-2010 scores among participants with hypertension in NHANES 2007–2014.

Characteristic	HEI-2010 scores HR (95% CI)					
	Q1	Q2	Q3	Q4	*P*-trend	Per-unit increment in ln-transformed HEI-2010 scores
Range	14.0–44.1	44.1–53.9	53.9–64.1	64.1–98.8		
All-cause mortality						
No. of deaths/total	320/1,668	329/1,682	323/1,667	287/1,673		
Model 1[a]	1.00	0.72 (0.61, 0.86)	0.63 (0.52, 0.76)	0.51 (0.41, 0.63)	<0.001	0.38 (0.29, 0.50) < 0.001
Model 2[b]	1.00	0.82 (0.70, 0.97)	0.80 (0.64, 0.95)	0.70 (0.56, 0.87)	0.002	0.58 (0.43, 0.79) < 0.001
Model 3[c]	1.00	0.82 (0.70, 0.97)	0.78 (0.64, 0.95)	0.68 (0.54, 0.85)	<0.001	0.57 (0.42, 0.77) < 0.001
Heart disease mortality						
No. of deaths/total	85/1,668	83/1,682	86/1,667	84/1,673		
Model 1[a]	1.00	0.54 (0.39, 0.75)	0.52 (0.36, 0.75)	0.46 (0.30, 0.70)	0.002	0.37 (0.22, 0.63) < 0.001
Model 2[b]	1.00	0.59 (0.43, 0.81)	0.59 (0.40, 0.88)	0.54 (0.35, 0.82)	0.014	0.46 (0.27, 0.78) 0.003
Model 3[c]	1.00	0.60 (0.44, 0.81)	0.59 (0.40, 0.89)	0.53 (0.35, 0.80)	0.010	0.45 (0.27, 0.76) 0.003

[a]Model 1 was adjusted for age (continuous), sex (men or women), and ethnicity (non-Hispanic white, non-Hispanic Black, Mexican American, and other race).
[b]Model 2 was adjusted for education (below high school, high school, and above high school), BMI (continuous), smoking status (never smoker, former smoker, and current smoker), drinking status (non-drinker, low-to-moderate drinker, and heavy drinker), recreational activity (inactive, moderately active, and vigorously active), and total energy intakes (in quartiles).
[c]Model 3 was further adjusted for blood pressure level (SBP/DBP ≥ 160/100 mmHg or SBP/DBP < 160/100 mmHg), anti-hypertensive medicine use (yes or no), hyperlipidemia (yes or no), diabetes (yes or no), and CVD (yes or no).

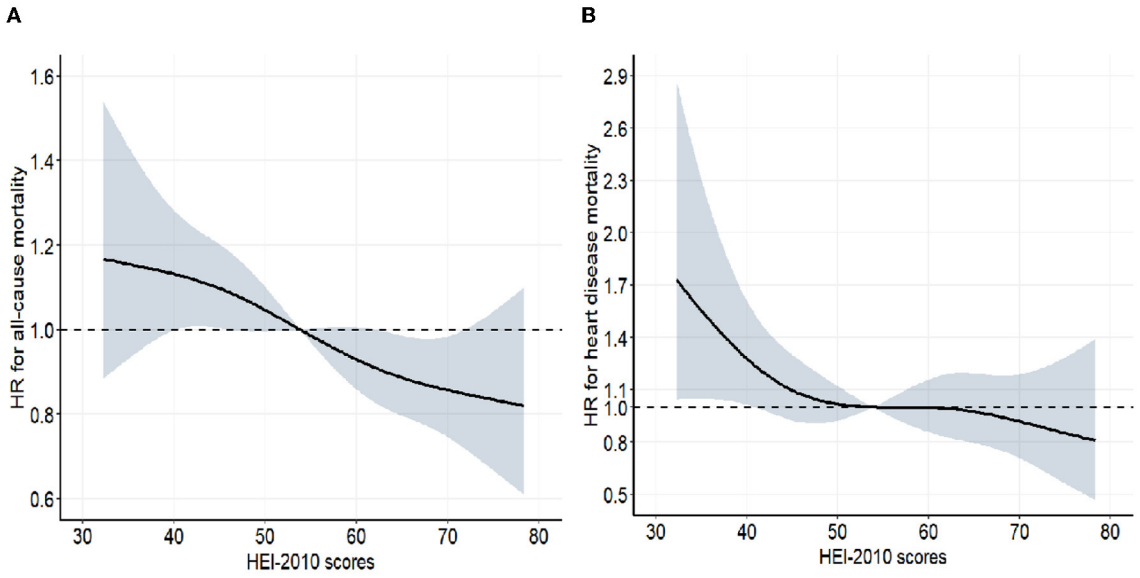

FIGURE 1
Associations between HEI 2010 and mortality from all-cause **(A)** and heart disease **(B)** among participants with hypertension from NHANES 2007–2014 (n = 6,690). The dose–response relationships between HEI 2010 scores and all-cause and heart disease mortality were assessed by a restricted cubic spline regression model with four knots (5th, 35th, 65th, and 95th percentiles) adjusted for age (continuous), sex (men or women), ethnicity (non-Hispanic white, non-Hispanic Black, Mexican American, and other race), education (below high school, high school, and above high school), BMI (continuous), smoking status (never smoker, former smoker, and current smoker), drinking status (non-drinker, low-to-moderate drinker, and heavy drinker), recreational activity (inactive, moderately active, and vigorously active), total energy intakes (in quartiles), blood pressure level (SBP/DBP ≥ 160/100 mmHg or SBP/DBP < 160/100 mmHg), anti-hypertensive medicine use (yes or no), hyperlipidemia (yes or no), diabetes (yes or no), and CVD (yes or no). Gray-shaded areas represent 95% confidence intervals. For all-cause mortality, *P*-linearity was <0.001, and for heart disease mortality, 0.010.

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TABLE 3 Stratified analyses of the associations between HEI-2010 scores and all-cause mortality among participants with hypertension.

Characteristic	HEI-2010 scores HR (95% CI)[a]				*P*-trend	*P*-interaction[b]
	Q1 14.0–44.1	Q2 44.1–53.9	Q3 53.9–64.1	Q4 64.1–98.8		
Age, y						0.649
<60 ($n = 3,205$)	1.00	0.90 (0.59, 1.37)	0.83 (0.52, 1.33)	0.78 (0.44, 1.39)	0.338	
≥60 ($n = 3,485$)	1.00	0.83 (0.68, 1.00)	0.83 (0.65, 1.06)	0.73 (0.57, 0.93)	0.034	
Sex						0.090
Women ($n = 3,471$)	1.00	0.96 (0.73, 1.26)	0.82 (0.61, 1.10)	0.81 (0.58, 1.14)	0.161	
Men ($n = 3,219$)	1.00	0.75 (0.57, 0.98)	0.78 (0.62, 1.00)	0.59 (0.42, 0.83)	0.002	
Ethnicity						0.961
Non-Hispanic white ($n = 2,922$)	1.00	0.83 (0.68, 1.03)	0.76 (0.60, 0.97)	0.66 (0.49, 0.88)	0.003	
Others ($n = 3,768$)	1.00	0.76 (0.58, 0.98)	0.78 (0.57, 1.07)	0.69 (0.50, 0.94)	0.040	
Education						0.617
Below/high school ($n = 3,611$)	1.00	0.81 (0.66, 1.00)	0.87 (0.66, 1.13)	0.81 (0.62, 1.06)	0.216	
Above high school ($n = 3,039$)	1.00	0.88 (0.62, 1.23)	0.68 (0.46, 1.01)	0.56 (0.39, 0.82)	0.001	
BMI, kg/m^2						0.793
<30 ($n = 3,319$)	1.00	0.97 (0.74, 1.27)	0.86 (0.64, 1.16)	0.70 (0.52, 0.93)	0.011	
≥30 ($n = 3,371$)	1.00	0.72 (0.56, 0.93)	0.66 (0.49, 0.88)	0.70 (0.49, 1.00)	0.043	
Recreational activity						0.126
Inactive ($n = 4,060$)	1.00	0.87 (0.72, 1.04)	0.87 (0.70, 1.01)	0.75 (0.59, 0.96)	0.025	
Active ($n = 2,630$)	1.00	0.69 (0.46, 1.03)	0.51 (0.34, 0.77)	0.50 (0.32, 0.77)	0.002	
Drinking status						0.660
Non-drinker ($n = 2,671$)	1.00	0.69 (0.54, 0.88)	0.70 (0.55, 0.88)	0.64 (0.49, 0.84)	0.003	
Drinker ($n = 4,019$)	1.00	0.97 (0.72, 1.31)	0.86 (0.62, 1.18)	0.67 (0.48, 0.92)	0.006	
Smoking status						0.022
Never ($n = 3,452$)	1.00	0.61 (0.46, 0.82)	0.70 (0.54, 0.92)	0.59 (0.43, 0.81)	0.0139	
Former/Current ($n = 3,238$)	1.00	0.93 (0.75, 1.16)	0.76 (0.59, 0.97)	0.62 (0.46, 0.84)	<0.001	
Hyperlipidemia						0.132
No ($n = 1,331$)	1.00	0.56 (0.34, 0.94)	0.82 (0.51, 1.31)	0.50 (0.30, 0.85)	0.036	
Yes ($n = 5,359$)	1.00	0.87 (0.69, 1.09)	0.75 (0.59, 0.96)	0.71 (0.54, 0.93)	0.007	
Diabetes						0.444
No ($n = 4,611$)	1.00	0.78 (0.61, 0.98)	0.72 (0.55, 0.94)	0.64 (0.48, 0.87)	0.007	
Yes ($n = 2,079$)	1.00	0.93 (0.65, 1.31)	0.90 (0.67, 1.20)	0.75 (0.51, 1.10)	0.100	
CVD						0.138
No ($n = 5,410$)	1.00	0.81 (0.66, 1.00)	0.68 (0.54, 0.85)	0.62 (0.47, 0.80)	<0.001	
Yes ($n = 1,280$)	1.00	0.86 (0.62, 1.17)	1.02 (0.75, 1.39)	0.84 (0.60, 1.19)	0.516	
Blood pressure level						0.910
SBP/DBP < 160/100 ($n = 5,976$)	1.00	0.81 (0.67, 0.98)	0.79 (0.64, 0.98)	0.71 (0.56, 0.91)	0.007	
SBP/DBP ≥ 160/100 ($n = 714$)	1.00	0.88 (0.47, 1.67)	0.71 (0.42, 1.22)	0.50 (0.28, 0.91)	0.011	
Anti-hypertensive drug use						0.664
No ($n = 5,579$)	1.00	0.91 (0.72, 1.15)	0.84 (0.67, 1.06)	0.72 (0.54, 0.95)	0.012	
Yes ($n = 1,111$)	1.00	0.47 (0.29, 0.76)	0.52 (0.34, 0.80)	0.72 (0.54, 0.95)	0.035	

[a]Data are expressed as HRs (95% CIs) adjusted for age (continuous), sex (men or women), ethnicity (non-Hispanic white, non-Hispanic Black, Mexican American, and other race), education (below high school, high school, and above high school), BMI (continuous), smoking status (never smokers, former smoker, and current smokers), drinking status (non-drinker, low-to-moderate drinker, and heavy drinker), recreational activity (inactive, moderately active, and vigorously active), total energy intakes (in quartiles), blood pressure level (SBP/DBP ≥ 160/100 mmHg or SBP/DBP < 160/100 mmHg), anti-hypertensive medicine use (yes or no), hyperlipidemia (yes or no), diabetes (yes or no), and CVD (yes or no). We did not include the strata variable in the model when stratifying by itself.

[b]The interaction between continuous HEI-2010 scores and stratification variables was examined using the Wald test.

TABLE 4 HR for all-cause mortality according to HEI-2010 components scores among participants with hypertension in NHANES 2007–2014[a].

HEI 2010 components	Receive max score[b], %	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)
Adequacy				
Total fruit**	25.12 (23.24,27.00)	0.73 (0.58,0.93)+	1.07 (0.85,1.35)	0.98 (0.78,1.24)
Whole fruit**	35.90 (33.15,38.64)	0.67 (0.55,0.80)+	0.90 (0.74,1.11)	0.88 (0.72,1.08)
Total vegetables***	27.03 (24.71,29.34)	0.64 (0.53,0.79)+	0.71 (0.58,0.88)+	0.71 (0.57,0.88)+
Greens and beans**	20.84 (19.03,22.65)	0.67 (0.55,0.80)+	0.76 (0.63,0.92)+	0.77 (0.63,0.94)+
Whole grains****	6.39 (5.63,7.15)	0.79 (0.66,0.94)+	0.94 (0.78,1.13)	0.91 (0.76,1.09)
Dairy***	12.95 (11.42,14.48)	0.99 (0.79,1.24)	1.02 (0.82,1.27)	1.04 (0.83,1.29)
Total protein foods*	67.14 (62.63,71.65)	0.75 (0.65,0.87)+	0.75 (0.66,0.86)+	0.75 (0.66,0.85)+
Seafood and plant proteins**	34.00 (31.27,36.72)	0.60 (0.49,0.74)+	0.75 (0.61,0.93)+	0.76 (0.62,0.94)+
Fatty acids*****	15.25 (13.80,16.71)	0.78 (0.68,0.90)+1	0.81 (0.69,0.95)+	0.79 (0.68,0.93)+
Moderation				
Refined grains***	23.77 (21.46,26.08)	0.79 (0.66,0.94)+	0.94 (0.78,1.13)	0.91 (0.76,1.09)
Sodium****	5.12 (4.46,5.78)	0.96 (0.82,1.14)	1.09 (0.90,1.32)	1.10 (0.92,1.33)
Empty calories******	16.43 (15.06,17.80)	0.71 (0.59,0.85)+	0.78 (0.64,0.94)+	0.75 (0.62,0.90)+

[a]Data are expressed as HRs (95% CIs) adjusted for age (continuous), sex (men or women), ethnicity (non-Hispanic white, non-Hispanic Black, Mexican American, and other race), education (below high school, high school, and above high school), BMI (continuous), smoking status (never smokers, former smokers, and current smokers), drinking status (non-drinker, low-to-moderate drinker, and heavy drinker), recreational activity (inactive, moderately active, and vigorously active), total energy intakes (in quartiles), blood pressure level (SBP/DBP ≥ 160/100 mmHg or SBP/DBP < 160/100 mmHg), anti-hypertensive medicine use (yes or no), hyperlipidemia (yes or no), diabetes (yes or no), and CVD (yes or no).
[b]Weighted proportions of participants who obtained the maximum component score for each component of HEI-2010.
*Those with a maximum score of 5, 10, or 20 compared to those with a score below it (e.g., max vs. <max).
**Those with a maximum score of 5, 10, or 20 compared to those with a score of zero (e.g., max vs. zero).
***Those with a maximum score of 5, 10, or 20 compared to those with a score below the 25th percentile (e.g., max vs. below the 25th percentile).
****Those with above minimum score compared to those with a score of zero (e.g., min < vs. zero).
*****Those with a score above the 50th percentile compared to those with a score below the 50th percentile.
******Those with a score above the 75th percentile compared to those with a score below the 25th percentile.
+ P-value < 0.05.

not related to cerebrovascular mortality and cancer mortality (Supplementary Table 4).

4. Discussion

To date, it is the first research to examine the relationship of the HEI-2010 and its components with mortality from heart disease and all causes in adults with hypertension. We observed that higher HEI-2010 scores were linked to lower heart disease mortality and all-cause mortality risk independent of various factors, which included lifestyle and dietary factors, anti-hypertensive medicine use, and blood pressure levels. We demonstrated the robustness of our findings through stratified analyses and sensitivity analyses. According to our study, among the 12 components of HEI-2010, a higher intake of greens and beans, seafood and plant proteins, total protein foods, vegetables, and unsaturated fatty acids, as well as moderate consumption of empty calories, were linked to a lower risk of all-cause mortality.

Previous studies including some meta-analysis studies have investigated the associations of healthy dietary patterns with cardiovascular and all-cause mortality and reached consistent findings with ours. They indicated that the inverse relationships of healthy dietary patterns with cardiovascular and all-cause mortality were statistically significant in both general populations and other people (11, 12, 17–21). For instance, according to a linear dose-response meta-analysis, each 5-point increment in compliance with Dietary Approaches to Stop Hypertension (DASH) significantly reduced the all-cause mortality risk (assessed in 13 cohort studies, 9 publications, including 1,240,308 participants) and cardiovascular mortality (assessed in 12 cohorts, 9 publications, including 1,314,675 participants) for 5% (6–4%) and 4% (5–2%), respectively (20). In addition, in a prospective multiethnic cohort study, each healthy dietary pattern including HEI-2010, the Alternative Healthy Eating Index (AHEI-2010), DASH, and the Alternate Mediterranean Diet was linked to reduced risk of deaths from cardiovascular disease and all causes (11). The same results were also seen in two other prospective cohort studies that recruited older adults (12) and postmenopausal women in the United States (US) (18), respectively. One possible explanation for the consistent findings is that despite there being multiple dietary pattern index scores, they tend to converge in preventing major chronic diseases, such as diabetes (22, 23) and cardiovascular disease (24, 25), as they are derived from many of the same core principles emphasizing vegetables, whole grains, plant-based proteins, and fruits, food combinations that are primarily rich in antioxidants and anti-inflammatory nutrients. A systematic review with 16 observational and 13 interventional studies indicated an inverse relationship between healthy dietary patterns with oxidative stress and pro-inflammatory biomarkers (26). In addition, healthy dietary patterns may improve lipid metabolism, blood pressure, and endothelial

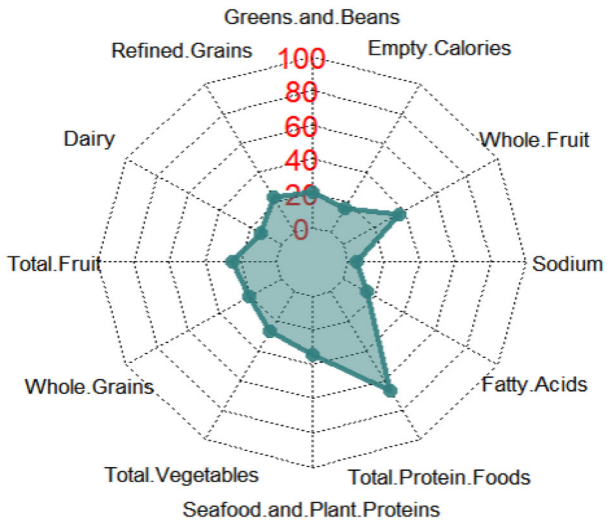

FIGURE 2
Radar graph depicting the weighted proportions of participants who obtained the highest component score for each component of HEI-2010. The radar graph shows all 12 components of HEI-2010, including total vegetables, greens and beans, total fruits, whole fruits, total dairy, total protein foods, seafood and plant proteins, whole grains and fatty acid ratio, sodium, refined grains, and empty calories.

function, and has anti-oxidative and anti-inflammatory properties (25, 27).

However, among adults with hypertension who tend to have endothelial dysfunction, increased oxidative stress, pro-inflammatory release, insensitivity to vasodilators, arterial vascular smooth stiffening (14, 15), and with a higher incidence of CVD and all-cause mortality, it is still not well known whether HEI-2010 has a long-term effect on mortality in this specific population. Although previous reviews and studies have reported beneficial effects on blood pressure control with HEI-2010 (8). Based on a nationally representative American adult sample with a long follow-up duration, the current study found inverse relationships between HEI-2010 and mortality from heart disease and all causes in adults with hypertension. Our results were consistent with a study performed on male diabetic physicians, where diabetes is characterized by increased pro-inflammatory and oxidative status. In this prospective cohort study of 1,163 male physicians with diabetes only, an inverse relationship between the AHEI-2010 score and all-cause mortality was found (HR = 0.59; 95% CI 0.44, 0.79) (21). A further analysis of the 12 individual components of HEI-2010 was conducted to determine possible dietary components that might affect all-cause mortality. It found that a higher intake of greens and beans, seafood and plant protein, total vegetables, total protein foods, unsaturated fatty acids, and moderate consumption of empty calories were associated with a 21–29% reduction in the all-cause mortality risk in adults with hypertension. The results can be explained as follows.

First, vegetables are rich in different nutrients and bioactive compounds, such as phytochemicals, vitamins, minerals, and fibers, which have cardioprotective effects, including anti-inflammation, anti-oxidation, anti-platelet properties, regulate blood pressure and lipid metabolism, improve endothelial function, and reduce myocardial injury (28, 29). As reported in one review, nitrate, which is rich in vegetables, is now considered a critical bioactive phytochemical with cardioprotective performances, increasing nitrogen oxide (NO) and other nitrogen oxides *via* the nitrate-nitrite-nitric oxide pathway to improve endothelial function, lower blood pressure, regulate arterial stiffness, reduce ischemia-reperfusion injury, modulate blood flow, and anti-platelet aggregation (30). In addition, vegetables are a significant source of potassium, and higher potassium intake was related to lower blood pressure, especially a high potassium/sodium ratio (31). Third, green vegetable soya bean is rich in carbohydrates, omega-3 fatty acids, protein, fiber, and a variety of micronutrients providing nutrients for humans, where steroids 7, saponins 2, alkaloids 6, and isoflavones 5 are found, exhibiting anti-oxidative and anti-inflammatory properties to some extent (32, 33). Fourth, the fatty acids ratio is expressed as monounsaturated and polyunsaturated fatty acids (PUFA) to saturated fatty acids. Omega-3 PUFA has been reported to reduce cardiovascular disease risk by regulating lipid metabolism and platelet aggregation (34). Also, seafood is a major source of omega-3 PUFA, which has been discovered to provide anti-inflammatory effects (35) and regulate blood lipids (36). Fifth, plant protein consumption has been found to lower the levels of total cholesterol, LDL cholesterol, and blood pressure (37, 38). Finally, in the HEI-2010, empty calories are those derived from added sugars and solid fats (7), there has been an association between solid fat intake as well as added sugar intake with mortality in previous studies (39, 40). Excessive added sugars intake is associated with elevated triglyceride levels (41) and inflammatory markers (42), which are crucial determinants in the pathogenesis of CVD. Therefore, it is necessary to limit the intake of added sugar. Through the mechanisms described earlier, the HEI-2010 may improve cardiovascular conditions and reduce all-cause mortality in adults with hypertension.

Furthermore, in adults with hypertension, HEI-2010 seemed to have a stronger protective effect against mortality events in non-smokers than in smokers. The finding may be due to the fact that smoking increases cardiovascular mortality and morbidity, which is supported by epidemiological studies (43, 44). When the analysis was stratified by anti-hypertensive medicine use (yes or no), the subgroup dataset analyses were all statistically significant, but the direction was not consistent across subgroups. The most common reason may be that there was an interaction between subgroup factors or between the observed subgroup factors with unknown factors. Positive results found in subgroup analyses have an extremely high probability of being false positive due to the fact that the subgroup analyses may not maintain randomization within subgroups, have an insufficient sample size, and low degree of certainty. Therefore, the essence of the evidence is a result of an observational study, which needs to be interpreted with caution and applied carefully to guide the work of clinical practice.

This study has several strengths. First, it is the first study to assess the relationship between the HEI-2010 and mortality from heart disease and all causes in adults with hypertension based on NHANES. Second, this study used data from NHANES, which collected and reported data using standardized procedures and

strict quality assurance. Third, we were able to generalize our results to the US adult population by utilizing a broad, nationally representative database to estimate diet quality. Finally, modeled upon the 2010 DGA recommendations, the HEI-2010 is a reliable and valid measurement of dietary quality for Americans.

There are also some potential limitations to the current study. First, the current study did not have detailed information on the severity of hypertension, although the results did not change significantly after further adjustment of blood pressure levels and anti-hypertensive medicine use. In addition, as some missing data in the database, we cannot include all potentially significant variables, for example, more than 50% of the data for CRP and LDL cholesterol were missing.

5. Conclusion

According to this prospective cohort study of adults with hypertension, we observed an inverse association between HEI-2010 and mortality from heart disease and all causes. Based on the findings, it may be helpful to guide the dietary intake of adults with hypertension. Further studies are needed to support these results.

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 human participants were reviewed and approved by National Center for Health Statistics (NCHS) Research Ethics Review Board. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

Study design: YZ, DL, and HZ. Data collection and analysis: YZ and DL. Writing the manuscript: YZ. 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.2023.1077896/full#supplementary-material

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Consumption of very low-mineral water may threaten cardiovascular health by increasing homocysteine in children

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Introduction: Homocysteine (Hcy) is a critical factor for cardiovascular injury, and the elevation of Hcy in children will inevitably increase the risk of cardiovascular disease in adulthood. This study explored the effect of very low-mineral water on children's Hcy and cardiovascular health.

Materials and methods: This was a retrospective cohort study that recruited two groups of 10–13-year-old children who had consumed direct drinking water (DDW) in school for 4years. The control group (NW) (119 boys, 110 girls) consumed normal DDW (conductivity 345μs/cm). The very low-mineral water consumption group (VLW) (223 boys, 208 girls) consumed very low-mineral DDW (conductivity 40.0μs/cm). Serum Hcy, Hcy metabolites, cofactors of Hcy metabolism, and cardiovascular biomarkers were assessed and standardized by age- and sex-specific Z-scores, and the differences between the two groups were analyzed with independent *t*-test. The relationships between Hcy metabolism biomarkers and key factors, cardiovascular biomarkers, serum Ca, and mineral intake were analyzed with linear regression.

Results: Compared with the NW group, the VLW group had significantly higher serum Hcy, Apo-B, Apo-B/A1, and oxLDL, and lower serum 1,25,$(OH)_2D_3$, vitamin B6 and B12, 5-methyltetrahydrofolate, and Apo-A1. Serum Hcy was positively associated with serum Apo-B and Apo-B/A1, and negatively associated with Ca intake from water and serum 1,25,$(OH)_2D_3$.

Conclusion: This study suggested that drinking very low-mineral water may increase Hcy level and oxidative stress, worsen lipid profile, and threaten the cardiovascular system in children. Reducing 1,25,$(OH)_2D_3$, and disordering of calcium metabolism might play important roles. This study first established an association between demineralized drinking water and cardiovascular health in children, suggesting a new environmental concern risk to cardiovascular health.

KEYWORDS

very low-mineral water, children, cardiovascular health, homocysteine, calcium, 1,25,$(oh)_2D_3$

1. Introduction

Cardiovascular diseases (CVD) are a major public health problem that can lead to death and disability. Although CVD usually happens in adulthood, there is evidence that these diseases may start in childhood and adolescence (1, 2). Recently, the incidence of asymptomatic cardiovascular pathological change has increased in children. In China, the prevalence of elevated blood pressure among 6–13 years old children had risen from 14.5% (in 2010, 16.1% in boys and 12.9% in girls) to 18.4% (in 2015, 20.2% in boys and 16.3% in girls) (3). Some risk factors for CVD in childhood and adolescents are well known, such as smoking, obesity, lack of exercise, or parental history of atherosclerotic diseases (1, 2, 4). High blood homocysteine levels are found to be associated with vascular endothelial damage in children, leading to CVD in adults (5). Homocysteine (Hcy) is an amino acid occurring as an intermediate in methionine metabolism. Homocysteine increases the intracellular concentration of reactive oxygen species (ROS), disturbs the lipoprotein metabolism, increases the formation of oxidized-low density lipoprotein (oxLDL), interferes with the production of nitric oxide, induces insulin resistance, and hurts vascular endothelial cells. Given that the causal risk factor for CVD may continue from early life to adulthood, homocysteine could be considered a critical link between pre-clinical vascular changes in youth and adult CVD (6).

There are two pathways of homocysteine metabolism (7). First, homocysteine can be recycled and remethylated back to methionine, and this path needs the presence of folate and vitamin B12 (8). Second, homocysteine can be metabolized and converted into cysteine by transsulfuration, which requires vitamin B6 and cystathionine β-synthase. Numerous factors are responsible for evaluating homocysteine in the blood, including genetic abnormalities, disturbed enzyme action, and nutritional deficiencies (9). Studies on dietary factors focus on insufficient B vitamins, especially folate, vitamin B12, and vitamin B6 (8). Hyperhomocysteinemia can be caused by the deficiency of vitamin B12, B6, or folate (10, 11). Some studies revealed that drinking mineral water fortified with B vitamins could reduce blood homocysteine (12, 13). Kim et al. reported a negative association between daily calcium (Ca) intake and plasma homocysteine level (14). But no further study has explored the effect of mineral intake on homocysteine.

In our previous study, drinking very low-mineral water could increase blood homocysteine, high-sensitivity C-reactive protein (hs-CRP), and arginase levels compared with drinking tap water, and induce cardiovascular pathological lesions including interstitial edema, localized higher acidophily of cytoplasm, focal fiber dissolution, and fracture in the heart, mucoid degeneration, localized endothelial cell exfoliation, scattered foam cells, and localized intimal thickening in the intima of the aortic arch in rabbits (15). Drinking very low-mineral water could increase serum triglycerides, low-density lipoprotein, apolipoprotein (Apo)-A1, Apo B, and atherosclerosis index (Apo B/Apo A1), and decrease high-density lipoprotein in young men (15). It indicated that minerals in the water are also crucial to homocysteine metabolism and cardiovascular health.

Our previous study found that direct drinking water (DDW) on many primary school campuses are very low-mineral water resulting from the wide use of the reverse osmosis technique (16). Drinking very low-mineral water may affect children's bone development and dental health (17, 18). Thus, children on campus also face health risks due to drinking very low-mineral water. However, there is no report about the effect of drinking very low-mineral water on children's homocysteine metabolism and cardiovascular health. Our previous study revealed that drinking very low-mineral water may disturb the body's Ca metabolism and decrease serum magnesium (Mg) in children, which are associated with homocysteine metabolism and cardiovascular health (17, 18). Calcium is an essential hemostatic cofactor and second messenger involved in intracellular signalings, such as the vascular system. Disturbed Ca homeostasis directly leads to increased levels of homocysteine and dyslipidemia (19). In addition, Ca may disturb mitochondrial b-oxidation and increase oxidative stress, facilitating lipid oxidation (20). Besides, consuming very low-mineral direct drinking water may decrease serum 1,25-dihydroxy vitamin D_3 (1,25,$(OH)_2D_3$) in children in our previous study (18). 1,25,$(OH)_2D_3$ is a cofactor in the transsulfuration of homocysteine by directly upregulating cystathionine β-synthase and is negatively associated with serum Hcy (21, 22). These results support the negative role of drinking very low-mineral water in children's homocysteine metabolism and cardiovascular system. However, studies are rare.

Considering the wild use of very low-mineral DDW on primary school campuses, investigating the effect of long-term consumption of very low-mineral water on cardiovascular health in children is necessary. This study aimed to explore the relationship between long-term consumption of very low-mineral DDW and homocysteine metabolism and its effect on cardiovascular health in children.

2. Methods

2.1. Recruiting, dietary assessment, socio-demographic characteristics collecting, and examination of the study population

This study was a continuation of our previous study (18). As we described in our previous article, it was a retrospective cohort study. The recruiting of the study population and the investigation of their dietary nutrition intake, developmental parameters, and socio-demographic characteristics were described in our previous article (18). Briefly, 1817 Han ethnic students (10–13 years old in 2013) who had annual health examinations records in 2009 were recruited from four schools that introduced the DDW systems in 2009 and had not changed them until September 2013, in Chongqing of Southwest China in March 2013.

All the subjects completed the questionnaire interview of socio-demographic characteristics (in March 2013), including sleep, socioeconomic status, outdoor exercise time outside class, medication, lifestyle factors, medical history, family history of development-associated diseases, and consumption history of mineral or vitamin supplements. Total outdoor exercise time was calculated by adding the

Abbreviations: direct drinking water, DDW; Hcy, homocysteine; The control group, NW; The very lowmineral water consumption group, VLW; CVD, cardiovascular diseases; ROS, reactive oxygen species; oxLDL. oxidized-low density lipoprotein; Calcium, Ca; hs-CRP, high-sensitivity C-reactive protein; Apo, apolipoprotein; Mg, magnesium; 1,25,(OH)2D3, 1,25-dihydroxy vitamin D3; SBP, systolic blood pressure; DBP, diastolic blood pressure; Cys, cysteine; Met, methionine; 5-MTHF, 5-methyltetrahydrofolate; VCAM- 1, vascular cellular adhesion molecule-1; sTM, soluble thrombomodulin; MDA, Malondialdehyde; 3-NT, 3- nitrotyrosine; RNI, recommended nutrient intake; AI, adequate intake.

outdoor exercise time outside class and the time for morning exercises and physical education. Participants with the following conditions were excluded: had bone fracture or transferred from other schools during 2009–2013, absented themselves from annual health examinations or summer remedial in 2013 (which lacked exposure to DDW from August to September 2013), consumed mineral or vitamin supplements, had cardiovascular disease, digestive system disease, metabolic syndrome, or development-associated diseases (hypoevolutism [assessed by height (23)], rickets, or poliomyelitis), or claimed that their family (including siblings, parents and their siblings, grandparents and their siblings) had above disease (Supplementary Figure S1). At last, 660 individuals were enrolled and completed the food records and examination in 2013. These students were divided into two groups by the mineral contents of their campus DDW. The control group (NW), including 119 boys and 110 girls, came from one school whose DDW had a mineral content close to municipal tap water (conductivity 345 μs/cm, Supplementary Table S1). The very low-mineral water consumption group (VLW) came from three schools, including 223 boys and 208 girls. The mineral content of their DDW was much lower than that of municipal tap water and lower than the recommendation by the WHO: 20 mg/l for calcium and 10 mg/L for magnesium (24) (conductivity 40.0 μs/cm, Supplementary Table S1).

The dietary mineral and nutrient, including B vitamins, intakes were obtained by 3-day food records (two weekdays and one weekend), which had been investigated twice (in March and August 2013). They were calculated according to China Food Composition (25). What is different from our previous report was that we took salt consumption into account [salt consumption data came from the study about the daily salt consumption of people in Chongqing in that period (26)].

The developmental parameters, including systolic blood pressure (SBP), diastolic blood pressure (DBP), and cardiovascular and development-associated disease information, were obtained from annual health examination records in 2009 and 2013. Ten milliliter of blood was obtained in the annual health examination in 2013 (September 2013) for the blood test.

2.2. Evaluation of Hcy, vitamins associated with Hcy metabolism, and biomarkers of the cardiovascular system of the study population

Serum Ca, Mg, and 1,25,$(OH)_2D_3$ were cited from our previous study (18). Serum Hcy and its metabolites [cysteine (Cys) and methionine (Met), vitamin B6, vitamin B12, 5-methyltetrahydrofolate (5-MTHF), 1,25,$(OH)_2D_3$, and biomarkers of the cardiovascular system [including Apo-A1, Apo-B, hs-CRP, vascular cellular adhesion molecule-1 (VCAM-1), soluble thrombomodulin (sTM), Resistin, OxLDL, Malondialdehyde (MDA), and 3-nitrotyrosine (3-NT)], were assessed by commercial ELISA kits (Beijing Andy Huatai technology co., LTD, Beijing, China). The ratio of Apo-B to Apo-A1 (Apo-B/A1) was calculated by Apo-B/Apo-A1.

2.3. Analysis of minerals in water and mineral intake from drinking water

Water samples (including tap water and DDW) were collected twice (October 2012 and May 2013). Their minerals were measured according to our previous study (16, 17, 27). Briefly, Ca and Mg were assessed by flame atomic fluorescence spectrometer. Potassium and sodium were measured by flame atomic absorption spectrophotometer (TAS-986, Purkinje General Instrument Co., Ltd., Beijing, China). Bicarbonate was assessed by indicator titration, and fluoride (F), chlorides, and sulfates were assessed by ion chromatographic method (SPD-20A, Shimadzu (China) Co., Ltd., Shanghai, China). Conductivity and pH values were detected twice per semester using a pure water tester and a pH tester (hi98308 and hi98108, Hanna Instruments, Inc., Woonsocket, RI, United States), respectively.

The mineral intake from drinking water and total mineral intake was calculated as follows:

Mineral intake from drinking water (including DDW and household drinking water, mg/d) = mineral content in DDW (mg/L) × daily consumption of DDW (L/d) + mineral content in tap water (mg/L) × daily water consumption at home (L/d).

Total mineral intake (mg/L) = mineral intake from drinking water (mg/L) + dietary mineral intake (mg/L).

2.4. Statistical analysis

All statistical analyses were performed with SPSS for Windows version 18.0 (SPSS Inc. Released 2009. PASW Statistics for Windows, Version 18.0. Chicago: SPSS Inc.). The independent-sample *t*-test was used to compare the difference in socio-demographic characteristics, lifestyle factors, blood pressure, and mineral intake between the two groups. Differences in the sexual distinction between the two groups were analyzed using the Chi-square test.

To avoid the influence of age and sex, standardized age- and sex-specific Z-scores of the mineral intake from drinking water and total mineral intake, serum Ca, Mg, Hcy, Cys, Met, vitamin B6, vitamin B12, 5-MTHF, 1,25,$(OH)_2D_3$, Apo-A1, Apo-1, Apo-B/A1, hs-CRP, VCAM-1, sTM, Resistin, OxLDL, MDA, and 3-NT (z-Hcy, z-Cys, z-Met, z-vitamin B6, z-vitamin B12, z-5-MTHF, z-1,25,$(OH)_2D_3$, z-Apo-A1, z-Apo-1, z-Apo-B/A1, z-hs-CRP, z-VCAM-1, z-sTM, z-Resistin, z-OxLDL, z-MDA, z-3-NT) were computed (28). The difference in Z-scores of serum Hcy, Cys, Met vitamin B6, vitamin B12, 5-MTHF, and biomarkers of the cardiovascular system was analyzed by the independent-sample *t*-test. To investigate the effects of very low-mineral DDW exposure on Hcy, Hcy metabolites, cofactors of Hcy metabolism, and biomarkers of the cardiovascular system. Hcy, Apo-A1, Apo-B, Apo-B/A1, and oxLDL were divided by their Z-scores (higher: Z-score > 0; lower: Z-score ≤ 0). Vitamin B6, B12, 5-MTHF, and Cys were divided by their Z-scores (higher: Z-score ≥ 0; lower: Z-score < 0). The effects were assessed by binary logistic regression. Effects of mineral intake and serum Ca and Mg (age- and sex-specific Z-score) on z-Hcy, z-vitamin B6, z-vitamin B12, z-5-MTHF, z-Apo-A1, z-Apo-1, z-Apo-B/A1, and z-OxLDL were assessed by single linear regression, and their combined effects were by multiple linear regression. The independent effect of serum Hcy (age- and sex-specific Z-score) on z-Apo-A1, z-Apo-1, z-Apo-B/A1, and z-OxLDL and their combined impact on mineral intake were assessed by single linear regression and multiple linear regression, respectively.

3. Results

3.1. Minerals in DDW

As we described in our previous paper (18), the mineral content and the conductivity of DDW in the school of the NW group were close to those of tap water. The mineral content of DDW in the schools of the VLW group sharply decreased compared with that of tap water and the NW group. The conductivity of the DDW is stable during 2009–2013 (Supplementary Table S1).

3.2. Baseline, characteristics, daily mineral, and nutrient intake of the subjects

As we described in our previous article (18), all the participants lived in the urban area. There were no significant differences in age, sex, water consumption, outdoor exercise time, sleep time, and family income between the two groups ($p \geq 0.05$, Supplementary Table S2). There were no significant differences in height, weight, and BMI in 2009 between the two groups when the DDW ($p \geq 0.05$, Supplementary Table S2), Children in the VLW group showed significantly lower height and weight after drinking DDW for 4 years (in 2013, $p < 0.05$, Supplementary Table S2). But the BMI in 2013 was not different between the two groups ($p \geq 0.05$, Supplementary Table S2). There were no significant differences in SBP, DBP, and pulse pressure between the two groups when the DDW system was introduced (2009) and 4 years later (2013) ($p \geq 0.05$, Supplementary Table S2).

There was no difference in daily dietary mineral intake, including Ca, Mg, Na, K, and Zinc, between the two groups in 2013 ($p \geq 0.05$, Supplementary Table S3). However, a significant decrease was observed in daily Ca, Mg, and Na intake from drinking water and in total daily intake of Ca and Mg in the VLW group after the introduction of DDW ($p < 0.01$, Supplementary Table S3). There was no difference in daily intake of energy and other nutrients (protein, fat, carbohydrates, and vitamins [including thiamin, riboflavin, niacin, and folic acid]) ($p \geq 0.05$, Supplementary Table S4).

3.3. Comparison of Hcy, metabolites of Hcy, and essential cofactors in Hcy metabolism between the two groups after long-term consumption of DDW

After drinking DDW for 4 years (during 2009–2013), children in the VLW group showed significantly higher z-Hcy, and lower z-Cys, z-vitamin B6, z-vitamin B12, z-5-MTHF, and z-1,25,$(OH)_2D_3$ than children in the NW group ($p < 0.01$, Figure 1). Furthermore, the higher serum Hcy, and lower serum cysteine, vitamin B6, vitamin B12, and 5-MTHF (divided by age- and sex-specific Z-scores) were positively associated with lower mineral DDW exposure ($p < 0.01$, Table 1).

3.4. Comparison of serum biomarkers of the cardiovascular system between the two groups after long-term consumption of DDW

After drinking DDW for 4 years (during 2009–2013), children in the VLW group showed significantly higher z-Apo-B, z-Apo-B/A1, and z-oxLDL, and lower z-Apo-A1 than children in the NW group ($p < 0.05$, Figure 2). Furthermore, the higher serum Apo-B, Apo-B/A1, and oxLDL, and lower serum Apo-A (divided by age- and sex-specific Z-scores) in the VLW group were positively associated with lower mineral DDW exposure ($p < 0.01$, Table 2).

3.5. Associations of mineral intake with serum Hcy, metabolites of Hcy, essential cofactors in Hcy metabolism, and biomarkers of the cardiovascular system

The Ca, Mg, and Na intake from drinking water (age- and sex-specific Z-scores) was negatively associated with serum Hcy, and positively associated with serum vitamin B12 and 5-MTHF (age- and sex-specific Z-scores) ($p < 0.05$, Table 3). The Ca, Mg, and K intake from drinking water (age- and sex-specific Z-scores) was

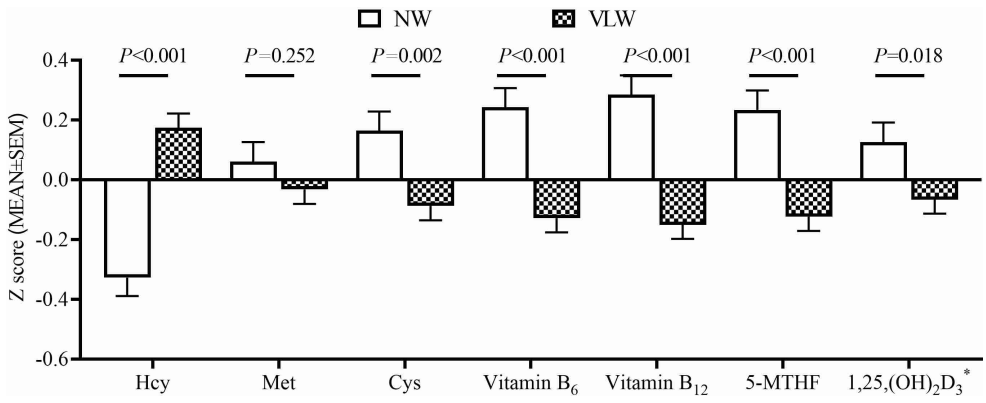

FIGURE 1
Comparison of Hcy and important associated cofactors between the two groups after consumption of DDW in children. Values were age- and sex-specific Z-scores (means ± SEM, NW: n=229, VLW: n=431). *Data of 1,25,$(OH)_2D_3$ were cited from Huang et al. (18).

TABLE 1 Associations of long-term low-mineral DDW exposure between Hcy, metabolites of Hcy, and important cofactors in Hcy metabolism.[a]

	NW	VLW	*p* value
	n =229	*n* =431	
Hcy[b]	Ref.	2.17 (1.56, 3.02)	<0.001
Cys[b]	Ref.	1.76 (1.27, 2.43)	0.001
Vitamin B6[b]	Ref.	1.71 (1.23, 2.36)	0.001
Vitamin B12[b]	Ref.	1.45 (1.05, 2.00)	0.023
5-MTHF[b]	Ref.	1.40 (1.01, 1.92)	0.042
$1,25,(OH)_2D_3$[b, c]	Ref.	1.36 (0.983, 1.87)	0.063

[a]Values were the rate ratio (95% Cl) analyzed by binary logistic regression.
[b]Hcy, Cys, Vitamin B6, Vitamin B12, 5-MTHF, and $1,25,(OH)_2D_3$ were divided by their age- and sex-specific Z-scores: Hcy: 1: higher, Z-score > 0; 0: lower, Z-score ≤ 0; Cys, Vitamin B6, Vitamin B12, 5-MTHF, and $1,25,(OH)_2D_3$: 1: lower: Z-score < 0; 0: higher: Z-score ≥ 0.
[c]Data of $1,25,(OH)_2D_3$ were cited from Huang et al. (18).

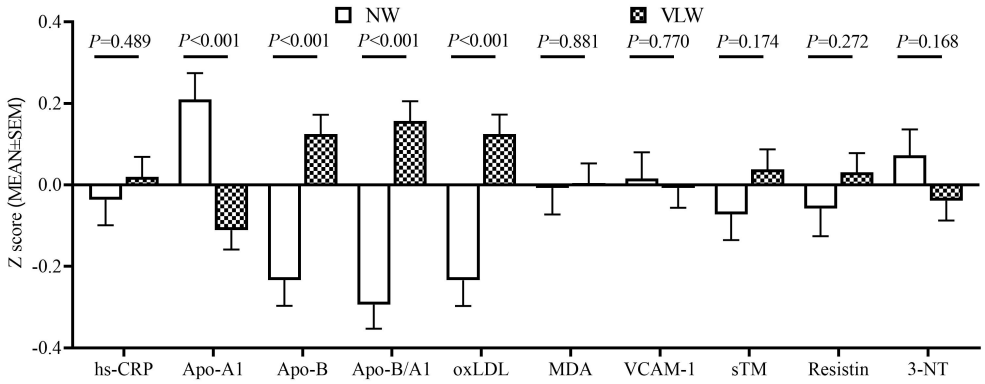

FIGURE 2
Comparison of serum biomarkers of the cardiovascular system between the two groups after consumption of DDW in children. Values were age- and sex-specific Z-scores (means ± SEM, NW: *n*=229, VLW: *n*=431).

positively associated with serum vitamin B6 (age- and sex-specific Z-scores) ($p < 0.05$, Table 3). The Ca intake from drinking water (age- and sex-specific Z-scores) was positively associated with serum $1,25,(OH)_2D_3$ (age- and sex-specific Z-scores) ($p < 0.05$, Table 3).

The Ca, Mg, and Na intake from drinking water was (age- and sex-specific Z-scores) positively associated with serum Apo-A1 (age- and sex-specific Z-score), and negatively associated with Apo-B/Apo-A1 and oxLDL (age- and sex-specific Z-scores) ($p < 0.05$, Table 3). The Ca, Mg, Na, and K intake from drinking water was negatively associated with serum Apo-B (age- and sex-specific Z-score) ($p < 0.05$, Table 3). When we assessed the main factors of the four mineral intake from drinking water by multiple linear regression, the Na intake from drinking water (age- and sex-specific Z-score) was a key factor associated with z-Apo-A1 ($p < 0.05$, Table 3). Ca (age- and sex-specific Z-score) was a key factor with z-Apo-B and z-Apo-B/A1 ($p < 0.05$, Table 3). Ca and Mg intake from drinking water (age- and sex-specific Z-scores) exerted combined effects on z-Hcy and z-oxLDL (Ca: negative association; Mg: positive association; $p < 0.05$, Table 3), z-vitamin B6, z-vitamin B12, and z-5-MTHF (Ca: positive association; Mg: negative association; $p < 0.05$, Table 3). The total daily Ca intake (including drinking and diets, age- and sex-specific Z-score) was negatively associated with z-oxLDL ($p < 0.05$, Supplementary Table S5).

3.6. Associations of serum ca, mg, Hcy, metabolites of Hcy, essential cofactors in Hcy metabolism, and biomarkers of the cardiovascular system

The z-$1,25,(OH)_2D_3$ was negatively associated with z-Hcy [β (95% CI): −0.0885 (−0.165, −0.0123); $p < 0.05$]. The z-Hcy was positively associated with z-Apo-B and z-Apo-B/A1 ($p < 0.05$, Table 4). The z-Hcy had a combinative effect with Ca intake from drinking water (age- and sex-specific Z-scores) on z-Apo-B/A1 [β (95% CI): Ca: −0.1760 (−0.251, −0.100); Hcy: 0.0800 (0.0040, 0.157); $p < 0.05$]. Serum Ca (age- and sex-specific Z-score) was negatively associated with z-oxLDL ($p < 0.05$, Table 4). There was no association of serum Ca and Mg (age- and sex-specific Z-scores) with serum Hcy, metabolites of Hcy, and important cofactors in Hcy metabolism (age- and sex-specific Z-scores) ($p \geq 0.05$, Table 4 and Supplementary Table S6).

4. Discussion

In our previous study, we reported that children had seriously insufficient Ca intake from diets, which was in line with other studies (29). Drinking very low-mineral DDW aggravated children's lack of

10.3389/fnut.2023.1133488

TABLE 2 Associations between low-mineral DDW exposure and serum biomarkers of cardiovascular system.[a]

	NW	VLW	*p* value
	n =229	*n* =431	
ApoA1[b]	Ref.	1.60 (1.16, 2.21)	0.004
ApoB[b]	Ref.	1.81 (1.30, 2.50)	<0.001
Apo-B/A1[b]	Ref.	2.14 (1.53, 3.00)	<0.001
oxLDL[b]	Ref.	1.70 (1.23, 2.35)	0.001

[a]Values were the rate ratio (95% Cl) analyzed by binary logistic regression.
[b]Apo-A1, Apo-B, Apo-B/A1, and oxLDL were divided by their age- and sex-specific Z-scores: Apo-A1: 1: lower: Z-score < 0; 0: higher: Z-score ≥ 0; Apo-B, Apo-B/A1, and oxLDL: 1: higher, Z-score > 0; 0: lower, Z-score ≤ 0.

TABLE 3 Effects of mineral intake from daily drinking water on serum Hcy, lipid parameters, and related vitamines after consumption of DDW in children.[a]

	Ca^2	Mg^2	Na^2	K^2
Hcy[b, c]	−0.191 (−0.266, −0.116)**	−0.177 (−0.252, −0.101)**	−0.168 (−0.244, −0.0930)**	−0.0140 (−0.0900, 0.0630)
Vitamin B6[b, c]	0.144 (0.0680, 0.219)**	0.132 (0.0560, 0.208)**	0.00900 (−0.0680, 0.0850)	0.135 (0.0590, 0.211)**
Vitamin B12[b, c]	0.177 (0.102, 0.252)**	0.165 (0.0890, 0.240)**	0.188 (0.112,0.263)**	0.0180 (−0.0590, 0.0940)
5-MTHF[b, c]	0.162 (0.0870, 0.238)**	0.150 (0.0750, 0.226)**	0.141 (0.0650, 0.216)**	0.0100 (−0.0670, 0.0860)
$1,25,(OH)_2D_3$[b, c, e]	0.0780 (0.0010, 0.154)*	0.0710 (−0.0050, 0.147)	0.0090 (−0.0680, 0.0850)	0.0110 (−0.0660, 0.0880)
Apo-A1[b, c]	0.100 (0.0240, 0.176)**	0.0880 (0.0120, 0.165)*	0.117 (0.0410, 0.193)**	−0.0230 (−0.0990, 0.0540)
Apo-B[b, c]	−0.176 (−0.251, −0.100)**	−0.174 (−0.249, −0.0990)**	−0.125 (−0.201, −0.0490)**	−0.0990 (−0.175, −0.0230)*
Apo-B/A1[b, c]	−0.190 (−0.265, −0.115)**	−0.181 (−0.256, −0.106)**	−0.159 (−0.234, −0.0830)**	−0.0570 (−0.133, 0.0200)
oxLDL[b, c]	−0.144 (−0.219, −0.0680)**	−0.133 (−0.209, −0.0570)**	−0.141 (−0.217, −0.0650)**	−0.0050 (−0.0810, 0.0720)
Hcy[b, d]	−1.030 (−1.637, −0.424)**	0.846 (0.239, 1.45)**		
Vitamin B6[b, d]	0.834 (0.221, 1.45)**	−0.696 (−1.31, −0.0830)*		
Vitamin B12[b, d]	0.884 (0.275, 1.49)**	−0.712 (−1.32, −0.103)**		
5-MTHF[b, d]	0.856 (0.244, 1.47)**	−0.699 (−1.31, −0.0880)*		
$1,25,(OH)_2D_3$[b, d, e]	0.0780 (0.0010, 0.154)*			
Apo-A1[b, f]			0.117 (0.0410, 0.193)**	
Apo-B[b, f]	−0.176 (−0.251, −0.100)**			
Apo-B/A1[b, f]	−0.190 (−0.265, −0.115)**			
oxLDL[b, f]	−0.784 (−1.40, −0.171)*	0.646 (0.0320, 1.26)*		

[a]Values were the β (95% CI) analyzed by linear regression ($n = 660$).
[b]The mineral intake from daily drinking water (including DDW and household drinking water, mg/d), serum Hcy, Vitamin B6, vitamin B12, 5-MTHF, $1,25,(OH)_2D_3$, Apo-A1, Apo-B, Apo-A1/B, and oxLDL were standardized by age- and sex-specific Z-scores.
[c]The association was analyzed by single linear regression ($n = 660$).
[d]The association was analyzed by multiple linear regression of all the factors which had a significant association in single linear regression and combined effects on Z score of serum Hcy ($n = 660$).
[e]Data of $1,25,(OH)_2D_3$ were cited from: Huang et al. (18).
[f]The association was analyzed by multiple linear regression of all the factors which had a significant association in single linear regression ($n = 660$).
*$p < 0.05$; **$p < 0.01$.

total daily Ca and Mg intake, which disturbed Ca metabolism and decreased serum Mg level (18). But Na intake was lower than the recommendation in our previous report (775 mg/d and 780 mg/d in NW and VLW, respectively) and other studies. However, they did not estimate sodium intake reliably, resulting from the lack of salt consumption records. When we took the daily salt consumption [using the daily salt consumption of people in Chongqing in that period (26)] into account, the total daily Na intake was much higher than the recommended (more than two times). These people may have a high risk of cardiovascular disease due to their high daily Na intake (30). Drinking very low-mineral DDW cannot significantly moderate the excessive Na intake and may not benefit cardiovascular health *via* dampening the excessive Na intake.

Serum homocysteine increase has been associated with more than 100 diseases, including cardiovascular disease (5, 6). This study showed that children in the VLW group had higher serum homocysteine. In our previous study, consuming VLW increased serum Ca in children (18). Increased serum Ca can increase serum homocysteine by mediating atherothrombosis (19). But the serum homocysteine was not associated with the serum Ca in this study. The Ca intake from drinking water was a key factor for high serum homocysteine. It indicated that the homocysteine increase *via*

TABLE 4 Associations of serum Hcy and calcium, magnesium, 1,25,$(OH)_2D_3$ with biomarkers of cardiovascular disease in children.[a]

	Serum Hcy[b]	*p* value	Serum calcium[b]	*p* value	Serum magnesium[b]	*p* value	Serum 1,25,$(OH)_2D_3$[b]	*p* value
Apo-A1[b]	−0.0460 (−0.123, 0.0300)	0.235	−0.0220 (−0.0990, 0.0540)	0.568	0.0340 (−0.0420, 0.111)	0.382	0.0010 (−0.0760, 0.0770)	0.982
Apo-B[b]	0.100 (0.0240, 0.176)	0.010	0.0230 (−0.0530, 0.100)	0.552	0.0460 (−0.0310, 0.122)	0.240	−0.0060 (−0.0830, 0.0700)	0.877
Apo-B/A1[b]	0.114 (0.0380, 0.190)	0.003	0.0400 (−0.0370, 0.117)	0.306	0.0210 (−0.0550, 0.0980)	0.587	−0.0170 (−0.0930, 0.0600)	0.666
oxLDL[b]	0.0580 (−0.0190, 0.134)	0.140	0.0920 (0.0160, 0.168)	0.018	−0.0060 (−0.0830, 0.0700)	0.874	−0.0190 (−0.0960, 0.0570)	0.622

[a]Values were the β (95% CI) analyzed by single linear regression ($n = 660$).

[b]The serum calcium, magnesium, 1,25,$(OH)_2D_3$, Hcy, important cofactors in Hcy metabolism, and biomarkers of the cardiovascular system were standardized by age- and sex-specific Z-scores.

consuming VLW might be associated with the lower Ca intake, as Tanaka reported in postmenopausal women (31). Ca plays a key role in the absorption process of vitamin B12 (32, 33). In this study, although there was no difference in the folic acid intake between the two groups, the serum vitamin B6, vitamin B12, and 5-MTHF decreased in the VLW group and were associated with Ca intake from drinking water. Furthermore, serum 1,25,$(OH)_2D_3$ was associated with serum homocysteine. 1,25,$(OH)_2D_3$ can directly upregulate cystathionine β-synthase, an enzyme involved in the transsulfuration of homocysteine, which is mediated by vitamin D receptor *via* binding together with the retinoid X receptor and acetylated histone H4 in the intergenic region of the cystathionine β-synthase gene (34). In our previous study, serum 1,25,$(OH)_2D_3$ decreased in children consuming very low-mineral water and was negatively associated with Ca intake from drinking water (18). In this study, methionine, a metabolite of homocysteine remethylating, was not different between the two groups, and cysteine, a metabolite of homocysteine transsulfuration, decreased in children drinking VLW. In another study in rats, consuming purified water decreased cystine, an oxide of cysteine, and 2-hydroxybutyric acid, the by-product of homocysteine transsulfuration (35) (data not shown). These findings supported that drinking very low-mineral water may repress homocysteine transsulfuration. Disturbing serum B vitamins and 1,25,$(OH)_2D_3$ status due to Ca deficiency in drinking water may be the key reason. Low cysteine levels will aggregate the insufficient Ca intake and Ca disorders by decreasing the absorption of vitamin D and K *via* decreasing taurine, which is synthesized from cysteine (36).

Dyslipidemia and lipid oxidation are risk factors for cardiovascular diseases (37–40). Both homocysteine metabolism and Ca homeostasis disorders can disturb lipid metabolism and induce oxidative stress (19, 20, 41). The serum Apo B, Apo B/Apo A1, and oxLDL was higher in children drinking very low-mineral DDW. Serum Apo B and Apo B/Apo A1 are biomarkers of lipid metabolism and may reflect the higher risk of atherosclerosis in adulthood (38). The serum homocysteine was associated with elevated serum Apo B and Apo B/Apo A1 in this study. And the Ca intake from drinking water had a combinative effect with serum homocysteine. Based on these findings, Ca deficiency in DDW may disturb lipid metabolism by increasing serum homocysteine, which may increase the risk of atherosclerosis in adulthood. The oxidation of LDL was considered a biomarker of oxidative stress cardiovascular system and the main atherogenic modification of LDL (42, 43). It has antigenic potential and contributes heavily to atherosclerosis-associated inflammation (44, 45). In this study, the serum oxLDL was only associated with the Ca, either the Ca intake (from the drinking water and total Ca intake) or the serum Ca level. Calcium can disturb mitochondrial b-oxidation and regulate the cellular oxidation of low-density lipoprotein by arterial smooth muscle cells (20, 46). Calcium channel blockers can significantly inhibit the increase in ox-LDL levels in Dahl salt-sensitive rats receiving a high salt diet (47). Though oxidative stress is considered the major cause of homocysteine-induced toxicity, the main pro-oxidant nature of homocysteine is forming disulfides induced by metals (40). Some reports provide that the effects of homocysteine on vascular smooth muscle cells and endothelial cells are mediated by Ca (48, 49). These indicate that deficient Ca in drinking water threatens the cardiovascular system *via* inducing lipid oxidation, which relies mainly on serum Ca disorders, rather than high homocysteine. Though the serum Ca was not associated with serum 1,25,$(OH)_2D_3$ in this study, the disturbing of bone metabolism, which increased serum Ca when Ca intake was insufficient, was associated with serum 1,25,$(OH)_2D_3$. Therefore, serum 1,25,$(OH)_2D_3$ can disturb either homocysteine metabolism or Ca metabolism, and then played a key role in cardiovascular risk by consuming very low-mineral water.

Some limitations to this study were reported in our previous paper (18). For example, we only recorded the minerals in DDW of the four schools and the dietary intake of these children in 2012 and 2013. Besides, the present study lacked data on these children's daily vitamin B12 and B6 intake resulting from the lack of vitamin B12 and B6 contents in food in the China Food Composition (25). We cannot exclude the influence of dietary vitamins B12 and B6. But those students lived in the same area and shared similar nutritional habits. And we excluded participants who consumed mineral or vitamin supplements. We may postulate that the dietary intake of vitamin B12 and B6 was similar between the two groups. Second, these children had no symptoms or signs of cardiovascular damage, as well as higher blood pressure or hs-CRP. Children are in development, and their organs have a strong repair ability. They may not show a significant sign of cardiovascular dysfunction or morbidity. We can only use the cardiovascular biomarkers that can predict the risk of cardiovascular disease in adulthood, such as apolipoproteins and oxLDL, to evaluate the cardiovascular health of these children (38). However, we did not collect blood samples of these children in 2009. Lack of the baseline of serum homocysteine, B vitamins, and biomarkers of the cardiovascular system makes it impossible to show the causal

relationship between very low-mineral water consumption and cardiovascular damage. Although the blood pressure of these children was similar in 2009, it was also similar in 2013 and cannot support the baseline of cardiovascular system status was not different (2009). Thus, more studies are required to confirm this finding.

5. Conclusion

This study was the first trial to evaluate the association between long-term consumption of very low-mineral water and cardiovascular health in children. We found that consumption of very low-mineral water, even though it is not the only source of daily drinking water, might disturb homocysteine and lipid metabolism, increase oxidative stress, and then threaten cardiovascular health in children. Calcium and $1,25,(OH)_2D_3$ disorders induced by insufficient Ca intake might play a key role. Although further studies are required to confirm this finding, we still suggest that children drinking very low-mineral water or reverse-osmosis purified water are exposed to many health risks besides retarded bone development.

Data availbility 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 Ethics Committee of Army Medical University, Chongqing, China. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

WS conceived the investigation and designed the exposure estimates. YH designed the exposure estimates, performed the experiment and statistical analyses, and drafted the manuscript. LL made substantial contributions to the data collection. YT and LW made substantial contributions to performing the experiments. JL and HZ performed the statistical analyses. JW assisted with and checked the statistical analyses and modified the 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.

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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.2023.1133488/full#supplementary-material

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The value of the MIND diet in the primary and secondary prevention of hypertension: A cross-sectional and longitudinal cohort study from NHANES analysis

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Background: The Mediterranean-Dietary Approaches to Stop Hypertension for neurodegenerative delay (MIND) has been regarded as a novel healthy dietary pattern with huge benefits. However, its value in preventing and treating hypertension has not been investigated. The objective of this study is to investigate the impact of adhering to the MIND diet on the prevalence of hypertension in the entire population and long-term mortality in hypertensive patients.

Methods: In this cross-sectional and longitudinal study, 6,887 participants consisting of 2,984 hypertensive patients in the National Health and Nutritional Examination Surveys were analyzed and divided into 3 groups according to the MIND diet scores (MDS; groups of MDS-low [<7.5], MDS-medium [7.5–8.0] and MDS-high [≥8.5]). In the longitudinal analysis, the primary outcome was all-cause death and the secondary outcome was cardiovascular (CV) death. Hypertensive patients received a follow-up with a mean time of 9.25years (median time: 111.1months, range 2 to 120months). Multivariate logistics regression models and Cox proportional hazards models were applicated to estimate the association between MDS and outcomes. Restricted cubic spline (RCS) was used to estimate the dose–response relationship.

Results: Compared with the MDS-low group, participants in the MDS-high group presented a significantly lower prevalence of hypertension (odds ratio [OR] 0.76, 95% confidence interval [CI] 0.58, 0.97, p=0.040) and decreased levels of systolic blood pressure (β=−0.41, p=0.033). Among hypertensive patients, 787 (26.4%) all-cause death consisting of 293 (9.8%) CV deaths were recorded during a 10-year follow-up. Hypertensive patients in the MDS-high group presented a significantly lower prevalence of ASCVD (OR=0.71, 95% CI, 0.51, 0.97, p=0.043), and lower risk of all-cause death (hazard ratio [HR]=0.69, 95% CI, 0.58, 0.81, p<0.001) and CV death (HR=0.62, 95% CI, 0.46, 0.85, p for trend=0.001) when compared with those in the MDS-low group.

Conclusion: For the first time, this study revealed the values of the MIND diet in the primary and secondary prevention of hypertension, suggesting the MIND diet as a novel anti-hypertensive dietary pattern.

KEYWORDS
hypertension, prevention, the MIND diet, dietary pattern, nutrition, prognosis

1. Introduction

Hypertension, known as one of the standard modifiable cardiovascular risk factors, greatly contributes to atherosclerotic cardiovascular disease (ASCVD) development and health burden worldwide (1). Investigations exploring dietary approaches with anti-hypertensive value have been extensively performed. In previous studies, the Dietary Approaches to Stop Hypertension (DASH) diet and the Mediterranean (MED) diets have been widely demonstrated to confer huge benefits in preventing hypertension (2, 3). Recently, the MED-DASH Intervention for Neurodegenerative Delay (MIND) diet, a promising dietary pattern designed from most of the components in the MED and DASH diets, attached great attention for its great protective values in cognitive performance (4). As for its components, the MIND diet emphasizes the consumption of whole grains, green leafy vegetables, olive oil, nuts, beans, berries, poultry, and seafood, and restricts the intake of fast-fried foods, sweets, butter, and margarine (5). In addition to the cognitive protection, benefits brought by the MIND diet are ongoingly revealed, such as preventing ASCVD (6), protecting physical function through strengthening muscles (7), reducing depression symptoms (8), and lowering the risk of breast cancer (9). Since the MIND diet is designed from the DASH and MED diets and has shown great therapeutic potential in numerous aspects, the value of adhering to the MIND diet in the prevention and treatment of hypertension raised interest. However, evidence for this aspect is scarce.

In this study, we analyzed 6,887 participants consisting of 2,984 hypertensive patients based on The U.S. National Health and Nutrition Examination Survey (NHANES), aiming to investigate the value of the MIND diet in the primary and secondary prevention of hypertension.

2. Materials and methods

2.1. Study design and participants

In this study, we utilized data from the 2 continuous cycles of NHANES from 2003 to 2006 because of no available questionnaire data on the MIND diet in the other years. Adult participants were included in this study, and the exclusion criterion was a lack of data on the components of the MIND diet. A total of 7,205 adult participants with complete data on dietary patterns were included initially. After excluding participants without information on smoking status ($n = 309$), mortality data ($n = 7$), and blood lipid levels ($n = 2$), we analyzed 6,887 participants (2,984 hypertensive patients) in the final analysis (Figure 1). Generally, 6,887 participants were ultimately included in this study. Participants in this study were allocated into 3 groups according to the MIND diet scores (MDS): groups of MDS-low (< 7.5), MDS-medium (7.5–8.0), and MDS-high (≥ 8.5). The optimal MDS cut-offs were defined as the tertiles of MDS in all participants. The main focus of this study is the value of the MIND diet in primary prevention (the association of MDS with the levels of blood pressure [BP] and the prevalence of hypertension in the entire population) and secondary prevention (the association of MDS with the prevalence of ASCVD, and the risk of all-cause death, and CV death in hypertensive patients) of hypertension.

Hypertension was defined as a self-reported medical history of high blood pressure, receiving antihypertensive drugs, or blood pressure measurement $\geq$140/90 mmHg (10), and ASCVD was defined as a series of coronary artery disease (CAD), heart attack, angina, congestive heart failure, stroke, and peripheral artery disease.

2.2. Dietary assessment

In this study, we analyzed each diet component relevant to the MIND diet according to the Food Frequency Questionnaire during the NHANES 2003 to 2006-year cycles. The food frequency questionnaire (FFQ) of this study was only conducted at baseline, and concrete information was presented in Supplementary Text S1. MDS was applicated to evaluate adherence to the MIND diet. The MIND diet includes 10 brain-healthy food groups (green leafy vegetables, other vegetables, nuts, berries, beans, whole grains, seafood, poultry, olive oil, and wine) and 5 unhealthy food groups (red meats, butter, and stick margarine, cheese, pastries and sweets, and fried/fast food). Olive oil consumption was scored 1 if identified by the participant as the primary oil usually used at home and 0 otherwise. For all other diet score components, we summed the frequency of consumption of each food item portion associated with that component and then assigned a concordance score of 0, 0.5, or 1. The total MDS was computed by summing over all 15 of the component scores, concrete information on the calculation of MDS was presented in Supplementary Table S1 (4).

2.3. Follow-up and outcomes

The primary outcome of this study was all-cause and the secondary outcome was CV death. Mortality status was ascertained with death certificate records by linkage to the National Death Index through December 31, 2019. The specific cause of death was determined based on the International Statistical Classification of Disease, Tenth Revision (ICD-10). CV death was defined as deaths from heart diseases (ICD-10 codes I00-I09, I11, I13, I20-I51) or cerebrovascular diseases (ICD-10 codes I60-I69). The follow-up time was calculated from the NHANES Mobile Examination Center (MEC) date to the date of death or end of follow-up (December 31, 2019), whichever came first. These final mortality statuses, follow-up time, and the underlying leading causes of death files are available for online access.[1]

1 https://ftp.cdc.gov/pub/Health_Statistics/NCHS/datalinkage/linked_mortality

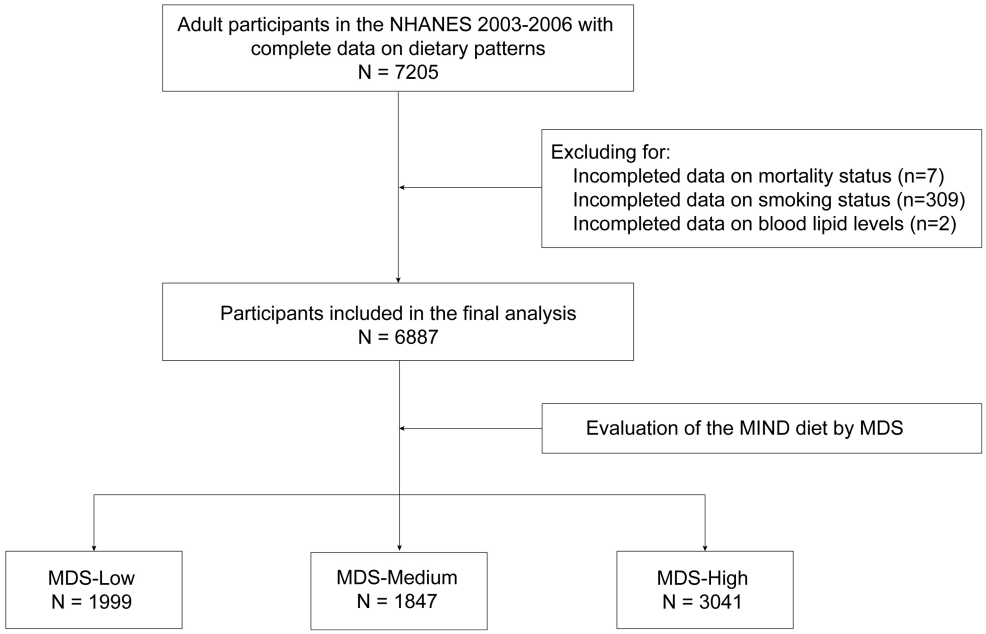

FIGURE 1
Flowchart of participant selection. MDS-Low, Low MIND score, the MIND diet score<7.5; MDS-Mdeium, Medium MIND score, the MIND diet score≥8 and<8.5; MDS-High, High MIND score, the MIND diet score≥8.5. NHANES, National Health and Nutrition Examination Survey; MIND diet, Mediterranean-DASH Diet Intervention for Neurodegenerative Delay diet; MDS, the MIND diet scores.

2.4. Covariates

Covariates were collected at baseline (NHANES 2003–2004). Information on age, sex, race/ethnicity, smoking status, alcohol consumption, physical activity, and self-reported medical conditions were obtained through standardized questionnaires during in-home interviews by trained interviewers. Heights, weights, waist circumferences, blood pressures, and blood samples were collected from physical examinations at Mobile Examination Center (MEC) using standard protocols.

Race/ethnicity was categorized as non-Hispanic White people, non-Hispanic Black people, Mexican American people, and others. Smoking status was categorized as never (smoked less than 100 cigarettes in life), former (smoked more than 100 cigarettes in life but quit smoke now), and current (smoked more than 100 cigarettes in life and still smoke some days or every day). Physical activity was measured as the weekly minutes of moderate and vigorous activities multiplied by the metabolic equivalent (MET) level and divided into four categories: sedentary (without regular physical activity, MET-minutes/week = 0), insufficient (0 < MET-minutes/week <500), moderate (500 ≤ MET-minutes/week ≤1,000), and high (>1,000 MET-minutes/week) (10), Body mass index (BMI, kg/m^2) was calculated as weight in kilograms divided by height in meters squared. Diabetes mellitus was defined as a self-reported medical history of diabetes, receiving oral hypoglycemic agents or insulin, fasting glucose level ≥ 126 mg/dl, or hemoglobin A1c (HbA1c) level ≥ 6.5% (11). Hyperlipidemia was defined as serum triglycerides (TG) ≥ 150 mg/L, total cholesterol (TC) ≥200 mg/dl, low-density lipoprotein cholesterol (LDL-C) ≥ 130 mg/dL, high-density lipoprotein cholesterol (HDL-C) ≤ 40 mg/dl in men or ≤ 50 mg/dL in women, or receiving medication for hyperlipidemia (12). The biochemical parameters, including TG, TC, HDL-C, LDL-C, and HbA1c were measured among partial participants who provided blood samples (95.7%, 6590/6887) at MEC.

2.5. Statistical analysis

As part of the NHANES complex sampling design, we utilized appropriate weights to ensure a representative sample of the US national population.[2] The results of baseline characteristics were presented as weighted means ± standard error for continuous variables and frequency (weighted percentages) for categorical variables. We compared the differences among groups using ANOVA for continuous variables and $\chi 2$ tests for categorical variables. The percentages of missing data for covariates were lower than 5% (BMI [1.7%], and energy intake [5.0%]). Imputation with the median of each variable was used to incorporate all data for modeling.

The analysis mainly included three parts: (1) In the first part of our analysis, we made a cross-sectional analysis of the entire population to investigate the association of adhering to the MIND diet with the prevalence of hypertension and levels of BP, (2) Next, we focused on hypertensive patients and made a cross-sectional analysis to explore the association of adhering to the MIND diet with the prevalence of ASCVD, and (3) At last, we performed a longitudinal analysis (a 9.25-year clinical follow-up) for hypertensive patients with the outcomes of all-cause and cardiovascular death to explore the value of the MIND diet in the secondary prevention of hypertension.

2 https://wwwn.cdc.gov/nchs/nhanes/tutorials/module3.aspx

The odd ratios (ORs) and 95% confidence intervals (CIs) for the association of MDS with the prevalence of hypertension and ASCVD were estimated using multi-variate Logistics regression models (cross-sectional analysis), and the hazard ratios (HRs) and 95% CIs for the association of MDS with the risk of all-cause death and CV death were explored using multivariate Cox proportional hazards models (longitudinal analysis). The correlation of MDS with levels of BP was estimated in the linear regression with the fully adjusted model. Restricted cubic spline (RCS) with 4 knots (5^{th}, 35^{th}, 65^{th}, and 95^{th} percentiles) in the fully adjusted model was used to estimate the dose–response relationship between MDS and outcomes. Nonlinearity was tested using the likelihood ratio test. Apart from the crude model, we adjusted potential covariates progressively in the 3 models. Model 1 was adjusted for age (continuous), sex (male or female), and race/ethnicity (non-Hispanic White people, non-Hispanic Black people, Mexican American people, and other). Model 2 was further adjusted for all covariates in Model 1 and smoking status (never, former, and current), physical activity (sedentary, insufficient, moderate, and high), and BMI (< 25.0, 25.0–29.9, and ≥ 30.0 kg/m2). Model 3 (fully adjusted model) was further adjusted for all covariates in Model 2 and diabetes, hyperlipidemia, and energy intake.

Subgroup analysis was performed by age (< 60 or ≥ 60 years), sex (male or female), race/ethnicity (White people or non-White people), smoking status (never or former and current), BMI (<30.0 or ≥ 30.0 kg/m2), physical activity (sedentary and insufficient or moderate and high), and diabetes (yes or no), and examined the significance of multiplicative interaction terms between the stratification variables and MDS by the Wald test.

Sensitivity analyzes were conducted based on the fully adjusted model. Firstly, we excluded non-Hispanic Black participants because of the higher prevalence of mortality among non-Hispanic Black individuals. Secondly, we excluded Mexican American people and other participants because of the oversampled non-Hispanic participants. Thirdly, we excluded participants who died within 1 year of follow-up to minimize the potential reverse causation bias. Finally, we excluded participants with cerebral diseases because of the brain-protective effects of the MIND diet which might enlarge its protective effects on long-term mortality.

All analyzes were performed with *R* version 4.1.3 (*R* Foundation for Statistical Computing, Vienna, Austria) using the "survey" package. A 2-tailed value of $p < 0.05$ was considered significant.

3. Results

3.1. Characteristics of the study population

Generally, 6,887 participants (age range:20 to 85 years old) were ultimately included in this study. In this study, MDS in all participants ranged from 4.5 to 13 points (Supplementary Table S2; Supplementary Figure S1). Table 1 showed the baseline characteristics of participants grouped by MDS. The overall weighted mean age of all participants was 47.13 years and 53.8% of them were female. Participants who better adhered to the MIND diet were older, more likely to be non-Hispanic white people, non-smokers, and have higher levels of DBP, physical activity, and less likely to combine cerebral diseases. The baseline characteristics of excluded participants with incomplete data were presented in Supplementary Table S3.

3.2. Association of adhering to the MIND diet with the prevalence of hypertension in the whole population

Table 2 and Figure 2A presented the logistic regression results of the association of adhering to the MIND diet with the prevalence of hypertension in 3 different models. Although no significant association was found in the crude model, results in other models presented that the MDS-high group showed a significantly lower prevalence of hypertension compared with participants in the low MDS group (model 3, HR 0.76, 95% CI 0.58, 0.97, $p = 0.040$). Besides, per one-score increase in MDS was shown to be associated with a 9% lower prevalence of hypertension (model 2, HR 0.91, 95% CI, 0.86, 0.97) (Table 2), and RCS showed a linear association of MDS with the prevalence of hypertension (p for non-linearity = 0.259) (Figure 3A).

Linear regression analysis presented that MDS was inversely correlated with the levels of SBP ($\beta = -0.41$, $p = 0.033$) in the whole population (Supplementary Table S5).

3.3. Association of adhering to the MIND diet on prevalence of ASCVD and BP levels in hypertensive patients

The baseline characteristics of hypertensive participants in this study were presented in online Supplemental files (Supplementary Table S4), and 641 (21.5%) of them combined ASCVD. Table 3 showed that hypertensive participants in the MDS-high group presented a significantly lower prevalence of ASCVD (model 3, OR = 0.80, 95% CI, 0.51, 0.97, p for trend = 0.043) compared with the MDS-low group in all models (Figure 2B). Moreover, per one-score increase in MDS was found to be associated with a 10% lower prevalence of ASCVD (HR = 0.90, 95% CI, 0.82, 0.99) (Table 3), and RCS showed a linear association of MDS with the prevalence of ASCVD (p for non-linearity = 0.614) in hypertensive participants (Figure 3B). No significant correlation was found between MDS and BP levels in hypertensive patients (Supplementary Table S5).

Besides, the inverse association of MDS with the prevalence of ASCVD was significant in the entire population (Supplementary Table S6), but not in participants without hypertension (Supplementary Table S7).

3.4. Association of adhering to the MIND diet with risk of all-cause death and CV death in hypertensive patients

During the follow-up, a total of 787 (26.4%) all-cause deaths and 293 (9.8%) CV deaths in hypertensive patients were recorded. As is shown in Table 3, Compared with participants in the low MDS group, hypertensive patients in the MDS-high group showed a significantly lower risk of all-cause death (model 3, HR = 0.69, 95% CI, 0.58, 0.81, P for trend <0.001) and CV death (model 3, HR = 0.62, 95% CI, 0.46, 0.85, P for trend = 0.001) in the all models (Figures 2C,D). Per one-score increase in MDS was associated with a 10% lower risk of all-cause death (HR = 0.90, 95% CI, 0.86, 0.95) and a 13% lower risk of CV death (HR = 0.87, 95% CI, 0.79, 0.96)

TABLE 1 Baseline characteristics of all participants based on the MIND diet score.

Characteristics	MDS tertile				*p* trend
	Total (*N*=6,887)	MDS-L (*N*=1999)	MDS-M (*N*=1847)	MDS-H (*N*=3,041)	
Age (years)	47.13 ± 0.45	42.97 ± 0.52	47.37 ± 0.57	49.66 ± 0.61	< 0.001
Sex, *n* (%)					< 0.001
Male	3,181 (46.19)	1,051 (52.29)	876 (49.14)	1,254 (39.13)	
Female	3,706 (53.81)	948 (47.71)	971 (50.86)	1787 (60.87)	
Race/ethnicity, *n* (%)					< 0.001
Non-Hispanic White people	3,809 (55.31)	1,080 (70.53)	993 (70.51)	1736 (75.53)	
Non-Hispanic Black people	1,333 (19.36)	478 (15.09)	369 (12.02)	486 (8.67)	
Mexican American people	1,272 (18.47)	318 (7.11)	353 (8.44)	601 (8.20)	
Others	473 (6.87)	123 (7.27)	132 (9.03)	218 (7.60)	
Smoking status, *n* (%)					< 0.001
Never	3,526 (51.2)	923 (43.95)	964 (49.76)	1,639 (53.92)	
Former	1920 (27.88)	478 (20.01)	485 (25.40)	957 (30.43)	
Current	1,441 (20.92)	598 (36.04)	398 (24.84)	445 (15.65)	
BMI (kg/m2), *n* (%)					0.07
<25.0	2082 (30.71)	610 (35.08)	531 (32.15)	941 (33.80)	
25.0–29.9	2,356 (34.75)	639 (29.51)	635 (34.03)	1,082 (34.85)	
≥30.0	2,341 (34.53)	717 (35.41)	653 (33.82)	971 (31.35)	
Physical activity, *n* (%)					< 0.001
Sedentary	1774 (25.76)	610 (23.94)	504 (19.68)	660 (15.03)	
Insufficient	2,621 (38.06)	728 (39.66)	726 (43.71)	1,167 (41.41)	
Moderate	1,129 (16.39)	302 (17.10)	289 (16.32)	538 (19.04)	
High	1,363 (19.79)	359 (19.30)	328 (20.29)	676 (24.52)	
MDS (score)	8.16 ± 0.05	6.45 ± 0.02	7.75 ± 0.01	9.49 ± 0.03	< 0.001
DBP (mmHg)	54.61 ± 0.31	51.75 ± 0.60	53.74 ± 0.42	56.93 ± 0.52	< 0.001
SBP (mmHg)	123.26 ± 0.45	122.41 ± 0.55	123.71 ± 0.74	123.53 ± 0.55	0.23
Hypertension, n (%)	2,984 (43.33)	846 (36.03)	841 (40.34)	1,297 (38.27)	0.21
Diabetes, *n* (%)	1,021 (14.83)	304 (11.01)	277 (11.07)	440 (10.78)	0.96
Hyperlipidemia, n (%)	4,954 (71.93)	1,428 (69.18)	1,347 (71.10)	2,179 (69.96)	0.68
Cerebral diseases, *n* (%)	287 (4.17)	96 (3.82)	83 (2.80)	108 (2.15)	0.003
TG (mg/dL)	142.74 ± 2.53	150.65 ± 5.04	141.39 ± 4.38	138.86 ± 4.20	0.21
HbA1c (%)	70.47 ± 0.28	70.70 ± 0.54	70.32 ± 0.50	70.41 ± 0.38	0.87
Fast blood glucose (mg/dL)	5.47 ± 0.02	5.45 ± 0.03	5.50 ± 0.03	5.46 ± 0.02	0.48
Waist circumference (cm)	97.53 ± 0.45	98.50 ± 0.59	97.89 ± 0.62	96.71 ± 0.63	0.08
Energy intake (Kcal)	2117.02 ± 15.62	2219.03 ± 28.08	2093.35 ± 21.63	2065.08 ± 23.42	< 0.001

Data are presented as weighted means ± SEs for continuous variables and unweighted numbers (weighted percentages) for categorical variables.
MDS-L, Low MIND score, the MIND diet score < 7.5; MDS-M, Medium MIND score, the MIND diet score ≥ 8 and < 8.5; MDS -H, High MIND score, the MIND diet score ≥ 8.5.
MDS, the MIND diet scores; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglyceride; HbA1c, glycosylated hemoglobin, type A1C.

(Table 3). Besides, RCS showed linear associations of MDS with the risk of all-cause death (p for non-linearity = 0.585) and CV death (p for non-linearity = 0.662) in hypertensive participants (Figures 3C,D).

Kaplan–Meier curves for all-cause mortality and CV mortality of 3 groups among hypertensive patients were further performed (Supplementary Figure S2). Consistently, groups with higher MDS showed a significantly lower risk of all-cause death (Log-rank test, $p < 0.001$) and CV death (Log-rank test, $p = 0.014$).

Besides, the inverse associations of MDS with the risk of all-cause death and CV death were significant in the entire population (Supplementary Table S6). As for participants without hypertension, the inverse associations of MDS with the risk of all-cause death, but not CV death, was significant (Supplementary Table S7).

TABLE 2 Logistic regression analysis for the risk of hypertension according to the MIND diet score in the whole population.

Model	Per one-score increases in MDS OR (95% CI)	OR (95% CI)			*p* trend
		MDS-L	MDS-M	MDS-H	
Crude	1.04 (0.99, 1.10)	1.00	1.20 (1.01, 1.42)	1.10 (0.91, 1.34)	0.414
Model 1	0.91 (0.86, 0.97)	1.00	0.92 (0.73 1.15)	0.71 (0.56, 0.90)	0.005
Model 2	0.93 (0.87, 1.00)	1.00	0.92 (0.71, 1.19)	0.74 (0.57, 0.96)	0.020
Model 3	0.94 (0.88, 1.01)	1.00	0.93 (0.73, 1.20)	0.76 (0.58, 0.97)	0.040

Model 1, adjusted for age, sex, and race/ethnicity.
Model 2, further adjusted (from Model 1) for smoking status, BMI, and physical activity.
Model 3, further adjusted (from Model 2) for diabetes, dyslipidemia, and energy intake.
MDS-L, Low MIND score, the MIND diet score < 7.5; MDS-M, Medium MIND score, the MIND diet score ≥ 8 and < 8.5; MDS -H, High MIND score, the MIND diet score ≥ 8.5.
MIND, the Mediterranean-DASH Diet Intervention for Neurodegenerative Delay diet score; MDS, the MIND diet scores; OR, odds ratios; CIs, confidence intervals.

3.5. Verification of results

Subgroup analyzes for the prevalence of hypertension in the whole population (Supplementary Table S8; Supplementary Figure S3), the prevalence of ASCVD (Supplementary Table S9; Supplementary Figure S4), and the risk of all-cause death (Supplementary Table S10; Supplementary Figure S5), and CV death (Supplementary Table S11; Supplementary Figure S6) in hypertensive patients were presented in supplemental files. Analyzes were stratified by age (<60 or ≥ 60 years), sex (male or female), race/ethnicity (non-Hispanic White people or other), smoking status (never or former/current), hypertension (yes or no), diabetes (yes or no), BMI (<30 or ≥ 30 kg/m^2) and physical activity (sedentary/insufficient or moderate/high). Results in subgroup analyzes did not change. Specifically, significant interactions were found in the subgroup analysis of age for the risk of all-cause death, the subgroup analysis of sex for the prevalence of ASCVD, and all-cause death, and the subgroup analysis of race for the risk of CV death.

When it came to the sensitivity analysis for the risk of all-cause death and CV death in hypertensive participants (Supplementary Table S12), the results remained consistent after excluding Hispanic participants, Mexican American and other participants, individuals who died within 1 year of follow-up, and participants with cerebral diseases.

To further validate the results above, we compared subjects with the mean score of each MDS category and found that the results were consistent (Supplementary Table S13). Besides, we also explored the protective effect of each food component in Supplementary Table S14. Results showed that the points were largely from restricted intake of butter and red meat. High intakes of fish, green leafy vegetables, nuts, and poultry, limited consumption of red meat, and proper intake of wine were the main protective contributors.

4. Discussion

In this cross-sectional and longitudinal study, a total of 6,887 participants consisting of 2,984 hypertensive patients were ultimately included. The main findings of this study include (1) better adherence to the MIND diet is associated with a lower prevalence of hypertension in the whole population, (2) hypertensive patients who adhered better to the MIND diet presented a lower prevalence of ASCVD, and a lower risk of all-cause death, and CV death, and (3) The inverse associations of MDS with the prevalence of hypertension, ASCVD, and the risk of all-cause death, and CV death all presented as linear relationships, and per 1-score increase in MDS was shown to significantly reduce the risk above. To date, this study documented the protective value of adhering to the MIND diet in both primary and secondary prevention of hypertension for the first time.

Investigations for anti-hypertensive dietary patterns have nowadays been widely performed. In previous studies, the DASH and MED diets have been revealed to confer great value in the prevention of hypertension, since numerous randomized control trials (RCT) reported that the MED and DASH diets significantly decreased both SBP and DBP in the whole population (2, 3). The MIND diet was initially designed based on the dietary components of the MED and DASH diets, including the great emphasis on natural plant foods and restricted consumption of animal and high saturated fat foods (4). However, the anti-hypertensive value of the MIND diet has not been investigated so far. For the first time, this study revealed that better adherence to the MIND diet was associated with decreased SBP and lower prevalence of hypertension in the whole population, documenting the significant value of the MIND diet in the primary prevention of hypertension.

Another major finding of this study is firstly revealing the values of the MIND diet in the secondary prevention of hypertension. Numerous studies have confirmed the therapeutic benefits in hypertensive patients who adhered to the DASH diet (3, 13–15) and the MED diet (2, 16). As for the MIND diet, its benefits of lowering long-term all-cause mortality in old participants have been reported recently (17), however, no research explored the therapeutic value of the MIND diet among hypertensive patients. In this study, we focused on patients with hypertension and revealed the improved prognosis in those with better adherence to the MIND diet. In addition to all-cause mortality, the cardioprotective potential of the MIND diet was recently discussed. In a current prospective cohort study with 2,863 participants, Mahdieh et al. revealed a significant inverse relationship between MDS and CVD (comprised of CAD, stroke, and CV mortality) risk (6). Besides, a recent case–control study focused on patients with stroke also presented similar results (18). Consistent with previous studies, a significantly lower risk of ASCVD and CV death was also reported in the entire population and hypertensive patients who better adhered to the MIND diet, further supporting that the MIND diet was a cardioprotective dietary pattern and concreting the therapeutic value of the MIND diet in the secondary prevention of hypertension.

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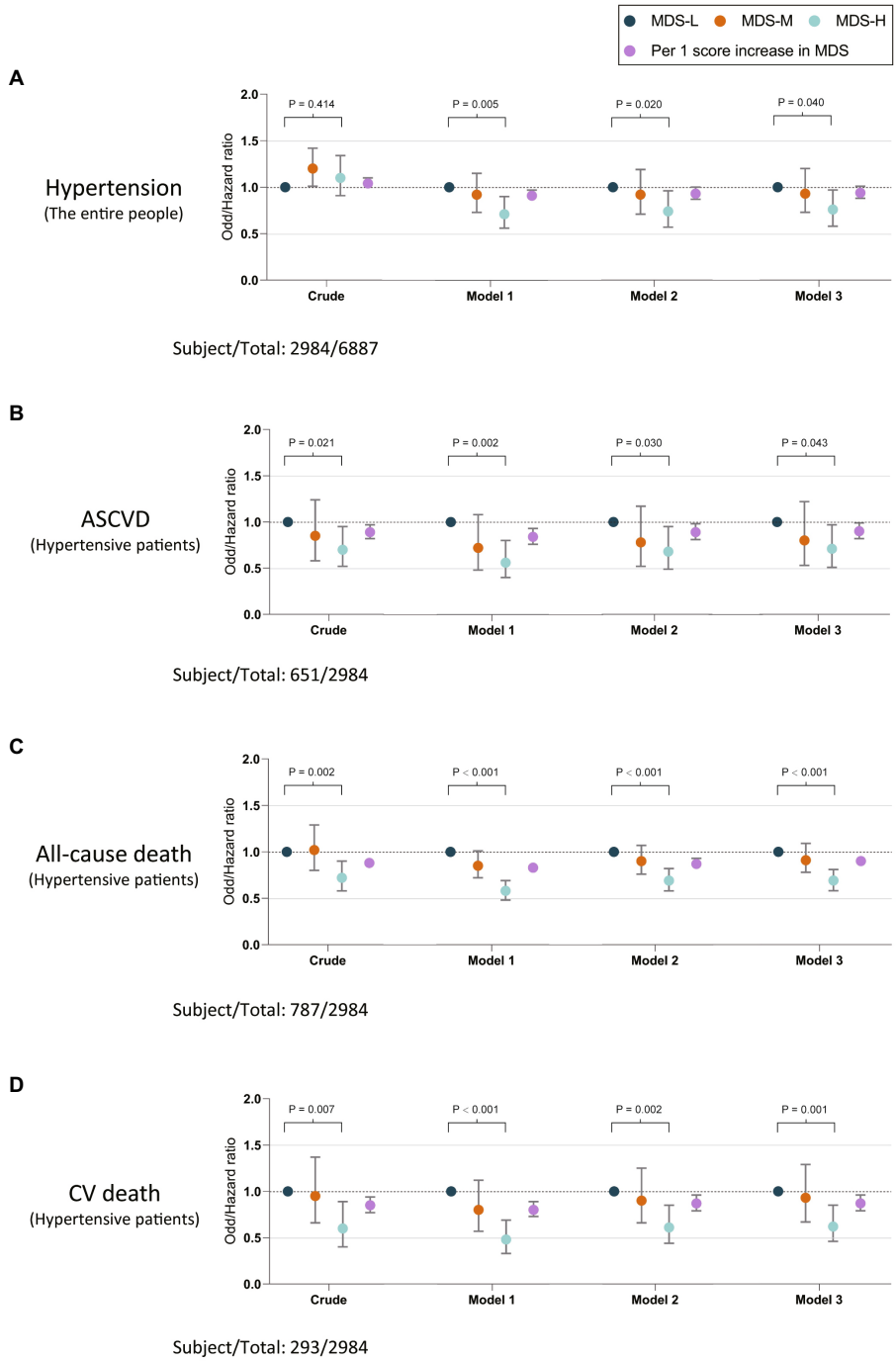

FIGURE 2
Odds/hazard ratios and 95%CI for the associations of MDS with the risk of hypertension in entire participants **(A)**, and the risk of ASCVD **(B)**, all-cause death **(C)**, and CV death **(D)**. MDS-L, Low MIND score, the MIND diet score<7.5; MDS-M, Medium MIND score, the MIND diet score≥8 and<8.5; MDS -H, High MIND score, the MIND diet score≥8.5. ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; MIND diet, Mediterranean-DASH Diet Intervention for Neurodegenerative Delay diet; MDS, the MIND diet scores.

In the subgroup analyzes of this study, we reported that the protective anti-hypertensive impact of the MIND diet was more significant in old people, females, and non-white people. These results indicated the protective roles of the MIND diet might be various in different people. Thus, future studies are also expected to compare the beneficial impact of adhering to the MIND diet on participants with different age groups, sex, and races to further illuminate the anti-hypertensive roles of the MIND diet.

In the components of MIND diets, we found that MDS was largely coming from a restricted intake of butter and red meat. High intakes of fish, green leafy vegetables, nuts, and poultry, limited consumption of red meat, and proper intake of wine were the main protective contributors. In previous studies, the high intake of fish with huge

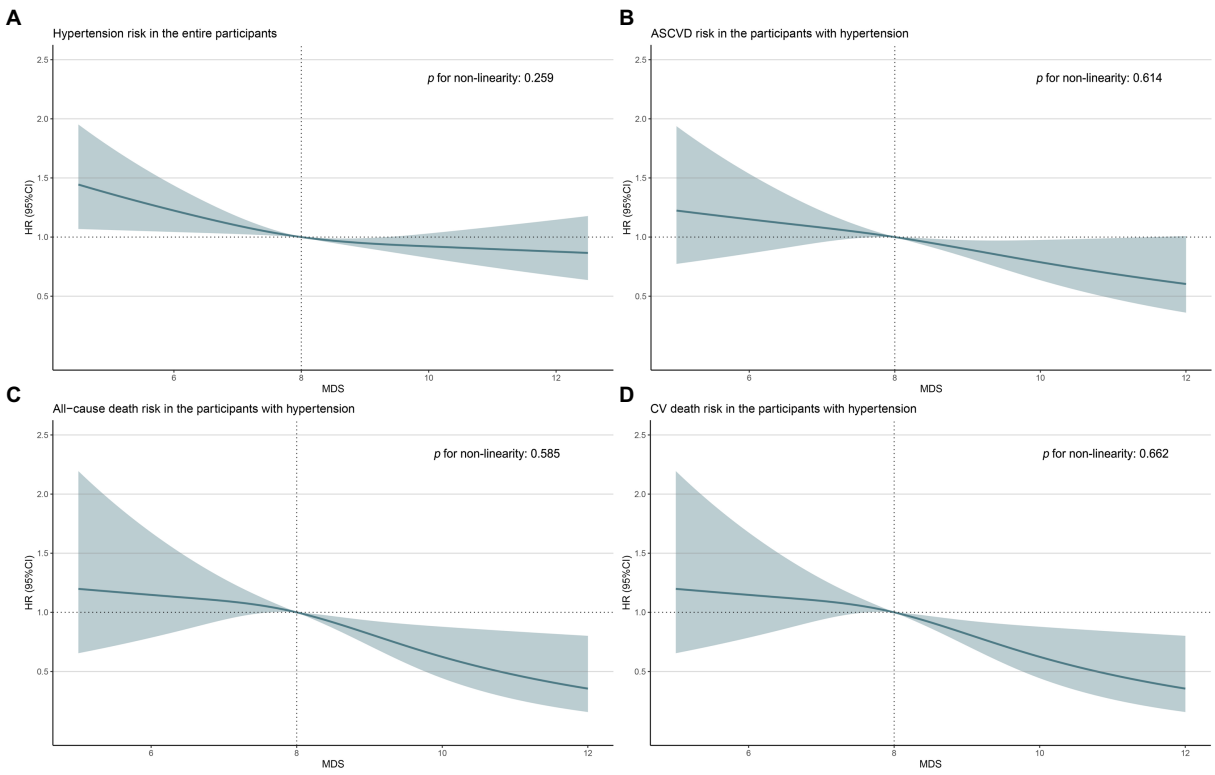

FIGURE 3
Restricted cubic spline models for the associations of MDS with the risk of hypertension in the entire participants **(A)**, and the risk of ASCVD **(B)**, all-cause death **(C)**, and CV death **(D)** in hypertensive patients. ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; MIND diet, Mediterranean-DASH Diet Intervention for Neurodegenerative Delay diet; MDS, the MIND diet scores.

sources of α-linolenic acid and marine omega-3 fatty acids (19), and high consumption of whole grains (20), olive oil (21), beans (22), and nuts (23), which were also emphasized in the DASH or MED diet, have been demonstrated as great anti-hypertension dietary components in previous studies. In addition, the MIND diet uniquely emphasized the consumption of berries and green leafy vegetables for dementia prevention, and these components also presented anti-hypertensive effects. In a rigorous investigation performed on hypertensive rats, Melissa et al. reported that the 6 week consecutive consumption of an experimental diet containing 4% green leafy vegetables significantly decreased SBP (24). Moreover, the consumption of berries was also indicated to hold great therapeutic potential in both the prevention and treatment of hypertension, as numerous recent clinical trials and RCT reported that the consumption of berries brought a significant reduction in levels of SBP and DBP regardless of the combination of hypertension (25–27). As for the mechanisms, great sources of quercetin, flavonoid, and folate from green leafy vegetables and berries were shown to be the main contributors through great anti-oxidative effects and vascular protection (28–30). As for the red meat, poultry, and wine intake, their associations with hypertension were still controversial, our results need to be further validated in future studies.

In the subgroup analysis, we found that the protective effect of the MIND diet was more significant in females. This conclusion was also reported by a recent study that focused on the relationship between the MIND diet and the risk of dementia, as the result showed that MIND adherence contributed to a decrease in the risk of dementia in females but not males (31). Besides, a more significant association between adherence to the MIND diet and a decrease in mortality among olde people was reported in the current study. Although there is no study comparing the protective effects of the MIND diet between old people and young people before, scholars have previously focused on old people and determined that closer adherence to the MIND diet is significantly associated with lower all-cause mortality (17). The interaction between race and the MIND diet has not been discussed previously, and the current study reported that the MIND diet-related reduction in the risk of CV death was more significant in white people for the first time. This conclusion was warranted to be further validated in future studies focusing on white people.

The main strength of this study is the first illustration of the impact of adhering to the MIND diet on the prevalence of hypertension in the whole population, and the prevalence of ASCVD and prognosis in hypertensive patients. However, there were several limitations in this study. Firstly, the association of adhering to the MIND diet with the prevalence of hypertension and ASCVD was investigated in cross-sectional analyzes, which might not have identified robust causal inferences. Secondly, the diagnosis of ASCVD was based on questionnaires without medical records, laboratory tests, or imaging, which might cause misdiagnosis. Thirdly, the 24 h dietary recall data was not applied in this study for the reason that these data mostly presented as "g/day" but not

TABLE 3 Logistic regression analysis for the risk of ASCVD and Cox regression analysis for all-cause and cardiovascular mortality according to the MIND diet score among hypertensive patients.

Model	Per one-score increases in MDS OR/HR (95% CI)	ORs/HRs (95% CI)			*p* trend
		MDS-L	MDS-M	MDS-H	
ASCVD					
Number of ASCVD/totals	641/2984	203/846	183/841	255/1297	
Crude	0.89 (0.82, 0.97)	1.00	0.85 (0.58, 1.24)	0.70 (0.52, 0.95)	0.021
Model 1	0.84 (0.76, 0.93)	1.00	0.72 (0.48 1.08)	0.56 (0.40, 0.80)	0.002
Model 2	0.89 (0.81, 0.98)	1.00	0.78 (0.52, 1.17)	0.68 (0.49, 0.95)	0.030
Model 3	0.90 (0.82, 0.99)	1.00	0.80 (0.53, 1.22)	0.71 (0.51, 0.97)	0.043
All-cause mortality					
Number of deaths/totals	787/2984	254/846	234/841	299/1297	
Crude	0.88 (0.83, 0.93)	1.00	1.02 (0.80, 1.29)	0.72 (0.58, 0.90)	0.002
Model 1	0.83 (0.79, 0.87)	1.00	0.85 (0.72 1.01)	0.58 (0.48, 0.69)	<0.001
Model 2	0.87 (0.83, 0.93)	1.00	0.90 (0.76, 1.07)	0.69 (0.58, 0.82)	<0.001
Model 3	0.90 (0.86, 0.95)	1.00	0.91 (0.78, 1.09)	0.69 (0.58, 0.81)	<0.001
CV mortality					
Number of deaths/totals	293/2984	97/846	88/841	108/1297	
Crude	0.85 (0.77, 0.94)	1.00	0.95 (0.66, 1.37)	0.60 (0.40, 0.89)	0.007
Model 1	0.80 (0.73, 0.89)	1.00	0.80 (0.57, 1.12)	0.48 (0.33, 0.69)	<0.001
Model 2	0.87 (0.79, 0.96)	1.00	0.90 (0.66, 1.25)	0.61 (0.44, 0.85)	0.002
Model 3	0.87 (0.79, 0.96)	1.00	0.93 (0.67, 1.29)	0.62 (0.46, 0.85)	0.001

Model 1, adjusted for age, sex, and race/ethnicity.
Model 2, further adjusted (from Model 1) for smoking status, BMI, and physical activity.
Model 3, further adjusted (from Model 2) for diabetes, dyslipidemia, and energy intake.
MDS-L, Low MIND score, the MIND diet score < 7.5; MDS-M, Medium MIND score, the MIND diet score ≥ 8 and < 8.5; MDS -H, High MIND score, the MIND diet score ≥ 8.5.
ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; MDS, the MIND diet scores; ORs, odd ratio; HRs, hazard ratios; CIs, confidence intervals; MDS, the MIND diet score, the Mediterranean-DASH Diet Intervention for Neurodegenerative Delay diet score; BMI, body mass index.

"serving/week" which is not suitable for the calculation of the MIND diet scores. Fourthly, the non-Hispanic participants were oversampled in the NHANES database. To decrease the bias from ethnicity, we made the related subgroup and sensitivity analysis. Nevertheless, it is still worthy to be validated in a population with proper percentages of ethnicity. Fifthly, the intake of each component of the MIND diet was collected based on a questionnaire without correction from specialists and continuous follow-up, which might contribute to bias. At last, the small or moderate sample size of this study limited the strength of the conclusions. Therefore, future exploration for the association of the MIND diet with hypertension is expected to be performed in large cohort studies or RCTs.

5. Conclusion

In conclusion, this study focused on the whole population and hypertensive patients and revealed the therapeutic potential of the MIND diet in the primary and secondary prevention of hypertension. These results documented the MIND diet as a novel anti-hypertensive dietary pattern for the first time.

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

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements.

Author contributions

KD and YS: conceptualization. QD, YS, and ZCh: methodology. YS and ZCh: software and formal analysis. YS and KC: validation. YS, ZCh, KC, and ZCa: investigation. KD and QD: resources. ZCh: data curation. YS, ZCh, KC, CS, and BS: writing—original draft preparation. QD and KD: writing—review and editing. YS: visualization. KD: supervision, project administration, and funding acquisition. 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.2023.1129667/full#supplementary-material

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Effects of different n-6/n-3 polyunsaturated fatty acids ratios on lipid metabolism in patients with hyperlipidemia: a randomized controlled clinical trial

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Background and aims: Intake of n-3 polyunsaturated fatty acids (PUFA) is helpful for cardiometabolic health. It improves lipid metabolism, and increasing n-3 PUFA is often considered beneficial. However, the role of n-6/n-3 in the regulation of lipid metabolism has been much debated. Therefore, this study was performed on the effect of different proportions of n-6/n-3 diet on lipid metabolism, and quality of life in patients with hyperlipidemia, aiming to explore appropriate proportions of n-6/n-3 to provide the theoretical basis for the development and application of nutritional blended oil in the future.

Methods: These 75 participants were randomized and assigned into three groups, which received dietary oil with high n-6/n-3 PUFA ratios (HP group: n-6/n-3=7.5/1), dietary oil with middle n-6/n-3 PUFA ratios (MP group: n-6/n-3=2.5/1) or low n-6/n-3 PUFA ratios (LP group: n-6/n-3=1/2.5). All patients received dietary guidance and health education were monitored for hyperlipidemia. Anthropometric, lipid and blood glucose parameters and quality of life were assessed at baseline and 60days after intervention.

Result: After 60days, high-density lipoprotein cholesterol (HDL-c) level was increased (p=0.029) and Total cholesterol (TC) level was decreased (p=0.003) in the MP group. In the LP group, TC level was decreased (p=0.001), TG level was decreased (p=0.001), but HDL-c level was not significantly increased. At the end of intervention, quality of life' score was improved in both MP and LP groups (p=0.037).

Conclusion: Decreasing the intake of edible oil n-6/n-3 ratio can improve blood lipids and quality of life. This is significant for the prevention of cardiovascular disease (CVD). It is also essential to note that an excessive reduction of the n-6/n-3 ratio does not further improve the blood lipid metabolism. In addition, the application of perilla oil in nutritional blended oil has particular significance.

Clinical Trial Registration: https://www.chictr.org.cn/indexEN.html, identifier ChiCTR-2300068198.

KEYWORDS

n-6/ n-3 polyunsaturated fatty acids ratio, cardiometabolic health, hyperlipidemia, lipid metabolism, perilla oil

1. Introduction

Hyperlipidemia, also known as dyslipidemia (1, 2), is an essential risk factor leading to cardiovascular disease (CVD), including atherosclerosis and ischemic cerebrovascular accidents (3, 4). Hyperlipidemia has become one of the most common health problems in humans (5, 6), which seriously affects the quality of life of patients. Nevertheless, high-fat diets are commonly regarded as contributing factors to excess body fat accumulation. Moreover, excessive fat intake, particularly when derived from saturated fatty acids (SFAs), has been linked to an elevated risk of obesity and hyperlipidemia.

Dietary fats encompass a diverse array of fatty acids (FA), derived from various sources, each exhibiting distinct chemical structures and biological functions (7, 8). Numerous studies have demonstrated that dietary polyunsaturated fatty acids (PUFA) intake is associated with positive effects on obesity and CVD (9, 10). Among PUFAs, n-3 PUFAs and n-6 PUFAs play particularly significant biological roles. N-3 PUFAs including docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), alpha-linolenic acid (ALA), possess neuroprotective properties, reduce the expression of eicosane, pro-inflammatory factors, modulate other inflammatory mediators, and suppress inflammatory responses (14–16). Primary sources of ALA include perilla and flaxseed oils. Prior research has indicated that n-3 PUFA-rich foods or n-3 supplements can decrease body weight and mitigate the risk of CVD stemming from dyslipidemia, such as coronary atherosclerosis (11–13). However, it has also been reported that no improvement in disease risk with n-3 PUFA intake (14, 15). N-6 PUFAs, primarily composed of linoleic acid (LA) and arachidonic acid (AA), can be found in edible oils like peanut oil and soybean oil, as well as animal-derived foods. As an EPA precursor, LA facilitates inflammatory processes and stimulates immune responses, thereby exacerbating inflammatory damage (16). Research on n-6 PUFAs has shown that their consumption in a typical diet reduces both good and bad cholesterol levels. Furthermore, n-6 and n-3 PUFAs cannot be interconverted within the body. These PUFAs compete for desaturase and *carbon-chain elongase*, with the conversion of LA to AA, and ALA to EPA and DHA mediated by desaturation and elongation reactions. An increase in one type of PUFA intake results in a decreased in the synthesis of the other PUFA in the body (17). An imbalance in the dietary n-6/n-3 PUFA ratio can leads to chronic low-grade inflammatory responses, promoting inflammation (18). The development of dyslipidemia or CVD is associated with inflammation. Thus, emphasizing an importance of maintaining an optimal n-6 and n-3 PUFA ratio for overall health (19).

Dietary therapy, as an effective alternative measure to control dyslipidemia, is currently attracting increasing attention from experts and scholars, including the use of dietary oils (20, 21). Studies of dietary intervention clinical trials focusing on hypercholesterolemic subjects revealed that plasma triglycerides (TG) may be reduced through n-3 PUFA and supplementation or used the oil blend with the higher concentration of n-3 PUFA, while also exhibiting a trend toward decreased total and LDL cholesterol (LDL-c) (22). This highlights the significance of n-3 PUFAs in reducing the risk of CVD, as extensively investigated in previous research (15). *Perilla frutescens* (L.) Britt. (PF) is a prominent oilseed crop utilized as a source of edible vegetable oil, traditionally considered a health food in Asian countries such as Korea, China, and Japan (23, 24). In comparison to other edible vegetable oils, perilla seed oil (PO) is primarily consists of PUFA (76 ~ 93%), ALA(57 ~ 62%) and LA(14 ~ 18%) (25), with ALA, an essential n-3 PUFA, being the most abundant (26). Past studies have demonstrated that perilla oil exhibits beneficial effects on weight loss, decreased fat mass (FM) reduction, waist circumference (WC) reduction, and appetite responses is improvement, and lipid profile enhancement (27, 28). Consequently, the properties of perilla oil have been suggested for use in the treatment and prevention of obesity (29).

We hypothesized that a reduced n-6/n-3 PUFA ratio might mitigate some of the detrimental effects of dyslipidemia on cardiovascular function. Therefore, the aim of this study was to evaluate the effects of n-6/n-3 PUFA plant blend oils prepared with different proportions of soybean oil and perilla oil on body weight, blood lipids and blood glucose in middle-aged and older patients with hyperlipidemia.

2. Materials and methods

2.1. Subjects and study design

This study was a double-blind, randomized, placebo-controlled trial conducted in the Third Affiliated Hospital of Nantong University (later renamed the Affiliated Hospital of Jiangnan University) from April 2022 to October 2022 for 6 months. This trial was approved by the Ethics Committee of the Affiliated Hospital of Jiangnan University (ID: LS2021010) and registered in the Chinese Clinical Trial Registry with registration (ChiCTR-2,300,068,198). Written informed consent was obtained from all participants by completing a consent form before the intervention.

Seventy-five hyperlipidemic patients, with body mass index (BMI) between 28 and 34.9 kg/m^2, aged 45 to 75 years, diagnosed with dyslipidemia and met any of the following criteria: TC $\geq$ 6.2 mmol/L, TG $\geq$ 2.3 mmol/L, HDL-c < 1.0 mmol/L, LDL-c $\geq$ 4.1 mmol/L. Furthermore, without a diagnosis of neurological, malignant hypertension, cancer or gastrointestinal disease, unrestricted diet, and no use of dietary supplements, herbal medicines, or lipid-lowering drugs in the last 2 months. Subjects with poor compliance or protocol violation or unwillingness to continue the clinical trial were asked to withdraw from this study. In the end, seventy-one participants were eligible and decided to participate in this study and completed. All subjects were randomly assigned to the control group (HP group) and the experimental groups (MP group, LP group) at a

ratio of 1:1:1. The demographic data of all subjects were recorded after enrollment, including gender, age, disease history, medication, and lifestyle. Anthropometric data were collected, including BMI, waist circumference (WC), hip circumference (HC), waist-hip ratio (WHR), etc. Based on previous studies (30), we calculated the sample size based on the primary outcome. Considering 20% drop-out and nonadherence, a total of 75 study subjects were required for the HP, MP, and LP groups at a 1:1:1 ratio. All eligible participants were asked to complete a 3-day dietary record and maintain physical activity. Dietitians questioned and recorded the participants' diets during the first 3 days of the formal experiment. Refer to the Chinese food composition table's standard edition to better understand the participants' diets. At the first enrollment, volunteers arrived at the Affiliated Hospital of Jiangnan University after a 12-h fast for blood collection and anthropometric assessment. Participants who met the diagnostic criteria of dyslipidemia were enrolled in the study and were given the corresponding cooking oil according to the random sequence. Participants were asked to replace the daily cooking oil at home and use perilla oil for cooking every day. The amount of oil used per person was 25 g per day, and they followed the prescribed dietary plan for 60 days.

The clinical trial was double-blinded because neither the subjects nor researchers knew which group every subject was assigned to, and the grouping of all subjects was unblinded by a statistician after they had completed their experiment. In the middle of the trial, volunteers were given oil for the next stage. Intervention adherence was assessed by perilla oil use diary.

TABLE 1 Qualitative analysis of fatty acids in perilla oil and soybean oil.

Fatty acids (FA)		Perilla oil	Soybean oil
Palmitic acid (C16:0)	%(A/A)	6.04	10.88
Stearic acid (C18:0)	%(A/A)	1.67	4.56
Arachidic acid (C20:0)	%(A/A)	ND	0.45
Behenic acid (C22:0)	%(A/A)	ND	0.47
Lignoceric acid (C24:0)	%(A/A)	ND	0.18
Oleic acid (C16:1, 9c)	%(A/A)	ND	0.09
Oleic acid (C18:1, 9c)	%(A/A)	11.8	24.27
Cis-vaccenic acid (C18:1, 11c)	%(A/A)	ND	0.04
Eicosenoic acid (C20:1)	%(A/A)	0.12	0.23
Linoleic acid (C18:2, 9c, 12c, n-6)	%(A/A)	13.5	52.49
α-linolenic acid (C18:3, 9c,12c, 15c n-3)	%(A/A)	66.4	5.99
Total saturated FA(SFA)	%(A/A)	1.67	16.54
Total monounsaturated FA (MUFA)	%(A/A)	11.92	24.63
Total polyunsaturated FA(PUFA)	%(A/A)	79.9	58.54
Total	%(A/A)	99.53	99.71

ND, not detect.

2.2. Intervention

In this part, the study intervention will be described in detail. All participants were randomly assigned (allocation ratio: 1:1:1) to groups HP, MP and LP. In both the control and experimental groups, we administered the oil at a dose of 25 g per day, and all subjects received the same dose of oil. In the HP group, subjects received soybean oil, while the MP and LP groups received perilla blend oil with n-6/n-3 = 2.5/1 and n-6/n-3 = 1/2.5, respectively (Tables 1, 2). The duration of the intervention was 60 days. The soybean oil used in the study was extracted from soybeans and produced by the Huanan Nongshengyuan Food Co., Ltd. of China Longjiang Forest Industry General Company. Perilla oil was extracted from perilla seed and supplied by the Huanan Nongshengyuan Food Co., Ltd. of China Longjiang Forest Industry General Company. Both oils were cold-pressed and stored in identical black bottles. Both oils were kept in the shade according to the manufacturer's instructions. During the intervention, participants were instructed to not change their dietary habits and physical activity. Importantly, the doses of applied oils were exchanged for the same amount of oil used in the diet. Therefore, the energy contents of the diet did not change during the intervention. Moreover, during the intervention, subjects were supervised over the telephone by the nutritionist to check compliance with the study protocol, especially regular administration of the appropriate oil. To verify adherence to the study protocol, participants were instructed to regularly return empty oil bottles to the research team. No deviation from the study protocol was noted.

In addition, health education for patients by endocrinology nurses, mainly including improving the understanding of dyslipidemia, correcting misconceptions about the cause of illness (i.e., providing information about the nature of the disease and that dyslipidemia is multifactorial, has multiple effects, and is often related to genetics and poor daily living habits), and reducing their fear of hyperlipidemia and its complications. Telephone-based Health follow-up service, asked about participant's daily, weekly, and monthly oil consumption, and received telephone guidance on daily living and exercise.

2.3. Anthropometric evaluation

Anthropometry and body weight was measured by an electronic weight scale with 150 kg of capacity and 100 g of precision, and height was measured by a vertical rangefinder measured height. Both variables were used to calculate BMI. WC was measured at the midpoint between the last rib and the top edge of the iliac crest, and HC was measured in the largest area of the hip to evaluate the WHR. WC higher than 102 cm was considered a risk of metabolic complications associated with obesity, and WHR higher than 0.90 was considered a cardiovascular risk. According to the principle that different biological tissues and organs have different electrical properties. Body fat measuring instrument (Biospace Inbody270, Biospace Corporation, Korea) is used to measure the resistance of different parts of the human body. The composition information of the corresponding parts is analyzed, such as fat, muscle mass, protein, inorganic salts, water, and so on.

TABLE 2 Ratio of soybean oil to perilla oil.

Group	Soybean oil: perilla seed oil	LA (%)	ALA (%)	n-6: n-3 ratio
HP	25:0	13	1.7	7.5:1
MP	20:5	10.9	4.7	2.5:1
LP	5:20	5.2	13.6	1:2.5

HP group: High proportion of n6/n3 group (n6/n3 = 7.5/1). MP group: Middle proportion of n6/n3 group (n6/n3 = 2.5/1). LP group: Low proportion of n6/n3 group (n6/n3 = 1/2.5).

2.4. Biochemical evaluation

The primary outcome of lipid change was measured before and after the intervention. Lipid metabolism indicators included total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-c), and low-density lipoprotein cholesterol (LDL-c). Secondary outcomes included changes in fasting plasma glucose (FBG) and uric acid level (UA). The above indicators were tested by an automatic biochemical analyzer (Beckman Coulter au680; Beckman Coulter Corporation, America).

2.5. Quality of life measurement

The MOS 36-Item Short Form Health Survey (SF-36) was used to measure the improvement of the quality of life of the study subjects. SF-36 is a concise health questionnaire developed by the Boston Institute of Health Research (31). It is widely used in the measurement of quality of life in the general population, the evaluation of clinical trials, and the evaluation of health policies. As a simple health questionnaire, SF-36 comprehensively summarizes the quality of life of the respondents from eight aspects: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health. In addition to the eight components of the SF-36, a health change measure was also included to assess the overall change in health status over the past year (32). The SF-36 scale has good reliability and validity, and its application range is wide, which is suitable for the evaluation of the health level of Chinese residents.

2.6. Statistical analysis

Statistical analysis was performed using SPSS software version 26.0 (SPSS Inc., Chicago, IL, USA), considering significant $p < 0.05$. Shapiro Wilks (normally). Test was performed to evaluate the distribution of the variables. Differences among the three tested groups at baseline and at the end of the study were assessed by one-way ANOVA test or Kruskal-Wallis test. When within-group comparison before and after intervention and between-group comparison, the distribution was normal being used the Student's *t* test and non-normal being used the Wilcoxon or Mann–Whitney test. Quality of life scales were analyzed by covariance analysis.

3. Results

3.1. Study population

The participant flowchart is presented in Figure 1. During the intervention period, two participants dropped out of the HP group, one out of the MP group and one out of the LP group. Finally, a total of 71 patients with hyperlipidemia completed the study.

3.2. Anthropometric evaluation

The baseline characteristics are presented in Table 3. All parameters of participants were similar between the three groups at baseline. Diet with a lower n-6/n-3 PUFA ratio did not change body fat or WHR of the participants after intervention. Body weight and BMI decreased in three groups, as shown in Table 3. The delta values of body weight and BMI of each group were summarized as follow: Δ Body weight-HP group: −0.93 ± 4.44, MP group: −1.44 ± 3.97, LP group: −2.84 ± 5.88, $p = 0.376$; Δ BMI-HP group: −0.34 ± 1.9, MP group: −0.57 ± 1.53, LP group: −1.12 ± 2.36, $p = 0.386$).

3.3. Blood lipid parameters

There were significant differences in the mean values for partial outcomes between groups at the end of the dietary intervention (Table 4). The dietary intervention with perilla oil treatment was effective in improving the serum levels of TC ($p = 0.002$) and TG ($p = 0.006$). A declining trend was observed for LDL-c levels in the MP group and LP group, although the difference was not significant.

The results of the three groups before and after intervention were shown in Table 5. After the end of the intervention, HDL-c levels in the MP group increased from 1.313 to 1.500 mmol/L ($p = 0.029$). The difference in the TC, TG and LDL-c levels before and after intervention was statistically significant ($p < 0.05$, paired *T*-test). LP group showed decreased TC levels (6.711 ± 1.104 vs. 5.843 ± 0.596, $p = 0.001$) and TG: (2.332 ± 0.737 vs. 1.741 ± 0.617, $p = 0.001$) with no change in HDL levels before and after intervention. In addition, as shown in Table 5, all differences of ΔTC, ΔTG and ΔHDL-c between the three groups were statistically significant (ΔTC: $p = 0.023$, ΔTG: $p = 0.003$, ΔHDL-c: $p = 0.002$). Despite not being statistically significant, a clear reduction in LDL-c in HP and LP group were observed: ΔLDL-c = −0.171 ± 0.395 (HP group) and ΔLDL-c = −0.230 ± 0.888 (LP group).

3.4. The SF-36 quality of life score

Quality of life scores among the three groups before and after intervention were shown in Table 6. Perilla oil intervention had significantly different effects on vitality scores (HP vs. MP vs. LP): (66.09 ± 9.648 vs.69.17 ± 7.470 vs. 68.96 ± 7.799, $p = 0.008$) and the total scores (68.841 ± 4.586 vs. 70.613 ± 4.817 vs. 71.277 ± 4.195, $p = 0.037$) had significant difference. After the intervention, the MP group's scores had significant differences in vitality, social functioning, and total score compared with pre-intervention (VT: 63.13 ± 9.066 vs. 69.17 ± 7.470, $p = 0.001$, SF: 69.29 ± 11.686 vs. 2.96 ± 9.720, $p = 0.029$,

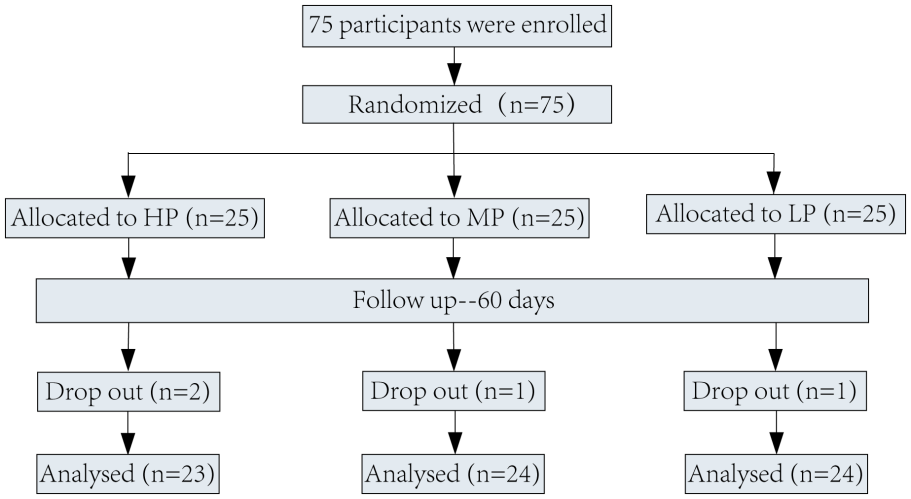

FIGURE 1
Flow-diagram of volunteers of the study. HP group: High proportion of n6/n3 group (n6/n3=7.5/1). MP group: Middle proportion of n6/n3 group (n6/n3=2.5/1). LP group: Low proportion of n6/n3 group (n6/n3=1/2.5).

TABLE 3 Baseline characteristics of study participants.

Variables		HP (*n*=23)	Δ	MP (*n*=24)	Δ	LP (*n*=24)	Δ	Value of *p*
Sex (male/female)		10/13		11/13		10/14		0.958
Age (years)		58.13 ± 6.73		60.88 ± 5.44		60.08 ± 5.59		0.273
Height (m)		162.22 ± 6.91		160.71 ± 6.86		161.28 ± 5.37		0.629
Anthropometry								
Body Weight (kg)	Baseline	78.96 ± 6.58		76.91 ± 8.63		77.93 ± 6.17		0.691
	Final	78.03 ± 7.00	−0.93 ± 4.44	75.47 ± 8.54	−1.44 ± 3.97	75.09 ± 6.12	−2.84 ± 5.88	0.500
	Value of *p*	0.328*		0.088*		0.027*		0.376#
BMI (kg/m2)	Baseline	30.03 ± 2.10		29.75 ± 2.40		30.10 ± 2.12		0.810
	Final	29.65 ± 1.94	−0.34 ± 1.69	29.18 ± 2.24	−0.57 ± 1.53	28.97 ± 1.81	−1.12 ± 2.36	0.500
	Value of *p*	0.294*		0.083*		0.030*		0.386##
WHR	Baseline	0.873 ± 0.036		0.875 ± 0.036		0.873 ± 0.034		0.892
	Final	0.867 ± 0.040	−0.006 ± 0.019	0.870 ± 0.044	−0.005 ± 0.026	0.872 ± 0.041	−0.001 ± 0.024	0.913
	Value of *p*	0.144*		0.341*		0.799*		0.754##
Body fat (%)	Baseline	27.23 ± 3.18		28.22 ± 2.76		27.28 ± 2.62		0.424
	Final	27.37 ± 2.57	0.12 ± 1.80	27.23 ± 2.52	−0.99 ± 1.72	26.45 ± 2.34	−0.83 ± 1.993	0.393
	Value of *p*	0.749*		0.010*		0.054*		0.093##

HP group: High proportion of n6/n3 group (n6/n3 = 7.5/1). MP group: Middle proportion of n6/n3 group (n6/n3 = 2.5/1). LP group: Low proportion of n6/n3 group (n6/n3 = 1/2.5). BMI: body mass index. WC: waist circumference. WHR: waist-hip ratio. Δ: delta (final value-after intervention value). * Student's *t* test, paired. # One-way ANOVA. ## Kruskal-Wallis.

Total score: 67.034 ± 6.899 vs. 70.613 ± 4.817, $p = 0.009$). Additionally, the scores of LP group had significant differences in role-physical, role-emotional, mental health, and total score compared with pre-intervention (RP: 61.46 ± 28.532 vs. 69.79 ± 20.824, $p = 0.029$, VT: 61.67 ± 8.427 vs. 68.96 ± 7.799, $p = 0.000$, MH: 60.67 ± 10.277 vs. 64.42 ± 10.450, $p = 0.001$, Total score:67.411 ± 6.283 vs.71.277 ± 4.195, $p = 0.001$).

4. Discussion

Hyperlipidemia, a significant causal risk factor for CVD, is a chronic condition linked to metabolic complications (33). Effective interventions are crucial for treating and preventing dyslipidemia and its associated complications (34). Dietary intervention is regarded as an efficacious and safe treatment approach. In this context,

TABLE 4 Multiple comparisons of the mean values at the end of follow up in all intervention groups in individuals with patients.

Endpoints at the end of follow up	All groups (*n*=71)	HP vs. MP	HP vs. LP	MP vs. LP
	Value of *p*	Value of *p*	Value of *p*	Value of *p*
Body Weight (kg)	0.500*	0.430**	0.431**	0.854**
BMI (kg/m2)	0.500*	0.670**	0.580**	0.720**
WHR	0.913*	0.971**	0.964**	0.970**
Body fat (%)	0.393*	0.845**	0.503**	0.504**
Serum TC (mmol/L)	0.002*	0.004**	0.012**	0.580**
Serum TG (mmol/L)	0.006#	0.005##	0.098##	0.192##
Serum HDL-c (mmol/L)	0.109*	0.131**	0.632**	0.227**
Serum LDL-c (mmol/L)	0.165#	0.219##	0.651##	0.334##
Plasma glucose (mmol/L)	0.769*	0.868**	0.879**	0.868**
Plasma uric acid (mmol/L)	0.330#	0.362##	0.656##	0.656##

HP group: High proportion of n6/n3 group (n6/n3 = 7.5/1). MP group: Middle proportion of n6/n3 group (n6/n3 = 2.5/1). LP group: Low proportion of n6/n3 group (n6/n3 = 1/2.5). BMI: body mass index. WC: waist circumference. WHR: waist-hip ratio. the data was showed as mean ± standard deviation. * One-way ANOVA. # Kruskal-Wallis Test. ** Student's t test, unpaired. ## Mann–Whitney.

we examined the hypothesis that a diet with a lower n-6/n-3 ratio would promote weight loss and improved lipid levels. Our finding revealed that the diet characterized by a reduced n-6/n-3 ratio led to increased HDL-c level and decreased TC, TG and LDL-c levels in hyperlipidemic patients. In the present study, we observed a decrease in LDL level in the MP group, while HDL levels increased following perilla oil consumption. Elevated HDL levels facilitate the reverse transport of cholesterol from peripheral tissues to the liver for more efficient utilization. As PUFAs intake increases, there is a corresponding rise in HDL synthesis to facilitate this reverse transport. Although limited evidence has suggested that LA may contributes to weight control, our study does not support this claim. The primary outcomes assessed were body weight, blood lipids and BMI, which significantly influence obesity. However, in our study, there was no effect on body weight and BMI were observed. This lack of effect may be due to the possibility that excessive doses of linolenic acid could significantly impact appetite, leading to higher calorie intake, which would be counter-productive for weight management.

To the best of our knowledge, this study represents the first randomized controlled trial that compares the efficacy of two distinct lower n-6/n-3 interventions, i.e., 1/2.5 and 2.5/1, in hyperlipidemic patients as a means to regulate lipid metabolism in this population. In our investigation, we compared MP group with LP group in pairs. Notably, the improvement within blood lipids in the LP group did not become more pronounced as the n-6/n-3 ratio decreased when compared to the enhancement observed in the MP group. No significant differences emerged in blood lipid parameters between the MP and LP groups. Serum TC, TG, and LDL levels were decreased in the MP group, while the favorable HDL level increased. Previous

TABLE 5 Multiple comparisons of the mean values at the end of follow up in all intervention groups in individuals with patients.

Blood biochemistry		HP (*n*=23)	Δ	MP (*n*=24)	Δ	LP (*n*=24)	Δ	Value of *p*
Serum TC (mmol/L)	Baseline	6.567 ± 0.914		6.124 ± 0.889		6.711 ± 1.104		0.220
	Final	6.562 ± 1.064	−0.004 ± 1.042	5.703 ± 0.887	5.703 ± 0.887	5.843 ± 0.596	−0.868 ± 1.140	0.002
	Value of *p*	0.984*		0.041*		0.001*		0.023#
Serum TG (mmol/L)	Baseline	2.111 ± 0.827		1.933 ± 1.019		2.332 ± 0.737		0.186
	Final	2.169 ± 0.834	0.058 ± 0.694	1.461 ± 0.748	1.461 ± 0.748	1.741 ± 0.617	−0.591 ± 0.573	0.006
	Value of *p*	0.691*		0.003**		0.001**		0.003##
Serum HDL (mmol/L)	Baseline	1.433 ± 0.328		1.433 ± 0.328		1.391 ± 0.308		0.389
	Final	1.316 ± 0.313	−0.117 ± 0.253	1.500 ± 0.254	1.500 ± 0.254	1.360 ± 0.354	−0.031 ± 0.211	0.109
	Value of *p*	0.038*		0.029*		0.476*		0.002#
Serum LDL (mmol/L)	Baseline	4.137 ± 0.685		3.832 ± 0.758		4.180 ± 0.880		0.356
	Final	4.180 ± 0.880	−0.083 ± 0.500	3.661 ± 0.744	3.661 ± 0.744	3.950 ± 0.788	−0.230 ± 0.888	0.165
	Value of *p*	0.406*		0.045**		0.218**		0.745#
Plasma glucose (mmol/L)	Baseline	5.66 ± 0.66		5.69 ± 0.55		5.85 ± 0.51		0.318
	Final	5.80 ± 0.57	0.14 ± 0.45	5.72 ± 0.58	5.72 ± 0.58	5.83 ± 0.53	−0.03 ± 0.23	0.769
	Value of *p*	0.159*		0.759*		0.572*		0.329#
Plasma uric acid (mmol/L)	Baseline	314.46 ± 26.49		300.40 ± 25.37		307.28 ± 27.66		0.116
	Final	315.03 ± 23.45	0.57 ± 29.67	303.32 ± 30.92	303.32 ± 30.92	309.68 ± 25.31	2.41 ± 20.41	0.330
	Value of *p*	0.927**		0.425*		0.569*		0.935##

HP group: High proportion of n6/n3 group (n6/n3 = 7.5/1). MP group: Middle proportion of n6/n3 group (n6/n3 = 2.5/1). LP group: Low proportion of n6/n3 group (n6/n3 = 1/2.5). Δ: delta (final value – after intervention value). *Student's *t* test, paired. **Wilcoxon test. #One-way ANOVA. ##Kruskal-Wallis.

TABLE 6 Quality of life scores among the three groups before and after the intervention.

SF-36	HP (n=23)		MP (n=24)		LP (n=24)		F^a	p-value
	Pre	Post	Pre	Post	Pre	Post		
PF	85.43 ± 4.980	85.65 ± 4.599	86.46 ± 4.773	87.29 ± 3.895	87.71 ± 4.165	88.13 ± 3.555	1.189	0.331
RP	63.04 ± 27.041	67.39 ± 17.573	60.42 ± 25.449	67.71 ± 18.765	61.46 ± 28.532	69.79 ± 20.824*	0.371	0.692
BP	64.65 ± 19.676	63.96 ± 18.656	65.46 ± 19.204	68.92 ± 14.407	64.92 ± 20.151	66.50 ± 17.230	0.899	0.412
GH	55.978 ± 17.524	57.337 ± 16.499	58.854 ± 18.237	60.156 ± 13.266	59.375 ± 15.309	59.635 ± 12.766	0.078	0.925
VT	65.43 ± 9.404	66.09 ± 9.648	63.13 ± 9.066	69.17 ± 7.470*	61.67 ± 8.427	68.96 ± 7.799*	5.231	0.008
SF	70.83 ± 13.917	71.78 ± 11.878	69.29 ± 11.686	72.96 ± 9.720*	71.13 ± 13.300	73.42 ± 9.127	0.811	0.419
RE	72.65 ± 19.201	74.17 ± 13.917	71.00 ± 20.449	75.25 ± 14.597	72.38 ± 21.262	79.38 ± 16.320	1.045	0.357
MH	63.86 ± 9.064	64.35 ± 9.335	61.67 ± 10.277	63.67 ± 9.649	60.67 ± 10.277	64.42 ± 10.450*	1.699	0.191
Total	67.731 ± 4.944	68.841 ± 4.586	67.034 ± 6.899	70.613 ± 4.817*	67.411 ± 6.283	71.277 ± 4.195*	3.452	0.037

HP group: High proportion of n6/n3 group (n6/n3 = 7.5/1). MP group: Middle proportion of n6/n3 group (n6/n3 = 2.5/1). LP group: Low proportion of n6/n3 group (n6/n3 = 1/2.5). PF: Physical Functioning. RP: Role-Physical. BP: Bodily Pain. GH: General Health. VT: Vitality. SF: Social Functioning. RE: Role-Emotional. MH: Mental Health. Value of p: Analysis of covariance; *Compared with the group pre-intervention, $p < 0.05$.

research has similarly reported that a lower n-6/n-3 PUFA ratio is not necessarily superior (35) and that the "optimal ratio" of LA and ALA may not represent the most accurate measure of PUFA balance (36). It has been suggested that PUFAs is intake is more effective means of achieving dietary n-6 and n-3 PUFAs balance than simply focusing on proportions (37). The World Health Organization (WHO) also posits that, provided unsaturated fatty acids (USFA) fall within the recommended range, there are no well-founded recommendations for the n-6 to n-3 PUFA or LA to ALA ratios (38). In this context, individual doses of n-6 and n-3 PUFAs should be carefully considered alongside their proportions. In conclusion, both the MP and LP groups demonstrated improved lipid levels, and reducing the n6/n3 ratio proved beneficial for enhancing cardiometabolic health and decreasing the risk of CVD.

To ensure that participants adhered to the required daily cooking oil consumption, we supplied them with specialized oil pots featuring clearly marked scales. This facilitated facilitate control over the quantity of oil utilized during cooking and provide participants with a clear understanding of their daily oil usage, which is a distinguishing aspect of our trial. Furthermore, we acknowledge that prior studies needed to address the impact of individual compliance on experimental outcomes, as they were population-based investigations. Thus, enhance participant compliance during the intervention phase of our trial, we conducted weekly telephone follow-ups while allowing for unrestricted eating. Health education was provided to inform the patients about disease-related knowledge, such as dietary precautions, and to understand their daily eating habits. However, we did not impose restrictions on participants' energy intake or food types were not restricted. Regular follow-ups and health guidance ensured participants' compliance, rendering the regulatory effects of n-3 PUFA on blood lipids and body weight more persuasive.

It is important to note that our evaluation of quality of life serves as a reliable indicator of lipid-regulating therapy efficacy in hyperlipidemic patients, and holds significant value in guiding subsequent treatment. We employed the SF-36 quality of life scale to assess changes in participants' physical function, bodily pain, social function, and other aspects before and after the intervention. Our findings revealed no differences in scores across all p aspects among participants prior to the intervention. However, following the 2-month perilla oil intervention significant between-group differences in energy and total score were observed in the experimental group. In both the MP and LP groups, scores for physical function, vitality, social function, and mental health were significantly improved after the intervention. A possible explanation is that reducing the n-6/n-3 ratio can enhance patients' blood lipid levels, regulate neurological function and mood, and mitigate the detrimental effects of negative emotions on the disease. Consequently, the quality of life scores for the MP and LP groups improved post-intervention. Other studies have also shown that change dietary changes can reduced blood lipids and body weight while improving mood in hyperlipidemic patients. Although this study did not involve a comprehensive dietary pattern in this study, the rich linolenic acid in perilla oil increased the intake of n-3 PUFAs intake and adjusted the proportion of dietary fatty acids in the diet, further substantiating the aforementioned conclusions.

Oil is a fundamental component of the diet, with its nutritional value determined by both the quantity of oil consumed and the composition of FAs within it. The edible mixed oils, created by blending various fats in specific proportions, address the limitations of single-source fats, which may lack certain nutritional elements. Mixed oils not only satisfy the body's requirement for various fatty acids but also enhance the flavor of fats. Different fats contain distinct fatty acids, with varying ratios of SFA, monounsaturated fatty acids (MUFA), and PUFA, which impact their nutritional effects. Research has demonstrated that soybean oil is abundant in PUFAs and phytosterols, which can lower blood lipids and protect against cardiovascular and cerebrovascular diseases. However, the insufficient oleic acid content in soybean oil leads to an imperfect nutritional profile. Flaxseed oil, vegetable oil, is rich in n-3 PUFA components and vitamin E, offering antioxidant, anti-inflammatory, and anti-cancer properties. Additionally, flaxseed oil shows considerable potential in preventing CVD and treating diabetes and neurological disorders. Since single-oil nutrition is inadequate to meet the demand for nutritious and healthy oil, a more balanced fatty acid composition is needed for cooking oil. Notably, the distinct fishy taste of deep-sea fish oil can negatively affect the flavor of cooking oil, while flaxseed oil, another vegetable oil, also contains ample n-3 PUFA. Consequently, in this study utilized soybean oil and ALA-rich perilla oil as base oils to prepare the relevant oils. Our findings revealed that both the MP and LP groups experienced similar improvements in blood lipids and quality of life. However, the LP group required more perilla oil, resulting in higher production costs compared to the MP group,

potentially posing a financial burden for consumers seeking to increase their ALA intake. Furthermore, the greater perilla oil content in the LP group influenced its flavor and taste. This research can serve as a theoretical foundation for the development and application of nutritionally balanced oil blends.

5. Conclusion

Adopting a dietary habit with a lower n-6/n-3 ratio dietary habit positively impacts lipid parameters and quality of life for individuals with hyperlipidemia. Furthermore, it has the potential to enhances patients' cardiometabolic health and provides protection against CVD. Importantly, excessively reducing the n6/n3 ratio does not lead to additional improvements in blood lipids. These findings reveal an alternative approach for reducing total cholesterol and triglycerides while simultaneously increasing HDL-c level. To substantiate the results of this study, further research involving larger samples is required. Moreover, a deeper exploration of the mechanisms by which different n-6/n-3 ratios influence lipid regulation would be an intriguing subject for future investigations.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by the ethical review board of the Affiliated Hospital of Jiangnan University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

YY was responsible for the operation of the experiment, data collection, data interpretation, and writing and revision of the manuscript, under the direction and assistance of BZ, YW, and FZ, who assisted with each step in the study and completion of the manuscript. YX and DL assisted in the completion of the experiment. JiY, HC, and JS were in charge of grouping and followed-up on the trial. All authors have read and agreed to the published version of the manuscript.

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Conflict of interest

YX, DL, JiY, JuY, JS, HC, YW, and FZ are employed by Yixing Institute of Food and Biotechnology Co., Ltd.

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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Glossary

CVD	Cardiovascular disease
BMI	Body mass index
FA	Fatty acid
ALA	Alpha-linolenic acid
LA	Linolenic acid
AA	Arachidonic acid
MUFA	Monounsaturated fatty acids
PUFA	Polyunsaturated fatty acids
SFA	Saturated fatty acids
USFA	Unsaturated fatty acids
FM	Fat mass
WC	Waist circumference
WHR	Waist-hip ratio
TC	Total cholesterol
TG	Total triglyceride
HDL-c	High- density lipoprotein cholesterol
LDL-c	Low-density lipoprotein cholesterol

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Trends in research on dietary behavior and cardiovascular disease from 2002 to 2022: a bibliometric analysis

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Background: Dietary behaviors and cardiovascular disease are two major health issues that have attracted a lot of attention from researchers worldwide. In this study, we aimed to provide a comprehensive analysis of the publication trends, authorship patterns, institutional affiliations, country/region contributions, journal outlets, highly cited documents, and keyword clusters in the field of dietary behaviors and cardiovascular disease research over the past two decades.

Methods: We conducted a systematic literature review of peer-reviewed articles published from 2002 to 2022 in the Web of Science Core Collection database. We extracted and analyzed data on the annual publication volume, authorship patterns, institutional affiliations, country/region contributions, journal outlets, highly cited documents, and keyword clusters using bibliometric methods and visualization tools.

Results: Our study analyzed 3,904 articles, including 702 reviews and 3,202 research articles. The results revealed a continuous increase in the number of publications in this field over the past two decades. The top 10 authors, institutions, and countries/regions with the highest publication output were identified, indicating the leading contributors to this field. Moreover, the most frequently cited documents and highly clustered keywords were identified, providing insights into the research themes and topics in this field.

Conclusion: Our study provides a comprehensive analysis of the publication trends, authorship patterns, institutional affiliations, country/region contributions, journal outlets, highly cited documents, and keyword clusters in the field of dietary behaviors and cardiovascular disease research over the past two decades. The findings provide valuable information for researchers, policymakers, and stakeholders to understand the research landscape, identify research gaps, and develop future research directions in this field.

KEYWORDS

dietary behavior, cardiovascular disease, bibliometric analysis, VOSviewer, visualization

Introduction

Cardiovascular diseases (CVDs) continue to pose a significant global health burden, contributing to substantial morbidity and mortality worldwide (1). The prevalence of CVDs has reached epidemic proportions, warranting urgent attention and comprehensive strategies for prevention and management (2). Among the various modifiable risk factors associated with

CVDs, dietary behaviors have emerged as crucial contributors to the development and progression of these conditions (3).

A growing body of evidence suggests that an individual's dietary choices and patterns play a pivotal role in determining their cardiovascular health status (4). The intricate interplay between nutrients, bioactive compounds, and dietary components can significantly influence the pathophysiological processes underlying CVDs, including inflammation, oxidative stress, endothelial dysfunction, dyslipidemia, and hypertension (5–8). Furthermore, the impact of dietary factors extends beyond traditional risk factors, encompassing novel markers such as gut microbiota composition, metabolomic profiles, and epigenetic modifications, which further shape an individual's cardiovascular risk profile (9–11).

Understanding the intricate relationship between dietary behaviors and cardiovascular health is essential for the development of effective preventive and therapeutic interventions (12). Moreover, unraveling the mechanisms underlying these associations can provide valuable insights into the etiology of CVDs and guide personalized dietary recommendations tailored to individuals at risk (13, 14). Additionally, exploring the cultural and social determinants that shape dietary behaviors is crucial for addressing health disparities and promoting equitable access to cardiovascular health (15).

Thus, this study aims to conduct a bibliometric analysis of studies examining dietary behavior and cardiovascular disease, published from 2002 to 2022, utilizing the Web of Science database. This study examines information on keywords, authors, institutions, countries/regions, and journals, employing VOSviewer to analyze the data. Ultimately, a deeper understanding of the intricate relationship between dietary behaviors and cardiovascular health can inform evidence-based strategies to promote heart health, empower individuals to make informed dietary choices, and alleviate the burden of cardiovascular diseases on a global scale.

Materials and methods

Data source

The research process is illustrated in Figure 1. We collected the data from the Web of Science Core Collection database. The timespan covered the last 21 years (from 2002 to 2022). The "topic" field was used to search for articles related to a specific research field. TS = ("behavior, feeding" or "feeding behaviors" or "eating behavior" or "behavior, eating" or "eating behaviors" or "feeding-related behavior" or "behavior, feeding-related" or "feeding related behavior" or "feeding-related behaviors" or "feeding patterns" or "feeding pattern" or "pattern, feeding" or "food habits" or "food habit" or "habit, food" or "eating habits" or "eating habit" or "habit, eating" or "dietary habits" or "dietary habit" or "habit, dietary" or "diet habits" or "diet habit" or "habit, diet" or "habits, diet") and ("cardiovascular disease" or "disease, cardiovascular" or "cardiovascular diseases" or "diseases, cardiovascular"). The "document type" field was set to "article" and "review" to ensure that we only included articles in our analysis. The language of the included literature was limited to English in order to ensure consistency and minimize potential language bias.

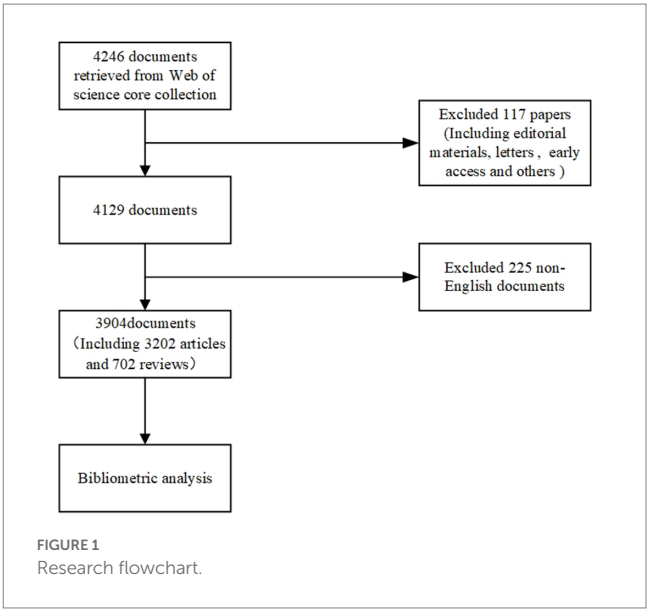

FIGURE 1
Research flowchart.

Data analysis

We used VOSviewer, a bibliometric analysis software, to analyze the data. VOSviewer uses co-occurrence analysis to identify relationships between different terms and keywords in the articles. The software generates a map that shows clusters of related terms. The size of each term on the map indicates its importance and the thickness of the lines between the terms represents the strength of the relationship between them.

To generate the map, we first exported the search results from Web of Science Core Collection into a text file and then imported it into VOSviewer. We conducted keyword clustering analysis using the following parameters, with a minimum occurrence frequency set at 50 for each term to be included in the analysis. We used the VOSviewer default settings for the remaining parameters.

Data visualization

We used the VOSviewer software to generate the visualization of the co-occurrence analysis results. The visualization is presented in a map format, where each cluster of keywords is represented by a different color. The size of each keyword on the map is proportional to its frequency of occurrence in the articles, and the proximity of two keywords on the map indicates their degree of co-occurrence.

Results

Annual publication volume

In our study, we analyzed a total of 3,904 articles consisting of 702 reviews and 3,202 articles within the field of dietary behaviors and cardiovascular diseases. Our findings reveal that the number of publications in this area has been on the rise from 2002 to 2022. This trend is visually presented in Figure 2, which illustrates the number of

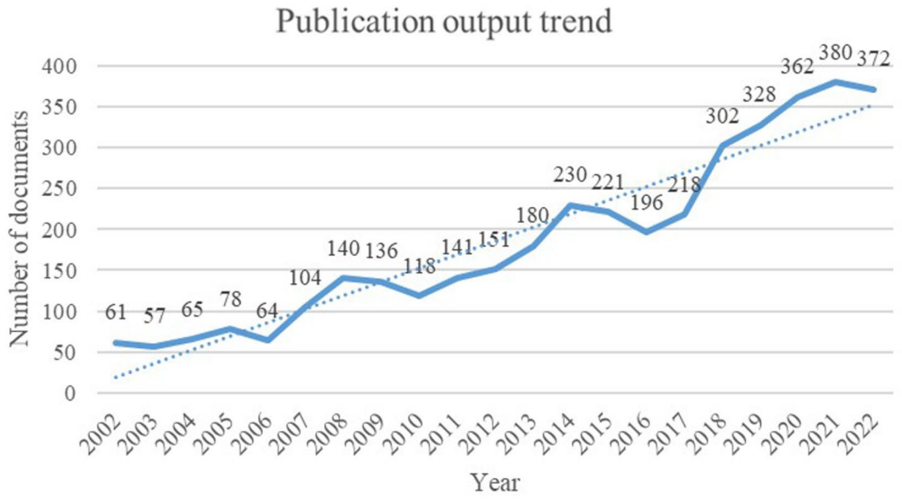

FIGURE 2
Trend of publications on dietary behavior and cardiovascular disease from 2002 to 2022.

publications related to dietary behaviors and cardiovascular research from 2002 to 2022.

Author analysis

From 2002 to 2022, a total of 20,640 authors have published documents in this field. Table 1 presents the top 10 authors ranked by the number of publications in the field of dietary behavior and cardiovascular disease. At the top of the list is Panagiotakos DB, who has published a remarkable 83 documents, indicating his significant contribution to the field. Pitsavos C follows closely behind with 57 publications, while Stefanadis C ranks third with 47 publications. Figure 3 shows the co-authorship of the authors.

TABLE 1 Top 10 authors ranked by the number of publications.

Ranking	Authors	Documents
1	Panagiotakos DB	83
2	Pitsavos C	57
3	Stefanadis C	47
4	Chrysohoou C	40
5	Martinez-Gonzalez MA	34
6	Panagiotakos DB	24
7	Iacoviello L	20
8	Polychronopoulos E	19
9	Tyrovolas S	19
10	Zeimbekis A	18

Institutional analysis

In the past 21 years, a total of 5,244 research institutions have published papers in this field. Table 2 presents the top 10 institutions with the highest number of publications in the field of study. Harvard University leads the list with a remarkable 147 publications, followed closely by Harokopio University Athens with 124 publications. Ciber Centro de Investigacion Biomedica En Red ranks third with 116 publications, while National Kapodistrian University of Athens and University of California System round out the top five with 111 and 97 publications, respectively. The remaining institutions in the list include Athens Medical School, University of London, Harvard T. H. Chan School of Public Health, Harvard Medical School, and Ciberobn, all of which have made significant contributions to the field through their numerous publications. Figure 4 shows the co-authorship of institutions.

Journal analysis

A total of 1,301 journals have published papers related to the field. Table 3 presents the top 10 journals ranked by the number of publications in this field. The journal with the highest number of publications is Nutrients, with 192 papers. Following closely is PLoS One with 80 publications, and BMC Public Health and International Journal of Environmental Research and Public Health with 70 papers each. Other journals that made the top 10 list include Public Health Nutrition, Nutrition Metabolism and Cardiovascular Diseases, European Journal of Clinical Nutrition, American Journal of Clinical Nutrition, and Journal of Nutrition. The Figure 5 shows the visualization map of journal citations.

Country/regions analysis

In the past 21 years, a total of 121 countries/regions have published papers related to this field. Table 4 presents the top 10 countries/regions ranked by the number of publications in this field. The United States holds the leading position with 1,102 publications, followed by Italy with 371 publications and Spain with 325 publications. England, Australia, and People's Republic of China also have a significant number of publications with 302, 221, and 210 documents, respectively. Greece, Japan, Canada, and Brazil are also among the top 10 countries/regions. Figure 6 shows the co-authorship of countries/regions.

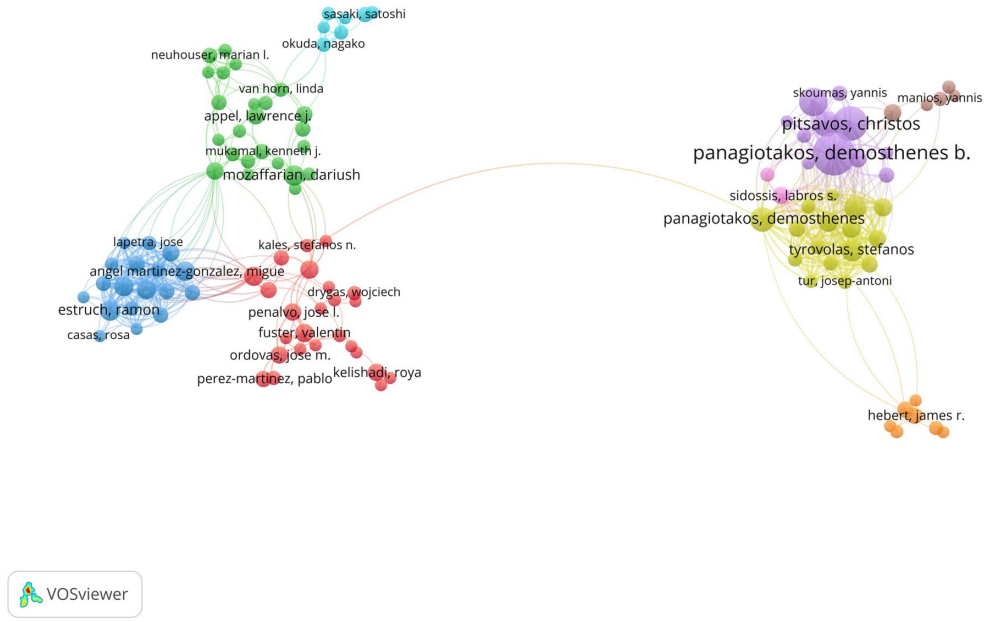

FIGURE 3
The co-authorship of authors.

TABLE 2 Top 10 institutions with the highest number of publications.

Ranking	Institution	Documents
1	Harvard University	147
2	Harokopio University Athens	124
3	Ciber Centro de Investigacion Biomedica En Red	116
4	National Kapodistrian University of Athens	111
5	University of California System	97
6	Athens Medical School	88
7	University of London	86
8	Harvard T. H. Chan School of Public Health	85
9	Harvard Medical School	80
10	Ciberobn	74

Documents analysis

In the past 21 years, a total of 3,904 papers related to this field have been published. Table 5 shows the top 10 highly cited documents in the field. The expert committee recommendations regarding the prevention, assessment, and treatment of child and adolescent overweight and obesity: summary report, published in Pediatrics in 2007, ranked first with 3,119 citations. The report provides comprehensive recommendations on the prevention, assessment, and treatment of child and adolescent obesity, which is a major public health problem worldwide. The second most cited document is Youth Risk Behavior Surveillance—United States, 2015, published in MMWR Surveillance Summaries in 2016, with 1,223 citations. The document presents the results of a survey of risk behaviors among high school students in the United States, including behaviors related to obesity, physical activity, and nutrition. Ranked third is Youth Risk Behavior Surveillance—United States, 2013, published in Sports Medicine in 2014, with 1,143 citations. Similar to the second-ranked document, it reports on the results of a survey of risk behaviors among high school students in the United States. Figure 7 shows the visualization knowledge maps of highly cited documents.

Keyword analysis

There are a total of 12,855 keywords. Figure 8 illustrates the results of the keyword clustering analysis, where the keywords are categorized into four clusters represented by the colors red, blue, yellow, and green. The red cluster is dominated by keywords such as cardiovascular disease, obesity, body mass index, and overweight. The blue cluster includes keywords such as Mediterranean diet, heart disease, olive oil, mitochondrial dysfunction, stroke, and coronary heart disease. The yellow cluster is mainly composed of keywords such as diet, exercise, intervention, and prevention. The green cluster includes keywords such as oxidative stress, metabolic syndrome, insulin resistance, adipose tissue, blood pressure, cholesterol, inflammation, and C-reactive protein. This analysis provides a comprehensive understanding of the key themes and concepts in the field of diet and cardiovascular disease research.

Discussion

General information

This study analyzed the literature related to diet behavior and cardiovascular disease over the past 21 years, revealing a trend of increasing research output in this field. This suggests a growing interest among researchers and the general public in the link between diet behavior and cardiovascular health. Notably, Panagiotakos DB emerged as one of the most prolific authors in this field, having published 83 articles that highlight

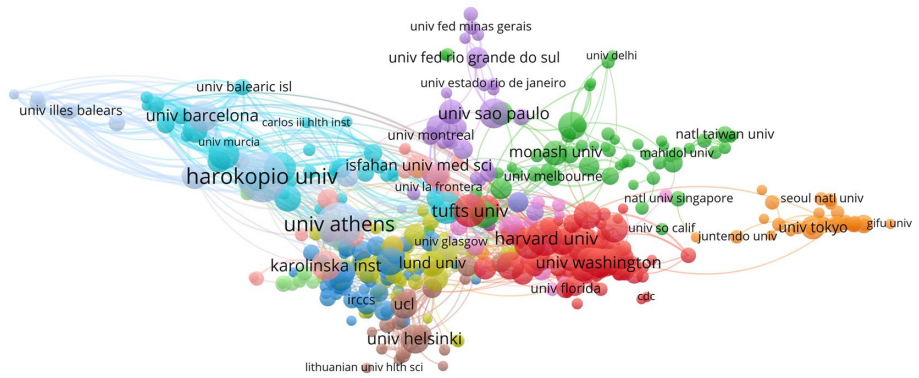

FIGURE 4
The co-authorsship map of institutions.

TABLE 3 Top 10 journals ranked by number of publications.

Ranking	Journal	Documents
1	Nutrients	192
2	PLoS One	80
3	BMC Public Health	70
4	International Journal of Environmental Research and Public Health	70
5	Public Health Nutrition	60
6	Nutrition Metabolism and Cardiovascular Diseases	58
7	European Journal of Clinical Nutrition	56
8	American Journal of Clinical Nutrition	45
9	Journal of Nutrition	42
10	Nutrients	37

his significant contributions. Collaboration among authors also emerged as an important factor in advancing research in this area. Harvard University, Harokopio University Athens, and Ciber Centro de Investigacion Biomedica En Red were the top institutions in terms of research output, indicating their pivotal role in this field. Meanwhile, contributions from diverse institutions worldwide underscore the global reach of this research. The United States led the way in research output with 1,102 published articles, followed by Italy, Spain, England, Australia, and mainland China. This highlights the global nature of research in this field and the widespread interest among researchers worldwide. Nutrients, PLoS One, BMC Public Health, and International Journal of Environmental Research and Public Health were among the most prolific journals publishing in this field, covering a wide range of topics related to diet behavior and cardiovascular health. Keyword analysis revealed 12,855 keywords clustered into four groups represented by red, blue, yellow, and green. Red keywords included those related to cardiovascular disease, obesity, body mass index, and overweight. Blue keywords included Mediterranean diet, heart disease, olive oil, mitochondrial dysfunction, stroke, and coronary heart disease. Yellow keywords were related to diet, exercise, intervention, and prevention. Green keywords included oxidative stress, metabolic syndrome, insulin resistance, adipose tissue, blood pressure, cholesterol, inflammation, and C-reactive protein.

Research trends, knowledge gaps, and future directions

Taken together, these findings highlight the expanding scope of research on diet behavior and cardiovascular disease, encompassing a wide range of topics and concepts. Notable contributions from authors, institutions, and countries, such as Panagiotakos DB, Harvard University, and the United States, provide valuable insights for future research and practice to reduce the incidence of cardiovascular disease and promote public health.

Although the relationship between diet behavior and cardiovascular disease has been extensively studied, there are still some gaps that need to be further explored. One of these gaps is the impact of diet on the risk of cardiovascular disease in different races and cultural backgrounds. While some studies have suggested a correlation between dietary habits and the incidence of cardiovascular disease, most of these studies have focused on Western populations (16–18), and further research is needed for other ethnic and cultural groups. Another gap is the personalized design of dietary intervention measures. While some dietary intervention measures have been shown to improve the risk of cardiovascular disease (19–21), there is significant biological variation between individuals. Therefore, further research is needed to explore how to design personalized dietary intervention measures based on individual characteristics such as genes, metabolites, and microbiomes. Based on the trends and gaps in research, we can predict future research directions and focuses in this field. Firstly, we can expect to see more research on the relationship between dietary behavior and cardiovascular health in different cultural and geographical

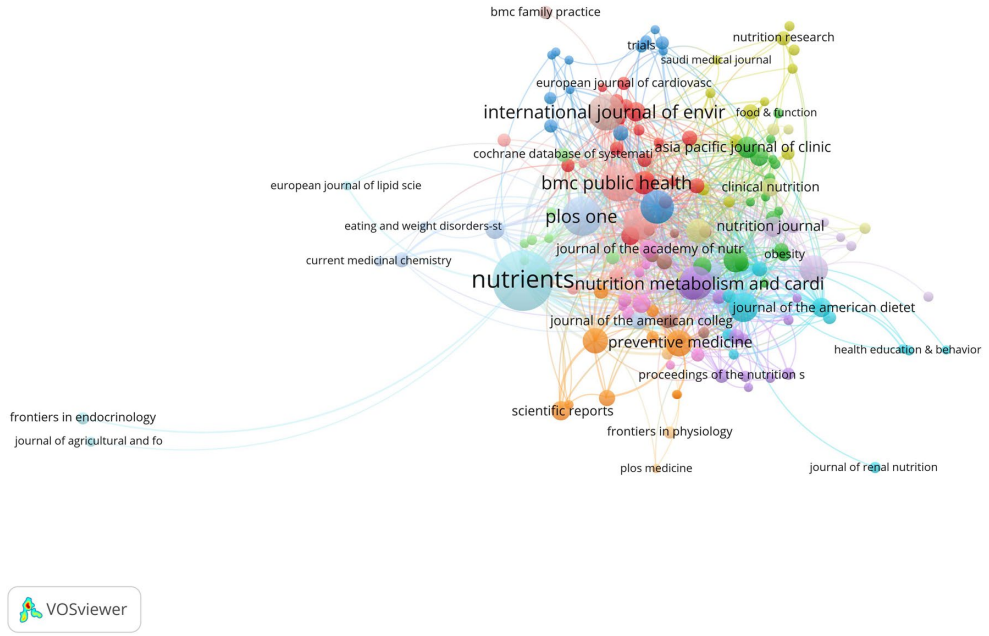

FIGURE 5
Visualization map of journal citations.

TABLE 4 Top 10 countries/regions by number of publications.

Ranking	Country/region	Documents
1	United States	1,102
2	Italy	371
3	Spain	325
4	England	302
5	Australia	221
6	People's Republic of China	210
7	Greece	204
8	Japan	186
9	Canada	180
10	Brazil	172

contexts. Another possible direction is the study of differences in dietary behavior and cardiovascular health between different individuals. This includes research on individuals of different genders, ages, ethnicities, and health statuses, as well as differences between dietary habits and nutrient requirements. Overall, we expect the research field of the relationship between dietary behavior and cardiovascular disease to continue to develop and expand, with future research focusing more on individual differences, the relationship between dietary patterns and nutrients, and the effects of food processing and cooking.

Strengths and limitations

In this study, a comprehensive analysis of publication trends, authorship patterns, institutional affiliations, country/region contributions, journal outlets, highly cited documents, and keyword clusters in the field of dietary behaviors and cardiovascular disease research over the past two decades was conducted. The use of systematic literature review and bibliometric methods ensured a rigorous and objective approach to analyzing the 3,904 articles included in the study, providing a representative sample of the research in this field. However, the limitations of this study include the reliance on articles from the Web of Science Core Collection database, which may not encompass all relevant publications, and the restriction to publications in English, which may limit generalizability to non-English speaking countries.

Conclusion

In conclusion, our analysis of the literature related to diet behavior and cardiovascular disease over the past 21 years reveals a trend of increasing research output in this field, indicating a growing interest among researchers and the general public. Notable contributions from authors, institutions, and countries provide valuable insights for future research and practice to reduce the incidence of cardiovascular disease and promote public health. However, there are still gaps in our understanding of the relationship between diet behavior and cardiovascular disease that need to be addressed in future research. We expect the research field in this area to continue to develop and expand, with a focus on individual differences, the relationship between dietary patterns and nutrients, and the effects of food processing and cooking.

Data availability statement

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

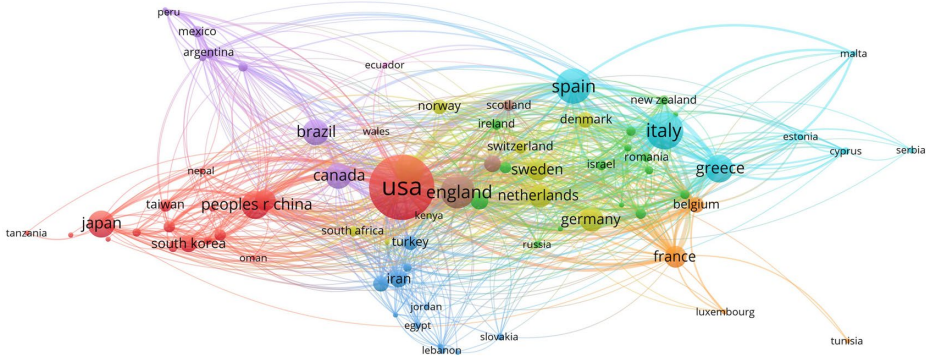

FIGURE 6
The co-author ship map of countries/regions.

TABLE 5 Top 10 highly cited documents.

Ranking	Title	Journal	Citation	Year
1	Expert committee recommendations regarding the prevention, assessment, and treatment of child and adolescent overweight and obesity: summary report	Pediatrics	3,119	2007
2	Youth risk behavior surveillance—United States, 2015	MMWR Surveillance Summaries	1,223	2016
3	Youth risk behavior surveillance—United States, 2013	Sports Medicine	1,143	2014
4	Central effects of stress hormones in health and disease: understanding the protective and damaging effects of stress and stress mediators	European Journal of Pharmacology	1,134	2008
5	Diabetic nephropathy: diagnosis, prevention, and treatment	Diabetes Care	1,111	2005
6	Dietary and policy priorities for cardiovascular disease, diabetes, and obesity a comprehensive review	Circulation	809	2016
7	Gender differences in food choice: the contribution of health beliefs and dieting	Annals of Behavioral Medicine	771	2004
8	Consumption of fish and n-3 fatty acids and risk of incident Alzheimer disease	Archives of Neurology	765	2003
9	The meter of metabolism	Cell	683	2008
10	Dietary intake and the development of the metabolic syndrome—the atherosclerosis risk in communities study	Circulation	609	2008

Author contributions

JW served as the first author and wrote the manuscript. QY contributed to the analysis and interpretation of the data and provided valuable insights during the manuscript writing process. NL and KN conducted the literature search and assisted in the drafting of the manuscript. XS provided valuable insights and expertise in data analysis, refining the research methodology. XS also played a crucial role in editing the manuscript to ensure clarity and coherence. LX as the corresponding author, reviewed and revised the manuscript and oversaw the overall process, providing guidance and coordination among the authors. 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.

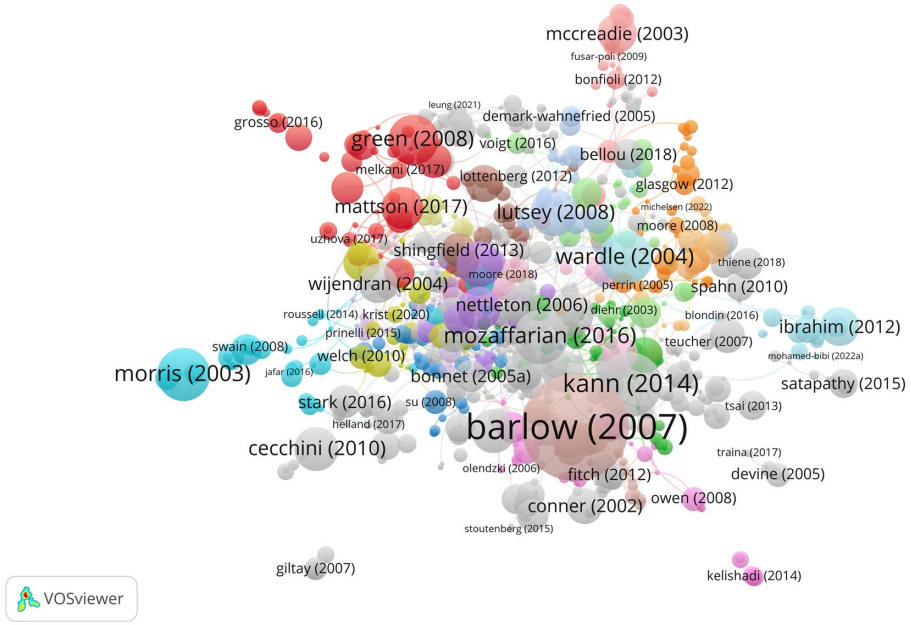

FIGURE 7
Visualization knowledge maps of highly cited documents.

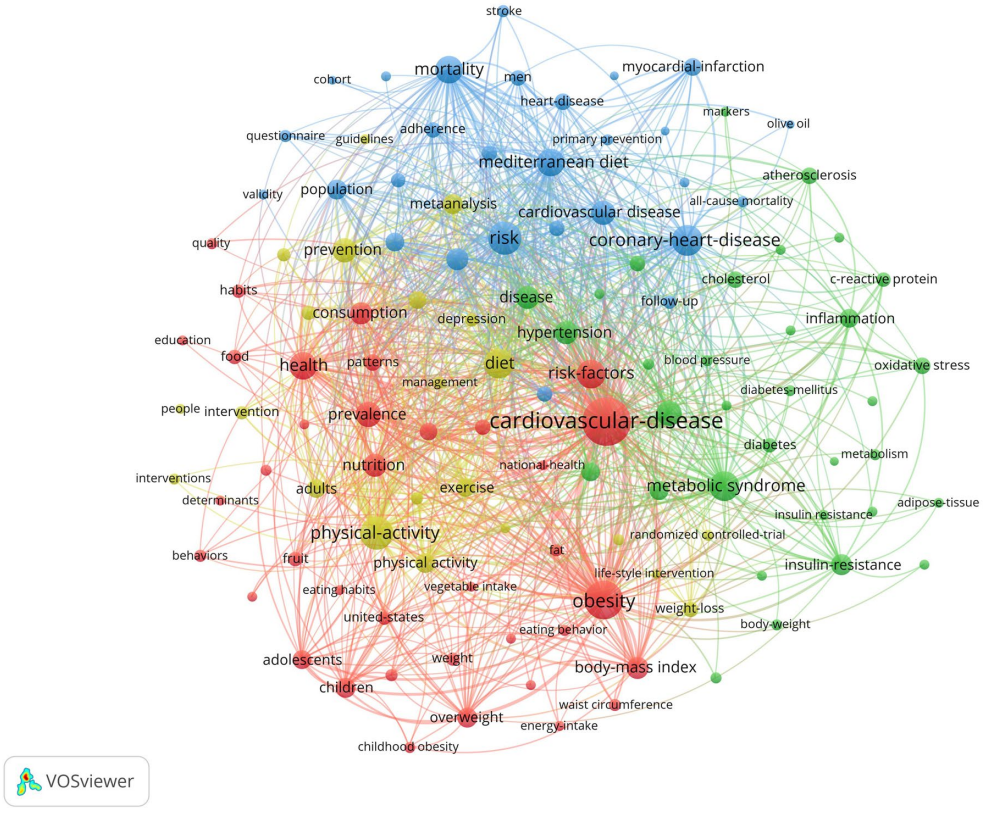

FIGURE 8
Visualization of co-occurrence analysis for keywords.

Publisher's note

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Risk assessment of dietary factors in global pattern of ischemic heart disease mortality and disability-adjusted life years over 30 years

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Objectives: The aim of this study was to investigate differences in the burden of ischemic heart disease (IHD)-related mortality and disability-adjusted life years (DALYs) caused by dietary factors, as well as the influencing factors with age, period, and cohort effects, in regions with different social-demographic status from 1990 to 2019.

Methods: We extracted data on IHD mortality, DALYs, and age-standardized rates (ASRs) related to dietary risks from 1990 to 2019 as IHD burden measures. Hierarchical age–period–cohort analysis was used to analyze age- and time-related trends and the interaction between different dietary factors on the risk of IHD mortality and DALYs.

Results: Globally, there were 9.2 million IHD deaths and 182 million DALYs in 2019. Both the ASRs of death and DALYs declined from 1990 to 2019 (percentage change: −30.8% and−28.6%, respectively), particularly in high and high-middle socio-demographic index (SDI) areas. Low-whole-grain, low-legume, and high-sodium diets were the three main dietary factors that increased the risk of IHD burden. Advanced age [RR (95%CI): 1.33 (1.27, 1.39)] and being male [1.11 (1.06, 1.16)] were independent risk factors for IHD mortality worldwide and in all SDI regions. After controlling for age effects, IHD risk showed a negative period effect overall. Poor diets were positively associated with increased risk of death but were not yet statistically significant. Interactions between dietary factors and advanced age were observed in all regions after adjusting for related variables. In people aged 55 and above, low intake of whole grains was associated with an increased risk of IHD death [1.28 (1.20, 1.36)]. DALY risks showed a similar but more obvious trend.

Conclusion: IHD burden remains high, with significant regional variations. The high IHD burden could be attributed to advanced age, sex (male), and dietary risk factors. Dietary habits in different SDI regions may have varying effects on the global burden of IHD. In areas with lower SDI, it is recommended to pay more attention to dietary problems, particularly in the elderly, and to consider how to improve dietary patterns in order to reduce modifiable risk factors.

KEYWORDS

ischemic heart disease, global burden, death, dietary, temporal trends

Introduction

Ischemic heart disease (IHD), which is the leading cause of death globally, also accounts for the highest loss of disability-adjusted life years (DALYs). Income inequality, demographic changes, environmental risks, and unhealthy lifestyles pose challenges to the prevention and control of IHD in different regions, and it is expected that IHD will continue to pose a significant health threat to populations and societies (1, 2).

Research has indicated that metabolic risk factors are the main drivers of cardiovascular and cerebrovascular diseases (3). Metabolic abnormalities, however, can be largely attributed to modifiable risk factors such as poor lifestyle behaviors and unhealthy dietary habits (4, 5). For example, a high-sugar diet can lead to the increase of human uric acid level, impaired glucose tolerance, and changes in platelet function, thereby increasing the risk of coronary heart disease (6). Dietary risks were the most important level 2 risk factor leading to the highest IHD mortality and DALY rates in the Global Burden of Disease study (GBD) estimation (7). Among the 15 dietary risk factors involved in the GBD study, 87% were related to IHD, confirming the close relationship between diet and IHD (8).

In recent years, the Mediterranean diet, which focuses on olive oil, vegetables, fruits, nuts, and seeds, has been praised as the most comprehensive dietary pattern and has swept the world (9). This pattern promotes healthy metabolism and helps prevent cardiovascular disease (CVD) (9–11). Nevertheless, the high burden of IHD in the population suggests that this general awareness of health behaviors may not be effective in changing those behaviors in different regions or that there are regional differences in the transition from knowledge to action (12). Therefore, the current status of diet-related disease burden of IHD in different areas and its pattern changes across generations need to be further studied. The purpose of this study was to explore the differences in burden trends of IHD mortality and DALYs caused by dietary factors in different regions from 1990 to 2019, as well as the influencing factors such as age, period, and cohort effects.

Materials and methods

Data source

We collected and used the attributable burden of IHD data from the GBD 2019 study, obtained through the Global Health Data Exchange (GHDx) query tool,[1] which is an ongoing global collaboration that uses all the latest available epidemiological data sources and improved standardized methodologies (13). GBD 2019 provides location, year, age, and sex estimates of 369 diseases and injuries and 87 risk factors in 204 countries and territories over the past 30 years (14). The input sources details and estimation methods used in GBD 2019 have been described elsewhere, and the data quality is globally recognized (1).

As a secondary study, we extracted estimates for deaths, DALYs, mortality, DALY rates, age-standardized death rates (ASDRs), age-standardized DALY rates, and their 95% uncertainty intervals (UIs) as primary measures of IHD burden. Data were collected from 1990 to 2019 by gender, selected dietary risk factors, and regions. ASRs were age-standardized using the GBD standard and reported per 100,000 population.

Definition of disease and regions

IHD was defined based on the WHO clinical criteria and the International Statistical Classification of Diseases (GBD cause code B.2.2; ICD-10 codes I20-I25.9; ICD-9 codes 410–414.9). The socio-demographic index (SDI) (15) is calculated based on lag distributed income *per capita*, average educational attainment over the age of 15, and total fertility rate under 25 in order to evaluate the social development level comprehensively. It is used to position countries on the development continuum and to categorize the countries into five regions (high, high-medium, medium, low-medium, and low levels). We used this indicator as the basis for regional grouping.

Identify risk factors

In GBD 2019, risks were organized into five hierarchical levels (7). Among the second-level risks in the GBD estimation system, the dietary factor was the leading cause of IHD deaths and DALYs. Therefore, we selected the top five dietary factors at the most detailed level 4—low whole grains (WG), low legumes, high sodium, high trans fatty acids (TFA), and low nuts and seeds (NS)—to generate attributable risk factors for IHD burden.

Outcome variables

According to the comparative risk assessment (CRA), assuming that exposure levels of other risk factors remain unchanged, the theoretical minimum risk exposure distributions of various dietary risks were compared with the exposure distributions of a specific population. Next, the population attributable fractions (PAF) of each dietary risk were estimated (7), that is, the proportion of the IHD burden due to different dietary factors in the total IHD burden in a certain population. Based on the definition of PAF and the exposure distribution and exposure risk estimates at different exposure levels, the IHD deaths and DALYs attributable to dietary factors in different populations were estimated as:

$$PAF = \frac{\sum_i^n p_i\left(RR_i - 1\right)}{\sum_i^n p_i\left(RR_i - 1\right) + 1}$$

where p_i is the percentage of the population exposed to level i of risks, n is the total number of exposure level, and RR_i is the relative risk at level i.

IHD deaths attributable to dietary factors were calculated by multiplying the PAFs and total disease-specific deaths. DALYs were calculated as the sum of years of life lost (YLL) and years lived with disability (YLD) (8). YLLs for IHD were calculated by subtracting the age at death from the life expectancy for a person of that age. YLDs

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

were determined by multiplying the prevalence of each sequela by its disability weight. For DALYs attributed to dietary factors, YLL and YLD for IHD were multiplied by the corresponding PAF for each dietary factor. This resulted in the calculated attributable YLL and YLD, which were then added together to obtain the total DALYs caused by a certain dietary factor for IHD. We therefore obtained the absolute number and ASRs of deaths and DALYs for IHD due to dietary risks globally and in different SDI regions.

Statistical analysis

Basic information

Descriptive analysis was used to characterize the burden of IHD worldwide and in various regions. The numbers of death cases, DALYs, and respective age-standardized rates (ASRs) in both genders combined over different years were compared. The trends in the ASRs reflect the alterations in disease patterns and risk factors. Additionally, the estimated annual percentage change (EAPC) was introduced to describe the ASR trend from 1990 to 2019.

Stratified association of risk with DALY and mortality

To measure the potential changes in IHD burdens associated with dietary factors in different SDI areas, we also described the mortality and DALYs of IHD stratified by different risk factors of age, period, and cohort. In the hierarchical age–period–cohort model (HAPC) framework, we analyzed the multivariate relationships between outcomes and three main sources for spatiotemporal variation: age, year, and cohort for each SDI region and globally. The patterns of IHD outcomes may be relevant to various socio-demographic and dietary risks and their ethnicity, using longitudinal panel evidence to indirectly assess the cohort effect. Since cohort effects can be calculated indirectly as a variation in time effects encountered by different age groups, we used the mixed-effects framework of hierarchical age–period–cohort to calculate the longitudinal panel data model (16).

Several mixed-effects models with fixed and random population-level effects and random slopes were used to explicitly assess differences in IHD mortality and DALYs among group levels over age (age effects) and time (period effects), in addition to, implicitly, the assessment period effect across populations of different age groups (cohort effects). Indeed, the mixed-effects model can make the three elements of age, period, and cohort effects nested so that they are no longer at the same level, which can solve the unrecognizable problem caused by collinearity problem in APC model (17, 18). In other words, the model can turn the period and cohort dimensions at the high-level into environmental variables and reflect their impact on the individual or population levels through the regression intercept and coefficient. Some individuals/population will be higher than the population mean (β_0) at baseline, and some will be smaller. Some will have greater slopes than the population mean of β_1, and some will be lower. This makes the model more flexible and versatile as it allows for heterogeneity of the baseline responses and responses over time. For IHD mortality analysis, the series of models were analyzed as follows:

$$DR_{it} = (\beta_0 + b_{0i}) + (\beta_1 + b_{1i}) Age_{it} + (\beta_2 + b_{2i}) Year_{it} + (\beta_3 + b_{3i}) Gender_i + (\beta_4 + b_{4i}) Risks_{it} \quad (1)$$

$$DR_{it} = (\beta_0 + b_{0i}) + (\beta_1 + b_{1i}) Age_{it} + (\beta_2 + b_{2i}) Year_{it} + (\beta_3 + b_{3i}) Gender_i + (\beta_4 + b_{4i}) Risks_{it} + (\beta_5 + b_{5i}) Age_{it} \times Risks_{it} + (\beta_6 + b_{6i}) Gender_i \times Risks_{it} + \varepsilon_{it} \quad (2)$$

$$DR_{it} = (\beta_0 + b_{0i}) + (\beta_1 + b_{1i}) Age_{it} + (\beta_2 + b_{2i}) Year_{it} + (\beta_3 + b_{3i}) Gender_i + (\beta_4 + b_{4i}) Risks_{it} + (\beta_5 + b_{5i}) Age_{it} \times Risks_{it} + (\beta_6 + b_{6i}) Gender_i \times Risks_{it} + (\beta_7 + b_{7i}) Year_{it} \times Risks_{it} + \varepsilon_{it} \quad (3)$$

$$DR_{it} = (\beta_0 + b_{0i}) + (\beta_1 + b_{1i}) Age_{it} + (\beta_2 + b_{2i}) Year_{it} + (\beta_3 + b_{3i}) Gender_i + (\beta_4 + b_{4i}) Risks_{it} + (\beta_5 + b_{5i}) Age_{it} \times Risks_{it} + (\beta_6 + b_{6i}) Gender_i \times Risks_{it} + (\beta_7 + b_{7i}) Year_{it} \times Risks_{it(\beta_8 + b_{8i})} Age_{it} \times Year_{it} + \varepsilon_{it} \quad (4)$$

where DR_{it} is the IHD mortality of population i at time t, $\beta_0,\ldots,\beta_k$ are the population mean intercept and slopes for related variables (fixed effects), b_{0i} is the difference between β_0 and the intercept of i (random effect), $b_{1i},\ldots, b_{ki}$, are the differences between $\beta_1,\ldots,\beta_k$ and the slopes of i (random effects), and ε_{it} is the random error within the population over time.

In the above series of models, the coefficient for age group can be interpreted as the overall age effect on IHD mortality after controlling for gender, year, and risk effects. The coefficient for year can be interpreted as the overall period effect after controlling for other variables. The coefficient of risks were the effects of different dietary risks on IHD mortality. The coefficients for age and risk interaction terms can be interpreted as differences in the experienced risk effect between different ages. The coefficients for gender and risk interaction terms can be interpreted as differences in the experienced risk effect between female (reference) and male people. The coefficients for the age and year interaction can be interpreted as differences in the experienced period effect across populations of varying ages (cohort effect). Overall, the exponential value of difference (coefficients) denoted the mortality/DALYs relative risk (RR) of a particular age group, period, and interactions terms relative to the reference groups. Similarly, DALYs were estimated using the same set of models. A likelihood ratio test was used to evaluate the existence of interaction effects. The degree of model fitting was evaluated by deviance, the Akaike information criterion (AIC), and Bayesian information criterion (BIC) to select the most appropriate model. After comparison, model 2 was finally selected to be included in the study.

Age, period, and cohort effects on IHD burden by major dietary risks

We additionally analyzed the age, period, and cohort effects on IHD burden (mortality and DALYs) attributable to the top three

TABLE 1 The death cases, DALYs, and related age-standardized rates (ASRs) of ischemic heart disease in 1990 and 2019 and its temporal trends from 1990 to 2019.

Types	1990		2019		1990–2019
	Cases [No.×10³ (95% UI)]	ASR per 100,000 [No. (95% UI)]	Cases [No.×10³ (95% UI)]	ASR per 100,000 [No. (95% UI)]	EAPC [No. (95% UI)]
Death					
Overall	5,695.89 (5,405.19, 5,895.40)	170.45 (159.61, 176.94)	9,137.79 (8,395.68, 9,743.55)	117.95 (107.83, 125.92)	−30.8 (−34.83, −27.17)
Sex					
Male	3,022.46 (2,895.63, 3,133.48)	205.24 (194.29, 213.05)	4,968.25 (4,591.34, 5,344.57)	144.6 (132.87, 154.96)	−29.55 (−34.72, −24.81)
Female	2,673.43 (2,478.70, 2,815.92)	141.73 (130.00, 149.72)	4,169.54 (3,680.48, 4,521.72)	95.07 (83.91, 103.11)	−32.92 (−37.96, −28.36)
SDI					
High SDI	1,688.79 (1,572.96, 1,744.99)	162.39 (150.62, 168.15)	1,447.27 (1,270.02, 1,553.84)	67.1 (60.07, 71.54)	−58.68 (−60.30, −56.69)
High-middle SDI	1,870.95 (1,782.68, 1,923.52)	209.2 (196.25, 216.23)	2,658.29 (2,411.87, 2,832.48)	135.41 (122.68, 144.44)	−35.28 (−39.01, −31.69)
Middle SDI	1,151.13 (1,087.98, 1,217.99)	143.11 (133.18, 152.13)	2,824.55 (2,576.47, 3,047.02)	134.12 (121.51, 145.22)	−6.28 (−14.41, 1.84)
Low-middle SDI	712.69 (654.08, 773.46)	144.21 (132.05, 156.58)	1,646.06 (1,488.07, 1,801.77)	136.59 (122.96, 149.50)	−5.28 (−15.25, 5.09)
Low SDI	269.14 (240.68, 301.92)	139.20 (124.00, 156.79)	556.60 (495.17, 627.06)	127.99 (113.13, 143.90)	−8.05 (−20.59, 3.17)
DALYs					
Overall	1,21,068.87 (1,16,357.40, 1,25,633.90)	3,143.28 (3,012.81, 3,257.17)	1,82,030.14 (1,70,206.78, 1,93,504.63)	2,243.54 (2,098.70, 2,385.01)	−28.62 (−24.16, −33.28)
Sex					
Male	72,227.38 (69,305.13, 75,003.87)	4,003.52 (3,840.47, 4,147.26)	1,10,683.66 (1,02,235.95, 1,18,954.62)	2,899.51 (2,681.07, 3,117.87)	−27.58 (−33.40, −21.84)
Female	48,841.50 (46,134.15, 51,457.89)	2,366.31 (2,222.27, 2,491.26)	71,346.48 (64,769.33, 77,093.70)	1,637.86 (1,486.52, 1,769.83)	−30.78 (−36.85, −25.39)
SDI					
High SDI	29,372.65 (28,133.32, 30,043.01)	2,833.48 (2,714.36, 2,898.17)	22,126.94 (20,524.86, 23,331.05)	1,188.04 (1,115.22, 1,246.49)	−58.07 (−59.46, −56.20)
High-middle SDI	37,654.49 (36,362.34, 38,712.49)	3,692.48 (3,539.46, 3,799.84)	46,960.74 (43,498.58, 49,829.05)	2,346.48 (2,172.97, 2,492.22)	−36.45 (−40.41, −32.47)
Middle SDI	28,068.28 (26,555.47, 29,665.87)	2,755.61 (2,603.65, 2,909.61)	59,649.47 (54,813.58, 64,435.73)	2,476.04 (2,273.77, 2,675.65)	−10.15 (−18.26, −2.17)
Low-middle SDI	18,861.31 (17,327.36, 20,460.10)	3,040.68 (2,796.16, 3,299.79)	39,251.98 (35,477.77, 43,178.51)	2,831.95 (2,564.04, 3,104.29)	−6.86 (−17.50, 4.31)
Low SDI	7,044.40 (6,312.59, 7,911.42)	2,908.58 (2,609.96, 3,254.17)	13,935.07 (12,423.47, 15,691.65)	2,606.43 (2,330.38, 2, 923.57)	−10.39 (−22.27, 1.36)

DALYs, disability-adjusted life years; ASR, age-standardized rate; UI, uncertain interval; EAPC, estimated annual percentage change; SDI, socio-demographic index.

dietary risks of diet low in whole grains, diet low in legumes, and diet high in sodium in different SDI regions by using an APC model based on intrinsic estimation (IE) algorithm (19):

$$Y = \log(M) = \mu + \alpha Age_i + \beta Period_j + \gamma Cohort_k + \varepsilon_{it}$$

where M is defined as the mortality rates and DALYs. α, β, and γ refer to the coefficients of three dimensions, and μ and ε are defined as the intercept and random error. The standard error (SE) coefficient and risk ratios were calculated. The above statistical description and analyses were all performed using the R program (Version 4.1.2, R core team). Results with $p < 0.05$ were considered statistically significant.

Results

Overall trend in mortality and DALYs of ischemic heart disease

Globally, the number of death cases of IHD has increased by 60.43% from 5.70 million in 1990 to 9.14 million in 2019, and the number of DALYs increased by 50.35% from 121.07 million to 182.03 million (Table 1). The overall ASRs of death decreased in the same period (EAPC = −30.8% [95% UI: −34.83 to −27.17]) from 170.45 to 117.95 per 100,000 persons. In terms of SDI regions, the number of deaths and DALYs increased in all subregions except for high-SDI regions. In contrast, the ASDRs in all regions decreased, but the corresponding decrease was only significant in high- and high-middle-SDI areas. The variation trend of DALYs during this period was similar to that of ASDRs, and the decrease was not obvious in low- and low-middle-SDI regions.

IHD mortality and DALYs attributable to dietary factors

As shown in Supplementary Figure S1, the ASDR attributable to high diet in TFA was highest in 1990 in high-SDI regions, but it declined the most, reaching the lowest point by 2019. Apart from high TFA intake, IHD mortality from all other four dietary factors was highest in high-middle-SDI regions in 1990 and remained high in 2019, despite a decline over 30 years. In addition, deaths attributed to five dietary factors in high-SDI regions all fell to their lowest levels in 2019.

The trends of IHD mortality caused by diets with low levels of legumes and whole grains were similar in all regions, being highest in 2019 in high-middle-SDI regions, as noted above. By 2019, IHD mortality attributable to high-sodium levels was higher in middle-SDI regions than in others. The attributable mortality of the diet high in TFA and low in nuts and seeds was at the highest level in low-middle-SDI regions in 2019. The attributed DALYs showed a similar trend (Figure 1), but the fluctuations were more obvious than that of mortality. DALY caused by low whole-grains intake was highest in areas with low SDI. This suggests that different dietary habits in different SDI regions may affect the burden of IHD populations worldwide to varying degrees.

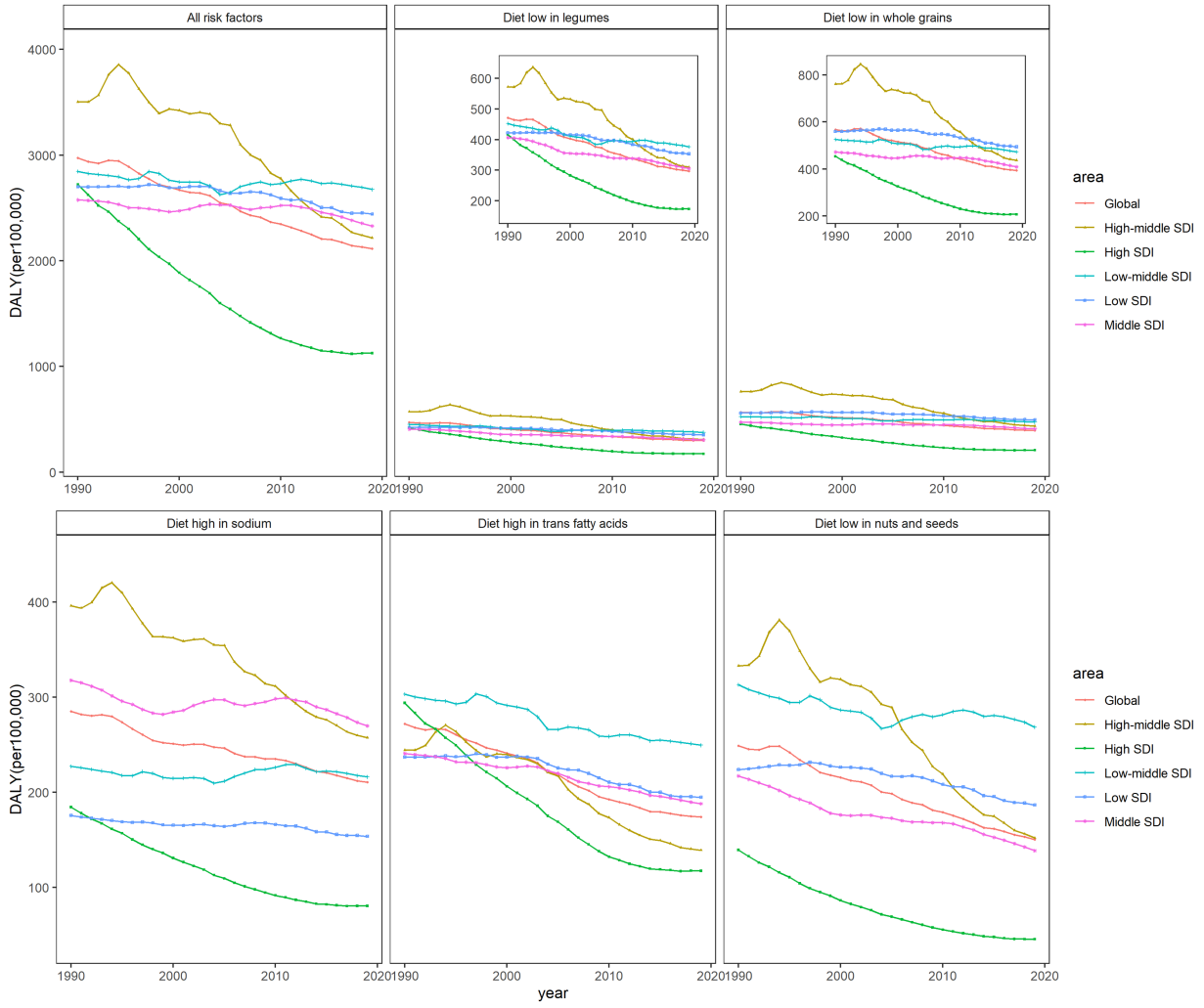

FIGURE 1
The age-standardized rates of DALYs attributable to dietary factors from 1990 to 2019 in world SDI regions and globally, both sexes.

Age-, period-, and cohort-related trends and interaction with dietary risks

In terms of age, period, and their risk interaction effects, we observed a significant increase in the risk of death among age groups of 55 years and older compared with the younger populations, both globally and in all SDI regions, assuming the impact of other variables remained unchanged (Table 2). The area with the highest age-related risk of death was the high-middle-SDI region (RR = 1.50, 95%CI: 1.41, 1.60), followed by the middle-SDI region [RR (95%CI): 1.37 (1.33, 1.42)]. The risk of death in male people was higher than that of female people in all regions, and the RR (95%CI) in the high-middle-SDI area was the highest [1.18 (1.11, 1.26)].

After controlling for age effects, there was a negative period effect on IHD mortality from 1990 to 2019. In high-SDI areas, the risk of death declined significantly over time, with a 12% reduction in 2019 compared with 1990. These correlation effects were not statistically significant in the middle- or lower-SDI regions. Globally, diet-related risks were positively associated with the increased risk of death, but the difference was not statistically significant. A significant interaction between risk and age was observed in the global population aged 55 and older, and it was associated with low intake of legumes and whole grains. The risk of death from IHD was increased in people aged 55 years and older who consumed low levels of whole grains (RR = 1.28, 95%CI: 1.20, 1.36). Low level of whole grains increased the risk of death from IHD among people aged 55 and above (RR = 1.28, 95% CI: 1.20, 1.36). As shown in Supplementary Table S1, a similar but more pronounced trend can be found in the risk analysis of DALYs.

Comparison of estimated APC effects by SDI regions in major dietary factors

We further separately analyzed the age, period, and cohort effects of the three major dietary factors (diet low in whole grains, diet low in legumes, and diet high in sodium) in different SDI regions (Supplementary Tables S2–S7). The age, period, and cohort effects on DALYs and mortality attributed to three dietary factors were globally similar, with slightly different separation trends for different SDI

TABLE 2 Mixed-effect model estimates (RR, 95% CIs) predicting ischemic heart disease (IHD) death risk, globally, and by SDI region separately.

Value	Global	High SDI	High-middle SDI	Middle SDI	Low-middle SDI	Low SDI
Age group (year)						
10–54	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
≥55	1.33 (1.27, 1.39)	1.20 (1.13, 1.27)	1.50 (1.41, 1.60)	1.37 (1.33, 1.42)	1.25 (1.20, 1.29)	1.20 (1.17, 1.24)
Sex						
Female	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Male	1.11 (1.06, 1.16)	1.07 (1.01, 1.14)	1.18 (1.11, 1.26)	1.12 (1.08, 1.16)	1.08 (1.04, 1.12)	1.05 (1.02, 1.08)
Year						
1990	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
1999	0.98 (0.95, 1.00)	0.95 (0.91, 0.99)	0.98 (0.95,1.02)	0.99 (0.97, 1.01)	0.99 (0.97, 1.01)	1.00 (0.98, 1.02)
2009	0.95 (0.92, 0.98)	0.90 (0.86, 0.93)	0.94 (0.90, 0.97)	0.99 (0.97, 1.01)	0.99 (0.97, 1.01)	0.99 (0.97, 1.01)
2019	0.93 (0.91, 0.96)	0.88 (0.85, 0.92)	0.90 (0.86, 0.93)	0.98 (0.96, 1.00)	0.99 (0.96, 1.01)	0.98 (0.96, 1.00)
Risks						
Diet high in sodium	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Diet high in TFA	1.03 (0.98, 1.09)	1.01 (0.94, 1.09)	1.07 (0.99, 1.15)	1.04 (1.00, 1.08)	1.01 (0.97, 1.06)	1.01 (0.97, 1.05)
Diet low in legumes	1.02 (0.97, 1.08)	1.01 (0.93, 1.08)	1.05 (0.97, 1.14)	1.03 (0.99, 1.07)	1.01 (0.96, 1.05)	0.99 (0.96, 1.03)
Diet low in nuts and seeds	1.03 (0.98, 1.09)	1.02 (0.95, 1.10)	1.06 (0.98, 1.15)	1.04 (1.00, 1.08)	1.01 (0.97, 1.06)	1.01 (0.97, 1.05)
Diet low in whole grains	1.02 (0.96, 1.07)	1.00 (0.93, 1.08)	1.04 (0.96, 1.12)	1.02 (0.98, 1.06)	1.00 (0.95, 1.04)	0.98 (0.95, 1.02)
Risk age interaction						
≥55 × Diet high in TFA	0.96 (0.90, 1.02)	1.09 (1.00, 1.19)	0.84 (0.77, 0.92)	0.90 (0.86, 0.95)	1.03 (0.98, 1.08)	1.02 (0.98, 1.07)
≥55 × Diet low in legumes	1.15 (1.08, 1.22)	1.23 (1.13, 1.34)	1.15 (1.06, 1.26)	1.04 (0.99, 1.09)	1.16 (1.10, 1.21)	1.20 (1.15, 1.25)
≥55 × Diet low in nuts and seeds	0.93 (0.87, 0.99)	0.95 (0.87, 1.04)	0.91 (0.83, 0.99)	0.87 (0.83, 0.91)	1.03 (0.98, 1.08)	1.00 (0.95, 1.04)
≥55 × Diet low in whole grains	1.28 (1.20, 1.36)	1.28 (1.17, 1.40)	1.41 (1.29, 1.54)	1.14 (1.08, 1.19)	1.26 (1.20, 1.32)	1.37 (1.31, 1.43)
Risk sex interaction						
Male×Diet high in TFA	0.94 (0.88, 1.00)	0.98 (0.90, 1.07)	0.87 (0.80, 0.96)	0.93 (0.88, 0.97)	0.98 (0.93, 1.03)	0.99 (0.95, 1.04)
Male×Diet low in legumes	0.97 (0.91, 1.03)	1.01 (0.92, 1.10)	0.92 (0.84, 1.00)	0.96 (0.91, 1.00)	1.01 (0.96, 1.06)	1.03 (0.99, 1.08)
Male×Diet low in nuts and seeds	0.93 (0.88, 0.99)	0.96 (0.88, 1.05)	0.88 (0.81, 0.96)	0.92 (0.88, 0.97)	0.99 (0.94, 1.04)	0.99 (0.95, 1.04)
Male×Diet low in whole grains	0.99 (0.93, 1.05)	1.02 (0.94, 1.12)	0.95 (0.87, 1.04)	0.98 (0.93, 1.02)	1.03 (0.99, 1.09)	1.06 (1.01, 1.11)
AIC	450.01	494.23	497.17	418.60	422.36	409.01
BIC	497.66	541.87	544.81	466.24	470.00	456.65

SDI, Socio-demographic index; TFA, trans fatty acids; AIC, Akaike information criterion; BIC, Bayesian information criterion; CI, confidence intervals; RR, relative risk.

regions and dietary factors, and relatively larger fluctuations in DALYs can be seen (Figure 2). As shown in Figure 3, DALYs caused by low levels of whole-grains intake increased with age, while the period effect did not change significantly, and the cohort effect showed an overall downward trend.

The risk of DALYs attributable to diet with low whole-grains intake increased significantly with age in both men (Figure 3A) and women (Figure 3B). For male people, the risk of attributable DALYs with age slowed down from 55 to 75 years old and then increased again. In female people, however, age-related DALY risk has been increasing almost linearly compared with that of male people. The risk of DALY in high- and high-middle-SDI areas decreased slightly over the years, but in middle-SDI areas and below, the DALY risk increased slightly since 2009. The period effect trends were not significant in both genders. Specifically, in middle-SDI regions, men in 2019 had the highest DALY risk attributable to low levels of whole-grains intake, with the RR and 95% CI of 1.13 (1.09, 1.18), an increase of 34% compared with 1994 (Supplementary Table S5). For cohort effects, the trend decreased linearly with birth year in almost all SDI regions and reached the lowest point in the 1994–1998 birth cohort. For DALYs caused by low whole-grains intake, the RRs of cohort effects continuously decreased globally from 2.00 (1.90, 2.10) in the 1904–1908 cohort to 0.62 (0.47, 0.82) in the 1989–1993 cohort for male people and from 2.38 (2.19, 2.58) to 0.49 (0.30, 0.80) for female people (Supplementary Table S5). As for the diet low in legumes, the effect was similar to that for the diet low in whole grains (Supplementary Table S6).

Discussion

In this GBD-based study, we revealed patterns and the latest overall trends in mortality, DALYs, associated socio-economic levels, and dietary risk factors related to the occurrence and progression of

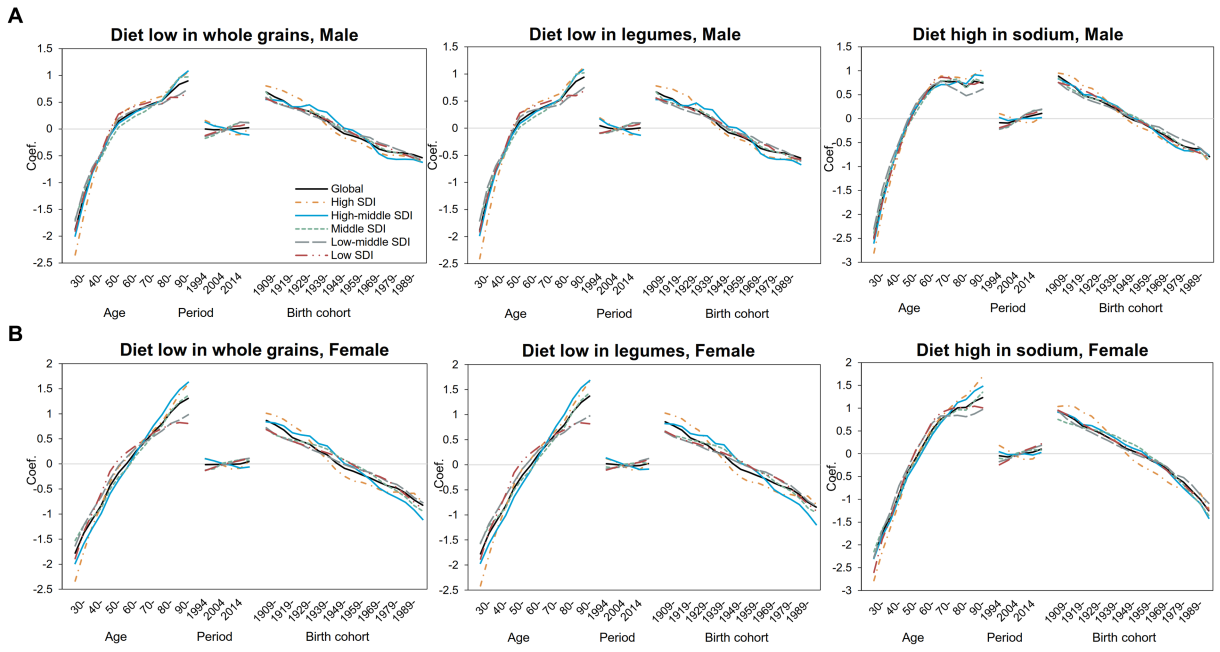

FIGURE 2
Age–period–cohort-related trends in IHD DALYs from 1990 to 2019 globally and SDI quintiles attributable to most common dietary risks stratified by sex **(A)** Male **(B)** Female.

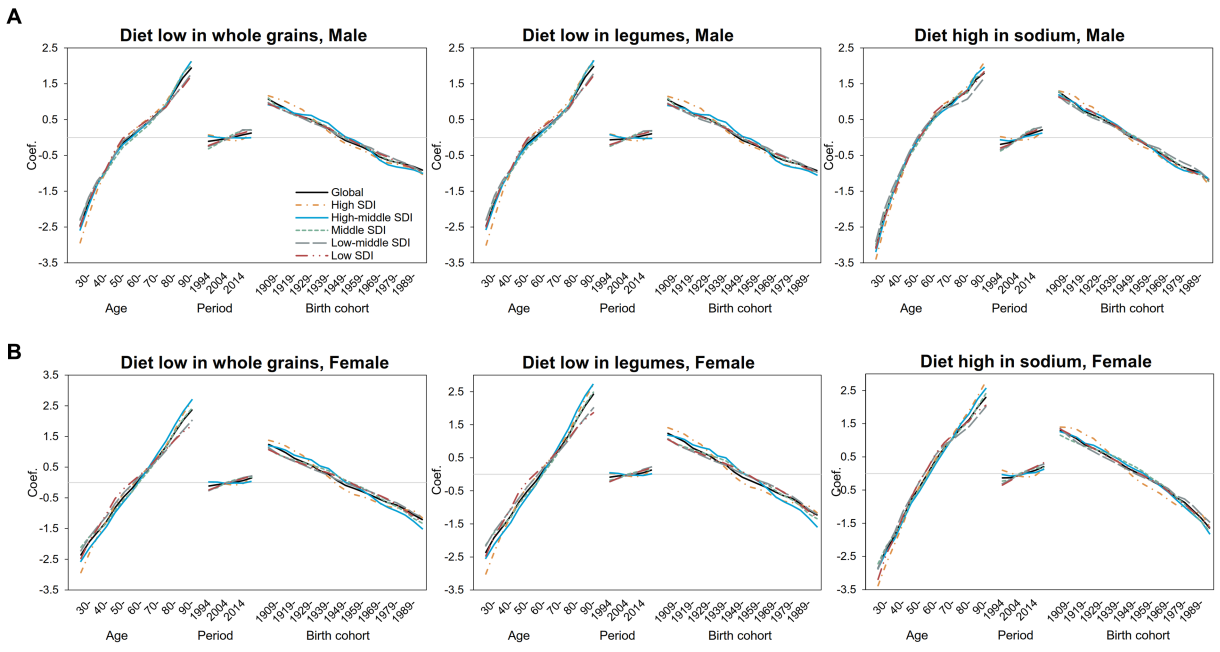

FIGURE 3
Age–period–cohort-related trends in IHD mortality from 1990 to 2019 globally and SDI quintiles attributable to most common dietary risks stratified by sex **(A)** Male **(B)** Female.

IHD worldwide. We found that although ASRs of IHD death and DALYs decreased from 1990 to 2019, the absolute number increased by more than half, indicating that IHD still caused a high social burden. Therefore, not only ASR indicators but also the absolute values are equally important for policymakers and health planners when measuring the effectiveness of IHD prevention and treatment in different regions over time.

From a regional perspective, among all SDI regions, the absolute value of IHD burden decreased only in high-SDI areas, which also had the greatest reduction in ASRs. Compared with high-SDI countries,

the burden of IHD remains high in middle- and low-SDI regions (20). More than 80% of deaths occurred in low-income and lower-middle-income countries (LLMICs) (21, 22), where universal health coverage or access to healthcare services is often limited, resulting in huge economic loss (23). Epidemic and burden trends of IHD vary significantly among countries and regions due to the differences in socioeconomic development level, dietary behavior, and living habits (24, 25). That is, due to the aging of the population, the differences in regional economic development, and the risks faced, the low- and middle-SDI regions will bear an increasing burden. The burden caused by IHD has adverse economic consequences at multiple levels for individuals, families, governments, and society as a whole. Furthermore, not only targeted, effective prevention and treatment strategies are needed, but it must also be judged whether the existing prevention strategies are effective. Therefore, we conducted an in-depth analysis of various factors and found that age, gender, time, and dietary risks were potential causes of increased IHD mortality and DALYs.

Age effects

The adverse outcome of vascular-related diseases was related to age and gender. The global increase in crude death rate and the decrease in ASDR of IHD since 1990 can be attributed to the change of population structure, especially the aging of the social population, and it may also be related to the advancements of global healthcare. According to the World Population Prospects, the proportion of the global population aged 65 and over is expected to rise from 10 to 16% from 2022 to 2050 (26).

Consistent with previous studies, when other variables remained unchanged, the risk of IHD burden among people aged 55 and above was significantly increased compared to the younger population, both globally and in each SDI region (8). According to the APC analysis, the risk of IHD burden increased with age, that is, the oldest age group had the highest risk of death and DALYs. In terms of regional differences, the most significant age effect was concentrated in high-middle-SDI regions, which also indicates a significant gap between developed and developing countries in early death intervention (3).

Although both genders suffer from similar IHD-related risks, the risk of adverse outcomes was higher in men than in women. In contrast to women, the risk of IHD burden continued to increase with age, while the trend slowed down for men in the middle-aged group, especially for DALY risks, with more significant differences. This may be related to the decrease of estrogen level in elderly women after menopause and the disappearance of the protective effect of estrogen on the heart (27). In addition to biological factors, gender differences can also be explained from the perspective of differences in many behavioral risk factors (3, 28). The risk of IHD morbidity and adverse outcomes increased in both genders after the age of 55.

Period effects

With the rapid development of the social economy, environmental changes, and the improvement of living conditions, it can be assumed that the risk of adverse outcomes of IHD should be reduced (29). In the mixed-effect model, it can be seen that IHD mortality and DALY rates decreased with years, which is consistent with this assumption. However, after controlling for age and birth cohort effects, the overall period effect showed a slight upward trend in the risk of death and DALYs. Considering regional differences in development rates, further differentiation of the subsamples from different SDI regions revealed that the risk of IHD burden decreased in both high- and high-middle-SDI areas. This suggests that in high-income North America, Australia, Europe, and other areas with high social and economic development levels, transient external environmental changes—such as the improvement of screening technology, which facilitates the early detection and treatment of IHD patients and thus the improvement of disease diagnosis and treatment that can reduce the risk of death from IHD—may have beneficial effects on the progression of disease and the occurrence of adverse outcomes. In addition, factors such as the increase in life expectancy *per capita* may also prove beneficial.

Correspondingly, in low-income Africa and other regions with low- or middle-SDI levels, the period effect increased the risk of IHD mortality and DALY, partly reflecting the insufficient screening, diagnosis, and treatment of IHD in these regions (30). Moreover, the expected reduction in period effects may also be influenced by environmental deterioration and strong cohort effects. On the other hand, the overall fluctuation range of the period effect value is relatively small, and there are not too many groups, which may increase the instability of the results. Of course, the overall fluctuation range of the period effect value is small, and the period grouping is small, which may increase the data instability. Therefore, this interpretation can only be used as a relevant reference.

Cohort effects

The cohort effect was more obvious compared with the period effect, and the overall risk was gradually reduced in different regions. Disease burden was high in birth cohorts before 1949. The earliest birth cohort (1904–1908) had the highest risk coefficient, which also reflected that the quality of the latest birth cohort was relatively high regardless of the regional economic development level. However, it should also be noted that the cohort effects for people in high-SDI regions with higher levels of economic development decreased at a relatively earlier stage than that of people in lower-SDI areas, suggesting a negative correlation between social development and risk outcomes.

Those born in the early years experienced more social unrest, such as the Russo-Japanese War in 1904, World War I in 1914, the October Revolution in Russia in 1917, and the May Fourth Movement in China in 1919. By the early 1950s, capitalist economic development in the West ushered in a golden age. The United Nations was established in 1945, many African countries became independent in 1960, the European Union was formed in 1993, and so on. Such social stability and sustainable development have greatly improved the quality of the birth population and reduced the risk of adverse disease outcomes.

Diet-related risk factors

The most effective strategy for reducing the burden of IHD is early prevention targeting the risk factors. In the early stages of IHD, prevention measures targeting various risk factors should be carried out at the population level. IHD risk factors include metabolic,

behavioral, and environmental factors. Studies have suggested that IHD-related mortality in recent years is largely attributed to metabolic risk factors, such as high systolic blood pressure (SBP) and high low-density lipoprotein (LDL) cholesterol (3, 31). Our previous study also reached this conclusion (8). In addition, we observed 23 level 3 risk factors for IHD, indicating that high SBP, high LDL cholesterol, and a diet low in nuts and seeds are the top three risk factors. The trend of IHD burden attributed to risk factors in recent years suggests that intervention and management of risk factors are effective. Although metabolic risk factors have been emphasized in many studies, considering that dietary behavior is modifiable and universally applicable, dietary risks should not be ignored.

Balanced diet is a well-known consensus, but poor dietary habits still affect disease burden and its changing trends in IHD patients (32). Dietary control is of universal importance in all regions, but prevention policies should be tailored to priorities and local dietary habits. The majority of level 2 risk factors related to IHD DALYs were accounted for by dietary risks among behavioral risk factors, suggesting a need for concerted efforts to address dietary risks in order to effectively reduce the burden of IHD globally. The first step is to understand the differences of dietary attribution burden in different regions. Different from the traditional tertiary prevention, the Blue Book on the prevention and treatment of cardiovascular diseases in China focuses on "balanced diet, reasonable exercise, smoking cessation, healthy psychology, healthy sleep and healthy environment" as its zero-level prevention in view of the pressure of disease prevention and control. Similarly, not only in China, but in many developing regions, the situation of early prevention is not optimistic.

Almost all countries recommend adequate intake of foods such as vegetables, fruits, beans, and legumes in their dietary guidelines. IHD burden attributable to poor dietary habits of low whole grains, low legumes, and low nuts and seeds has shown similar trends over the past 30 years. In high-SDI regions such as high-income North America, this burden declined to the lowest point by 2019. Previous studies demonstrated that whole grains, such as oats and wheat, improved CVD to some extent (30). People with type 2 diabetes will experience health benefits if they consume more than 60 g of whole grains per day (33). In the early stage, most developed countries with high- and high-middle-SDI were based on animal food, which can also be called excessive nutritional diet structure, to provide high energy, high fat, and high protein, but this contained low dietary fiber content, leading to higher risk of CVD. However, since the late 1960s, the CVD mortality in Western developed countries has shown a significant downward trend, which is attributed to the improvement of health concepts and primary prevention measures, that is, the effective control of risk factors. For example, Finland, a country with high SDI, was once the country with the highest CVD incidence in the MONICA Project report (34). Since 1972, Finland has implemented the North Karelia Project with a series of policy-led community participation projects including increasing the availability of low-fat foods, effectively improving the lifestyle and diet structure of its residents and reducing their IHD mortality rate. Lee S. et al. (35) reported that the structure and quality of IHD-related diets among adults in the US had improved during the 20 years since 1980, and the intake of whole grains, fruits, and vegetables increased.

In contrast, in low- and low-middle-SDI regions such as South Asia, the attributable burden caused by insufficient intake of legumes and nuts/seeds has had no significant difference over the years. Studies have shown that CVD has become a major and growing cause of death and disability in Southeast Asia, and CVD has become one of the top ten causes of death in countries such as Bangladesh (36–38). The 2018 Astana Declaration highlighted the important role of primary care in strengthening health systems, and the WHO also provided cost-effective interventions. In middle-SDI countries such as Brazil, increased investment in national primary care since the early 1990s has somewhat reduced the risk of death from IHD (39, 40). However, in many low- and middle-income countries such as Bangladesh, investment in primary healthcare is still lacking (40, 41), accompanied by unhealthy dietary patterns (22), which has not achieved ideal results.

This study has certain limitations. Firstly, the data in our study came from the GBD dataset, and thus all limitations of the GBD methodology were also applicable to this study. In some countries, IHD-related data sources were not available, and their results were derived only from the GBD modeling process. However, these regions also tend to have relatively high disease burden, which may hinder the estimation of actual local IHD burden and may have further affected our findings. Our secondary analysis of regional differences based on SDI indicators can reduce this deficiency to some extent. Secondly, we only focused on the IHD burden attributable to diet-related risk factors and did not examine other risk factors. Since the attributable risks of IHD were assumed to be independent, this may inflate our estimated PAF values. On the other hand, it makes it feasible for us to analyze dietary factors separately. Although dietary factors are not the most important risk factors for IHD, considering that dietary behavior is modifiable and universally applicable, it is meaningful to explore dietary risk factors alone on the basis of such a large number of bases. Thirdly, we did not estimate results for units smaller than the country, nor did we conduct a more detailed analysis of the different subtypes of IHD disease.

Conclusion

In summary, our study systematically delineated the burden of IHD from 1990 to 2019. Diet-related attributable burden suggested that effective control of these selected risk factors is required for effective IHD management. In addition, the results of different regions show that the national conditions and development realities of different countries should be combined. Therefore, the regional classification used in the GBD study can also be used as the regional classification for IHD prevention. Developing countries with heavy IHD burden can learn from the experience of relatively more developed countries in the same region to address what has been described as "our generation's social justice issue," to further promote health equity and social justice, so as to formulate more effective and targeted cardiovascular protection and treatment strategies, effectively implement effective health education and health promotion, and reduce the risk caused by controllable adverse behaviors.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found at: http://ghdx.healthdata.org/gbd-results-tool.

Ethics statement

The list of all data sources used in GBD 2019 is publicly available at the Global Health Data Exchange website (http://ghdx.healthdata.org/gbd-results-tool); therefore, ethical proof is not applicable to this study.

Author contributions

FW, CY, and YZ: conceptualization and methodology. FW and SM: software and visualization. FW: writing—original draft preparation. FW, SM, YZ, WS, and CY: writing—review and editing. All authors have read and agreed to publish 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

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Population food intake clusters and cardiovascular disease incidence: a Bayesian quantifying of a prospective population-based cohort study in a low and middle-income country

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Aims: This study was designed to explore the relationship between cardiovascular disease incidence and population clusters, which were established based on daily food intake.

Methods: The current study examined 5,396 Iranian adults (2,627 males and 2,769 females) aged 35 years and older, who participated in a 10-year longitudinal population-based study that began in 2001. The frequency of food group consumption over the preceding year (daily, weekly, or monthly) was assessed using a 49-item qualitative food frequency questionnaire (FFQ) administered *via* a face-to-face interview conducted by an expert dietitian. Participants were clustered based on their dietary intake by applying the semi-parametric Bayesian approach of the Dirichlet Process. In this approach, individuals with the same multivariate distribution based on dietary intake were assigned to the same cluster. The association between the extracted population clusters and the incidence of cardiovascular diseases was examined using Cox proportional hazard models.

Results: In the 10-year follow-up, 741 participants (401 men and 340 women) were diagnosed with cardiovascular diseases. Individuals were categorized into three primary dietary clusters: healthy, unhealthy, and mixed. After adjusting for potential confounders, subjects in the unhealthy cluster exhibited a higher risk for cardiovascular diseases [Hazard Ratio (HR): 2.059; 95% CI: 1.013, 4.184] compared to those in the healthy cluster. In the unadjusted model, individuals in the mixed cluster demonstrated a higher risk for cardiovascular disease than those in the healthy cluster (HR: 1.515; 95% CI: 1.097, 2.092). However, this association was attenuated after adjusting for potential confounders (HR: 1.145; 95% CI: 0.769, 1.706).

Conclusion: The results have shown that individuals within an unhealthy cluster have a risk that is twice as high for the incidence of cardiovascular diseases. However, these associations need to be confirmed through further prospective investigations.

KEYWORDS

Bayesian cluster analysis, cardiovascular diseases, food intake patterns, dietary pattem, heart health

Introduction

Non-communicable diseases (NCDs) are the leading cause of death worldwide, accounting for 63% of all deaths. Traditionally, NCDs have been perceived as a burden predominantly on developed countries. However, recent evidence suggests a reverse trend and a dramatic increase in NCDs in low- and middle-income countries (LMICs) (1). NCDs primarily include chronic respiratory diseases, cancers, diabetes, and cardiovascular diseases (CVDs), which are the most frequent causes of mortality in most Western Pacific, South-East Asian, European, Eastern Mediterranean, and American countries (2).

Risk factors for NCDs such as harmful alcohol consumption, a sedentary lifestyle, tobacco use, and an unhealthy diet—characterized by high consumption of foods rich in sugar, salt, trans and saturated fats—can increase the risk of complications in individuals with NCDs (3). Among these established risk factors, diet plays a pivotal role, particularly concerning CVDs. Over the past few decades, numerous studies have improved our understanding of the correlation between diet and cardiovascular health (4, 5). The focus of these studies has shifted from investigating individual nutrients and foods to evaluating dietary patterns, reflecting the synergistic and combined effects of various foods and beverages (6). Dietary pattern analysis considers the cumulative effects of the overall diet and the complex interactions between foods and nutrients (7).

A traditional approach to dietary pattern analysis is factor analysis, which empirically derives dietary patterns by reducing the dimensionality of dietary data. In factor analysis, the covariance matrix of food intakes is used to generate linear combinations (factors), and participants are assigned a score based on these derived factors (8). However, since each participant may belong to more than one factor, interpreting these scores can be challenging (9, 10). Another approach is cluster analysis, which, unlike factor analysis, classifies participants into mutually exclusive, non-overlapping clusters based on the similarity of their dietary intake. This means members of each cluster have similar dietary intakes and are different from members of other clusters (9). Cluster analysis has advantages over factor analysis as it can classify individuals into distinct groups, enabling the comparison of nutritional differences among people in different groups and determining whether there is a relationship between dietary pattern subgroups and health outcomes (11).

The majority of current literature exploring the link between dietary patterns and the risk of CVDs employs factor analysis and suggests an inverse relationship between healthy eating patterns and the incidence of CVDs (12–15). However, less evidence is available regarding the use of cluster analysis to examine the relationship between diet and the risk of CVDs (16–18). In addition to the conflicting findings of previous studies, most of them have primarily focused on high-income and industrialized nations (19).

In recent decades, Iran has experienced significant changes in various social and economic aspects (20). As a middle-income country, Iran's economic growth has been subject to fluctuations, influenced by international sanctions, global oil prices, trade policies, domestic economic policies, and geopolitical tension. These economic changes have prompted many Iranians to modify their dietary patterns due to the need for lower-cost options. Social changes have also significantly influenced this transition. The nutritional transition in Iran has led to a shift toward Western dietary patterns (21).

Given the significant burden of cardiovascular diseases in Iran and the importance of identifying their underlying causes, this cohort study aimed to identify major dietary clusters among the general adult population of Iran using Bayesian cluster analysis. Moreover, the study sought to explore the relationship between these dietary clusters and the incidence of CVDs.

Method

Study participants and setting

The present study involved 5,396 individuals who participated in the Isfahan Cohort Study (ICS). The ICS is a population-based, longitudinal study that includes participants who were at least 35 years old at baseline and resided in urban or rural areas of three central counties of Iran, namely Isfahan, Arak, and Najaf-Abad (22). These cities exhibit similar general population characteristics and geographic variables. These participants had previously engaged in the Isfahan Healthy Heart Program (IHHP) baseline survey, which is a community trial for CVD prevention and control (22). The ICS study was executed by the World Health Organization (WHO) collaborating center, the Ethical Committee of the Isfahan Cardiovascular Research Center (ICRC). The primary aim of the ICS study was to determine the individual and combined impacts of different risk factors on the incidence of CVD events, including fatal and nonfatal coronary artery diseases and stroke. Participants have been monitored since 2003, with follow-ups conducted *via* phone calls for cardiovascular events every 2 years and risk factor interviews every 5 years (22). The selection of participants was facilitated

through a multistage cluster random sampling method based on the distributions of sex, age, and residential areas (urban/ rural). A detailed protocol for the study has been previously described (22). The study included those who had lived for at least 6 months in Isfahan, Arak, or Najaf-Abad, had Iranian nationality and were mentally competent. Exclusions from the ICS baseline survey were made for participants with a history of myocardial infarction (MI), stroke, heart failure, or pregnancy. After 2001, participants were followed up through biennial phone interviews until 2013 to record cardiovascular outcomes. The phone interviews included inquiries about the participant's survival, cause of death (if applicable), cardiovascular events, cerebrovascular events, neurological symptoms, and hospitalizations. If any outcomes of interest occurred, participants were asked for further information. This included reviewing relevant health records and questionnaires, and in the case of non-hospital deaths, examining death certificates from the death database, and conducting a verbal autopsy. A team of cardiologists and neurologists made the final decision about cardiovascular and cerebrovascular accidents based on all the collected information for each patient. The loss to follow-up rate was 404 (6.4%), 249 (3.9%), and 191 (2.9%) for the second to third follow-ups, respectively. Despite this, a preliminary study of the individuals lost to follow-up, compared with a random sample of the remaining population, revealed no significant difference in basic characteristics (Supplementary Table S1). It's worth noting that all participants provided written informed consent after receiving comprehensive explanations from qualified specialists.

Dietary intakes assessment

In 2003, an expert dietitian obtained participants' dietary intakes through face-to-face interviews using a 49-item qualitative Food Frequency Questionnaire (FFQ). The validity and reliability of the FFQ have been previously examined (23). For each food item, participants were asked, "During the past year, how often have you eaten these foods?" The questionnaire offered five predefined frequency categories: "never," "rarely," "daily," "weekly," and "monthly." In our FFQ, no portion sizes were specified; however, our validation study demonstrated that discrepancies are mainly because of variations in the frequencies rather than the portion size (23). Hence, portion size data are rather unimportant, since most of the variation in food intake is justified by consumption frequency (23). To calculate dietary clusters, the 49 food items were categorized into 12 food groups based on nutrient similarities as follows: fruits (fresh fruit, fruit juice, and dried fruit), vegetables (fresh, cooked, and dried vegetables), dairy products (cheese, low and whole fat milk, and yogurt), legumes (lentils, peas, beans, etc.), nuts (almonds, hazelnuts, pistachios, and seeds), white meat (chicken, poultry, fresh fish), grains (bread, rice), red meat, processed meat (sausages and burgers), sweets (sweets, cake, biscuits, chocolate, and pizza), non-hydrogenated vegetable oils (solid oil), and hydrogenated vegetable oils (liquid oil, olive oil) (24). It is important to note that all grains were classified as unhealthy, primarily because they are largely refined. Furthermore, due to the lack of information on low- and high-fat dairy products, these were considered healthy foods in our study.

Clinical and laboratory measurements

Participants were invited to their nearest health center, where a team of trained physicians and nurses conducted an extensive medical interview and physical examination. Subjects completed general questionnaires to gather information on demographics and risk factors for CVDs, including age, sex, family history of CVD, socioeconomic status, residency areas, anthropometric measures, physical activity, smoking status, hypertension, and dyslipidemia. Smoking status was categorized as a smoker, non-smoker, or ex-smoker (25). The Baecke questionnaire was used to assess physical activity, which was reported in equivalent metabolic minutes per week (METs-min/wk) (26). To estimate each person's total METs-min/wk., we calculated the METs-min/wk. for each activity (days per week × MET equivalent of exercise minutes) and then summed up all METs-min/wk. values. Anthropometric and blood pressure measurements were performed following standard protocols (27, 28) using calibrated instruments. Abdominal obesity was determined by the waist-to-hip ratio (WHR), with cut-off values set at WHR $\geq$ 0.90 cm for men and WHR $\geq$ 0.85 cm for women. Obesity was determined by a body mass index (BMI) $\geq$ 30 kg. Hypertension was defined as individuals with systolic blood pressure (SBP) $\geq$ 140 mmHg, diastolic blood pressure (DBP) $\geq$ 90 mmHg, or those taking antihypertensive medication, as per WHO guidelines (29).

In this study, dyslipidemia was considered as an abnormal value of at least one of the lipid profile components, including total cholesterol (TC) $\geq$ 200 mg/dL, triglyceride (TG) $\geq$ 150 mg/dL, low-density lipoprotein cholesterol (LDL-C) $\geq$ 130 mg/dL, or high-density lipoprotein cholesterol (HDL-C) $\leq$ 40 mg/dL in men and HDL-C $\leq$ 50 mg/dL in women. Those taking lipid-lowering drugs were also classified as having dyslipidemia (30, 31).

Statistical analysis

To cluster individuals based on their food intake and identify dietary patterns, we utilized the semi-parametric Bayesian approach of the Dirichlet Process (32). The Dirichlet Process is less susceptible to outliers and deviations from normality compared to the commonly used method of a mixture of Gaussian distributions. This was particularly useful when dealing with significant overlap between observations. The Dirichlet Process evaluates an unknown distribution G over all possible distributions, focused around a base distribution G0, with dispersion around this measure regulated by a dispersion parameter. Although G0 is typically assumed to be a Gaussian distribution, other distributions have been proposed [e.g., (20)]. The Dirichlet Process' capacity to generate discrete distributions was employed by many researchers to cluster data with complex structures, as shown in previous studies (33–35). We implemented the Gaussian Dirichlet process mixture model (36, 37) to generate clusters. We considered the stick-breaking representation of the Dirichlet process for

implementation in the OpenBUGs software (38). In our model-based clustering approach, each individual was assigned to the cluster with the highest probability density. Within a Bayesian framework, we estimated the distribution parameters of all clusters, calculated the probability density of individual observations in each cluster, and assigned each individual to the cluster with the highest density. We used the Markov chain Monte Carlo (MCMC) simulation method to obtain the Bayesian estimates of the parameters. After discarding 1,000 simulated values as burn-in for MCMC convergence, we averaged 20,000 MCMC samples for each parameter to obtain the Bayes estimates. The clustering approach was detailed previously (34, 39). We labeled the three main dietary clusters as healthy, unhealthy, and mixed.

In this study, we conducted all analyses on 5,396 individuals who completed all food-item questions on the FFQ. Continuous data were expressed as mean ± standard deviation (SD), and categorical data were presented as percentages. Differences between groups were evaluated by an independent samples t-test for continuous variables and a Chi-squared test for categorical variables. We used one-way analysis of variance (ANOVA) to compare continuous variables across three dietary clusters, and the Chi-square test for categorical variables.

We utilized Cox proportional hazards regression analysis to obtain the hazard ratio (HR) and 95% confidence intervals (CI) for the association between the derived dietary clusters and the incidence of CVDs. The first model was adjusted for age (continuous), gender, and socioeconomic status (low/moderate/high). The subsequent model was additionally adjusted for smoking (smoker/non-smoker/ex-smoker), physical activity (continuous), and general obesity (yes/no). Additional adjustments were made for residency areas (urban/rural), family history of CVDs (yes/no), abdominal obesity (yes/no), hypertension (yes/no), and dyslipidemia (yes/no).

Results

Table 1 displays the demographic and clinical characteristics of the study participants, segmented by the incidence of cardiovascular events. We identified 401 males (15.3%) and 340 females (12.3%) with cardiovascular diseases (CVD). The prevalence of CVDs was significantly higher in males than females ($p < 0.05$). Factors such as mean age, anthropometric measures (WHR and BMI), and lipid profile components (LDL-C, TG, TC) were significantly higher in individuals with CVDs compared to those without CVDs (all $p < 0.05$). Notably, HDL levels were not significantly different between these two groups. Participants with CVDs exhibited lower physical activity levels, a higher proportion of urban residency, and generally had lower socioeconomic status.

We identified three dietary clusters: healthy, unhealthy, and mixed. Table 2 demonstrates the dietary consumption of frequently consumed food items (consumed > times/portion/week), stratified by dietary clusters. The unhealthy cluster consumed more white meat, processed meat, sweets, non-hydrogenated vegetable oils, and hydrogenated vegetable oils. Conversely, the healthy cluster consumed more fruits, vegetables, dairy products, legumes, nuts, red meat, and grain.

Table 3 outlines the demographic and clinical characteristics of the study population, stratified by dietary clusters. Participants in the mixed cluster were typically older, more likely hypertensive, and had lower socioeconomic status and physical activity levels than those in healthy and unhealthy clusters. Moreover, the information across dietary clusters at different follow-up points was presented in Supplementary Table S2.

The study sample comprised 5,396 subjects, including 741 with CVDs. Of the 97 individuals in the unhealthy dietary cluster, 13 (13.4%) had CVDs, while 84 (86.6%) were censored. Among 4,954 participants in the mixed dietary cluster, 689 (13.9%) had CVDs, with 4,265 (86.1%) censored. In the healthy dietary cluster, 39 out of 345 participants (11.3%) had CVDs, and 306 (88.7%) were censored. Loss of follow-up was due to various factors such as changes in phone numbers, addresses, and geographical challenges. These losses were considered random and not biased. Detailed reasons for participant drop-outs are presented elsewhere (40).

Table 4 shows the hazard ratio (HR) and corresponding 95% confidence intervals (CI) for the association between dietary clusters and CVD risk. In the crude model, participants in the mixed cluster had a higher CVD risk than those in the healthy cluster (HR: 1.515; 95%CI: 1.097, 2.092). However, after adjusting for age, gender, socioeconomic status, smoking, physical activity, general obesity, residency areas, family history of CVDs, abdominal obesity, hypertension, and dyslipidemia, these findings were attenuated (HR: 1.145; 95%CI: 0.769, 1.706). The crude model did not show a significant association between the unhealthy dietary cluster and cardiovascular event risk compared to the healthy cluster (HR: 1.418; 95%CI: 0.757, 2.658). Nevertheless, the fully-adjusted model indicated that participants in the unhealthy cluster had a higher CVD risk than those in the healthy cluster (HR: 2.059; 95%CI: 1.013, 4.184) (Figure 1).

Discussion

Through the use of Bayesian cluster analysis, we identified three primary dietary patterns among the Iranian adult population: 'unhealthy', 'mixed', and 'healthy'. The analysis revealed that individuals within the unhealthy cluster had nearly twice the risk for cardiovascular diseases (CVDs), independent of potential confounders. Furthermore, the association between mixed clusters and a higher risk for CVDs was found to be influenced by variables such as age, gender, socioeconomic status, smoking habits, level of physical activity, general obesity, residency areas, family history of CVDs, abdominal obesity, hypertension, and dyslipidemia.

Our findings suggest that adopting a healthy dietary pattern, similar to the one identified in this study, could significantly reduce the risk of CVDs. This conclusion aligns with the results of other research, showing a positive association between the consumption of vegetables, fruits, and dairy products and improvements in variables such as lipid profile, adiposity measures, diastolic blood pressure (DBP), and fasting glucose concentration (41).

Moreover, our findings align with studies highlighting the benefits of a dietary pattern characterized by high vegetable consumption, often referred to as 'healthy' or 'cautious', in improving cardiovascular risk factors (42, 43). A separate study conducted among Brazilian adults found that adherence to a healthy dietary pattern led to

TABLE 1 Demographic and clinical characteristics of the study population stratified by the development of cardiovascular events.

	Cardiovascular disease			
	Total (*n* =5,396)	Yes (*n* =741)	No (*n* =4,655)	*p*-value
Demographic variables				
Age (year)	50.67 ± 11.61	57.31 ± 11.66	49.61 ± 11.25	0.001[a]
Sex				
Male	2,628 (48.7)	401 (54.1)	2,227 (47.8)	0.001[b]
Female	2,768 (51.3)	340 (45.9)	2,428 (52.2)	
Family history of CVD				
Yes	268 (4.6)	64 (8.7)	204 (4.3)	0.024[b]
No	5,128 (95.4)	677 (91.3)	4,451 (95.7)	
Socioeconomic status				
Low	5,353 (99.2)	733 (98.9)	4,622 (99.3)	0.032[b]
Moderate	27 (0.5)	2 (0.3)	23 (0.5)	
High	16 (0.3)	6 (0.8)	10 (0.2)	
Residency areas				
Urban	3,907 (72.4)	576 (77.7)	3,330 (71.6)	< 0.001[b]
Rural	1,489 (27.6)	165 (22.3)	1,325 (28.4)	
Anthropometric measures				
Waist-to-hip ratio	0.93 ± 0.8	0.95 ± 0.07	0.92 ± 0.08	< 0.001[a]
Body mass index (kg/m^2)	26.79 ± 4.6	37.27 ± 4.84	26.69 ± 4.64	0.001[a]
Lifestyle variables				
Physical Activity (MET/min/wk)	873.44 ± 549.26	778.71 ± 563.54	888.72 ± 545.63	< 0.001[a]
Smoking status				
Smoker	842 (15.6)	129 (17.4)	712 (15.3)	0.006[b]
Ex-smoker	346 (6.4)	64 (8.6)	282 (6.1)	
Non-smoker	4,208 (78.0)	548 (74.0)	3,661 (78.6)	
Co-complications				
Hypertension				
Yes	755 (14.0)	205 (27.7)	550 (11.8)	< 0.001[b]
No	4,637 (86.0)	536 (72.3)	4,105 (88.2)	
HDL-C (mg/dL)	46.93 ± 10.45	47.05 ± 10.73	46.91 ± 10.41	0.901[a]
LDL-C (mg/dL)	128.43 ± 42.14	135.3 ± 45.34	127.3 ± 41.54	< 0.001[a]
TG (mg/dL)	193.42 ± 118.97	225.02 ± 51.64	210.3 ± 49.56	< 0.001[a]
Total cholesterol (mg/dL)	212.39 ± 50.1	222.13 ± 139.6	188.8 ± 114.6	< 0.001[a]

Data are presented as mean ± SD or number (%). $p < 0.05$ was considered statistically significant. CVD: Cardiovascular disease, MET: Metabolic Equivalents, HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, TG: Triglyceride.
[a]Calculated by an independent samples *t*-test.
[b]Calculated by the Chi-square test.

favorable outcomes related to obesity, including lower waist circumference (WC), Body Mass Index (BMI), and Waist-to-Hip Ratio (WHR), along with lower systolic blood pressure (SBP) and improved lipid profile (44).

Moreover, adherence to a diet rich in fruits and vegetables has been linked to a higher intake of dietary fiber, folate, and potassium (45–47). Fruits and vegetables are known to contain biologically active compounds such as flavonoids and antioxidants, which may have beneficial effects against CVDs (45–48). While the exact cardioprotective properties of these substances are not fully understood, their consumption has been linked to a reduced risk of CVDs (46–49).

Various studies have further demonstrated the beneficial effects of fruit and vegetable consumption in preventing CVDs (50, 51). Data from a cohort study conducted in Sudan has shown that lifestyle modifications, including a healthy diet, could potentially prevent up to 80% of CVDs (52, 53). This underscores the importance of population-based strategies focusing on lifestyle modifications, including nutrition, in CVD prevention (54, 55).

TABLE 2 Dietary consumption of the most commonly consumed food items (>3 times/portion/week) stratified by the dietary clusters.

Food groups	Dietary clusters			
	Unhealthy (*n* =97)	Mixed (*n* =4,954)	Healthy (*n* =345)	*p*-value[a]
Fruits (time/wk)	8.4 ± 5.5	7.4 ± 4.6	9.7 ± 5.7	< 0.001
Vegetables (time/wk)	6.6 ± 4.1	6.2 ± 3.8	7.4 ± 4.4	< 0.001
Dairy products (time/wk)	0.63 ± 1.9	0.65 ± 1.6	1.1 ± 2.3	< 0.001
Legumes (time/wk)	3.2 ± 2.9	3.03 ± 2.2	3.7 ± 2.7	< 0.001
Nuts (time/wk)	1.5 ± 2.2	0.6 ± 0.9	8.1 ± 3.5	< 0.001
White meat (time/wk)	2.7 ± 2.5	2.3 ± 2.2	2.5 ± 2.3	0.019
Red meat (time/wk)	3.7 ± 2.9	4.1 ± 2.7	4.8 ± 3.07	< 0.001
Processed meat (time/wk)	5.7 ± 2.2	0.3 ± 0.6	0.8 ± 1.1	< 0.001
Grain (time/wk)	23.9 ± 7.7	23.5 ± 6.02	24.3 ± 6.4	0.037
Sweets (time/wk)	5.7 ± 7.5	1.8 ± 3.1	4.7 ± 6.1	< 0.001
HVOs (time/wk)	9.3 ± 5.2	8.08 ± 4.8	8.5 ± 5.03	0.009
NHVOs (time/wk)	3.2 ± 4.6	2.4 ± 3.9	2.9 ± 4.7	0.021

Data are presented as mean ± SD. $p < 0.05$ was considered statistically significant. HVOs, Hydrogenated vegetable oils; NHVOs, Non-hydrogenated vegetable oils. [a]Calculated by one-way analysis of variance (ANOVA).

In recent years, numerous studies have been conducted to investigate the effects of different food groups on CVD prevention and related mechanisms. These studies suggest that certain food groups, such as fruits, vegetables, legumes, nuts, grains, low-fat dairy products, and fish, confer beneficial effects in preventing CVDs (29). Recent research from the Swedish Mammography Cohort has demonstrated that adherence to a healthy dietary pattern can significantly lower the risk of myocardial infarction (MI) (56).

A longitudinal analysis conducted among Finnish adults underscored that adherence to a healthy eating pattern, characterized by high consumption of vegetables, legumes, nuts, tea, rye, and dairy products, was associated with reduced cardiovascular risk factors (57). In a cross-sectional study by Amini et al., the relationship between dietary patterns and visceral adiposity, lipid accumulation product (LAP), and triglyceride-glucose (TyG) index was examined among adults aged 18–45 years living in Tehran (58). The healthy dietary pattern in this study included vegetables, fruits and fruit juices, legumes, poultry, nuts, fish, eggs, low-fat dairy products, olives, and olive oil. The results revealed no significant associations between the healthy dietary pattern, TyG index, and visceral adiposity index, after adjusting for potential confounders. However, stronger adherence to the healthy dietary pattern was associated with a decrease in LAP (58).

In a distinct population-based cross-sectional study, Sauvageot et al. used stability-based validation of dietary patterns acquired through cluster analysis to investigate the association between these patterns and cardiovascular risk factors (59). This study suggested that a healthy dietary pattern was less associated with cardiovascular risk factors compared to an unhealthy one. The unhealthy dietary pattern was linked to higher systolic blood pressure (SBP) and diastolic blood pressure (DBP), and a significant association with fasting plasma glucose (FPG), but not with hemoglobin A1C (HbA1C) levels (59).

In a meta-analysis of observational studies, there was no observed association between saturated fatty acid (SFA) intake and the risk of CVDs or type 2 diabetes, or with all-cause and CVD mortality. However, the 2015 Dietary Guidelines Advisory Committee's scientific report proposed that replacing 1% of energy intake from SFA with polyunsaturated fatty acids (PUFA) may reduce the incidence of coronary heart disease by 2–3% (60, 61). Conversely, trans fatty acids, which are primarily found in products like cakes, cookies, and salad dressings, and mainly derived from the hydrogenation of industrial vegetable oils, have been associated with an increased risk of CVDs in numerous clinical studies (62–66). Trans fatty acid intake has been shown to elevate LDL-C levels, decrease HDL levels, and increase inflammation and endothelial dysfunction (67–69).

Consumption of an unhealthy diet has been linked with a higher intake of processed meat, which is known to contain 400% more sodium than raw meat (70). High sodium intake is a recognized risk factor for CVDs due to its potential to elevate blood pressure (71). Hence, reducing processed meat consumption could contribute to lowering the incidence of CVDs. A study by Rouhani et al. (72) explored the correlation between fast-food consumption and obesity among adolescent girls in Isfahan province and found that higher consumption of fast food was linked to lower diet quality, leading to increased cardiovascular risk factors such as dyslipidemia. Fast foods are typically energy-dense and are rich in saturated and trans fats. Recent research revealed that trans fats account for 24 and 31% of total fats in typical sausages and burgers in Iran, respectively (73). Saturated and trans fats have been demonstrated to negatively impact lipid profiles, metabolic syndromes, systemic inflammation, and endothelial function (74).

Research indicates compelling evidence supporting the assertion that red meat, a significant source of protein and fat, may not be optimal for dietary health due to predicted increases in total cholesterol (TC) and LDL-C (75). As a result, dietary health recommendations often limit red meat consumption or suggest replacing it with leaner options such as white meat (75). Several systematic reviews and meta-analyses have revealed an

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TABLE 3 Demographic and clinical characteristics of the study population stratified by dietary clusters.

	Dietary clusters			
	Unhealthy	Mixed	Healthy	*p-value*
Demographic variables				
Age (year)	45.23 ± 9.52	51.07 ± 11.68	46.47 ± 9.74	< 0.001[a]
Sex				
Male	46 (47.4)	2,421 (48.9)	160 (46.4)	0.640[b]
Female	51 (52.6)	2,533 (51.1)	185 (53.6)	
Family history of CVD				
Yes	5 (5.2)	223 (4.5)	20 (5.8)	0.520[b]
No	92 (94.8)	4,731 (95.5)	325 (94.2)	
Socioeconomic status				
Low	78 (97.5)	4,229 (99.3)	274 (98.6)	0.010[b]
Moderate	2 (2.5)	17 (0.4)	4 (1.4)	
High	0 (0.0)	13 (0.3)	0 (0.0)	
Residency areas				
Urban	79 (81.4)	3,589 (72.4)	239 (69.3)	0.059[b]
Rural	18 (18.6)	1,365 (27.6)	106 (30.7)	
Anthropometric measures				
Waist-to-hip ratio	0.925 ± 0.084	0.93 ± 0.080	0.921 ± 0.089	0.052[a]
Body mass index (kg/m^2)	27.65 ± 4.5	26.76 ± 4.7	26.9 ± 4.3	0.160[a]
Lifestyle variables				
Physical Activity (MET/min/wk)	960.01 ± 503.64	867.91 ± 548.94	928.50 ± 562.46	0.041[a]
Smoking status				
Smoker	21 (21.6)	760 (15.3)	60 (17.4)	0.350[b]
Ex-smoker	7 (7.2)	320 (6.5)	19 (5.5)	
Non-smoker	69 (71.2)	3,874 (78.2)	266 (77.1)	
Co-complications				
Hypertension				
Yes	8 (8.2)	714 (14.4)	34 (9.9)	0.010[b]
No	89 (91.8)	4,240 (85.6)	311 (90.1)	
HDL-C (mg/dL)	45.88 ± 10.28	47.00 ± 10.43	46.21 ± 10.85	0.250[a]
LDL-C (mg/dL)	123.92 ± 44.85	128.6 ± 41.93	127.36 ± 44.45	0.520[a]
TG (mg/dL)	208 ± 50.05	212.58 ± 49.93	210.9 ± 52.5	0.570[a]
Total cholesterol (mg/dL)	195.42 ± 104.69	192.53 ± 114.59	205.63 ± 171.88	0.140[a]

Data are presented as mean ± SD or number (%). $p < 0.05$ was considered statistically significant. CVD, Cardiovascular disease; MET, Metabolic Equivalents; HDL-C, High-density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol; TG, Triglyceride.
[a]Calculated by one-way analysis of variance (ANOVA).
[b]Calculated by the Chi-square test.

inverse relationship between red meat consumption and overall health (76). Additionally, red meat consumption has been linked to non-communicable diseases (NCDs) (75). For instance, World Cancer Research has reported strong evidence connecting the consumption of red and processed meat to an increased risk of colorectal cancer (77). Studies have also shown associations between red meat consumption and type 2 diabetes (78) and cardiovascular diseases (CVDs) such as coronary artery disease, stroke, and heart failure (70, 75, 79).

Our research further indicated that most individuals within unhealthy dietary clusters have poor social and economic statuses, consistent with previous study findings (80–82). Research has demonstrated that individuals with higher socioeconomic status tend to follow healthier food shopping patterns than those with lower socioeconomic status. For instance, a 2010 survey of British families revealed that lower socioeconomic status groups purchased more energy from less healthy foods and beverages, while those of higher status prioritized healthier food choices

TABLE 4 Hazard ratio (HR) and 95% confidence interval (CI) for the association between dietary clusters and the risk of cardiovascular disease.

Dietary clusters	*p*-value	HR (95% CI)
Crude		
Healthy	–	Ref
Unhealthy	0.276	1.418 (0.757, 2.658)
Mixed	0.012	1.515 (1.097, 2.092)
Model-1		
Healthy	–	Ref
Unhealthy	0.173	1.615 (0.811, 3.216)
Mixed	0.691	1.077 (0.748, 1.550)
Model-2		
Healthy	–	Ref
Unhealthy	0.187	1.591 (0.798, 3.171)
Mixed	0.708	1.072 (0.744, 1.544)
Model-3		
Healthy	–	Ref
Unhealthy	0.046	2.059 (1.013–4.184)
Mixed	0.506	1.145 (0.769–1.706)

Data are presented as HR (95% confidence interval) and obtained from Cox proportional hazard regression analysis. $p < 0.05$ was considered statistically significant. Crude: Unadjusted. Model 1: Adjusted for age, sex, and socioeconomic status. Model 2: Model 1+ smoking status, physical activity, general obesity. Model 3: Model 2 + residency areas, family history of cardiovascular disease, abdominal obesity, hypertension, and dyslipidemia.

(82). Furthermore, international research in Latin America showed that participants with low socioeconomic status consumed less fruit, vegetables, whole grains, fiber, fish, and shellfish, but consumed more legumes than those with higher status (83). Lower adherence to the Mediterranean diet has also been observed in groups with lower socioeconomic status (84). The higher cost of healthier diets may pose a barrier for low-income individuals to adopt healthy eating habits, as diets rich in quality and nutritious foods, such as lean meats, fish, vegetables, and fruits, are often more expensive than diets high in added sugars, fats, and refined grains (81). For example, an American study found that a healthy food basket could cost $14 to $32 more than a standard food basket due to the higher costs of whole grains, lean meats, and skinless chicken, which could constitute over 35 to 40 percent of the food budget of low-income consumers (85). This underscores the challenges faced by individuals with lower socioeconomic status in making healthy food choices due to financial constraints. These findings suggest that socioeconomic status significantly shapes dietary patterns, and addressing economic and social factors is vital in promoting healthy eating habits for cardiovascular disease prevention and management (80–85).

The results of our study suggest that individuals with unhealthy dietary patterns tend to be younger, aligning with findings from previous research (86–88). For instance, a study conducted in Spain found that younger people tend to follow a Western diet, characterized by high consumption of red and processed meat, refined grains, fried food, and high-fat foods. This dietary pattern is considered unhealthy in contrast to the Mediterranean diet, which is regarded as a healthy dietary pattern and includes more fruits, seafood, legumes, and nuts (87). Another study also demonstrated an inverse relationship between age and healthy eating patterns, with younger individuals more inclined to follow unhealthy eating patterns than older individuals (88). This may be attributed, in part, to the higher consumption of unhealthy foods, such as hamburgers and pizza, among young people (87). These findings suggest that age plays a role in shaping dietary patterns, with younger individuals being more susceptible to unhealthy eating patterns. Understanding these age-related differences in dietary choices can inform targeted interventions to promote healthy eating habits among younger populations for cardiovascular disease prevention.

The current study on dietary patterns in developing countries is scarce and often limited to cross-sectional studies. However, the present study, based on a population-based sample, enhances the external validity of the findings. Additionally, the study utilizes the Bayesian clustering method in a cohort study, which represents a novel approach.

However, some limitations should be considered when interpreting the results. The choice of variables used for clustering can affect the results, and different variables may yield different clustering outcomes. Nonetheless, clustering can be a valuable tool for identifying patterns in data, including dietary patterns and providing insights for further analysis and interpretation. In this regard, it is important to note that the nutritional performance of individuals in this study was determined using a standard food frequency questionnaire, which may have limitations such as a lack of access to detailed food intake information. This limitation could have affected the categorization of food items into food groups. For example, grains should ideally be divided into whole and refined grains, but in this study, all available grains were classified as unhealthy due to the prevalence of refined grains in Iran. Another

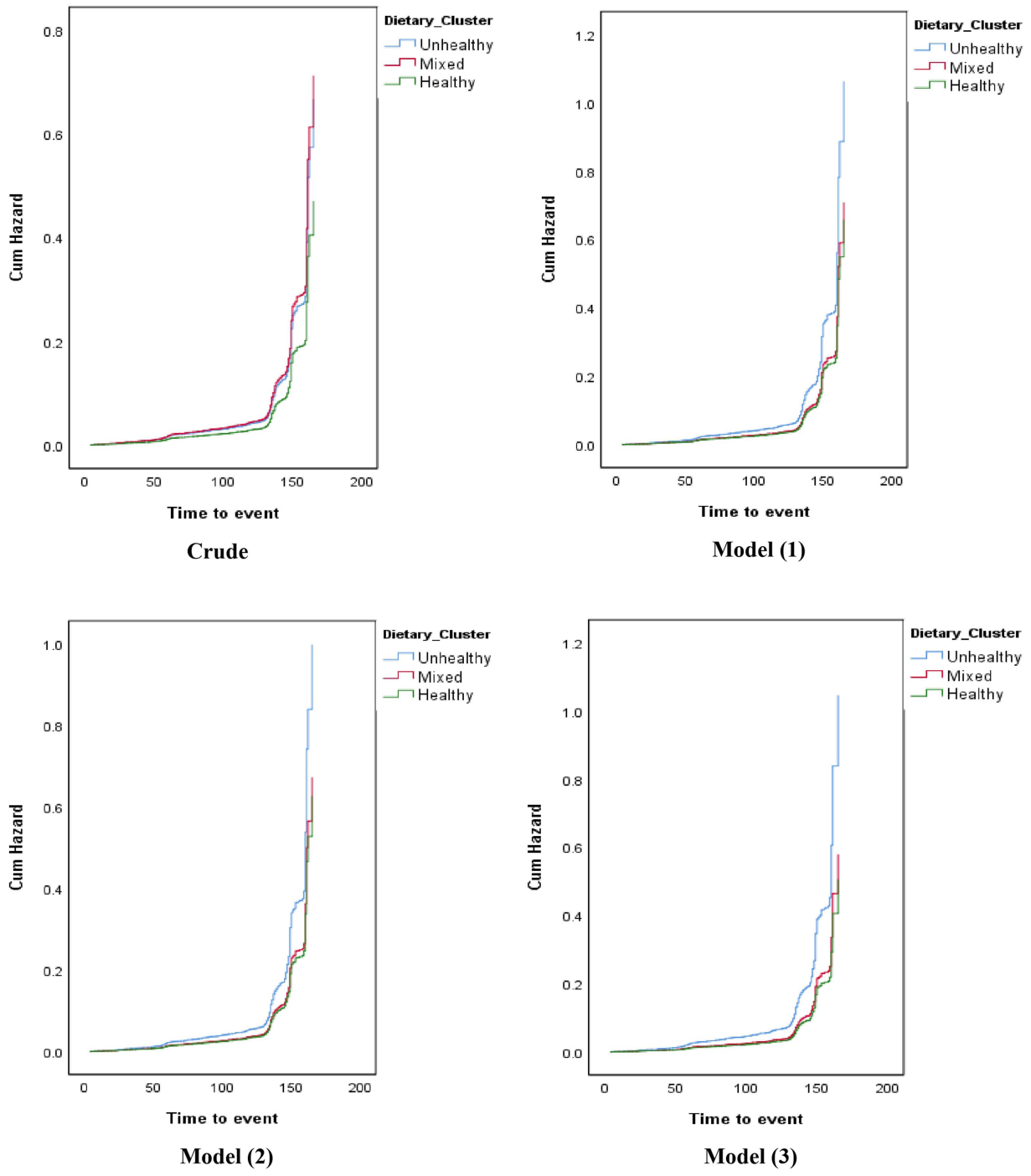

FIGURE 1
Hazard ratio (HR) for the association between dietary clusters and the risk of cardiovascular events.

limitation is that the questionnaire did not differentiate between low-fat and high-fat dairy products, resulting in all dairy products being categorized as healthy. Although our FFQ was validated, it did not provide us with data on portion sizes. Therefore, we did not have any data about total energy intake in this study.

The foundation of combating non-communicable diseases, including cardiovascular diseases (CVDs), lies in empowering individuals and policymakers through education and implementing supportive laws and regulations to create an environment conducive to healthy behaviors and lifestyles. By implementing the right societal interventions, we can eliminate or reduce many risk factors for CVDs. Community-based interventions that target risk factors such as smoking, unhealthy diets (high in fat but lacking in fruits and vegetables), physical inactivity, and other environmental, social, and behavioral variables are suggested for prevention.

In conclusion, dietary clusters within the Iranian population can be associated with the risk of CVDs. An essential aspect of the "health transition" is the emergence of CVD patterns associated with changes in dietary patterns, which should alert policymakers. Further prospective investigations are required to confirm such associations.

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 current study was conducted in accordance with the ethical guidelines of the 1975 Declaration of Helsinki and the protocol was approved by the Ethical Committee of Isfahan Cardiovascular Research Center. The patients/participants provided their written informed consent to participate in this study.

Author contributions

NS, MM, NM, and RR: conception and design. RR, NM, and KS: acquisition of data. MM, RR, KS, and ER: analysis and interpretation of data. RR, KS, MM, and AA: drafting the manuscript. RR, KS, ER, AA, FN, NM, MM, and NS: revising it for intellectual content. 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.2023.1150481/full#supplementary-material

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Socioeconomic status may affect association of vegetable intake with risk of ischemic cardio-cerebral vascular disease: a Mendelian randomization study

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Background: Previous studies found that increasing vegetable intake benefits are reduced after adjustment for socioeconomic factors. Using genetic variation as an instrumental variable for vegetable intake and socioeconomic status, we investigated the relationship between vegetable intake and ischemic cardio-cerebral vascular diseases and focused on whether socioeconomic status was a possible confounder.

Methods: From three independent genome-wide association studies, we extracted instrumental variables reflecting raw and cooked vegetable intake, which were used to perform Mendelian randomization analysis. To evaluate the effects of socioeconomic factors on vegetable intake, univariate and multivariate Mendelian randomization analyses were performed using single nucleotide polymorphisms representing education attainment and household income reported in the literature. We also performed outlier assessment and a series of sensitivity analyses to confirm the results.

Results: Genetically predicted raw and cooked vegetable intake were not associated with any ischemic cardio-cerebral vascular diseases and lipid components after Bonferroni correction. Univariate Mendelian randomized analysis revealed that raw vegetable intake was positively correlated with education attainment ($\beta = 0.04$, $p = 0.029$) and household income ($\beta = 0.07$, $p < 0.001$). Multivariate Mendelian randomized model showed a positive correlation between household income and raw vegetable intake ($\beta = 0.06$, $p = 0.004$). Socioeconomic status was closely associated with eating habits and lifestyle related to the risk of cardiovascular diseases.

Conclusion: Genetically determined raw and cooked vegetable intake was not associated with significant benefits in terms of ischemic cardio-cerebral vascular diseases while genetically determined socioeconomic status may have an impact on vegetable intake. Socioeconomic status, which was closely associated with other eating habits and lifestyle, may affect the association between vegetable intake and ischemic cardio-cerebral vascular diseases.

KEYWORDS

vegetable intake, socioeconomic status, ischemic cardiovascular disease, ischemic cerebrovascular disease, Mendelian randomization

Introduction

Ischemic cardio-cerebral vascular diseases are the leading cause of death and decreased quality of life worldwide (1–3). Increased vegetable intake is widely recommended in the cardiovascular disease (CVD) field (4, 5). Many observational studies support the benefits of increased vegetable intake (6, 7), including lowering serum lipids and preventing chronic disease. However, the independent effects of raw and cooked vegetables on ischemic cardiovascular disease are poorly understood, and results vary in traditional epidemiological studies (8–12).

Socioeconomic status (SES), such as education attainment and household income, has a significant impact on the occurrence of cardiovascular disease (13). A large study found that those with primary education had an increased risk of cardiovascular disease, cardiovascular event mortality, and all-cause mortality compared with those with higher education (14). Patients with financial barriers are at higher risk of future CVD events (15). Socioeconomic status can limit access to fresh vegetables and fruits due to a lack of health literacy and high prices (16, 17). Several studies found that increasing vegetable intake benefits are reduced after adjustment for socioeconomic factors (8, 10, 18). And the risk of ischemic cardio-cerebral vascular disease is related to various lifestyle factors, including diet, smoking, drinking, physical inactivity, etc. (19–22), which are also closely related to education attainment and household income (14, 23, 24).

The Mendelian randomization (MR) approach has been widely used to assess the causal effects of risk factors on disease. Relying on pooled data from genome-wide association studies (GWAS) (25), the MR approach uses genetic variants, randomly assigned to individuals at conception, as instrumental variables (IVs) to analyze causal relationships between exposure and outcome. When performed carefully, MR analysis largely overcomes the limitations of confounders and avoids the bias of typical observational studies (26). Several previous Mendelian randomization studies (12, 27, 28) have found that vegetable intake did not reduce certain metabolic risk factors and the risk of some cardiovascular events. We aimed to estimate the effects of vegetable intake on ischemic cardio-cerebral vascular disease risk and serum lipids and to focus on the influence of socioeconomic status on vegetable intake, other eating habits, and lifestyle.

Methods

Study design

We designed a one-sample Mendelian Randomization study to evaluate how vegetable intake was related to ischemic heart disease and ischemic stroke. We selected angina, acute myocardial infarction, chronic ischemic heart disease, and cerebral infarction as our outcome variables. Considering the genetic connection between instrumental variables used for the intake of raw and cooked vegetables, both univariable and multivariable MR studies were used to assess the causal relationship between exposure and outcome. After discovering a lack of clear causal relationship between vegetable intake and ischemic cardiovascular events, we further conducted a multivariable Mendelian Randomization study to estimate the potential impact of socioeconomic status on vegetable intake, and we also attempted to prove that this impact is equally widespread in other dietary habits and lifestyle (Figure 1).

Instrumental variable selection

Genetic instrumental variables reflecting vegetable intake were derived from three independent UK Biobank-based GWAS (Supplementary Table S1) (29–31). The measures of dietary intake, including vegetable intake, in UK Biobank are based on self-reported questionnaire data. We identified single nucleotide polymorphisms (SNPs) with a genome-wide significant p value ($<5\times10^{-8}$) associated with phenotypes. After removing duplicate SNPs, we obtained 39 SNPs reflecting raw vegetable intake, and 25 reflecting cooked vegetable intake. The SNP rs12629972 was excluded because it reflected both raw and cooked vegetable intake. We also excluded palindrome SNPs with intermediate allele frequencies (>0.42) or indel genetic variants. To account for the possibility that the three GWAS may have identified interrelated SNPs as reflecting vegetable intake, we used LDlink to remove SNPs in linkage disequilibrium (32). If a pair of SNPs had LD $R^2>0.01$, the SNP with the higher p value was removed. Finally, we used PhenoScanner, a curated database of publicly available results from large-scale genetic association studies in humans (33), to check whether each SNP was associated with potential confounders ($p<5\times10^{-8}$, proxies for European: $R^2>0.8$). Rs11191193 was excluded because of its significant genetic association with educational attainment, and rs838133 because it was directly associated with total cholesterol. Finally, we used 18 SNPs reflecting raw vegetable/salad intake and 11 SNPs reflecting cooked vegetable intake for MR analysis (Supplementary Tables S2, S3). Supplementary Figures S1, S2 show the detailed selection process. Proxy SNPs (minimum linkage disequilibrium $R^2=0.8$) were used for vegetable intake-associated SNPs that were unavailable in outcome datasets. Some studies have shown that these SNPs may influence people's dietary preferences and alter genetically determined raw and cooked vegetable intake through senses such as olfaction and taste (34, 35).

In addition, in order to get a more definite conclusion, we also directly extracted the instrumental variables from MRC-IEU. The visualization results of the exposed GWAS can be obtained in Supplementary Figures S3, S4. 18 and 17 SNP were used to reflex raw and cooked vegetables, respectively. Considering that some of the SNPs may have never been reported or used, we calculated the F statistic ($F=\frac{N-k-1}{k}\times\frac{R^2}{1-R^2}$) for each SNP to test for a weak instrumental variable bias. F statistics for all variables were over 10, and weak instrument bias was avoided in principle (Supplementary Tables S4, S5) (36).

Genetic associations with education attainment were obtained from the GWAS conducted under the auspices of the Social Science Genetic Association Consortium, which reported 74 genome-wide significant loci associated with educational attainment in people of European descent ($n=293{,}723$) (37). Educational attainment was

Abbreviations: ApoB, apolipoprotein B; CI, confidence interval; CVD, cardiovascular disease; IEU, Integrative Epidemiology Unit; IVs, instrumental variables; IVW, inverse-variance weighted; GWAS, genome-wide association studies; LDL-C, low-density lipoprotein cholesterol; MR, Mendelian randomization; MVMR, multivariable Mendelian randomization; OR, odds ratio; SES, socioeconomic status; SNPs, single nucleotide polymorphisms.

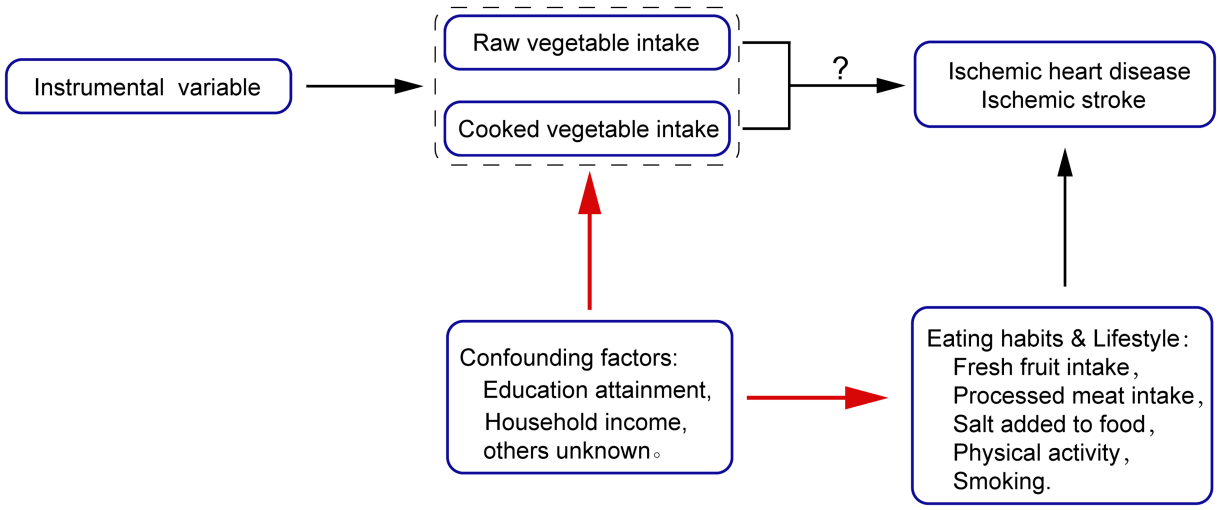

FIGURE 1
Mendelian Randomization (MR) Model of our study.

measured by the number of years of schooling completed (EduYears, mean = 14.3, SD = 3.6). 12 loci that were unavailable in the target data-set were removed and the remaining 62 loci have been retained (Supplementary Table S6). The SNPs used as instrumental variables related to household income were derived from Shi et al. (38). The same method was used to extract the genetic association of the 54 SNPs with education attainment and vegetable intake. Of 54 SNPs, 5 were unavailable and removed; the remaining 49 SNPs were retained to perform further analysis (Supplementary Table S7). SNPs associated with education attainment may affect years of education by altering neurodevelopment at different stages. For example, rs4500960 may be related to developmental biology, brain size, and cerebra core methodology, while rs61160187 is closely related to transcription factor binding and negative regulation of signal transmission (37). And SNPs associated with household income are associated with intracranial volume, infant head circumference, and level of cognitive ability (39).

Data sources for outcome of the Mendelian randomization analysis

The primary outcomes included ischemic cardio-cerebral vascular diseases diagnosed by the International Classification of Diseases version, Tenth Version, with the following ICD-10 codes: I20 (angina pectoris), I21 (acute myocardial infarction), I25 (chronic ischemic heart disease), and I63 (cerebral infarction). Data were acquired from the UK Biobank summary statistics curated in the MRC-IEU Open GWAS database or provided by Neale Lab (40). Serum lipid and lipoprotein levels were measured using the Nightingale high-throughput NMR metabolomics platform in 2020, and blood samples were provided by UK Biobank. GWAS results based on these metabolic biomarkers can be obtained from MRC-IEU (European, $N = 115{,}078$).

The raw and cooked vegetable intake as well as vegetarian alternatives intake used as outcome variables in MVMR were obtained from MRC-IEU. To illustrate the broad impact of education attainment and household income on IHD risk was not limited to the preferences for vegetable intake, we also obtained a series of outcome variables related to diet and lifestyle, including fresh fruit intake, processed meat intake, salt add to food and smoking (from MRC-IEU) and physical activity (from Within family GWAS consortium). Source and relevant information of result variables used in the study can be acquired from Supplementary Table S8.

Statistical analysis

We used the inverse-variance weighted (IVW) method as the main method to evaluate the causal effect of exposure and outcome. Due to the potential genetic association between raw and cooked vegetables, as well as between education and household income, we used the multivariate Mendelian method to analyze their independent effects. The SNPs used to conduct multivariable MR were combinations of instrumental variables of each exposure in univariable MR. We calculated the odds ratio (OR) and 95% confidence interval (CI). Cochrane's Q-statistic was used to assess the heterogeneity of SNP effects (Supplementary Tables S15, S16). If significant heterogeneity was observed, a random-effects IVW model was applied. For sensitivity analyses, we used three complementary methods with different assumptions for valid estimates. MR-Egger lacks statistical power for assessment of causal effects and provides wider confidence intervals, but can detect horizontal pleiotropy by p value for its intercept term (Supplementary Table S14) (41). A weighted median method generates homogeneous causal estimates, although >50% of weights derived in the analysis arise from invalid instrumental variables (42). Mendelian Randomization Pleiotropy RESidual Sum and Outlier (MR-PRESSO) can identify outlying SNPs and correct for horizontal pleiotropy through their exclusion (Supplementary Table S13) (43). Additionally, we performed leave-one-out sensitivity analysis to identify potentially highly influential SNPs (Supplementary Figures S5–S12).

All statistical analyses were performed in R (version 4.1.3, R Foundation for Statistical Computing, Vienna, Austria), with MR analyses performed using the TwoSampleMR package (version 0.5.6) (44), MRPRESSO package (version 1.0) (43), and MVMR package

(45). Statistical significance was set at a two-sided p value < 0.05. Bonferroni correction of the evidential threshold was based on the number of exposures (p value <0.05/the number of exposures).

Results

Association of genetically predicted vegetable intake with ischemic cardio-cerebral vascular disease and lipid profile

Genetically predicted raw and cooked vegetable intake (IVs from three UK biobank based GWAS) were not associated with any ischemic cardiovascular diseases according to IVW analysis (P>0.05) (Table 1). The multivariate MR (IVs from three UK biobank based GWAS) observed a correlation between cooked vegetable intake and an increased risk of Chronic ischemic heart disease (OR 1.02; 95% CI 1.00, 1.04; $p = 0.042$) (Table 1), but did not exceed the significance level of Bonferroni correction ($p > 0.0125$). IVW analysis also showed that genetically predicted raw and cooked vegetable intake (IVs from MRC-IEU) were not associated with any ischemic cardiovascular diseases (Supplementary Table S9; Supplementary Figures S13, S14).

IVW analysis showed that genetically predicted raw vegetable intake (IVs from three UK biobank based GWAS) was associated with reduced low-density lipoprotein cholesterol (LDL-C) (β −0.25; 95% CI −0.44, −0.07; $p = 0.006$) and apolipoprotein B (ApoB) (β −0.28; 95% CI −0.43, −0.12; $p < 0.001$) (Supplementary Tables S10, S11). MVMR analysis showed that raw vegetable intake was only associated with reduced ApoB (β −0.22; 95% CI −0.38, −0.06; $p = 0.013$), but did not exceed the significance level of Bonferroni correction ($p > 0.0083$) (Supplementary Tables S10, S11). Cooked vegetable intake did not significantly influence serum lipid components according to the IVW and MVMR analysis. Results of Mendelian randomization analysis of genetically predicted vegetable intake (IVs from MRC-EU) and lipid profiles are presented in Supplementary Tables S12; Supplementary Figures S15, S16.

Impact of social-economic conditions on vegetable intake

We conducted univariable MR analysis to explore the impact of education attainment and household income on raw and cooked vegetable intake. People with higher education attainment tended to eat more raw vegetables (IVW: β 0.04; 95% CI 0.00, 0.08; $p = 0.029$). Similarly, people with higher household income tended to eat more raw vegetables (IVW: β 0.07; 95% CI 0.03, 0.11; P<0.001) and vegetarian alternatives intake (IVW: β 0.02; 95% CI 0.00, 0.04; $p = 0.042$), while we did not find the impact of social-economic conditions on cooked vegetable intake (Figure 2).

TABLE 1 Estimates given as odds ratios (ORs) and 95% confidence intervals for the effect of raw and cooked vegetable intake on ischemic cardio-cerebral vascular diseases.

Outcomes	Method	Raw vegetable intake				Cooked vegetable intake			
		SNPs	OR	95% CI	*p*-value	SNPs	OR	95% CI	*P*-value
Angina pectoris	MR-Egger	18	1.01	0.98 ~ 1.05	0.405	11	0.97	0.91 ~ 1.02	0.243
	Weighted median	18	1.00	0.99 ~ 1.02	0.782	11	1.01	0.99 ~ 1.02	0.587
	Inverse variance weighted	18	1.01	0.99 ~ 1.02	0.421	11	1.00	0.98 ~ 1.01	0.692
	MR-PRESSO(Outlier-corrected)	NA	NA	NA	NA	NA	NA	NA	NA
	MVMR	18	1.00	0.99 ~ 1.01	0.915	11	1.00	0.98 ~ 1.01	0.659
Myocardial infarction	MR-Egger	18	1.01	0.99 ~ 1.04	0.341	11	1.02	0.96 ~ 1.08	0.51
	Weighted median	18	0.99	0.98 ~ 1.01	0.372	11	1.02	1.00 ~ 1.04	0.038
	Inverse variance weighted	18	1.00	0.99 ~ 1.01	0.909	11	1.01	1.00 ~ 1.02	0.18
	MR-PRESSO(Outlier-corrected)	NA	NA	NA	NA	11	1.01	1.00 ~ 1.03	0.05
	MVMR	18	0.99	0.98 ~ 1.00	0.202	11	1.01	1.00 ~ 1.03	0.056
Chronic ischaemic heart disease	MR-Egger	18	1.04	1.00 ~ 1.08	0.067	11	1.04	0.95 ~ 1.14	0.443
	Weighted median	18	1.00	0.98 ~ 1.02	0.786	11	1.02	0.99 ~ 1.04	0.229
	Inverse variance weighted	18	0.99	0.98 ~ 1.01	0.424	11	1.02	0.99 ~ 1.04	0.156
	MR-PRESSO(Outlier-corrected)	NA	NA	NA	NA	NA	NA	NA	NA
	MVMR	18	0.98	0.97 ~ 1.00	0.075	11	1.02	1.00 ~ 1.04	0.042
Cerebral infarction	MR-Egger	18	1.01	0.99 ~ 1.02	0.573	11	0.99	0.95 ~ 1.03	0.582
	Weighted median	18	1.00	0.99 ~ 1.01	0.701	11	1.00	0.99 ~ 1.01	0.933
	Inverse variance weighted	18	1.00	0.99 ~ 1.01	0.417	11	1.00	0.99 ~ 1.01	0.561
	MR-PRESSO(Outlier-corrected)	NA	NA	NA	NA	NA	NA	NA	NA
	MVMR	18	1.00	0.99 ~ 1.01	0.874	11	0.99	0.98 ~ 1.00	0.285

Considering that education and income are related genetically and socially, we next performed MVMR. In the MVMR model, education attainment had a weakened influence on raw vegetable intake (β 0.01; 95% CI −0.02, 0.05; $p = 0.440$). Household income was still positively related to raw vegetable intake (β 0.06; 95% CI 0.02, 0.10; $p = 0.004$) and vegetarian alternatives intake (IVW: β 0.02; 95% CI 0.00, 0.04; $p = 0.019$) (Figure 2).

Impact of social-economic conditions on other eating habits and lifestyle

Finally, we conducted univariable MR analysis to explore the impact of education attainment and household income on other eating habits and lifestyle to show that socioeconomic status has an extremely broad impact on ischemic cardio-cerebral vascular diseases. People with higher education attainment and household income tended to eat more fresh fruit intake (IVW: β 0.09; $p < 0.001$) (IVW: β 0.09; $p < 0.001$), eat less processed meat (IVW: β −0.06; $p = 0.028$) (IVW: β −0.10; $p = 0.001$), add less salt to food (IVW: β −0.15; $p < 0.001$) (IVW: β −0.14; $p < 0.001$), have more physical activity (IVW: β 0.07; $p = 0.002$) (IVW: β 0.06; $p = 0.004$) and smoke less (IVW: β −0.23; $p < 0.001$) (IVW: β −0.42; $p < 0.001$; Figure 3).

Discussion

Our results showed that genetic variant-determined increases in raw or cooked vegetable intake did not confer a benefit in terms of ischemic cardio-cerebral vascular diseases. Increased raw vegetable intake may reduce LDL-C and ApoB levels. In addition, socioeconomic status, including income and education, have positive effects on raw vegetable intake in persons of European ancestry. Meanwhile, socioeconomic status had an extremely broad impact on other eating habits and lifestyle.

Worldwide dietary guidelines (4, 5) include recommendations for increased vegetable intake to reduce the risk of CVD, but the independent effects of raw versus cooked vegetables by different epidemiological studies have yielded inconsistent results. Leenders et al. (9) reported that vegetable intake was associated with lower CVD mortality, with a stronger association for raw vegetables. Miller et al. (10) showed that CVD incidence was only associated with high cooked vegetable intake. In a large prospective cohort study (8), total and raw vegetable intake was

Outcome	Method	SNPs	P value	95% CI
Raw vegetable consumption				
Education attainment	MR−Egger	62	0.18	0.12 (−0.06 to 0.31)
	Weighted median	62	<0.001	0.07 (0.03 to 0.10)
	Inverse variance weighted	62	0.029	0.04 (0.00 to 0.08)
	MVMR	62	0.44	0.01 (−0.02 to 0.05)
Household income	MR−Egger	49	0.287	0.09 (−0.08 to 0.27)
	Weighted median	49	<0.001	0.07 (0.03 to 0.11)
	Inverse variance weighted	49	<0.001	0.07 (0.03 to 0.11)
	MVMR	49	0.004	0.06 (0.02 to 0.10)
Cooked vegetable consumption				
Education attainment	MR−Egger	62	0.834	0.02 (−0.16 to 0.20)
	Weighted median	62	0.833	0.00 (−0.04 to 0.05)
	Inverse variance weighted	62	0.462	0.01 (−0.02 to 0.05)
	MVMR	62	0.652	0.01 (−0.03 to 0.05)
Household income	MR−Egger	49	0.976	0.00 (−0.18 to 0.19)
	Weighted median	49	0.375	−0.02 (−0.06 to 0.02)
	Inverse variance weighted	49	0.887	−0.00 (−0.05 to 0.04)
	MVMR	49	0.977	0.00 (−0.04 to 0.04)
Vegetarian alternatives intake				
Education attainment	MR−Egger	54	0.545	0.04 (−0.09 to 0.16)
	Weighted median	54	0.192	0.02 (−0.01 to 0.04)
	Inverse variance weighted	54	0.343	0.01 (−0.01 to 0.03)
	MVMR	54	0.374	−0.01 (−0.02 to 0.01)
Household income	MR−Egger	41	0.209	0.08 (−0.04 to 0.19)
	Weighted median	41	0.048	0.03 (0.00 to 0.05)
	Inverse variance weighted	41	0.042	0.02 (0.00 to 0.04)
	MVMR	41	0.019	0.02 (0.00 to 0.04)

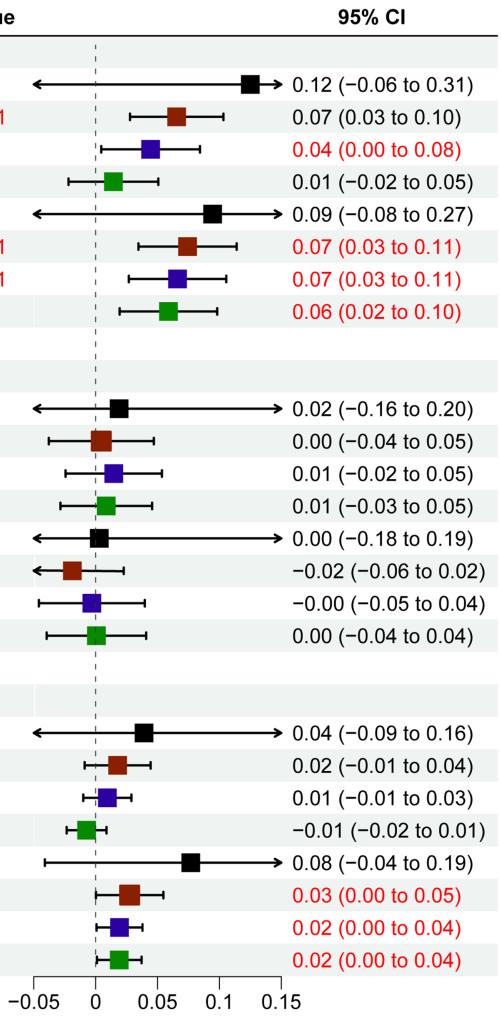

FIGURE 2
Estimates Given as Beta and 95% Confidence Intervals for the Effect of Education Attainment and Household Income on Vegetable Consumption.

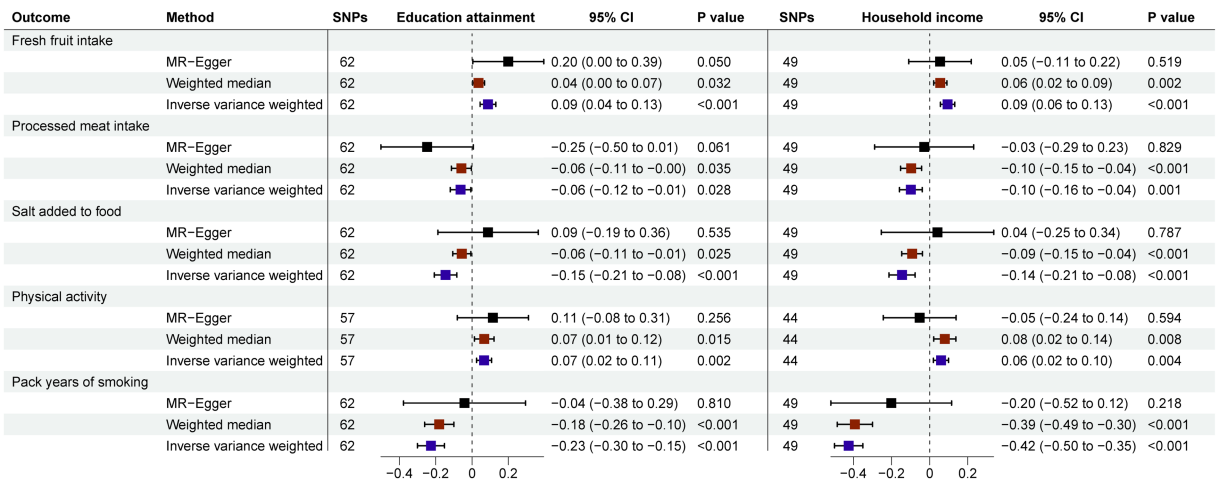

FIGURE 3
Estimates Given as Beta and 95% Confidence Intervals for the Effect of Education Attainment and Household Income on Eating Habits and Lifestyle.

inversely associated with cardiovascular disease outcomes. Systematic reviews have shown that total vegetable intake is associated with reduced CVD incidence and stroke risk (46–48). A Mendelian randomization study (27) has found no evidence of an association between cooked and raw vegetable intake and coronary heart disease, heart failure, or atrial fibrillation. Since the Mendelian randomization method can reduce the unknown confounders, different results between conventional epidemiological studies and Mendelian randomization studies may be related to differences in study populations and research methods, and insufficient adjustment for confounding factors in conventional epidemiological studies. High-vegetable diets are generally lower in calories, fat, sodium, and glycemic load, which are well-established risk factors for ischemic cardio-cerebral vascular diseases (11, 49). It may be a lack of significance in merely increasing vegetable intake without controlling for other variables such as salt intake and total energy intake. And the impact of diet on health outcomes is complex. It is important to control for consistency in overall dietary patterns when assessing the health effects of single foods or nutrients (30).

LDL-C and other apolipoproteins play central roles in ischemic cardio-cerebral vascular disease occurrence and progression (50–52). Increased vegetable intake may improve plasma lipid profiles, potentially protecting against ischemic cardio-cerebral vascular diseases. Our findings indicated that increased vegetable intake did not significantly improve lipoproteins, except that raw vegetable intake may be associated with improved LDL-C and ApoB. Although increased vegetable intake has been associated with lower plasma LDL-C in observational studies (53, 54), randomized controlled trial results suggest that increased vegetable intake has negligible effects on plasma cholesterol component concentrations (55, 56). This suggests that although increased vegetable intake may have some beneficial influence on lipid profile, the benefits may be insufficient to yield clinical effects. There are several possible reasons for the different effects of raw and cooked vegetables on lipoproteins. Cooking vegetables may increase salt and fat intake, which are linked to CVD morbidity and mortality (57, 58). Cooking improves food safety and food digestibility but also impairs food quality, resulting in the loss of certain nutrients (59–61). Moreover, different types of vegetables may be eaten differently (8).

Low socioeconomic status has been associated with the development of ischemic cardio cerebral vascular disease and may confer comparable cardiovascular risks to traditional risk factors (62, 63). A prospective cohort study demonstrated that adults with low SES are at higher risk of CVD mortality and cardiovascular events than adults with high SES, partly mediated by lifestyle (64). The increased CVD burden in low SES populations may be due to a range of biological, behavioral, and psychosocial risk factors (13). In our screening of instrumental variables of vegetable intake, rs11191193 had significant genetic associations with educational attainment. Roos et al. (65) showed that household education level is an important determinant of raw vegetable intake. A large study found that individuals with primary school education had an increased risk of cardiovascular disease and cardiovascular mortality compared with those with higher education (14). An MR study (66) reported an inverse association between genetically determined educational attainment and CAD risk. And there is a strong association between genetically determined educational attainment and risk factors such as smoking, body mass index, and hypertension (66). One analysis suggested that most CHD risk among individuals with low education is due to behavioral and biological risk factors, with the main contributors being smoking, physical inactivity, and hypertension (23). The level of education may affect the ability to develop health literacy and access to healthy lifestyle and dietary recommendations (16, 67), leading to changes in vegetable intake as well as other lifestyle. Income levels have been consistently associated with CVD risk (14). Population analysis studies of atherosclerosis risk in communities have shown that living in deprived areas is associated with a higher incidence of coronary heart disease (68). The increased risk of CVD in low-income groups may be related to poor dietary choices and increased costs of healthy foods. In low-income areas with limited access, there are more fast food restaurants, fewer supermarkets, and fewer brand options, resulting in limited access to fresh fruits and vegetables (17, 69–71). Economic differences can affect not only the availability of resources but also the promotion or maintenance of a healthy lifestyle (72, 73).

Higher income and higher education attainment may be associated with improved health perceptions and lifestyle factors (74, 75), potentially explaining the positive conclusions of studies that did not fully adjust for socioeconomic status. In a large prospective cohort study (8), total and raw vegetable intake was inversely associated with cardiovascular disease outcomes. However, these associations significantly decreased after

adjustment for potential confounders, such as socioeconomic status and lifestyle factors. Results from a cohort study (10) showed that higher vegetable intake was inversely associated with major cardiovascular disease, myocardial infarction, and cardiovascular mortality in models adjusted only for age, sex, and center. After multivariable adjustment including socioeconomic status, the association was significantly attenuated, and only non-cardiovascular mortality and total mortality remained significant. Similarly, in another study from China (18), higher vegetable intake was associated with lower CVD mortality risk in a minimally adjusted model, and the association was no longer significant after adjustment for factors such as socioeconomic status. Given the complex interrelationships between socioeconomic status, eating habits, lifestyle, and health outcomes, it is important to adjust for socioeconomic status to reduce bias.

Strength

Our study has several strengths. We investigated the independent effects of raw and cooked vegetable intake on ischemic cardio-cerebral vascular diseases and lipid profiles. Compared with traditional observational studies, MR studies reduce the effects of unknown confounders and reverse causality (30). Especially, by using the Mendelian randomization analysis, we examined the impact of socioeconomic factors on vegetable intake, other eating habits, and lifestyle, confirming that the effects of education and income on dietary habits and lifestyle are relatively common and may be extremely important confounders in previous studies.

Limitations

Our work had several limitations. Our selected GWAS for vegetable intake did not report specific intake characteristics, such as vegetable type. Therefore, we could not perform a stratified MR analysis by vegetable type, which would help draw more valuable causal inferences. Additionally, our MR study was restricted to individuals of European ancestry (76). Due to differences in genetic background and eating habits, similar studies should be conducted on a larger scale around the world. Moreover, the SNPs of the utilized GWAS were all self-reported, which may differ from the actual intake, potentially introducing some bias to the results. Individuals tend to report more healthy foods and less unhealthy foods, and people with a high BMI tend to report less food intake (77, 78). Diet changes over time may also be a potential limitation (79). Furthermore, we selected two sample datasets with a large proportion of the population overlapping, which may increase the bias in the direction of the observed association and the inflation of the Type I error rate and false-positive results (80). Finally, MR relies on assumptions that genetic tools are associated with exposure, independent of potential confounders and that genetic tools are associated with outcomes only through exposure. Although we speculated about the possible mechanism of action of the instrumental variable SNPs, the effect of the SNP on the function of the gene product is unknown and is based only on a statistical association between gene and apparent effect (81). We cannot completely avoid horizontal pleiotropic effects because it is difficult to determine the biological function of exact genetic variants. There remains a need for further high-quality GWAS and MR analyses.

Conclusion

Our results showed that genetically determined raw and cooked vegetable intake was not associated with significant benefits related to ischemic cardio-cerebral vascular disease. Genetically determined socioeconomic status may have an impact on vegetable intake. Additionally, socioeconomic status, which was closely associated with other eating habits and lifestyle, may affect the association between vegetable intake and ischemic cardio-cerebral vascular diseases.

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.

Author contributions

JH and ZH: design the study and draft the work. MX and JD: data collection and statistical analysis. Y-tZ: design the study and revise it critically for important intellectual content. 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.2023.1161175/full#supplementary-material

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Insulin resistance surrogate markers and risk of hyperuricemia among patients with and without coronary artery disease: a cross-sectional study

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Background: Although emerging evidence emphasizes the associations between both insulin resistance and hyperuricemia with coronary artery disease (CAD) risk, no definite relationship has yet been established. In this respect, time-efficient and affordable methods to estimate insulin resistance (IR) status, and to predict risk of hyperuricemia, are needed. Thus, the goal of this investigation was to examine the associations between IR, as assessed by novel surrogate markers [triglyceride-glucose (TyG) and TyG–body mass index (TyG-BMI)], and risk of hyperuricemia in patients with and without diagnosed CAD.

Methods: This cross-sectional study used data from the medical records of 1,170 patients who were referred to the cardiology outpatient clinic. Medical records, anthropometrics, and serum analytes were determined at the initial visit. Hyperuricemia was defined as serum uric acid ≥ 5.6 mg/dL. IR was estimated through surrogate markers (TyG and TyG-BMI). Multiple regression analysis was performed to assess the relationship between these indices and odds of hyperuricemia among patients with and without CAD.

Results: Overall, 814 angiographically-confirmed CAD cases (mean age (SD) = 52 (8)yrs) were compared with 356 patients without CAD (mean age (SD) = 48 (8)yr). There were positive associations between TyG and TyG-BMI indices and odds of hyperuricemia in CAD patients after controlling for confounders (adjusted odds ratio (aOR) = 1.60; 95%CI: 1.02–2.51; *p*-value = 0.036; and aOR = 1.83; 95%CI: 1.24–2.70; *p*-value = 0.002, third tertiles for TYG and TYG-BMI, respectively).

Conclusion: The present findings suggest that higher levels of the IR surrogate markers, TyG and TyG-BMI, are associated with higher odds of hyperuricemia in patients with CAD. However, given the cross-sectional design of this study, the sensitivity and specificity of these novel markers could not be determined for

confirming the diagnosis of IR and hyperuricemia, further studies are needed to determine such outcomes and to confirm the current findings.

KEYWORDS

hyperuricemia, insulin resistance, coronary artery disease (CAD), triglyceride, insulin sensitivity

Introduction

A high blood uric acid level is known as hyperuricemia. There have been several definitions proposed for diagnosing hyperuricemia, but from a clinical point of view, anything above the typical maximum limit of 6.8–7 mg/dL is regarded as saturated uric acid, and symptoms may appear accordingly that indicate the presence of gout (1). More recent evidence provided by research from the Uric Acid Right for heart Health (URRAH), a polycentric Italian cohort study investigating the threshold for serum uric acid (SUA) that is associated with the risk of cardiovascular disorders, suggested that SUA could independently predict risk for cardiovascular events and all-cause mortality when above 4.7–5.7 mg/dL (2–4). This elevated level is typically brought on by reduced uric acid excretion, elevated production of uric acid, or a combination of both factors (5). Approximately 21% of the general population and 25% of hospitalized patients have asymptomatic hyperuricemia (5), and it is far more common in men as compared with women (4,1 ratio) (6). This condition is not considered to be a health concern when patients are asymptomatic, though its most common and well-known complication is gout, which has a prevalence rate of approximately 3.9% in the U.S. population. Notably, hyperuricemia has become more prevalent in the past few decades, since it is frequently comorbid with obesity, metabolic diseases, type 2 diabetes mellitus (T2DM), dyslipidemia, hypertension, metabolic syndrome, chronic kidney disease, cardiovascular diseases, and cardiometabolic-related complications (5–7). The elevated occurrences of T2DM and metabolic syndrome, which frequently coexist with hyperuricemia, have emerged as prominent public health concerns. The interrelationships among these conditions have garnered scientific attention due to their potential implications for disease pathogenesis and management (7, 8). As reported in a meta-analysis of 11 cohort studies, T2DM risk is elevated by 17% for each 1 mg/dL elevation in SUA levels (9). Additionally, in accordance with the available evidence, people with metabolic syndrome may experience hyperuricemia due to insulin resistance, fatty liver, and dyslipidemia (7, 10).

Insulin resistance has been acknowledged as a general risk factor in many pathological conditions, including abnormal glucose tolerance, T2DM, metabolic syndrome, dyslipidemia, and obesity (11). Not only can insulin resistance begin up to two decades prior to the appearance of T2DM in non-diabetic patients, but it may also independently predict incident cardiovascular disorders (CVDs) and mortality (11). Impaired insulin sensitivity is thought to play an important role in the development of hyperinsulinemia and the progression of atherosclerotic-related conditions including hypertension, dysmetabolism, inflammation, endothelial dysfunction, and coronary artery disease (CAD), even among individuals without T2DM, or in the absence of any other clinical signs of insulin resistance. Although the underlying pathological mechanisms of these associations are not well-established, an accumulating body of research supports the potential for a causal role for reduced insulin sensitivity in increasing the risk of morbidity related to atherosclerosis, particularly for CAD and ischemic stroke (12–19).

Of note, in recent studies, the associations between insulin resistance as the principal symptom of T2DM and metabolic syndrome with elevated levels of SUA as emerging risk factors for CVDs have gained attention (7, 20, 21). Although emerging evidence emphasizes the link between both insulin resistance and hyperuricemia with CAD, no definite relationship has been established yet (7, 20). As such, it has been hypothesized that hyperinsulinemia might cause hyperuricemia, and that the reverse would not be true. Additionally, lowering serum urate levels is unlikely to improve insulin resistance and associated cardiometabolic consequences; conversely, alleviating insulin resistance may decrease serum urate levels and subsequent gout risk (22, 23).

Therefore, conducting a comparative investigation of patients with CAD and without CAD to assess the presence of insulin resistance and hyperuricemia could offer valuable insights into the potential associations between these risk factors and CVDs. Although the hyperinsulinemic-euglycemic clamp is considered the gold standard for determining insulin resistance, given the fact that it is invasive, time consuming, and expensive, conventionally in epidemiological studies and clinical practice, the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) has been recognized as a reliable and popular method to gauge insulin resistance, using fasting blood glucose and insulin (24, 25). However, there are also additional practical and feasible indirect methods that do not require serum insulin levels to approximate insulin resistance status. Therefore, predicting insulin resistance status through novel surrogate indicators, including the triglyceride glucose (TyG) and TyG-body mass index (BMI) indices, taking into account a combination of fasting triglycerides, glucose, and BMI status (as an indicator of obesity and excess body weight), may be more feasible and practical than the other costly methods (7, 26–29). TyG and TyG-BMI have been shown to accurately indicate lipotoxicity and glucotoxicity status (30, 31). Furthermore, similar to more well-known markers of insulin resistance, such as HOMA-IR, these novel biomarkers have also been shown to be significantly associated with CVD risk factors such as metabolic syndrome, arterial stiffness, diabetes, hypertension, coronary stenosis, and all-cause and/or cardiovascular (CV) mortality (30–36). In particular, Cho et al. conducted a cross sectional study that indicated that the TyG index was correlated with risk of obstructive CAD and CAD incidence, even following adjustment for traditional cardiovascular risk factors (25). Therefore, we sought to determine insulin resistance status using novel surrogate indices including TyG and TyG-BMI, along with SUA among patients with and without

CAD, as these indices may serve as feasible and practical clinical assessments approximate insulin resistance, and to determine risk for hyperuricemia, and atherosclerotic-related conditions.

Methods

Participants

In this single-center cross-sectional study, data were obtained from 2019 to 2021, when about 12,000 Iranian individuals visited the cardiology outpatient clinic at Dr. Heshmat Hospital in Rasht, Iran. Reasons for visiting the clinic varied from routine check-ups to having clinical signs of cardiac disorders. Expert cardiologists examined all patients to determine CAD diagnosis. Following reviews of a total of 12,000 medical records, those of 2000 patients were randomly selected for inclusion in the current study. Of the 2000 patients selected, cardiologists ruled out a CAD diagnosis in 1000 patients following the initial examination and assessment of clinical or laboratory signs of atherosclerotic conditions or angina pectoris. These assessments were also based on negative results for non-invasive tests (i.e., exercise stress tests, and/or echocardiography). For the remaining 1,000 patients, angiographic findings were then used to confirm CAD diagnosis in accordance with "*ESC 2019 guidelines for the diagnosis and management of chronic coronary syndromes*" (37). All patients who had the required demographic, medical history, and anthropometric data (such as weight and height) were considered for study inclusion. Patients with medical histories indicating a serious cardiac disorder, liver, kidney, neurologic diseases, cancer, thyroid dysfunction, gout according to physicians' diagnosis or those who reported use of alcohol, vitamin C supplements, theophylline, or warfarin 3 months prior to study were excluded from the study. Accordingly, 644 subjects in the non-CAD group (134 did not meet the inclusion criteria, and 510 did not have anthropometric, clinical, and biochemical laboratory data past medical history, physician examination data, triglycerides, uric acid, and blood glucose), and 286 subjects in the CAD group (69 did not meet the inclusion criteria, and 117 lacked anthropometric, clinical, and biochemical laboratory data) were excluded from the analysis. In total, 1,170 patients (356 non-CAD and 814 CAD) between the ages of 30 and 75 years, with BMIs between 18.5 and 39 kg/m^2 were included for analysis (Figure 1).

All research procedures were in line with the guidelines outlined in the 2013 version of the Declaration of Helsinki. The study protocol was assessed and approved by the Cardiovascular Diseases Research Center Institutional Review Board [affiliated with Guilan University of Medical Sciences (GUMS)] (registered with research number = 4,246). The GUMS' Ethics Committee also approved this study (ethics code number = IR.GUMS.REC.1401.174). Formal oral and written assent were obtained when the patients were informed of the study objectives.

Measurements of anthropometry and clinical data collection

Measurements of obesity indices such as weight (kg), height (m), and BMI (kg/m^2) were performed. To achieve precise measures, professional healthcare staff measured weight without shoes and with minimal clothing. A Seca 755 dial was used to determine weight via medical scale column (weighing accuracy of 0.5 kg). Height was measured to the nearest 0.1 cm via standard stadiometer. Height was measured without shoes and with shoulders in a neutral position. BMI was computed by dividing weight (kg) by height (m) squared. A BMI of $\geq$25 or $\geq$ 30 is considered overweight or obese, respectively. Prior to initiation of the study, all patient demographic and anthropometric data were collected. Past medical history was determined (including history of hypertension, T2DM, hyperlipidemia, and ever-smoking) as well as history of medications consumption and medications prescribed after angiography for patients with a CAD diagnosis: antihypertensive drugs [particularly beta blockers, thiazides, angiotensin II receptor blockers (ARBs); angiotensin-converting enzyme inhibitors (ACE inhibitors); calcium channel blockers (CCBs); antidiabetic medications (including metformin, and/or sulfonylureas); antihyperlipidemic medications (mainly statins); proton-pump inhibitors (PPIs); and antiplatelets including aspirin and clopidogrel (Plavix)].

Angiography of the coronary arteries

Two cardiologists, based on the Judkin technique, used a femoral approach to perform coronary angiographs, and the severity of atherosclerosis was examined visually. Normal angiograms showed no apparent atherosclerotic changes in the coronary arteries, interpreted by cardiologists who were blinded to study details. The presence of stenosis in one, two, or three main coronary arteries was used as evidence of single-, two-, or three-vessel coronary artery disease. All patients with CAD underwent echocardiology in fewer than 3 days from hospitalization, in order to estimate left ventricular systolic ejection (LVEF). Based on the International Simpson method, two independent echocardiologists assessed the graphs again.

Laboratory analyses

All patients were fasted for at least 8 h before 10 mL venous blood samples were drawn. To prevent coagulation, the samples were stored with sodium citrate in tubes at −20 degrees Celsius until the concentrations of fasting blood glucose (FBS) and total cholesterol were determined using the enzymatic-colorimetric method in accredited laboratories based on the manufacturer's instructions (38). The enzymatic method (MAN CO., Tehran, Iran) was used to estimate high-density lipoprotein cholesterol (HDL-C) levels and serum uric acid levels, applying the uricase–peroxidase system (39). Triglyceride levels were measured using the enzymatic method through applying glycerol phosphate oxidase and using Bionic corporation commercial kits (MAN Co., Tehran, Iran). Themethod and Fried Wald formula was used in order to estimate low-density lipoprotein cholesterol (LDL-C) levels (40–42). Additionally, hemoglobin A1c (HbA1c) levels were measured and compared only among patients with a past medical history of T2DM (n = 399). As mentioned in the URRAH Study, total and cardiovascular mortality were predicted based on the level of SUA in diabetic patients using a 5.6 mg/dL cut point as a clinical margin (3). Thus, we considered those with SUA $\geq$ 5.6 mg/dL to have hyperuricemia.

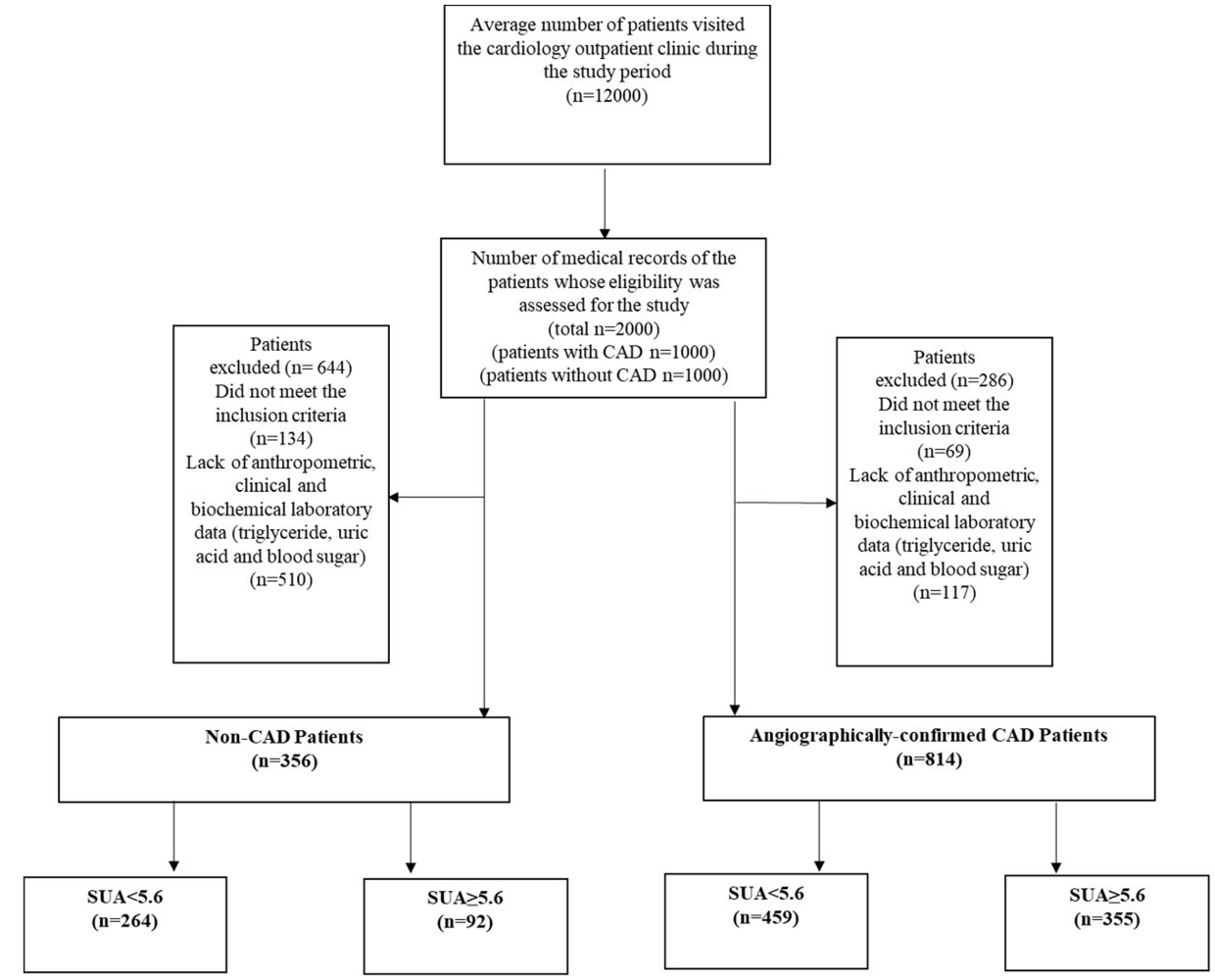

FIGURE 1
Participant flow diagram. CAD, coronary artery disease; SUA, serum uric acid.

Novel insulin resistance surrogate markers

According to reported methods from previous studies, the insulin resistance surrogate indicators were calculated using the following formulas:

$$\text{Triglyceride glucose}\left(\text{TyG}\right)\text{index} = \text{Ln}\left(\frac{\text{fasting triglycerides}\left(\frac{\text{mg}}{\text{dL}}\right)\times\text{fasting glucose}\left(\frac{\text{mg}}{\text{dL}}\right)}{2}\right) \quad 31$$

$$\text{Triglyceride glucose}\left(\text{TyG}\right)-\text{BMIindex} = \left(\text{TyGindex}\times\text{BMI}\right) \quad 31,35$$

Statistical methods

No apriori statistical power calculations were performed. Hence, the current sample size (n = 2,000 non-CAD and CAD subjects) was determined according to our previous experience with this design. Due to the study methods, there were no missing data. Shapiro–Wilk tests were used to determine whether data were normally distributed. Categorical data were determined as frequency and %, and chi-squared or Fisher's exact tests were used to analyze between-group differences. For continuous data, differences in the mean values were determined via independent samples t-tests and means and standard deviations (SD) were reported. The odds of hyperuricemia were examined for the novel markers under study using logistic regression. Biological sex, age, and history of hypertension, T2DM, hyperlipidemia, or using antihypertensive, antidiabetic, or anti-hyperlipidemic medications, in addition to ever-smoking status were all added as control variables for the fully adjusted model. By treating the median values of each tertile as continuous variables, we also tested for linear trends (p-values for trend) corresponding with odds of hyperuricemia across tertiles of insulin resistance surrogate markers, and odds ratios (OR) with corresponding 95% confidence intervals (CIs) were provided. Besides, Pearson correlation tests used for the analysis of correlation between serum uric acid and TyG index and TyG-BMI levels among CAD and non-CAD patients, and the correlation coefficient, 95%

confidence intervals (CIs) and *p*-values are presented. IBM SPSS software was used for all analyses (version 24.0; SPSS, Chicago, IL).

Results

Baseline characteristics

Baseline demographic, anthropometric, and clinical characteristics of study participants, with and without CAD according to hyperuricemia status, are provided in Table 1. Overall, 1,170 patients were enrolled in the present cross-sectional study, with an average age of 52 (8) and 48 (8) years for patients with CAD ($n = 814$) and without CAD ($n = 356$), respectively. Participants were then divided into two groups on the basis of whether or not they had hyperuricemia (SUA levels above 5.6 mg/dL). Among the 814 patients with CAD, 355 had hyperuricemia, of whom 47.3% were male. Out of 356 patients without CAD, 92 had hyperuricemia, of whom 44.6% were male (Table 1). Patients with CAD who had hyperuricemia were more likely to be men and ever-smokers, had higher BMIs, and were more likely to have a history of hypertension, hyperlipidemia, and use of anti-hyperlipidemic medications (*p*-values < 0.05). Additionally, these patients had higher levels of SUA, triglycerides, TyG, and TyG-BMI, as compared to patients with CAD who did not have hyperuricemia (*p*-value < 0.001). However, there were no significant differences between the groups for total cholesterol or FBS levels (Table 1). Similarly, patients without CAD with hyperuricemia had significantly greater concentrations of SUA, triglycerides, TyG, and TyG-BMI than those without hyperuricemia, whereas patients in these subgroups were similar in terms of proportion of males/females, age, BMI, past medical histories, medication use, and other clinical and laboratory characteristics. Moreover, the HbA1c levels of diabetic patients, both with and without CAD, were not significantly different (Table 1).

CAD patients' clinical characteristics, including categorization of CAD types (the numbers of involved vessels based on angiographic findings), LVEF, and prescribed medications according to hyperuricemia status, are provided in Table 2. About one-third of CAD patients without hyperuricemia had nonobstructive CAD (32.2%), while a greater proportion of those with hyperuricemia were diagnosed with three-vessel coronary disease (33.2%). Those with hyperuricemia also tended to have lower LVEF. All CAD patients were prescribed antiplatelets, statins, PPIs, and antihypertensive medication, regardless of hyperuricemia status (Table 2).

Table 3 and Figures 2A–D present the unadjusted and adjusted ORs and associated 95%CIs for hyperuricemia according to the tertiles of insulin resistance surrogate indicators, in patients with and without CAD. According to the crude regression models, when exploring the relationship between TyG and odds of hyperuricemia among those with CAD, compared to patients in the 1st tertile of TyG (median = 8.37), the patients in both the 2nd (median = 8.95) (OR = 1.62, 95% CI 1.128–2.34) and 3rd tertiles (median = 9.62) (OR = 1.85, 95% CI 1.30–2.63) had significantly higher odds of hyperuricemia (*p*-value for trend = 0.001). Likewise, after controlling for potential confounders including age, biological sex, history of T2DM, hyperlipidemia, and hypertension, using antihypertensive, antidiabetic, or antihyperlipidemic medications, and ever-smoking status in the multiple regression models, it was found that those in the 2nd and 3rd tertiles of TyG had 60–65% higher odds of hyperuricemia (OR = 1.65, 95% CI 1.12–2.42; and OR = 1.60, 95% CI 1.02–2.51, respectively) compared with patients in the 1st tertile (*p*-value for trend = 0.036) (Table 3; Figure 2A). In the patients without CAD, although an overall significant association between TyG and hyperuricemia was detected (*p*-value for trend = 0.043) in the unadjusted model, only those in the 2nd tertile of TyG (median = 8.95) had elevated odds of hyperuricemia (OR = 1.81, 95% CI 1.05–3.10). Nonetheless, after multivariable model adjustment for relevant confounders, no significant associations remained (*p*-value for trend = 0.072) (Table 3; Figure 2B).

With respect to the relationship between TyG-BMI index and hyperuricemia among the studied groups, according to the crude regression models, significant increases in odds of hyperuricemia were noted among patients with CAD in the 3rd tertile of the TyG-BMI index (median = 296.45) (OR = 1.97, 95% CI 1.38–2.82) as compared with those in the 1st tertile (median = 217.61) (*p*-value for trend < 0.001). This elevated odds of hyperuricemia remained significant following adjustment for confounding factors and was approximately 83% for CAD patients in the highest tertile of TyG-BMI as compared to the lowest (OR = 1.83, 95% CI 1.24–2.70; *p*-value for trend = 0.002) (Table 3; Figure 2C). However, no significant relationships between TyG-BMI index and hyperuricemia were indicated among patients without CAD in either unadjusted or multiple regression models (Table 3; Figure 2D).

Figures 3A–D plots SUA levels by insulin resistance surrogate markers (TyG and TyG-BMI indices) among patients with and without CAD. The correlation between TyG and SUA levels was not significant among the patients without CAD. Whereas, among patients with CAD, there was a weak positive correlation between TyG and SUA levels ($r = 0.127$; *p*-value < 0.001) (Figures 3A,B). Figures 3C,D plot SUA levels against TyG-BMI in the two studied groups. There were significant weak positive correlations between TyG-BMI and SUA concentrations among both patients with CAD ($r = 0.218$; *p*-value < 0.001) and without CAD ($r = 0.212$; *p*-value < 0.001).

Discussion

The primary purpose of the current study was to examine the associations between insulin resistance status as assessed by novel surrogate markers including TyG and TyG-BMI, and odds of hyperuricemia among patients with and without CAD. Results indicated that these novel indices could predict risk of hyperuricemia among CAD patients, regardless of potential confounders. Although neither the unadjusted (except for TyG index), nor the multiple regression models revealed statistically significant relationships in patients without CAD, there were significant weak positive correlations between TyG-BMI and SUA concentration in both the CAD and non-CAD groups. However, high TyG index showed a weak positive association with high levels of SUA only among the CAD group.

Physiological concentration of SUA, the metabolic byproduct of purine nucleotides, has beneficial powerful antioxidant effects and works as a free radical scavenger. Moreover, the protective effects of SUA include DNA damage resistance, anti-osteoporotic action, and postponement of cognitive decline. With excessive concentrations,

TABLE 1 Baseline demographic, anthropometric, and clinical characteristics of study participants, with and without coronary artery disease (CAD) according to hyperuricemia status.

	Studied group					
	Non-CAD patients (n = 356)			CAD patients (n = 814)		
	Hyperuricemia status			Hyperuricemia status		
	SUA < 5.6 (n = 264)	SUA ≥ 5.6 (n = 92)	P-value	SUA < 5.6 (n = 459)	SUA ≥ 5.6 (n = 355)	P-value
Biological sex number of males (percentage)	97 (36.7%)	41 (44.6%)	0.214	169 (36.8%)	168 (47.3%)	0.003
Hypertension history number (percentage)	13 (4.9%)	9 (9.8%)	0.128	202 (44.0%)	182 (51.3%)	0.040
Using antihypertensive medications [α] (percentage)	11 (4.2%)	8 (8.7%)	0.109	185 (40.3%)	162 (45.6%)	0.134
T2DM history number (percentage)	30 (11.4%)	13 (14.1%)	0.464	203 (44.2%)	153 (43.1%)	0.776
Using antidiabetic medications [β] (percentage)	29 (11.0%)	13 (14.1%)	0.454	193 (42.0%)	141 (39.7%)	0.518
Hyperlipidemia history number (percentage)	21 (8.0%)	13 (14.1%)	0.099	112 (24.4%)	135 (38%)	<0.001
Using antihyperlipidemic medications [γ] (percentage)	20 (7.6%)	10 (10.9%)	0.383	97 (21.1%)	117 (33.0%)	<0.001
Ever- smokers	18 (6.8%)	6 (6.5%)	1.000	56 (12.2%)	92 (25.9%)	<0.001
Age, (years) (mean, SD)	49 (8)	48 (8)	0.507	53 (8)	52 (8)	0.757
BMI, kg/m^2 (mean, SD)	28.05 (4.78)	29.02 (4.60)	0.093	27.99 (3.81)	29.04 (4.07)	<0.001
Serum biochemical analysis [mean (SD)]						
SUA (mg/dL)	3.0 (1.6)	6.5 (1.0)	<0.001	4.4 (0.7)	7.4 (2.1)	<0.001
Triglycerides (mmol/L)	1.51 (0.65)	1.67 (0.63)	0.043	1.69 (0.96)	1.98 (1.01)	<0.001
Total cholesterol (mmol/L)	4.57 (0.79)	4.51 (0.92)	0.532	4.59 (1.04)	4.64 (1.15)	0.533
Fasting blood sugar (mmol/L)	5.47 (1.45)	5.55 (1.44)	0.630	7.57 (3.78)	7.40 (3.53)	0.505
HbA1c (%) *	6.27 (1.29)	6.68 (1.36)	0.359	6.54 (1.46)	6.47 (1.67)	0.690
Triglyceride glucose (TyG) index	8.66 (0.58)	8.80 (0.54)	0.049	9.01 (0.66)	9.18 (0.65)	<0.001
Triglyceride glucose (TyG)-BMI	243.62 (47.40)	255.64 (44.8)	0.034	252.23 (38.45)	266.76 (44.35)	<0.001

CAD, coronary artery disease; BMI, body mass index; SUA, serum uric acid; SD, standard deviation.
[α] Mainly include beta blockers, thiazides, ARBs (Angiotensin II receptor blockers), ACE inhibitors (Angiotensin-converting enzyme inhibitors), and CCBs (calcium channel blockers).
[β] Mainly include metformin, and/or sulfonylureas.
[γ] Mainly include statins.
* Measured and compared only among patients with a history of T2DM (n = 399).

high uric acid levels or hyperuricemia followed by aggregated production of reactive oxygen species (ROS) under conditions of stress, such as hypoxia and ischemia would occur (8). Ongoing epidemiological studies suggest that there are global increases in circulating levels of SUA (43). Hence, a definitive threshold level for diagnosis of hyperuricemia associated with increased risk of chronic metabolic disorders, that might also be considered as an important routine clinical test for patients with such disorders, could be clinically beneficial (44). Results from the URRAH research indicated that regardless of age, gender, the history of T2DM or hypertension, patients with metabolic syndrome had a greater risk of cardiovascular death when they had hyperuricemia, as assessed by a cut-off level of 5.6 mg/dL (3). Additionally, one cohort study conducted in China, showed that increased SUA was considered as a risk factor for CAD, regardless of obesity status (45). The same results were obtained in a cohort study conducted in the United States, where a positive correlation between elevated SUA levels and CVD disease risk factors was shown (46). Recently, some research has studied the correlations between hyperuricemia or elevated SUA levels and not only CVD, but also several metabolic disorders such as T2DM, kidney disease, and hypertension (20, 22, 47–49).

With respect to this evidence, in the current cross-sectional study, we aimed to explore two novel insulin resistance surrogate markers (TyG and TyG-BMI) as predictors for odds of hyperuricemia among patients with and without CAD. TyG index, as a promising surrogate measure for insulin resistance in large-scale epidemiological investigations given its simplicity of use and affordability, had a strong correlation with TyG-BMI, TyG-waist circumference (TyG-WC), HOMA-IR, and HbA1c (50). This novel biomarker has been considered as an effective marker in diagnosis of some chronic diseases such as metabolic syndrome and T2DM (51). Interestingly, a recently published study reported the higher the TyG index value, the higher the risk of CVDs over a 10-year period (29). Moreover, the inclusion of this index in the Framingham risk score (FRS) showed an added value, enhancing the predictive power of this score for CVD risk evaluation (52).

Similarly, TyG-BMI, which measures the TyG index multiplied by the BMI, is thought to be another reliable marker for diagnosing insulin resistance as compared with conventional lipid measures including blood lipid ratios, blood glucose markers, and obesity-related parameters. Additionally, TyG-BMI has been linked to prehypertension, nonalcoholic fatty liver disease, and stroke in a number of recent investigations (53–55).

TABLE 2 Clinical characteristics of patients with CAD according to hyperuricemia status.

	CAD patients (n = 814)	
	Hyperuricemia status	
	SUA < 5.6 mg/dL (n = 459) Cases (%)	SUA ≥ 5.6 mg/dL (n = 355) Cases (%)
Nonobstructive CAD	148 (32.2%)	96 (27.0%)
One-vessel coronary disease	91 (19.8%)	80 (22.5%)
Two-vessel coronary disease	81 (17.6%)	61 (17.2%)
Three-vessel coronary disease	139 (30.3%)	118 (33.2%)
LVEF mean (SD)	47 (10)	44 (12)
Prescribed medications after angiography		
Antiplatelets [α] (number, percentage)	459 (100%)	355 (100%)
Statins [β] (number, percentage)	459 (100%)	355 (100%)
Antihypertensive [γ] (number, percentage)	459 (100%)	355 (100%)
PPIs [ε] (number, percentage)	459 (100%)	355 (100%)

CAD, coronary artery disease. LVEF, left ventricular ejection fraction. PPIs, proton-pump inhibitors.
[α] Mainly include aspirin, clopidogrel (Plavix).
[β] Mainly include atorvastatin.
[γ] Mainly include ARBs (Angiotensin II receptor blockers), ACE inhibitors (Angiotensin-converting enzyme inhibitors), CCBs (calcium channel blockers).
[ε] Mainly include pantoprazole.

The present research outcomes indicate positive correlations between TyG and SUA only among patients with CAD, and between TyG-BMI and SUA in patients both with and without CAD, though correlations were weak, further supporting the associations between higher insulin resistance and hyperuricemia particularly among patients suffering from CAD. However, it should be noted that there might be some possibility of spurious correlations, or statistically significant results found by random chance as the observed correlation coefficients between the studied parameters were not very strong. Regardless of this limitation, these findings expand the currently available evidence indicating that elevated levels of serum lipids and blood glucose, as indicated in insulin resistance alternative markers particularly TyG-BMI, were significantly associated with the odds of hyperuricemia (7, 8, 56–62). Shi et al. (58), conducted a case–control study on hyperurecemic patients (n = 339) compared to control subjects (n = 6,127), aiming to explore the utility of the TyG index for estimating hyperuricemia risk among a Chinese population. In parallel with the current study, results indicated that subjects in the fourth quartile of TyG index had a significant increased risk for hyperuricemia than those in the first quartile. More importantly, results indicated that simultaneous lipid and glycemic control is necessary for hyperuricemia prevention (58). Align with these findings, Kahaer et al. investigated the relationship between a number of obesity-related risk factors and risk of hyperuricemia (defined as an SUA level > 7.0 mg/dL) among a total of 2,243 Chinese subjects, an even more robust association was revealed when exploring the TyG index in relation to hyperuricemia risk (56). Additional reports have indicated that the TyG index could significantly predict the risk of hyperuricemia among subjects diagnosed with hypertension (7, 57, 60). For example, in a cross-sectional study among Chinese older adults in which TyG and TyG-BMI indices were used as insulin resistance biomarkers, these markers were shown to be significantly associated with increased risk of hyperuricemia or hypertension alone or in combination (60). Interestingly, such relationships seem to be consistent in patients with T2DM (8, 20, 62). In a cross-sectional study conducted by Hang et al., it was reported that in patients with T2DM, a weak but significant correlation was detected between SUA and insulin resistance as indicated by TyG (r = 0.406, p-value < 0.05) and the triglyceride to HDL-C ratio (r = 0.493, p-value < 0.05). Additionally, TyG-BMI (r = 0.272, p-value < 0.05) and METS-IR (r = 0.238, p-value < 0.05) showed very weak, but still significant correlations with insulin resistance (8). These results were consistent with another study showing a significant association between elevated SUA and higher risk of insulin resistance, especially in women with T2DM (20). A recently published study by Qi et al., additionally confirmed that TyG could be considered as a risk factor for developing hyperuricemia among patients suffering from nonalcoholic fatty liver disease (NAFLD), regardless of potential confounders (63). Of note, another recent study suggested that either of the factors, hyperuricemia or elevated TyG index, could independently predict the risk of major adverse cardiovascular event (MACE) occurrence among those who underwent coronary artery bypass grafting (CABG). Intriguingly, the two predictivefactorsshowed a synergistic interaction. As such, the highest risk of reporting MACE was noted among the subjects presenting with increased TyG index and serum uric acid levels simultaneously, as compared to those with lower levels of either of these factors (64). These reports confirm the added value of considering both insulin resistance and hyperuricemia indicators when assessing risk for CVDs and comorbid complications.

Since a causal relationship between insulin resistance and SUA has not been determined, a definite mechanism underlying the association between these two conditions cannot be confirmed. Notably, one of the primary predictors of insulin resistance is believed to be excess adipose tissue, which then could be involved in inducing oxidative stress (65). Additionally, insulin resistance promotes SUA synthesis via the hexose monophosphate route, while decreasing SUA renal excretion (66, 67). One more important point is that insulin escalates renal reabsorption of uric acid via stimulation of glucose transporters (Glut 9) (encoded by SLC2A9) and other renal urate transporters participate in reabsorption of uric acid (10). In other words, insulin resistance and resultant hyperinsulinemia encourage the renal tubules to reabsorb uric acid. Accordingly, this condition could then enhance the creation of fat cells in the liver, leading to aberrant purine metabolism and a subsequent increase in SUA levels (68). However, some studies have also suggested that central adiposity and SUA accumulation may contribute to insulin resistance (67). As mentioned, augmented SUA levels may lead to oxidative stress, which then may impair glucose metabolism and reduce insulin sensitivity, and might contribute to insulin resistance by upregulating insulin receptor substrate 1 phosphorylation, as well as increased production of excessive ROS (66–68). Additionally, the ROS formation escalation following hyperuricemia could result in a decrease in the transcription factors necessary for the expression of the insulin gene, and a reduction in insulin synthesis and release (69).

TABLE 3 Odds ratios and 95% confidence intervals for hyperuricemia according to tertiles of insulin resistance surrogate markers.

	Tertiles of insulin resistance surrogate markers			*P*-value[d]
	1st tertile	2nd tertile	3rd tertile	
Triglyceride glucose (TyG) index				
CAD patients				
Cases/non-cases	76/148	122/146	157/165	
Median	8.37	8.95	9.62	
Crude model	1.00	1.62 (1.12–2.34)	1.85 (1.30–2.63)	0.001
Multivariable adjusted model [a]	1.00	1.65 (1.12–2.42)	1.60 (1.02–2.51)	0.036
Non-CAD patients				
Cases/non-cases	33/132	38/84	21/48	
Median	8.23	8.95	9.38	
Unadjusted model	1.00	1.81 (1.05–3.10)	1.75 (0.92–3.31)	0.043
Multivariable adjusted model [a]	1.00	1.72 (0.98–3.01)	1.81 (0.77–4.20)	0.072
Triglyceride glucose (TyG)-BMI				
CAD patients				
Cases/non-cases	86/158	129/171	140/130	
Median	217.61	251.90	296.45	
Crude model	1.00	1.38 (0.97–1.96)	1.97 (1.38–2.82)	<0.001
Multivariable adjusted model [a]	1.00	1.35 (0.94–1.95)	1.83 (1.24–2.70)	0.002
Non-CAD patients				
Cases/non-cases	29/116	28/63	35/85	
Median	200.81	253.82	294.84	
Crude model	1.00	1.77 (0.97–3.24)	1.64 (0.93–2.90)	0.088
Multivariable adjusted model [a]	1.00	1.81 (0.97–3.40)	1.71 (0.93–3.13)	0.087

CAD, coronary artery disease; SUA, serum uric acid; BMI, body mass index.

[a] Multiple regression model adjusted for biological sex; age, and history of hypertension, T2DM, or hyperlipidemia, using antihypertensive [α], antidiabetic [β], or antihyperlipidemic medications [γ], and ever-smoking status.

[α] Mainly include beta blockers, thiazides, ARBs (Angiotensin II receptor blockers), ACE inhibitors (Angiotensin-converting enzyme inhibitors), and CCBs (calcium channel blockers).

[β] Mainly include metformin, and/or sulfonylureas.

[γ] Mainly include statins.

[d] *p*-value less than 0.05 considered as statistical significant.

The clinical importance of the current findings

Despite the fact that the cross-sectional design of the current study limits the ability to determine causal relationships between the studied exposures and outcomes, as well as their clinical interpretation, the present study suggested that TyG and TyG-BMI indices, along with SUA levels may serve as feasible and practical clinical assessments to determine risk for hyperuricemia and atherosclerotic-related conditions. Accordingly, it seems that employing these available and inexpensive measures could assist in risk stratification and early detection of CAD patients who may require more comprehensive treatment options in association with insulin resistance. Nonetheless, long-term prospective cohort investigations are necessary to confirm the diagnostic value of these novel indices for early detection of insulin resistance and hyperuricemia, as well as associated CAD comorbidities. Future studies should also consider establishing cut points for optimal balance between positive and negative-predictive values of the surrogate markers of insulin resistance.

Study strengths and limitations

Several strengths are attributed to the current study. Foremost, this is the first study to assess the odds of hyperuricemia based on novel insulin resistance surrogate markers among patients with and without CAD in a sample of the Iranian population. Another strength is that CAD diagnosis was established using findings from angiograms, interpreted by two expert interventional cardiologists. Consequently, miscategorization of CAD cases was minimized.

The present research study has also limitations which should be considered when interpreting findings. First, the cross-sectional, retrospective, and single-center properties of the study limit interpretation as well as generalizability. Associations between the novel insulin resistance indices and incidence of future hyperuricemia events, gout, and related morbidity and mortality could not be explored because of absence of follow-up data. Additionally, due to absence of data on a number of relevant explanatory variables including waist circumference, dietary intakes, sleeping habits, and physical activity, the potential effects of these variables on the study biomarkers and outcomes could not be considered.

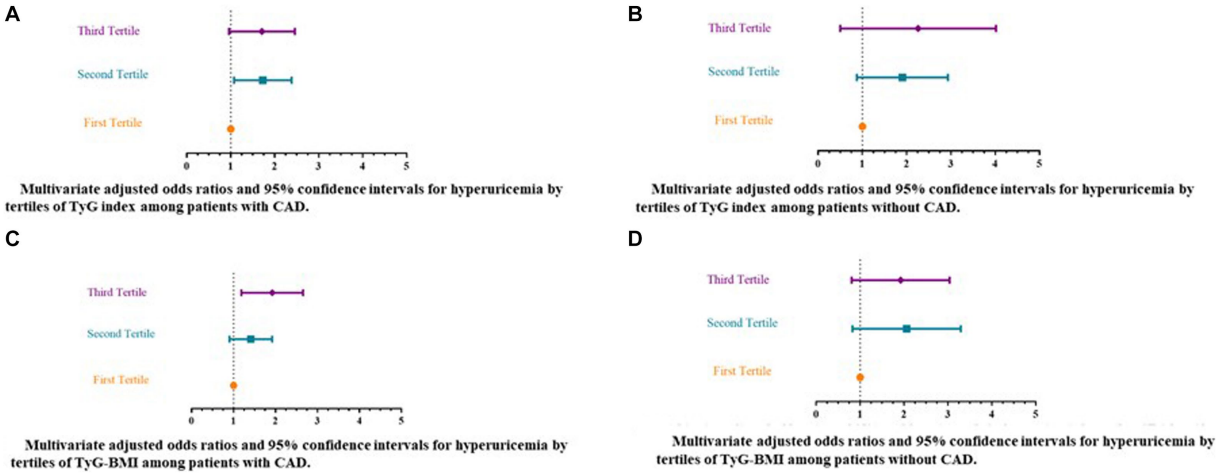

FIGURE 2
Multivariate adjusted odds ratios and 95% confidence intervals for hyperuricemia by tertiles of insulin resistance surrogate markers [triglyceride-glucose (TyG) index and triglyceride-glucose-body mass index (TyG-BMI)]. **(A)** Multivariate adjusted odds ratios and 95% confidence intervals for hyperuricemia by tertiles of TyG index among patients with CAD. **(B)** Multivariate adjusted odds ratios and 95% confidence intervals for hyperuricemia by tertiles of TyG index among patients without CAD. **(C)** Multivariate adjusted odds ratios and 95% confidence intervals for hyperuricemia by tertiles of TyG-BMI among patients with CAD. **(D)** Multivariate adjusted odds ratios and 95% confidence intervals for hyperuricemia by tertiles of TyG-BMI among patients without CAD. [a] Multiple regression model adjusted for biological sex; age, and history of hypertension, T2DM, or hyperlipidemia, using antihypertensive [α], antidiabetic [β], or antihyperlipidemic medications [γ], and ever-smoking status. [α] Mainly include Beta blockers, Thiazides, ARBs (Angiotensin II receptor blockers), ACE inhibitors (Angiotensin-converting enzyme inhibitors), and CCBs (calcium channel blockers). [β] Mainly include metformin, and/or sulfonylureas. [γ] Mainly include statins. TyG, triglyceride-glucose index. CAD, Coronary artery disease. TyG-BMI, triglyceride-glucose-body mass index.

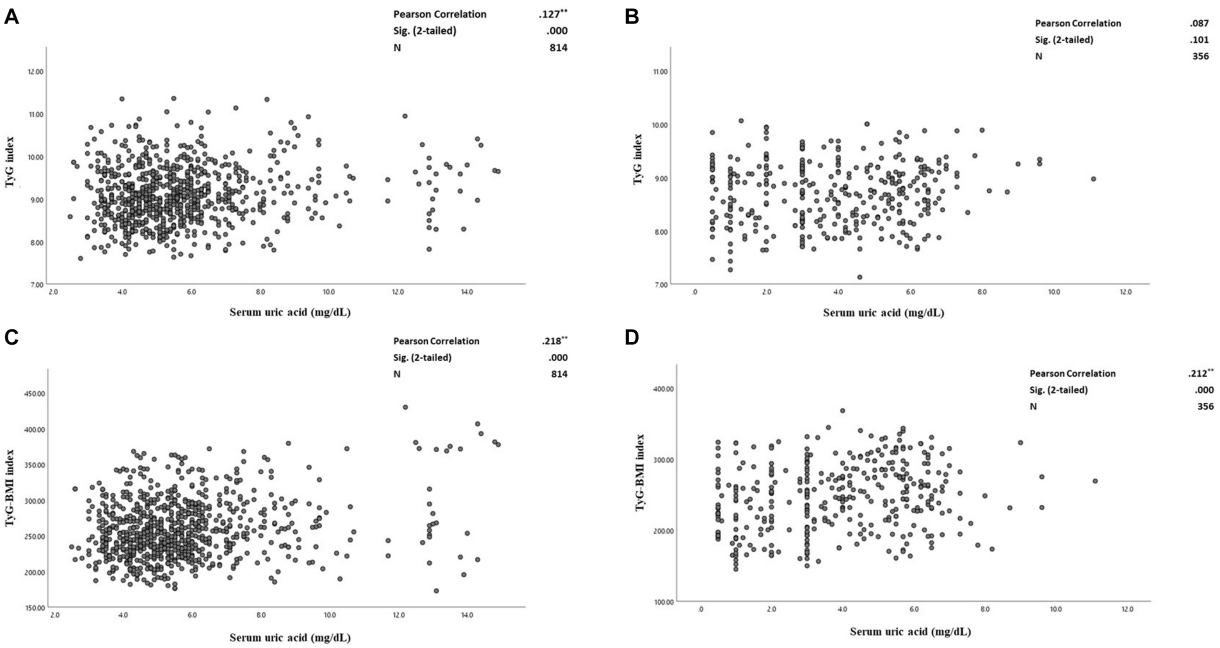

FIGURE 3
(A–D) The correlation between serum uric acid and triglyceride-glucose (TyG) index and triglyceride-glucose-Body mass index (TyG-BMI) levels among CAD and non-CAD patients. **(A)** The correlation between serum uric acid and TyG index among the patients with CAD. **(B)** The correlation between serum uric acid levels and TyG index among the patients without CAD. **(C)** The correlation between serum uric acid and TyG-BMI indices among the patients with CAD. **(D)** The correlation between serum uric acid levels and TyG-BMI indices among the patients without CAD. Pearson correlation tests used and the correlation coefficient, 95% confidence intervals (CIs) and *p*-values are presented. TyG, triglyceride-glucose index. CAD, Coronary artery disease. TyG-BMI, triglyceride-glucose-body mass index.

Conclusion

The current cross-sectional study of 814 angiographically-confirmed patients with CAD and 356 patients without CAD, revealed that two novel insulin resistance surrogate markers, TyG and TyG-BMI indices, were associated with increased odds of hyperuricemia, regardless of potential confounders. For patients with CAD, those in the highest tertiles for both TyG and TyG-BMI, had increased odds for hyperuricemia by 60 and 83%, respectively. Although no significant relationships were indicated for patients without CAD, significant positive and weak correlations between TyG-BMI and SUA concentrations among patients with and without CAD were noted. However, the correlation between elevated TyG index scores, and elevated levels of SUA appeared to be significant only among patients with CAD.

All together, the present study findings indicate that stratifying the patients based on their SUA levels and insulin resistance surrogate indices may facilitate primary screening and early diagnosis of CAD patients who may require more comprehensive treatment options associated with insulin resistance. However, further research with stronger study designs is needed to confirm these outcomes.

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 protocol was assessed and approved by the Cardiovascular Diseases Research Center Institutional Review Board [affiliated with Guilan University of Medical Sciences (GUMS)] (registered with research number = 4246). The GUMS' Ethics Committee also approved this study (ethics code number = IR.GUMS.REC.1401.174). 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

MM-R and ZG conceived and designed the research. MM-R, ZG, SA, and AH played an important role in data collection and reviewing the patients' documents. MM-R, ZG, and NS acquired data and performed data analysis. MM-R, ZG, SM, NS, and SR played an important role in results interpretation and drafted and revised the manuscript. All authors reviewed and approved the final version of the submitted manuscript.

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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A qualitative study of food sociality in three provinces of South China: social functions of food and dietary behavior

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Background: Food sociality refers to the exploration of food production, exchange, distribution, and consumption and influences on cultural communication and social meaning. This study aimed to investigate food sociality in three provinces of South China to provide theoretical and practical evidence of food sociality in the region and to revise nutrition policies.

Materials and methods: We conducted a qualitative study comprising 25 experts in the fields of nutrition, sociology, food science, and agriculture from Hainan, Guangdong, and Guangxi Province by using a semi-structured in-depth interview, which included 28 pre-determined questions covering six topics. The interviews were conducted between November 2020 and March 2021. Verbatim transcripts were analyzed thematically using NVivo 11.0.

Results: Of the 25 experts, the mean age was 50.6 (SD = 8.4) years, 15 (60%) were male, and 22 (88%) held a master's degree or above. The analysis showed that food sociality in three provinces of South China mainly comprises social functions of food and dietary behavior. Regarding social functions of food, the experts expressed that food represents local culture (72%, 18 experts), presents social status and economic power (40%, 10 experts), and is central to special occasions, traditional customs, and etiquette activities (60%, 15 experts). In terms of social functions of dietary behaviors, the majority of experts indicated that food is a social communication tool (72% experts), has geographical characteristics (80% experts), and, to some extent, is used as a proxy for reward or punishment. Furthermore, festivals are one of the core elements of food sociality in the region, although food safety is a major concern. Some dietary behaviors, such as overindulgence in afternoon tea and encouraging drinking, may increase the risk of chronic diseases.

Conclusion: Food sociality in three provinces of South China is mainly related to the social function of food and dietary behavior. It is a combination of local culture, social status and economic power, traditional customs, rewards and punishments, geographical food preference, and social communication tools. The authors recommend increasing food safety at festivals and promoting healthy eating behaviors in order to improve the overall health of the population in this region.

KEYWORDS

South China, food, dietary behavior, social function, qualitative research, sociality

1. Introduction

Food sociality refers to the exploration of food production, exchange, distribution, and consumption as a special way to describe cultural communication and communicate social meaning (1). As a behavior with biological and cultural attributes, diet provides an excellent starting point for understanding all social behaviors, concepts, and theories of human groups (2). Though eating is fundamentally a basic physiological need, it is also a symbol and is given many social meanings. This means that the human diet evolves (3). People can understand the meaning of social life and culture of a social network via food, so food sociality is an understanding of the social nature of food.

From ancient times to the present, food has been endowed with expressive and profound cultural connotation by human beings. Under the condition that most people in society can meet their food requirements, human beings not only need food to survive and maintain health, but also to carry out social practices with interactive attributes (4).

Food preferences and consumption can be influenced by economics, politics, culture, and other factors. Food is not only about eating, drinking, nutrition, and digestion, but also about placing the food and eating habits of a regional group in the context of historical movements, thus gaining a unique perspective on the culture of individual and group life (5). Dietary behaviors facilitate "dialogue" between people and food and reflect people's desire to maintain and construct their social orders (6). From an anthropological perspective, food is part of a society that establishes relationships between people, environment, and beliefs (7).

However, many studies exploring food culture in three provinces of South China often overlook the social function of food (8–10). Ma believes that the social functions of food in the world generally include establishing and maintaining interpersonal relationships, expressing the degree of interpersonal relationships, representing social status, explaining group characteristics, celebrating important events, holding symbolic significance, and use as reward or punishment (11), but this study did not focus on South China, and the research on food sociality in the three provinces of South China is still missing. In addition, through reviewing literature, we found that the occurrence of chronic diseases and some special diseases in three provinces of South China may be related to the sociality of their food (12–16). Therefore, this study aimed to investigate food sociality in three provinces of South China, and explain under which conditions and activities the food sociality will emerge, to provide theoretical and practical evidence of food sociality in this region, to reduce the gap between South China and the rest of the world in the interpretation of food culture, and to provide recommended diet-related policies and interventions if necessary.

2. Materials and methods

2.1. Study design and settings

This qualitative study was conducted in three provinces of South China, namely Guangdong, Guangxi, and Hainan, where the residents' dietary practices and food culture differ significantly from the remaining regions of China. The region has a population of 187 million, a daily average temperature over 20°C, and an annual precipitation of 1,400–2,000 mm, i.e., a hot and rainy, four-season evergreen tropical-subtropical southern zone, with a unique research significance from a geographic perspective (17). Our study focused on the understanding of food sociality of locals by interviewing food-related experts from this region.

The data in this study are qualitative. As an important qualitative research and analysis software, Nivio can enable us to conduct content analysis and research based on Grounded theory, which is applicable to the processing of non-quantitative information such as group discussions, interviews, surveys, videos, audio, and social media. The extraction of files in different formats can be completed through nodes and encoding. Nvivo can significantly improve the quality of research. This software does indeed reduce a large number of manual tasks, giving researchers more time to discover trends, identify themes, and draw conclusions, which is conducive to the rigorous nature of the research and further improves its effectiveness. The analysis of qualitative data has become easier and the results have become more reliable.

2.2. Sampling

We used non-random sampling and snowball sampling methods to recruit the study participants, i.e., food-related experts. We identified experts who appeared frequently in academic journals, newspapers, and other authoritative media by using the key words "diet," "culture," and "nutrition." After a pilot study, theme saturation can be achieved by interviewing two experts in each field in each region. Therefore, 24 experts were planned to be recruited, and 25 experts were recruited overall. The inclusive criteria were: ① 10 years or more of working experience in nutrition, sociology, food, or agriculture; ② holding an intermediate or above level of professional or technical title; ③ with a bachelor degree or above; and ④ willing to participate in this study.

2.3. Interview

A one-to-one in-depth interview was given to the recruited 25 experts from the nutrition, sociology, and food or agriculture fields.

On the basis of Guansheng Ma's understanding of food sociality, we focused on food sociality from different biological and social perspectives, and discussed the development of the interview outline on this basis, such as the function of food and the meaning of dietary behaviors, putting together specific and subtle activity elements (18). In addition, considering the characteristics of South Chinese residents who like to eat together, we also added the hygiene problem of using serving chopsticks and serving spoons. After a pilot study, the feasibility of the food sociality interview outline was assessed by interviewing three experts from Guangdong, Guangxi, and Hainan, and the interview outline was adjusted according to the test results. Finally, the semi-structured

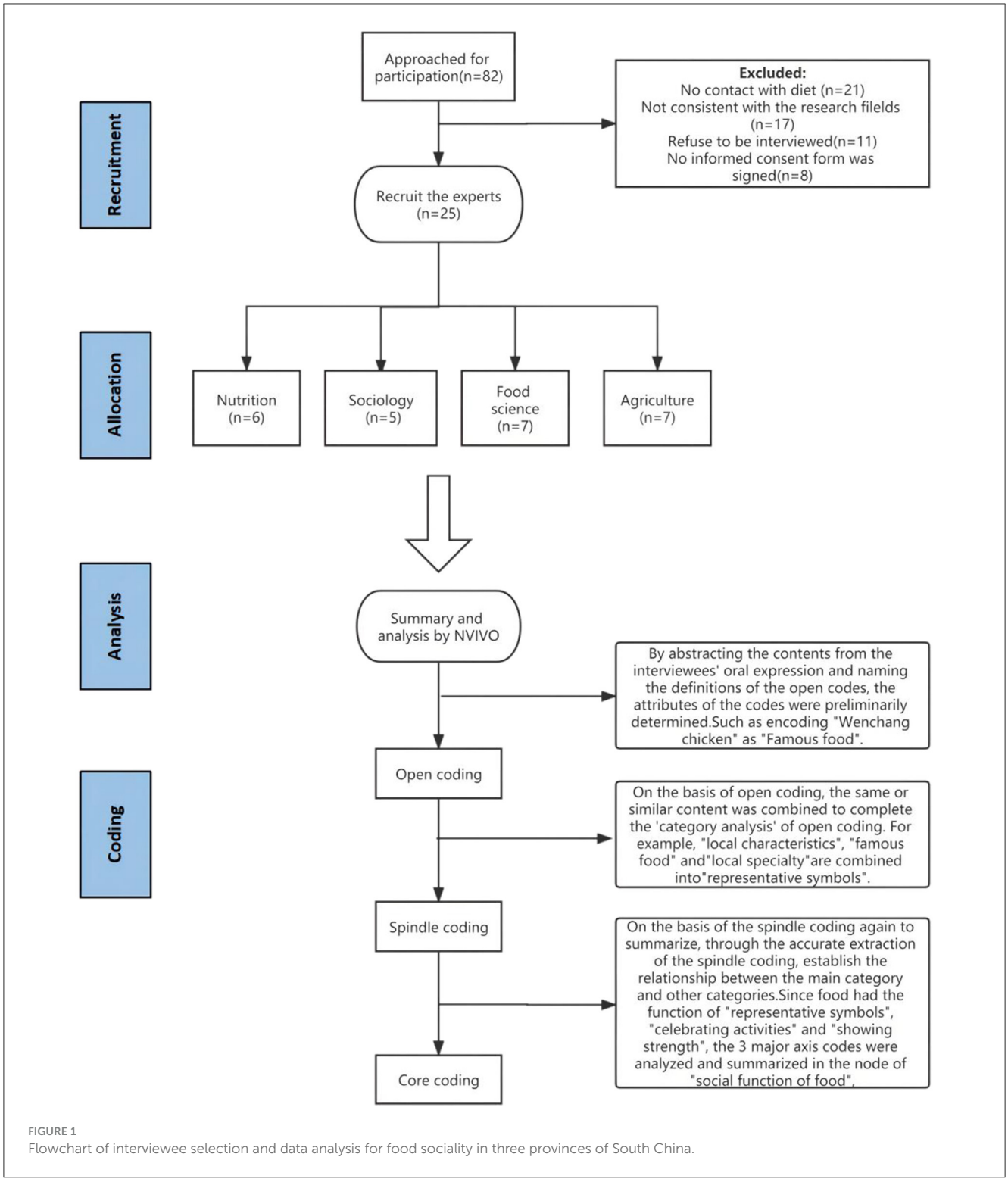

FIGURE 1
Flowchart of interviewee selection and data analysis for food sociality in three provinces of South China.

interview outline included 28 pre-determined questions covering six topics (Supplementary Table 1).

The interviews were conducted in Hainan, Guangdong, and Guangxi provinces from November 2020 to March 2021. The total amount of time interviewing 25 experts was 1,322 minutes with an average of 53 minutes (range 47–83 minutes) per interview. Due to the COVID-19 pandemic, three interviews were conducted via video calls using WeChat App; the rest were face-to-face. In the beginning of the interview, the interviewees were asked to describe their experience with food socialization, and then a semi-structured interview started following the pre-determined interview outline. However, during the interview process, the trained interviewers could make certain adjustments according to the interviewee's response. For example, when the interviewees talked about local

TABLE 1 Open coding (part).

Open coding	Original text
A1* Famous food	*"The four famous dishes of Hainan: Wenchang Chicken, Jiaji Duck, Hele Crab, and Dongshan Goat. Other dishes included Small Yellow Cattle, Hainan Vegetarian Pot, Salted Dried Fish, Huangliu Old Duck, Hainan Rice Noodles, Lingao Roast Suckling Pig, Shishan Goat Hot Pot, Raw Betel Nut, Coconut Chicken, Coconut Rice, Coconut Boat, Wenchang Chicken rice, and Braised Dongpo Pork."*
A2* Geographic characteristics	*"If you see someone eating Hainan Rice Noodles and Wenchang Chicken in a foreign country, and loved to drink Afternoon Tea and sit there chatting all day, you will think he comes from Hainan, right? That's our characteristic, right? For example, people in South China are used to ironing their bowls and chopsticks before eating. And people in Guangdong like to drink soup, which is also an obvious feature."*
A4* Traditional festival food	*"Eating Zongzi is definitely a tradition in the Dragon Boat Festival, and before that there were some customs like drinking Realgar Wine in the north. Then the Mid-autumn Festival would eat Moon Cakes. And we had Glue Pudding for the Lantern Festival."*
A25* Express the relationship	*"It's also easy to understand that eating with different people have different means. For example, a couple would liked to have a candlelit dinner to express how much they love each other. And he was very particular about dates, such as Chinese Valentine's Day, which needs more attention."*
A33* Symbol of reunion	*"For people in southern China, we stress social life, morality, emotion, and we eat together with family and friends at the Round Table. Why? Because it means 'Reunion together'."*
A34* Light taste	*"Hainan was a coastal area with plenty of seafood. Hainan's local diet is a branch of Cantonese style dish, which is relatively light, and we encourage it to be light now."*

*A1, main open code 1; A2, main open code 2; A4, main open code 4; A25, main open code 25; A33, main open code 33; A34, main open code 34.

food, they were asked to describe the significance of the food, and which local festivals the food was associated with.

2.4. Data analysis

A total of 25 interview texts were collected, coded, and summarized for information extraction, node coding, and analysis to summarize the food sociality in three provinces of South China (Figure 1). Three coding stages were used in this study, which were open coding, spindle coding, and core coding.

The first stage was open coding. Based on 25 interviews transcribed, we summarized, re-grouped, re-organized, defined, and coded. A total of 37 open-code nodes were generated. Table 1 illustrates six nodes which showed the most frequent key words mentioned by the interviewees (the rest of nodes are available upon request).

By abstracting the contents from the interviewees' oral expression and naming the definitions of the open codes, the attributes of the codes were preliminary determined. For example, "The four famous dishes of Hainan: Wenchang Chicken, Jiaji Duck, Hele Crab, and Dongshan Goat." The analysis was summarized as "Famous food," encoding related content to form 48 reference points. The corresponding Chinese names of the food appearing in the article are shown in Supplementary Table 2.

TABLE 2 Spindle coding.

Category	Initial concept
B1* Representative symbols	A1 Famous food, A2 Local specialties, and A3 Local specialties
B2* Celebrating activities	A4 Traditional festival food, A5 Ancestor worship activities, A6 Weddings and funerals, and A7 Emotional sustenance
B3* Showing strength	A8 Economic strength, A9 Curious ingredients, A10 Social status, A11 Rare for expensive, and A12 Show off economic power
B4* Social communication tools	A13 Reach cooperation, A14 Dining together, A15 Establish relations, A16 Drinking Afternoon tea, A17 Contact feelings, A18 Persuade alcohol drinking, A19 Talk about business, A20 Dinner guests, A21 Having Dimsum, A22 Drinking together, A23 Entertainment, A24 Entertain guests, and A25 Express the relationship
B5* Geographic characteristics	A26 Become a habit, A27 Pay attention to atmosphere, A28 Pay attention to emotion, A29 Like to drink soup, A30 Like to eat together, A31 Diet taboo, A32 Original taste, A33 Pay attention to reunion, A34 Light taste, A35 Like fresh ingredients, A16 Drink Afternoon tea, and A21 Having Dimsum
B6* Rewards and punishments measures	A36 As a reward and A37 As a punishment

*B1, main spindle code 1; B2, main spindle code 2; B3, main spindle code 3; B4, main spindle code 4; B5, main spindle code 5.

The second stage was spindle coding, which is also known as relational coding or secondary coding. On the basis of Guansheng Ma's understanding of food sociality and open coding, similar contents were combined for "category analysis" (19). For example, "local characteristics," "famous food," and "local specialty" were combined into "representative symbols." Finally, we identified six spindle codes among 37 open codes based on their similarities and semantic connections, and presented them in Table 2.

The third stage was core coding. We established connections between the main and other categories by extracting the spindle coding to define the concept of food sociality in three provinces of South China. Different from Guansheng Ma's study, we focused on the food sociality of the three provinces of South China, and made a new summary according to its characteristics. We believe that food has social significance. After the core coding process, we finally generated two main concepts of food sociality in three provinces of South China: the social function of food and the social function of dietary behavior.

3. Results

3.1. Demographic characteristics of the interviewees

Table 3 shows the demographic characteristics of 25 interviewees. The mean age was 50.6 (SD = 8.4) years, 15 (60%) were male, and 22 (88%) were experts with a master's degree or above.

TABLE 3 Demographic characteristics of interviewees ($N = 25$).

Variable		Number	Percentage
Gender	Male	15	60.0
	Female	10	40.0
Ethnicity	Han	20	80.0
	Hui	2	8.0
	Li	2	8.0
	Zhuang	1	4.0
Professional field	Nutrition	6	24.0
	Sociology	5	20.0
	Food science	7	28.0
	Agriculture	7	28.0
Education	Bachelor	3	12.0
	Master	12	48.0
	Doctor	10	40.0
Working institute	University	17	68.0
	CDC	3	12.0
	Hospital	2	8.0
	Media	3	12.0
Positional titles	Senior	25	100.0
Province	Guangxi	8	32.0
	Guangdong	10	40.0
	Hainan	7	28.0
Religion	Buddhism	2	8.0
	None	23	92.0

CDC, Center for Disease Control and Prevention.

3.2. Social characteristics of food in three provinces of South China

Based on the analysis and summary of the data from the 25 transcribed texts of the interviews, food sociality in three provinces of South China was found to include two main core codes, six principal codes, and 310 reference points of social function of food and social function of dietary behavior. Core coding results showed the social functions of food are representative symbols, showing strength, and celebration activities. And the social functions of dietary behavior are rewards and punishments, geographic characteristics, and social communication tools. Table 4 and Figure 2 present the content of the food sociality in three provinces of South China both in detail and in overlap, for instance, people communicate with others when they use food for celebrating activities.

3.2.1. Social functions of food

There were 140 key points for the social functions of food, including three spindle codes: representative symbols, celebrating activities, and showing strength.

3.2.1.1. Representative symbols

There were 18 (72%) experts who expressed that food was considered to be representative symbols. The most frequently mentioned words were "chicken" and "rice."

> "*Such as Guangdong Rice Rolls, Chaozhou's Casserole Porridge, Hakka Sampan Porridge, Congee with Sweet Potato, Cantonese Style Dumplings. Guangxi's famous Guilin Rice Noodles, Liuzhou River Snails Rice Noodles, Five-color Glutinous rice, Wenchang Chicken rice, Chinese Pudding, Coconut Rice, Bamboo Rice, Hainan Rice Noodles, Danzhou Rice Rotten, Jin Dui, Qingbuliang, Yiba, Hainan Ding An Black Pig Zongzi, and so on*" Guangdong's nutritionist 2 said.

What all of these foods have in common is that they are made of "rice," which plays an important dietary role in the three provinces of South China, and the residents make full use of local ingredients, all kinds of seafood, poultry, livestock, and vegetables to combine with rice to form its own unique characteristics and become local symbols for the region.

3.2.1.2. Celebrating activities

More than half (15, 60%) of the experts thought that food was used to celebrate activities, such as traditional festivals, ancestor worship activities, weddings, funerals, etc. The most frequently mentioned word was "festival."

> "*People will make many foods that handed down from generation to generation to celebrate the festival. The Three-color Rice, Five-color Rice, and Seven-color Rice of the Li nationality on March The Third. The Mountain Wine, Rice Wine, and Meat Wine that they brewed themselves would be drunk on the festival. During the Spring Festival, there were always allegories. For example, Chickens (pronounced as 'Ji') are always eaten during the Spring Festival because it means good luck and good wishes (pronounced also as 'Ji'). Like Celery (pronounced as 'Qin') means diligent (pronounced also as 'Qin'), Lettuce (pronounced as 'sheng') means make money (pronounced also as 'sheng'), those were very particular because of their pronunciations have particular meanings! Cantonese eat Jishiteng Dessert on the Tomb Sweeping Day. On the morning of the wedding day, you should lay peanuts, Red Dates, Lotus Seeds and rice on your new bed to bless the new couple having babies earlier. You should have New Year Cake and Dumplings for the new year, otherwise there would be no meaning of the Spring Festival. South China's traditional festivals and life rituals are closely related to diet. In traditional festivals, 'chicken' is homophonic to 'lucky,' which represents auspicious meaning [sic]*" Hainan's agricultural scientist 2 said.

Festivals are important components of culture, and festivals around the world vary, with food playing a crucial role. The residents in the three provinces of South China appreciate eating food with rich meaning in festivals, such as eating food that would result in good prospects. Various foods have unique meanings due to various histories or pronunciations. Due to this, food is used to celebrate different kinds of activities.

TABLE 4 Core coding.

Main categories	Corresponding category	Corresponding category specific meaning	Material source	Reference point
			N (%)	
M1* The social function of food	B1* Representative symbols	Representative food of the three provinces of South China	18 (72)	73
	B2 Celebrating activities	Food prepared for various activities in three provinces of South China	15 (60)	43
	B3 Showing strength	Representative of the strength of food in three provinces of South China	10 (40)	24
M2 The social function of dietary behavior	B4 Social communication tools	Part of the local residents' dietary behaviors could be used as social tools	18 (72)	101
	B5 Geographic characteristics	Some dietary behaviors have become the representative characteristics of local residents	20 (80)	58
	B6 Rewards and punishments measures	Some dietary behaviors could be used as rewards and punishments	7 (28)	11

*M1, main core code 1; M2, main core code 2.
*B1, main spindle code 1; B2, main spindle code 2; B3, main spindle code 3; B4, main spindle code 4; B5, main spindle code 5.

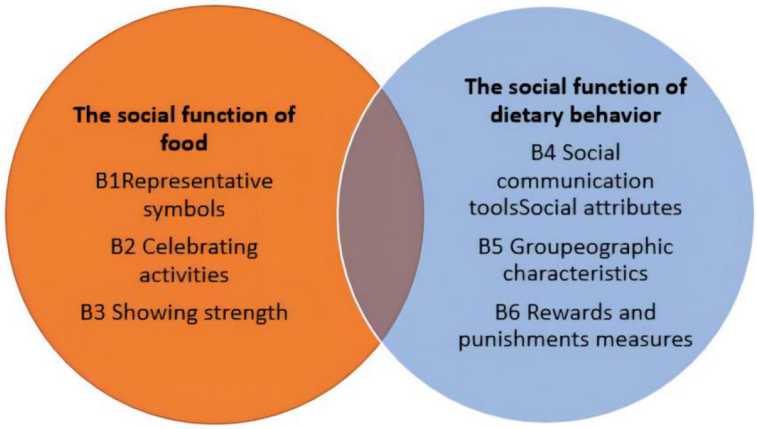

FIGURE 2
Core codes of food sociality in three provinces of South China.

3.2.1.3. Showing strength

Showing strength includes social status and economic power. Unique ingredients are rare and expensive, so using these ingredients demonstrates wealth. Showing strength is one of the social functions of food that was agreed upon by 40% of experts interviewed. The most frequently mentioned word was "precious."

> "*Generally speaking, the harder to get something, the more valuable it is. Just like the Wealthy Shrimp, which used to be cheap and common when the number of shrimps was large, but now the price of shrimp is becoming expensive and it is often eaten at reception parties. If I need to ask somebody for help, I'll take the one to taste precious things to show my sincerity, and maybe the one never eats that food before. It shows that I take the one very seriously [sic]*" Guangxi's sociologist 1 said.

In general, the rarer and more expensive the food provided, the higher the social and economic status of the provider.

3.2.2. Social functions of dietary behaviors

There were 170 reference points on the social functions of dietary behavior. This includes three spindle codes: social communication tools, geographic characteristics, and reward and punishment measures.

3.2.2.1. Social communication tools

In this survey, the majority (72%) of experts suggest that dietary behaviors can be social communication tools. The most frequently mentioned words were "together" and "friends."

> "*The Afternoon Tea and Guangdong Dimsum, Ah, a group of people sitting together to chat, people liked to eat while talking. It's a great way to enjoy food, connect (with each other), exchange information, and even close a deal [sic]*" Guangdong's agricultural scientist 1 said.

> "*Intimate Lovers would eat candlelit dinners together, guests were often treated with respect through expensive and rare food, and close friends or colleagues often go to food stalls or restaurants for meals and drinks*" Guangxi's nutritionist 2 said.

In human society, food is used to build and express relationships between people. Dietary behaviors are social. Food consumed by one person alone does not have social properties, but when it is consumed or eaten by a group of people, the sociality of food is determined. Different dining ingredients, environments, and places represent different relationships among diners.

3.2.2.2. Geographic characteristics

After coding and analyzing the group characteristics, a total of 58 reference points were established. Of the experts, 80% believed that food behaviors show geographic characteristics. The most frequently mentioned words were "tea" and "drink."

> "*If you see someone eating Hainan Rice Noodles and Wenchang Chicken in a foreign country, and who loved to drink Afternoon Tea and sit there chatting all day, you will think he comes from Hainan, right? That's our characteristic, right? For example, people in South China are used to heating their bowls and chopsticks before eating. And people in Guangdong like to drink soup, which is also an obvious feature*" Hainan's sociologist 2 said.
>
> "*There is another kind of wine that Guangxi people like to drink. It is called Rice Wine, which is made by ourselves. Self-brewed Rice Wine in many places in Guangxi, including our Liuzhou, Guilin, etc. Rice Wine is also very distinctive. It's actually rare in other provinces, because it's local, cottage and home-brewed [sic]*" Guangxi's food scientist 1 said.

When food becomes a part of the local culture, it remains even after migration. Figure 3 illustrates the role of local symbolic food and dietary behaviors in three provinces of South China. Due to differences in taste and growth environment, food preferences and dietary behavior can be defined as part of geographic characteristics.

3.2.2.3. Reward and punishment measures

Food in this region, in some cases, is used for rewards or punishments (28% experts mentioned), especially to motivate children to behave to meet parents' wishes and expectations. The most frequently mentioned word was "drinking."

> "*For example, when you do well in school, your parents may reward you with candy or promise to take you to a good restaurant. People often use mustard, lemons, and other food as props for punishment when they play games. If you are late for a party, your friends will punish you by drinking wine*" Hainan's sociologist 1 said.
>
> "*In fact, drinking is not all a bad thing. Proper drinking can activate the atmosphere, right? Some people appreciate to drink. Without wine, they are not active in eating. However, on some occasions, some people are unconscious after drinking. It is your fault to persuade them to drink. This phenomenon does exist [sic]*" Guangxi's sociologist 2 said.

To a certain extent, persuading people to drink shows a kind of hospitality. For some people who like wine, drinking is a reward, but when it exceeds a certain standard, it becomes a punishment.

4. Discussion

Our study shows that food sociality in three provinces of South China is mainly related to social functions of food and dietary behavior. Social functions of food mainly comprise three aspects: food as a symbol of local culture, food to demonstrate social status and economic power, and food to represent traditional customs and etiquette activities. Social functions of dietary behaviors are expressed by food as a social communication tool, with geographical characteristics, and, to some extent, in use as a proxy for reward or punishment.

Different from Guansheng Ma's understanding, we believe that the social function of food does not represent all characteristics of food sociality, because dietary behavior as a human activity has its social function, while food acts as a bridge between abstract sociality and concrete dietary behavior. In one sense, food has more typical regional characteristics than common dietary behavior. Symbolically, the people in three provinces of South China believed that "chicken" (pronounced as 'ji') means "lucky" (also pronounced as 'ji'), lettuce (pronounced as 'sheng') means to make money (also pronounced as 'sheng'). The existence of this phenomenon largely depends on the same sound production. They can exist independently of eating behavior. It is a phenomenon that people think of chicken first when they think of lucky. Dietary behavior as a human activity also has its social function; people in the three provinces of South China are used to heating their bowls and chopsticks before eating, so this is an eating behavior with regional characteristics, as people in other places do not have this habit.

Because of the geographical characteristics of the three provinces of South China being rich in rice, where it is the so-called "one land and one people," rice plays an important dietary role, and the living there make full use of local ingredients to form their own unique dishes that become local symbols (20). Chicken rice, Rice with Chinese Pudding, Coconut Rice, Bamboo Rice and Hainan Rice Noodles from Hainan, Rice Rolls from Guangdong, and Guilin Rice Noodles and Liuzhou River Snail Rice Noodles from Guangxi are the typical local food in three provinces of South China (Figure 3). In northern China, wheat and sorghum are the main food materials, therefore, there are steamed buns, bread rolls, and other steamed or fried wheat food, such as fried hard sticks and fried wheat cakes (21). The dimensions of Japan and three provinces of South China are similar, and Japan is surrounded by the sea, so Japan's fishery has developed very well. Seafood accounts for a large proportion of people's daily diet, so they formed a local culture with "Sushi" as the symbol (22). Each of these local foods is unique and becomes a symbol of region identity, which gives visitors an idea of the local culture.

The development of food is closely related to politics, economy, and culture. It is one of the ways in which society is divided into classes. Rare and expensive food used to be and still is a symbol of social status and wealth (23). This study found that in three provinces of South China, in most situations, people pay more attention to attitude than the price of food. But on some special

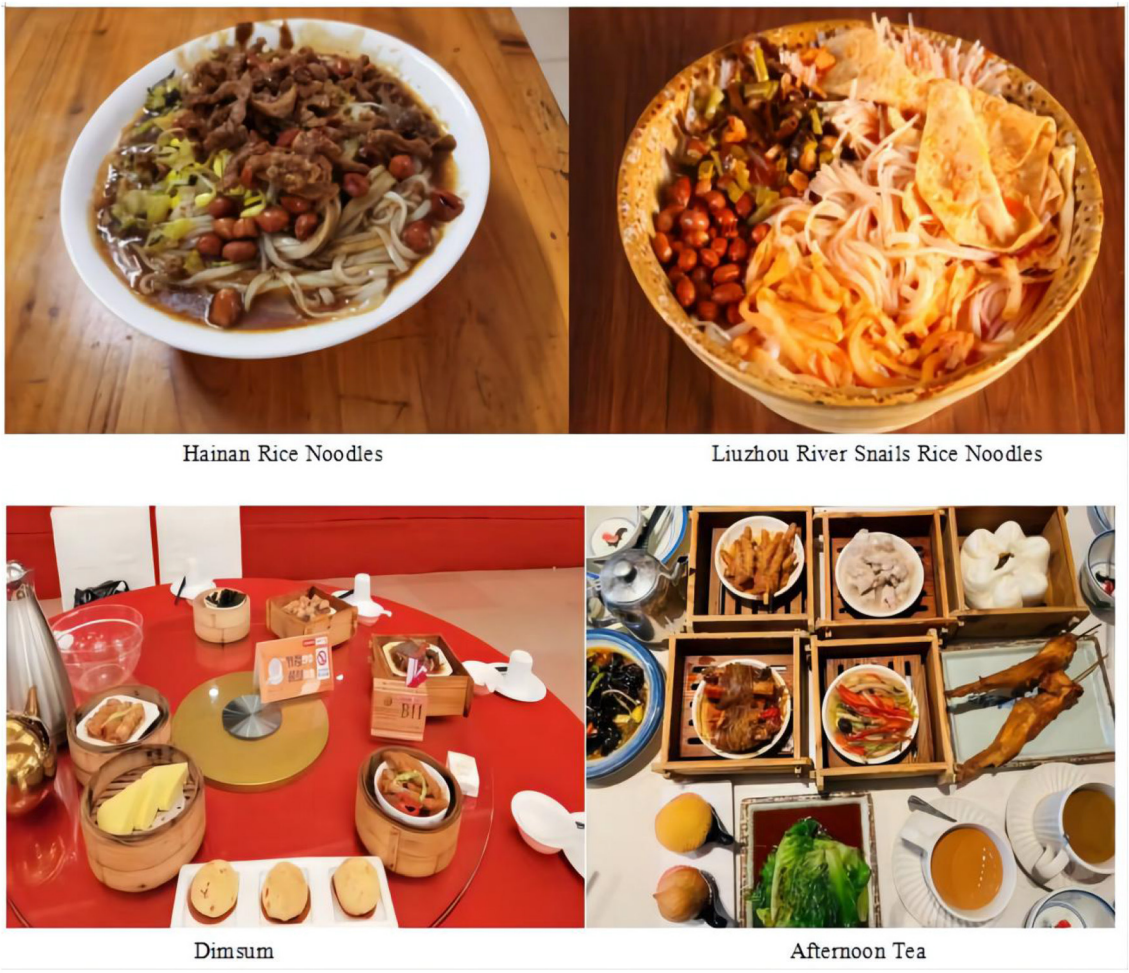

FIGURE 3
Local symbolic food and dietary behaviors in three provinces of South China (part).

occasions, such as the occasion where a company or family needs to show their strength, the more expensive the food consumed, the higher the social status the company or family has. As it is still difficult to catch fresh seafood in the deep sea, the price of this kind of food is very expensive in China. The distinctive seafood products are rich shrimp, abalone, etc. This finding is in line with other studies (24, 25). It is the same elsewhere in the world; an English anthropologist, Jack Goody, in his book "*Cooking, Dishes and Class*" describes that differences in food production, distribution, and consumption correspond with differences in social and economic structure. Food distributions are made according to particular classes and ranks (24). A few decades ago in France, food was used as a tool to gain reputation (wealth and social status) by sharing food; other people intended to legitimize their own societal power using food (25).

The social function of food is also reflected in important events such as festivals, weddings, and funerals. In Chinese culture, food is a symbol for the delivery of messages, and is more symbolic than nutritional. This trait can be influenced by different societies and cultures (26). For thousands of years, Northern China has celebrated the Spring Festival by eating dumplings (27), very similar to the tradition of consuming turkey for Thanksgiving in the United States (28). Our study interpreted that in three provinces of South China, the word "chicken" is homophonic to the word "Ji" (lucky), which stands for auspicious meaning, so the character and food appear during the Spring festival, for weddings, Hainan Public Holidays (ancestor worship activities), and other important social occasions, and because of the light taste of the local population, the chicken is generally made into Blanched Chicken. Red Dates, Peanuts, Longan, and Lotus Seeds are laid a couple's bed on the morning of their wedding, which is symbolic of wishing increased fertility and children for the new couple.

Festivals play an important role in food sociality; in Hainan, "Chicken rice" is often used for the "Ancestor Worships" festival, and after the festival, local people gather and share the "Chicken rice" to "*Unite the family ties and connect with the past* (29)." But there is no unified standard for the preservation and manufacture of festival food, and it may become a potential safety hazard. Most festivals are accompanied by banquets, which increases the risk of poor food safety (30). It is recommended to provide better health education during the festival, popularize the knowledge of food production and preservation, formulate corresponding

standards, strengthen food hygiene supervision, and prevent food safety accidents.

Moreover, for Chinese immigrants living overseas, food is a symbol of home, especially hometown-food. For instance, some people in Hainan (originally from Wenchang, Hainan) in Malaysia use local Malaysian ingredients to make Wenchang-style "Chicken rice" for "Ancestor Worship." Anna, who was born and grew up in Macao but currently lives in Portugal, often cooks "Techo," i.e., a combination of a Portuguese and Macanese dish for the Chinese New Year's Eve and Portuguese Christmas Eve (31).

Dietary behaviors have geographic characteristics. Due to differences in taste and growth environment, food preferences and dietary behavior can be seen as related to geographic characteristics. One's character is shaped by the land they live in and the food they eat. The food in Northeast China is characterized by its "Big serving size." The Northeast Chinese mostly eat meat and drink alcohol in larger size than people from other regions. Therefore, Northeast Chinese are renowned for their generous, hospitable, easygoing and straightforward attitudes (32). Especially when they host guests, the dish sizes must be more than enough in order to demonstrate the guests are served well. However, in three provinces of South China, gathering together has more meaning than eating. In our research, most experts believe that it is difficult for people in the three provinces of South China to use serving chopsticks and serving spoons. This is related to tradition and habits, which may increase the risk of infectious diseases (33).

In addition, drinking soup and having "Dimsum" and "Afternoon Tea" are popular amongst residents from three provinces of South China and it shows in their geographic characteristics. A study has shown that Dimsum consumers mainly have problems with unbalanced energy intake, high fat intake, insufficient carbohydrate intake, and low intake of vegetables and fruits, all of which increases the risk of chronic diseases such as hypertension and diabetes (34). Therefore, the abundance of Afternoon Tea and Dimsum may be risk factors for chronic diseases. It is suggested that the government should formulate relevant policies to intervene in the moderate intake of high calorie food.

In this study, the experts described how food not only expresses but also builds relationships between eaters. Amongst Cantonese people, having Dimsum is regarded as a way of communicating. People are used to going to tea houses for friends' gathering and business negotiation. While eating, people enjoy the food, connect with each other, exchange information, and even close business deals. Afternoon Tea is also popular in Hainan; as Hainan is located in the tropics, it is hot in the afternoon, the local people are usually used to farming in the morning and evening, and drink Afternoon Tea in the afternoon to rest, known locally as "Dad's Tea." The sociality of food also existed in the ancient world. The people in western Sudan believe that "*Food can only be shared with relatives and acquaintances, and will never be shared with enemies and strangers* (35)." "*The cultural expression of the public diet becomes an important ethical basis of the community.*" A quotation from the Azander's *sorcery, oracles and magic* reads: "*If a person was not invited to share their food, the absence of that person was often discussed by the neighbors* (36)." "*The sociality of food had become a force to be reckoned with that sustains tradition. Banquet and drinking were the social glue in ancient Greek, they could strengthen civic functions, values, maintain social order, and state stability* (37)." Food or diet alone does not create a social network. Social networks are also developed through special processes, media, and other forms. The ritual and the food create a permanent interaction. Like the "Drinking Ceremony" in ancient Chinese society, "*The Confucian Christian incorporated the idea of respect and caring for the elderly into the village banquets, so that people could be educated when they gathered together for banquets* (38)." Some regard eating as a "Social Act" that is ritualistic. People share food as a communication method and to build connections. It can transcend the meaning of behavior itself and highlight the meaning of other social behavior (39). For instance, through social media such as WeChat (a Chinese social media APP), Twitter, Facebook, or other online platforms, people share delicious food pictures to portray self-satisfaction and build social networks (40).

Food as a means of reward and punishment can be seen all over the world, such as through the use of chocolate or candy (41). Our study found that drinking as a form of punishment and reward were common dietary practices in southern China. Drinking is very common at weddings, workplace dinners, family dinners, and friends' gatherings (42). To a certain extent, encouraging people to drink is a kind of hospitality. For some people who like wine, drinking is a reward, but if it exceeds a certain standard, for example, when it has caused damage to others' bodies, it becomes a punishment. The phenomenon of encouraging people to drink alcohol also appears in other regions of China. What is more distinctive is that northern China tends to drink Erguotou and beer (32), while the residents from three provinces of South China have a habit of brewing their own Rice Wine and sharing it at events. The home-brewed wine contains strong alcohol and causes more damage to different organs through absorption, distribution, metabolism, and excretion than other types of commercial wine (43). We suggest the local government revise policies and implement interventions to promote healthier eating behaviors.

This study summarized the conceptual framework of two dimensions and six aspects of food sociality. Based on insights gained from interviews with the experts, it becomes evident that food is an inseparable element of contemporary human existence. Once food is a part of human activity, its sociality will emerge, so its value is universal and can be used as a reference for other regions to study the local food sociality.

In summary, through this study, we can understand the food sociality in the three provinces of South China, understand under what conditions and activities food sociality will appear, provide theoretical and practical evidence for food sociality, and provide a basis for promoting dietary related policies and intervention measures.

4.1. Strengths and limitations

We recruited 25 experts in the fields of nutrition, sociology, food science, and agriculture to increase opportunities for greater participation, which allowed the collection of a wider range of views. To minimize researcher bias in analysis, the third author (LL) checked the coding framework and, importantly, participants

were invited to comment on whether findings represented the views shared during interview.

However, this study has limitations. The interview outlines (questions), although tested for their feasibility, were created subjectively without validity. This may lead to selection bias (44).

We only interviewed experts from food-related fields without including local residents with diverse backgrounds. This selection bias may lead to our study being less generalizable; interpreting our results may need caution. In addition, we only included 25 experts from three provinces. Further studies should expand the sample size to increase validity.

5. Conclusion

Food sociality in three provinces of South China is a result of the social functions of food and dietary behaviors, which in turn are a result of local culture, social status, economic power, traditional customs, rewards and punishments, geographical food preference, and social communication tools. We suggest strengthening health education, especially for festival food hygiene and healthy eating behaviors, in order to achieve improved population health in this region. Through this study, we have contributed to the summary of food sociality in the three provinces of South China, provided ideas for the summary of food sociality around the world, and provided a basis for modifying dietary policies and intervention measures based on local food sociality in various regions.

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 humans were approved by the Ethics Committee of Hainan Medical University (HYLL-2022-024). 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

FZ initiated the study. JC, LL, XL, and GJ collected and analyzed data. YY drafted the manuscript. JDP revised the manuscript mainly. All authors provided comments for the manuscripts and agreed on the final 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.2023.1058764/full#supplementary-material

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Identifying barriers and facilitators to adopting healthier dietary choices in clinical care: a cross-sectional observational study

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Background and aims: Adopting healthier diets can drastically improve societal health. Our environment plays a crucial role in daily dietary choices and hospitals in particular can stimulate patients to adopt healthier eating habits. Unfortunately, no robust clinically applicable cuing tools exist to help guide in-hospital dietary interventions. The purpose of this study was to identify patient-related barriers and facilitators to adopting healthier dietary choices.

Methods and results: This cross-sectional observational study was conducted on the cardiology ward of a university medical center between June 2020 and January 2021. Of the 594 patients asked and the 312 completed surveys on healthy eating intentions, 285 responses were considered for analysis. Notably, the majority of respondents were male (68.8%), with an average hospital stay of 3.3 days. The results indicate that cardiac patients attribute significantly greater influence on their dietary behavior to doctors compared to other caregivers, including dieticians ($X^2 = 37.09$, $df = 9$, $p < 0.001$). Also, younger patients (below 70 years of age) were more inclined to plan changing dietary behavior than older patients. Most mentioned facilitators for adopting a healthier diet were more information/counseling, help in preparing food, support from family and friends, and more emphasis from a doctor.

Conclusion: The study highlights the importance of involving doctors in formulating dietary policies and patient-directed interventions within hospital settings. It also sheds light on the barriers and facilitators for promoting healthier dietary behaviors among patients during their hospitalization.

KEYWORDS

nudge, healthy diet, cardiovascular disease, teachable moment, choice behavior

Introduction

Cardiovascular disease (CVD) accounts for 24.7% of all deaths in the Netherlands (1). Dutch healthcare expenditures on CVD progressed to over 10 billion euros in 2017, amounting to 11.7% of total healthcare expenditures (2). The elimination of unhealthy risk behaviors such as unhealthy diet, smoking, or physical inactivity may prevent at least 80% of CVD (3). Even changing to a healthy diet alone could reduce the incidence of CVD by as much as 30% (4).

Recognizing the pivotal role of diet in CVD prevention and management, adherence to dietary guidelines has been emphasized as a cornerstone of treatment and prevention strategies for cardiac patients (5–7). However, motivating individuals to adopt healthier behaviors is a complex challenge, and national campaigns have struggled to achieve significant impact, resulting in low adherence rates to dietary guidelines in the Netherlands, estimated at just 20–30% (8, 9).

A crucial factor contributing to this low adherence is the environment in which individuals make their dietary choices (10, 11). The increasing overabundance of cheap, highly processed, convenient, energy-dense, and nutrient-poor foods and drinks contributes to adverse dietary choices (12). These adverse dietary choices can lead to obesity early in life, and CVD, obesity and many other chronic diseases later in life (13, 14). For this reason, our environment has been called "obesogenic" (15). Obesity leads to CVD and CVD mortality, even independently of other CVD risk factors (16). Thus the dietary environment influences CVD incidence and mortality in many ways. Fortunately, our dietary environment can also be part of the solution (17). Many public places such as schools, supermarkets and workplaces can contribute to an environment that nudges toward healthier diets. However, stimulating lifestyle behavior change is especially relevant in healthcare.

It is known that hospitals can influence the health of patients, visitors and employees (18, 19). For example, research has shown that fast food can be perceived as healthier when available within a hospital (20). Therefore, it is seen as the responsibility of the health service to serve as a role model for healthy eating behaviors (18). Fortunately, hospitals collectively gear toward promoting healthier dietary choices. Multiple examples of healthy diet promoting interventions are reported in the literature. A first example are so called nudges, which are environmental cues that are used to help people make healthier dietary choices (21–23). An effective example of using nudging in a hospital setting is a traffic light labeling system that influences healthy food choices in hospital cafeteria (24). Other examples include healthy meal-deliveries after discharge, 100% plant-based menus in hospitals, improvements in food presentation, preparation and purchasing, outpatient education and app-based coaching (25–29). In-hospital interventions are especially important as recent studies show that patients are more susceptible to health-related advice and more prepared to change health-related behavior during admission to the hospital (30, 31). Thus, a hospital stay can and should serve as a "teachable moment." However, at present it is unclear how to best capitalize on this momentum for change and "what works best for whom."

Dietary interventions can aim at multiple aspects of behavior to instigate a change. A psychological theory often used to dissect these aspects of behavior is the Theory of Planned Behavior (TPB) (32). According to this theory, intention is the most influential aspect of behavior change and intention is influenced by attitude, subjective norm and self-efficacy. In a previous study we showed the development and tested the internal reliability of a novel questionnaire based on the TPB (33). This questionnaire can be used to explore the normative referents, attitudes and intentions of hospitalized cardiovascular patients. Exploring potential handholds could give direction to future dietary interventions in multiple ways. It could provide information regarding what role should be used to provide the intervention (normative referent). Also the patients most motivated or unmotivated for behavior change (attitude, intention) could be identified and targeted specifically. Lastly, it could further clarify what the intervention should aim for (attitude, subjective norm, and perceived behavioral control).

In light of these considerations, the present study aims to explore potential barriers and facilitators for encouraging patients to embrace healthier dietary choices. Specifically, our research seeks to determine which healthcare providers should deliver dietary advice, identify patient groups most receptive to adopting a healthy diet based on their reason for admission, gender, and age, and map the attitudes, subjective norms, and perceived barriers and motivators of CVD patients. This information will be invaluable in tailoring effective dietary interventions and ultimately mitigating the burden of cardiovascular disease.

Methods

Design and study population

This cross-sectional observational study was conducted at the cardiology ward of the Leiden University Medical Center in the Netherlands. All patients admitted to the cardiology ward between July 2020 and January 2021 were invited to participate in the study. Researchers visited the cardiology ward daily to recruit newly admitted patients during their stay. Patients were asked to fill out a one-time, anonymous questionnaire if they were 18 years of age of older and had eaten at least one meal at the hospital ward. Exclusion criteria were absence of email address, insufficient meal consumption (no evening meals consumed), previous participation in this study, inability to provide consent and language barrier. Participants were asked to fill out the questionnaire after their last evening meal in the hospital, this could be done in the hospital or at home. The majority did so in the hospital. Participation to the online survey was on voluntary basis and informed consent was obtained at the beginning of the survey. Castor EDC (Castor, Amsterdam) was used to send and manage the questionnaires (34). All protocols and the process of obtaining informed consent were approved by the Medical Ethics Committee Leiden-Den Haag-Delft.

Questionnaire

The 20-item long Dutch Dietary Intention Evaluation Tool (DIETI) was used to assess multiple facets of healthy eating. This questionnaire has been specifically developed to assess healthy eating intentions of hospitalized patients and has been found te be reliable (33). The DIETI is based on the TPB and consists of the following subscales; intention (4 items), attitude (5 items), self-efficacy (3 items), subjective norm (3 items) and normative referent (5 items). For the intention, attitude, self-efficacy and subjective norm subscales, 7-point Likert scales were used with higher scores representing stronger intentions, more positive attitudes,

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higher self-efficacy and higher subjective norms. A scale of 1–10 was used for the normative referent subscale where a higher response endorsed a higher influence. Demographic data included gender, age, reason for admittance, history of cardiac ischemia, healthiness of current diet and number of meals consumed, and were obtained from a self-report questionnaire. The influence of different healthcare professionals were measured using a 10-point scale. The healthiness of current diet was measured using a single question on a 10-point scale where 10 means healthiest and 1 means least healthy. The English and Dutch versions of the questionnaire can be found in Supplementary Table 1 respectively.

Data cleaning

Data cleaning was performed to identify and correct lacks or excesses of data, outliers and logical inconsistencies. Data entry validation, statistical outlier detection, flatliner detection and fixed algorithms for logical inconsistencies were used. Examples of these algorithms are; age >100 years or a difference > 3 between the number of breakfast- lunch- or evening meals.

Statistical analysis

Descriptive statistics were used for the demographics. Patients were stratified according to age (based on distribution of age in sample), gender and reason for admission, namely arrythmia, angina/myocardial infarction, heart failure or other. The influence of doctors on dietary behavior of participants was compared to the influence of the other identities and institutions using a chi-square test for trend. The Mann–Whitney–Wilcoxon *U*-test was used to investigate the influence of gender on the various subscales. Moreover, the Kruskal–Wallis test was used to assess the differences in the behavior change subscales between the age groups and reasons of admission followed by the *post-hoc* Dunn multiple comparisons test. Statistical significance was set at $p < 0.05$ for the chi-square test, the Mann-Whitney-Wilcoxon U test as the Kruskal–Wallis test. All statistical analyses were performed using SPSS Statistics version 25.0 (35). Figures were made using R statistical software and Graphpad Prism version 8.0.0 for Windows (36, 37).

Results

A total of 505 (out of 594 assessed) patients were deemed eligible and 494 (98%) agreed to participate. Of all participants, 312 (63%) completed the survey, 136 (27.5%) were non-responders and 48 (9.7%) provided incomplete surveys. After data cleaning, 285 responses were used for further analysis (Table 1). The participants had a mean age of 63.1 ($SD = 12.8$) years, were predominantly male (68.8%), had an average hospital stay of 3.3 days ($SD = 3.8$) and the majority was admitted for cardiac arrythmia (42.1%). The mean self-rated healthiness of diet was 7.32 ($SD = 1.2$) on a scale of 1 to 10.

TABLE 1 Characteristics of the study participants ($n = 285$).

Characteristic	Value
Total	285
Age (years), mean (SD)	63 (12.81)
Age, n (%)	
<50	38 (13.3)
50–69	141 (49.5)
70–89	106 (37.2)
Gender, n (%)	
Female	89 (31.2)
Male	196 (68.8)
Reason of admission, n (%)	
Arrhythmia	120 (42.1)
AP/MI	72 (25.3)
Heart failure	17 (6.0)
Other	76 (26.7)
Admission duration (days), mean (SD)	3.29 (3.79)
Special diet, n (%)	30 (10.5)
Myocardial infarction in medical history, n (%)	77 (27.0)
Diet health score, mean (SD)	7.34 (1.2)

n, number of participants; SD, standard deviation; AP, angina pectoris; MI, myocardial infarction.

Normative referent

In the DIETI subscale of the normative referent participants were asked to evaluate the influence on dietary habits for various identities and institutions, including the Nutrition Center, hospital dietary policies, food assistant, doctor and dietician. The responses were recorded on a 10-poitn scale and visualized in a color-coded graph (Figure 1). In this graph, green marks indicate higher scores and red marks indicate lower scores. The figure clearly shows that doctors receive the highest number of sufficient marks (≥6, in green). A chi-square test for trend confirms that doctors have a significantly higher influence on dietary behavior than the others combined ($X^2 = 37.09$, $df = 9$, $p < 0.001$) and even than the dietician separately ($X^2 = 24.6$, $df = 9$, $p = 0.003$).

Attitude and intention based on age and gender

The mean scores for the dietary subscales on a scale of one to seven were; intention $M = 5.23$ ($SD = 1.07$), attitude $M = 5.76$ ($SD = 0.70$), subjective norm $M = 5.06$ ($SD = 0.85$), self-efficacy $M = 5.76$ ($SD = 5.75$).

Based on the distribution of age, patients were divided into three groups, <50 ($n = 39$), 50–69 ($n = 138$) and 70–89 ($n = 107$) years. Regarding the intention to eat a healthier diet, the youngest group ($M = 5.46$, $SD = 1.06$) had a significantly higher intention

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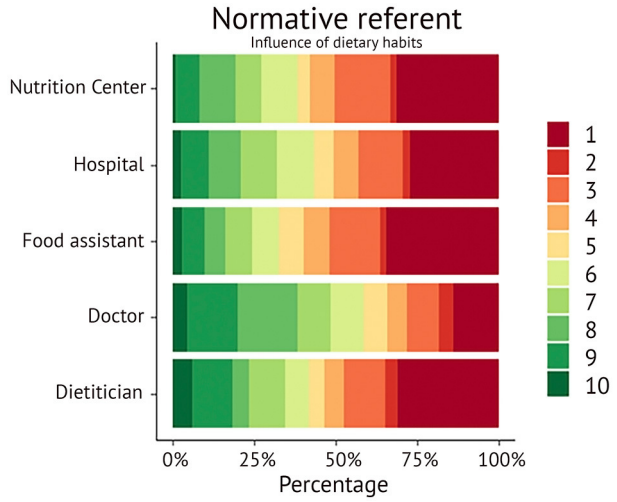

FIGURE 1
Visual representation of responses of influence on dietary habits by different providers and institutions. The gradient changes from forest green (highest influence of 10) to dark red (lowest influence of 1).

than the oldest group ($M = 4.86$, $SD = 1.07$), $U = 1387.00$, $p = 0.002$ (Figure 2). This was also seen when comparing the middle age group ($M = 5.45$, $SD = 0.95$) to the oldest age group ($M = 4.86$, $SD = 1.07$), $U = 5087.00$, $p = 0.000$. A similar difference was seen in the attitude regarding a healthy diet as the youngest age group had a significantly more positive attitude than the oldest age group ($M = 5.96$, $SD = 0.65$ vs. $M = 5.63$, $SD = 0.69$, $U = 1402.50$, $p = 0.003$). Notably, females had a significantly more positive attitude regarding a healthy diet than their male counterparts ($M = 5.95$, $SD = 0.60$ vs. $M = 5.67$, $SD = 0.72$, U = 6679.50, $p = 0.002$). All significant results remained significant after correction of the p-value for multiple testing.

Barriers and facilitators of healthy dietary choices according to patients

To gain further insights into attitude, intention, subjective norm, and self-efficacy, participants were questioned about the barriers and facilitators to healthy dietary choices. A total of 150 out of 285 participants reported at least one limiting factor (Figure 3). The most frequently mentioned hindrances to healthy eating included habits and tradition ($n = 47$, 31.3%), a dislike for the taste of healthy food ($n = 36$, 24.0%), the effort required to prepare a healthy meal ($n = 30$, 20.0%), dependency on others for meals ($n = 24$, 16.0%), time constraints ($n = 23$, 15.3%), high costs ($n = 21$, 14.0%), and a lack of perseverance to consistently prepare healthy meals ($n = 20$, 13.3%). A total of 212 (out of 285) participants reported at least one facilitating factor. The most frequently mentioned facilitating factors for altering dietary patterns were additional nutritional information ($n = 72$, 34.0%), a helping hand with food preparation ($n = 66$, 31.1%), nutritional counseling ($n = 53$, 25%), support from family and friends ($n = 50$, 23.6%) and emphasis on the importance of a healthy diet by healthcare professionals ($n = 41$, 19.3%). Other facilitating factors mentioned were weekly boxes with groceries and recipes ($n = 23$, 10.8%), groceries begin brought by someone ($n = 21$, 9.9%) and cooking classes ($n = 19$, 9.0%).

Discussion

The primary objective of this study was to identify effective strategies for future interventions aimed at promoting healthier dietary choices within clinical care. The key findings of our study are: (1) doctors are the most influential on dietary choices of patients, exceeding all other identities and institutions, and even than dieticians separately, (2) patients rate themselves quite highly on a healthy eating scale, and (3) younger and female patients are more inclined to eat healthy. Below we interpret these results to formulate practical recommendations to guide future interventions aiming to stimulate healthier dietary choices in clinical care.

Firstly, Our study unequivocally highlights the pivotal role of doctors in influencing patients' dietary choices, surpassing other healthcare providers and even dieticians. This is partly in line with a Dutch study conducted in 2015 that asked 1,063 patients to rate the credibility of doctors and dieticians regarding dietary advice. Both roles had very high reliability scores, 95 and 93% respectively (38). However, in our study, doctors were clearly found to be more credible than dieticians when it came to dietary advice. The credibility of a source is important as it can influence the impact of messages on one's health behavior (39). We know that a brief advice from doctors can increase the chance of successful lifestyle alterations in patients in the long term (40). Furthermore, our study resonates with a systematic review of behavior change techniques in cardiac rehabilitation, revealing that interventions emphasizing source credibility correlate with significant improvements in cardiovascular disease risk factors, such as systolic blood pressure and physical performance (41). These results further emphasize that involving a doctor in dietary interventions for in-hospital cardiac patients can increase the effect of the intervention.

Secondly, patients in our study consistently provided high self-ratings regarding their current healthy eating habits, intentions to eat healthier, attitudes toward a healthy diet, and self-efficacy. Previous literature showed that perceived diet quality is overrated when compared to actual diet (42–44), which could mean the self-ratings may be structurally higher than the actual value. While these self-assessments may be influenced by social desirability bias, they remain important indicators for assessing cardiometabolic disease risk. Notably, higher self-rated diet quality has been found to correlate with superior scores on the Healthy Eating Index-2015 and reduced cardiometabolic disease risk factors (e.g., BMI, waist circumference, insulin, cholesterol) (45). So, even though current healthy eating, intention, attitude and self-efficacy seem rather high and might not represent real diet quality, they can be relevant parameters for cardiometabolic disease risk.

Thirdly, our research underscores age and gender as influential factors in motivating dietary behavior change. We found that the intention to eat healthier and the attitude toward a healthy diet were higher for the two younger cardiac patient groups (<50 and 50–69 years old) compared to the relatively older cardiac patients (age

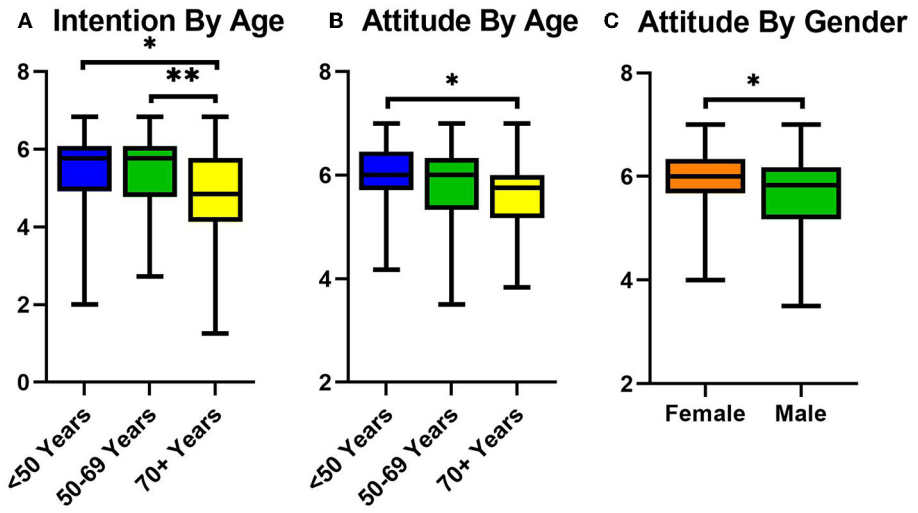

FIGURE 2
(A) Box and whiskers plot showing mean intention for healthy eating across the three age groups; <50 in blue (left), 50–69 in green (middle) and 70+ in yellow (right). **(B)** Box and whiskers plot showing mean attitude for healthy eating across the three age groups; <50 in blue (left), 50–69 in green (middle) and 70+ in yellow (right). **(C)** Box and whiskers plot showing mean attitude for healthy eating classified by gender; female in orange (left) and male in green (right). *$p < 0.01$, **$p < 0.0001$.

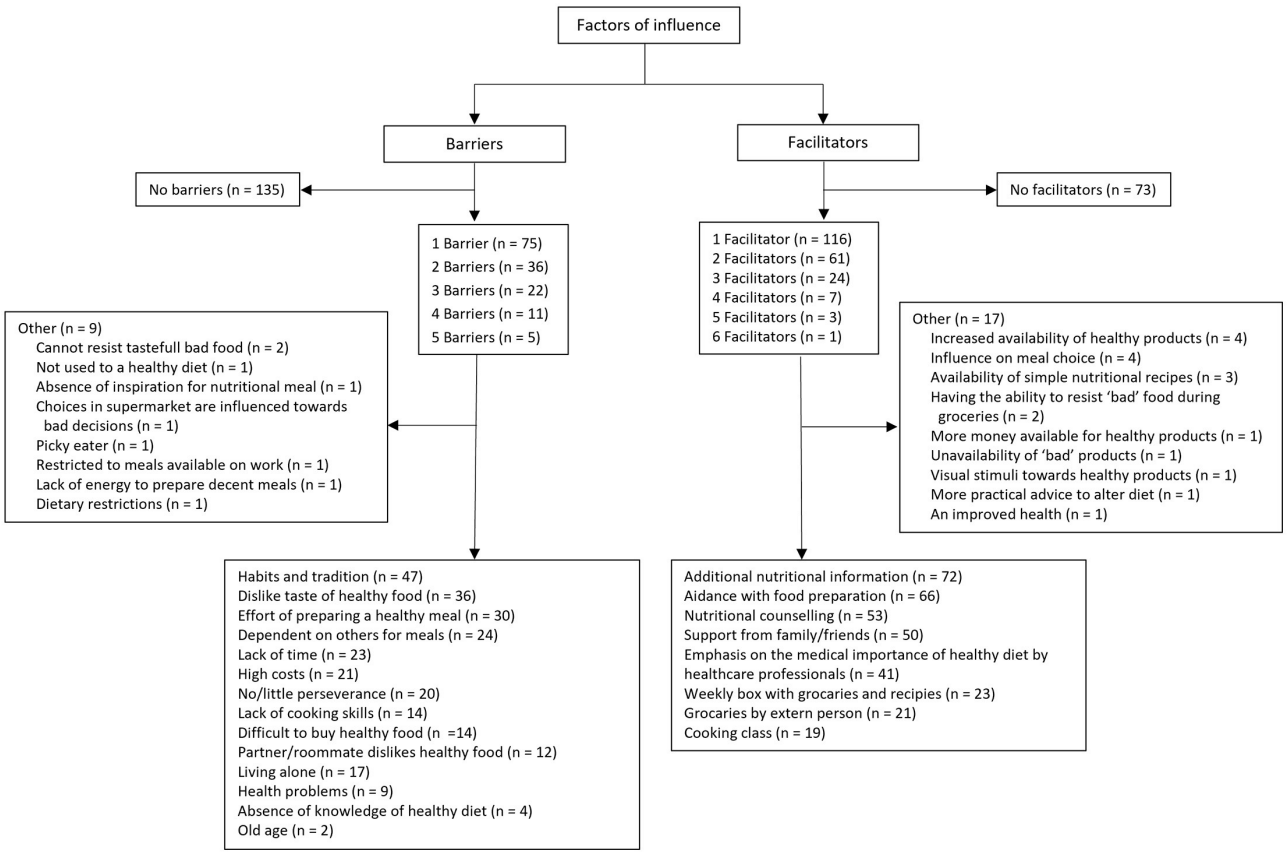

FIGURE 3
Overview of responses regarding factors of influence. *N* = the number of times a certain response was given.

<70 years). This would suggest that younger cardiac patients are more inclined to alter dietary behavior. These results are in line with previous research that showed younger people in general to be more likely to change behavior compared to older counterparts (46). That young cardiac patients are more inclined to alter behavior emphasizes the general idea that is it essential to start implementing lifestyle medicine as early as possible. Similarly, we found that female patients in our study have a more positive attitude toward healthy a diet. Previous studies also suggested that females in the general population have stronger beliefs in healthy eating (47, 48). Given the predominantly male demographic among cardiac patients, this finding highlights the importance of acknowledging that, generally, male patients may be less motivated to adopt healthier eating habits.

Finally, we explored what dietary interventions should form the target (attitude, subjective norm, perceived behavioral control). When asking patients about limiting factors for healthy eating, the most reported limitations are a habit of unhealthy diets, the dislike of healthy food, and the effort of preparing healthy meals. This is in line with the general idea that breaking old habits should be a considerable part of promoting healthier eating behavior. Stimulating cardiac patients into preparing some healthy meals could enable them to create new habits, appreciate healthy food and lower the threshold for preparing a healthy meal. A total of 19 patients mentioned that cooking classes could stimulate them to eat healthier. Indeed, research has shown that cooking sessions in cardiac rehabilitation are associated with a reduction in myocardial infarctions (49). Furthermore, a study on 28 patients during the COVID-19 pandemic showed that even culinary coaching via Telemedicine can improve cooking skills and promote self-care (50). This suggests that incorporating cooking sessions into healthcare may be an effective way of helping patients change health behavior. When asked for factors that would help them eat healthier, more information/counseling ($n = 72$)/($n = 53$), help in preparing food ($n = 66$), support from family and friends ($n = 50$), and more emphasis from a doctor ($n = 41$) are mentioned most. Surprisingly, lack of information was only mentioned four times as a limiting factor. We also know that only providing information does not necessarily change behavior (8). However, the results of this study implicate that patients sometimes miss nutritional information. In terms of supportive factors, over a third of patients responded that further emphasis of a doctor would help them eat healthier. This further highlights the need to involve doctors in interventions about healthier diets for patients.

One limitation of this study is the explorative design of the study. Due to privacy regulations we were unable to compare responders to non-responders. This means that with these results we can only speculate about the aim and shape of dietary interventions in hospitals. Another limitation is the narrow study population of cardiac patients in a single center. However, different patient populations in hospitals may be fairly similar in terms of healthy eating intentions.

The main implication of the results of this study is to include doctors in interventions aimed to improve dietary behavior of cardiac patients. At present, even in high-risk patients with CVD, diabetes or hyperlipidemia, only 1 in 5 receive nutrition counseling from their healthcare professional (51). Reasons for the minimal provision of nutrition counseling are lack of training, time, and reimbursement (52). Time and funding may help, but it is also important to note that doctors are not adequately educated in the basics of healthy diets or their promotion (53, 54). Teaching doctors the basics of nutrition counseling and the principles of motivational interviewing with regard to a healthy diet, might be a means to capitalize on the authority of doctors (55). Other recommendations include aiming interventions at patients as young as possible and being aware that female patients might be more inclined to change their behavior compared to male patients. Furthermore, nutritional information, support from family and friends, and cooking sessions are aspects that can support patients in adopting healthier behavior. Even though providing information does not equal behavior change, it might be helpful to have a simple, solid and trustworthy place of information on healthy diets. An example is the website of the Dutch Heart Foundation (Hartstichting) (56).

The results of this study emphasize the need for involving doctors in dietary policies and interventions in hospitals. Further, this study provides handholds for the future dietary interventions in a clinical setting. Future research could focus on conducting trials to evaluate in-hospital patient-centered dietary interventions.

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 Medische Ethische Toetsingscommissie Leiden-Den Haag-Delft. 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

DF cleared the study for the ethics committee, wrote the first version of the manuscript, and set up the study with help from NK, DA, and VJ. DF and HW managed participants inclusion and created the figures. HW performed the analyses. ZB checked the statistical analyses. HW, ZB, NK, DA, and VJ performed substantial revisory work on the manuscript. All authors read and approved the final 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.

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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.2023.1178134/full#supplementary-material

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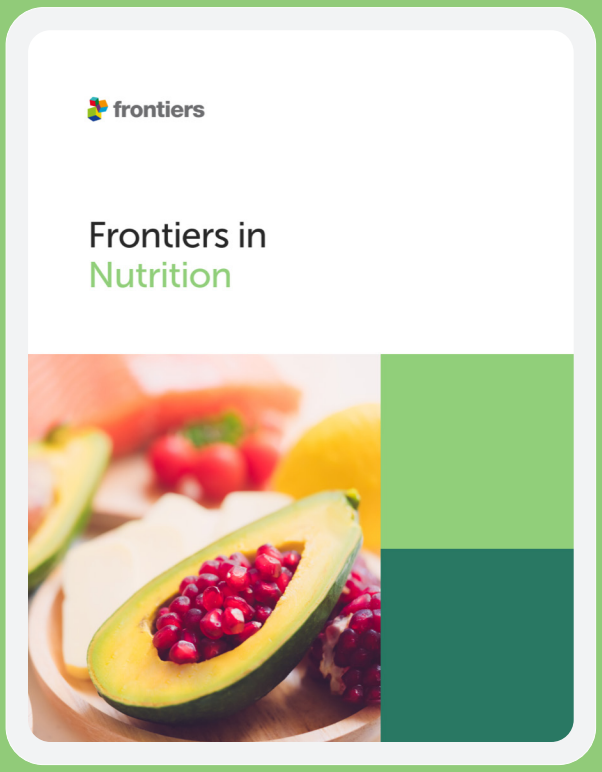

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