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Eating behavior and chronic diseases: Research evidence from population studies

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Eating behavior and chronic diseases: Research evidence from population studies

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Editorial: Eating behavior and chronic diseases: research evidence from population studies

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Editorial on the Research Topic
Eating behavior and chronic diseases: research evidence from population studies

Non-communicable diseases (NCDs), such as overweight/obesity, cardiovascular diseases (CVDs), cancer, diabetes, and chronic respiratory disease, have been becoming a major global public health problem (1). NCDs account for over 70% of all deaths and impose significant economic burdens worldwide (1). Therefore, it is in urgent need on a global scale to implement effective and feasible actions against NCDs from either public health or economic viewpoint. NCDs are usually preventable, as they share key modifiable lifestyle and behavioral risk factors, including unhealthy eating behavior (1).

As a major lifestyle-related modifiable factor of NCDs, eating behavior is particularly important for the prevention of NCDs. Typically, eating behavior refers to not only dietary patterns but also nutrient intake. From the public health nutrition perspective, population-based evidence on healthy eating is of significance for sharpening policies aimed at preventing NCDs. Thus, this Research Topic was designed to provide population-level evidence on the relationship between eating behavior (both dietary patterns and nutrient intake) and selected NCDs across diverse sub-populations, with particular interest in the interactive associations between eating behavior and other lifestyle/behaviors (e.g., physical activity) in relation to NCDs.

In the paper *Associations of healthy eating index-2015 with osteoporosis and low bone mass density in postmenopausal women: a population-based study from NHANES 2007-2018* (Wang et al.), it was observed that diet quality indicated with healthy eating index-2015 (HEI-2015) was in negative association with the risk of osteoporosis but had no link with low bone mass density (BMD) among postmenopausal women aged 50 years and older in the USA. Osteoporosis, a common metabolic bone disorder, has been emerging as a significant public health issue with a prevalence of 19.7% in the general population worldwide (2). In addition to existing evidence on the association of nutrients intake with osteoporosis and BMD, this study reported the potential link between overall dietary patterns and osteoporosis as well as BMD. It is of important public health meaningfulness to examine the associations of both overall dietary patterns and nutrients intake with osteoporosis.

The correlation between fruit intake and all-cause mortality in hypertensive patients: a 10-year follow-up study (Sun et al.). Based data derived from the National Health and Nutrition Examination Survey (NHANES), this cohort study found that,

among the common five fruits (apple, banana, pear, pineapple, and grape), intake of apple or banana was associated with decreased risk of all-cause mortality for American hypertensive people. As one of major types of daily foods, fruit is essential to human health. Previously, it has been well-documented that fruit intake was negatively associated with the risk of developing hypertension (3). Meanwhile, it is also important to investigate the relationship between eating behaviors and the risk of death. The present study made a contribution to literature, as it provided another scenario of the association between fruit intake and human health in that increased consumption of specific fruits can reduce the risk of all-cause death for hypertensive individuals.

Compliance with the EAT-Lancet diet and risk of colorectal cancer: a prospective cohort study in 98,415 American adults (Ren et al.). With a mean follow-up period of 8.82 years, this study identified that the EAT-Lancet diet (ELD) can reduce the risk of colorectal cancer (CRC) among American adults. ELD, a universally applicable dietary pattern introduced in 2019, encourages the intake of plant-based foods (including vegetables, whole grains, fruits, unsaturated oils, legumes, and nuts) and fish, but limits the consumption of meat and animal products (e.g., beef and lamb, pork, poultry, eggs, and dairy), potatoes and added sugar (4). Different from traditional dietary patterns, the ELD pattern integrated the concepts of nutrition-based health promotion approaches and environmental sustainability (4). In terms of human health promotion, ELD has been examined that it can decrease the incidence and mortality of NCDs such as stroke, CVDs, and cancers (5–8). On the other hand, in terms of environmental sustainability, compliance with the ELD was investigated to be associated with a significant reduction in either greenhouse gas emissions or freshwater consumption (9). Therefore, the ELD may be a scientifically optimized dietary pattern for human long-term development on the earth.

Soft and energy drinks consumption and associated factors in Saudi adults: a national cross sectional study (Aljaadi et al.). This study reported a high prevalence of weekly consumption of energy-dense drinks among Saudi adults based on nationally representative data collected in 2021. Energy-dense drinks consumption has been examined to be associated with adverse health outcomes, including obesity, type 2 diabetes (T2D), and CVDs (10–12). It is crucial to implement interventions aimed at reducing the consumption of energy-dense drinks to prevent and alleviate NCDs. The findings regarding energy-dense drinks consumption in this study were similar to those documented in a nationwide survey conducted among Saudi adults in 2013 (13), unfortunately showing that it is not easy for people to modify their preference or habit of food consumption at the population level. Therefore, for the purpose of population-based NCDs prevention through precision lifestyle/behavior intervention, it is important to dynamically investigate population-level eating behaviors and the associated factors.

Patient-centered nutrition education improved the eating behavior of persons with uncontrolled type 2 diabetes mellitus in North Ethiopia: a quasi-experimental study (Gebreyesus et al.). This study presented that a 3-month patient-centered nutrition education intervention could significantly improve both specific and overall eating behaviors for T2D patients with HbA1c $\geq$ 7.0% in Ethiopia. Additionally, the nutritional intervention was effective in lowering the HbA1c levels among the participants in this study. It highlighted that nutrition education as an intervention approach would be effective to improve eating behavior and glycemic control for diabetic patients in a resource-limited country. Adopting and maintaining healthy eating are always encouraged for diabetic patients to effectively manage the blood glucose (14). However, the biggest challenge is not to have people's eating behaviors modified with an intervention program, but to have the favorably-changed eating behaviors maintained for a lifetime or, at least, as long as possible.

Population-based comprehensive lifestyle and behavior intervention is of particular importance and effectiveness for NCDs prevention, and it is often viewed as a feasible and cost-effective approach for preventing NCDs. It is necessary to document the updated findings on the association of lifestyle and behavior with NCDs from nutritional epidemiological studies. The papers related to our Research Topic could offer valuable information to assist researchers, clinicians and policy-makers in designing and implementing dietary-specific intervention programs or policies, thus contributing to the prevention of NCDs.

In summary, eating behavior is time and economic status dependent, which may change as an individual's age or/and socio-economic status changes. This may occur in both developing societies and economically settled communities. Meanwhile, updating the dietary patterns and nutrient intake levels of different sub-populations is also necessary for precision eating behavior intervention. Therefore, although relationships between eating behaviors (dietary pattern, nutrients intake) and specific NCDs have been examined in different societies, studies are always welcome to continuously investigate population-level associations between eating behavior and NCDs in sub-populations with culturally and linguistically diverse background, and especially to further examine the interaction between eating behavior and other factors, such as physical activity, on NCDs. In future, research in these two areas needs to be encouraged to provide evidence supporting healthy dietary guidelines or policies for the prevention of NCDs.

Author contributions

FX: Conceptualization, Supervision, Writing – original draft, Writing – review & editing. XX: Conceptualization, Writing – original draft, Writing – review & editing. LZ: Conceptualization, Writing – original draft, Writing – review & editing. ZS: Conceptualization, Writing – original draft, Writing – review & editing.

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Sex differences in intuitive eating and its relationship with body mass index among adults aged 18–40 years in Saudi Arabia: a cross-sectional study

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Introduction: Intuitive eating (IE) is eating without judgment, relying only on physiological hunger and satiety. Sex differences in IE have been reported; however, none of the studies have explicitly examined IE and its relationship with body mass index (BMI) in the Saudi Arabian population. Thus, this study aimed to investigate sex differences in IE and its relationship with BMI in the Saudi population.

Subjects/methods: A cross-sectional online survey of 360 participants (18 years or older) with self-reported weight and height was conducted. IE was measured using the Intuitive Eating Scale-2 (IES-2). Separate multiple linear regression analyses were conducted to determine if total IE and its subscale scores differed across sexes. It was also conducted to assess the relationship between IE and BMI across sexes.

Results: Women had higher total IE score, eating for physical rather than emotional reasons (EPR), and body-food choice congruence (BFCC) scores compared to men ($p = 0.013$, $p = 0.01$, $p < 0.001$, respectively). The analysis showed a significant negative association between total IE, BFCC, EPR scores, and BMI in women compared to men ($p = 0.023$, $p = 0.01$, $p = 0.003$, respectively).

Conclusion: The data on the sex differences in IE and its subscales and their different association with BMI encourage tailing nutrition-related recommendations in the context of intuitive eating based on sexes. Future studies are needed to explore how intuitive eating functions differently in women compared to men and explore the causal relationship between IE and BMI in this population.

KEYWORDS

intuitive eating, IES-2, Saudi Arabia, body mass index, obesity, sex

1. Introduction

Globally, the prevalence of obesity has increased. Saudi Arabia has a higher rate of overweight individuals and obesity, with three out of five adults being overweight or obese in the year 2019 (1). Obesity is a complex disease associated with mental problems and several chronic diseases that are known as the leading cause of death worldwide such as type 2 diabetes, cardiovascular diseases, and some cancers (2, 3). In the Middle East, Saudi Arabia has the second highest rate of diabetes and ranks seventh worldwide (4). It is noteworthy that this disease is primarily linked to obesity and can be managed by preventing weight gain and obesity. The adverse impact of obesity on health as well as the alarming rate of increased prevalence indicate the need for more effective prevention and treatment strategies.

Traditional weight loss approaches, such as food restriction or high-intensity exercises, might be unsuccessful for long-term weight loss and could be physically and mentally detrimental to the individual (5). Studies have shown that long-term food restriction may lead to disturbed eating behavior and improper food and body relationships (6). In addition, this may result in repeated cycles of weight loss and regain, a reduction in self-trust with food, and eventually obesity or eating disorders (7). The effectiveness of long-term dieting on weight loss and healthy lifestyle is limited; therefore, an alternative to traditional restrictive eating is needed to reduce these disordered eating attitudes and related psychological problems.

A growing body of research supports the anti-dieting approach, which involves recognizing and reacting to individuals' signals of hunger and satiety. There has been a shift in the dieting approach, and it now focusses on connecting with the body and trusting its need to adopt a healthy lifestyle (8, 9). One of the approaches that applies this concept is known as Intuitive eating (IE). In 1995, clinical dietitians Evelyn Tribole and Elyse Resch identified and suggested IE as an off-diet approach for unsuccessful long-term weight loss. IE is an eating behavior which is guided by physiological hunger and satiety sensations (i.e., eating when hungry and stopping when full). The principles of IE encouraged a healthy relationship that connect food, mind, and body. They also promote an appreciation of emotions and enjoyment of food. Therefore, it allows individuals to trust their body to make choices around nutritious and energetic food; and gives a sense of pleasure without the effect of emotional or external cues, such as altered mood (10, 11).

IE is measured by the Intuitive Eating Scale-2 (IES-2) (12). IES-2 includes four subscales which reflect the essential aspects of IE. "Unconditional permission to eat (UPE)" subscale assesses the act of eating whatever food is desired at the moment. "Eating for Physical Rather Than Emotional Reasons" (EPR) subscale assesses the act of eating that is governed by energy needs rather than eating that is driven by emotions. "Reliance on Hunger and Satiety Cues (RHSC)" subscale assesses individuals' ability to tune into their body's hunger and satiety signals in relation to food intake. "Body-Food Choice Congruence (B-FCC)" subscale assesses the choice of tasty and healthy nutrition in line with the bodily needs (12, 13). Combining the scores of these aspects provides a total IE score that reflects whether individuals are intuitively eating.

The IES-2 scale has been used in both female and male populations and has demonstrated invariance across sexes. This means that scores can be compared and interpreted across sexes. Interestingly, researchers have shown inconclusive results when comparing the scores of men to women as they might be equal, higher, or lower (12, 14–18). Furthermore, it has also been demonstrated that women and men may have different associations with IES subscales (15, 19). Several factors could have contributed to this sex discrepancy, such as cross-cultural differences in food. Understanding the interaction between sex and IE will aid in understanding how IE works for both men and women. Therefore, examining sex differences in IE practices across different cultures is imperative.

Research on IE holds promise for improving weight management, physiological and psychological health, dietary quality, as well as quality of life (7, 20, 21). Clinical studies have indicated that IE is related to weight stability as opposed to other weight loss diets approaches (20, 22). Researchers examining the IE approach found a relationship between IE and anthropometric measurements (12, 16, 18, 19, 23). The higher the IE, the lower was the Body Mass Index (BMI), body weight, waist circumference, and waist-to-hip ratio (23). Research on early adolescents, young adults, college students, and adults have also shown a negative relationship between IE and BMI (12, 16, 18, 19). Moreover, a mounting body of evidence indicates that intuitive eaters have lower BMI and higher life satisfaction and self-esteem (5, 12, 18, 24, 25). Previous studies have found that EPR and RHSC are negatively correlated with BMI; however, the findings are inconsistent for UPE and B-FCC (12, 19, 26). Therefore, it is important to examine the relationship between IE, and its subscales and BMI as a potential approach to compete with obesity and promote weight maintenance (27, 28).

While existing research on IE is promising, little is known about IE practices and their relationship with BMI across sexes in Saudi Arabia. Therefore, the current study aimed to (1) examine sex differences in IE practices using IES-2 in Saudi Arabian population and (2) assess the relationship between IE and its subscales with BMI based on sexes within the target population. This might contribute to the development of alternatives to the current strategies of obesity management programs used in Saudi Arabia. Consequently, the prevalence of obesity, diabetes, and other diseases would also decrease. Based on prior findings, we hypothesized that women would have lower IE scores compared to men. Additionally, we also hypothesized a significant negative relationship between IE and BMI.

2. Materials and methods

2.1. Participants and procedures

For this cross-sectional study, we aimed to recruit at least 360 participants (1:1.3 ratio; men to women). The potential sample size was determined using a two-sided *t*-test, with confidence level of 95%, power of 80%, and estimated effect size 0.3. Data was collected from October 2020 to August 2021. An anonymous online survey was created and circulated among community members via social media (such as twitter) and word of mouth. Before answering the questionnaire, the survey presented information on the study objectives, protocol, confidentiality statements, and consent statements. Sociodemographic characteristics, anthropometric measurements, and the IES-2 were included as part of the questionnaire.

A convenient sample of 360 participants was included in the study, of which 153 were men (42.5%) and 207 women (57.5%). Adults between the ages of 18 and 40 years of either sex with a BMI of 18.5 or above, who were fluent in English and Arabic, and were living in Saudi Arabia were included in the study. The exclusion criteria included history of bariatric surgery or surgery within the next 12 months; history or current eating disorder; history of metabolic or mental health disorders; use of prescription medications that affect eating or metabolism, pregnancy, or breastfeeding within the last 12 months; attempt to lose more than 4.5 kilograms during the last 3 months; food allergies or special diets; and individuals residing outside Saudi Arabia. Approval to conduct the study was obtained from the Research and Ethics Committee of the Faculty of Applied Medical Sciences of King Abdulaziz University (reference no. FAMS-EC2020-0016).

2.2. Measures

2.2.1. Sociodemographic characteristics

Data regarding participants' sex, age, region of residence, education status, employment status, socioeconomic status, and weight loss dieting practices was collected via the questionnaire. Participants reported their current weight and height which were used to calculate their body mass (kg/m^2). World Health Organization classification of BMI was used in this study (4).

2.2.2. Intuitive eating scale (IES-2)

IES-2 was used to assess intuitive eating (IE). The IES-2 consists of 23 items and four subscales. The subscales included: (1) 'Unconditional Permission to Eat' (UPE; six items, e.g., "If I am craving a certain food, I allow myself to have it."); (2) 'Eating for Physical Reasons Rather than Emotional Reasons' (EPR; eight items, e.g., "I am able to cope with my negative emotions (e.g., anxiety, sadness) without turning to food for comfort."); (3) 'Reliance on Hunger and Satiety Cues' (RHSC; six items, e.g., "I rely on my hunger signals to tell me when to eat."); (4) 'Body-Food Choice Congruence' (B-FCC; three items, e.g., "I mostly eat foods that give my body energy and stamina."). Participants were asked to rate each item on the scale using a 5-point Likert scale for scoring ranging from one (strongly disagree) to five (strongly agree). The IES-2 yields separate scores for each subscale as well as a composite total score. After reversed scoring items in the scale, the total score was created by summing the results of each item and dividing them by 23 for a total average score (12). Similarly, subscales scores were calculated by summing up the responses and dividing them by the number of items for each subscale individually. Possible scores on the scale range from 1 to 5 with higher scores indicating greater intuitive eating. Previous research has supported the validity and reliability of the total IES-2 and its subscales scores, as it showed good internal consistency, test–retest reliability, and construct validity (12, 15). Moreover, it has also been applied to cross-cultural samples and shown to be invariant across men and women.

2.2.3. Statistical analysis

Participant characteristics based on sex were assessed via independent samples *T*-test and Chi-squared testing. The intercorrelations of the study variables were examined using Pearson's Product Moment Correlation analysis. For all of the mentioned statistical methods, assumptions were evaluated before. In this study, descriptive statistics were presented as percentages "%." Mean ± standard deviation (SD) was used to present the scores for the IES-scores and its subscales. Separate multiple linear regression analyses were conducted to determine if total IE and its subscale scores differed across sexes. It was also conducted to assess the relationship between IE and BMI across sexes. The regression models were adjusted for income as well as education except for EPR subscale which only adjusted for income due to its significant correlation with the study variables. Statistical significance was set at p-value < 0.05. All statistical analyses were performed using two-sided tests, carried out by SPSS software version 27 (IBM Corporation, Armonk, New York, United States). For the total IES-scores, RHSC, and BFCC regression models, a bootstrapping technique was implemented instead of the conventional computing techniques because the normality assumption was violated.

TABLE 1 Demographic characteristics of the study population (N = 360; Women = 207; Men = 153).

Demographic characteristics	Mean (SD) or %
Age (Years)	26.5 (6)
Women	25.0 (5.2)
Men	28.5 (6.4)
BMI (kg/m^2)	24.4 (4.9)
Women	24.7 (5.3)
Men	24 (4.3)
Education	
High school	
Women	54.5%
Men	45.5%
Diploma	
Women	13.8%
Men	86.2%
Bachelor or higher education	
Women	62.7%
Men	37.7%
Income (Saudi riyal)	
<5,000	48%
5,000–15,000	36%
16,000–30,000	13%
>30,000	3%
Nationality	
Saudi	92.8%
Women	54.8%
Men	45.2%
Non-Saudi	7.2%
Women	92.3%
Men	7.7%

3. Results

A total of 360 participants who were 26.5 ± 6 years of age (57.5%, n = 207 women; and 42.5%, n = 153 men) were included in the analyses. Participants demographic characteristics, including age, education, and income, are presented in Table 1. Participants had a mean BMI of 24.4 ± 4.9 kg/m^2. The mean BMI of women and men included in the study were 24.7 ± 5.3 and 24 ± 4.3 kg/m^2, respectively. More than half of the participants (76.7%) had a Bachelor's degree or higher education. Nearly half of the participants were classified in the lowest category of income (48%). A majority of participants (92.8%) were Saudis. No significant differences were observed between men and women in terms of the demographic data. Means and standard deviations for the Intuitive Eating Scale-2 (IES-2) total score and the four subscales by sex, are presented in Table 2.

Results for the multiple linear regression analyses are shown in Table 3. For the total IE scores, there was a significant effect of sex, such that intuitive eating in women was greater than men [β (standardized beta coefficient) = 0.73, 95% CI: 0.22, 1.32, p = 0.01].

The model for the total IE score revealed a significant interaction between sex and BMI on IES after controlling for education, and income ($\beta = -0.02$, 95% CI: −0.05, −0.01, $p = 0.01$). This significant negative association means when the individual is female, the total IE score decreased by 0.02 for every unit increase in BMI. Figure 1 shows the association between total IE scores and BMI between sex.

Regarding UPE subscale, sex has no significant effect ($\beta = 0.53$; 95% CI: −0.2, 1.30; $p = 0.17$). The model did not display a significant interaction between sex and BMI on UPE after controlling for education, and income ($\beta = -0.02$, $p = 0.07$). Moreover, for EPR subscale, there was a significant effect of sex, such that EPR score in women was greater than men ($\beta = 0.83$, 95% CI: 0.15, 1.52, $p = 0.01$). The model for the EPR subscale revealed a significant interaction between sex and BMI on EPR subscale after controlling for income ($\beta = -0.03$, 95% CI: −0.02, 0.03, $p = 0.01$). This significant negative association means when the individual is female, the EPR score decreased by 0.03 for every unite increase in BMI.

Additionally, for RHSC subscale, sex has no significant effect ($\beta = 0.13$; 95% CI: −0.87, 1.13; $p = 0.80$). The model did not display a significant interaction between sex and BMI on RHSC after controlling for education, and income ($\beta = 0.01$, $p = 0.74$). Furthermore, for B-FCC subscale, there was a significant effect of sex, such that B-FCC

TABLE 2 Means and standard deviations for the Intuitive Eating Scale-2 (IES-2) total score and the four subscales by sex.

Scale	Women (n = 207)	Men (n = 153)
IES-total	2.90 (0.50)	2.79 (0.46)
UPE	2.87 (0.69)	3.02 (0.65)
EPR	3.18 (0.65)	3.16 (0.53)
RHSC	2.60 (0.90)	2.26 (0.92)
BFCC	2.81 (1.36)	2.38 (1.25)

IES-2, Intuitive Eating Scale-2; UPE, Unconditional permission to eat; EPR, Eating for physical rather than emotional reasons; RHSC, Reliance on hunger and satiety cues; B-FCC, Body-food choice congruence; n, number of participants.

TABLE 3 Multiple regression analysis assessing the association between intuitive eating scores and body mass index (BMI)[a].

Scale	Variable	β	SE_b	P-value	95% CI
Total IE scores[b]					
	(Constant)	2.82	0.32	<0.001	2.13, 3.43
	Sex	0.73	0.28	0.013*	0.22, 1.32
	BMI	0.004	0.01	0.60	−0.01, 0.02
	Interaction	−0.02	0.01	0.012**	−0.05, −0.01
UPE subscale					
	(Constant)	3.55	0.37	<0.001	2.82, 4.30
	Sex	0.53	0.39	0.17	−0.24, 1.30
	BMI	−0.01	0.01	0.28	−0.04, 0.01
	Interaction	−0.02	0.01	0.07	−0.06, 0.003
EPR subscale					
	(Constant)	3.26	0.32	<0.001	2.62, 3.62
	Sex	0.83	0.34	0.01*	0.15, 1.52
	BMI	0.004	0.01	0.70	−0.02, 0.03
	Interaction	−0.03	0.01	0.01**	−0.61, −0.01
RHSC subscale[b]					
	(Constant)	2.20	0.56	<0.001	1.15, 3.33
	Sex	0.13	0.51	0.80	−0.87, 1.13
	BMI	0.01	0.01	0.44	−0.01, 0.04
	Interaction	0.01	0.02	0.74	−0.03, 0.04
BFCC subscale[b]					
	(Constant)	1.34	0.76	0.06	−0.22, 2.81
	Sex	2.44	0.73	<0.001*	0.99, 3.94
	BMI	0.03	0.02	0.17	−0.01, 0.07
	Interaction	−0.08	0.02	0.003**	−0.14, −0.03

IE, Intuitive Eating; BMI, Body mass index; UPE, Unconditional permission to eat; EPR, Eating for physical rather than emotional reasons; RHSC, Reliance on hunger and satiety cues; B-FCC, Body-food choice congruence; β, unstandardized beta coefficient; SE_b, SE for the unstandardized β; CI, confidence interval.

[a]Income and education were controlled in the model for total IES-2 score, UPE, EPR, RHSC, B-FCC except for EPR, which controlled for income only.

[b]Bootstrapped for coefficient.

*Statistically significant effect of sex on total IE score, EPR and, B-FCC subscale, $p = 0.013$, $p = 0.017$, $p < 0.001$, respectively.

**Statistically significant negative association between sex and BMI on total IE score, EPR and, B-FCC subscale, $p = 0.0128$, $p = 0.016$, $p = 0.003$, respectively.

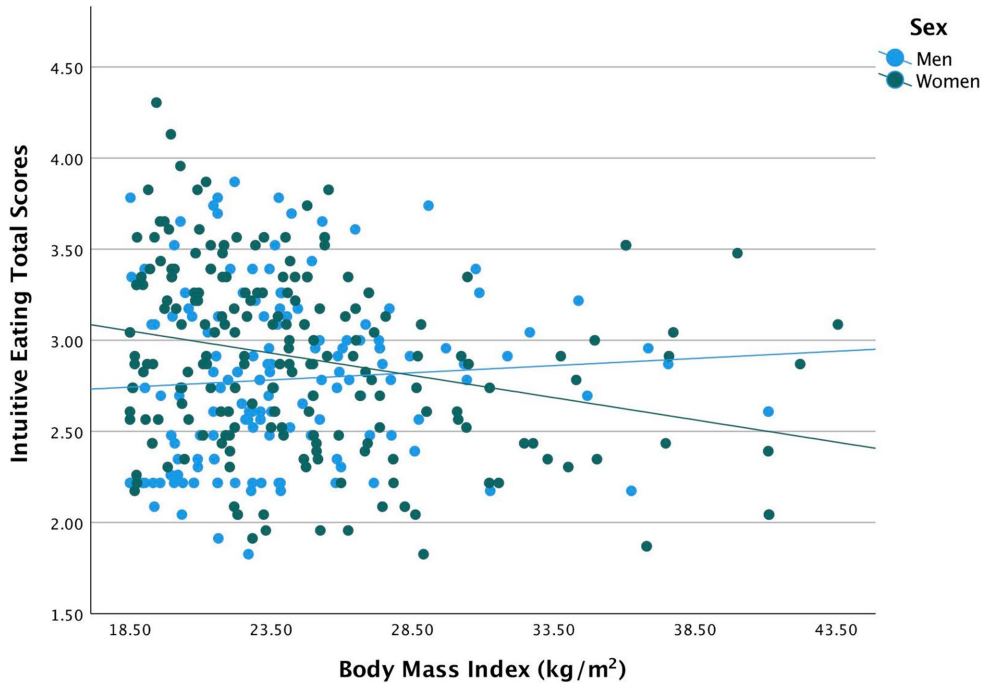

FIGURE 1
Indicates a negative association between total IE scores and BMI among women.

score in women was greater than men ($\beta = 2.44$, 95% CI: 0.99, 3.94, $p < 0.001$). The model for the B-FCC subscale revealed a significant interaction between sex and BMI on B-FCC subscale after controlling for education, and income ($\beta = -0.08$, 95% CI: −0.14, −0.03, $p = 0.003$). This significant negative association means when the individual is female, the B-FCC score decreased by 0.08 for every unite increase in BMI.

4. Discussion

The present study examined the differences in IE and its subscales across sexes (women vs. men) in Saudi Arabia. In addition, the study assessed the relationship between IE and its subscales with body indices, specifically BMI, across sexes. The study findings indicated that women had significantly higher levels of IE compared to men. Results also suggested that women scored significantly higher on two of the IE subscales [Body-food choice congruence (BFCC) and Eating for physical rather than emotional reasons (EPR)] compared to men. The study also revealed a significant negative relationship between BMI and BFCC as well as EPR only in women.

Findings on IE across sexes have been inconsistent. Previous studies have reported equal level of IE, or one sex with a higher score than the other, mostly men (12, 15, 26, 29). On the contrary, our study revealed a significant sex difference in the total IE score, with higher scores in women than men. A possible explanation for this may be the fact that our sample excluded individuals who were current dieters. The researchers noted that IE was significantly higher among individuals who were never dieters compared to those who were former as well as current dieters (15). The author speculated that dieting might disrupt the innate ability of an individual to take notice of the body signals that regulate food intake. This disturbance may in turn affect individuals' ability to differentiate physical from emotional hunger. Presumably, this may not apply to our women sample as they not only ate more intuitively but they also eat in response to physical needs rather than emotional ones compared to men. Therefore, studies should consider diet-related behaviors and their influence on food regulation signals when examining IE.

This inconsistency regarding study findings could also be attributed to the existence of other eating behaviors, such as restraint vs. emotional eating. In line with a previous study, researchers reported that women had lower IE than men. In addition, they also reported that these women had higher levels of restraint as well as emotional eating (29). These eating patterns rely on external guidance and predetermined rules that dictate eating decisions, whereas IE involves internal guidance and a willingness to eat when the body is in need (29). In our sample, these could be reflected in women reporting higher eating for physical rather than emotional reasons and body-food choice congruence subscales, and their BMI association with the subscales compared to men. However, these women may or may not practice restraint overeating, but, according to the EPR scores, they attenuated overeating in response to emotional triggers. One may assume that inner tuning, connecting, and listening to the body needs, may increase women's senses toward hunger and satiety signals, thus, an appropriately response to triggers and a healthier body-food relationship. As mentioned, the sample of this study ruled out dieters or eating disorders but did not include an objective assessment of other eating behaviors that were not within the scope of the study. We assumed that the women in our sample did not follow extensive restrictive eating behaviors which could have resulted in a high IE score. Therefore, adding objective measures of other eating behaviors which may interfere with IE is worth considering.

Interestingly, the correlational findings of the current study were consistent with other studies, which reported an inverse relationship between IE and BMI (12, 14, 15, 30, 31). Our findings observed a conflicting directional correlation in women and men, contrary to some studies which reported similar relationships in both sexes. Consistent with our study, researchers reported the same inverse relationship in older women (32). Similar findings were noted in another study with younger women, which reported that BMI decreased with an increase in IE scores (14). In accordance with these studies, our findings may suggest that women who scored high on IE tended to have lower BMI while men scored high on IE tended to have high BMI. It is worth noting that the average BMI for women and men in this study was similar compared to other studies (14, 33). We hypothesize that women with normal BMI may be at minimum risk for the sociocultural pressure of thinness and dieting; thus, they might be more aware of and in harmony with their emotions and physical need for food (29, 34). This hypothesis could be supported by the negative correlation between BFCC, EPR and BMI in women as observed by other studies (19, 30). Another possible explanation might be related to the freedom from preoccupying food thoughts and the pressure of dieting that allows oneself to pay attention to the body's needs, which promotes a healthier food-mind–body connection and, thus, a healthier BMI. This may suggest that eating for non-emotional reasons where food choices in agreement with body needs are the main contributors in the overall relationship between IE and BMI. This also suggests that the link between IE and BMI becomes more pronounced in women with low BMI. These data suggest that IE principles (BFCC and EPR) might be relevant for weight management in women but not in men in Saudi Arabia. In addition, IE and its subscales could be used as a screening tool to identify women who are likely to eat in response to emotional triggers and may be less likely to choose foods that are congruent with their body's needs and preferences. Further studies are required to prove these hypotheses.

Important factors that might play a role in the observed discrepancies between our results and those of previous studies are the cross-cultural differences in foods and the mentality toward dieting. To the best of our knowledge, this is the first study to examine IE and its subscales across sexes and its relationship with BMI in the Saudi Arabian population. Eating styles and practices have been suggested to differ across cultures. In addition, reciprocal interactions between sex and sociocultural factors are known to influence food intake and choice (35). Thus, more studies should be conducted to identify the influence of cross-cultural differences on IE.

Our findings have several important clinical implications. The findings from this cross-sectional survey suggest that women eat more intuitively when they have a lower BMI whereas men eat less intuitively with a higher BMI. In addition, women with lower BMI tend to eat according to physical reasons rather than non-emotional reasons where food choices are in agreement with their body needs. The link between this non-restrictive eating approach and body mass may suggest the use of this approach to promote and maintain a healthy weight in this specific sample. Therefore, to encourage healthier weight-related outcomes, dietitians in Saudi Arabia should discuss the concept of IE with their patients, especially women. In addition, the findings may encourage facing the obesity dilemma differently by adopting an approach that focuses on the mentality of "body wisdom" instead of dieting itself or may necessitate the combination of both approaches.

The current study had a few limitations. First, it is worth noting that the distributed survey used the English version of IES-2 due to the unavailability of the Arabic version. Considering that Arabic is the native language of Saudi Arabia, the study sample may not be fully reflective of the general population. Second, the underrepresentation of the general population may limit the generalizability of the results. A representative sample would include Arabic speakers as well as more non-Saudis as they represent 41.6% of the population in Saudi Arabia (36). In addition, it would also include participants from different educational levels, such as middle and high school graduates as they represent 22.6 and 26.6% of the population; respectively. More individuals with an income between 5,000 and 15,000 would also make the sample more representative (37). Third, the use of a cross-sectional design limits the development of cause-and-effect relationships (38). Fourth, we recruited a convenience sample that led to half of the sample being within normal BMI in both groups, thus resulting in an underrepresentation of overweight and obese people. Despite these limitations, this study had several strengths that need to be mentioned. First, to the best of our knowledge, this study is the first to consider sex differences in the context of IE and its relation to BMI in Saudi Arabian population. This is an important first step in understanding how IE varies across sexes and how it is related to body status in this understudied population. Second, the study had a relatively large sample size, with diverse age ranges and educational levels.

The findings from the present study are promising and suggest the need for future research on this topic. To the best of our knowledge, no adaptation of the scale has been conducted in the Saudi population; therefore, this study is novel as it highlights the potential value of translating and validating the IES-2 in Arabic. Additionally, the cross-sectional design of the current study does not establish causality; therefore, it was ambivalent whether lower BMI resulted in an increase in IE or whether having the ability to eat intuitively lead to a normal BMI. Further evidence is needed to investigate the potential association between self-regulation and BMI in the general population. Additionally, our findings indicate the necessity of evaluating IE in a larger sample with different BMI categories and eating styles across sexes. Future research should also use longitudinal study designs which would aid in tracking individuals' weight changes and its impact on levels of IE. Exploring IE practices and its relationship with BMI could reveal possible mediating effects of eating styles in the Saudi Arabian population. Future studies should attempt to replicate the sex disparities discovered in this study with a sample of dieters vs. non-dieters. The significant inverse association between IE and BMI warrants the need for intervention studies that would examine the effect of IE training on weight status in women with higher BMI.

5. Conclusion

This study revealed that women eat more intuitively, rely on physical hunger cues rather than emotional triggers, and their food choices are related to their body's needs compared to men. Women's BMI was inversely associated with total IES, BFCC, and EPR while in men, BMI was positively associated with total IES. This suggests that IE and some of its principles may be a protective strategy against weight gain at a certain BMI in the women population in Saudi Arabia. The current findings highlight the importance of translating and validating the IES in the Arabic language, to better represent and

understand Saudi culture. Prospective studies in the Saudi population are required to investigate the temporal and causal relationships between IE and BMI. Taken together, the current and previous findings should encourage dietitians in Saudi Arabia to discuss the concept of IE and its components (BFCC and EPR) with their patients, especially women as a helpful tool in weight management practice to promote healthier 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 studies involving human participants were reviewed and approved by the Ethical Committee of the Faculty of Applied Medical Sciences, King Abdulaziz University (FAMS-EC2020-0016). The patients/participants provided their written informed consent to participate in this study.

Author contributions

EA and MN conceived the study, conducted part of the analyses, interpreted the results, and wrote the manuscript. All authors critically reviewed the manuscript and approved the final version submitted for publication.

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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Long-term impact of post COVID-19 pandemic quarantine on eating habits changes among adult residents of Riyadh, Saudi Arabia

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Background: COVID-19 outbreak and quarantine measures clearly had an impact on the population's eating habits-related behavior.

Objective: This study aimed to explore the long-term impact of the COVID-19 pandemic and physical quarantine on eating habits after quarantine among Riyadh city residents, Saudi Arabia.

Methods: A cross-sectional study was conducted through an online survey between December 2022 and April 2023 on a convenient sample of Saudi adults in Riyadh, Saudi Arabia. A valid questionnaire was used to measure study outcomes. A comparison between dietary habits before and after COVID-19 was performed to identify the changes in dietary habits.

Results: 1,451 Saudi adults residing in Riyadh completed the online survey. The majority (88.6%) of the respondents reported changes in dietary habits after COVID-19. About 50% had 1–3 dietary habits changes and slightly more than one-third had 4–7 dietary habits change. About 33.8% of the participants reported stable weight during the COVID-19 pandemic. However, 40.9% reported weight gain, and 20.7% reported weight loss. The participants reported several unhealthy dietary changes most commonly eating fast food (33%), eating junk food/fast food due to boredom/distress/disappointment (29.8%), and high sugar such as sweet porridge, pastry, sweets, and chocolate (28.5%). On the other side, the participants showed healthy dietary habits such as having a balanced healthy ingredients diet (34.4%), an increase in the consumption of fruits and vegetables, and a decrease in the intake of junk foods (28.9%). Males were more likely to exhibit unhealthy dietary habits than females (Odd Ratio:1.43, p =0.038, CI: 1.02–2.02). Increasing age was associated with a reduction in the likelihood of exhibiting unhealthy dietary habits (OR: 0.98, p =0.011, CI: 0.96–0.99). Moreover, participants who reported stable weight or weight loss during COVID-19 were 0.29 (p =0.043, 0.09–0.96) and 0.34 (p =0.020, 0.07–0.79), respectively, less likely to have unhealthy dietary habits.

Conclusion: Although healthy dietary habits have been reported in this study, such as consumption of fruits and vegetables, COVID-19 confinement has also led to negative dietary behaviors reflected by high consumption of fast/junk food and sugar intake resulting in weight gain, a potential adverse impact on the population wellbeing.

KEYWORDS

COVID-19 pandemic, dietary changes, healthy/unhealthy, Saudi Arabia, impact, long-term

Introduction

The World Health Organization (WHO) declared the coronavirus (COVID-19), a serious acute respiratory condition, to be a pandemic and a public health threat in March 2020 (1). Saudi Arabia announced the first COVID-19 case on March 2, 2020 (2). In step with international efforts to counter and mitigate the spread of COVID-19, Saudi Arabia's Ministry of Health has applied several preventive measures and restrictions to limit the spread of infection including physical distancing. Physical distancing was implemented in various ways including quarantines, travel restrictions, distance work, and closing of stores, crowded areas including universities, schools, and gym/sport centers (3, 4). Individuals were informed by law of physical distancing methods by staying at home, limiting travel, avoiding overcrowded spots, using non-contact greetings, and physically distancing themselves from others (3, 5). Accordingly, changes in health and socio-economic status have been reported locally and globally (6).

As a result of preventive restrictions, new habits and routines have been developed that need attention (6). A number of studies have shown positive modifications in persons' lifestyle such as eating habits, and increasing the number of consumed and cooked meals at home (6–8). On the other hand, a home quarantine and limited practice of normal activities had a negative impact on the individual daily habits, such as increased food consumption "emotional eating" to deal with emotional triggers as many persons' experience undesirable feelings and distress due to fear of infection and of the loss of loved one (6, 7). Additionally, working from home leads to less physical activity (9). An aggravated sedentary lifestyle, increased sitting time, fewer chances for performing physical activity, and extended time spent on smart devices have adversely affected people's sleep quality (8–14).

By the end of 2021, normal life activities returned gradually particularly for people who completed the doses of COVID-19 vaccine. Several studies have assessed and reported the short-term effect of home isolation and lockdown (8–12). Nevertheless, few studies have evaluated the long-term impact of quarantine including post pandemic effect. However, there is a gap in knowledge on the long-term impact of quarantine on dietary habits from Saudi Arabia and regional countries. It is probable that the pandemic left a heritage of doubt and psychological disturbance among people. It is imperative to investigate whether these alterations in physical activity, eating habits, and sleep quality have a significant impact on people's daily quality of life (15). Therefore, this study aims to explore the long-term impact of COVID-19 pandemic and physical quarantine on eating habits after quarantine among Saudi adults in Riyadh City, Saudi Arabia.

Materials and methods

Study design and setting

An analytical observational cross-sectional study was conducted among a sample of Riyadh City Saudi adults between December 2022 and April 2023.

Study sample and sampling technique

This study included the Saudi population aged >18 years, were residents in Riyadh city during the quarantine, have no mental disorders or physical disabilities, and were willing to participate in this online survey. A convenient sampling technique was used to recruit study participants. The total population of Saudi Arabia is 32.12 million, and adult Saudis represent about 68% of the total population. The potential participants were identified by three study coordinators for eligibility and shared with the survey via email or WhatsApp upon fulfilling the inclusion criteria. The survey was designed in compliance with the CHERRIES guidelines for web survey (16).

Data collection procedure

The data collection tool is composed of two sections parts. Section 1 included sociodemographic and anthropometric parameters such as age, sex, height, and weight. The second section assessed the dietary habits changes before and after the COVID-19 pandemic using a previously validated questionnaire (17). The questionnaire was originally written in English and underwent linguistic validation using a forward-backward translation technique by expert translators, and was reconciled by an expert panel. The questionnaire was administered to the participants in the Arabic language. A face validity testing was also conducted by expert researchers and medical physicians to assess the comprehensiveness of the designed questions, and the clarity of wording. Following the face validity testing, a pilot study was performed on 30 parents to compute the reliability of the questionnaire. A Cronbach alpha test showed a score of 0.83 suggesting a good internal consistency. The questionnaire was composed of 12 questions and was completed twice at the same time point. The questionnaire addressed questions about the frequency of maintaining a regular meal pattern, consumption of fast food, fried food, junk food, fruits, and vegetable intake, having a balanced diet with healthy ingredients, intake of milk and its products, pulses, eggs, or meat. In addition, the questionnaire included questions about the frequency of teaspoons consumption of sugar/honey/jiggery, sugar-sweetened beverages, foods with high sugar, and lastly about how often frequency of eating junk food/fast food is due to boredom/distress/disappointment. Questions 1–8 and 10–12 were measured and coded as follows: (Not routinely: 1; 1–2 times/week: 2; 3–4 times/week: 3; 5–6 times/week: 4; and almost daily: 5). For question 9, it was measured as follow: (Zero teaspoons/day, I do not add sugar in my meals/ beverages: 1; 1–2 teaspoons/day: 2; 3–4 teaspoons/day: 3; 5–6 teaspoons/day: 4, and > 6 teaspoons/day: 5).

Data analysis

We used the SPSS version 22.0 (IBM Corporation, Armonk, NY, United States) 22 to analyze the data. Determination of whether the participants have changes in dietary habits (healthy or unhealthy) was done by deducting the post COVID-19 reported score from the pre COVID-19 reported score. For questions (unhealthy habits) 2–4 and 9–12, if the score is positive [possible range 1–4] then the participants have unhealthy dietary changes, and if the score is negative (worse

TABLE 1 Demographic characteristics of participants and frequency of dietary habits change after COVID-19 pandemic.

Characteristics	*n* (%)	Male (*n* = 690)	Female (*n* = 761)	*p* value
Age (mean ± SD)	34.72 ± 12.38	35.59 ± 13.12	33.93 ± 11.63	**0.011**
Marital status				
Single	579 (39.9)	289 (41.9)	290 (38.1)	0.231
Married	726 (50)	329 (47.7)	397 (52.2)	
Divorced/widowed	146 (10.1)	72 (10.4)	74 (9.7)	
Height (cm)	165.52 ± 9.336	172.22 ± 7.54	159.45	**<0.001**
Weight (Kg)	69.78 ± 12.34	74.41 ± 11.62	65.59 ± 11.45	**<0.001**
Body mass index (mean ± SD)	25.47 ± 4.10	25.07 ± 3.59	25.83 ± 4.45	**<0.001**
Underweight (>18.5)	22 (1.5)	18 (2.6)	4 (0.5)	
Healthy weight (18.5–24.9)	728 (50.2)	349 (50.6)	379 (49.8)	
Overweight (25.0–29.9)	507 (34.9)	257 (37.2)	250 (32.9)	
Obese (≥30)	194 (13.4)	66 (9.6)	128 (16.8)	
Weight during COVID-19 pandemic				0.115
Was stable	491 (33.8)	236 (34.2)	255 (33.5)	
Lost weight	301 (20.7)	130 (18.8)	171 (22.5)	
Gained weight	593 (40.9)	285 (41.3)	308 (40.5)	
I do not know	66 (4.5)	39 (5.7)	27 (3.5)	
Change in dietary habits (mean ± SD)	3.09 ± 2.26	3.26 ± 2.12	2.95 ± 2.29	**0.009**
No	165 (11.4)	67 (9.7)	96 (12.9)	
Yes	1,286 (88.6)	623 (90.3)	663 (87.1)	
1–3 habits	732 (50.4)	329 (47.7)	403 (53)	
4–7 habits	499 (34.4)	272 (39.4)	227 (29.8)	
8–11 habits	55 (3.8)	22 (3.2)	33 (4.3)	

Bold value of *p*: statistically significant at < 0.05; (*n* = 1,451).

dietary habit), then the participants have healthy dietary changes. For questions (healthy habits) 1 and 5–8, if the score is negative, then the participants have unhealthy dietary changes, and if the score is positive, then the participants have healthy dietary changes. The number of changes in dietary habits was classified into three categories (1–3 habits, 4–7 habits, and 8–11 habits). The study data were normally distributed. Categorical variables were summarized using descriptive statistics as frequencies, percentages, and continuous variables as means and standard deviation. The chi-square test was used to compare categorical variables. An independent sample *t*-test was used to compare two means, and a one-way ANOVA between the means of two or more continuous variables. The change in dietary habits was transformed into a binary variable (yes/no). We carried out a binary logistic regression to determine the predictors of change in dietary habits. The variables included in the binary logistic regression model were selected based on statistical significance variables with values of $p < 0.025$ on the univariable analysis were included in the model. *p* values of less than 0.05 were considered significant.

Sample size calculation

The online Epi Info sample size calculator was used to calculate the sample size based on a previous similar study conducted in Saudi Arabia (18) and the Saudi General Authority for Statistics in 2021 (19). The anticipated non-response rate was 20%, with a 99.99% confidence level, a 5% margin error, and a design effect of 1,453 participants required.

Results

A total of 1,451 participants completed the survey. Males represented 47.6% of the respondents with statistically significant higher age (35.59 ± 13.12, $p = 0.011$), height (172.22 ± 7.54, $p < 0.001$), and weight (65.59 ± 11.45, $p < 0.001$) than females. About one-third of the participants (33.8%) reported stable weight during COVID-19 pandemic. However, 40.9% reported weight gain, and 20.7% reported weight loss. A total of 1,286 (88.6%) indicated changes in their dietary habits after COVID-19 pandemic. Half of them (50.4%) had 1–3 dietary habits change and slightly more than one-third (34.4%) had 4–7 dietary habits change. Further details are presented in Table 1.

Table 2 displays the percentages of dietary habits change before and after COVID-19. The results showed statistically significant difference in the consumption (before and after COVID-19 pandemic) of fast food (worse consumption; $p < 0.001$), fried food (worse consumption; $p < 0.001$), fruits and vegetables (better consumption; $p < 0.001$), balanced healthy ingredients diet (better consumption; $p < 0.001$), sugar/honey/jiggery ($p < 0.001$), sugar-sweetened beverages (worse consumption; $p < 0.001$), and junk food/fast food due to boredom/

TABLE 2 Comparison of dietary habits change before and after COVID-19.

Dietary habits	Before COVID-19	After COVID-19	*p* value
1. *How often do you maintain a regular meal pattern?*			0.750
Not routinely	462 (31.8)	446 (30.7)	0.643
1–2 times/week	215 (14.8)	237 (16.3)	0.335
3–4 times/week	460 (31.7)	454 (31.3)	0.862
5–6 times/week	167 (11.5)	176 (12.1)	0.645
Almost daily	147 (10.1)	138 (9.5)	0.610
2. *How often do you consume fast food such as pizza, burger, pasta or noodles as snacks or meals?*			**<0.001**
Not routinely	415 (28.6)	371 (25.6)	0.163
1–2 times/week	543 (37.4)	486 (33.5)	0.126
3–4 times/week	347 (23.9)	409 (28.2)	**0.044**
5–6 times/week	112 (7.7)	124 (8.5)	0.452
Almost daily	34 (2.3)	61 (5.2)	**0.006**
3. *How often do you consume fried food (fried bread/poori, fried snack such as fries)?*			**<0.001**
Not routinely	530 (36.5)	541 (37.3)	0.751
1–2 times/week	450 (31.0)	441 (30.4)	0.812
3–4 times/week	358 (24.7)	296 (20.4)	**0.030**
5–6 times/week	86 (5.9)	119 (8.2)	**0.024**
Almost daily	27 (1.9)	54 (3.7)	**0.029**
4. *How often do you consume junk foods (popcorn, chips, candies, and chocolate) as snacks?*			0.641
Not routinely	367 (25.3)	397 (27.5)	0.313
1–2 times/week	367 (25.3)	370 (25.6)	0.888
3–4 times/week	452 (31.2)	419 (29.0)	0.349
5–6 times/week	150 (15.3)	145 (10.1)	0.802
Almost daily	115 (7.9)	114 (7.9)	0.969
5. *What was the frequency of your fruits and vegetables intake?*			**0.010**
Not routinely	334 (23.0)	279 (19.2)	**0.043**
1–2 times/week	334 (23.4)	336 (23.2)	0.944
3–4 times/week	479 (33.0)	478 (32.9)	0977
5–6 times/week	178 (12.3)	182 (12.5)	0.842
Almost daily	126 (8.7)	176 (12.1)	**0.006**
6. *How often do you have a balanced diet by including healthy ingredients (whole wheat, pulses, legumes, eggs, and nuts) in your meals?*			**<0.001**
Not routinely	331 (22.8)	241 (16.6)	**<0.001**
1–2 times/week	289 (19.9)	288 (19.8)	0.969
3–4 times/week	530 (36.5)	557 (38.4)	0.484
5–6 times/week	190 (13.1)	214 (14.7)	0.263
Almost daily	111 (7.6)	151 (10.4)	**0.017**
7. *How often do you have 2–3 servings of milk or its products (curd, buttermilk, cheese, paneer etc.) in a day?*			0.769
Not routinely	228 (15.7)	207 (14.3)	0.347
1–2 times/week	309 (21.3)	316 (21.8)	0.799
3–4 times/week	494 (34.0)	506 (34.9)	0.743
5–6 times/week	221 (15.2)	211 (14.5)	0.653
Almost daily	199 (13.7)	211 (14.5)	0.579
8. *How often do you have one or more servings of pulses, egg or meat in a day?*			
Not routinely	137 (9.4)	129 (8.9)	0.173
1–2 times/week	206 (14.2)	212 (14.6)	0.638
3–4 times/week	432 (29.8)	377 (26.0)	0.983

(Continued)

TABLE 2 (Continued)

Dietary habits	Before COVID-19	After COVID-19	*p* value
5–6 times/week	254 (17.5)	275 (19.0)	0.087
Almost daily	422 (29.1)	458 (31.6)	0.401
9. *How many teaspoons of sugar/honey/jiggery do you consume in a day?*			**<0.001**
Zero teaspoons/day, I don' t add sugar in my meals/beverages	270 (18.6)	411 (28.3)	**<0.001**
1–2 teaspoons/day	611 (42.1)	536 (36.9)	0.060
3–4 teaspoons/day	406 (28.0)	330 (22.7)	**0.012**
5–6 teaspoons/day	128 (8.8)	124 (8.5)	0.809
More than 6 teaspoons/day	36 (2.5)	50 (3.4)	0.136
10. *How often do you consume sugar-sweetened beverages (juice, soft drinks, and flavored soda)?*			**<0.001**
Not routinely	461 (31.8)	531 (36.6)	0.054
1–2 times/week	326 (22.5)	313 (21.6)	0.641
3–4 times/week	427 (29.4)	336 (23.2)	**0.003**
5–6 times/week	119 (8.2)	126 (8.7)	0.667
Almost daily	118 (8.2)	145 (10.0)	0.110
11. *How often do you consume foods with high sugar such sweet porridge, pastry, sweets and chocolate etc.?*			**0.062**
Not routinely	524 (36.1)	553 (38.1)	0.450
1–2 times/week	401 (27.6)	352 (24.3)	0.111
3–4 times/week	358 (24.7)	365 (25.1)	0.840
5–6 times/week	114 (7.9)	103 (7.1)	0.471
Almost daily	54 (3.7)	78 (5.4)	**0.041**
12. *How often do you eat junk food/fast food due to boredom/distress/disappointment?*			
Not routinely	630 (43.4)	615 (42.4)	**0.003**
1–2 times/week	396 (27.3)	348 (24.0)	0.722
3–4 times/week	325 (22.4)	333 (22.9)	0.116
5–6 times/week	51 (3.5)	86 (5.9)	0.778
Almost daily	49 (3.4)	69 (4.8)	**0.003**

Bold *p* values: statistically significant at < 0.05; ($n = 1,451$).

distress/disappointment (worse consumption; $p = 0.003$). No other significant differences were found in the remaining dietary habits (Table 2).

The participants reported several unhealthy dietary changes most commonly eating fast food (33%), eating junk food/fast food due to boredom/distress/disappointment (29.8%), and high sugar such as sweet porridge, pastry, sweets, and chocolate (28.5%). In contrast, the top healthier reported dietary habits changes were having a balanced healthy ingredients diet (34.4%), an increase in the consumption of fruits and vegetables, and a decrease in the intake of junk foods (28.9%: Table 3).

The univariate analyses showed a significant association between age ($p = 0.010$) and weight status during COVID-19 ($p < 0.001$) with unhealthy dietary habits changes after COVID-19. A logistic regression was performed to ascertain the effects of age, sex, BMI, marital status, and weight during COVID-19 pandemic on the likelihood that participants exhibit unhealthy dietary habits. Males were 1.43 times more likely to exhibit unhealthy dietary habits than females ($p = 0.038$, CI: 1.02–2.02). Increasing age was associated with a reduction in the likelihood of exhibiting unhealthy dietary habits (OR: 0.98, $p = 0.011$, CI: 0.96–0.99). Moreover, participants who reported stable weight or weight loss during COVID-19 were 0.29 ($p = 0.043$, 0.09–0.96) and 0.34 ($p = 0.020$, 0.07–0.79), respectively, less likely to have unhealthy dietary habits (Table 4).

Discussion

COVID-19 outbreak and quarantine measures clearly had an impact on the population's lifestyle-related behavior. To control the outbreak of COVID-19, many countries, including Saudi Arabia, have implemented quarantine measures. The quarantine had the beneficial results of lowering the pandemic level due to the measures implemented. However, the fear of illness and death as well as quarantine measures boosted people's stress levels and made them change their regular behaviors. Our study evaluated the long-term impact of the COVID-19 quarantine on the eating habits of adults from Riyadh, Saudi Arabia.

The results from the current study showed that 40.9% of participants reported weight gain during the COVID-19 quarantine. Our results are in line with previous studies that have reported weight gain during lockdown periods in Saudi Arabia (10, 18, 20–22). These studies have reported a prevalence of weight gain between 29.1 and 62.3%. Our findings are consistent as well with previous findings from different regions worldwide. A recent meta-analysis published by Anderson et al. (23) showed a small but potentially clinically significant increase in weight gain, BMI, and prevalence of obesity in both children and adults during COVID-19. Another systematic review and meta-analysis on the effects of COVID-19 lockdown on eating disorders and obesity reported 52% pooled prevalence of

TABLE 3 Changes in dietary habits.

Questions	*n* (%)
■ How often do you maintain a regular meal pattern?	
No change	674 (46.5)
Unhealthy change	390 (26.9)
Healthy change	387 (26.6)
■ How often do you consume fast food such as pizza, burger, pasta, or noodles as snacks or meals?	
No change	642 (44.2)
Unhealthy change	**478 (33.0)***
Healthy change	331 (22.8)
■ How often do you consume fried food (fried bread/poori, fried snack such as fries)?	
No change	689 (47.5)
Unhealthy change	404 (27.8)
Healthy change	358 (24.7)
■ How often do you consume junk foods (popcorn, chips, candies, and chocolate) as snacks?	
No change	654 (45.1)
Unhealthy Change	377 (26.0)
Healthy Change	**420 (28.9)** [¥]
■ What was the frequency of your fruits and vegetables intake?	
No change	670 (46.2)
Unhealthy Change	340 (23.4)
Healthy Change	**441 (30.4)** [¥]
■ How often do you have a balanced diet by including healthy ingredients (whole wheat, pulses, legumes, eggs, nuts,) in your meals?	
No change	630 (43.4)
Unhealthy change	322 (22.2)
Healthy change	**499 (34.4)** [¥]
■ How often do you have 2–3 servings of milk or its products (curd, buttermilk, cheese, paneer etc.) in a day?	
No change	652 (45.0)
Unhealthy change	392 (27.0)
Healthy change	407 (28.0)
■ How often do you have one or more servings of pulses, egg or meat in a day?	
No change	770 (53.1)
Unhealthy Change	305 (21.0)
Healthy Change	376 (25.9)
■ How many teaspoons of sugar/honey/jiggery do you consume in a day?	
No change	791 (54.5)
Unhealthy change	258 (17.8)
Healthy change	402 (27.7)
■ How often do you consume sugar-sweetened beverages (juice, soft drinks, flavored soda)?	
No change	647 (46.5)
Unhealthy change	377 (26.0)
Healthy change	400 (27.5)
■ How often do you consume foods with high sugar such sweet porridge, pastry, sweets and chocolate etc.?	
No change	659 (45.4)
Unhealthy change	**414 (28.5)***
Healthy change	378 (26.1)
■ How often do you eat junk food/fast food due to boredom/distress/disappointment?	
No change	709 (48.9)
Unhealthy change	**433 (29.8)***
Healthy change	309 (21.3)

*Top 3 unhealthy dietary habit changes; [¥]Top 3 unhealthy dietary habit changes; ($n = 1,451$). The bold values in table indicate the statistically significant p - values at < 0.05.

TABLE 4 Predictors of dietary habits changes ($n = 1,451$).

Characteristics	*n* (%) of participants in each dietary habits change category			Multivariate analysis			
	Unhealthy change	Healthy change	*p* value	Unadjusted OR [95% CI]	*p* value	Adjusted OR [95% CI]	*p* value
Age	34.42 ± 12.35	37.07 ± 12.48	**0.010**	0.98 [0.97–0.99]	0.010	098 [0.96–0.99]	**0.011**
Sex							
Male	623 (48.4)	67 (40.6)	0.058	1.37 [0.99–1.91]	0.058	1.43 [0.97–1.07]	**0.038**
*Female**	663 (51.6)	98 (59.8)		-		-	
BMI (Kg/m^2)	25.51 ± 4.11	25.09 ± 4.03	0.218	1.03 [0.99–1.07]	0.218	1.02 [0.97–1.07]	0.444
Marital status							
Single	523 (40.7)	56 (33.9)	0.120	0.99 [0.54–1.83]	0.976	0.71 [0.35–1.42]	0.327
Married	631 (49.1)	95 (57.6)		0.70 [0.93–1.27]	0.246	0.69 [0.38–1.27]	0.241
*Divorced/Widow**	132 (10.3)	14 (8.5)		-		-	
Weight during COVID-19 pandemic							
Was stable	419 (32.6)	72 (43.6)	**<0.001**	0.28 [0.09–0.91]	0.034	0.29 [0.09–0.96]	**0.043**
Lost weight	250 (19.4)	51 (30.9)		0.23 [0.07–0.77]	0.017	0.34 [0.07–0.79]	**0.020**
Gained weight	554 (43.1)	39 (23.6)		0.68 [0.20–2.25]	0.424	0.68 [0.21–2.27]	0.524
*I do not know**	63 (4.9)	3 (1.8)		-		-	-

*Reference variable; ($n = 1,451$). The bold values in table indicate the statistically significant *p* - values at < 0.05.

increased weight (24). Additionally, a combined systematic review and a meta-analysis have reported a prevalence change in body weight of 11.1–72.4% during COVID-19 lockdown (25). People often overstocked their kitchens with different foods out of fear of COVID-19, which may have resulted in overeating, particularly canned foods, which are high in calories. Given that many people stopped their regular daily routine activities, gyms were closed, and they were forced to work from home, weight gain is a reasonable result of this drop in physical activity and energy expenditure (10, 26, 27). Overall, 80.6% of the participants reported changes in dietary habits due to COVID-19 pandemic.

We found a statistically significant increment in healthy eating habits related to fruits and vegetables and healthy ingredients diet before and after COVID-19 pandemic. This is in accordance with studies of surveyed individuals who have increased their intake of fruits and vegetables (10, 22, 28, 29), and healthy ingredients diet (17, 30). Nonetheless, other studies have reported a decrease in the consumption of fruits and vegetables and healthy ingredients diet. Lippi et al. (31) concluded there is a reduction in fruits and vegetables intake. Similarly, a study in Zimbabwe showed that 57.8% of participants indicated a decrease in the consumption of fruits and vegetables (32). On the other side, we also observed a statistically significant increment in the consumption of fast food, fried food, sugar, consume sugar-sweetened beverages. In previous studies evaluating different perspectives on eating, the participants reported increased consumption of such unhealthy foods (13, 33–37). Conversely, few studies reported a downward trend consumption of fast food during the lockdown restrictions (22, 24, 25, 38).

Boredom has been associated with unhealthy eating behaviors such as higher fat, carbohydrate, and weight gain (39). Staying home for long periods and the high prevalence of sleep disorders during COVID-19 might increase the feeling of boredom, which is often linked with overeating to escape boredom (40). Our results were consistent with the aforementioned where around 30% have eaten junk food/fast food due to boredom/distress/disappointment.

We found that high age, being male, and maintaining or losing weight were significantly associated with reporting healthy dietary behaviors. Younger adults were more likely to have undesired changes in healthy dietary behaviors as consumption of fast food compared with old adults (41). A previous study has reported that females reported unhealthier dietary behaviors and weight gain during COVID-19 pandemic (29).

Nevertheless, our study findings imply that the COVID-19 pandemic and associated regulations have a significant impact on people's eating habits and food consumption patterns. Although several health recommendations were publicized for healthy eating during the COVID-19 pandemic and distributed information on how an adequate diet can support the immune system, the majority of our study participants did not adopt these recommendations into practice during and after the pandemic.

This work represents one of the few studies on the impact of COVID-19 quarantine on dietary habits changes, some limitations must be recognized. First, this study was cross-sectional, completed at one-time point and the self-reporting by participants on dietary habits changes before COVID-19 can introduce recall bias. The convenient sampling method might have introduced selection bias such that people with negative health and dietary changes were more likely to be interested in and completed the survey and It is still possible that selection bias influenced the results of this study.

Conclusion

Although healthy dietary habits have been reported in this study, such as the consumption of fruits and vegetables, COVID-19 confinement has also led to negative dietary behaviors reflected by

high consumption of fast/junk food and sugar intake resulting in weight gain, a potential adverse impact on the population wellbeing.

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 King Fahad Medical City—institutional review Board. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because No risk is anticipated in this survey-based.

Author contributions

MohA and IA: designed the study, statistical analysis, and supervision. MonA, ArA, AfrA, and AfnA: data collection, literature review, and prepare the draft manuscript. MohA, MonA, and IA: critical revision of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

MonA was employed by Nutrition and Dietetics, Eurofins-Ajal.

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

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Compliance with the EAT-Lancet diet and risk of colorectal cancer: a prospective cohort study in 98,415 American adults

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Background: The EAT-Lancet diet (ELD) is a recommended dietary pattern for achieving simultaneous improvements in both individual health and environmental sustainability. While research on the association between ELD and colorectal cancer (CRC) remains scarce, the potential impact of nutrition on CRC prevention and progression is a topic of growing interest. This study aims to investigate the relationship between adherence to the ELD and the risk of CRC, shedding light on the role of nutrition in CRC prevention.

Methods: A total of 98,415 participants were included. A Diet History Questionnaire (DHQ) was used to collect dietary information, and an ELD score was used to assess adherence to ELD. Higher scores indicated greater adherence. Cox hazard regression analyses were conducted to examine whether there were associations between the ELD score and CRC risk. The restricted cubic spline (RCS) model was used to further explore the dose-response association between the ELD score and CRC incidence. Subgroup analyses were conducted to identify potential modifiers that interacted with ELD on CRC incidence, and sensitivity analyses were performed to evaluate the robustness of the established association.

Results: During a mean follow-up of 8.82 years, a total of 1,054 CRC cases were documented. We found a statistically significant correlation between the ELD score and CRC risk (Q4 vs. Q1: HR 0.81, 95% CI 0.67–0.98; P for trend = 0.034) after adjusting for potential confounders. No statistically significant associations were discovered between ELD adherence and CRC by anatomical site. Subgroup analyses found no interactional factor, sensitivity analyses, and the RCS model showed a robustness and linearity association (P-linearity >0.05).

Conclusion: We concluded that adherence to ELD contributes to the prevention of CRC.

KEYWORDS

EAT-lancet diet, colorectal cancer, cox hazards regression analysis, prostate, lung, colorectal, ovarian cancer screening trial

1. Introduction

In the United States, colorectal cancer (CRC) is an important cause of cancer burden. It is reported to be the third most commonly diagnosed cancer and the third cause of cancer-associated death in both men and women (1). In 2023, it is estimated to have 153,020 new cases of CRC and 52,550 CRC deaths in the United States (1). The occurrence and development of CRC is a slow and long-term process, which provides opportunities for some preventive measures (2). In Western countries, diet is one of the most important risk factors for CRC, making it a possible preventive target (1).

Epidemiological research suggests that many foods can reduce the risk of CRC (3–6). In a prospective study of UK Biobank, participants eating more red and processed meat had a higher risk of CRC (3), while a meta-analysis by Schwingshackl et al. (4) found an inverse association between vegetables, fruit, and whole grains and CRC. A systematic review showed a protective effect of fish on CRC (5), while a study in two prospective US cohorts found an adverse effect of added sugars (6). These studies focused on specific foods and thus may not offer a comprehensive understanding of an ideal diet for overall health. Dietary patterns, which characterize a variety of foods, nutrients, and beverages, may serve as useful tools to represent the overall effects of diet on the risk of health outcomes.

Recently, the EAT-Lancet diet (ELD) was introduced as a scientifically optimized diet for nutrition and certain environmental indicators (7). In 2019, the EAT–Lancet Commission, made up of experts from diverse fields such as human health, agriculture, political science, and environmental sustainability, proposed for the first time the ELD, which is universally applicable to all food cultures and production systems in the world with high potential for local adaptation and scalability (7). Further research showed that ELD is affordable in most countries, including the United States (8). The ELD encourages the intake of vegetables, fruits, whole grains, legumes, nuts, unsaturated oils, and fish while limiting the intake of beef, lamb, pork, poultry, eggs, dairy products, potatoes, and added sugars. The dietary components of ELD are similar to those of the Mediterranean diet (MD) (high intakes of vegetables (excluding potatoes), fruits, whole grains, legumes, nuts, and fish, while a low intake of red and processed meats) (9), which has been widely recognized for its health benefits (10–12). Compared to MD, ELD is more environmentally friendly and requires less water (13). Adherence to ELD may greatly benefit human health. For example, adherence to ELD could reduce annual mortality by 19.0–23.6% (14) and could also reduce the risk of cardiovascular disease and diabetes (15–17). However, Berthy et al. (18) comprehensively analyzed the association between ELD, cardiovascular disease (CVD), and cancer risk. They concluded that adherence to the ELD could decrease the risk of cancer only in some subgroups but found no association with CVD risk.

To date, research focused on the ELD and CRC risks is scarce. Therefore, we conducted this analysis to explore the relationship between ELD adherence and CRC risk in 98,415 subjects aged 55 to 74 years from the Prostate, Lung, Colorectal, and Ovarian (PLCO) cohort.

Abbreviations: ELD, EAT-Lancet diet; CRC, colorectal cancer; PLCO, Prostate, Lung, Colorectal, and Ovarian; RCS, Restricted cubic spline; MD, Mediterranean diet; DHQ, Diet History Questionnaire; BQ, Baseline Questionnaire; SQX, Supplementary Questionnaire; DRC, Death Review Committee; NCI, National Cancer Institute; NIH, National Institutes of Health; FFQ, food frequency questionnaire; BMI, body mass index; HRs, hazards ratios; CIs, confidence intervals; NCDs, non-communicable diseases; EPIC, European Prospective Investigation into Cancer and Nutrition.

2. Methods

2.1. Study population

The PLCO Cancer Screening Trial is a large multicenter randomized controlled trial designed to evaluate the effectiveness of screening methods for prostate, lung, colorectal, and ovarian cancer. More information about the PLCO Cancer Screening Trial has been described elsewhere (19). In 10 selected screening centers nationwide in the United States, 154,887 men and women aged 55 to 74 years were enrolled in the PLCO cancer screening trial between 1993 and 2001 and then randomized to control or intervention arms in a 1:1 ratio (control arm received usual care, while intervention arm received additional screening care) (20). At baseline, participants were administered some self-reported questionnaires, such as the Baseline Questionnaire (BQ), Supplementary Questionnaire (SQX), and Diet History Questionnaire (DHQ), to collect individual characteristics, including diet and other cancer risk factors. All screening procedures and individual medical record abstracting were performed by trained and certified specialists, and the cause of death was certified by the Death Review Committee (DRC) (19, 21). The PLCO Cancer Screening Trial was approved by the National Cancer Institute (NCI), one of the components of the National Institutes of Health (NIH) (20), and each of the 10 screening centers involved in the study, all participants provided explicit, informed, and written consent. Our research was carried out with the approval of the NCI (project number: PLCO-1231).

In consideration of the objective of our study, we further excluded subjects as follows: (1) did not complete the BQ (n = 4,918); (2) did not complete a valid DHQ (valid DHQ refers to DHQ with date of completion, <8 missing frequency responses, still alive when completed DHQ, and participants with no extreme calorie intake, which means participants in the first or last percentile by gender) (n = 38,462); (3) had a history of any cancer (except non-melanoma skin cancer) (n = 9,684); (4) exited before accomplishing the DHQ (n = 114); (5) had unbelievable energy intake unbelievable energy intake refers to food energy intake from a diet <800 kcal or >4200 kcal for men and <600 kcal or >3500 kcal for women (22) (n = 3,294). Finally, 98,415 participants were included in our analyses (Figure 1).

2.2. EAT-lancet diet compliance

Dietary information was collected by the above-mentioned DHQ, a food frequency questionnaire (FFQ) developed by members of the Risk Factor Monitoring and Methods Branch

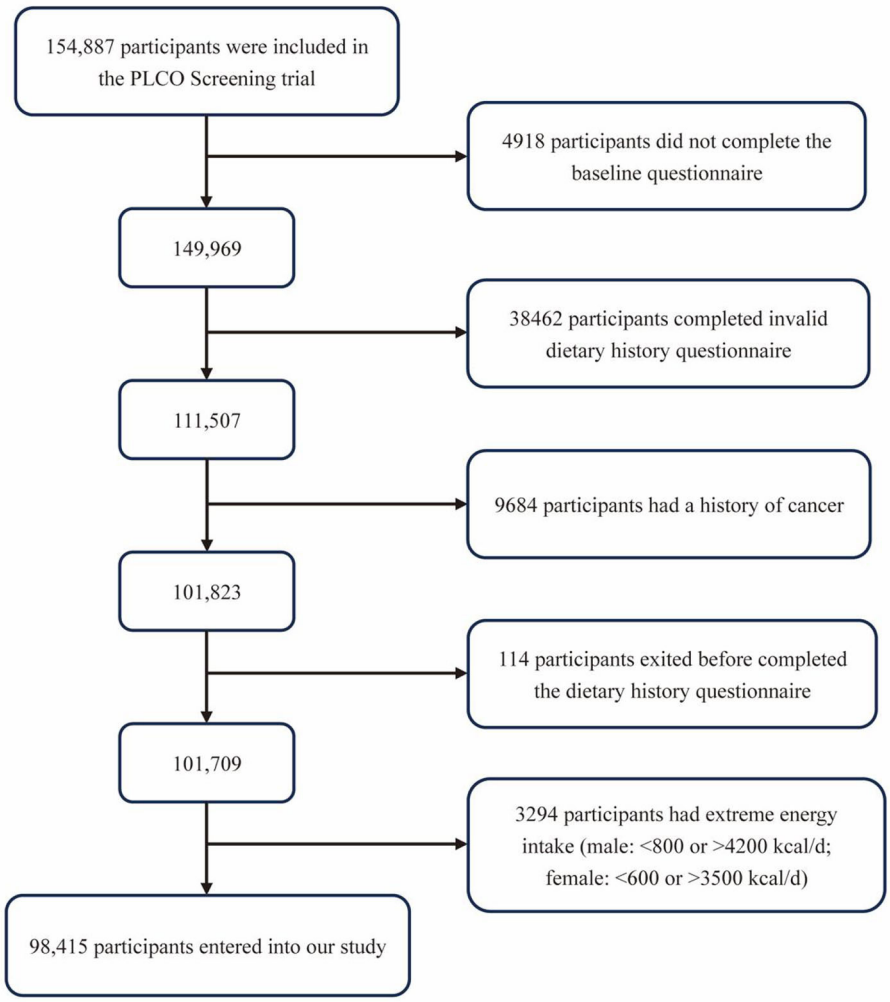

FIGURE 1
The flowchart for identifying eligible subjects. PLCO, Prostate, Lung, Colorectal, and Ovarian.

(RFMMB). The DHQ consists of 124 food items, includes portion size and dietary supplement questions, and provides reliable estimates of nutrient intake. The validity and reliability of DHQ have been tested elsewhere (23).

Compliance with ELD was assessed using the ELD scores, which are derived from the study of Stubbendorff et al. (24), who established ELD scores based on the recommendation of the EAT-Lancet Commission. In their research, a total of 14 food components were described as "emphasized foods" or "limited foods." Emphasized food components included whole grains, vegetables (except starch vegetables), fruits, legumes, nuts, unsaturated oils, and fish, while limited food components consisted of potatoes, dairy, eggs, poultry, pork, beef, lamb, and added sugar. Food components were described in grams per day and were dealt with based on an energy intake of 2500 kcal, consistent with the dietary target intake recommended by the EAT-Lancet Commission (7). According to the quantity of individual food intake, each component ranged from 0 to 3 points, with a possible total score of 0 to 42 (Supplementary Table 1). Specifically, emphasized food groups were given positive scores, while limited food groups were given negative scores. In other words, 3 points indicated high compliance, and 0 points indicated low compliance. Higher scores indicated greater adherence to ELD.

2.3. Assessment of covariates

The BQ, DHQ, and SQX were used to collect information involving demographic and lifestyle factors, such as age, sex, race, body mass index (BMI), smoking status, pack-year of smoking, drinking status, physical activity level, aspirin or ibuprofen consumption, family history of CRC, history of diverticulitis, history of colorectal polyps, history of colon comorbidities (including ulcerative colitis, Crohn's disease, Gardner's syndrome, or familial polyposis), energy intake from diet, protein intake from diet, carbohydrate intake from diet, and fat intake from diet. Diet-associated covariates, such as energy intake from diet, protein intake from diet, carbohydrate intake from diet, and fat intake from diet, were collected by DHQ, physical activity level was derived

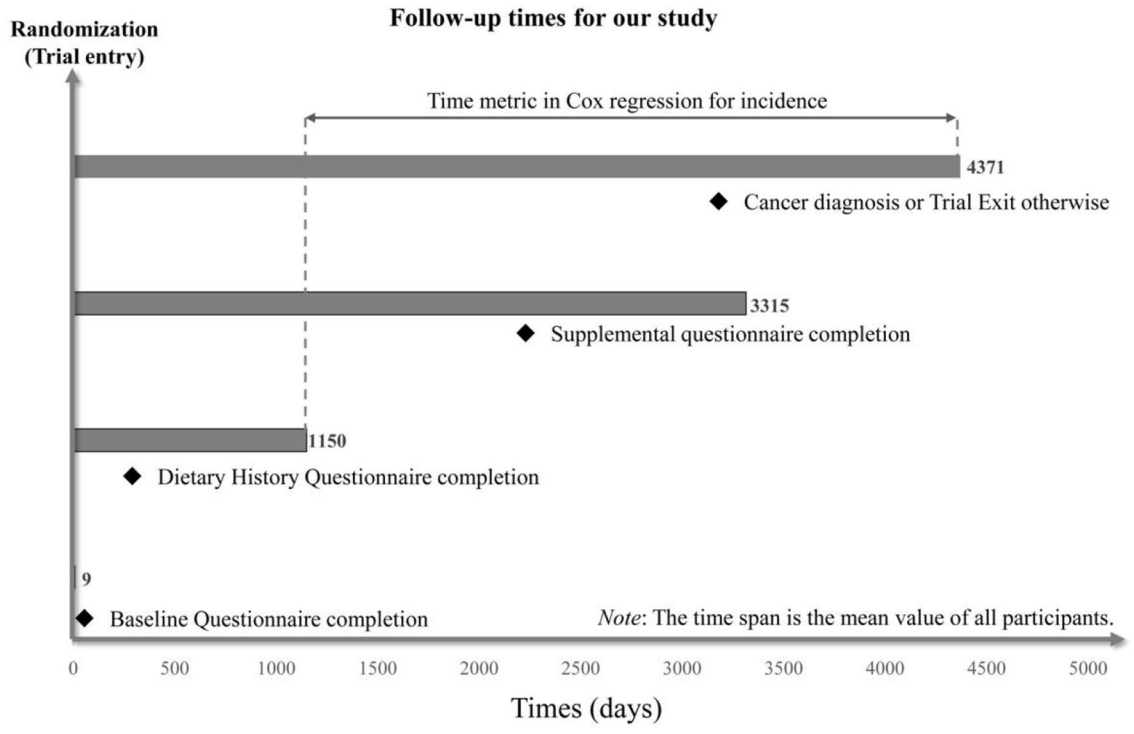

FIGURE 2
The timeline and follow-up scheme of our study.

from SQX, and all the other covariates were taken from BQ. Race was classified as white or non-white. BMI was calculated as weight in kilograms divided by height in meters squared. Smoking status was described as non-smokers and previous/current smokers. Physical activity level was calculated as the sum of self-reported minutes of moderate to vigorous activity in a week.

2.4. Ascertainment of outcomes

In this study, the primary outcome was the diagnosis of CRC. CRC was defined based on the definitions by the International Classification of Diseases for Oncology (ICD-O-2; codes: proximal colon cancer: C180-C185, distal colon cancer: C186-C187, and rectal cancer: C19-C20) (25). Proximal colon cancer includes cecum, appendix, ascending colon, hepatic flexure, transverse colon, and splenic flexure colon cancer. Distal colon cancer includes descending and sigmoid colon cancer (26). Participants were sent a self-reporting annual study update form to report any new CRC diagnoses they received, including the date and type of cancer diagnoses. If the annual study update form did not return, a repeated one or telephone would be conducted to contact the participant. Medical records were used as Supplementary material to certify the diagnoses. Family reports were collected if participants died, and death certificates, available autopsy reports, pathology slides, and pathology and other medical forms were used to ascertain the underlying cause of death (27), thus providing Supplementary material to certify the diagnoses.

2.5. Statistics analyses

For variables with <5% missing values, we used the modal value to impute the missing values for categorical covariates, including family history of any cancer, smoking status, aspirin consumption, ibuprofen consumption, history of diverticulitis, history of colorectal polyps, history of colon comorbidities, and family history of CRC. The median value was used to impute the continuous covariates, namely BMI and pack-years of smoking. For variables with more than 25% missing values, that is, physical activity level, we used the multiple imputation method to impute (Supplementary Table 2).

Cox proportional hazards regression analyses were utilized to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations between ELD adherence and subsite-specific CRC risk (colorectum, proximal colon, distal colon, and rectum). The follow-up period lasted from the completion of DHQ to the date of CRC diagnosis, death, loss to follow-up, and the end of follow-up (December 31, 2009), whichever came first (Figure 2) and was used as the time variable.

Based on ELD scores, we divided participants into quartiles and considered the first quartile to be the control group. The median scores of each quartile were assigned to each participant in the quartile to conduct Cox regression analyses and acquire P for trend. Some predefined confounders were included in the Cox regression models: Model 1 was adjusted for age, sex, and

TABLE 1 The baseline information of participants included in the study according to their EAT-Lancet diet scores*.

	ALL	Quartiles of EAT-lancet diet scores			
		Q1 (≤18)	Q2 (19–21)	Q3 (22–24)	Q4 (≥25)
	N = 98,415	*N* = 25,468	*N* = 26,969	*N* = 25,611	*N* = 20,367
ELD score	21.19 ± 4.10	16.07 ± 1.93	20.05 ± 0.81	22.92 ± 0.81	26.91 ± 2.02
Age	65.52 ± 5.73	64.75 ± 5.64	65.50 ± 5.74	65.88 ± 5.73	66.05 ± 5.73
Sex					
Male	47,183 (47.94%)	15,615 (61.31%)	13,219 (49.02%)	10,620 (41.47%)	7,729 (37.95%)
Female	51,232 (52.06%)	9,853 (38.69%)	13,750 (50.98%)	14,991 (58.53%)	12,638 (62.05%)
Race					
White	91,179 (92.65%)	24,491 (96.16%)	25,600 (94.92%)	23,777 (92.84%)	17,311 (85.00%)
Non-white	7,236 (7.35%)	977 (3.84%)	1,369 (5.08%)	1,834 (7.16%)	3,056 (15.00%)
BMI (kg/m^2)	27.20 ± 4.79	27.84 ± 4.74	27.46 ± 4.79	27.07 ± 4.80	26.21 ± 4.65
Smoke status					
Never	47,216 (47.98%)	10,595 (41.60%)	12,851 (47.65%)	12,986 (50.70%)	10,784 (52.95%)
Current/former	51,199 (52.02%)	14,873 (58.40%)	14,118 (52.35%)	12,625 (49.30%)	9,583 (47.05%)
Pack years of smoking	17.49 ± 26.39	23.07 ± 30.44	17.68 ± 26.32	15.28 ± 24.29	13.03 ± 21.98
Drinking					
No	26,666 (27.10%)	6,399 (25.13%)	6,962 (25.81%)	7,026 (27.43%)	6,279 (30.83%)
Yes	71,749 (72.90%)	19,069 (74.87%)	20,007 (74.19%)	18,585 (72.57%)	14,088 (69.17%)
Use aspirin regularly					
No	52,218 (53.06%)	13,373 (52.51%)	14,323 (53.11%)	13,487 (52.66%)	11,035 (54.18%)
Yes	46,197 (46.94%)	12,095 (47.49%)	12,646 (46.89%)	12,124 (47.34%)	9,332 (45.82%)
Use ibuprofen Regularly					
No	70,843 (71.98%)	18,171 (71.35%)	19,209 (71.23%)	18,414 (71.90%)	15,049 (73.89%)
Yes	27,572 (28.02%)	7,297 (28.65%)	7,760 (28.77%)	7,197 (28.10%)	5,318 (26.11%)
Physical activity (min/week)	122.03 ± 108.98	104.30 ± 101.93	116.51 ± 105.53	126.85 ± 109.28	145.45 ± 116.69
Arm					
Intervention	50,113 (50.92%)	12,701 (49.87%)	13,715 (50.85%)	13,086 (51.10%)	10,611 (52.10%)
Control	48,302 (49.08%)	12,767 (50.13%)	13,254 (49.15%)	12,525 (48.90%)	9,756 (47.90%)
Family history of colorectal cancer					
No	86,008 (87.39%)	22,207 (87.20%)	23,481 (87.07%)	22,467 (87.72%)	17,853 (87.66%)
Yes/possibly	12,407 (12.61%)	3,261 (12.80%)	3,488 (12.93%)	3,144 (12.28%)	2,514 (12.34%)
Had colonoscopy or test for blood in stool in past 3 years					
No	55,017 (55.90%)	15,606 (61.28%)	15,089 (55.95%)	13,842 (54.05%)	10,480 (51.46%)
Yes	43,398 (44.10%)	9,862 (38.72%)	11,880 (44.05%)	11,769 (45.95%)	9,887 (48.54%)
History of diverticulitis					
No	91,783 (93.26%)	23,915 (93.90%)	25,082 (93.00%)	23,832 (93.05%)	18,954 (93.06%)
Yes	6,632 (6.74%)	1,553 (6.10%)	1,887 (7.00%)	1,779 (6.95%)	1,413 (6.94%)
History of colon-related comorbidity					
No	97,109 (98.67%)	25,113 (98.61%)	26,634 (98.76%)	25,272 (98.68%)	20,090 (98.64%)
Yes	1,306 (1.33%)	355 (1.39%)	335 (1.24%)	339 (1.32%)	277 (1.36%)

(Continued)

TABLE 1 (Continued)

	ALL	Quartiles of EAT-lancet diet scores			
		Q1 (≤18)	Q2 (19–21)	Q3 (22–24)	Q4 (≥25)
	N = 98,415	*N* = 25,468	*N* = 26,969	*N* = 25,611	*N* = 20,367
History of colorectal polyps					
No	91,874 (93.35%)	23,791 (93.42%)	25,166 (93.31%)	23,926 (93.42%)	18,991 (93.24%)
Yes	6,541 (6.65%)	1,677 (6.58%)	1,803 (6.69%)	1,685 (6.58%)	1,376 (6.76%)
History of hypertension					
No	66,613 (67.69%)	17,388 (68.27%)	18,078 (67.03%)	17,181 (67.08%)	13,966 (68.57%)
Yes	31,802 (32.31%)	8,080 (31.73%)	8,891 (32.97%)	8,430 (32.92%)	6,401 (31.43%)
History of heart attack					
No	90,356 (91.81%)	23,332 (91.61%)	24,820 (92.03%)	23,537 (91.90%)	18,667 (91.65%)
Yes	8,059 (8.19%)	2,136 (8.39%)	2,149 (7.97%)	2,074 (8.10%)	1,700 (8.35%)
Food energy from diet (kcal/day)	1728.59 ± 658.00	1874.06 ± 694.00	1749.03 ± 660.54	1652.40 ± 625.11	1615.41 ± 611.27
Protein from diet (g/day)	96.48 ± 18.29	97.25 ± 19.08	96.84 ± 18.39	96.60 ± 17.86	94.90 ± 17.56
Carbohydrate from diet (g/day)	324.96 ± 58.52	302.29 ± 53.43	318.98 ± 55.64	332.99 ± 55.97	351.11 ± 59.04
Total fat from diet (g/day)	88.28 ± 20.88	95.44 ± 19.19	89.67 ± 19.95	85.58 ± 20.44	80.88 ± 21.53
Fiber intake from diet (g/day)	11.86 ± 5.45	9.46 ± 4.06	11.24 ± 4.69	12.54 ± 5.28	14.82 ± 6.44
Components of ELD score (g/day)					
Vegetables	315.39 ± 221.43	183.93 ± 123.41	274.36 ± 167.06	361.36 ± 213.12	476.29 ± 267.26
Fruits	276.34 ± 218.69	149.09 ± 135.33	247.30 ± 183.02	322.80 ± 210.57	415.46 ± 254.27
Unsaturated oils	2.39 ± 4.72	1.79 ± 3.34	2.02 ± 3.75	2.36 ± 4.50	3.64 ± 6.88
Legumes	52.92 ± 61.84	27.64 ± 25.81	42.57 ± 37.82	58.36 ± 53.21	91.40 ± 98.65
Nuts	13.45 ± 19.04	8.60 ± 11.61	11.48 ± 15.78	14.18 ± 19.50	21.21 ± 26.09
Whole grains	94.15 ± 91.02	55.37 ± 51.28	79.95 ± 71.12	103.95 ± 89.74	149.13 ± 120.96
Fish	22.84 ± 24.71	14.74 ± 15.93	20.09 ± 19.77	25.18 ± 25.29	33.66 ± 33.08
Beef and lamb	53.58 ± 33.15	65.23 ± 35.35	57.56 ± 32.23	50.56 ± 29.95	37.53 ± 28.01
Pork	8.59 ± 10.88	12.26 ± 13.63	9.35 ± 10.75	7.22 ± 8.93	4.72 ± 7.17
Poultry	52.45 ± 53.91	51.76 ± 51.48	54.08 ± 53.67	53.96 ± 55.19	49.27 ± 55.39
Eggs	20.98 ± 25.39	29.71 ± 30.09	22.04 ± 25.40	17.77 ± 22.36	12.68 ± 17.91
Dairy	399.51 ± 373.77	471.35 ± 423.48	421.29 ± 382.57	381.42 ± 348.62	303.59 ± 295.80
Potatoes	87.49 ± 65.32	106.49 ± 73.75	92.51 ± 65.60	81.36 ± 59.05	64.81 ± 51.87
Added sugar	71.16 ± 37.21	84.34 ± 45.15	73.33 ± 36.51	66.58 ± 31.42	57.59 ± 26.50

*Values are mean ± standard deviation or counts (percentage) as indicated.

race. Model 2 was further adjusted for BMI, smoking status, pack-year of smoking, drinking status, physical activity level, regular consumption of aspirin, regular consumption of ibuprofen, family history of CRC, history of diverticulitis, history of colorectal polyps, history of colon comorbidities, energy intake from diet, protein intake from diet, carbohydrate intake from diet, and fat intake from diet. To further explore whether there was a linear dose-response association of ELD with CRC risk, we constructed a restricted cubic spline (RCS) model. Of note, we conducted the dose–response analysis in Model 2. Prespecified subgroup analyses were conducted to identify potential modifiers interacting with ELD, including age (≤65 vs. >65 years), sex (male vs. female), BMI (≤30 vs. >30 kg/m^2), physical activity level (≤medium vs. >medium), smoking status (never vs. current/former), current alcohol drinking (yes vs. no), regular consumption of aspirin (yes vs. no), family history of colorectal cancer (yes vs. no), history of colorectal polyps (yes vs. no), history of colorectal comorbidities (yes vs. no), and energy intake from diet (≤medium vs. >medium). The following sensitivity analyses were conducted to testify to the robustness of our study: (1) First, we excluded participants with a history of diabetes, which is one of the risk factors for CRC (28); (2) Second, subjects with a history of heart attack were excluded; (3) third, the participants who had a colonoscopy or test for blood in stool in the past 3 years were

excluded; (4) Finally, participants diagnosed in 2 years of follow-up were excluded.

3. Results

3.1. Baseline characteristics

A total of 98,415 participants aged 55–74 years were divided into quartiles according to their ELD scores [Q1 (ELD score $\leq$ 18), n = 25,468; Q2 (ELD score: 19–21), n = 26,969; Q3 (ELD score: 22-24), n = 25,611; Q4 (ELD score $\geq$ 25), n = 20,367]. As shown in Table 1, the mean age (SD) was 65.52 (5.73), and the mean ELD score (SD) was 21.19 (4.10). Higher ELD scores indicated greater adherence to the ELD. Among all included participants, we found that those who adhered more closely to ELD tended to be women (Q4, 62.05%; Q1, 38.69%) and non-white (Q4, 15.00%; Q1, 3.84%), have lower BMI (Q4, 26.21 $\pm$ 4.65 kg/m^2; Q1, 27.84 $\pm$ 4.74 kg/m^2), were more likely to be a non-smoker (never smoke: Q4, 52.95% vs. Q1, 41.60%), nondrinker (never drink: Q4, 30.83% vs. Q1, 25.13%), were less likely to use aspirin or ibuprofen regularly, and exercised more (Q4, 145.45 min/week vs. Q1, 104.30 min/week; Table 1). Consistent with expectation, mean daily intakes of emphasized components increased with higher adherence to ELD, while the opposite was observed for the intake of limited components. Furthermore, subjects in Q4 had a higher dietary intake of carbohydrates but a lower dietary intake of energy, protein, and total fat than in Q1 (Table 1).

3.2. ELD scores and CRC incidence

During a mean follow-up of 8.82 years, we documented 1054 CRC cases, which consisted of 626 proximal colon cancers, 214 distal colon cancers, and 194 rectal cancers. Compared with those in the lowest quartile (Q1), participants in the highest quartile of ELD scores (Q4) had a decreased CRC risk after adjusting for potential CRC risk factors ($HR_{Q4vs.Q1}$: 0.81; 95% CI: 0.67, 0.98; P-trend = 0.034; Table 2). We did not record any significant association between the ELD scores and anatomic CRC (proximal colon cancer: $HR_{Q4vs.Q1}$: 0.85; 95% CI: 0.67, 1.09; P-trend = 0.160; distal colon cancer: $HR_{Q4vs.Q1}$: 0.73; 95% CI: 0.47, 1.12; P-trend = 0.258; rectal cancer: 0.69; 95% CI: 0.43, 1.11; P-trend = 0.205; Supplementary Table 3).

3.3. Additional analyses

In the RCS model, we found a linear association between the ELD score and CRC incidence (P-nonlinearity = 0.920) (Figure 3). Subgroup analyses showed no significant modifiers interacting with ELD, including age, sex, BMI, physical activity level, smoking status, drinking status, regular consumption of aspirin, family history of CRC, history of colorectal polyps, history of colorectal comorbidities, and energy intake from diet (all P-interaction > 0.05; Table 3).

After excluding participants with a history of diabetes, a history of heart attack, those who had colonoscopy or test for blood in stool in the past 3 years, and those diagnosed with CRC in 2 years, the inverse association between the ELD score and CRC incidence still existed (all P-trend < 0.05), which demonstrated the robustness of our finding (Table 4).

4. Discussion

In the cohort of the PLCO Cancer Screening Trial, we used *a priori*-defined ELD score to assess adherence to ELD and evaluated its relationship with CRC risk. During a mean follow-up of 8.82 years, we found that greater adherence to the ELD was associated with a lower risk of CRC in a linear dose–response manner in American adults. Subgroup analyses showed no significant effect modifiers interacting with ELD on CRC, and our result was robust. We did not observe any significant association between ELD adherence and the risk of specific subsites of CRC.

In the realm of dietary approaches promoting health and sustainability, the ELD and the MD stand as two distinct paradigms marked by notable disparities in their historical origins and core principles. The ELD, guided by a global perspective and a resolute commitment to environmental sustainability, places a pronounced emphasis on the consumption of plant-based foods while advocating for a reduction in meat intake (7). In stark contrast, the MD remains region-specific, deeply entrenched in the rich culinary traditions of Mediterranean nations, and underscores a well-balanced dietary pattern characterized by the incorporation of olive oil, whole grains, fruits, vegetables, and moderate portions of fish and poultry (28). The ELD's accentuation of plant-based foods, restricted consumption of meat and animal products, integration of sustainable agricultural practices, and adaptability to diverse cultural contexts collectively position it as a dietary choice with enhanced environmental sustainability. While both diets share commonalities in their promotion of healthful and sustainable eating habits, the fundamental principles of the ELD take precedence in prioritizing the reduction of the environmental impact associated with dietary choices. Thus, the ELD emerges as an appealing option for individuals seeking a dietary approach that promotes health and demonstrates a steadfast commitment to sustainable practices on a global scale.

With improved living standards, residents' income, and urbanization, eating behavior of humans is gradually shifting to unhealthy diets that are high-energy, high-animal-origin, and ultra-processed (7). This dietary habit is threatening human health and environmental sustainability, and an unhealthy diet has become the largest burden to diseases and premature death, surpassing smoking and drinking (7). Therefore, in 2019, the EAT–Lancet Commission proposed a plant-based diet that was good for human health and environmental sustainability (7). The effectiveness of ELD has been confirmed by many studies. In terms of environmental sustainability, a meta-analysis by Springmann et al. (14) showed that compliance with the ELD was associated with a 42% reduction in greenhouse gas emissions and a 10% reduction in freshwater consumption. These advantages were further confirmed by the study of Cambeses-Franco et al. (29). In terms of human health, ELD has been believed to decrease the incidence and mortality from non-communicable diseases (NCDs) (7, 16, 18, 24, 29–31). In the Malmö Diet and Cancer study cohort,

TABLE 2 Hazard ratios of the association of the EAT-Lancet diet score with the risk of colorectal cancer.

Quartiles of ELD scores	No. of participants	No. of cases	Person-years	Hazard ratio (95% confidence interval)		
				Unadjusted	Model 1[a]	Model 2[b]
Quartile 1 (≤18)	25468	314	221736.80	1.00 (reference)	1.00 (reference)	1.00 (reference)
Quartile 2 (19–21)	26969	273	238353.80	0.81 (0.69, 0.95)	0.79 (0.67, 0.93)	0.81 (0.69, 0.95)
Quartile 3 (22–24)	25611	266	227230.70	0.83 (0.70, 0.97)	0.80 (0.68, 0.94)	0.84 (0.70, 0.99)
Quartile 4 (≥25)	20367	201	180807.70	0.79 (0.66, 0.94)	0.74 (0.62, 0.89)	0.81 (0.67, 0.98)
P for trend				0.009	0.001	0.034

[a] Adjusted for age (years), sex (male, female), and race (white, non-white). [b] Adjusted for model 1 plus body mass index (kg/m^2), smoking status (never, current or former), pack-year of smoking, drinking status (no, yes), physical activity level (min/week), aspirin and ibuprofen consumption (no, yes), family history of colorectal cancer (no, yes), history of diverticulitis (no, yes), colorectal polyps (no, yes), colon comorbidities (including ulcerative colitis, Crohn's disease, Gardner's syndrome, or familial polyposis) (no, yes), energy intake from diet (kcal/day), protein intake from diet (g/day), carbohydrate intake from diet (g/day), and fat intake from diet (g/day).

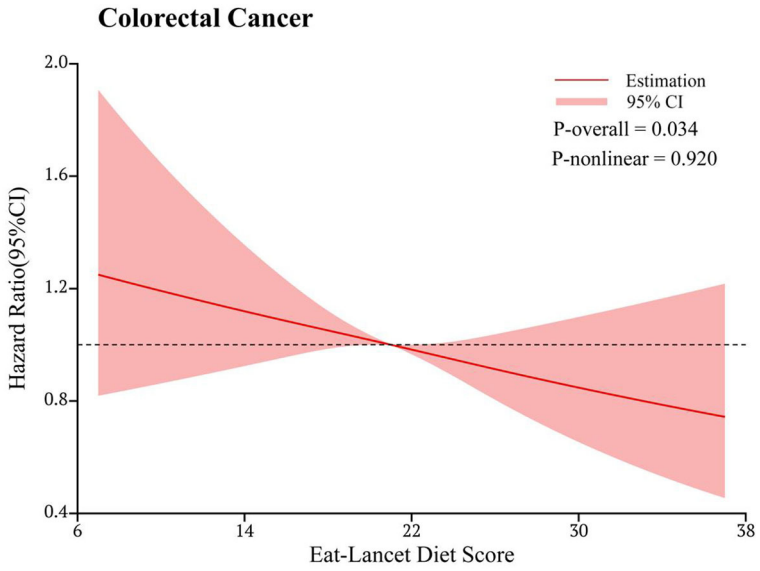

FIGURE 3
Dose-response analysis of the association of the EAT-Lancet diet score with the risk of colorectal cancer. The hazard ratio was adjusted for age (years), sex (male and female), race (white and non-white), body mass index (kg/m^2), smoking status (never, current or former), pack-year of smoking, drinking status (no, yes), physical activity level (min/week), aspirin and ibuprofen consumption (no, yes), family history of colorectal cancer (no, yes), history of diverticulitis (no, yes), colorectal polyps (no, yes), colon comorbidities (including ulcerative colitis, Crohn's disease, Gardner's syndrome, or familial polyposis) (no, yes), energy intake from the diet (kcal/day), protein intake from the diet (g/day), carbohydrate intake from the diet (g/day), and fat intake from the diet (g/day).

adherence to ELD can reduce the risk of type 2 diabetes by 18% (30). In the Swedish population, adherence to ELD can reduce the risk of coronary events by 20% (31) and can reduce the risk of all-cause mortality by 25%, cardiovascular disease death by 32%, and cancer-related death by 24% (24).

In previous research on ELD, only two studies involved the incidence of cancer (18, 32). Research by Laine et al. (32) showed that adherence to ELD over a 20-year period could effectively decrease 10%-39% of cancer risk in a large prospective cohort of the European Prospective Investigation into Cancer and Nutrition (EPIC). A prospective cohort study of the French population focused for the first time on ELD adherence and the risk of specific types of cancer. They found that adherence to ELD was associated with a decreased risk of lung cancer while not associated with the risk of breast cancer, prostate cancer, and CRC (18). In our study, we found a statistically significant association between adherence to ELD and the risk of CRC. The possible reason may be that the study populations were different: the study of Berthy et al. (18) was conducted in France, while our study was conducted in America. There was a difference in their dietary habits. Compared to the French, Americans are less likely to eat fruits and vegetables, which are determined by their respective cultural background (33).

ELD emphasizes the intake of vegetables, whole grains, fruits, unsaturated oils, legumes, nuts, and fish and limits the intake of beef and lamb, pork, poultry, eggs, potatoes, dairy, and added sugar. All the emphasized food components have been proven to reduce the CRC risk (34–38), and most of the restricted components, such as beef and lamb, pork, eggs, potatoes, and added sugar (6, 39–43), were reported to increase the CRC incidence. As for dairy, there are many types. Certain types, such as cheese and low-fat dairy,

TABLE 3 Subgroup analyses on the association of the EAT-Lancet diet scores with the risk of colorectal cancer.

Subgroup variable	No. of cases		Hazard ratio (95% confidence interval) EAT-lancet diet scores				P for trend	P for interaction
		Person-years	Quartile 1 (≤18)	Quartile 2 (19–21)	Quartile 3 (22–24)	Quartile 4 (≥25)		
Age (years)								0.528
≤65	384	454117.86	1.00 (reference)	0.70 (0.54, 0.92)	0.82 (0.63, 1.09)	0.74 (0.54, 1.02)	0.068	
>65	670	414011.15	1.00 (reference)	0.89 (0.72, 1.10)	0.87 (0.70, 1.08)	0.87 (0.68, 1.10)	0.214	
Sex								0.270
Male	571	411493.40	1.00 (reference)	0.88 (0.72, 1.09)	0.88 (0.70, 1.10)	0.74 (0.56, 0.97)	0.037	
Female	483	456635.61	1.00 (reference)	0.70 (0.54, 0.92)	0.77 (0.60, 1.00)	0.83 (0.63, 1.09)	0.344	
Body mass index (kg/m^2)								0.582
≤30	799	675555.72	1.00 (reference)	0.80 (0.66, 0.97)	0.84 (0.69, 1.03)	0.76 (0.61, 0.95)	0.027	
>30	255	192573.28	1.00 (reference)	0.84 (0.61, 1.15)	0.80 (0.57, 1.13)	0.96 (0.65, 1.42)	0.523	
Physical activity (min/week)								0.299
≤medium[a]	651	430488.15	1.00 (reference)	0.84 (0.69, 1.03)	0.77 (0.62, 0.96)	0.82 (0.64, 1.06)	0.035	
>medium[a]	403	437640.85	1.00 (reference)	0.77 (0.57, 1.03)	0.95 (0.72, 1.26)	0.81 (0.59, 1.10)	0.439	
Smoking status								0.876
Never	470	422690.59	1.00 (reference)	0.75 (0.59, 0.97)	0.82 (0.64, 1.06)	0.79 (0.60, 1.05)	0.182	
Current/Former	584	445438.42	1.00 (reference)	0.85 (0.69, 1.06)	0.84 (0.67, 1.06)	0.81 (0.62, 1.05)	0.082	
Drinker								0.425
No	279	233353.73	1.00 (reference)	0.70 (0.50, 0.99)	0.87 (0.62, 1.23)	0.87 (0.58, 1.30)	0.744	
Yes	775	634775.27	1.00 (reference)	0.86 (0.71, 1.03)	0.83 (0.68, 1.02)	0.81 (0.64, 1.01)	0.052	
Regular consumption of aspirin								0.524
No	578	464200.11	1.00 (reference)	0.76 (0.60, 0.95)	0.85 (0.68, 1.07)	0.78 (0.60, 1.01)	0.119	
Yes	476	403928.90	1.00 (reference)	0.87 (0.68, 1.10)	0.81 (0.62, 1.04)	0.83 (0.62, 1.10)	0.124	
Family history of colorectal cancer								0.611
No	895	758790.68	1.00 (reference)	0.83 (0.69, 0.99)	0.82 (0.68, 0.98)	0.81(0.66, 1.00)	0.044	
Yes/possible	159	109338.33	1.00 (reference)	0.69 (0.45, 1.06)	0.92 (0.61, 1.41)	0.74 (0.45, 1.22)	0.440	
History of colorectal polyps								0.694
No	963	810317.57	1.00 (reference)	0.81 (0.68, 0.96)	0.83 (0.69, 0.99)	0.79 (0.65, 0.97)	0.026	
Yes	91	57811.44	1.00 (reference)	0.78 (0.43, 1.41)	0.91 (0.51, 1.63)	1.00 (0.53, 1.88)	0.893	
History of colorectal comorbidities								0.455
No	1038	856685.97	1.00 (reference)	0.80 (0.68, 0.95)	0.82 (0.69, 0.98)	0.81 (0.67, 0.98)	0.033	
Yes	16	11443.03	1.00 (reference)	1.84 (0.41, 8.17)	2.20 (0.50, 9.71)	0.71 (0.10, 5.00)	0.991	
Energy intake from the diet (kcal/day)								0.517
≤Medium[b]	535	434541.58	1.00 (reference)	0.82 (0.64, 1.04)	0.92 (0.72, 1.17)	0.84 (0.64, 1.09)	0.379	
>Medium[b]	519	433587.42	1.00 (reference)	0.82 (0.65, 1.02)	0.75 (0.59, 0.96)	0.79 (0.60, 1.04)	0.029	

The hazard ratio was adjusted for age (years), sex (male, female), race (white, non-white), body mass index (kg/m^2), smoking status (never, current or former), pack-year of smoking, drinking status (no, yes), physical activity level (min/week), aspirin and ibuprofen consumption (no, yes), family history of colorectal cancer (no, yes), history of diverticulitis (no, yes), colorectal polyps (no, yes), colon comorbidities (including ulcerative colitis, Crohn's disease, Gardner's syndrome, or familial polyposis) (no, yes), energy intake from diet (kcal/day), protein intake from diet (g/day), carbohydrate intake from diet (g/day), and fat intake from diet (g/day). [a]The median of physical activity is 104 min/week. [b]The median dietary energy intake in this study is 1615 kcal/day.

contribute to the prevention of CRC, while whole-fat dairy, which is the component we used to construct the ELD score, may increase the risk of CRC (44). The impact of an individual diet on disease is limited, but the synergies and interactions between multiple diets, combined with long-term accumulation, may eventually contribute to the onset, delay, or prevention of NCDs (45–47).

TABLE 4 Sensitivity analyses on the association of the EAT-Lancet diet scores with the risk of overall colorectal cancer[a].

Categories	No. of participants	No. of cases	Hazard ratio (95% confidence interval) of the EAT-lancet diet Scores[a]				
			Quartile 1 (≤18)	Quartile 2 (19–21)	Quartile 3 (22–24)	Quartile 4 (≥25)	P for trend
Excluded participants with a history of diabetes[b]	91,950	952	1.00 (reference)	0.79 (0.67, 0.94)	0.82 (0.69, 0.98)	0.81 (0.66, 0.99)	0.044
Excluded participants with a history of heart attack[c]	90,356	953	1.00 (reference)	0.79 (0.66, 0.94)	0.83 (0.69, 0.99)	0.80 (0.65, 0.97)	0.035
Excluded participants had colonoscopy or test for blood in stool in the past 3 years[d]	55,017	594	1.00 (reference)	0.90 (0.73, 1.11)	0.83 (0.66, 1.04)	0.64 (0.48, 0.84)	0.001
Excluded participants diagnosed in 2 years	98,180	819	1.00 (reference)	0.84 (0.69, 1.01)	0.85 (0.70, 1.03)	0.79 (0.63, 0.98)	0.040
Repeated analysis of participants with unfilled data	98,415	1,054	1.00 (reference)	0.84 (0.69, 1.04)	0.79 (0.63, 0.98)	0.77 (0.60, 0.99)	0.024

[a]HR was adjusted for age, sex (male and female), race (white, non-white), body mass index (kg/m^2), smoking status (never, current or former), pack-year of smoking, drinking status (no, yes), physical activity level (min/week), aspirin and ibuprofen consumption (no, yes), family history of colorectal cancer (no, yes), history of diverticulitis (no, yes), colorectal polyps (no, yes), colon comorbidities (no, yes), energy intake from diet (kcal/day), protein intake from diet (g/day), carbohydrate intake from diet (g/day), and fat intake from diet (g/day). [b]The hazard ratio was not adjusted for a history of diabetes. [c]The hazard ratio was not adjusted for a history of heart attack. [d]Hazard ratio did not exclude participants who had colonoscopies or tests for blood in stool in the past 3 years.

The occurrence of CRC is a heterogeneous process that is influenced by the environment, microbial exposure, diet, and host immunity. Evidence suggests that CRC is caused by gradual interference with changes in gut microbiota composition attributed to food composition or diet and changes in oncogenes and tumor suppressor genes (48). Intestinal microorganisms can promote CRC development by metabolizing food to produce different substances and causing chronic inflammation, affecting host immunity and genetic susceptibility of the body (48). These may help explain the impact of food on CRC.

Our study has some limitations. First, our study had fully adjusted covariates available in the PLCO Cancer Screening Trial. However, we could not rule out the possibility that our finding was biased by unmeasured or unrecognized confounders. Second, all diet-associated information used to calculate the ELD score was assessed using a questionnaire that was only collected once at baseline, without considering the change of dietary habits over time. However, a study has suggested that compared to assessing a dietary pattern using the cumulative averages, baseline diet data can help acquire a similar statistical association for disease risk analysis (49). Third, we found no significant interaction in the incidence of CRC between the ELD score and potential effect modifiers in subgroup analyses, so we cannot provide guidance for specific subgroups based on our results. Fourth, in the Cox regression analyses of subsite CRC, there was no statistically significant association between the ELD score and proximal colon cancer, distal colon cancer, or distal cancer. The reason may be attributed to the limited number of cancer cases in the proximal colon, distal colon, and rectum, leading to insufficient statistical power for these analyses. Finally, this study was conducted on Americans aged 55–74 years. It is unknown whether the result can be extended to populations of other ages or countries with different physical characteristics, dietary cultures, and genetic backgrounds, so more studies need to be conducted.

5. Conclusion

In conclusion, in American adults, great adherence to ELD is associated with decreased CRC risk in a linear dose-response manner. Our result supports the role of ELD in preventing CRC, which provides new evidence for ELD in cancer prevention. Therefore, it is crucial to publicize the ELD.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: The raw data used in this article is not available because of the National Cancer Institute's data policy. Requests to access these datasets should be directed to NCIinfo@nih.gov.

Ethics statement

The studies involving humans were approved by the NCI (Project ID: PLCO-1231). The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

XR: Writing—review and editing, Data curation, Investigation, Writing—original draft. CY: Data curation, Writing—original draft. LP: Funding acquisition, Writing—review and editing, Project administration. HG: Funding acquisition, Writing—review and editing. YX: Writing—review and editing. YT: Writing—review and editing. HH: Writing—review and editing. LX: Writing—review and editing. YW: Writing—review and editing, Funding acquisition. YJ: Writing—review and editing.

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Conflict of interest

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

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2023.1264178/full#supplementary-material

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Associations between homocysteine, vitamin B12, and folate and the risk of all-cause mortality in American adults with stroke

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Objective: Associations between plasma homocysteine (Hcy), vitamin B12, and folate and the risk of all-cause mortality are unclear. This study aimed to examine whether plasma Hcy, vitamin B12, and folate levels independently predict the risk of all-cause mortality in American adults with stroke.

Methods: Data from the United States National Health and Examination Survey (NHANES; 1999–2006) were used and linked with the latest (2019) National Death Index (NDI). Cox proportional hazards models and restricted cubic splines were used to estimate the hazard ratios (HR) and 95% confidence intervals (CI) of all-cause mortality for Hcy, folate, and B12 levels in adults with stroke. Sample weights were calculated to ensure the generalizability of the results.

Results: A total of 431 participants were included (average age: 64.8 years). During a median follow-up of 10.4 years, 316 deaths occurred. Hcy was positively associated with all-cause mortality in adults with stroke (HR, 1.053; 95% CI: 1.026–1.080). Stroke patients with plasma Hcy levels in the fourth quartile had a 1.631-fold higher risk of all-cause mortality (HR, 1.631; 95% CI: 1.160–2.291) than those in the first quartile. The association between plasma Hcy and all-cause mortality was strong significant in older patients (*p* for interaction = 0.020). Plasma folate and vitamin B12 concentrations were inversely correlated with Hcy concentrations [B-value (95% CI): −0.032 (−0.056– −0.008), −0.004 (−0.007– −0.002), respectively]. No significant associations were observed between folate, vitamin B12 levels, and all-cause mortality in adults with stroke.

Conclusion: Plasma Hcy levels were positively associated with all-cause mortality in older adults with stroke. Folate and vitamin B12 levels were inversely correlated with Hcy. Plasma Hcy may serve as a useful predictor in mortality risk assessment and targeted intervention in adults with stroke.

KEYWORDS

stroke, all-cause mortality, homocysteine, folate, vitamin B12

Introduction

Stroke is the second leading cause of death worldwide (1). In the United States (US), stroke ranks fifth among all causes of death, and on average, in 2020, one person died of stroke approximately every 3 min (2). A recent study showed a 0.8% decrease in stroke mortality and a 23.8% increase in actual stroke deaths (2). Stroke imposes a great burden

on families and society owing to its poor prognosis and high mortality rates. The improvement of stroke outcomes is a major global public health concern. Given the limited effective treatments for stroke, the emphasis should be on prevention, via early detection and proactive management of modifiable risk factors.

Elevated plasma homocysteine (Hcy) is one of the most easily modifiable risk factors for stroke and can be caused by deficiency of either vitamin B12 or folate (vitamin B9) (3, 4). Hcy can damage vascular structures through oxidative stress and inflammation, promote atherosclerosis, and increase the risk of stroke (5). Hcy also has a strong and direct effect on stroke severity and prognosis via neurotoxicity and increased brain damage (6). Although controversial (7, 8), clinical studies have shown that hyperhomocysteinemia (HHcy) is associated with a poor prognosis for stroke (7, 9, 10). However, whether plasma Hcy levels predict the mortality risk in stroke patients remains unclear.

Folate and vitamin B12 are the major nutritional determinants of homocysteinemia. Folate and vitamin B12 effectively reduce the Hcy concentration by participating in its metabolic pathways (4). In the United States, a folate fortification policy was implemented in 1998, which significantly increased folate levels and reduced Hcy levels in Americans (11). One study suggested that the decline in stroke-related mortality in the United States tripled after folate fortification (12). B vitamins exert a protective effect on stroke prognosis (4, 13, 14). However, some studies suggest that vitamin B12 and folate do not improve stroke prognosis (15, 16) and excessive B vitamin supplementation may increase the risk of hip fractures (17) and cancer (18). There are limited studies on the correlation between B vitamins and the long-term prognosis of adults with stroke, and the results are inconsistent with respect to B vitamin levels, comorbidities, and age (8, 19–21).

Homocysteine concentrations represent a modifiable risk factor for stroke that can be prevented and treated by B vitamin supplementation. Therefore, understanding the effects of Hcy and B vitamin levels on all-cause mortality in adults with stroke is clinically relevant. Given this context, we aimed to examine the associations between Hcy, vitamin B12, and folate and all-cause mortality in United States adults with stroke using data from the National Health and Nutrition Examination Survey (NHANES).

Materials and methods

Study population

This cohort study used data from the NHANES 1999–2006 and was linked to the most recent (2019) National Death Index (NDI). The NHANES is a nationally representative cross-sectional survey of the non-institutionalized United States civilians with data collected in 2-year cycles. During each cycle, the NHANES was conducted based on a stratified multistage probability sampling design and included two components: a household interview and a health examination. The health examination component consisted of medical, dental, and physiological examinations, as well as laboratory tests administered by trained medical personnel in a fully equipped mobile examination center (MEC). Additional information on the design and procedures of the NHANES are available at the Center for Disease Control and Prevention website.[1]

The study included individuals aged >20 years with stroke who participated in the 1999–2006 NHANES survey cycles. We excluded 799 participants with stroke owing to missing data on Hcy, B vitamin levels ($n = 263$) and other covariates of interest ($n = 104$), as well as those with missing mortality data ($n = 1$). The final sample consisted of 431 participants (Figure 1). All participants provided written informed consent prior to participation. The NHANES survey was approved by the Research Ethics Review Board of the National Center for Health Statistics (NCHS) and the procedures followed the principles of the Declaration of Helsinki. The NHANES data used in this study are publicly available and did not require ethical or administrative approval.

Covariates

Sociodemographic and lifestyle information, including age, sex, race, marital status, smoking status, and educational status, were obtained from household interviews using standardized questionnaires. Race was classified as non-Hispanic white, non-Hispanic black, Mexican American, or other. Past and current smokers were defined as smokers. Non-smokers were defined as those who had never smoked. Education was defined as high school or below, and college or above. Body mass index (BMI) data and plasma Hcy, folate, and vitamin B12 levels were obtained from the MEC.

The BMI was calculated as the weight (kg)/height squared (m^2) by trained medical personnel. Blood samples were collected in the MEC by trained laboratory technicians, and processed and transported to central laboratories following validated procedures. Plasma Hcy levels were measured using fluorescence polarization immunoassay (FPIA) method (Abbott Laboratories, Chicago, IL, United States). Serum folate and vitamin B12 concentrations were measured simultaneously by the National Center for Environmental Health at the Centers for Disease Control and Prevention using a radioprotein binding assay kit (Quantaphase II; Bio-Rad Laboratories, Hercules, CA, United States) (22, 23). History of stroke, hypertension, or diabetes was assessed using a combination of questionnaires and examination results. Stroke was defined as a diagnosis of stroke by a physician or health professional. Hypertension was defined as: (1) an average systolic blood pressure/average diastolic blood pressure $\geq$ 140/90 mmHg, (2) previous diagnosis by a doctor or health professional, or (3) currently being treated with antihypertensive medications. Diabetes was defined as follows: (1) based on the participants' self-reported diagnosis of diabetes or (2) currently being treated with hypoglycemic drugs. Death outcomes were defined as the final mortality status determined by the mortality data from the NDI until December 31, 2019. Follow-up for each individual was defined as the year between the date of the NHANES interview and death, the last known survival date, or being censored in the death file. Details of these variables can be found on the official NHANES website.

1 https://wwwn.cdc.gov/nchs/nhanes

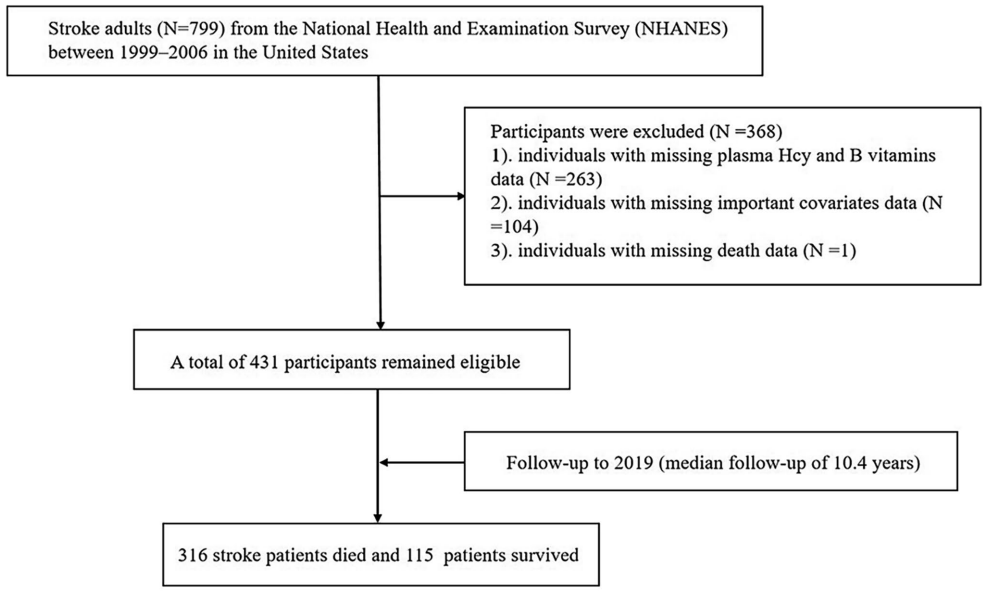

FIGURE 1
Flow chart of the study.

Statistical analysis

Descriptive data on participants' baseline characteristics are expressed as weighted means and standard error (SE) or medians and interquartile ranges (IQRs) for continuous variables, and numbers and weighted percentages for categorical variables. One-way ANOVA and chi-squared tests were used to compare continuous and categorical variables, respectively.

Trends in all-cause mortality across the Hcy, folate, and vitamin 12 quartiles were tested using weighted logistic regression. Hazard ratios (HRs) and 95% confidence intervals (CIs) for all-cause mortality were assessed using weighted Cox proportional hazards models. The proportional hazard assumption by estimation of Schoenfeld's residuals was fulfilled for Cox's regression model. Restricted cubic splines (RCS) based on adjusted Cox proportional hazards models were used to test the linear or nonlinear associations between Hcy, B vitamins, and all-cause mortality. Weighted Kaplan–Meier plots were used to visualize the cumulative survival rate across Hcy quartiles. Linear regression analyses were used to estimate the B-values and 95% CIs for the associations between Hcy and B vitamins in adults with stroke. Two adjusted models were applied. Model 1 shows the age-adjusted results. Variables were entered in the multivariate regression models if the value of p was ≤0.05 in the univariate analysis. In the multivariate-adjusted Model 2, we adjusted for baseline age, sex, race, educational status, BMI, and history of diabetes.

In stratified analyses, the association between baseline Hcy and all-cause mortality was ascertained in subgroups by age (<65 and ≥ 65 years), sex (female and male), and history of hypertension (no/yes) and diabetes (no/yes) with the fully adjusted model except for stratification factors. The survey-weighted Wald test was adopted to assess the potential interaction. Data were weighted using complex survey sampling analysis methods to ensure that they were representative of United States adults. All data analyses were performed using R software (version R-4.1.0; Cary, NC, United States). Two-tailed values of $p < 0.05$ were considered statistically significant.

Results

Characteristics of the study population

This study included 431 adults with stroke, representative of the 3,466,111 adults with stroke in the total population. The mean age of the group was 64.8 years, and 206 participants (47.8%) were women. Among the 431 participants, the weighted mortality rate was 66.3% (316) in 2019.

Table 1 presents the characteristics of the participants stratified according to their survival state. Compared with those who were still alive, participants who had died were more likely to be older, male, non-Hispanic white, have a lower BMI, have a history of diabetes, and have higher plasma folate and Hcy concentrations. Additionally, they were less likely to be educated. There were no significant differences in the distribution of vitamin B12 concentrations, marital status, smoking status, or history of hypertension.

Associations between Hcy, B vitamins, and all-cause mortality

Table 2 shows that the plasma Hcy concentration (both as categorized and as continuous variables) were positively correlated with all-cause mortality in adults with stroke. A significant correlation was observed between plasma Hcy as a continuous variable and risk of all-cause mortality (multivariate-adjusted HR 1.053, 95% CI 1.026–1.080, $p < 0.001$). A one-unit increase in plasma Hcy level was associated with a 5.3% higher risk of death in adults with stroke. There was no significant continuous correlation between serum folate, vitamin B12, and all-cause mortality.

Using the Hcy level as the categorical variable, participants in the highest quartile of Hcy had a 63.1% higher risk of all-cause mortality than those in the lowest quartile (multivariate-adjusted HR 1.631, 95% CI 1.160–2.291, p for trend <0.001). We also found no significant

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TABLE 1 Baseline characteristics of all included participants by survival state from NHANES 1999–2006.

Characteristic	Total (n = 431)	Alive (n = 115)	Death (n = 316)	p value
Age, in years[a]	64.77 (1.07)	51.89 (1.47)	71.32 (0.85)	< 0.001
Female, n (%)	206 (47.80)	76 (70.95)	130 (51.78)	0.010
Race, n (%)				0.009
Non-Hispanic White	252 (58.47)	47 (65.45)	205 (82.92)	
Non-Hispanic Black	84 (19.49)	32 (15.20)	52 (9.18)	
Mexican American	72 (16.71)	26 (6.15)	46 (3.12)	
Other Race	23 (5.34)	10 (13.20)	13 (4.78)	
Education status, n (%)				< 0.001
College or above	150 (34.8)	49 (58.52)	101 (34.12)	
High school or below	281 (65.2)	66 (41.48)	215 (65.88)	
Smoking status, n (%)				0.093
Former	168 (38.98)	35 (24.17)	133 (38.07)	
Never	186 (43.16)	53 (45.47)	133 (42.68)	
Now	77 (17.87)	27 (30.36)	50 (19.25)	
Marital status, n (%)				0.205
Married/Living with partner	239 (55.45)	65 (57.16)	174 (55.27)	
Never married	21 (4.87)	10 (9.69)	11 (4.38)	
Widowed/Divorced/Separated	171 (39.68)	40 (33.15)	131 (40.4)	
Body mass index (kg/m^2)[a]	29.78 (0.39)	31.00 (0.70)	29.16 (0.46)	0.031
Homocysteine (μmol/L)[b]	11.44 (0.32)	9.75 (0.68)	12.31 (0.41)	0.004
Folate (nmol/L)[b]	39.98 (2.11)	33.39 (2.86)	43.34 (2.41)	0.005
Vitamin B12 (pmol/L)[b]	408.51 (15.58)	414.92 (27.10)	405.24 (19.07)	0.771
Medical history, n (%)				
Diabetes	133 (30.86)	25 (17.11)	108 (33.30)	0.010
Hypertension	351 (81.44)	87 (72.73)	264 (81.56)	0.134

[a]Mean (SE); [b]Median (interquartile ranges).

correlation between the quartiles of folate, vitamin B12, and risk of all-cause mortality in adults with stroke. The adjusted HRs (95% CIs) from the bottom to the top quartile of serum folate and folate for all-cause mortality were 1.00 (reference), 1.00 (0.710–1.408), 0.726 (0.494–1.067), and 0.971 (0.670–1.408; p for trend = 0.374) and 1.00 (reference), 1.010 (0.669–1.525), 1.079 (0.678–1.717), and 1.086 (0.730–1.616; p for trend = 0.092), respectively. Restricted cubic splines showed the linear relationship between Hcy, folate, vitamin B12, and all-cause mortality risk in adults with stroke (p for non-linearity > 0.05).

Figure 2 presents Kaplan–Meier curves for the cumulative survival rate stratified by Hcy quartiles. The higher the Hcy level of adults with stroke, the lower their survival rate.

Correlations between folate, vitamin B12, and Hcy levels

Table 3 shows the results of the multivariate linear regression analysis of serum folate, vitamin B12, and Hcy levels. Serum folate and vitamin B12 levels are inversely correlated with plasma Hcy levels. The multi-adjusted B-values (95% CI) of Hcy for folate and vitamin B12 were −0.032 (−0.056 to −0.008; p = 0.011) and −0.004(−0.007 to −0.002; p = 0.002), respectively.

Stratification analysis

In stratified analyses (Figure 3), the association of plasma Hcy with increased risk of all-cause mortality was largely consistent in most subgroups. As shown in the forest plot, no interactions were observed between plasma Hcy concentration and sex (p for interaction = 0.371), diabetes (p for interaction = 0.056), or hypertension (p for interaction = 0.657); therefore, none of these variables significantly modified the association between Hcy levels and all-cause mortality in adults with stroke. However, Hcy significantly increased the risk of all-cause mortality in older adults with stroke, and age and Hcy had an interaction effect (p for interaction = 0.020).

Discussion

In a representative United States cohort of adults with stroke with a median follow-up of 10.4 years, we found that higher plasma Hcy levels were significantly associated with lower long-term survival in older adults with stroke; however, no significant association was observed between folate, vitamin B12, and all-cause mortality. In addition, higher folate and vitamin B12 levels were associated with

TABLE 2 Associations of homocysteine and B vitamins with all-cause mortality in adults with stroke.

Variables	Mortality	Model 1 HR (95%CI)	*p* value	Model 2 HR (95% CI)	*p* value	*p* for non-linearity
Continuous						
Homocysteine	316/431	1.057 (1.034, 1.081)	<0.001	1.053 (1.026, 1.080)	<0.001	>0.05
Folate	316/431	1.003 (0.999, 1.007)	0.156	1.002 (0.998, 1.006)	0.374	>0.05
Vitamin B12	316/431	1.000 (1.000, 1.001)	0.329	1.000 (1.000, 1.001)	0.092	>0.05
Categorical						
Homocysteine						
Quartile1 (<8.5)	50/108	reference		reference		
Quartile2 (8.5,10.8)	83/109	1.314 (0.940, 1.838)	0.110	1.123 (0.781, 1.615)	0.532	
Quartile3 (10.8,13.3)	88/106	1.969 (1.385, 2.798)	<0.001	1.750 (1.197, 2.558)	0.004	
Quartile4 (>13.3)	95/108	1.919 (1.407, 2.617)	<0.001	1.631 (1.160, 2.291)	0.005	
p for trend		<0.001		<0.001		
Folate						
Quartile1 (<21.2)	70/108	reference		reference		
Quartile2 (21.2,30.8)	74//108	0.931 (0.673, 1.287)	0.665	1.000 (0.710, 1.408)	0.998	
Quartile3 (30.8,51.1)	81/107	0.660 (0.446, 0.976)	0.038	0.726 (0.494, 1.067)	0.103	
Quartile4 (>51.1)	91/108	0.994 (0.647, 1.527)	0.978	0.971 (0.670, 1.408)	0.878	
p for trend		0.156		0.374		
Vitamin B12						
Quartile1 (<248.0)	83/109	reference		reference		
Quartile2 (248.0,332.8)	77/108	0.873 (0.584, 1.307)	0.510	1.010 (0.669, 1.525)	0.963	
Quartile3 (332.8,475.3)	79/106	0.919 (0.618, 1.368)	0.678	1.079 (0.678, 1.717)	0.749	
Quartile4 (>475.3)	77/108	0.909 (0.595, 1.389)	0.660	1.086 (0.730, 1.616)	0.682	
p for trend		0.329		0.092		

Model 1: Adjusted for age.
Model 2: Adjusted for age, sex, race, educational status, body mass index, and history of diabetes.

lower Hcy levels. These findings suggest that plasma Hcy levels might be a useful indicator for assessing risk of all-cause mortality in clinical practice.

The association between Hcy and all-cause mortality risk in adults with stroke has not been well established. Our study found a linear and positive correlation between Hcy and all-cause mortality in adults with stroke. Every 1 μmol/L increase in Hcy concentration increased mortality in these patients by 5.3%. Data specific to the stroke population are unavailable; however, previous studies of the general, non-stroke population have reported a higher all-cause mortality risk with high plasma Hcy levels (24, 25). Many previous studies have reported the effect of Hcy levels on stroke prognosis and the results have been controversial (7, 9, 20, 26, 27). A 16.4- and 6-year follow-up study in Norway found that Hcy significantly increased long-term stroke mortality (20, 26). However, in a 2-year cohort study, a moderate reduction in total Hcy in patients with non-disabling cerebral infarction had no effect on vascular outcomes (8). A Chinese stroke study showed that Hcy was significantly associated with poor functional outcomes at discharge but not with in-hospital mortality in patients with spontaneous intracerebral hemorrhage (10). However, most studies have focused on the short-term prognosis of patients with stroke. Evidence shows that the risk factors for long- and short-term mortality from stroke differ partially (26). In addition, it should be noted that after the introduction of the folate fortification program in the United States, the Hcy level in the United States population was significantly reduced (11) and the mortality rate for stroke was reduced by a factor of 3 (12). Stroke is the second leading cause of death worldwide (1), but ranks fifth among all causes of death in the United States population (2), which indicates that the distribution of Hcy concentration and death composition differ in different regions. Therefore, different population backgrounds are likely to influence the effect of Hcy on mortality in adults with stroke. Further studies are needed to indicate the underlying biological mechanisms.

We further stratified our analysis by age, sex, hypertension, and diabetes to explore the relationship between Hcy and all-cause mortality in different settings among United States adults with stroke. Higher levels of Hcy were found to increase the risk of mortality only in the association between age and Hcy (p-interaction = 0.020), indicating that Hcy is a strong risk factor for all-cause mortality in older adults with stroke. In previous studies, old age, male, history of hypertension, and diabetes were found to be risk factors for stroke (2, 28) and had a synergistic effect on stroke with Hcy (29, 30). Screening for risk factors in high-risk populations to develop more personalized Hcy treatment strategies, as well as controlling traditional risk factors, such as blood pressure, blood glucose, and smoking status, are important for improving stroke outcomes. Our analysis adds to the literature by

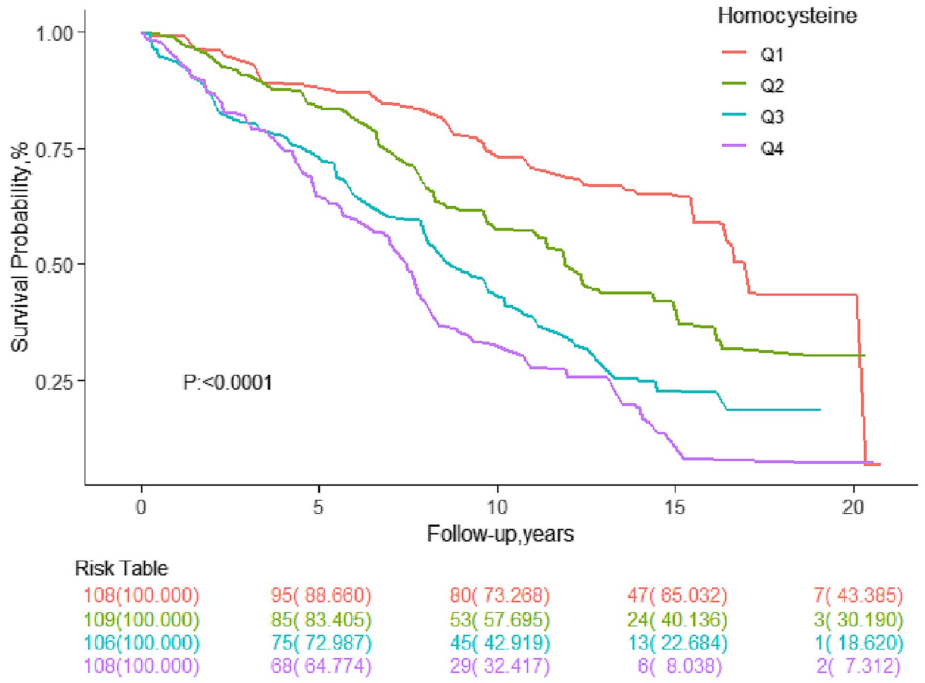

FIGURE 2
Survival curve of the stroke population.

TABLE 3 Associations of homocysteine with B vitamins in adults with stroke.

Variables	Model 1	*p* value	Model 2	*p* value
	B-value (95% CI)		*B*-value (95% CI)	
Folate	−0.031 (−0.054, −0.008)	0.010	−0.032 (−0.056, −0.008)	0.011
Vitamin B12	−0.004 (−0.007, −0.002)	0.002	−0.004 (−0.007, −0.002)	0.002

Model 1: Adjusted for age.
Model 2: Adjusted for age, sex, race, education status, body mass index, and history of diabetes.

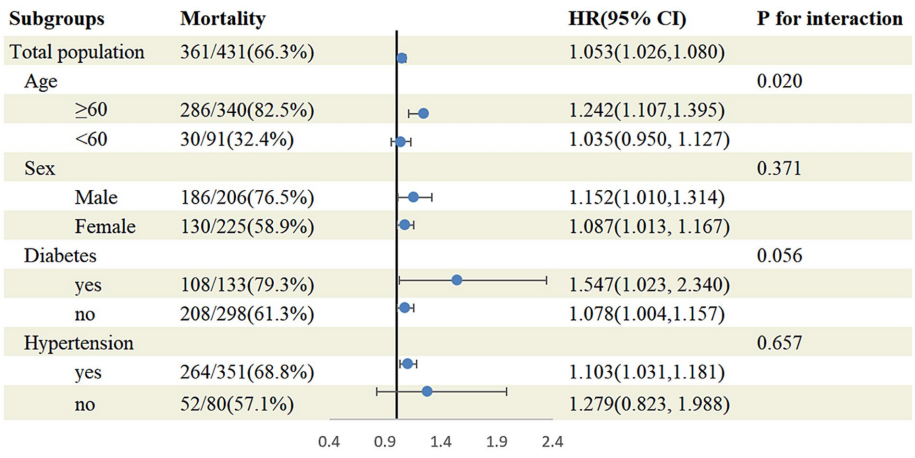

FIGURE 3
Subgroup analysis of the association between homocysteine and all-cause mortality. Results were adjusted for all covariates except the corresponding stratification variable.

showing that age could greatly increase the adverse effects of Hcy on all-cause mortality in adults with stroke. It is unclear why higher Hcy concentrations would be associated with higher all-cause mortality risk among adults with stroke, especially in older adults. A possible explanation is that B vitamins are the major nutritional determinants of Hcy levels, and their dietary deficit, along with a physiological age-related reduction in renal function, is responsible for most cases of HHcy in older adults (31, 32).

No association was observed between serum folate and long-term mortality in adults with stroke in our study. In this study, participants underwent folate fortification, which generally improves blood folate levels (11). One study has shown that low-dose (0.4 mg/day) folate supplementation is sufficient to improve vascular endothelial function, while increasing the dose to 5 mg/day has no additional benefit (33). This may be why our study suggests that further folate increases did not reduce mortality in adults with stroke who had already received folate fortification. The effects of folate on mortality are inconsistent in different populations. In the general population included in the NHANES from 1999 to 2010, Peng et al. (34) found that low folate levels were significantly associated with a higher risk of all-cause mortality. In the population with cardiovascular diseases, folate treatment was not significantly associated with all-cause mortality (21). In a hemodialysis population, folate supplementation reduced total mortality (19). However, Leung et al. (35) found that neither low-nor high-dose folate intake was significantly associated with stroke mortality in individuals with kidney disease. These studies suggest that the association between folate levels and mortality may be influenced by disease background and causes of death.

No protective effects of vitamin B12 on long-term mortality in adults with stroke were observed in this study. The association between vitamin B12 levels and mortality rates is inconsistent. A NHANES study showed that low serum vitamin B12 levels were associated with increased all-cause mortality in the general population (36). Mendonça et al. (37) found that higher vitamin B12 levels were associated with a higher risk of all-cause and cardiovascular mortality in women. Consistent to our results, there was no association of vitamin B12 levels with all-cause mortality was found in older people in the United Kingdom (38). The United States Preventive Services Task Force concluded that the current evidence to assess the balance of benefits and harms of using multivitamin supplements to prevent cardiovascular disease is insufficient (39). Measurements of vitamin B12 was based on a single B12 concentration at baseline and its high intra-individual variability, are likely to underestimate the association with mortality due to regression dilution bias in our cohort as well as in others (38).

In this study, we explored the correlations between folate, vitamin B12, and Hcy levels in adults with stroke. Consistent with a previous study (4), folate and vitamin B12 levels were inversely correlated with Hcy levels, indicating that supplementation with folate and vitamin B12 can reduce Hcy levels. A few studies have shown that folate and vitamin B12 indirectly reduce the risk of stroke (40) and death (41, 42) by reducing the Hcy levels. Further research is required to explore the impact of interventions targeting Hcy levels using folate and vitamin B6 supplementation on mortality in stroke patients.

Our results extend the previously reported associations of Hcy with all-cause mortality and the absence of associations between folate and vitamin B12 with all-cause mortality in the older stroke population. These results highlight the potential advantages of monitoring and evaluating Hcy status in the prevention of all-cause mortality for adults with stroke. In addition, the strengths of this study are its prospective design, long-term follow-up period, and ascertainment of mortality by validated NDI data.

Despite its critical findings, this study has a few limitations. First, causality cannot be concluded due to the observational study design. The genetic variants in Hcy metabolism-related genes may provide more information for the causal relationship between Hcy and outcomes. Second, stroke was self-reported, which is likely to introduce bias. However, this questionnaire has been widely used in studies assessing self-reported stroke. Third, although this study accounted for major covariates, the possibility of residual confounding factors cannot be excluded. Fourth, measurements of plasma Hcy, folate, and vitamin B12 were based on single blood samples. This is likely to underestimate the associations with mortality due to regression dilution bias. Finally, the relationships explored in this study were based on United States adults (1999–2006 NHANES data), a country where folate fortification is administered; therefore, caution must be taken when generalizing these findings to populations without folate fortification. Further studies are required to explore the relationship between plasma Hcy and B vitamins and long-term mortality in adults with stroke among different populations. Additional analyses are needed to examine Hcy-lowering over the course of the trial on all-cause mortality in adults with stroke.

Conclusion

In this prospective American study, plasma Hcy was linearly and positively associated with the risk of all-cause mortality in older adults with stroke. Folate and vitamin B12 levels were inversely correlated with Hcy levels but had no effect on long-term survival in adults with stroke. Further research are needed to indicate the potential mechanisms underlying the observed associations and the impact of interventions targeting Hcy levels by folate and vitamin B6 supplementation in stroke patients.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found at: https://wwwn.cdc.gov/nchs/nhanes/.

Ethics statement

The studies involving humans were approved by the Research Ethics Review Board of the National Center for Health Statistics (NCHS). 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

PZ: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Software, Validation, Writing

– original draft. XX: Investigation, Validation, Writing – review & editing. YZ: Conceptualization, Formal analysis, Funding acquisition, Methodology, Supervision, Visualization, Writing – review & editing.

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Conflict of interest

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

Publisher's note

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Ingestion of triglycerides containing medium- and long-chain fatty acids can increase metabolism of ingested long-chain triglycerides in overweight persons

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Introduction: Medium-chain fatty acids (MCFAs) have attracted considerable attention for preventing or improving obesity, which is a recognized risk factor for lifestyle-related diseases. Medium- and long-chain triglycerides (MLCTs) are expected to improve the metabolism of ingested long-chain triglycerides (LCTs). However, previous studies have reported mixed results. In this study, the effect of ingestion of MLCTs was evaluated on the metabolism of LCTs and compared to the ingestion of rapeseed oil (control oil).

Methods: A randomized, double-blind, placebo-controlled crossover study was performed among sedentary participants with BMIs ranging from 25 below 30 kg/m^2. Thirty participants were asked to ingest either 14 g of MLCTs or a control oil for 4 weeks. The metabolism of ingested LCTs was evaluated by measuring isotopically labeled carbon dioxide released by the degradation of carbon-13 (13C)-labeled LCTs.

Results: Ingestion of MLCTs markedly enhanced the metabolism of ingested LCTs by comparison to the control oil.

Conclusion: The findings of this study suggest that ingestion of MLCTs may enhance the metabolism of dietary LCTs through activation of β-oxidation in liver mitochondria, which may increase the metabolic kinetics of ingested long-chain fatty acid (LCFAs).

Clinical trial registration: https://center6.umin.ac.jp/cgi-open-bin/ctr/ctr_view.cgi?recptno=R000053101, identifier: UMIN000046604.

KEYWORDS

medium- and long-chain triglycerides, obesity, metabolism of ingested fat, medium-chain fatty acid, postprandial metabolism

1 Introduction

Obesity augments the chances of developing dyslipidemia, hypertension, and type 2 diabetes, which are related to cardiometabolic diseases and metabolic syndrome (1). Mitochondrial dysfunction often occurs in metabolic diseases, including metabolic syndromes (2). Improved mitochondrial function may play an important role in increased energy expenditure and fat oxidation, which contribute to weight loss and maintaining a healthy weight (3). The diet-induced thermogenesis (DIT) and metabolism of ingested LCTs were lower in obese individuals compared to normal weight individuals (4, 5).

MCFAs, comprising unbranched saturated fatty acids with 6–12 carbon atoms, are dietary ingredients that promote improved mitochondrial function (2, 6). As such, ingestion of MCTs, containing 8- and 10-carbon MCFAs, has been investigated. MCTs ingestion is reported to elicit an anti-obesity function by suppressing the accumulation of body and visceral fat (7, 8), enabling postprandial increase in DIT (9–11), and increasing both 24-h energy expenditure (12), fat oxidation during physical activity (13–15), as well as the metabolism of dietary fat (16).

Although MCTs prevent or improve obesity their physicochemical characteristics cause them to smoke during the cooking process at high temperatures (150–200°C). Moreover, heating a mixture of cooking oil and MCTs together causes foaming. To resolve these issues, we prepared MLCTs by mixing 80%–90% rapeseed oil and 10%–20% MCTs before initiating an enzymatic catalyzed ester exchange reaction. The net result of this reaction was to randomize the fatty acids on the glycerides. These MLCTs increase the smoke point and reduce foaming during cooking. Moreover, these improvements allow MLCTs to be regularly used in the same wide range of cooking applications as fats and oils (17). Human studies have been conducted to analyze the ingestion of MLCTs. Akin to the results for MCTs, MLCTs ingestion was found to inhibit the accumulation of body fat and visceral fat (18–21), enhance postprandial DIT (22, 23), and increase the oxidation of fat during physical activity (24). Results from animal studies suggest ingestion of MLCTs increase the hepatic degradation of LCFAs (25, 26). Therefore, MLCTs are expected to act in the same way as MCTs to improve the metabolism of ingested LCTs. However, previous studies using butter and coconut oil (which contain small amounts of octanoic and decanoic acids) have reported mixed results (27, 28).

Based on these results, the present study was designed to establish whether 4-week ingestion of MLCTs in humans enhances the metabolism of ingested fat. Specifically, overweight volunteers were selected. Obesity is defined as a BMI of 25 kg/m^2 or more (29) and BMIs ranging from 25 below 30 kg/m^2 is classified as obese class-1 (30) in Japan. According to this definition, about 30% of men and 20% of women in Japan are considered obese (31). After the initial 4 week feeding period, metabolism of dietary fat was investigated using isotopically labeled LCTs by monitoring the release of labeled carbon dioxide.

2 Methods

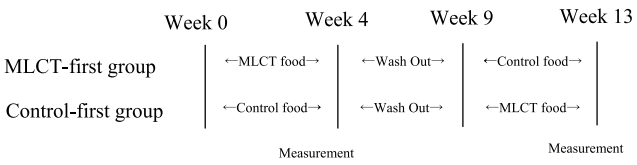
2.1 Ethical considerations and participant

This study complied with the Declaration of Helsinki. The investigation was performed with assistance from a physician at the Kouwa Clinic, Kouwa-kai Medical Corporation (Tokyo, Japan) and Fuji Medical Science Co., Ltd. (Chiba, Japan) as a contract research organization (CRO, Huma R&D Co., Ltd., Tokyo, Japan). The proposed experimental procedures were reviewed by the Yoga Allergy Clinic Clinical Research Ethics Review Committee (approval number: RD10012KW04). This study was registered with UMIN-CTR prior to initiating the investigation (UMIN CTR ID: UMIN000046604).

Thirty volunteers were recruited for this study. Previous studies have examined the fat oxidation rate during physical activity (15) and metabolic rate of dietary fat after meals (16) containing 2 g of MCTs for 2 weeks in overweight persons. The least number of subjects required for this analysis was evaluated to be 28.

Volunteers were recruited from the participant registration bank of the contract research organization. Potential subjects were screened by conducting an interview, testing blood pressure, and performing a range of biochemical analyses of the blood. Participants were eligible for the study if: (i) selection criteria were met, (ii) administrative requirements throughout the study period could be fulfilled, and (iii) involvement in the study was judged by the principal investigator to be safe.

A double-blind study was performed using a crossover method. Participants were randomly allocated into two groups. One group was given MLCT first (MLCT-first group) and the other group received the control food first (control-first group). The two groups were equivalent with respect to sex and age. The washout period was 5 weeks between the two intervention periods (period-1 and period-2). The schedule for this study is shown below.



2.2 Test food

MLCTs (Nisshin OilliO Group, Ltd., Tokyo, Japan) was used as the test oil, and rapeseed oil (Nisshin OilliO Group, Ltd.) was used as the control oil. The fatty acid composition of their oils is shown in Table 1. The MLCTs comprised inter-esterified triglycerides containing 1.6 g of MCFAs in 14 g (32). During the intervention period, test foods containing MLCTs (MLCT food), or control oil (control food) were ingested (303 kcal energy, 8.5 g protein, 14.3 g fat, 35.1 g carbohydrate).

TABLE 1 The fatty acid composition of the control and test oils.

g/100 g fatty acids	Control oil	Test oil
Saturated fatty acids	9.0	19.5
Medium-chain fatty acids	0.0	11.6
Mono-unsaturated fatty acids	63.9	56.5
Poly-unsaturated fatty acids	27.2	24.0
n-6 fatty acids	19.5	17.2
n-3 fatty acids	7.7	6.8

Participants who ingested MLCT food comprised the MLCT group, and those who ingested control food comprised the CO group. Both the test and control food diets were ingested for 4 weeks. Throughout the study period patients were asked to continue their usual lifestyle and not to engage in vigorous exercise, eating small meals, overeating, and excessive consumption of alcohol.

2.3 Nutritional survey

On the 25th, 26th, and 27th days following ingestion of the MLCT or control food, the participants were asked to photograph their meals and record details on a survey form over the three day period. From the information provided by the participants, nutrient calculations were performed to determine the daily intake of energy, protein, fat, carbohydrate, saturated fatty acids, MCFAs, monounsaturated fatty acids, polyunsaturated fatty acids, n-6 polyunsaturated fatty acids, and n-3 polyunsaturated fatty acids (33).

2.4 Measurement

After ingesting the test foods for 4 weeks and then fasting overnight, metabolic rate was measured in the laboratory. Here, participants were asked to enter relevant details in the human calorimeter. The accurateness of the readings were confirmed as previously reported (15, 16). During the study period both oxygen consumption and carbon dioxide production recoveries were within 100 ± 2%.

Each participant ingested a test meal containing 14 g of either MLCTs or the control oil and 400 mg of 13C-labeled triolein (481 kcal energy, 22.4 g protein, 18.7 g fat, 57.6 g carbohydrate). 13C-labeled triolein was TRIOLEIN (1,1,1–13C3; Cambridge Isotope Laboratories, Inc., Tewksbury, MA, United States).

Participants rested for 4 h before and after ingestion of the test meal. Exhaled breaths were collected with a gas bag approximately every hour before and after ingestion of the test meal.

2.5 Experimental determination of the metabolic rate of ingested LCTs

Metabolism of dietary fat was determined from the rate of excretion of 13C-labeled carbon dioxide. The metabolic rate of ingested 13C-labeled triolein was determined using the same formula as previously reported, and cumulative values were calculated using the same method (15).

2.6 Statistical analysis

Data for participant period-1 or period-2 were analyzed. When missing values occurred, multiple imputations were conducted. Dietary intake and body weight during the intervention period were checked for normality by the Shapiro–Wilk test to evaluate the two intervention groups (MLCT and CO groups). Cumulative metabolic rate of ingested LCTs at 4 h were postprandial. For cases of no normality, the Mann–Whitney U test was performed, and if normality was found, equal variances were confirmed by an F test. Student's *t*-test was performed if there was equal variance, and Welch's t-test was used if there was no equal variance.

The intervention effect values for the cumulative metabolic rate of ingested LCTs at 4 h postprandial (values for the MLCT group minus values for the CO group) were confirmed for normality by the Shapiro–Wilk test. If no normality was found, a Mann–Whitney U test was performed. If there was normality, a linear mixed model was used. Restricted maximum likelihood estimation was performed with a random intercept model equation with group, time, and order of intake as fixed effects and participants as variable effects. Significance, estimates, and 95% confidence intervals were obtained for fixed effects. Measurement indicators that showed significant differences were analyzed for carryover effects, and results were withheld if the significance of the difference was found.

Basic statistical analysis was performed using Microsoft Excel for Office365 (Microsoft Japan Co., Ltd., Tokyo, Japan). All statistical processing was done using the R package (ver. 4.1.0; R Core Team, Vienna, Austria). Note, *p*-values of <5% indicated a significant difference.

3 Results

3.1 Participant

In all, 80 individuals who gave informed consent were evaluated for eligibility to participate in the study. Of these, 33 were excluded (4 for not meeting the selection criteria, 4 due to their own free will, 8 for personal reasons other than their own free will, and 17 for other reasons). The remaining 47 eligible participants were randomly split into two groups: 24 in the MLCT-first group and 23 in the control-first group.

After commencement of the study, 1 participant in the MLCT-first group discontinued before the period-1 visit and 1 participant in the control-first group dropped out of the study. In all, 15 participants from each group were analyzed in period-1 (i.e., the target number of patients, 30, was measured). A total of 14 participants, 7 participants in each group, were not measured at the end of period-1. One participant in the MLCT-first group discontinued before coming to the hospital for period-2, and 14 participants in the MLCT-first group and 15 participants in the control-first group were evaluated in period-2. Thus, measurement data was obtained from 30 participants in the MLCT group and 29 participants in the CO group. All reasons for discontinuation were related to restrictions on outdoor activity due to the COVID-19 pandemic. Subject details are shown in Table 2.

TABLE 2 Details of the participants (male *n* = 14, female *n* = 16).

	n = 30		
Age, year	50.5	±	8.0
Height, cm	164.7	±	6.1
Weight, kg	73.6	±	7.0
BMI, kg/m^2	27.0	±	1.4

Values are expressed as mean ± SD.

No adverse events attributable to the ingestion of the test food (including the MLCT food and the control food) were observed during the study period. Two participants in the CO group each reported one adverse event (1 with diarrhea; 1 with bloating, belching, and soft stools) that could have been caused by the ingestion of the control food. However, the physician decided to continue the study because these adverse events are commonly observed following the ingestion of foods.

There were 30 participants in the analysis with measurement data from either period-1 or period-2. Data analysis was performed after multiple imputations to the nutrient intake and cumulative metabolic rate data of dietary LCTs for 1 participant who discontinued the study in period-2.

3.2 Nutrient intake

Nutrient intakes based on dietary surveys during the intervention period are shown in Table 3, the calculated nutrient intakes include the test foods. A difference in intake of MCFAs was seen between the two groups, reflecting the intake of the different test foods.

3.3 Metabolic rate of ingested LCTs

TRIOLEIN (1,1,1–13C3) was ingested at 2.14% (w/w) per fat in meal, at an average of 5.4 mg/kg body weight per participant. The aggregate metabolic rate of dietary LCTs for each diet group and their intervention effect values are shown in Table 4. The intervention effect value for the cumulative metabolic rate of dietary LCTs was significantly higher in the MLCT group than in the CO group ($p < 0.05$, Mann–Whitney's U test, Table 4).

4 Discussion

When verifying the effectiveness of dietary elements in combating obesity, major techniques for analyzing changes in metabolism after a meal include energy expenditure (which may be distinguished by fat and carbohydrate oxidation), the dynamics of blood lipids, and the degradation of specific fatty acids using 13C isotope labeling. Numerous studies indicate augmented postprandial energy expenditure utilizing MCTs and MLCTs (9–12, 22, 23, 34). Conversely, there are conflicting conclusions concerning fat and carbohydrate oxidation reported across studies. MCTs effectively reduce postprandial chylomicron concentrations and hinder the elevation of TG concentrations in blood lipids (35–37). In contrast, no noticeable differences result on the blood lipid from the ingestion of MLCTs [coconut oil (38)], as they contain LCFAs within the MLCTs. To differentiate fat metabolism in the body from the metabolic process of ingested fat, the optimal method is considered to evaluate the decomposition of targeted fatty acids via ingested 13C isotopes. Studies analysing the degradation of 13C-labelled fatty acids have demonstrated a distinct escalation in the oxidation of MCFAs (5, 39). However, a growth in the metabolism of ingested LCTs has only recently been documented when ingested MCTs (14) but not MLCTs. Previous studies of short-term (11 days) butter ingestion have shown increased net postprandial oxidation of dietary myristic acid but not palmitic acid, depending on the fatty acid composition of the test meal, compared with tallow ingestion (27). The combined ingestion of butter and coconut oil for 14 days increased postprandial net saturated LCFAs oxidation but did not increase dietary saturated LCFAs oxidation more than tallow ingestion (28).

Here, we evaluated metabolism of ingested 13C-labeled triolein in overweight participants following a 4-week period of ingestion of either MLCTs or control oil. The findings indicated that participants in the MLCT group displayed significantly increased metabolism of

TABLE 3 Nutrient intake during the intervention period.

	CO group			MLCT group		
Energy, kcal	2035	±	58	2029	±	62
Protein, g	70.3	±	2.7	71.8	±	2.4
Fat, g	80.5	±	3.6	80.6	±	3.4
Carbohydrate, g	247	±	8	244	±	9
Saturated fatty acids, g	19.6	±	1.1	20.7	±	1.1
Medium-chain fatty acids, mg	276	±	36	1925	±	53*
Mono-unsaturated fatty acids, g	31.3	±	1.5	31.5	±	1.3
Poly-unsaturated fatty acids, g	20.0	±	0.8	18.8	±	0.8
n-6 fatty acids, g	16.3	±	0.7	14.9	±	0.7
n-3 fatty acids, g	3.5	±	0.2	3.7	±	0.2

Values given as mean ± SD. The calculated nutrient intakes include the test foods. * Significant difference from CO group ($p < 0.05$).

TABLE 4 Cumulative value of metabolic rate of dietary LCTs.

	Cumulative value (4 h of AUC)							Intervention effect			
	CO group				MLCT group			(MLCT-CO)			
Metabolic rate of ingested LCTs, %	1.8	±	0.3		2.3	±	0.3	0.5	±	0.3	#

Values given as mean ± SE. # Significant difference ($p < 0.05$, Mann-Whitney's U test).

ingested triolein compared to those given control oil (CO group). This study found similar results for increased metabolism of ingested LCTs to those reported from studies with small amounts of MCTs ingested (16), but different results from those with butter and coconut oil ingested (27, 28). The fat energy in the test meals in which postprandial metabolism was assessed in the studies with MCTs and MLCTs (this study) was 7%–8% per day, whereas the test meals in the studies with butter and coconut oil were high in fat energy, around 30%–50%. It is speculated that differences in the amount of total fat in the test meals may have affected the metabolism of ingested fat after the meal. In addition, the present study investigated the effect of fats and oils high in unsaturated fatty acids, comparing rapeseed oil and its inter-esterified counterpart, MLCTs. While previous studies using butter and coconut oil have examined the metabolism of ingested saturated LCFAs in the diet of mainly saturated fats and oils, this study measured the metabolism of oleic acid as a monounsaturated fatty acid in the diet. It has been discussed that the degree of postprandial oxidation varies with the type of fatty acid, and it is generally thought that the increase in postprandial oxidation is saturated fatty acids < monounsaturated fatty acids < polyunsaturated fatty acids. However, the differences between these fatty acids are not clear, as some studies have found no difference between saturated and monounsaturated fatty acids (40).

The present investigation was conducted using a crossover study design, with no significant differences in energy and energy-producing nutrient intake between the two groups. Furthermore, the analysis of the carryover effect with respect to the influence of the order of allocation was not significant. These findings confirmed that there was no significant difference between the effects of energy and nutrient intake and allocation during the test food ingestion period, and that the results obtained were due to the effects of MLCTs ingestion. In this study, we used rapeseed oil as the control oil. Rapeseed oil is the most widely used edible oil in Japan. Therefore, the test oil, which was prepared by inter-esterification of rapeseed oil and MCTs, was considered to be highly acceptable to the Japanese and easy to substitute. As shown in the Table 1, rapeseed oil contains n-3 and n-6 polyunsaturated fatty acids in addition to monounsaturated fatty acids. MLCTs reduce the monounsaturated fatty acids and n-3 and n-6 polyunsaturated fatty acids that are provided by consuming rapeseed oil, depending on the amount of MCFAs. However, rapeseed oil and MLCTs have generally equivalent cooking oil properties. Replacing edible oil with MLCTs, which do not differ markedly except for containing the low-level of MCFA, would increase the metabolism of ingested LCTs, as shown in this study, suggesting that ingestion of MLCTs may help prevent or ameliorate obesity.

Previous studies allow for inference that the fatty acid degrading system is activated in the liver due to the functional properties of the MLCTs obtained in this study. Ingested LCTs are absorbed from the intestinal tract as LCFAs and LCFA-bound monoacylglycerol, which are then resynthesized into LCTs to form lipoproteins and released into the blood via the lymphatic system. In the bloodstream, LCTs are degraded by lipoprotein lipase and converted to LCFAs, which are then transferred to adipose tissue, muscle tissue, and the liver (i.e., major organs in the body that utilize LCFAs) (40, 41). Crucially, the liver actively expends energy, even at rest after eating (42), and dietary LCFAs are oxidized when they reach the liver. Previous animal studies examined the effects of MLCTs ingestion on hepatic β-oxidation activity (25). Specifically, rats were fed either MLCTs or LCTs over a 4 week period. The expression of long-chain acyl-CoA dehydrogenase at the mRNA level in the MLCTs group was significantly higher compared to LCTs group, while PPARα mRNA expression was the same in both groups. This observation suggested that the increase in peroxisomal fatty acid oxidation may be unaffected by the ingestion of LCTs. In another study involving rats, the activity of liver acyl-CoA dehydrogenase was measured 1 h after a single ingestion of either MLCTs or LCTs and palmitoyl-CoA as substrate (26). Long-chain acyl-CoA dehydrogenase enzyme activity was significantly elevated together with the corresponding level of mRNA in the MLCTs group compared to the LCTs group. Taken together, these results suggest that the activity and corresponding gene expression of enzymes that oxidize LCFAs in the mitochondrial β-oxidation system may be increased in the liver of animals fed MLCTs, and that the oxidation of LCFAs is accelerated in the liver. MCFAs absorbed from the intestinal tract are not as easily resynthesized into triglycerides as LCFAs, and most of MCFAs are quickly metabolized in the liver (6). Studies in animals have also shown that the oxidation of MCFAs (i.e., octanoic acid) in hepatocytes is five-fold faster than that of LCFAs (i.e., oleic acid), partly because MCFAs and albumin exist in a bound state at a lower ratio than LCFAs and are more readily taken up by the hepatocytes (43). Indeed, previous human studies have shown that ingested MCTs are oxidized at a faster rate than ingested LCTs (5, 39). Furthermore, previous animal studies have shown mRNA expression of long-chain acyl-CoA dehydrogenase was significantly upregulated after ingestion of both MCTs and MLCTs instead of LCTs (26). The post-absorption metabolic kinetics of MCFAs may also alter the activation of fatty acid oxidation of LCFAs in the liver.

A limitation of this study was that it exclusively involved Japanese participants. Thus, it is unclear whether similar results would be obtained for other ethnicities. Moreover, Asians reportedly differ from Caucasians in body composition, as evidenced from the difference in body fat percentage and fat-free mass (44). Consequently, it is not obvious whether similar results would be obtained if different dietary compositions were used to assess metabolism of ingested fat. Another limitation of the study is that it did not examine populations with different exercise habits or higher levels of obesity.

5 Conclusion

The present study showed that 4 weeks of MLCTs ingestion could significantly enhance the metabolism of ingested LCTs in overweight individuals with no exercise habits. Our findings suggest that MCFAs exhibit different metabolic kinetics than LCFAs and contribute to enhanced degradation of ingested fatty acid by activating the β-oxidation system in liver mitochondria.

At present, people who need fats and oils with metabolic functions select and consume them, but in the future, edible oils will be developed that contain fatty acids with metabolic functions that are needed by each individual, such as MLCTs. With progress, it may be possible to consume optimal fats and oils without increasing fat intake.

Data availability statement

The datasets presented in this article are not readily available because data not available due to commercial restrictions. Requests to

access the datasets should be directed to NN, n-nosaka@nisshin-oillio.com.

Ethics statement

The studies involving humans were approved by Yoga Allergy Clinic Clinical Research Ethics Review Committee. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

NN: Conceptualization, Methodology, Writing – original draft. ST: Conceptualization, Writing – review & editing. SS: Formal analysis, Writing – review & editing. NA: Formal analysis, Writing – review & editing. KK: Supervision, Writing – review & editing.

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Conflict of interest

The authors NN, ST, SS, and NA are employees of The Nisshin OilliO Group, Ltd. Author KK was employed by medical cooperation Kato Clinic.

Publisher's note

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Soft and energy drinks consumption and associated factors in Saudi adults: a national cross-sectional study

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Introduction: The consumption of soft and energy drinks poses a significant risk for non-communicable diseases, such as diabetes and heart disease. Studies in Saudi Arabia have reported elevated consumption of soft/energy drinks, but nation-wide data is not available. Therefore, this study aims to explore the prevalence of soft and energy drinks consumption and its associated factors among a representative sample of Saudi adults.

Methods: The present research is a secondary data analysis of the 2021 Sharik Diet and Health National Survey (SDHNS). Current analysis used data on socio-demographics, anthropometrics, physical activity, and soft and energy drink consumption. The frequency of soft and energy drinks consumption is assessed on a weekly basis.

Results: Of the 5,194 Saudi adults, 3,928 were analyzed. Overall, 67% consumed soft drinks weekly, while 30% consumed energy drinks weekly. In multiple logistic regression, consumption of either soft drinks or energy drinks was associated with males, a younger age, lower income, and lower physical activity. Individuals with overweight or obesity were less likely to consume energy drinks [OR (95%CI): 0.83 (0.71, 0.99) and 0.73 (0.60, 0.90), respectively] than those with healthy weight. However, education level was not associated with either soft or energy drink consumption. These findings highlight the need for targeted interventions designed to reduce soft and energy drinks consumption in Saudi adults.

KEYWORDS

soft drink, energy drink, Saudi Arabia, overweight, adults, consumption, survey, obesity

1 Introduction

Energy drinks, also referred to as power drinks, are liquid refreshments that typically incorporate a variety of ingredients, such as caffeine, sugar, amino acids like taurine, and other energizing substances such as guarana and ginseng (1). These beverages are often promoted because of their apparent advantages, including enhanced energy levels, sharpened mental focus, and improved physical capabilities (2, 3). Nevertheless, they can pose potential health hazards, particularly among youth (4–6).

Conversely, soft drinks are non-intoxicating beverages primarily composed of carbonated water, a sweetening agent, and either natural or synthetic flavorings (7). The sweetener can take various forms, including sugar, high-fructose corn syrup, fruit juice, or artificial sweeteners in the case of diet versions (8–10). Soft drinks can also contain caffeine, colorants, and preservatives, among other constituents. They are a subset of the broader group of sugar-enriched beverages, which have been linked to obesity and other health concerns when ingested in sizable volumes (11, 12).The intake of energy drinks and soft drinks has been progressively associated with adverse health outcomes, including obesity, dental diseases, and type 2 diabetes mellitus (6, 10, 13, 14). Energy drinks have been also associated with arrhythmias, including atrial fibrillation and supraventricular tachycardia, particularly among young consumers due to its high caffeine contents (15–17).

From a behavioristic viewpoint, numerous factors can impact the consumption of energy drinks and soft drinks. These factors encompass taste preferences, the perceived energy surge or mood elevation, influences from marketing and advertising, societal norms, and easy availability (18, 19). The sweet flavor of these beverages, often amplified by their high sugar content, can stimulate the brain's reward system, promoting habitual consumption (20, 21). Energy drinks are frequently consumed due to their supposed benefits in boosting energy and alertness, appealing to individuals coping with intense work or academic stress, or those aiming to augment physical performance (22). Advertisements and marketing campaigns often depict these beverages as stylish, enjoyable, or vital for peak performance, thereby influencing consumer attitudes and actions. Moreover, the ubiquitous presence and societal acceptance of these drinks in different contexts (like social gatherings, workplaces, and vending machines) can encourage regular consumption (23).

The strategy of increasing taxes on energy drinks and soft drinks is a policy that has been implemented by Saudi Arabia in 2017 to curb overconsumption and alleviate related health implications (24, 25). This tactic is based on the principle that pricing significantly influences consumer habits (26). Preliminary studies indicate that such taxation increased prices and reduced purchasing, but whether this reduced consumption in Saudi Arabia remains unclear (25).

A number of factors contribute to the consumption of soft and energy drinks worldwide. For example, consumption of soft or energy drinks is commonly associated with males, young people, and people of lower socioeconomic status (26, 27). Moreover, individuals with higher BMI or physically inactive people are more likely to consume soft and energy drinks (28). Understanding these factors facilitates targeted interventions to reduce consumption and improve public health. Nonetheless, to date, national prevalence data regarding the consumption of soft and energy drinks among Saudis and their associated factors are lacking. We aim in this study to determine the consumption of soft and energy drinks among Saudi adults and investigate associated factors.

2 Materials and methods

2.1 Study design and sampling

This study is a secondary data analysis of the 2021 Sharik Diet and Health National Survey (SDHNS) (29). The SDHNS, an annual nationwide cross-sectional survey conducted in Saudi Arabia, employs phone interviews (29). For a balanced distribution of participants, the SDHNS uses a proportional quota sampling method, stratified by age, gender, and region across Saudi Arabia's 13 administrative regions. The SDHNS integrates ZDataCloud®, a data collection tool that minimizes sampling bias without human interaction (30). The dataset used in this research was collected in 2021 encompassing $n = 5{,}194$ participants. A detailed methodology of the SDHNS is available in a separate document published by the Sharik Association for Research and Studies (29). Ethical approval was obtained from the ethics committee of Sharik Association for Research and Studies (Approval no.06–2021).

2.2 Measurements

The weekly consumption was measured based on the frequency of the consumption of soft and energy drinks in separate questions. Participants were asked "During the past week, how many times per week have you consumed soft drinks?" and "During the past week, how many times per week have you consumed energy drinks?." Answers ranged from "none" to "seven times per week." Participant answers were classified into two groups for the regression analyses: those who drunk any soft drink per week ("none" = 0) and at least once per week ("yes" = 1). Similar classification was used for energy drinks consumption question.

Sociodemographic information, including age, sex, education level, and monthly income, was provided by the SDHNS database. Level of income was measured by asking the participant about the monthly range of their income. The possible answers were: (1) I do not have stable monthly income, (2) less than SR 5000, (3) between SR 5,000 and SR 16,000, (4) more than SR 16,000. Those who answered "I do not have stable income" were excluded, $n = 1{,}239$ as we were interested in gradient relationship across income categories. Education was measured by asking the participant about the highest attainable degree.

BMI was calculated from self-reported height and weight. Weight status was classified as underweight (BMI <18.5 kg/m^2), healthy (BMI: 18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), and obesity (BMI ≥ 30 kg/m^2) (31). Extreme BMI values were excluded (<15 kg/m^2 or ≥ 50 kg/ m^2). The participants' level of physical activity adhered to the World Health Organization's (WHO) recommendations, which include engaging in moderate-intensity activity for at least 30 or 20 min of high-intensity activity in the past week (32). Subsequently, the activity level was categorized as: (1) none: when the participants did not engage in any type of physical activity, (2) less than recommended level: when the participants engage in some physical activity but did reach the recommended level and (3) follow recommended level: when the participants met the WHO recommendations (32).

2.3 Statistical analyses

Categorical variables are presented as frequencies (n) and percentages (%) across four levels of weekly consumption: never, 1–2 times, 3–4 times, and 5 times or more per week. Bivariate analyses were conducted using a chi- square test of association (proportions) to identify factors associated with weekly consumers versus

non-consumers. Logistic regression models were used to identify factors and the magnitude of association with frequency of soft or energy drinks consumption. The outcome was categorized as the consumption of at least one time per week or none. Factors that showed significant association in the bivariate analyses with weekly soft or energy consumption ($p < 0.05$) were included in the adjusted models.

3 Results

The study sample included $n = 5{,}194$ participants. Participants who reported unstable income ($n = 1{,}239$, 24%) or extreme BMI values ($n = 45$, <1%) were excluded. Overall, a total of $n = 3{,}928$ were included in the analyses, 57% of which were males, 43% were 30–49 years, 65% had a post-secondary education, and 54% had overweight or obesity (BMI $\geq 25\,kg/m^2$).

3.1 Soft drinks consumption

Soft drinks consumption is shown by participants' characteristics in Table 1. About 67% reported consuming soft drinks at least once a week, with more males than females reporting weekly consumption (69% vs. 65%, $p < 0.01$). Consumption of soft drinks also differed by age, monthly income, physical activity level, and weight status. Education level did not differ between consumers and non-consumers.

3.2 Energy drinks consumption

Energy drinks consumption is shown by participants characteristics in Table 2. Nearly, 30% reported consuming energy drinks at least once a week, with more males than females reporting weekly consumption (34% vs. 25%, $p < 0.001$). Significant differences in consumption of energy drinks were observed by age, monthly income, physical activity level, and weight status. Education level did not differ between consumers and non-consumers.

3.3 Factors associated with soft and energy drinks consumption

Table 3 presents unadjusted and adjusted logistic regression models of factors associated with weekly soft drinks consumption. Females had lower odds of consuming soft drinks weekly compared to males [crude OR (95%CI) = 0.84 (0.73, 0.96)]. Adults over the age of 50 y and those 30–49 y were less likely to consume soft drinks [crude ORs (95%CI): 0.26 (0.22, 0.31) and 0.70 (0.60, 0.83), respectively] compared to younger adults <29 y. Overweight, but not obesity, was associated with lower odds of soft drinks consumption compared to healthy weight adults [crude OR (95%CI): 0.83 (0.71, 0.97)]. Participants with higher income >16,000 SAR and those following physical activity recommendations had lower odds of consuming soft drinks consumption than reference categories (<5,000 SAR and no physical activity, respectively). Interestingly, those who performed physical activity less than the recommended level had higher odds of consuming soft drinks than those with no physical activity. In the fully adjusted model, gender, age, monthly income, and physical activity remained significantly associated with soft drinks consumption following the same direction of association. Weight status was not associated with soft drinks consumption after adjusting for age, gender, monthly income, and physical activity.

Table 4 illustrates logistic regression analyses of unadjusted and adjusted odds ratios of factors associated with weekly energy drinks consumption. Similar to the pattern observed in soft drinks consumption, females had lower odds of consuming energy drinks weekly compared to males [AOR (95%CI): 0.53 (0.46, 0.62)]. Adults over the age of 50 y and 30–49 y were less likely to consume soft drinks compared to younger adults <29 y. Both overweight and obesity were associated with lower odds of energy drinks consumption compared to adults with healthy weight. Higher income >16,000 SAR was associated with lower odds of consuming energy drinks than those who earned <5,000 SAR. Education level was not associated with weekly energy drinks consumption as observed in soft drinks. Following physical activity recommendations was associated with lower odds of consuming energy drinks; however, less than the recommended physical activity was associated with higher odds of consumption than the reference category (no physical activity). In the fully adjusted model, gender, age, monthly income, weight status, and physical activity remained significantly associated with energy drinks consumption following the same direction of association in the bivariate analyses.

4 Discussion

Based on nationally representative data of Saudi adults, weekly consumption of soft drinks was 67% and energy drinks consumption was 30%. Analyses showed that Saudi females were less likely to consume soft and energy drinks compared to males and that adults less than 30 years old had the highest prevalence of consuming both soft and energy drinks. Interestingly, adherence to the WHO's physical activity recommendations was inversely correlated with the consumption of soft and energy drinks. Similarly, adults with obesity exhibited a lower likelihood of weekly consumption of energy drinks. However, weight status was not associated with soft drinks consumption after adjusting for age, gender, income, and physical activity level.

In this study, the prevalence of soft drinks consumption in Saudi adult population was 67% in any given week. Our findings support the evidence that Saudi Arabia is one of the biggest consumers of soft drinks in the Middle East region (33). Globally, Saudi Arabia ranks fifth in terms of calorie consumption derived from sugar-sweetened beverages (33). The findings of the current study are consistent with findings from a national study showing that ~71% of Saudi adults consume sugar-sweetened beverages, which include soft drinks, at least once a week using data collected in 2013, with 36% of adults consume these beverages on a daily basis (34). Saudi Arabia implemented a 50% tax on sugary drinks, including soft drinks in 2017, which aligns with a broader initiative to combat the escalating rates of obesity and type 2 diabetes mellitus, conditions correlated with the overconsumption of these beverages (24, 35). A 2019 study on 1,194 adults living in Saudi Arabia reported a lower rate of weekly soft drinks consumption (44%); of which, 6% reported consuming soft drinks daily (36). Consumption of soft drinks on a daily basis has been

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TABLE 1 Characteristics of study sample by soft drinks consumption.

	Soft drinks consumption				*P*-value
	Never	1–2 times/week	3–4 times/week	≥5 times/week	
Total	1,288 (32.3)	1,150 (29.3)	759 (19.3)	731 (18.6)	
Gender					
Male	694 (31.1)	597 (26.8)	451 (20.2)	490 (22.0)	0.009
Female	594 (35.0)	553 (32.6)	308 (18.2)	241 (14.2)	
Age group					
<30 years	309 (23.0)	361 (26.9)	304 (22.6)	370 (27.5)	0.000
30–49 years	503 (29.8)	537 (31.8)	357 (21.12)	293 (17.3)	
≥50 years	476 (53.2)	252 (28.19)	98 (11.0)	68 (7.6)	
Education level					
≤High school	467 (34.1)	374 (27.3)	272 (19.9)	256 (18.7)	0.154
Diploma and bachelor	748 (31.6)	719 (30.4)	452 (19.1)	449 (19.0)	
Master and PhD	73 (38.2)	57 (29.84)	35 (18.3)	26 (13.6)	
Income level					
<5,000 SAR	436 (29.9)	419 (28.7)	293 (20.1)	311 (21.3)	0.000
5,000–16,000 SAR	621 (31.5)	604 (30.7)	379 (19.2)	366 (18.6)	
>16,000 SAR	231 (46.3)	127 (25.5)	87 (17.4)	54 (10.8)	
Physical activity*					
None	419 (32.7)	370 (28.8)	226 (17.6)	268 (20.9)	0.000
Less than recommended level	512 (28.8)	584 (32.8)	384 (21.6)	299 (16.8)	
Follow recommended level	357 (41.2)	196 (22.6)	149 (17.2)	164 (18.9)	
BMI‡					
Underweight	44 (24.4)	62 (34.4)	32 (17.8)	42 (23.3)	0.001
Healthy weight	506 (31.0)	445 (27.3)	342 (21.0)	337 (30.7)	
Overweight	463 (35.1)	399 (30.3)	258 (18.8)	208 (15.8)	
Obesity	275 (34.4)	244 (30.5)	137 (17.1)	144 (18.0)	

Data are presented as n (%). Proportions are row total. *Includes intense and moderate. ‡BMI was used to define weight status as follows: underweight (BMI <18.5 kg/m^2), healthy (BMI: 18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), and obesity (BMI≥30 kg/m^2).

observed in developed nations, such as the UK (20.4%) (37) and the USA (40.0%) (38), with similar prevalence in South Africa (48.3%) (39). This may be due to the preference for fast food and soft drinks consumption in western and European countries. A trend toward a busy lifestyle with less emphasis on finding time to cook may also be emerging (40).

We found that around 30.0% Saudi adults consume energy drinks on a weekly basis, which is in agreement with the most recent study performed among Saudi young adults (29.3%) (41). However, the results of the present study are inconsistent and lower compared with earlier studies executed in Saudi Arabia. A 2017 study that included students from the Prince Sattam bin Abdulaziz University found that 81.3% of students consumed energy drinks, while in another study conducted at the University of Dammam, 45.3% of participants consumed energy drinks (42, 43). Both studies, however, did not report a clear frequency of consumption to facilitate comparison. Compared to Malaysian adults, weekly consumption appears to be higher in our study (30.0% vs. 18.8%) (27). It is suggested that these reduced consumption in recent years is due to the new rules of the Saudi Food and Drug Authority (SFDA) and the General Authority of Zakat and Tax (GAZT) related to energy drinks. In 2017, SFDA published few rules for handling energy drinks; one of these rules includes that manufacturers must write the warning phrases on the package (44). Weekly consumption has been observed in the 16 European countries (16.0%) (45) and Denmark (15.8%) (26). Energy drinks are considered new in the Danish soft drink market, which may be one reason why young adults in Denmark are less likely to consume energy drinks. Additionally, the above drinks tend to be more expensive than other drinks, which may also contribute to this phenomenon (26).

In the current study, gender, age, monthly income, and physical activity were identified as contributing factors to soft and energy drinks consumption. Gender was found to be significantly associated with soft and energy drinks consumption. Females had lower odds for consuming soft and energy drinks weekly [AOR (95%CI): 0.69 (0.60, 0.80) vs. AOR (95%CI): 0.53 (0.46, 0.62), respectively] compared to males. This finding is consistent with findings from several earlier population-based studies in Saudi Arabia (34), USA (38), and Australia (46), which revealed that males were more likely to consume soft and energy drinks than females. A study in Denmark found 25%

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TABLE 2 Characteristics of study sample by energy drinks consumption.

	Energy drinks Consumption				
	Never	1-2 times/week	3-4 times/week	≥ 5 times/week	*P* value
Total	2,747 (69.9)	667 (17.0)	343 (8.7)	171 (4.4)	
Gender					
Male	1,466 (65.7)	431 (19.3)	219 (9.8)	116 (5.2)	0.000
Female	1,281 (75.5)	236 (13.9)	124 (7.3)	55 (3.2)	
Age group					
<30 years	813 (60.5)	307 (22.8)	143 (10.6)	81 (6.03)	0.000
30–49 years	1,186 (70.2)	284 (16.8)	150 (8.9)	70 (4.1)	
≥50 years	748 (83.7)	76 (8.5)	50 (5.6)	20 (2.2)	
Education level					
≤High school	960 (70.1)	221 (16.1)	135 (9.9)	53 (3.9)	0.086
Diploma and bachelor	1,652 (69.8)	421 (17.8)	185 (7.8)	110 (4.7)	
Master and PhD	135 (70.7)	25 (13.1)	23 (12.0)	8 (4.2)	
Income level					
<5,000 SAR	985 (67.5)	289 (29.8)	116 (8.0)	69 (4.7)	0.000
5,000–16,000 SAR	1,353 (68.9)	331 (16.8)	197 (10.0)	89 (4.5)	
>16,000 SAR	409 (82.0)	47 (9.4)	30 (6.0)	13 (2.6)	
Physical activity*					
None	926 (72.2)	206 (16.1)	91 (7.1)	60 (4.7)	0.000
Less than recommended level	1,168 (65.7)	365 (20.5)	183 (10.3)	63 (3.5)	
Follow recommended level	653 (75.4)	96 (11.1)	69 (8.0)	48 (5.5)	
BMI‡					
Underweight	112 (62.2)	40 (22.2)	17 (9.4)	11 (6.1)	0.000
Healthy weight	1,068 (65.5)	315 (19.3)	158 (9.7)	89 (5.5)	
Overweight	953 (72.3)	192 (14.6)	117 (8.9)	56 (4.3)	
Obesity	614 (76.8)	120 (15.0)	51 (6.4)	15 (1.9)	

Data are presented as n (%). Proportions are row total. *Includes intense and moderate. ‡BMI was used to define weight status as follows: underweight (BMI < 18.5 kg/m^2), healthy (BMI: 18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), and obesity (BMI ≥ 30 kg/m^2).

of men consume energy drinks on a weekly basis, suggesting that the consumption of energy drink is predominantly observed among males (26). Another study in Cambodia found the men are more likely [AOR (95%CI): 1.49 (1.10, 2.00)] to consume soft drinks than women (40) This difference could be attributed to gender-driven roles, identities, and social norms. For example, men may be more likely to be influenced by advertising that targets males. It could be also that females tend to more health-conscious and the desire to be a positive role-model. Previous research in several populations (34, 41, 47, 48) has demonstrated a strong correlation between the age of an individual and their consumption of soft and energy drinks, and the current study's findings support this. Our result was that young adults <29 y are more likely to consume soft and energy drinks compared to adults over the age of 50 y and those 30–49 y. However, a study on Cambodian adults opposes this finding (40).

Monthly income was significantly associated with soft and energy drinks consumption. Those who earned higher income >16,000 SAR per month were less likely to consume soft and energy drinks compared to those who earned <5,000 SAR per month. This observation is in line with data from Singapore, which indicates that high and middle-income individuals consume fewer soft drinks in comparison to lower-income individuals (48). In addition, a 2022 Saudi study indicated that adults with higher incomes were less likely to consume soft drinks (34). Conversely, a study conducted in Australia found that individuals with a higher annual income tended to consume more soft drinks than those with a lower annual income (39). The reason that higher income participants in this study were less likely to consume soft and energy drinks could be explained by how high income can increase people access to knowledge, material, cultural, and psychosocial resources that can influence their engagement in such behaviors (49). However, our study did not observe any association between education level and energy and soft drinks consumption. Existing evidence indicates that the consumption of energy drinks was more common among individuals with lower educational attainment levels than those with higher educational attainment levels (26). Thus, examining several socioeconomic status indicators, such as income and education, can improve our understanding of how such indicators influence soft and energy drinks consumption, as they usually represent different social processes in health and health behaviors (50).

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TABLE 3 Odd ratios of factors associated with soft drink consumption and their 95% confidence intervals (n = 3,928).

	Weekly soft drinks consumption	
	Model 1	Model 2
	OR (95% CI)	AOR (95% CI)
Gender		
Male	1.00	1.00
Female	0.84 (0.73, 0.96)**	0.69 (0.60, 0.80)***
Age group		
<30 years	1.00	1.00
30–49 years	0.70 (0.60, 0.83)***	0.65 (0.54, 0.79)***
≥50 years	0.26 (0.22, 0.31)***	0.24 (0.19, 0.29)***
Education level		
≤High school	1.00	–
Diploma and bachelor	1.12 (0.96, 1.29)	–
Master and PhD	0.84 (0.61, 1.14)	–
Income level		
<5,000 SAR	1.00	1.00
5,000–16,000 SAR	0.93 (0.80, 1.07)	1.13 (0.95, 1.34)
>16,000 SAR	0.49 (0.40, 0.61) ***	0.72 (0.57, 0.91) **
Physical activity		
None	1.00	1.00
Less than recommended level	1.20 (1.03, 1.40)*	1.18 (1.00, 1.38)*
Follow recommended level	0.69 (0.58, 0.83)***	0.60 (0.50, 0.73)***
BMI‡		
Healthy weight	1.00	1.00
Underweight	1.39 (0.97, 1.99)	1.13 (0.78, 1.64)
Overweight	0.83 (0.71, 0.97)*	0.99 (0.84, 1.17)
Obesity	0.86 (0.72, 1.03)	1.16 (0.95, 1.40)

*p<0.05; **p<0.01; ***p<0.001. Results obtained from binary logistic regression models. Model 1 column reports crude odds ratio; Model 2 columns report estimate from models mutually adjust for gender, age group, income level, physical activity and BMI. AOR, adjusted odds ratio; CI, confidence interval.

TABLE 4 Odd ratios of factors associated with energy drink consumption and their 95% confidence intervals (n = 3,928).

	Weekly energy drinks consumption	
	Model 1	Model 2
	OR (95% CI)	AOR (95% CI)
Gender		
Male	1.00	1.00
Female	0.62 (0.54, 0.71)***	0.53 (0.46, 0.62)***
Age group		
<30 years	1.00	1.00
30–49 years	0.65 (0.56, 0.76)***	0.65 (0.55, 0.78)***
≥50 years	0.30 (0.24, 0.37)***	0.31 (0.24, 0.39)***
Education level		
≤High school	1.00	–
Diploma and Bachelor	1.02 (0.88, 1.18)	–
Master and PhD	0.97 (0.70, 1.36)	–
Income level		
<5,000 SAR	1.00	1.00
5,000–16,000 SAR	0.95 (0.82, 1.10)	1.08 (0.91, 1.28)
>16,000 SAR	0.46 (0.36, 0.59)***	0.60 (0.45, 0.79)***
Physical activity		
None	1.00	1.00
Less than recommended level	1.36 (1.16, 1.59)***	1.33 (1.13, 1.56)***
Follow recommended level	0.85 (0.69, 1.03)	0.72 (0.59, 0.89)**
BMI‡		
Healthy weight	1.00	1.00
Underweight	1.15 (0.84, 1.59)	1.02 (0.74, 1.42)
Overweight	0.73 (0.62, 0.85)***	0.83 (0.71, 0.99)*
Obesity	0.58 (0.47, 0.70)***	0.73 (0.60, 0.90)**

*p < 0.05; **p < 0.01; ***p < 0.001. Results obtained from binary logistic regression models. Model 1 column reports crude odds ratio; Model 2 columns report estimate from models mutually adjust for gender, age group, income level, physical activity and BMI. AOR, adjusted odds ratio; CI, confidence interval.

As expected, adhering to physical activity recommendations was associated with lower odds of consuming soft and energy drinks. This conclusion is in line with the findings of a population-based cross-sectional survey conducted in Spain, which showed that the prevalence of diet soda consumption was highest among inactive adolescents (51). Adolescents may consume diet soda in response to the realization that they are not consuming enough energy (51). In the context of our study in Saudi adults, it might be that participants who are following physical activity recommendations consuming less soft and energy drinks in order to follow healthy food choices and maintain overall health. Regarding weight status, we found that overweight/obesity were associated with lower odds of energy drinks consumption compared to adults with healthy weight. This result is inconsistent with previous evidence, which might reflect differences in population and methodology (52, 53). In three Eastern European cohorts have indicated positive correlation between consumption of sugar-sweetened beverage and BMI (52). A study on 515 Malaysian adults reported no bivariate association between energy drinks consumption and BMI (27). A recent systematic review of 26 observational studies showed that only one study reported no correlation between the intake of sugar-sweetened beverage and weight gain (53). It is possible that participants classified as overweight/obese in our study were avoiding the consumption of energy drinks for better weight control or under-reported consumption, causing social desirability bias and this needs to be further explored.

Advertisements and marketing campaigns frequently portray energy drinks as fashionable, pleasurable, or necessary for optimal performance, affecting consumer behaviors and attitudes (23, 54). A study in Canada indicated a considerable number of energy drink postings on social media in 2020–2021, with several posts have using marketing strategies on Twitter, Facebook and Instagram, that may be appealing to adolescents. Another study in Saudi Arabia found that advertising is the primary source of information regarding

energy drinks among 43% of Saudi adolescents (55). However, a recent study on n = 316 students from two Saudi universities reported no associations between social media platforms or watching relevant social media advertisements with sugary drinks consumption after adjusting for age, sex, nationality, marital status, academic year, monthly household income, and BMI; weekly users of Snapchat had lower odd of consuming sugary drinks than daily user 0.33 (0.11–0.98) (56). Further studies are needed to understand the impact of the media on soft and energy drinks consumptions in the Saudi Arabian context.

Finally, the present study measures the consumption of soft and energy drinks by asking the participants about their frequency of intake each week rather than the actual quantity of consumption. Using the frequency of consumption, as an index of actual amount consumption is easier and a relatively reliable tool to judge the amount of consumption which was adopted in many other studies (57–59). Studies have shown correlations between frequency of consumption and quantity of soft drinks consumption (57–59). Frequency of consumption has been associated with adverse health behaviors and higher rates of overweight/obesity among children, adolescents, and adults from several countries (6, 60, 61).

The current study has many strengths, which includes a relatively large sample size representative of Saudi adults from all regions of Saudi Arabia by using multistage quota sampling. This sampling technique was limiting the risk of selection bias and allowing for the recruitment of a balanced study sample in terms of gender and age that representing all the regions of the kingdom. On the other hand, the use of a research participant database might introduce bias, given that participation in the database was voluntary. Data integrity checks, inherent to the QPlatform data collection system, minimize invalid or erroneous data entry. The study was also able to report on soft drinks and energy drinks separately. However, the study has some limitations. The cross-sectional design might affect the causative relationship between the soft and energy drinks consumption and possible associations. The self-reported data is commonly used in nutrition research and public health surveillance, but it is vulnerable to recall bias and social desirability bias, which may result in misreporting particularly among those who are overweight. Furthermore, the soft and energy drinks consumption was measured by frequency rather than actual quantity that ingested by participants on the weekly basis. Data was not available on the sizes or types of soft and energy drinks; some might be consuming non-sugar sweetened drinks that have a different impact compared to sugar-sweetened beverages.

5 Conclusion

Overall, this study on a representative sample of Saudi adults shows that 67% consume soft drinks and 30% consume energy drinks weekly. Males, younger adults, and those with higher incomes are more likely to consume soft drinks weekly than females, older adults, and those with lower incomes. The soft drinks consumption remains high despite the implementation of taxes and alarm action, particularly among young adults and men. Studies are needed on the type and quantity of drinks consumed and in-depth analyses of associated factors; this could inform targeted interventions for any future programs on the prevention and/or management of non-communicable diseases. The findings of this study highlight the need for public health interventions to the consumption of soft drinks and energy drinks in Saudi Arabia. These interventions should be based on a comprehensive understanding of the factors that influence consumption and tailored to the specific needs of the Saudi population.

Data availability statement

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

Ethics statement

The studies involving humans were approved by Ethics Committee of Sharik Association for Research and Studies (Approval no. 06–2021). 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

AA: Conceptualization, Investigation, Supervision, Writing – original draft, Writing – review & editing. AT: Investigation, Writing – original draft, Writing – review & editing. AG: Formal analysis, Investigation, Software, Writing – review & editing. FA-Q: Conceptualization, Writing – original draft, Writing – review & editing. NA: Methodology, Resources, Writing – original draft, Writing – review & editing. NB: Data curation, Funding acquisition, Resources, Writing – review & editing.

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Conflict of interest

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

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Association of major dietary patterns with socioeconomic status, obesity, and contracting COVID-19 among Iranian adults

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Background: The coronavirus disease 2019 (COVID-19) pandemic clearly affected the lifestyle and dietary habits of millions of people worldwide. The purpose of this study was to evaluate the association of major dietary patterns with socioeconomic status, obesity, and contracting COVID-19.

Methods: We conducted a cross-sectional study using an online survey for data collection with a total of 1,187 participants (over the age of 18 years) who reported their sociodemographic details, anthropometric index (weight and height), and dietary intake. Multivariable logistic regression models were applied to assess the association between major dietary patterns and study outcomes.

Results: A total of 1,106 adults were included in the current analysis. We identified three major dietary patterns (plant-based, meat, and Western dietary patterns). The mean age of participants was significantly higher in the upper tertile of plant-based dietary patterns (DPs) compared to the first tertile, while it was lower in the top tertile of meat and Western DPs. The percentage of participants who lived in urban areas was significantly higher in the third tertile of meat DP than in the first tertile ($p < 0.001$). Moderate adherence to Western DP was significantly associated with increased odds of obesity (OR: 1.79; 95% CI: 1.17, 2.74). In addition, high adherence to Western DP was significantly related to increased odds of obesity after controlling for confounders. Subjects in the second tertile of the Western DP had higher odds (95% CI: 1.04, 1.92) for COVID-19 infection than the first tertile.

Conclusion: This study showed that moderate and high adherence to a Western dietary pattern was associated with a higher risk of obesity and COVID-19 infection during the pandemic. Future studies are needed to confirm these findings.

KEYWORDS

dietary pattern, weight, COVID-19, socioeconomic status, adults

1 Introduction

Coronavirus disease-2019 (COVID-19), caused by a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has become a global public health crisis of this century (1). The pandemic situation and the measures needed to control the spread of the disease have resulted in lockdowns and many restrictions on daily living, with probable consequences on lifestyle, particularly affecting physical activity, sleep quality, eating habits, and mental health (2–4). Available evidence has shown several unhealthy lifestyles during the COVID-19 pandemic, including increased sedentary behavior and less time spent on physical exercise (5).

Moreover, negative emotions (e.g., stress and boredom), sleep disorders, and sedentary behaviors caused by home confinement could promote overconsumption, change dietary patterns, and reduce diet quality (6). These changes result in higher consumption of "comfort foods" and energy imbalance. These foods, mainly rich in simple carbohydrates, unhealthy fat, and sugar, are associated with an increased risk for more severe complications of COVID-19 (7, 8), thereby increasing the risk of developing non-communicable diseases (NCDs), such as obesity, diabetes, and cardiovascular disease (9).

On the other hand, obese subjects are one of the groups with a higher risk for COVID-19 complications (10). Kompaniyets et al. (11) reported that obesity is associated with a 3.07 times higher risk of hospitalization and a 1.42 times higher risk of severe illness when hospitalized. Obesity-induced adipose tissue expansion contributes to increased circulating levels of proinflammatory cytokines (12). This low-grade inflammation state could further exacerbate the inflammation in patients with COVID-19 (13).

Xu et al. observed that prudent dietary patterns, which are characterized by high intake of fresh fruits and vegetables, and low intake of soft drinks and fried food were negatively associated with weight gain among the Chinese population during the COVID-19 pandemic (13). In addition, a healthy dietary pattern, which is based on healthy fats, plant food (fruits, vegetables, cereals, and legumes), and low-fat protein foods, could support the immune system in fighting infections such as COVID-19 (14, 15). A recent meta-analysis showed that the effectiveness of a plant-based diet against COVID-19 infection was 50% (16). Moreover, an observational study indicated that unhealthy or traditional dietary patterns were associated with a higher risk of severe COVID-19 (17).

Dietary patterns are mainly shaped by income and food prices. A decrease in the financial capacity to purchase food due to job instability during the pandemic would lead to adjusting the items of food baskets with more affordable resources (18).

Therefore, the current study is conducted to determine the association of major dietary patterns with socioeconomic status, obesity, and contracting COVID-19 among Iranian adults.

2 Methods and materials

2.1 Study design and population

The present cross-sectional web-based survey was performed among Iranian adults during the COVID-19 pandemic.

The required sample size was calculated using Gpower software ($\alpha = 0.05$, $\beta = 0.2$) according to a previous study. Therefore, the estimated sample size for the study is 515 volunteers. A combination of convenience and snowball sampling was used to employ participants.

Participants aged 18 years or above and living in Iran were considered as inclusion criteria. Participants excluded from the study were those (1) who were pregnant or lactating, (2) who were on specific diets, and (3) who did not fill out the questionnaire appropriately or reported invalid data.

2.2 Study variables and tools

An online questionnaire with an invitation letter was posted through different social media portals (including Instagram and WhatsApp). To prevent duplicate responses, we used an online form that allows only one response per user. We also asked the participants to share the study link to increase the number of persons who receive the invitation link. The purpose of the survey was provided on the cover page of the online questionnaire to inform the participants.

An online questionnaire was prepared in which participants self-reported sections regarding categories of sociodemographic characteristics, food consumption, and anthropometric index (weight and height) during the COVID-19 pandemic.

Dietary intake was assessed using a modified food frequency questionnaire (FFQ). The validity and reliability of the FFQ were evaluated previously (18). The correlation coefficient for reliability was 0.77. Since this survey was conducted during the COVID-19 pandemic, we summarized the questionnaire to prevent the adverse effects of the length of the questionnaire on the response rate. Each item included a typical portion size. Participants reported each food consumption based on servings per week.

Self-reported data on weight and height were used to calculate BMI by dividing weight (kg) by high squared (m2) and interpreted according to the criteria of the World Health Organization. Following this, the participants were classified into groups: (i) underweight (BMI < 18.5), (ii) normal weight (BMI between 18.5 and 24.9), (iii) overweight (BMI between 25 and 29.9), and (iv) obese (BMI ≥ 30).

Data on age, gender, education level, place of living, marital status, and smoking during the pandemic were collected. Socioeconomic status (SES) was evaluated based on scoring variables related to their household asset and wealth (homeownership, personal vehicle, washing machine, LCD/LED TV, dishwasher, laptop/computer, refrigerator, and microwave), education, and income. The SES score was computed for each respondent, and participants were then classified into three categories (low, medium, and high) using tertiles of the distribution of the SES scores as cutoff points.

In addition, respondents reported their health status, such as chronic diseases (diseases with proven diagnosis) and whether they were previously infected with COVID-19. According to the UK NHS report, if participants had any of 10 medical conditions (e.g., diabetes, weakened immune system, chronic kidney disease, etc.), they were considered to be "high risk" for COVID-19.

The present online survey was reported based on the Checklist for Reporting Results of Internet E-Surveys (CHERRIES) guidelines (19).

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2.3 Ethics statement

The study protocol was approved by the ethics committee of Shiraz University of Medical Sciences (IR.SUMS.REC.1401.34).

2.4 Statistical analysis

The principal component analysis method was applied to identify dietary patterns. Dietary patterns were identified based on 18 food groups, eigenvalue (>1), factor interpretability, and the explained variance (>5%). Factors were rotated with varimax to achieve uncorrelated factors and improve the interpretability. Each food group received a factor loading associated with each dietary pattern. Factor loadings show the correlation coefficient between the food group and the dietary pattern. In the present study, food groups with factor loadings of more than 0.2 were considered to be important contributors to the pattern. After that, the factor score for each dietary pattern was computed by summing up intakes of food groups weighted by their factor loadings. Respondents received a factor score for each identified dietary pattern and were categorized into tertiles (three groups with equal sample size) of dietary patterns' scores. Participants in the lowest tertile (T1) had the lowest adherence to the identified dietary pattern, and those in the highest tertile (T3) had the highest adherence to that dietary pattern.

The normality of the data distribution was evaluated by the one-sample Kolmogorov–Smirnov test. The quantitative variables were expressed as mean ± SD and qualitative variables as frequency (percentage). To compare the quantitative variables across tertiles of dietary patterns, a one-way analysis of variance (ANOVA) was used, while for categorical variables, the chi-square test was applied. To determine the association of dietary patterns with weight status and contracting COVID-19, multivariable logistic regression was applied. The odds ratios (ORs) and their 95% confidence intervals (95% CIs) were calculated in crude and adjusted models. In Model I, adjustment was made for the main confounders (age and gender). In Model II, additional adjustments were conducted for smoking status, marital status, and SES. The first tertile of dietary patterns was considered the reference category in all analyses.

3 Results

In total, 1,187 subjects were participated in the current study. Removal of participants who were not eligible (e.g., under 18 years) and participants who did not complete the survey resulted in a final sample size of $N = 1{,}106$.

Three major dietary patterns were identified using principal components analysis, and they were labeled as "Plant-based dietary pattern (DP)," "Meat DP," and "Western DP." These three dietary patterns explained 39.34% of the total variation in dietary intakes in this population. The "Plant-based DP" was characterized by high consumption of legumes, onions/garlic, fruits, nuts, dried fruits, vegetables, whole breads, and dairy. The "Meat DP" was mainly loaded with red meat, poultry, fish, and canned fish. The "Western DP" was associated with higher intakes of fast foods, carbonated drinks, fruit juice, soy, egg, and seeds. All food groups and their loading factors for each dietary pattern are presented in Table 1.

TABLE 1 Loadings of foods and food groups across major dietary patterns.

Food groups	Component		
	Plant-based dietary pattern	Meat dietary pattern	Western dietary pattern
Legumes	0.591	0.122	0.111
Onion/garlic	0.583		0.106
Fruits	0.581	0.273	0.213
Nuts	0.578	0.309	
Dried fruits	0.555	0.275	
Vegetables	0.539		0.203
Whole breads	0.462		−0.144
Dairy	0.344	0.318	
Red meat	0.227	0.776	
Poultry	0.128	0.752	0.149
Fish	0.128	0.723	
Canned fish		0.457	0.239
Carbonated drinks			0.650
Fast foods	−0.164	0.120	0.644
Fruits juice	0.164	0.275	0.600
Soy	0.325		0.504
Egg	0.257		0.416
Seeds	0.372		0.378

Extraction method: principal component analysis. Rotation method: varimax with kaiser normalization[a].

The mean age and BMI of respondents were 34.5 ± 9.4 years and 26 ± 6.57 kg/m^2, respectively; 85.2% of included subjects were female. The sociodemographic characteristics of participants across tertiles of the dietary patterns are presented in Table 2. The mean age of subjects was significantly higher in the upper tertile of plant-based DP compared to the first tertile ($p = 0.01$), while it was lower in the top tertile of meat DP and Western DP ($p < 0.001$). The percentage of women in the first tertile of Western DP was more than that in the third tertile. The frequency of participants who lived in urban areas was significantly higher in the third tertile of meat DP than in the first tertile ($p < 0.001$). Most subjects had bachelor's and postgraduate degrees in the top tertile of plant-based DP and meat DP ($p < 0.001$), while a high frequency of the participants had bachelor's and postgraduate degrees in the first tertile of Western DP ($p < 0.001$). The percentage of married subjects in the highest tertile of meat DP ($p = 0.01$) and Western DP ($p < 0.001$) were significantly lower than the first one. The proportion of respondents who had low SES in the first tertile of the plant-based DP and meat DP were notably higher compared to the top tertile ($p < 0.001$(, while it was higher in the third tertile of Western DP ($p < 0.001$). Furthermore, the percentage of participants who had a high risk for COVID-19 and had been diagnosed with COVID-19 was significantly lower in the last tertile of Western DP ($p < 0.001$). Body weight and BMI were not

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TABLE 2 Sociodemographic characteristics of participants across tertiles of the dietary patterns.

Variables	Plant-based dietary pattern		*p*-value	Meat dietary pattern		*p*-value	Western dietary pattern		*p*-value
	Tertile 1	Tertile 3		Tertile 1	Tertile 3		Tertile 1	Tertile 3	
Sample size (*n*)	368	369		368	369		368	369	
Age (year)	33.37 ± 9.74	35.11 ± 9.67	0.01	35.22 ± 8.89	33.32 ± 10	<0.001	36 ± 9.2	32.14 ± 10	<0.001
Body weight (kg)	67.30 ± 13.42	69.24 ± 15.56	0.07	68.8 ± 14.9	68.32 ± 15	0.82	68.27 ± 14.79	68.49 ± 15.98	0.58
BMI (kg/m2)	25.72 ± 5.7	26.13 ± 5.8	0.49	26.27 ± 5.6	25.6 ± 5.48	0.30	25.94 ± 5.64	25.64 ± 5.86	0.61
Sex			0.76			0.31			<0.001
Male	54 (14.7)	51 (13.8)		46 (12.5)	60 (16.3)		37 (10.1)	76 (20.6)	
Female	314 (85.3)	318 (86.2)		322 (87.5)	309 (83.7)		331 (89.9)	293 (79.4)	
Place of living			0.76			<0.001			0.33
Urban	277 (75.3)	280 (75.9)		254 (69)	302 (81.8)		290 (78.8)	279 (75.6)	
Rural	91 (24.7)	89 (24.1)		114 (31)	67 (18.2)		78 (21.2)	90 (24.4)	
Education			<0.001			<0.001			<0.001
high school and less	80 (21.7)	50 (13.6)		83 (22.6)	45 (12.2)		47 (12.8)	78 (21.1)	
diploma	153 (41.6)	127 (34.4)		162 (44)	120 (32.5)		120 (32.6)	162 (43.9)	
Bachelor and Postgraduate	135 (36.7)	192 (52)		123 (33.4)	204 (55.3)		201 (54.6)	129 (35)	
Marital status			0.83			0.01			<0.001
Married (not separated)	270 (73.4)	290 (78.6)		300 (81.5)	270 (73.2)		291 (79.1)	262 (71)	
Widowed or divorced	7 (1.9)	7 (1.9)		8 (2.2)	3 (0.8)		4 (1.1)	9 (2.4)	
Single	91 (24.7)	72 (19.5)		60 (16.3)	96 (26)		73 (19.8)	98 (26.6)	
Smoking			0.37			0.83			<0.001
Non-smoker	344 (93.5)	351 (95.1)		347 (94.3)	346 (93.8)		358 (97.3)	328 (88.9)	
Smoker	24 (6.5)	18 (4.9)		21 (5.7)	23 (6.2)		10 (2.7)	41 (11.1)	
SES			<0.001			<0.001			<0.001
Low	260 (70.7)	197 (53.4)		283 (76.9)	173 (46.0)		199 (54.1)	253 (68.6)	
Moderate	100 (27.2)	152 (41.2)		81 (22)	161 (43.6)		38.9 (8.9)	105 (28.5)	
High	8 (2.2)	20 (5.4)		4 (1.1)	35 (9.5)		26 (7.1)	11 (3)	
At risk medical group for COVID			0.78			0.22			<0.001
Yes	116 (31.5)	112 (33.6)		133 (36.1)	112 (30.4)		127 (34.5)	99 (26.8)	
No	252 (33.9)	247 (33.2)		235 (63.9)	257 (69.6)		241 (65.5)	270 (73.2)	
Diagnosed COVID			0.44			0.41			<0.001
Yes	113 (30.7)	115 (31.2)		120 (32.6)	102 (27.6)		112 (30.4)	103 (27.9)	
No	368 (34)	369 (33.9)		255 (69.3)	254 (68.8)		256 (69.6)	266 (72.1)	

Quantitative variables: mean ± SD. Qualitative variables: frequency (percentage). *p* resulted from ANOVA for quantitative variables and the chi-square test for categorical variables.

significantly different among the tertiles of the various types of dietary patterns.

3.1 Association of dietary patterns with BMI and contracting COVID-19

Multivariable-adjusted ORs (95% CI) for the association of dietary patterns with BMI and contracting COVID-19 are shown in Table 3. In the crude and adjusted models, no significant association was found between plant-based DP with underweight, obesity, and contracting COVID-19. In the case of the association of plant-based DP with overweight, the moderate adherence (second tertile) to plant-based DP was significantly related to increased odds of overweight (OR: 1.41; 95% CI: 1.02, 1.96); however, the relationship disappeared after adjusting for potential confounders. In the crude model, participants in the highest tertile of the Western DP had 2.62-fold higher odds (95% Cl: 1.32, 5.2) for underweight than the first one. However, this association disappeared after considering potential confounding variables.

Moreover, moderate adherence to Western DP was significantly associated with increased odds of obesity (OR: 1.79; 95% CI: 1.17, 2.74). This relation remained significant even after adjusting for confounders. In addition, high adherence to Western DP was

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TABLE 3 Multivariate adjusted odds ratio (OR) and 95% confidence interval (CI) for the association of dietary patterns with BMI and contracting COVID-19.

	Tertile 1	Tertile 2	Tertile 3	*P*-trend
Plant-based dietary pattern				
Underweight				
Crude model	1	0.78 (0.38, 1.5)	1.12 (0.58, 2.14)	0.73
Model 1	1	0.96 (0.46, 2.02)	1.30 (0.66, 2.54)	0.44
Model 2	1	1.02 (0.48, 2.14)	1.14 (0.71, 2.80)	0.32
Overweight				
Crude model	1	1.41 (1.02, 1.96)	1.24 (0.89, 1.72)	0.19
Model 1	1	1.29 (0.92, 1.82)	1.12 (0.80, 1.58)	0.49
Model 2	1	1.28 (0.90, 1.81)	`1.14 (0.80, 1.62)	0.45
Obesity				
Crude model	1	1.25 (0.82, 1.90)	1.19 (0.78, 1.82)	0.39
Model 1	1	1.14 (0.74, 1.76)	1.07 (0.69, 1.65)	0.73
Model 2	1	1.17 (0.75, 1.82)	1.16 (0.74, 1.81)	0.49
Contracting COVID-19				
Crude model	1	1.19 (0.88, 1.63)	1.02 (0.74, 1.39)	0.90
Model 1	1	1.14 (0.83, 1.55)	0.97 (0.71, 1.34)	0.89
Model 2	1	1 (0.79, 1.48)	0.92 (0.67, 1.28)	0.64
Meat dietary pattern				
Underweight				
Crude model	1	0.58 (0.28, 1.21)	0.95 (0.49, 1.82)	0.92
Model 1	1	0.57 (0.27, 1.20)	0.74 (0.37, 1.46)	0.42
Model 2	1	0.59 (0.28, 1.26)	0.80 (0.39, 1.62)	0.56
Overweight				
Crude model	1	0.78 (0.56, 1.09)	0.83 (0.59, 1.15)	0.27
Model 1	1	0.78 (0.56, 1.01)	0.93 (0.66, 1.33)	0.73
Model 2	1	0.82 (0.58, 1.17)	1.04 (0.72, 1.51)	0.79
Obesity				
Crude model	1	0.75 (0.50, 1.14)	0.68 (0.44, 1.03)	0.07
Model 1	1	0.76 (0.50, 1.17)	0.78 (0.50, 1.21)	0.28
Model 2	1	0.85 (0.55, 1.31)	0.99 (0.62, 1.58)	0.99
Contracting COVID-19				
Crude model	1	1.17 (0.86, 1.59)	0.79 (0.57, 1.08)	0.14
Model 1	1	1.16 (0.85, 1.58)	0.81 (0.58, 1.11)	0.20
Model 2	1	1.12 (0.82, 1.53)	0.73 (0.52, 1.02)	0.75
Western dietary pattern				
Underweight				
Crude model	1	1.03 (0.45, 2.35)	2.62 (1.32, 5.2)	<0.001
Model 1	1	1.05 (0.45.2.40)	1.83 (0.89, 3.76)	0.76
Model 2	1	1.02 (0.44, 2.37)	1.73 (0.83, 3.62)	0.11
Overweight				
Crude model	1	1.05 (0.76, 1.45)	0.99 (0.71, 1.37)	0.97
Model 1	1	1.10 (0.79, 1.54)	1.31 (0.92, 1.85)	0.12
Model 2	1	1.02 (0.72, 1.43)	1.25 (0.87, 1.79)	0.22

(Continued)

TABLE 3 (Continued)

	Tertile 1	Tertile 2	Tertile 3	*P*-trend
Obesity				
Crude model	1	1.79 (1.17, 2.74)	1.37 (0.88, 2.12)	0.17
Model 1	1	1.93 (1.24, 2.98)	1.96 (1.23, 3.13)	<0.001
Model 2	1	1.70 (1.09, 2.66)	1.75 (1.08, 2.81)	0.02
Contracting COVID-19				
Crude model	1	1.41 (1.04, 1.91)	0.88 (0.64, 1.21)	0.46
Model 1	1	1.41 (1.04, 1.92)	0.92 (0.66, 1.28)	0.70
Model 2	1	1.41 (1.03, 1.93)	0.94 (0.67, 1.32)	0.80

[1]Adjusted for age and gender. [2]Adjusted for age, gender, smoking status, marital status, and SES.

significantly related to increased odds of obesity after controlling for confounders (model 1: OR: 1.96; 95% CI: 1.23, 3.13; model 2: OR: 1.75; 95% CI: 1.08, 2.81). Regarding contracting COVID-19, participants in the second tertile of the Western DP had 1.41-fold higher odds (95% Cl: 1.04, 1.92) for COVID-19 infection. This association remains significant after adjusting for confounding variables. However, neither crude nor adjusted models found any significant association among meat DP, BMI status, and contracting COVID-19.

4 Discussion

Our study aimed to investigate the association of major dietary patterns with socioeconomic status (SES), obesity, and contracting COVID-19 among Iranian adults. The findings from this cross-sectional survey provided valuable insights into the relationship between dietary patterns and these health outcomes. We found that participants with moderate and high adherence to Western DP had higher odds of obesity. In addition, we found that participants with moderate adherence to Western DP had higher odds of contracting COVID-19. However, we could not find any significant correlation between meat DP and plant-based DP with contracting COVID-19.

When examining the association between dietary patterns and BMI, we found that adherence to the Western DP was significantly associated with an increased likelihood of obesity. The Western DP is a widely followed eating pattern characterized by high salt, trans fats, saturated fats, and simple carbohydrates. However, it lacks complex carbohydrates and fibers. Moreover, it is considered a calorie-dense diet deficient in essential nutrients such as vitamins and minerals (20). These findings are consistent with previous studies that have shown the detrimental effects of Western DP on weight status. It has been reported in a population-based study that following the Western DP closely correlated with higher risks of obesity and weight gain (21). A cohort of healthy reproductive-age women study showed that adherence to the Western DP is associated with higher odds of obesity (OR: 2.68) (22). The findings of the cross-sectional study showed that modern dietary pattern (higher intake of soft drinks, fried foods, pickles, and lower intake of fresh vegetables) was positively associated with weight gain in men and women during the COVID-19 pandemic (23). In addition, our results align with a previous meta-analysis, indicating a 65% heightened risk of obesity linked to the Western DP (24). In terms of the mechanism, the Western DP led to hyperinsulinemia, which causes increased fat storage, appetite, hyperphagia, and carbohydrate craving (25).

Obesity is one of the main risk factors for increasing the risk of contracting COVID-19. Singh et al. (26) in a systematic review and meta-analysis study, showed that obesity was associated with an increased risk of severe disease and mortality rate among patients with COVID-19. In terms of odds of contracting COVID-19, we found that participants with moderate adherence to Western DP had significantly higher odds of COVID-19. In line with our findings, it has been reported in previous studies that moderate or higher adherence to Western DP led to a significant increase in the risk of infectious diseases such as COVID-19. Ebrahimzadeh et al. (17) in a cross-sectional study, showed that participants who followed unhealthy dietary patterns such as Western DP had a higher risk for COVID-19 and its related symptoms such as cough, fever, chilling, weakness, myalgia, nausea and vomiting, and sore throat.

Various mechanisms have been proposed that consumption of the Western diet increases the risk of chronic diseases such as fatty liver (27), cardiovascular diseases (28), metabolic syndrome (29), and infectious diseases. Long-term adherence to the Western dietary pattern increases the level of inflammatory factors (30), oxidative stress (31), and lipid peroxidation (32), all of which can be involved in the development of chronic diseases. In this study, unlike most of the previous studies, we considered the meat group as a separate dietary pattern, while in some studies, the high consumption of meats, especially red meat, is considered part of the Western dietary pattern.

Interestingly, the plant-based DP did not show a significant association with underweight, obese, or overweight and contracting COVID-19 in the adjusted models. In contrast to our findings, according to Kim et al.'s (33) population-based case–control study conducted in six countries, there was a significant 73% reduction in the likelihood of experiencing moderate-to-severe COVID-19 severity with a strong adherence to a plant-based DP. In addition, it has been reported in another study that higher adherence to plant-based DP caused a significant improvement against SARS-CoV-2 infection (16). Moreover, some studies indicated that higher adherence to the Mediterranean DP is negatively associated with COVID-19 infection-related deaths (34, 35).

Part of the contrast observed in our study with other studies could be due to the difference in the type of food selected in the plant-based DP and infection rates. Fruits and vegetables provide a wealth of vitamins, folate, fiber, and various phytochemicals such as carotenoids and flavonoids. In addition, whole grains are a rich source of group B

vitamins, which have the ability to strengthen the endogenous antioxidant system (36–38). These compounds possess immune-protective properties due to their anti-inflammatory, antibacterial, and antiviral effects (39–41). It has been reported in a previous study that consuming a minimum of 0.67 daily servings of vegetables (excluding potatoes, whether cooked or raw) has been linked to a reduced risk of contracting COVID-19 (42). According to recent ecological studies on COVID-19, countries that have a significant intake of food rich in antioxidants or foods with anti-angiotensin-converting enzyme (ACE) activity, like raw or fermented cabbage, show a lower rate of COVID-19-related fatalities when compared to other countries (43, 44).

We could not find any significant correlation among meat DP, BMI status, and contracting COVID-19. However, Chen et al. (45) reported that students with a higher BMI consumed more meat products than others during the COVID-19 pandemic. Another study indicated that lower consumption of legumes, vegetables, and fruits and a higher intake of meat, sweets, salty snacks, and fast food are associated with obesity during the COVID-19 lockdown in Poland (46). In a population base study among the participants in the UK, it has been reported that participants in the 4th quartile of processed meat intake had higher odds for COVID-19, but in line with our findings, they did not find any significant correlation between total meat intake and COVID-19 (42). Sausages, bacon, and ham are the primary sources of processed meat consumption in many countries, and they frequently contain salt enriched with nitrates/nitrites (47). This type of meat also contains many preservatives and additives, many of which are harmful to health. Processed meats tend to have higher concentrations of both total and saturated fat (48, 49). Consumption of processed meats, commonly associated with a Western DP, might have a negative impact on immunity (50). Therefore, other dietary habits connected to processed meat intake may be responsible for the observed link with susceptibility to COVID-19.

This finding suggests that although plant-based DP is generally considered a healthy dietary pattern, moderate adherence to it may not have a significant impact on weight status among Iranian adults. Further research is needed to explore the potential factors influencing this result.

As a novelty, this study is the first one to evaluate the association of major dietary patterns with the risk of COVID-19 contracting. Our study has other strong points, including a large and diverse population sample. This evidence can be used to develop preventive measures against COVID-19 contracting and weight gain during the COVID-19 pandemic.

In interpreting the results of our study, it is important to acknowledge some limitations. First, the cross-sectional nature of the study design limits our ability to establish causality between dietary patterns and health outcomes. Second, the self-reported dietary assessment method might introduce recall bias and measurement error. Additionally, the reliance on self-reported weight and height for BMI calculation may introduce inaccuracies in the classification of weight status. Finally, the study sample mainly consisted of female participants, which may limit the generalizability of the findings to the entire Iranian adult population.

In conclusion, our study highlights the associations between major dietary patterns, socioeconomic status, obesity, and contracting COVID-19 among Iranian adults. The Western DP showed unfavorable associations with obesity and increased odds of contracting COVID-19, while the plant-based DP did not show significant associations with weight status or COVID-19 infection in the adjusted models. These findings emphasize the importance of promoting healthy dietary patterns, such as plant-based diets, for preventing obesity and potentially reducing the risk of COVID-19 infection. Future research should focus on longitudinal designs and more diverse populations to further investigate these associations.

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

Studies involving humans were approved by Research Ethics Committee of Shiraz University of Medical sciences (IR. SUMS. REC.1401.344). The current study was conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was provided by participants.

Author contributions

MM: Conceptualization, Investigation, Methodology, Supervision, Writing – original draft. MR: Writing – original draft. AS: Writing – original draft, Investigation. SS: Data curation, Investigation, Methodology. SM: Conceptualization, Formal analysis, Methodology, Writing – original draft, Writing – review & editing.

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Conflict of interest

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

Publisher's note

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Convenience stores: an obesogenic promoter in a metropolitan area of northern Mexico?

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Introduction: The prevalence of obesity in the Mexican school-age (5–11 years old) population increased from 8.9 to 18.1% between 1999 and 2022. Although overweight and obesity (OW+Ob) is a complex and multifactorial phenomenon, alongside its increasing trend, changes in eating patterns as a result of obesogenic environments that promote higher energy intake have been documented. The objective of the present study was to detect possible associations between schools and their proximity to and density of convenience stores in Monterrey, Mexico from 2015 to 2018.

Materials and methods: Anthropometric data were obtained from a subset of measurements of the National Registry of Weight and Height (RNPT) performed in the Monterrey Mexico metropolitan area in 2015 and 2018, and obesity prevalence was computed and classified into quintiles at the school level. Convenience store data were obtained from the National Directory of Economic Units (DNUE). The analyses consisted of densities within 400-800m buffers, distance to the nearest stores, and cartographic visualization of the store's kernel density versus OW+Ob hotspots for both periods.

Results: A total of 175,804 children in 2015 and 175,964 in 2018 belonging to 1,552 elementary schools were included in the study; during this period, OW+Ob prevalence increased from 38.7 to 39.3%, and a directly proportional relationship was found between the quintiles with the higher OW+Ob prevalence and the number of stores for both radii. Hotspots of OW+Ob ranged from 63 to 91 between 2015 and 2018, and it was visually confirmed that such spots were associated with areas with a higher density of convenience stores regardless of socioeconomic conditions.

Conclusion: Although some relationships between the store's proximity/density and OW+Ob could be identified, more research is needed to gather evidence about this. However, due to the trends and the magnitude of the problem, guidelines aimed at limiting or reducing the availability of junk food and sweetened beverages on the school's periphery must be implemented to control the obesogenic environment.

KEYWORDS

childhood obesity, geographic information systems, obesogenic environment, spatial analisis, scholar population

1 Introduction

Overweight and Obesity (OW + Ob) is among the most challenging and urgent problems worldwide. In the last decade, no countries have controlled or even lowered their OW + Ob prevalence, particularly in countries with lower incomes, which report greater increases in this issue (World Obesity Federation Atlas) for the period between 2020 and 2025 on a worldwide scale. An increment is expected in the prevalence of obesity from 10 to 14% and 8 to 10% for boys and girls aged 5–19 years, respectively (1).

In Mexico, the OW + Ob problem was recognized in 2016 and ratified in 2018 as a national public health emergency (2). In the school-age population (5–11 years old), the National Nutrition Survey (ENSANUT) reported an alarming increase between 1999 and 2022, rising from 17.2 to 19.2% for overweight and from 8.3 to 18.1% for obesity (3, 4).

This rising trend in OW + Ob has occurred alongside changes in eating patterns, and Popkin et al. found a shift from home-prepared to processed and packaged foods (5). This is not unique to Mexico; in other countries such as Brazil, the increase in ultra-processed foods (junk food) during the last two decades has also been documented (6).

There is existing literature that demonstrates a link between junk food consumption and OW + Ob as a "cause-effect" relationship. One such study was developed by PAHO in 2015, wherein the authors analyzed data from 14 countries and found a significant relationship between the per-capita sales of these products and the OW + Ob levels. Moreover, in their conclusion, they encourage countries to reduce the consumption of ultra-processed food due to its negative impacts on the nutrition of the population (7). Longitudinal (cohort) studies (8) and literature reviews (9) have confirmed this relationship. Recently, a study conducted in eight countries (including Mexico) documented that increased consumption of ultra-processed foods was associated with higher energy and free sugar intake and stated that this association constituted a potential determinant of obesity in children and adolescents (10).

Numerous studies have been conducted to examine the obesogenic environment from a spatial perspective, some of them in Latin American countries such as Peru and El Salvador (11, 12), which are merely descriptive and aimed at characterizing the spatial distribution of OW + Ob. In the case of seeking spatial interactions between junk food offerings and OW + Ob, research is mainly based on developed countries, and one study conducted in the United Kingdom in 2012 established that areas with greater access to fast food stores also had greater OW + Ob prevalence (13). Similar studies have been carried out in the USA, Netherlands, Germany, Canada, Macao, and New Zealand, finding spatial interactions between food sources and OW + Ob (14–18).

In Mexico, recent studies have approached this issue by conducting a cross-sectional analysis to estimate the indirect association between food store density and OW + Ob among Mexican adolescents, using sugar-sweetened beverage (SSB) consumption as a mediator. Store density was directly associated with SSB consumption but not indirectly associated with OW + Ob mediated by SSB (19). Another study analyzed the change in the retail food environment in Mexican municipalities from 2010 to 2020 and assessed whether these trends were modified by socioeconomic deprivation. It was concluded that there has been a substantial expansion and rapid change in Mexico's food environment, driven mainly by the rise in convenience stores and supermarkets in the most deprived and least urbanized areas (20).

The present study was designed to measure the impact of convenience stores on OW + Ob prevalence in children, which is relevant because some authors have documented that although the home is still a place where a large number of calories is consumed, a significant proportion of the calories consumed (almost one-third) come from eating episodes conducted outside of the house (21, 22). A spatial approach using GIS techniques was proposed, considering that the periphery of schools could be a place where children acquire a significant proportion of their calories.

The objective of the present study was to assess the OW + Ob rates in children who attended schools in Monterrey, Mexico, between 2015 and 2018, and to detect possible associations between schools and their proximity to and density of convenience stores.

2 Materials and methods

The present work is an ecological study whose population was children (6 to 12 years old) from Monterrey, Mexico; the variable of interest was OW + Ob prevalence at the school level and its relation to spatial attributes – proximity and density – of convenience stores, as promoters of obesogenic environments. Considering the school as the unit of analysis, the study is longitudinal (2015–2018) since anthropometric data are present in both periods for the 1,552 schools.

2.1 Data sources

The study area encompasses the Monterrey Metropolitan Area, situated in the northern region of Mexico (25.67° N, 100.308° E), approximately 224 km southwest of the United States border in Laredo, Texas. As of the 2020 census, this region comprises 16 municipalities, analogous to county-level administrative units, with a total population of 5.3 million inhabitants. The economic landscape of the area is predominantly shaped by industrial activities, with a particular emphasis on key sectors such as beer, steel, and concrete production and the manufacture of cars and machinery.

Anthropometric data were obtained from the National Registry of Weight and Height (RNPT in Spanish) (23), a strategy implemented in Mexico to evaluate the nutritional status of children in elementary schools. Its main objective is to identify nutritional disorders such as malnutrition, overweight, and obesity. This initiative is jointly managed by the Health and Education Ministries (SSA and SEP in Spanish) and the National and State Systems for Integral Family Development (DIF) and is technically overseen by the National Nutrition and Medical Sciences Institute (INCMNSZ). This collaboration includes periodic visits to schools by trained personnel to conduct anthropometric measurements (24, 25). From these data, a subset consisting of 1,552 Elementary schools belonging to the urban areas of the municipalities (a county-like territorial division) conforms to the Metropolitan Area of Monterrey, as defined by the National Statistics Geography and Informatics Institute (INEGI) in its Metropolitan Areas Catalog (26). This dataset had an OW + Ob prevalence for each school of 454,217 and 447,792 children in 2015 and 2018, respectively. Nutritional status was defined using the WHO BMI/age indicator, defining overweight as individuals with a z-score

greater than +1 S.D. and obesity as those with a z-score > +2 S. D (27). To include socioeconomic data on the schools, a social exclusion index (SEI) variable built for the 2020 National Population and Household Census (28) was included, and the smallest geographic unit (suburb) was used to obtain the maximal resolution for characterizing the schools.

Convenience store data were extracted from the National Directory of Economic Units (DNUE) of INEGI (29), which includes information regarding all the businesses across the country, such as the type of activity, company name, number of employees, opening date, and, most important for the purposes of the present study, latitude and longitude. The final store dataset was constructed by filtering the DNUE database for the following criteria: "Convenience stores" as economic activity code, "OXXO" or "7-11" as company name, and – as in the case of the schools – being located in the urban areas of the Metropolitan Area of Monterrey. In 2015 and 2018, 1,394 and 1979 convenience stores were located, respectively (585 new stores were opened in the metropolitan area during this period).

2.2 Spatial and statistical analyses

All previously described data were clipped to the suburb polygon layer that included the SEI; quintiles for OW + Ob and the index were recoded to create categorical variables using QGIS 3.282 and SPSS 25, respectively (30, 31). Buffers (influence areas) of 400 and 800 m were constructed around every school using QGIS; these distances represent, in round numbers, walking times of 5 and 10 min, respectively, for an average pedestrian speed of 1.25 m/s (32).

As the geographic layers were not locally projected, we used the Python equidistance buffer plugin to generate buffer polygons with a precision of ±2 m (33). Once the polygons were generated, we used the QGIS *count points in the polygon* geoprocessing tool to determine the number of convenience stores within 400 m and 800 m radii from each school, which allowed us to estimate the density of such stores around the school-age population. Additionally, to establish ease of access to the stores from the schools, we computed the Euclidean distance from every school to its nearest store using the *distance to the nearest hub* geoprocessing tool. Once the spatial variables were calculated, cross-tabulations and scatter plots were performed to analyze the interaction between the density and ease of access of the population to stores with OW + Ob prevalence.

Additionally, to evaluate the impact of SEI characteristics on OW + Ob, a bootstrap analysis of 1,000 samples was performed to calculate the 95% confidence intervals for OW + Ob prevalence for every SEI quintile and determine whether the differences could be due to this and not necessarily because of the proximity and density of the convenience stores. Bootstrap analysis was performed using the SPSS v. 25.0, which uses the computer's calculation power to create a large number (1,000 in this case) of subsamples of the actual data to calculate a standard error, thus obtaining a confidence interval of the variable of interest (OW + Ob prevalence) (34).

Finally, the last analysis consisted of generating a raster Kernel Density Estimation (KDE) heatmap for the stores in 2015 and 2018, using the QGIS *KDE* geoprocessing tool with an Epanechnikov kernel shape, which is the most efficient and suitable for our data (35), and a bandwidth of 0.24° (degrees), defined by Scott's Rule for Bandwidth Selection (36) calculated for 2015 store data. The rasters corresponding to the density of the stores for the 2 years were clipped to the metropolitan area of Monterrey and cartographically represented with a pseudo-band color ramp for their visualization. Along with the previously described process, a *Getis*-Ord Gi* hotspot analysis was performed in ArcGIS desktop 3.0.3 (37) with the OW + Ob prevalence as the input field. This spatial statistical procedure allowed us to identify, with a significance level (90, 95, and 99%), those schools with a prevalence remarkably greater than their neighbors (38), and the resulting layer of this process was also included in the map along with the store density to visualize the relationship between them. This was performed for 2015 and 2018; therefore, changes over time can be observed when comparing the two maps.

3 Results

3.1 Overweight and obesity behaviors in schools

The number of children suffering from OW + Ob in the weight and height registry was 175,804 and 175,964 in 2015 and 2018, respectively, which are expressed as prevalence corresponding to 38.7 and 39.3%, respectively, which also modifies the Q4 and Q5 quintiles by year. The results are presented in Table 1.

3.2 Social exclusion index and its impact on OW + OB

To assess whether variations in socioeconomic status alone could account for differences in OW + Ob prevalence among schools, a bootstrap analysis of mean prevalence and 95% confidence intervals (CI) was conducted based on Socioeconomic Index (SEI) quintiles. The results, depicted in Figure 1, indicate that although Q4 consistently exhibited a higher prevalence in both years and the overall prevalence increased from the first to the second year of the study, no statistically significant differences were evident between the quintiles in 2015 and 2018 (with overlapping CIs).

TABLE 1 General characteristics of the elementary schools, Monterrey Metropolitan Area Mexico 2015–2018.

	2015	2018
Number of Schools	1,552	1,552
N total Children	454,218	447,792
N OW + Ob	175,804	175,964
Prevalence OW + Ob	38.70	39.30
OW + Ob Quintiles, N (interval)		
Q1	*n* = 310 (< 32.3)	*n* = 310 (<32.3)
Q2	*n* = 310 (32.3, 36.9)	*n* = 311 (32.3, 36.9)
Q3	*n* = 311 (36.9, 40.6)	*n* = 310 (36.9, 41.0)
Q4	*n* = 311 (40.6, 44.8)	*n* = 311 (41.0, 46.5)
Q5	*n* = 310 (>44.8)	*n* = 310 (>46.5)

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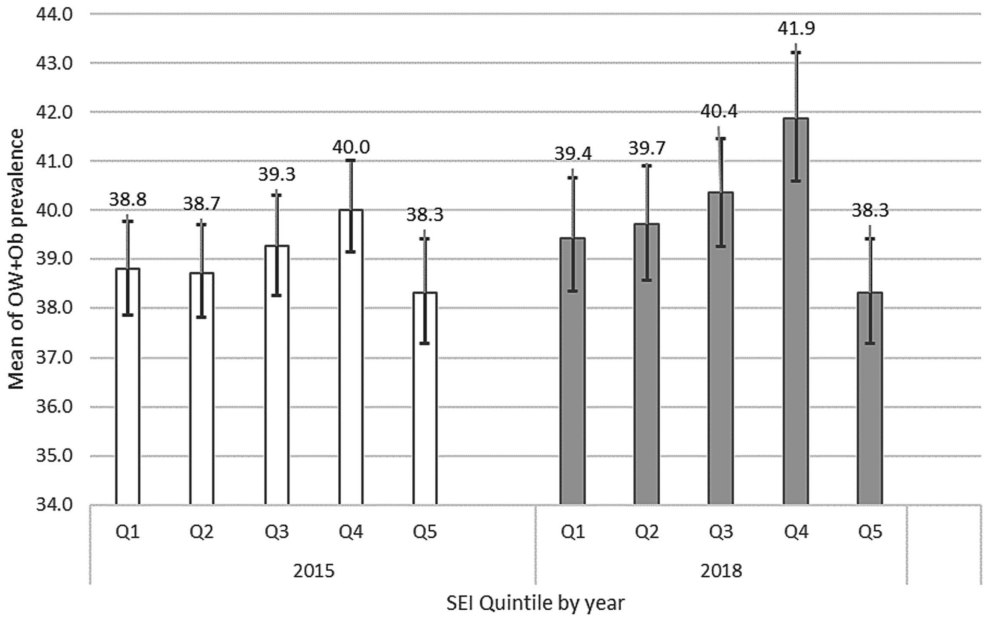

FIGURE 1
Mean and 95%CI of OW + Ob prevalence in schools in Monterrey Mexico Metropolitan Area by Social Economic Index (SEI) quintile 2015–2018.

3.3 Convenience store behavior between 2015 and 2018

Convenience stores registered in the National Directory of Economic Units (DNUE) in the geographical area of the study grew from 1,394 to 1979 in the 2015–18 period, which corresponds to a 42% relative increase in the number of stores in the cited period. Another way to describe this growth is that from 2015 to 2018, a new store was opened every 2.5 days in the Monterrey Metropolitan Area.

3.4 The number of stores and their impact on OW + Ob

Table 2 shows the mean and SD of the number of convenience stores in the OW + Ob quintile for the 2 years of the present study. The first aspect that is clear is that regardless of the store's density, in Q4 and Q5, OW + Ob increased between 2015 and 2018, showing a greater lower limit value in the most recent period (40.6 to 41.0 and 44.8 to 46.6, respectively). In other words, in the same proportion of the Q4 and Q5 quintiles, the actual prevalence is greater. Another interesting finding is that, between 2015 and 2018, in all quintiles and for both radii, the mean number of stores increased. If we consider that schools are spatially fixed, this necessarily indicates that a significant number of stores opened in the school's proximity during this time. A greater increment can be seen within the 400 m radius for Q1 schools, which increased from 0.82 schools to 1.27 (this corresponds to a 54% relative increment).

The relationship between the OW + Ob quintile and the number of stores in the two radii is shown in Figure 2A which graphically shows two trends: the OW + Ob quintile increases with the number of stores and, as shown in Table 2, the OW + Ob quintile and the store number increased between 2015 and 2018. The same Figure 2B shows an example of a school with 14 convenience stores within its 400 m radius and the remarkably high number of 46 within its 800 m radius.

The results show that, in all cases, a greater number of stores were present in the higher OW + Ob quintiles; moreover, a consistent trend was found as the quintile increased (perfect ladder view in Figure 2). It was quite concerning that by 2018, the children of the more prevalent OW + Ob schools could reach more than seven stores by walking for 10 min and at least two stores by walking for only 5 minutes. Another finding of this analysis was that over 3 years, all schools, regardless of their OW + Ob status, faced an increase in the density of convenience stores on their periphery.

3.5 Distance to the nearest convenience store and its impact on OW + Ob

Regarding the influence of the proximity of convenience stores and its effect on OW + Ob prevalence, Figure 3 shows a decreasing trend of the mean distance to the nearest store as the prevalence increases for 2015 and 2018; in other words, the schools in which the OW + Ob is greater have, on average, a convenience store nearer than those with lower prevalences (182 m for 2015 and 120 m for 2018). It is also clear that between 2015 and 2018, for all schools, regardless of the OW + Ob level, stores were actually nearer.

In this sense, we also found that by 2018, the average distance for the schools with the highest prevalence was only 338 m, but even for those with a lower prevalence, the average distance was 458 m, which indicates that in all cases, convenience stores and their food were near the schools. In this analysis, we confirmed the increase in the number of convenience store trends found in the density computations, which can be seen in Figure 3, in which the line of 2018 is well below the 2015 one, indicating that convenience stores and junk food offerings

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TABLE 2 Mean and standard deviation of the number of convenience stores around the elementary schools within 400 m and 800 m radii by OW + Ob quintile and year in Monterrey Mexico Metropolitan Area 2015–2018.

2015										
	Q1		Q2		Q3		Q4		Q5	
	N = 310 OW + Ob % (< 32.3)		*N* = 310 OW + Ob % (≥32.3–<36.9)		*N* = 311 OW + Ob % (≥36.9–<40.6)		*N* = 311 OW + Ob % (≥40.6– <44.8)		*N* = 310 OW + Ob % (≥44.8)	
	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
400 m radius	0.82	1.02	1.02	1.28	1.14	1.44	1.15	1.79	1.27	1.53
800 m radius	3.1	3.08	3.7	3.41	4.27	4.14	4.46	4.8	5.16	4.55
2018										
	Q1		Q2		Q3		Q4		Q5	
	N = 310 OW+ Ob % (< 32.3)		*N* =311 OW+Ob % (≥32.3–<36.9)		*N* =310 OOW+Ob % (≥36.9–<41.0)		*N* =311 OW+Ob % (≥41.0–<46.6)		*N* =310 OW+Ob % (≥46.6)	
	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
400 m radius	1.27	1.22	1.4	1.54	1.59	1.87	1.64	1.47	1.96	2.36
800 m radius	4.34	3.12	5.34	4.63	6.24	5.64	6.32	3.9	7.06	6.34

became nearer and thereby easier and faster to access during this period.

Another way to visualize the relationship between OW + Ob and distance to the nearest store is by plotting the schools as data hotspots using the school-store distance as the X-axis and the OW + Ob prevalence as the Y-axis and making a linear regression of the dataset, which can be seen for both years in Figure 4, where a negative slope of the linear fit can be seen and is confirmed by the negative β (beta) value, indicating that a trend for a lower prevalence of OW + Ob occurs as the schools have their nearest school at a greater distance. When viewing the same data not aggregated in quintiles but as continuous hotspots (Figure 4), one can confirm the cited behavior by inspecting the plot and linear regression negative coefficients that, again, not only confirm but also prove with statistical significance the inverse relationship between the distance to the nearest store and OW + Ob prevalence.

3.6 Cartographical visualization of OW + Ob and store density

Figure 5 shows two maps of the Metropolitan Area of Monterrey for 2015 (Figure 5A) and 2018 (Figure 5B), in which a raster layer in the background corresponding to the kernel density of convenience stores is presented as a white–red color ramp, where the more intense red color represents areas with a high density of stores. Another information layer presented as size-scaled hotspots shows those schools that were detected by the *Getis*-Ord Gi*algorithm as OW + Ob *hotspots*; in other words, the schools that presented a much higher prevalence of OW + Ob when compared to their neighbors. Point size indicates the confidence level of the categorization as a *hotspot* (90, 95, or 99%).

Looking at the maps side by side, it is clear that (regardless of the OW + Ob component) the store density grew from 2015 to 2018; it can be seen that (b) shows a more intense red background in the central area of the city and a slight increase in the periphery when compared to (a), which is a visual confirmation of the findings presented in Table 2. Regarding the hotspots, in (a), there are 63, whereas in (b), this cipher increased to 91, being an important proportion of such hotspots of 95–99% significance. It is also important to point out that in the central area of the city where the store density is greater, an important number of OW + Ob hotspots appeared over 3 years. Overall, the maps displayed a general concordance between the store's denser areas and the OW + Ob hotspots for both years, but this was more evident for the most recent period.

The store density and OW + Ob *Getis*-Ord Gi* Hotspots maps allow not only the visualization of the spatial distribution of the two variables but also the changes over time. Focusing on store density, it is clear that they are more abundant in the center of the metropolitan area and that they increased in number between 2015 and 2018 in the same center and also toward the periphery. The maps also show that in the areas of higher store density in the center and north, there are more schools with high OW + Ob, and the presence and significance levels of the hotspots increased between 2015 and 2018. It is also shown, in a more subtle way, that some new hotspots appeared in the periphery and some had an increased significance level.

4 Discussion and conclusions

Monterrey Mexico is a metropolitan area that belongs to the Nuevo León State, where, in the 2022 National Continuous Nutrition Survey, there was an OW + Ob prevalence of 34.2% (39), whereas the National was 37.1% (4). These data are strongly consistent with the prevalences found by us in 2015 and 2018 (Table 1). This region, especially the city, is highly industrialized, and its cultural and social patterns are strongly influenced by its proximity to the United States. One of the results of such an influence can be found in current eating behaviors, which have shifted from traditional food to fast food and energy-dense food (40). This is also where the main chain of convenience stores (OXXO) opened its first business more than 46 years ago (41, 42). This metropolitan area is also the second most

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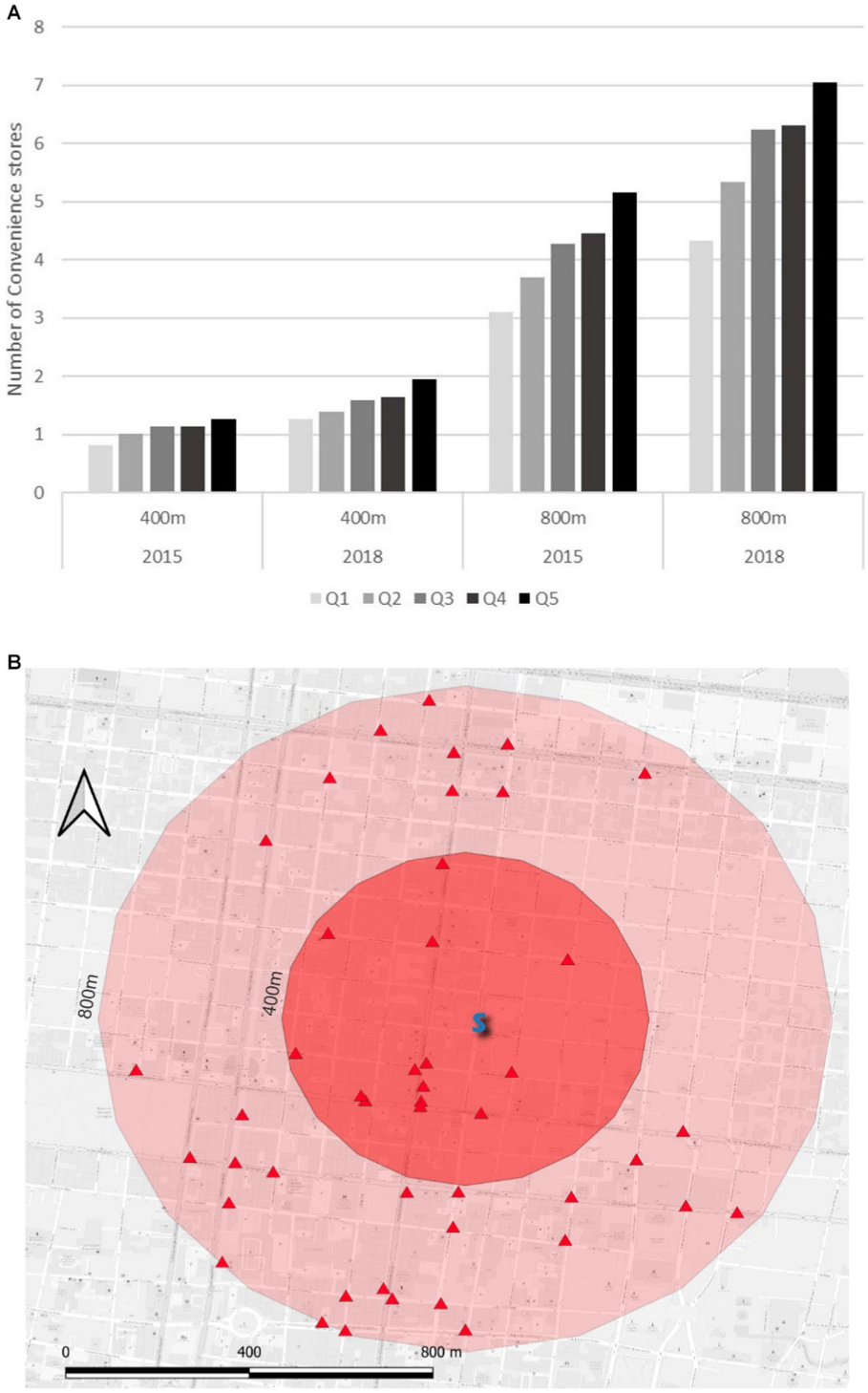

FIGURE 2
(A) Mean of the number of convenience stores around the elementary schools within 400 m and 800 m radii by OW + Ob quintile and year in Monterrey Mexico Metropolitan Area 2015–2018. **(B)** Extract of the actual data showing a school (S) surrounded by 14 and 46 convenience stores (Red triangles) in radii of 400 m and 800 m, respectively.

populated in the country (43), and all the previous factors make this place suitable for conducting the analyses of the present work.

It is well known that OW + Ob is a complex phenomenon that cannot be reduced to one or only a few factors. However, one of the main questions that could be addressed in this study is whether the stores themselves are the influencing factors for OW + Ob development or whether the mere presence of the stores in some places reflects the intrinsic economic characteristics of the regions inside the metropolitan area, and whether such characteristics are what finally determine or at least have an impact on OW + Ob. To control this

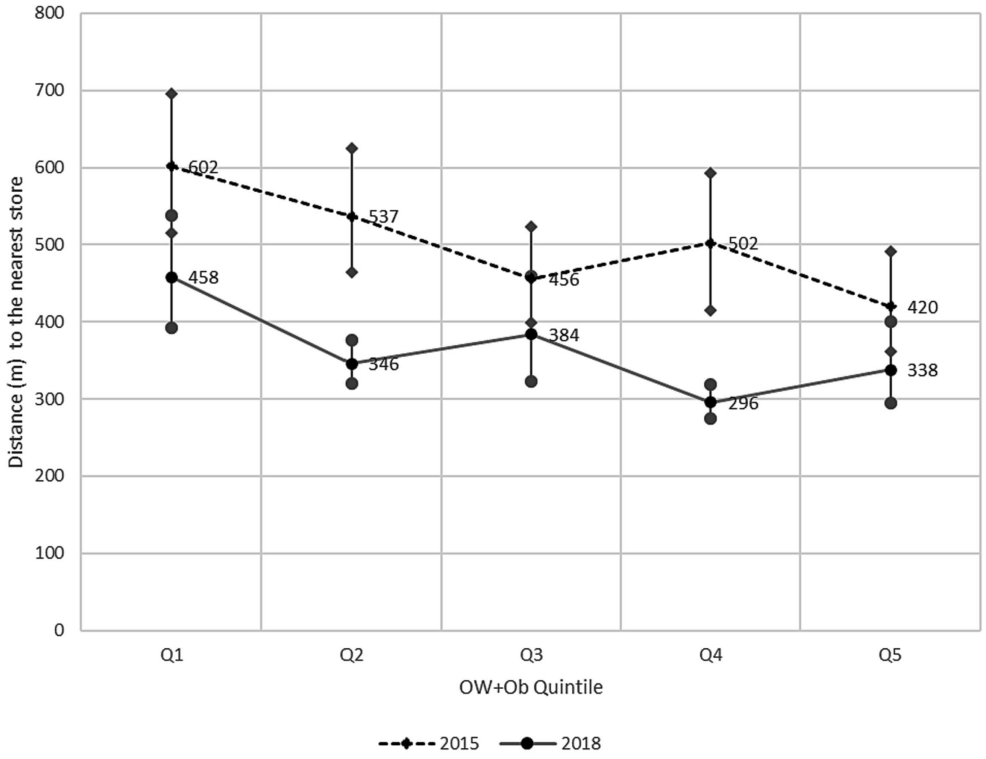

FIGURE 3
Mean Euclidean distance (m) and 95%CI between schools and the nearest convenience store by OW + Ob quintile, Monterrey Mexico Metropolitan Area 2015–2018.

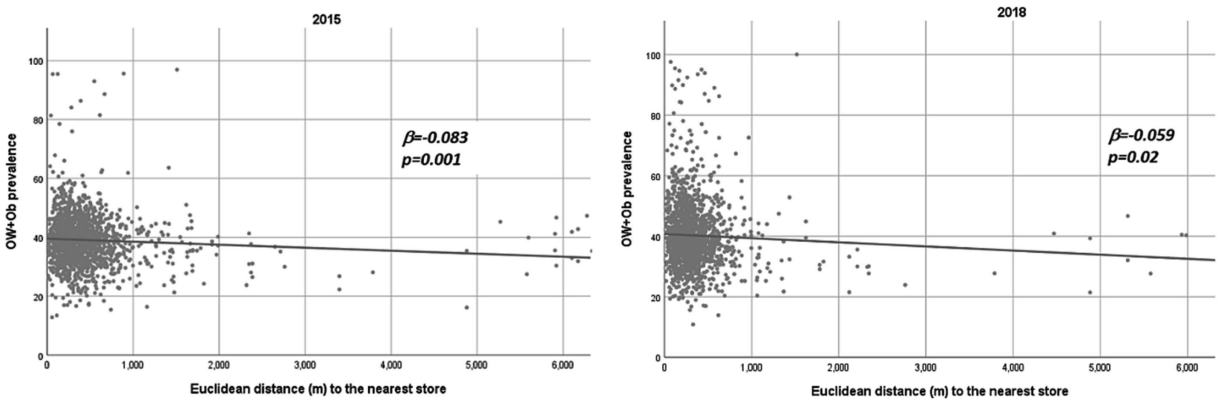

FIGURE 4
Scatterplot, linear fit, a negative beta value of *p* of the distance to the nearest convenience store (trimmed to 6 km) vs. OW + Ob prevalence in Monterrey Mexico Metropolitan Area 2015–2018.

issue, as the first step of the study, we calculated the distribution of OW + Ob using an SEI, finding no significative differences between the groups; this led us to discard the idea that inside the Monterrey Metropolitan area, the problem of OW + Ob in the children was determined mainly by socio-economic characteristics.

Approaching the research question from a spatial perspective, the first influencing factor from the stores that were studied was their density around the schools within 400 m and 800 m radii, corresponding to walking times of 5 and 10 min, respectively (32). This was important because we wanted to determine the number of junk/fast food offering hotspots available within those two radii around the schools. In other words, we considered these variables as a measure of the magnitude of this kind of food availability for all children who attended schools.

The other spatial property that we studied in the school–store interactions was nearness, which can be interpreted as the ease of access to junk/fast food by the children. These results are consistent with the density. The use of Euclidean distance constitutes the first approach; however, more sophisticated methods, such as distances over street networks (service areas) could be used in future research.

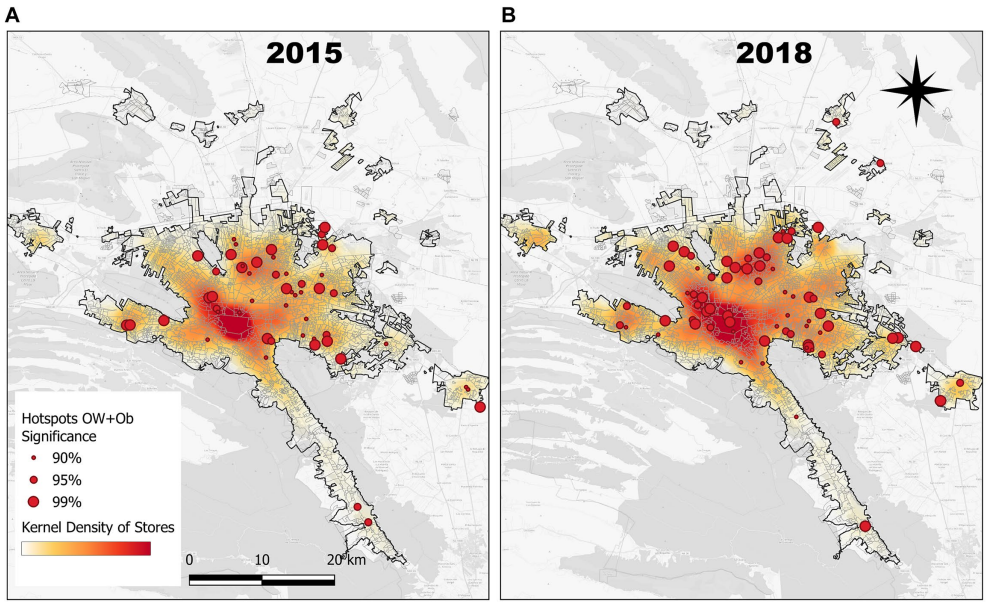

FIGURE 5
Getis-Ord Gi* Hotspots and significance level of OW + Ob in elementary school children in comparison to kernel density of convenience stores in Monterrey Metropolitan Area, Mexico in **(A)** 2015 and **(B)** 2018.

When viewing both maps side-by-side, it seems that the store presence and the obesity hotspots spread over time, increasing in the center and expanding these phenomena to the edges of the Metropolitan Area. Again, these analyses correspond to the first approach but are susceptible to being enhanced in many ways: updating the data (schools and stores) to more recent sets to confirm the cartographic findings, performing other analyses (i.e., map algebra) using density rasters, and perhaps replicating these same methods in other regions of the country. Although we cannot state that the store density, distance, and location are directly responsible for the OW + Ob condition of children attending school, we found interesting and consistent facts and trends that may point toward this. Although there are few spatial analyses of this issue in Mexico, the obtained results are consistent with those found by Zavala et al. in 2021 (44), but in the case of the present work, on a much larger scale (metropolitan area) and over a lapse of time. Furthermore, these results are consistent with numerous studies on urban areas in developed countries (45, 46).

According to a systematic review by Matsusaki et al. (47), a positive association exists between the nearness of fast food selling hotspots to schools and OW + Ob prevalence in children from Latin, Anglo-Saxon, and Afro-American ethnic groups from different continents, which was observed in all school degrees, but the authors remarked that this could be more important in younger individuals.

Hughey and collaborators (48) proposed a kernel density estimator methodology for an adolescent population to group the obesogenic environment components in the proximity of neighborhoods, such as processed food selling hotspots and fast food restaurants, and, on the other hand, positive elements such as parks and green/recreative areas used for physical activity. The authors recognize all of these places as relevant to the research because of the large amount of time spent by the individuals there.

In a similar study, Buszkiewicz et al. (49) established a relationship between the obesogenic environment and the presence of OW + Ob according to the place of residence. Their main findings agree with our work by showing that at smaller distances between households and junk food selling hotspots, OW + Ob prevalence increases. These results reinforce the idea that variables related to the food environment have an impact on weight gain.

The strengths of this study include its use of a large amount of data (census) on a homogeneous population (school-attending children), which results in robust OW + Ob ciphers, along with consistent and complete spatial information about convenience stores. This, in the context of a metropolitan area that does not have the enormous economic/social inequities present in other regions, allowed for the removal of some of the "noise" and facilitated a focus on the impact of the stores on OW + Ob. On the other hand, the study's weakness consists of the multifactorial complexity of the problem, which cannot be reduced only to junk food consumption and, thus, the stores' geographical locations. Another limitation could lie in the simplicity of some of the methods used (buffers and Euclidean distance), which could certainly be improved in future research. Despite the fact that it is not possible to confirm that all of the junk food and sweetened beverages come from convenience stores, it remains a hard fact that the number of such businesses has grown in recent years, reducing the distance of access to ultra-processed foods. This rapid spread of stores could not be explained without having significant sales, and in contrast to the supermarkets that are centralized meeting hotspots, these stores' strategies consist of "getting nearer" to the customers and readily offering the products.

In conclusion, investigating the relationship between convenience stores and their role in obesity in school-aged children, which is a growing global public health concern, requires an understanding of the potential role of convenience stores in contributing to this problem to support interventions and policies aimed at mitigating its impact, along with the use of spatial analysis, which provides valuable information for public health interventions

and urban planning and aids in tailoring interventions to specific geographic areas and formulating policy to promote healthier environments for children to grow and develop in. Considering this, it is important to conduct more research on this topic in Mexico using more recent datasets and more sophisticated methods to identify the precise role and possible negative impacts of convenience stores on the health of the population. It is necessary to promote guidelines that restrict the availability of junk food and sugar-sweetened beverages in schools.

Public policies aimed at effectively coping with this problem must include strategies for dealing with obesogenic environments. This implies limiting the number of convenience stores around schools and, at the same time, promoting the availability of healthy foods.

Data availability statement

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

Author contributions

MÁ: Writing – original draft, Investigation, Formal analysis, Conceptualization. TS: Writing – original draft, Supervision, Formal analysis, Conceptualization, Writing – review & editing. MD: Methodology, Data curation, Writing – review & editing. AC: Writing – review & editing, Project administration, Investigation, Conceptualization. AÁ: Writing – review & editing, Project administration, Investigation.

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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 pro-inflammatory diet with increased risk of gallstone disease: a cross-sectional study of NHANES January 2017–March 2020

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Background and aim: Gallstone disease (GSD) is a major public health problem worldwide. The dietary inflammatory index (DII) and the energy-adjusted DII (E-DII) have been used to describe dietary inflammatory potential. The current study sought to investigate the pro-inflammatory role of diet on GSD among outpatients in the United States.

Methods: Cross-sectional data from 7,334 individuals older than 20 years who participated in the National Health and Nutrition Examination Survey (NHANES) from January 2017 to March 2020 were obtained. The relationship between GSD and DII was assessed using self-reported data. An association between DII and the risk of GSD was determined using sample-weighted logistic regression and restricted cubic splines (RCS). Subgroup analyzes were conducted to assess the interaction between DII and related factors. Sensitivity analysis was further used to confirm the stability of the relationship. To control for the effect of total energy intake, E-DII was calculated and analyzed.

Results: A total of 10.5% of the study participants had GSD. The DII ranged from −5.52 to 5.51, and the median DII was significantly higher for participants with GSD than those without (1.68 vs. 1.23, $p < 0.001$). There was a significant and stable positive relationship between DII and GSD in adjusted models (OR 1.10, 95% CI 1.00–1.20). In the fully adjusted model, subjects with DII scores in the highest tertile were more likely to have GSD than those in the lowest tertile (OR 1.52, 95% CI 1.19–1.93). An apparent dose–response association between DII and GSD was detected. The association between E-DII and GSD remained stable.

Conclusion: Higher DII/E-DII scores linked to the intake of a pro-inflammatory diet were positively associated with a higher risk of GSD. These findings suggest that pro-inflammatory dietary patterns can promote the formation of gallstones.

KEYWORDS

National Health and Nutrition Examination Survey (NHANES), gallstone disease, pro-inflammatory diet, dietary inflammatory index (DII), population-based study

1 Introduction

Gallstone disease (GSD) is common in the general population and its incidence has increased in recent years. The prevalence rate of GSD among adults in Europe, the United States, and other developed countries is approximately 10–15% (1). More than 20% of patients with GSD will develop symptoms, including colic or infection, during their lifetime (2). The direct and indirect costs of GSD are a leading cause of gastrointestinal disease-related hospitalization, resulting in a significant economic burden on families and society (3, 4).

Based on their composition, gallstones can be classified into cholesterol stones, which account for >90% of all gallstones, and other stones represented by black and brown pigments (2). Gallstone formation is shown to be multifactorial (1, 5) and risk factors include age, ethnicity, genetics, female gender, and lifestyle. GSD is also linked to insulin resistance, obesity, metabolic syndrome, and diabetes, of which diet plays a vital role. Studies indicate that a high intake of cholesterol, fatty acids, carbohydrates, and legumes can increase the risk of GSD. In contrast, the consumption of unsaturated fat, coffee, fiber, ascorbic acid (vitamin C), and calcium may lower the risk of this condition (5, 6). The specific dietary pattern that contributes to the development of GSD remains poorly understood, however.

It is well established that inflammation plays an essential role in the formation of gallstones (7–9). Inflammatory processes can affect cholesterol and bile acid metabolism by changing the metabolism of protein and fat, increasing the level of bile salt, and promoting the formation of gallstones (9). While GSD is linked to inflammation, evidence on whether a pro-inflammatory diet increases the risk of GSD remains limited.

Several nutritional indices such as Diet Inflammatory Index (DII), Dietary Antioxidant Index (DAI), Dietary Phytochemical Index (DPI), Nutrition Index (NI), dietary insulin index, Dietary Approaches to Stop Hypertension (DASH), and Mediterranean diet (MED) were reported to evaluate the effect of diet on chronic diseases (10–16). Among these evaluation indicators, the DII was originally proposed in 2009 and recalculated in 2014 to quantify the potential inflammatory level of individual dietary components by giving them a score ranging from maximum anti-inflammatory to maximum pro-inflammatory (17, 18). In addition, to adjust the influence of total energy intake, the energy-adjusted DII (E-DII) was developed (19). The DII/E-DII index has been verified by several inflammatory biomarkers, including C-reactive protein (CRP), tumor necrosis factor (TNF-a), and interleukin-I (IL). In the past decade, this index has been widely used to explore the relationship between anti- or pro-inflammatory diets and disease morbidity and mortality (13, 14, 16, 20–22). However, only a few studies have explored the specific relationship between an inflammatory diet and the development of GSD.

The current study sought to assess the cross-sectional relationship between DII/E-DII and GSD using data from the National Health and Nutrition and Examination Surveys (NHANES). We found that exposure to a pro-inflammatory diet would increase the risk of GSD.

2 Methods

2.1 Data sources

Data were obtained from individuals who participated in the National Health and Nutrition Examination Survey (NHANES) from January 2017 to March 2020. NHANES is a stratified multi-stage sampling survey conducted by the National Center for Health Statistics (NCHS) and designed to assess the health and nutrition status of Americans. The survey, which includes a family interview and a health examination, has been approved by the NCHS research ethics review board since 1999.

The current study included 15,560 individuals who participated in NHANES from January 2017–March 2020. After excluding individuals <20 years of age ($n = 6{,}328$), those missing data on GSD ($n = 22$), DII ($n = 1{,}516$), and covariates ($n = 360$), 7,334 participants were included in the final dataset for DII analysis. Extreme values of energy intake, including <800 kcal/d or >4,200 kcal/d for men and <600 kcal/d or >3,500 kcal/d for women, were excluded when calculating the E-DII (n = 447) (23, 24). The inclusion and exclusion processes are shown in Figure 1.

2.2 Definition of GSD

The presence or absence of GSD is dependent on a patient's self-report response to the question: "Has a doctor or other health professional ever told you that you had gallstones?"

2.3 Dietary inflammation index calculation

The DII is a potential tool to assess the anti- or pro-inflammatory quality of an individual's diet by calculating the total potential inflammatory level of the dietary components consumed. This study calculated the exact nutritional intake of each participant using the nutritional intake information that was collected on day 1 and stored in the NHANES diet database. A total of 28 nutrients, including alcohol, vitamin A/B1/B2/B6/B12/C/D/E, β-carotene, caffeine, carbohydrate, cholesterol, energy, total fat, fiber, folic acid, iron, magnesium, zinc, selenium, monounsaturated fatty acids, niacin, n-3 fatty acids, n-6 fatty acids, protein, polyunsaturated fatty acids, and saturated fat, were used to determine the DII score in this study (Supplementary Table S2).

The specific calculation scheme of DII referred to the research of Shivappa et al. (18). Firstly, the dietary consumption information was compared to a worldwide daily intake database. The Z-score of each nutrient component was calculated based on the standard global daily mean intake and deviation (SD) values. Then it was transformed into a centered percentile, and multiplied by the respective overall inflammatory effect score to obtain the food parameter-specific DII score. Finally, all of the food parameter-specific DII scores were summated to gain an overall DII score for each individual. A higher DII score indicates that a diet is more pro-inflammatory in nature while a lower DII score indicates that a diet is more anti-inflammatory.

Accounting for the effect of total energy intake, density method was used to make energy adjustments for food and nutrient intake so

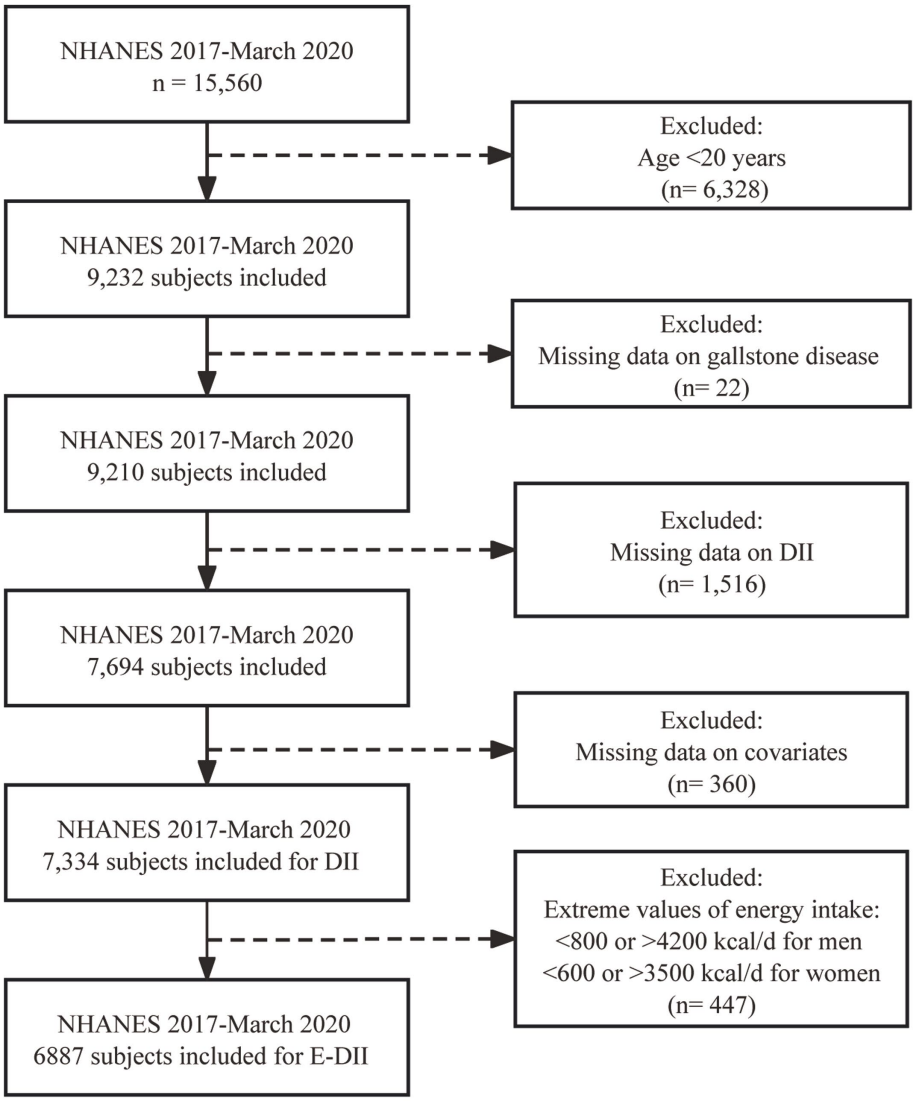

FIGURE 1
Flow diagram of study participant enrollment.

that each parameter was expressed per thousand kilocalories (1,000 kcal). Then, the steps similar to the DII calculation were repeated to obtain E-DII but using an energy-adjusted global database (19).

2.4 Covariate assessment

Based on prior studies (1, 2, 25, 26), several potential confounding variables were selected as covariates for the analysis. The following demographic information was obtained: age (<40, 40–60, >60 years), gender (male or female), and race (non-Hispanic Black, non-Hispanic White, Mexican American, Other Hispanic, and Other). Body mass index (BMI) was calculated using height and weight data obtained during the NHANES mobile physical examination. Patients with a BMI >30 were categorized as obese while those ≤30 were categorized as non-obese. Participants were considered sedentary if they had ≥600 min of sedentary activity in a typical day and categorized as non-sedentary if they had <600 min/d of sedentary activity. Smoking and drinking status were classified according to the participants' self-reported questionnaire responses. A respondent was defined as a non-smoker if they had smoked <100 cigarettes in their lifetime, and defined as a former smoker if they had smoked ≥100 cigarettes in their lifetime but did not smoke currently. Individuals who reported still smoking every day or on some days were defined as current smokers (27). Participants were further categorized as non-drinkers, light drinkers (1 to <30 drinks/month), or heavy drinkers (≥30 drinks/month). Diabetes, fatty liver, thyroid disease, and history of cancer were defined based on self-reported responses or confirmed clinical diagnoses (28–30).

2.5 Statistical analysis

Sample design and weights for the complex multi-stage cluster survey were considered using the Centers for Disease Control and

Prevention (CDC) guidelines for the analysis of NHANES data. Participant characteristics were presented as means with standard deviation, SD for continuous variables, and the unweighted number of participants and weighted percentages (%) for categorical variables. Continuous variables were compared among groups using the Wilcoxon rank-sum test for complex survey samples and categorical variables were compared among groups using a weighted Chi-square test.

Sample-weighted logistic regression models were used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) were used to measure associations between DII/E-DII scores and GSD. Four models were used after analyzing and adjusting for confounding factors. Model 1 represented the unadjusted crude model, model 2 was adjusted for sociodemographic variables (age group, sex, race, and ethnicity), and model 3 was based on model 2 and further adjusted for health-related and lifestyle factors, including sedentary activity, obesity, alcohol drinking status, smoking status, fatty liver, diabetes, and thyroid disease. To avoid over-adjustment, metabolic syndrome was defined as the presence of obesity, fatty liver, and/or diabetes (31). Model 4 was based on model 2 and further adjusted for sedentary activity, alcohol drinking status, smoking status, thyroid disease, and metabolic syndrome.

Restricted cubic splines were used to assess the dose–response relationship between GSD and DII scores, using four knots at prespecified locations according to the 5th, 35th, 65th, and 95th DII score percentiles. Subgroup analyzes were conducted using stratified multivariate regression analysis to assess the interaction between DII scores and specific covariates. p values for interactions across subgroups were calculated using the likelihood ratio test.

Given that the inclusion of the element of alcohol in the DII calculation, and data on alcohol consumption ($n = 205$) accounted for the largest proportion of the population participants with missing covariates ($n = 360$), sensitivity analyzes were performed to assess the robustness of the associations between DII and GSD after excluding alcohol intake ($n = 7{,}539$).

All statistical analyzes were performed with R software version 4.2.3 (R Core Team, Vienna, Austria. http://www.r-project.org/) using the survey package, version 4.1–1. All statistical tests were two-sided, and significance was considered at $p < 0.05$.

3 Results

3.1 Participant characteristics

A total of 7,334 participants were included in the study analyzes for DII. The general characteristics of the participants with and without GSD are shown in Table 1. Of these, 771 and 6,563 participants did and did not have GSD, respectively, for a prevalence of 10.5%. The DII scores ranged from −5.52 (highly anti-inflammatory) to +5.51 (highly pro-inflammatory). Participants with GSD had a significantly higher DII score than those without (1.68 vs. 1.23, $p < 0.001$, Table 2). Participants with GSD were older, more likely to be female, and had a higher BMI value than those without (all $p < 0.001$). Sedentary activity, alcohol drinking status, smoking status, fatty liver, diabetes, and thyroid disease were also significantly associated with GSD (all $p < 0.05$).

In further, the E-DII scores ranged from −5.25 to +5.33. There was no statistically significant difference of E-DII score between the two groups in the univariate analysis (Supplementary Table S1).

3.2 Association between DII/E-DII score and GSD risk

The association between the DII/E-DII score and the risk of GSD was determined using a sample-weighted multivariable logistic regression model (Table 3) and remained stable in each adjusted model. A higher DII score was associated with an increased risk of GSD (model 1, OR 1.22, 95% CI 1.12–1.32; model 2, OR 1.16, 95% CI 1.06–1.27; model 3, OR 1.10, 95% CI 1.00–1.20; model 4, OR 1.12, 95% CI 1.02–1.22). After full adjustment (model III), DII was associated with the presence of gallstones (OR 1.10, 95% CI 1.00–1.20). This association remained statistically significant after DII scores were grouped into tertiles. Subjects with the highest tertile DII scores had a higher risk of GSD than those with the lowest tertile DII scores (OR 1.52, 95% CI 1.19–1.93). The data also indicated that there was a linear relationship between DII scores and GSD (p for trend <0.05). Furthermore, multivariable-adjusted restricted cubic spline regression demonstrated a significant dose–response relationship between DII scores and the risk of GSD (Figure 2).

Similar results of E-DII with GSD were obtained when grouped into tertiles. Individuals with the highest tertile E-DII scores had a higher risk of GSD than those with the lowest tertile E-DII scores (model 1, OR 1.61, 95% CI 1.07–2.42; model 2, OR 2.33, 95% CI 1.61–3.36; model 3, OR 1.90, 95% CI 1.26–2.84; model 4, OR 2.07, 95% CI 1.36–3.16) (Table 3).

3.3 Subgroup analyzes

Results of the subgroup analyzes are shown in Figure 3. No significant interactions were identified (p for interaction >0.1 for all). Effect of DII on GSD was consistent across all nine pre-specified subgroups.

3.4 Sensitivity analyzes

Excluding alcohol intake did not reduce the statistical significance of the relationship between DII score and GSD in any of the models (model 1, OR 1.22, 95% CI 1.12–1.32; model 2, OR 1.16, 95% CI 1.06–1.27; model 3, OR 1.11, 95% CI 1.01–1.23; model 4 OR 1.14, 95% CI 1.03–1.26) (Table 4).

4 Discussion

This study investigated the association between DII scores and GSD using data from a nationally representative study, NHANES. A robust association between DII score and GSD was observed in US adults, indicating that a pro-inflammatory diet is positively associated with an increased risk of GSD. After adjusting for all confounding factors, individuals with the highest DII/E-DII scores were shown to be at higher risk of developing GSD than those with the lowest

TABLE 1 Characteristics of January 2017–March 2020 NHANES participants.

Characteristic	Overall *n* = 7,334	Without GSD *n* = 6,563 (89.5%)	With GSD *n* = 771 (10.5%)	*p*-value
Age, years	48.3 (17.4)	47.3 (17.2)	57.6 (15.8)	<0.001
Sex				<0.001
Male	3,593 (48.5%)	3,368 (51.0%)	225 (27.5%)	
Female	3,741 (51.5%)	3,195 (49.0%)	546 (72.5%)	
Race/ethnicity				0.068
Non-Hispanic White	2,659 (62.8%)	2,320 (62.2%)	339 (67.9%)	
Non-Hispanic Black	1,949 (11.3%)	1,793 (11.8%)	156 (7.3%)	
Other	1,137 (9.9%)	1,047 (10.0%)	90 (9.0%)	
Mexican American	849 (8.3%)	754 (8.4%)	95 (7.6%)	
Other Hispanic	740 (7.7%)	649 (7.6%)	91 (8.1%)	
Drinking status				0.003
Non/Light drinker	6,304 (83.2%)	5,603 (82.3%)	701 (90.4%)	
Heavy drinker	1,030 (16.8%)	960 (17.7%)	70 (9.6%)	
Smoking status				0.004
Non-smoker	4,223 (57.5%)	3,814 (58.1%)	409 (52.1%)	
Former smoker	1,775 (25.5%)	1,535 (24.7%)	240 (32.5%)	
Current smoker	1,336 (17.0%)	1,214 (17.2%)	122 (15.5%)	
Sedentary activity, min/day	350.0 (199.6)	347.1 (197.5)	375.2 (215.7)	0.011
BMI, kg/m^2	29.8 (7.2)	29.4 (6.9)	33.3 (8.6)	<0.001
Fatty liver				<0.001
No	4,609 (63.7%)	4,215 (64.9%)	394 (53.8%)	
Yes	2,725 (36.3%)	2,348 (35.1%)	377 (46.2%)	
Diabetes				<0.001
No	5,885 (85.3%)	5,362 (86.5%)	523 (74.9%)	
Yes	1,449 (14.7%)	1,201 (13.5%)	248 (25.1%)	
Thyroid disease				<0.001
No	6,470 (87.9%)	5,865 (89.3%)	605 (76.3%)	
Yes	864 (12.1%)	698 (10.7%)	166 (23.7%)	
Metabolic syndrome				<0.001
No	4,027 (58.4%)	3,711 (59.8%)	316 (46.2%)	
Yes	3,307 (41.6%)	2,852 (40.2%)	455 (53.8%)	

BMI, body mass index; GSD, gallstone disease.
Data are presented as unweighted numbers (weighted percentages) for categorical variables and means (SDs) for continuous variables.

TABLE 2 Dietary inflammatory index (DII) scores for January 2017–March 2020 NHANES participants with and without gallstone disease.

Characteristic	Overall *n* = 7,334	Without GSD *n* = 6,563(89.5%)	With GSD *n* = 771(10.5%)	*p*-value
DII	1.29 (−0.43, 2.66)	1.23 (−0.46, 2.63)	1.68 (0.01, 2.91)	<0.001
DII group				<0.001
Tertile 1	1,111 (17.2%)	1,022 (17.9%)	89 (11.2%)	
Tertile 2	3,977 (54.5%)	3,591 (54.6%)	386 (54.0%)	
Tertile 3	2,246 (28.3%)	1,950 (27.5%)	296 (34.9%)	

DII, dietary inflammatory index; GSD, gallstone disease.

DII/E-DII scores (OR 1.52, 1.19–1.93 95% CI, p trend <0.05 for DII, OR 1.90, 95% CI 1.26–2.84 for E-DII, Table 3). A dose–response relationship was observed between DII scores and GSD risk using restricted cubic spline regression. This association was generally consistent across subgroups. Sensitivity analysis confirmed the robustness of the primary analysis.

TABLE 3 Association between DII/E-DII and the presence of gallstone disease (GSD) among January 2017–March 2020 NHANES participants.

Characteristic	Model 1		Model 2		Model 3		Model 4	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
sqrt-trans DII, per 1 SD	1.22	1.12, 1.32	1.16	1.06, 1.27	1.10	1.00, 1.20	1.12	1.02, 1.22
Categorical DII								
Tertile 1	Ref.		Ref.		Ref.		Ref.	
Tertile 2	1.58	1.15, 2.17	1.42	1.03, 1.94	1.34	0.95, 1.90	1.39	1.00, 1.93
Tertile 3	2.03	1.54, 2.68	1.74	1.37, 2.21	1.52	1.19, 1.93	1.59	1.25, 2.02
p for trend		<0.001		<0.001		0.004		0.002
sqrt-trans E-DII, per 1 SD	1.02	0.92, 1.14	1.15	1.03, 1.29	1.08	0.96, 1.22	1.11	0.98, 1.25
Categorical E-DII								
Tertile 1	Ref.		Ref.		Ref.		Ref.	
Tertile 2	1.45	1.03, 2.03	1.71	1.23, 2.37	1.55	1.08, 2.22	1.65	1.17, 2.33
Tertile 3	1.61	1.07, 2.42	2.33	1.61, 3.36	1.90	1.26, 2.84	2.07	1.36, 3.16
p for trend		0.024		<0.001		0.007		0.003

OR, Odds Ratio; CI, Confidence Interval; DII, dietary inflammatory index; E-DII, energy-adjusted DII.
Sample-weighted logistic regression models were used.
Model 1: unadjusted.
Model 2: adjusted for sociodemographic variables (age group, sex, race and ethnicity).
Model 3: fully adjusted model: Model 2+ sedentary activity, obesity, alcohol drinking status, smoking status, fatty liver, diabetes, and thyroid disease.
Model 4: Model 2+ sedentary activity, alcohol drinking status, smoking status, thyroid disease and metabolic syndrome.

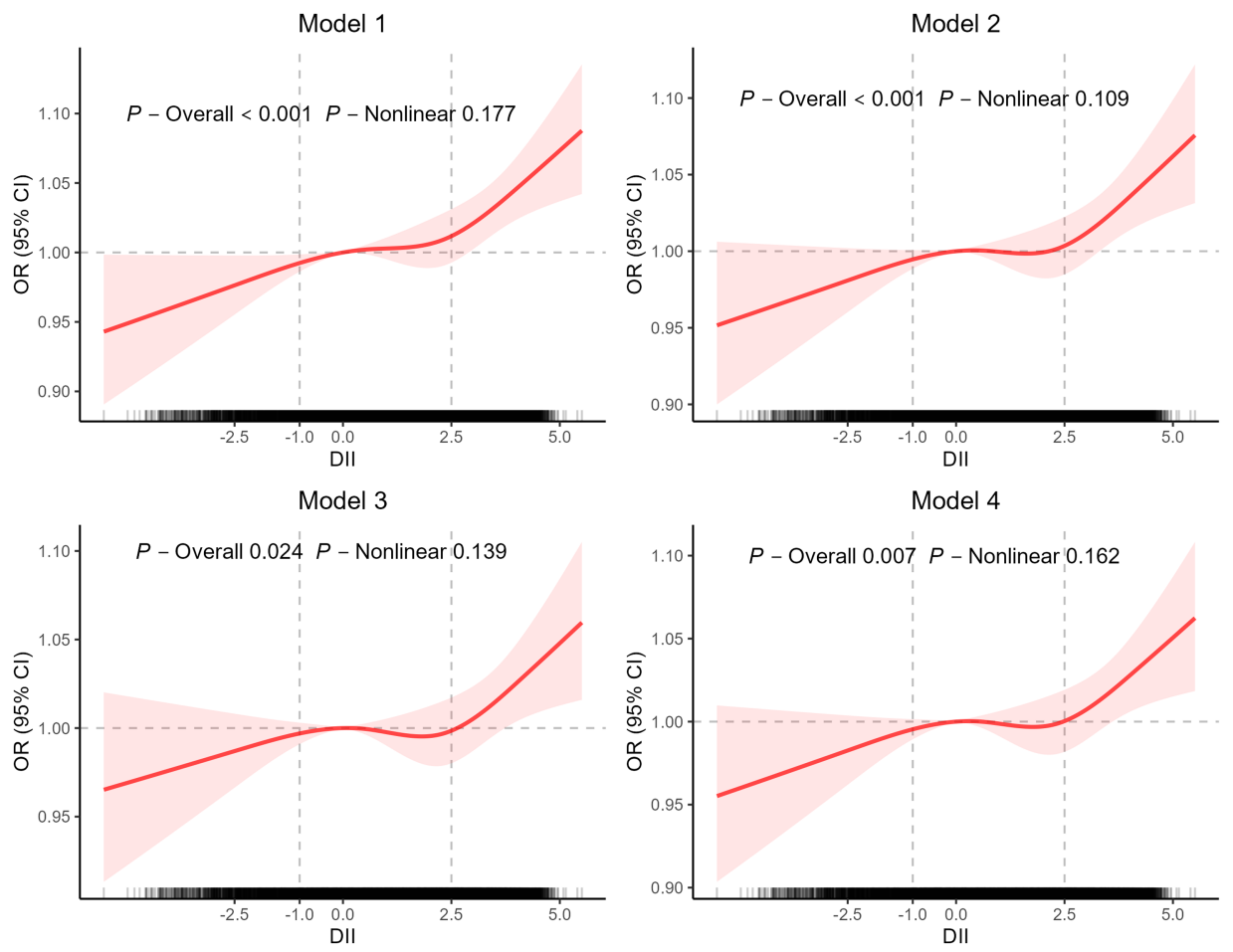

FIGURE 2
The restricted cubic spline for the association between dietary inflammatory index (DII) scores and gallstone disease (GSD).

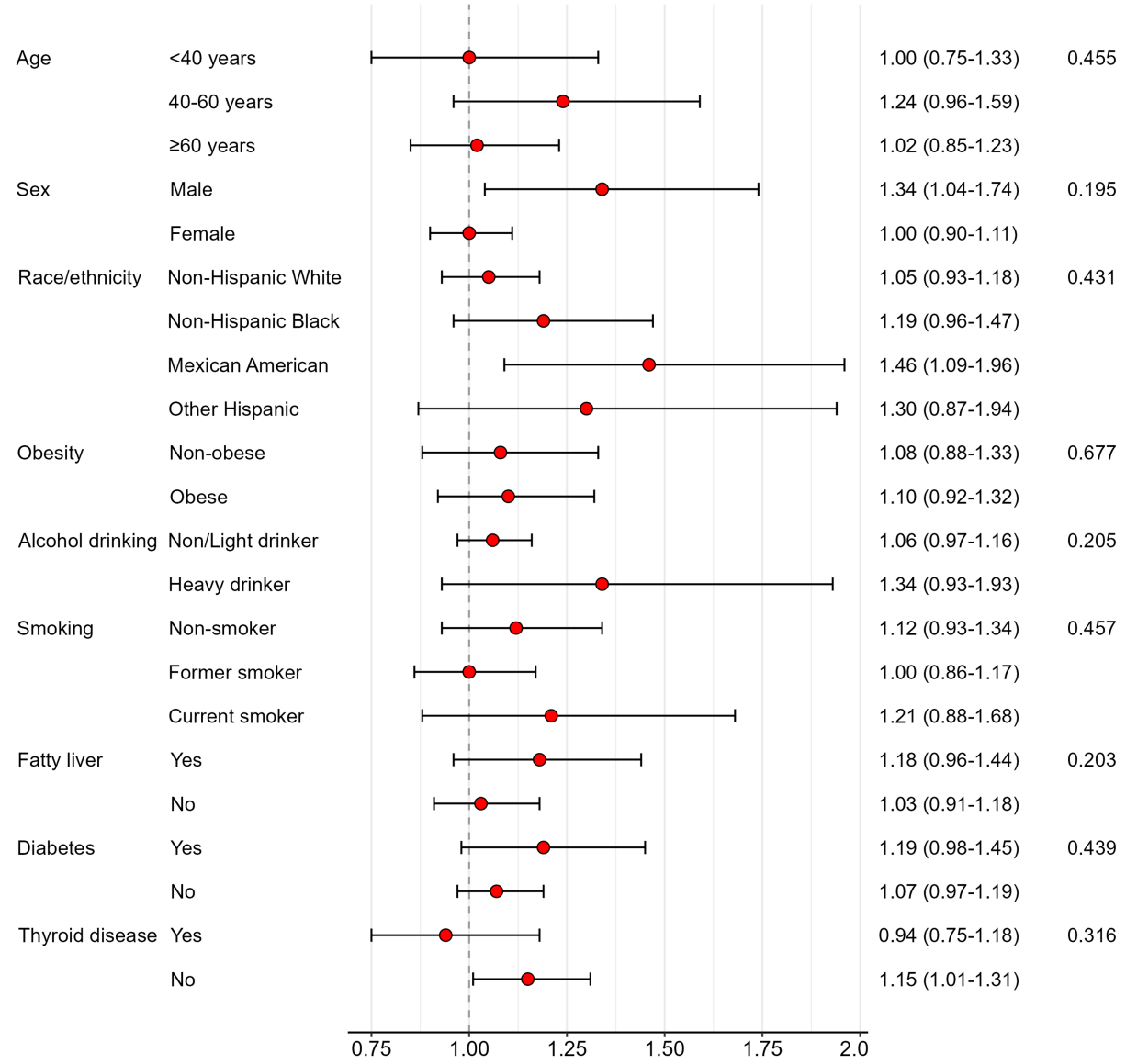

FIGURE 3
Subgroup analyzes of the association between dietary inflammatory index (DII) and the development of gallstone disease (GSD). OR, odds ratio; CI, confidence interval. Sample-weighted logistic regression models were applied. Each stratification was adjusted for confounding factors such as age group, sex, race and ethnicity, sedentary activity, obesity, alcohol drinking status, smoking status, fatty liver, diabetes, and thyroid disease except the stratification factor itself.

In recent years, the role of diet in regulating inflammation and affecting health has received widespread attention. The DII, developed by Shivappa et al. (18), is a reliable quantitative tool for evaluating the effects of diet on health by linking inflammatory cytokine levels in the blood to the outcomes of various chronic diseases (19). It was based on six of the most commonly studied inflammatory markers including IL-1β, IL-4, IL-6, IL-10, CRP, and TNF-α, and is used to quantitatively evaluate the anti- and pro-inflammatory effects of food (18, 19). A pro-inflammatory diet, that is, the higher DII score, is associated with an increased risk of several chronic noncommunicable diseases (NCD) (14, 20, 32–34), including metabolic syndrome and related diseases, cardiovascular and cerebrovascular diseases, cancers of various anatomic sites and depression and other mental health outcomes.

To the best of our knowledge, this is the first large population-based cross-sectional study to explore the association between a pro-inflammatory diet and GSD risk among a US population. One previous cross-sectional study, conducted using the Dena cohort, examined the association between DII scores and GSD (35). In contrast to findings from the current study, this report found that a pro-inflammatory diet was associated with a reduced risk of GSD. Due to the population restrictions of the geographic area, most of the participants had a similar diet and DII scores, which ranged from −0.4 to 1.43, so highly pro- or anti-inflammatory dietary data were lacking.

TABLE 4 Association between dietary inflammatory index (DII) and the presence of gallstone disease (GSD) among January 2017–March 2020 NHANES participants, excluding alcohol intake.

Characteristic	Model 1		Model 2		Model 3		Model 4	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
sqrt-trans DII, per 1 SD	1.22	1.12, 1.32	1.16	1.06, 1.27	1.11	1.01, 1.23	1.14	1.03, 1.26
Categorical DII								
Tertile 1	Ref.		Ref.		Ref.		Ref.	
Tertile 2	1.49	1.09, 2.05	1.35	0.97, 1.87	1.29	0.91, 1.83	1.35	0.97, 1.88
Tertile 3	1.94	1.47, 2.55	1.67	1.30, 2.15	1.51	1.16, 1.96	1.60	1.23, 2.09
p for trend		<0.001		<0.001		0.006		0.002

OR, Odds Ratio; CI, Confidence Interval.; DII, dietary inflammatory index.
Sample-weighted logistic regression models were used.
Model 1: unadjusted.
Model 2: adjusted for sociodemographic variables (age group, sex, race, and ethnicity).
Model 3: fully adjusted model: Model 2+ sedentary activity, obesity, smoking status, fatty liver, diabetes, and thyroid disease.
Model 4: Model 2+ sedentary activity, smoking status, thyroid disease, and metabolic syndrome.

Other studies that have synthesized and reviewed global database information have found that when the DII index covers all 45 food parameters, scores could range from −8.87 to +7.98. When it only refers to 25–30 parameters, the theoretical range of DII is usually from −5.5 to +5.5 (18, 19). Thus, the prior cross-sectional study may not be representative of people who consume a wide range of rich diets. While DII scores in the current study ranged from −5.52 (most anti-inflammatory) to +5.51 (most pro-inflammatory), which was consistent with most previous findings (18, 19). In addition, compared to the 4.3% incidence of GSD in the prior cross-sectional study (median DII −0.08), the GSD incidence in the current study was 10.5% (median DII 1.29). This reflects a likely correlation between the consumption of a pro-inflammatory diet and the development of GSD. Another case–control study was consistent with our results, in which the higher DII score, serum inflammatory and oxidative stress biomarkers were related to higher risk of GD in Iranian women (36). In our research, the E-DII was further calculated and analyzed for adjusting the effect of total energy intake, which indicated a stable and consistent correlation between E-DII and GSD.

Cholelithiasis is a critical public health issue and current researches suggest that three major pathogenic abnormalities are involved in the formation of gallstones: supersaturated gallbladder bile, precipitation and nucleation of excess cholesterol, and gallbladder hypomotility (1). Previous studies indicated that inflammation played an important role in the formation of gallstones (9, 37, 38). Higher levels of circulating inflammatory proteins and cytokines, including IL-1α, IL-6, IL-8, IL-10, IL-12 (p70), IL-13, CRP and tumor necrosis factor (TNF-α), were significantly associated with the increased risk of GSD (9, 37, 39–41). Inflammation-related histopathological changes occur in the gallbladder wall prior to the formation of cholesterol gallstones in both animal models and humans (37, 38, 42). Pro-inflammatory diet may increase the levels of circulating inflammatory proteins and cytokines in serum, which contributes to gallbladder wall fibrosis, and the impairment of gallbladder contractility (42). In addition, pro-inflammatory cytokines may lead to mucin hypersecretion, which plays an important role in the cholesterol nucleation process (41). The gallbladder hypomotility and mucin-related cholesterol nucleation predispose to the formation of gallstones (37, 43). The biological mechanisms underlying the association between pro-inflammatory diet and GSD would benefit from further researches.

This study had still several limitations. Firstly, given the cross-sectional study design of NHANES, the causal relationship between DII/E-DII scores and GSD could not be determined. Secondly, dietary data, GSD, and confounding factors were obtained from interviews or patient self-report questionnaires in the NHANES database, and are associated with an inevitable recall bias. Finally, while a sensitivity analysis was conducted, several participants were excluded due to the lack of data, which may have impacted the findings. A well-designed prospective cohort study will be necessary to explore the deeper relationship between DII/E-DII scores and GSD.

5 Conclusion

In conclusion, our findings indicate that a pro-inflammatory diet, that is, higher DII/E-DII scores, was positively associated with a higher risk of GSD. These findings indicate that pro-inflammatory dietary patterns can promote the formation of gallstones. Active dietary management and intervention should be considered to prevent the development of GSD.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found at: https://www.cdc.gov/nchs/nhanes/about_nhanes.htm.

Ethics statement

The studies involving humans were approved by the National Center for Health Statistics Institutional Review Board and Ethics Review Board. 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

JC: Writing – original draft, Conceptualization, Methodology, Funding acquisition. QZ: Software, Writing – original draft, Methodology. WW: Writing – review & editing, Conceptualization, Data curation. JL: Formal analysis, Resources, Writing – review & editing. LZ: Methodology, Visualization, Writing – review & editing. YX: Data curation, Writing – review & editing. HZ: Resources, Writing – review & editing. ZZ: Formal analysis, Visualization, Writing – review & editing. FZ: Investigation, Validation, Writing – review & editing. DY: Investigation, Validation, Writing – review & editing. YC: Project administration, Writing – review & editing, Funding acquisition. HP: Project administration, Writing – review & editing, Funding acquisition.

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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.2024.1344699/full#supplementary-material

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The correlation between fruit intake and all-cause mortality in hypertensive patients: a 10-year follow-up study

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Objective: Extensive research has consistently shown the beneficial impact of fruit consumption on overall health. While some studies have proposed a potential association between fruit consumption and hypertension management, the influence of fruit consumption on mortality rates among hypertensive individuals remains uncertain. Consequently, aim of this study is to evaluate whether fruit consumption is associated with all-cause mortality among hypertensive patients.

Methods: Data were obtained from the National Health and Nutrition Examination Survey (NHANES), conducted between 2003 and 2006. Ten-year follow-up data from the National Death Index (NDI) were used to assess all-cause mortality. Cox proportional hazard model was utilized to explore the impact of fruit intake on all-cause mortality among hypertensive individuals.

Results: The study included a cohort of 2,480 patients diagnosed with hypertension, and during the follow-up period, a total of 658 deaths from various causes were recorded. The COX regression analysis demonstrated that hypertensive patients who consumed apples three to six times per week exhibited a significantly reduced risk of all-cause mortality (HR = 0.60, 95%CI: 0.45–0.78, $p < 0.001$) in comparison to those who consumed apples less than once per month. Likewise, consuming bananas three to six times per week also led to a comparable outcome (HR = 0.76, 95%CI: 0.59–0.97, $p = 0.027$). Moreover, Combined consumption of bananas and apples three to six times per week exhibited a noteworthy decrease in all-cause mortality (HR = 0.57, 95%CI: 0.39–0.84, $p = 0.005$) when compared to individuals who consumed these fruits less frequently. Conversely, no significant association was found between the consumption of other fruits, including pears, pineapples, and grapes, and all-cause mortality.

Conclusion: The study discovered that moderate consumption of apples and bananas was associated with a reduced risk of all-cause mortality in patients with hypertension.

KEYWORDS

fruit consumption, apple consumption, banana consumption, hypertension, all-cause mortality

Introduction

Fruits play a pivotal role in promoting a nourishing diet on a global scale (1). The Dietary Guidelines for Americans 2015–2020 advocate for the inclusion of fruits in dietary patterns, with a particular emphasis on the consumption of whole fruits (2). Extensive research has consistently demonstrated a significant inverse association between the intake of substantial quantities of fruit and the risk of developing cardiovascular disease, obesity, diabetes, cancer, and stroke (3–7). Moreover, studies have indicated that fruit consumption can effectively mitigate the risk of all-cause mortality in individuals with diabetes and specific types of cancer (8, 9).

Hypertension is a widely prevalent cardiovascular disorder. The World Health Organization's global report on Hypertension reveals that approximately one third of the global population experiences this condition, resulting in over 10 million deaths annually attributed to elevated systolic blood pressure, with a substantial annual mortality rate (10). Hypertension remains the most significant modifiable risk factor for global all-cause mortality (11). The reportprimarily emphasizes the mitigation of hypertension through lifestyle modifications, with particular attention given to the impact of dietary patterns on blood pressure (10). Both the Dietary Approaches to Stop Hypertension and Mediterranean diets are recognized in the scientific community as effective dietary patterns for reducing high blood pressure (12–16). Both diets emphasize the consumption of fruits in their recommended meal plan (12–16).

Fruit-based diets, particularly those including apples, bananas, pears, and grapes, can have a positive impact on human health due to their high nutrient content. These fruits are rich in antioxidants, vitamins, and potassium (17). These nutrients can reduce blood pressure by improving endothelial function, modulating stress reflex sensitivity, and increasing antioxidant activity (18). Additionally, antioxidants can hinder the generation of reactive oxygen species, these species can scavenge excess and harmful free radicals that are produced during normal metabolism, prevent DNA damage, and ultimately reduce all-cause mortality (19). Nevertheless, a consensus regarding the optimal quantity of fruit intake has yet to be reached. Discrepancies in nutritional guidelines for fruit consumption persist across different nations. The World Health Organization advocates for the consumption of five fruit servings, the U.S. Dietary Guideline suggests at least 2 servings, whereas the Chinese Dietary Guideline suggests consuming 2.5–4.5 servings (20–22). Additionally, limited research has been conducted on the association between fruits intake and mortality rates among individuals with hypertension. Thus, the objective of this study is to assess the relationship between fruit consumption and all-cause mortality within a cohort of hypertensive patients.

Methods

Study design and population

Source of study population was from the National Health and Nutrition Examination Survey (NHANES), a public database that monitors human health conditions and nutrition across ethnic groups in the United States through continuous updates. NHANES obtained resident samples of all races in the United States through multi-stage stratified sampling, including people of all ages from all regions of the country. Therefore, NHANES data is a representative reflection of the health status of United States residents. Researchers can obtain NHANES data for free from the official website (Supplementary Table S1). The Ethics Review Board of the National Center for Health Statistics had approved the NHANES study. All participants provided written informed consent, allowing researchers to use the data as long as the data source is identified in the findings. The NHANES database included 11,183 adult participants from diverse ethnic and geographic backgrounds, between 2003 and 2006. Hypertension was identified through a computer-assisted personal interview system and a questionnaire. 3,390 participants were identified as having hypertension, while 908 participants were excluded due to not completing the Food Frequency Questionnaire (FFQ). Two participants lacked sufficient information to link to the National Death Index (NDI) data, resulting in missing follow-up survival status results and their exclusion from the study. Ultimately, 2,480 participants were enrolled in the study, as illustrated in Figure 1.

Fruit consumption assessment

The Food Frequency Questionnaire (FFQ) is a tool used to collect information about food intake frequency in the past 12 months, including fruit consumption habits. Participants in this study were asked about their average intake of apples over the last year by responding to the prompt: "How often did you eat apples/ bananas/ pears/pineapples/grapes?" Their eating habits were then analyzed. Fruit consumption data was obtained via an FFQ, which categorized intake levels as follows: unknow, less than once /month, 1–3 times/ month, 1–2 times/ week, three to six times/ week, or once or more / day for apples, pears, bananas, pineapples, and grapes.

Outcome assessment

All-cause mortality was examined using data from the National Death Index (NDI), which recorded death information for study participants from the survey's commencement through December 31, 2019. The NDI, published by the National Center for Health Statistics, a United States government agency, connects NHANES data with mortality records. Data perturbation techniques were utilized in the NDI to reduce the risk of participant re-identification and maintain patient confidentiality. Study period concludes 10 years after enrollment. For deceased patients, the follow-up duration since their interview was computed based on the quarter and year of their passing. For living patients, follow-up duration was determined using the end of the follow-up period. All NDI data used in this study were obtained from publicly released documents on the website (Supplementary Table S1).

Covariates assessment

The collection of baseline patient data was facilitated by a computer-assisted personal interview system and a questionnaire survey. This comprehensive dataset encompassed various

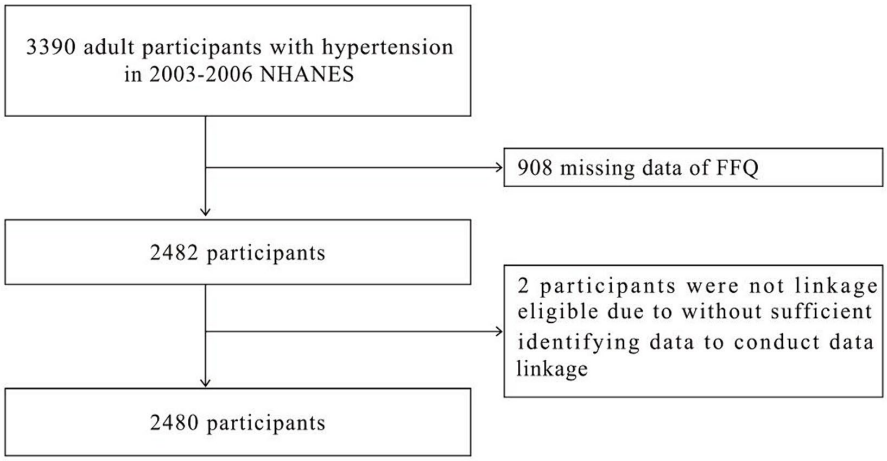

FIGURE 1
Flowchart of participant selection.

demographic factors such as gender, age, race, education level, ratio of family income to poverty, as well as health-related information including smoking and alcohol consumption, presence of hypercholesterolemia, diabetes, cardiovascular disease, stroke, lung disease, liver disease, and failing kidneys. Ethnicity was determined by categorizing patients as Mexican Americans, non-Hispanic Blacks, non-Hispanic whites, other Hispanics, or others. A smoking history of at least 100 cigarettes smoked throughout one's lifetime was used as the criterion for identifying individuals as smokers. A drinker was operationally defined as an individual who had consumed a minimum of 12 cups alcoholic beverages within the preceding 12-month period. The presence of hypertension, hypercholesterolemia, diabetes, stroke, liver disease, and renal failure was ascertained based on prior diagnoses made by the participant's healthcare provider. Participants who responded affirmatively to any of the following inquiries were categorized as having cardiovascular disease: "Have you ever been diagnosed with congestive heart failure, coronary heart disease, angina pectoris, or a heart attack by a healthcare professional?"

Statistical analysis

The median (first quartile, third quartile) was employed for continuous variables that did not adhere to a normal distribution. Categorical variables were expressed as numbers (percentages). The comparison of non-normally distributed continuous variables between two groups was conducted using the rank sum test. Furthermore, Chi-square tests were utilized to compare categorical variables between two groups. Cox proportional hazard model was utilized to examine the impact of fruit intake on all-cause mortality. Model 1 did not adjust any covariates. Model 2 made adjustments for gender, age, race, education level, and ratio of family income to poverty rate. In Model 3, covariates were selected based on the principle of covariate screening: confounding factors were compared before and after adding them to the regression model, and those resulting in a change in p value greater than 10% were included. Adjusting factors in the final Model 3 included sex, age, race, education level, ratio of family income to poverty rate, smoking history, history of hypercholesterolemia, diabetes, history of cardiovascular disease, stroke, lung disease, and history of failing kidneys. Before COX regression, collinearity screening was carried out for all covariates. The results indicated that the Variance Inflation Factor (VIF) for all covariates was less than 5. Splines smoothing plots were utilized to examine the linear or nonlinear correlation between the frequency of consuming different kinds of fruits and all-cause mortality. Additionally, stratified analyses were performed to confirm the consistency of the outcomes in the presence of different diseases. In addition, further elucidating the relationship between fruit intake and mortality was done by using a three-dimensional histogram and a time-mortality curve. The analysis of data was conducted using the R language package and EmPower software.[1] p-values less than 0.05 are considered statistically significant.

Results

Baseline characteristics of the participants

A total of 2,480 participants met the study's exclusion criteria and were included (Figure 1). The baseline characteristics of each participant are presented in Table 1. During the follow-up period, there were 1822 individuals who survived and 658 who died. The survivor group consisted of 44.5% males and 55.5% females. 15.8% of the population identified as Mexican American, 1.9% as other Hispanic, 53.4% as non-Hispanic white, 25% as non-Hispanic black, and 3.8% as belonging to other race. In regards to educational attainment, 45.4% of the population had education beyond high school. Concerning income, 40.3% of households had an income to poverty ratio greater than 3. Of the participants in survival group, 62.1% reported consuming alcohol, 48.9% smoked cigarettes, 47.3% had hypercholesterolemia, 17.8% suffered from diabetes, 14.2% from

1 http://www.Empowerstats.com

TABLE 1 Baseline characteristics of participants.

	All	Survival	All-cause death	*p*
Number	2,480	1822	658	
Age, years	64.0 (51.0–74.0)	60.0 (46.0–69.0)	75.0 (66.0–80.0)	<0.001
Sex				<0.001
Male	1,176 (47.4)	811 (44.5)	365 (55.5)	
Female	1,304 (52.6)	1,011 (55.5)	293 (44.5)	
Race				<0.001
Mexican American	369 (14.9)	288 (15.8)	81 (12.3)	
Other Hispanic	42 (1.7)	35 (1.9)	7 (1.1)	
Non-Hispanic White	1,404 (56.6)	973 (53.4)	431 (65.5)	
Non-Hispanic Black	583 (23.5)	456 (25.0)	127 (19.3)	
Other race	82 (3.3)	70 (3.8)	12 (1.8)	
Education level				<0.001
<High school	747 (30.1)	494 (27.1)	253 (38.4)	
High school graduate or general equivalency diploma	680 (27.4)	501 (27.5)	179 (27.2)	
>High school	1,052 (42.4)	827 (45.4)	225 (34.2)	
Unknown	1(0.1)	0 (0.0)	1 (0.2)	
Ratio of family income to poverty				<0.001
≤1	372 (15.0)	266 (14.6)	106 (16.1)	
1–3	1,094 (44.1)	745 (40.9)	349 (53.0)	
>3	898 (36.2)	735 (40.3)	163 (24.8)	
Unknown	116 (4.7)	76 (4.2)	40 (6.1)	
Alcohol use				0.278
No	955 (38.5)	690 (37.9)	265 (40.3)	
Yes	1,525 (61.5)	1,132 (62.1)	393 (59.7)	
Smoking				<0.001
No	1,176 (47.4)	931 (51.1)	245 (37.2)	
Yes	1,304 (52.6)	891 (48.9)	413 (62.8)	
Hypercholesterolemia				0.024
No	1,273 (51.3)	960 (52.7)	313 (47.6)	
Yes	1,207 (48.7)	862 (47.3)	345 (52.4)	
Diabetes				<0.001
No	1968 (79.4)	1,497 (82.2)	471 (71.6)	
Yes	512 (20.6)	325 (17.8)	187 (28.4)	
Cardiovascular Disease				<0.001
No	1972 (79.5)	1,563 (85.8)	409 (62.2)	
Yes	508 (20.5)	259 (14.2)	249 (37.8)	
Stroke				<0.001
No	2,264 (91.3)	1725 (94.7)	539 (81.9)	
Yes	216 (8.7)	97 (5.3)	119 (18.1)	
Lung Disease				<0.001
No	1969 (79.4)	1,483 (81.4)	486 (73.9)	
Yes	511 (20.6)	339 (18.6)	172 (26.1)	
Liver Condition				0.902
No	2,380 (96.0)	1748 (95.9)	632 (96.0)	

(Continued)

TABLE 1 (Continued)

	All	Survival	All-cause death	*p*
Number	2,480	1822	658	
Yes	100 (4.0)	74 (4.1)	26 (4.0)	
Failing Kidneys				<0.001
No	2,348 (94.7)	1762 (96.7)	586 (89.1)	
Yes	132 (5.3)	60 (3.3)	72 (10.9)	
Apple intake				<0.001
<1 times/month	953 (38.4)	670 (36.8)	283 (43.0)	
1–3 times/month	603 (24.3)	466 (25.6)	137 (20.8)	
1–2 times/week	423 (17.1)	317 (17.4)	106 (16.1)	
3–6 times/week	341 (13.8)	268 (14.7)	73 (11.1)	
≥1 times/day	101 (4.1)	66 (3.6)	35 (5.3)	
Unknow	59 (2.4)	35 (1.9)	24 (3.6)	
Banana intake				<0.001
<1 times/month	532 (21.5)	401 (22.0)	131 (19.9)	
1–3 times/month	500 (20.2)	392 (21.5)	108 (16.4)	
1–2 times/week	508 (20.5)	385 (21.1)	123 (18.7)	
3–6 times/week	592 (23.9)	429 (23.5)	163 (24.8)	
≥1 times/day	296 (11.9)	183 (10.0)	113 (17.2)	
Unknow	52 (2.1)	32 (1.8)	20 (3.0)	
Pear intake				0.689
<1 times/month	1,571 (63.3)	1,165 (63.9)	406 (61.7)	
1–3 times/month	498 (20.1)	367 (20.1)	131 (19.9)	
1–2 times/week	248 (10.0)	177 (9.7)	71 (10.8)	
3–6 times/week	85 (3.4)	61 (3.3)	24 (3.6)	
≥1 times/day	23 (0.9)	16 (0.9)	7 (1.1)	
Unknow	55 (2.2)	36 (2.0)	19 (2.9)	
Pineapple intake				0.761
<1 times/month	1722 (69.4)	1,260 (69.2)	462 (70.2)	
1–3 times/month	500 (20.2)	378 (20.7)	122 (18.5)	
1–2 times/week	151 (6.1)	110 (6.0)	41 (6.2)	
3–6 times/week	43 (1.7)	30 (1.6)	13 (2.0)	
≥1 times/day	12 (0.5)	9 (0.5)	3 (0.5)	
Unknow	52 (2.1)	35 (1.9)	17 (2.6)	
Grape intake				0.073
<1 times/month	1,074 (43.3)	758 (41.6)	316 (48.0)	
1–3 times/month	766 (30.9)	580 (31.8)	186 (28.3)	
1–2 times/week	359 (14.5)	273 (15.0)	86 (13.1)	
3–6 times/week	170 (6.9)	131 (7.2)	39 (5.9)	
≥1 times/day	44 (1.8)	34 (1.9)	10 (1.5)	
Unknow	67 (2.7)	46 (2.5)	21 (3.2)	

Continuous variables are presented as the median (Q1, Q3), and categorical variables are summarized as numbers (%). Differences in baseline characteristics were compared with the chi-square test for categorical variables and rank sum test for continuous variables. Q1, first quartile; Q3, third quartile.

cardiovascular disease, 5.3% from stroke, 18.6% from lung disease, 4.1% from liver disease, and 3.3% from failing kidneys. In the group that experienced death, 55.5% were male and 44.5% were female. By race, 12.3% identified as Mexican American, 1.1% as other Hispanic, 65.5% as non-Hispanic white, 19.3% as non-Hispanic black, and 1.8% as other race. In terms of educational attainment, 34.2% possessed a

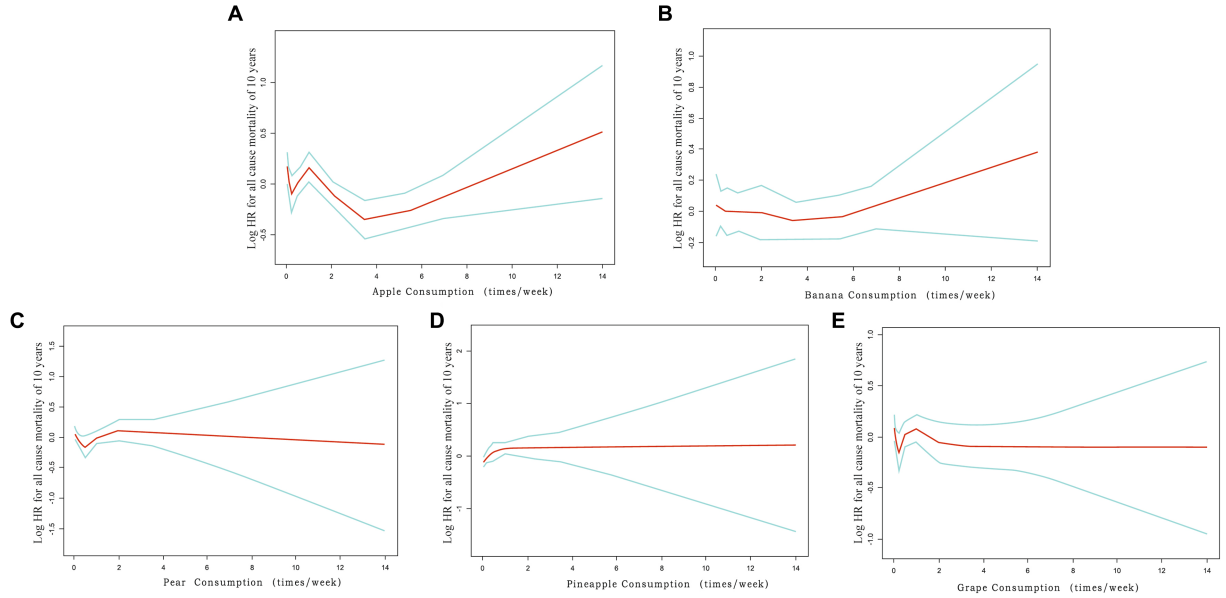

FIGURE 2
Splines smoothing plots of relationship between fruit consumption and all-cause mortality. **(A)** Splines smoothing plots of relationship between apple intake and all-cause mortality in patients with hypertension. **(B)** Banana intake. **(C)** Pear intake. **(D)** Pineapple intake. **(E)** Grape intake. HR has been fully adjusted for gender, age, race, education level, ratio of family income to poverty rate, smoking, hypercholesterolemia, diabetes, cardiovascular disease, stroke, lung disease, failing kidneys. HR, hazard ratio.

high school education or higher. Regarding income, 24.8% had a ratio of family income to poverty exceeding 3. Of all participants in all-cause death group, 59.7% reported alcohol consumption, 62.8% reported smoking, 52.4% had hypercholesterolemia, 28.4% had diabetes, 37.8% had cardiovascular disease, 18.1% had a history of stroke, 26.1% suffered from lung disease, 4% experienced liver disease, and 10.9% had failing kidneys.

Relationship between fruit consumption and all-cause mortality

The study examined the association between fruit consumption and all-cause mortality. The findings from splines smoothing plots analysis, as depicted in Figure 2, illustrated a decreasing trend in the risk of all-cause mortality when consuming apples and bananas three to six times per week. However, no significant changes in the risk of all-cause mortality were observed for other fruits, regardless of the intake levels.

The findings from the multivariable adjusted Model 3 reveal that individuals who consume apples or bananas three to six times per week have a reduced risk of all-cause mortality by 40% (HR = 0.60, 95% CI: 0.45–0.78, $p < 0.001$) and 24% (HR = 0.76, 95% CI: 0.59–0.97, $p = 0.027$), respectively, compared to those who consume them less than once per month (Table 2). However, no statistically significant correlation was found between other frequency of consumption of apples and bananas and the risk of all-cause mortality. Furthermore, it is worth noting that no significant association is identified between the consumption of other fruits (including pears, pineapples, and grapes) and all-cause mortality.

Relationship between apple intake and all-cause mortality

Subgroup analyses revealed that the association between apple consumption and all-cause mortality among individuals with hypertension remained unaffected by the presence or absence of comorbidities (all p values for the interaction were > 0.05) (refer to Table 3). Over the course of a 10-year follow-up period, our findings demonstrated that hypertensive individuals who consumed apples three to six times per week had a significantly lower risk of mortality compared to those who consumed them less than once a month. This observation is substantiated by the risk ratio results for all-cause mortality derived from the fully adjusted model, as illustrated in Figure 3 (log-rank test $p < 0.05$).

Relationship between banana intake and all-cause mortality

In a subgroup analysis, it was observed that the association between banana consumption and all-cause mortality among individuals with hypertension remained unaffected by the presence or absence of comorbidities (all p values for the interaction were > 0.05) (refer to Table 4). By employing COX regression analyses and accounting for confounding factors, the risk ratio for all-cause mortality was calculated. The results demonstrated that hypertensive individuals who consumed bananas three to six times per week had a significantly lower risk of mortality compared to those who consumed bananas less than once per month. The results are shown in Figure 4 (log-rank test $p < 0.05$).

Combined consumption of apple and banana with all-cause mortality

Further research was conducted to investigate the relationship between the consumption of a combination of apples and bananas and all-cause mortality rates. Participants were categorized into nine groups based on their frequency of consuming apples and bananas. Weekly consumption of apples and bananas was recorded as either three to six times, greater than three to six times, or less than three to six times. The Cox proportional hazard model was used to assess the risk of all-cause mortality. The findings (Figure 5; Supplementary Table S2) suggest that consuming apples and bananas three to six times per week significantly reduces the risk of all-cause mortality compared to consuming them less than three to six times per week (HR = 0.57, 95%CI: 0.39–0.84, $p = 0.005$). However, other consumption frequencies did not show a significant reduction in the risk of all-cause mortality.

Discussion

The study findings demonstrate that consuming apples or bananas three to six times per week is correlated with reduced all-cause mortality among individuals with hypertension, whereas no significant correlation was observed between the consumption of pears, pineapples, and grapes and lower all-cause mortality risks. Additionally, consuming a combination of apples and bananas three to six times per week may be associated with the greatest reduction in the risk of all-cause mortality. According to our knowledge, this is the first study to investigate the association between fruit consumption and all-cause mortality among individuals with hypertension.

Prior studies have demonstrated a connection between the intake of fruits and a decrease in mortality rates among populations afflicted with particular ailments. Chen et al. (8) sought to examine the association between fruit consumption and the dose–response relationship in relation to all-cause mortality in individuals diagnosed with type 2 diabetes in their study. The findings unveiled that a daily fruit consumption exceeding 42.9 g was associated with a 24% reduction in the risk of all-cause mortality (HR = 0.76; 95% CI 0.64–0.88) when compared to those who did not consume fruits. In a retrospective cohort study conducted by Martina et al. (9), it was observed that prostate cancer patients who consumed above-median quantities of fruits and vegetables exhibited a significantly higher likelihood of overall survival at 15 years in comparison to those with lower intake (71% versus 58%, $p = 0.04$; HR = 0.66, 95% CI: 0.47–0.93). These findings indicate a potential association between fruit and vegetable consumption and long-term survival among individuals diagnosed with prostate cancer. Similar to the aforementioned conditions, hypertension is a noteworthy health issue that affects a considerable portion of the population. Numerous studies have provided evidence that the consumption of fruit can reduce blood pressure levels in individuals with hypertension. However, the potential influence of fruit consumption on mortality rates among hypertensive populations has yet to be established. Our findings indicate that a moderate intake of apples and bananas is associated with a reduction in all-cause mortality among patients with hypertension, implying that fruit consumption may also confer survival benefits to hypertensive individuals.

Numerous studies have elucidated the positive impact of fruit consumption on health (23, 24). A meta-analysis has revealed that increased consumption of vegetables and fruits is associated with reduced all-cause mortality rates (24). The consumption of five servings of vegetables and fruits per day reached a point at which all-cause mortality no longer decreased. Our research suggests that consuming apples and bananas three to six times per week is associated with a decrease in mortality rates. However, increasing consumption beyond this range did not provide additional advantages. Further investigation into the relationship between fruit consumption and health is necessary to develop updated guidelines for optimal fruit intake.

Previous studies have primarily focused on the association between overall fruit consumption and mortality rates, with limited examination of the effects of specific types of fruit. Jonathan et al. found that increased apple consumption was associated with reduced all-cause mortality in elderly women (25). Our own research further supports this notion, demonstrating that the proper consumption of apples can effectively mitigate the risk of mortality. Jonathan's study demonstrates that there is no significant correlation between heightened banana consumption and all-cause mortality. Conversely, our study has identified a notable association between appropriate intake of bananas and all-cause mortality. Discrepancies in findings may be ascribed to multiple factors observed across various studies, including disparities in the study population, methods of measuring fruit consumption, adjustments for confounding variables, duration of follow-up, and characteristics of the cohort.

There is a lack of literature describing individual fruits, which makes it difficult to understand the mechanisms involved. Both apples and pears belong to the Rosaceae family and are excellent sources of dietary fiber and phenolic compounds (26, 27). Dietary fiber has been shown to have a positive impact on cholesterol levels, blood sugar, and blood pressure, as well as promoting a healthy intestinal flora (28, 29). Phenolic compounds possess antioxidant, anti-inflammatory, anti-cancer, anti-aging, antiviral (30, 31). The study found no significant difference in dietary fiber content between apples and pears. However, apple skin had the highest concentration of polyphenolic compounds. In terms of inhibiting DPPH free radicals, the apple peel extract was the strongest while the pear pulp extract was the weakest (32). A study found that apples are the primary source of phenolic compounds and antioxidants in Northern Europe and the United States (33). The potential health benefits of apple polyphenols may exceed those of pear polyphenols. The antioxidant effects of pear polyphenols have only been demonstrated *in vitro*, as they have received less attention in research (26). In addition to this, apples can alleviate the symptoms of chronic diseases and reduce the risk of cardiovascular disease and cancer, due in large part to apple polyphenols (27, 34). As one of the most commonly consumed fruits, grapes are rich in antioxidants such as polyphenols and flavonoids. These antioxidants can reduce atherosclerosis by inhibiting the oxidation of low-density lipoproteins and activating novel proteins that prevent cellular senescence. Additionally, they can help prevent cardiovascular disease (35, 36). However, compared to apples, grapes may contain less dietary fiber. Dietary fiber has a blood pressure-lowering effect, which may be one of the reasons why apples can help alleviate chronic diseases (28, 29). Pineapple contains polyphenols, dietary fiber, and minerals. Studies have shown that pineapple exhibits anti-inflammatory and antioxidant activity (37). The polyphenol content in pineapple is lower than in

TABLE 2 Hazard ratios and confidence intervals of all-cause mortality for fruit consumption.

		Model 1	Model 2	Model 3
	Number	HR (95%CI) *p*	HR (95%CI) *p*	HR (95%CI) *p*
Apple intake				
<1 times/month	953	Ref	Ref	Ref
1–3 times/month	603	0.73 (0.60, 0.90) 0.003**	0.79 (0.64, 0.98) 0.032*	0.81 (0.66, 1.01) 0.056
1–2 times/week	423	0.82 (0.66, 1.03) 0.082	0.80 (0.63, 1.00) 0.055	0.86 (0.68, 1.08) 0.199
3–6 times/week	341	0.69 (0.53, 0.89) 0.004**	0.56 (0.43, 0.73) <0.001***	0.60 (0.45, 0.78) <0.001***
≥1 times/day	101	1.19 (0.84, 1.69) 0.326	0.91 (0.63, 1.30) 0.592	0.94 (0.65, 1.35) 0.724
Banana intake				
<1 times/month	532	Ref	Ref	Ref
1–3 times/month	500	0.86 (0.67, 1.11) 0.240	0.78 (0.60, 1.01) 0.062	0.80 (0.61, 1.05) 0.105
1–2 times/week	508	0.98 (0.77, 1.26) 0.896	0.79 (0.61, 1.03) 0.077	0.82 (0.63, 1.06) 0.124
3–6 times/week	592	1.14 (0.90, 1.43) 0.274	0.74 (0.58, 0.94) 0.013*	0.76 (0.59, 0.97) 0.027*
≥1 times/day	296	1.69 (1.31, 2.17) <0.001***	0.95 (0.73, 1.23) 0.675	1.01 (0.77, 1.31) 0.958
Pear intake				
<1 times/month	1,571	Ref	Ref	Ref
1–3 times/month	498	1.04 (0.85, 1.26) 0.718	0.83 (0.68, 1.02) 0.080	0.82 (0.67, 1.01) 0.058
1–2 times/week	248	1.13 (0.88, 1.45) 0.341	0.93 (0.71, 1.21) 0.583	0.92 (0.70, 1.20) 0.538
3–6 times/week	85	1.14 (0.76, 1.73) 0.524	0.92 (0.59, 1.41) 0.690	0.87 (0.56, 1.34) 0.527
≥1 times/day	23	1.17 (0.56, 2.48) 0.674	1.21 (0.57, 2.58) 0.613	1.27 (0.60, 2.72) 0.535
Pineapple intake				
<1 times/month	1722	Ref	Ref	Ref
1–3 times/month	500	0.90 (0.74, 1.10) 0.319	0.96 (0.78, 1.18) 0.684	1.00 (0.82, 1.24) 0.963
1–2 times/week	151	1.05 (0.76, 1.44) 0.774	1.16 (0.83, 1.61) 0.391	1.00 (0.71, 1.40) 0.996
3–6 times/week	43	1.18 (0.68, 2.05) 0.553	1.33 (0.76, 2.31) 0.314	1.48 (0.84, 2.58) 0.172
≥1 times/day	12	0.87 (0.28, 2.71) 0.810	0.78 (0.25, 2.46) 0.675	0.86 (0.27, 2.78) 0.802
Grape intake				
<1 times/month	1,074	Ref	Ref	Ref
1–3 times/month	766	0.81 (0.68, 0.97) 0.023*	0.84 (0.70, 1.02) 0.072	0.84 (0.70, 1.02) 0.076
1–2 times/week	359	0.79 (0.62, 1.00) 0.047*	1.00 (0.78, 1.28) 0.978	1.01 (0.79, 1.30) 0.927
3–6 times/week	170	0.76 (0.55, 1.06) 0.111	0.76 (0.54, 1.07) 0.116	0.75 (0.54, 1.06) 0.109
≥1 times/day	44	0.74 (0.40, 1.40) 0.358	0.82 (0.42, 1.60) 0.566	0.80 (0.41, 1.56) 0.511

Model 1: Not adjusted.
Model 2: Adjusted for gender, age, race, education level, ratio of family income to poverty rate.
Model 3: Adjusted for gender, age, race, education level, ratio of family income to poverty rate, smoking, hypercholesterolemia, diabetes, cardiovascular disease, stroke, lung disease, failing kidneys.
CI, confidence interval; HR, hazard ratio; Ref, reference. *, $p < 0.05$, **, $p < 0.01$, ***, $p < 0.001$.

apples. Although some studies have shown that pineapple skin contains more bioactives, it is not edible. Therefore, it is recommended to consume processed pineapple products and extracts (38). As a highly popular fruit worldwide, bananas possess a diverse range of nutrients, including phenolic compounds, vitamins C and E, carotenoids, as well as potassium ions (39). Many of these compounds exhibit antioxidant activity that protects the body against oxidative stresses, potentially decreasing mortality rates (40). Vitamin E, vitamin C, and carotenoids react with free radicals, specifically peroxyl radicals, and monolinear molecular oxygen to achieve antioxidant effects (19). Vitamin E helps prevent the oxidation of unsaturated fatty acids to peroxides, while carotenoids possess the ability to scavenge single-linear oxygen. Vitamin C plays a role in the regeneration of vitamin E and the elimination of free radicals within the cytoplasm (19). Furthermore, vitamin E has the potential to decrease platelet aggregation by inhibiting the proliferation of smooth muscle cells and reducing platelet adhesion to collagen (41). When comparing the potassium content of commonly consumed fruits, bananas contain more potassium than pears, and green grapes (17). Studies have shown that the consumption of potassium from dietary sources can lead to a decrease in blood pressure and a reduction in overall mortality (42–45). These mechanisms may help explain the correlation between bananas and apples intake and all-cause mortality, but not other fruits, with lowered all-cause mortality in our results for

TABLE 3 Stratified analysis of relationship between apple intake and all-cause mortality.

		HR (95%CI)					P inter
	Number	<1 times/ month	1–3 times/ month	1–2 times/ week	3–6 times/ week	≥1 times/ day	
Hypercholesterolemia							0.843
No	1,273	Ref	0.75 (0.55, 1.03)	0.93 (0.66, 1.31)	0.60 (0.41, 0.89)	0.91 (0.50, 1.68)	
Yes	1,207	Ref	0.84 (0.62, 1.12)	0.77 (0.56, 1.07)	0.56 (0.38, 0.83)	0.95 (0.60, 1.52)	
Diabetes							0.913
No	1968	Ref	0.76 (0.59, 0.97)	0.83 (0.63, 1.09)	0.58 (0.42, 0.81)	0.99 (0.63, 1.58)	
Yes	512	Ref	0.94 (0.62, 1.43)	0.95 (0.59, 1.51)	0.59 (0.36, 0.95)	0.96 (0.52, 1.79)	
Cardiovascular Disease							0.797
No	1972	Ref	0.78 (0.59, 1.02)	0.80 (0.60, 1.08)	0.58 (0.42, 0.82)	1.06 (0.67, 1.67)	
Yes	508	Ref	0.84 (0.59, 1.19)	1.00 (0.68, 1.45)	0.56 (0.36, 0.89)	0.81 (0.43, 1.53)	
Stroke							0.242
No	2,264	Ref	0.78 (0.62, 0.99)	0.78 (0.60, 1.01)	0.60 (0.45, 0.80)	1.12 (0.75, 1.67)	
Yes	216	Ref	0.88 (0.53, 1.46)	1.35 (0.78, 2.34)	0.46 (0.20, 1.05)	0.73 (0.27, 1.96)	
Lung Disease							0.180
No	1969	Ref	0.79 (0.62, 1.01)	0.87 (0.67, 1.14)	0.56 (0.41, 0.77)	0.83 (0.55, 1.25)	
Yes	511	Ref	0.86 (0.56, 1.33)	0.84 (0.53, 1.34)	0.71 (0.40, 1.27)	3.46 (1.38, 8.67)	
Liver Condition							0.465
No	2,380	Ref	0.82 (0.66, 1.01)	0.87 (0.68, 1.10)	0.61 (0.46, 0.80)	0.93 (0.63, 1.36)	
Yes	100	Ref	2.01 (0.42, 9.56)	1.10 (0.22, 5.57)	0.62 (0.06, 6.45)	4.79 (0.45, 50.84)	
Failing Kidneys							0.920
No	2,348	Ref	0.81 (0.65, 1.02)	0.86 (0.68, 1.10)	0.61 (0.46, 0.80)	1.02 (0.70, 1.51)	
Yes	132	Ref	0.65 (0.31, 1.35)	0.64 (0.28, 1.45)	0.44 (0.12, 1.54)	0.61 (0.17, 2.20)	

Adjusted for gender, age, race, education level, ratio of family income to poverty rate, smoking, hypercholesterolemia, diabetes, cardiovascular disease, stroke, lung disease, failing kidneys, except the subgroup variable. HR, hazard ratio; CI, confidence interval; P inter, P interaction; Ref, reference.

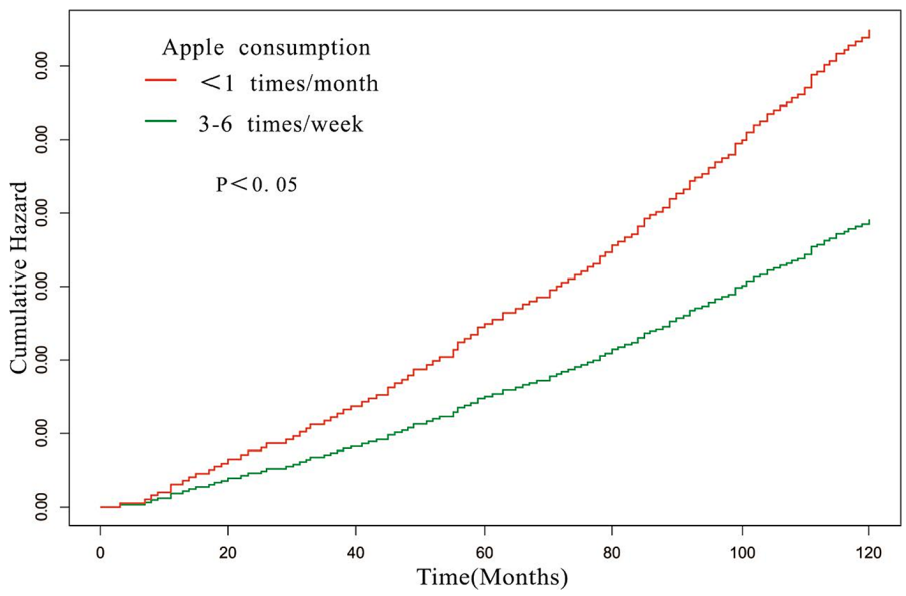

FIGURE 3
Time-mortality curve of the relationship between apple consumption and all-cause mortality. Adjusted for gender, age, race, education level, ratio of family income to poverty rate, smoking, hypercholesterolemia, diabetes, cardiovascular disease, stroke, lung disease, failing kidneys.

TABLE 4 Stratified analysis of relationship between banana intake and all-cause mortality.

		HR (95%CI)					P inter
	Number	<1 times/ month	1–3 times/ month	1–2 times/ week	3–6 times/ week	≥1 times/day	
Hypercholesterolemia							0.919
No	1,273	Ref	0.72 (0.48, 1.07)	0.86 (0.59, 1.26)	0.76 (0.53, 1.08)	0.99 (0.67, 1.46)	
Yes	1,207	Ref	0.86 (0.60, 1.24)	0.80 (0.55, 1.15)	0.77 (0.55, 1.09)	1.06 (0.73, 1.53)	
Diabetes							0.925
No	1968	Ref	0.76 (0.56, 1.03)	0.81 (0.60, 1.09)	0.75 (0.56, 1.00)	0.96 (0.70, 1.31)	
Yes	512	Ref	0.96 (0.56, 1.66)	0.85 (0.49, 1.48)	0.78 (0.48, 1.25)	1.15 (0.69, 1.92)	
Cardiovascular Disease							0.383
No	1972	Ref	0.88 (0.63, 1.25)	0.92 (0.66, 1.28)	0.90 (0.66, 1.23)	1.12 (0.79, 1.57)	
Yes	508	Ref	0.68 (0.44, 1.05)	0.70 (0.46, 1.08)	0.54 (0.36, 0.82)	0.84 (0.55, 1.28)	
Stroke							0.404
No	2,264	Ref	0.74 (0.55, 1.00)	0.82 (0.62, 1.10)	0.79 (0.61, 1.04)	0.94 (0.70, 1.26)	
Yes	216	Ref	1.07 (0.57, 1.99)	0.85 (0.45, 1.60)	0.60 (0.31, 1.14)	1.23 (0.66, 2.32)	
Lung Disease							0.959
No	1969	Ref	0.82 (0.60, 1.12)	0.86 (0.64, 1.17)	0.76 (0.57, 1.01)	1.04 (0.77, 1.41)	
Yes	511	Ref	0.75 (0.44, 1.26)	0.72 (0.43, 1.20)	0.75 (0.47, 1.19)	0.89 (0.51, 1.52)	
Liver Condition							0.117
No	2,380	Ref	0.79 (0.61, 1.04)	0.79 (0.61, 1.03)	0.74 (0.58, 0.95)	0.96 (0.73, 1.26)	
Yes	100	Ref	1.31 (0.20, 8.49)	0.93 (0.14, 5.93)	2.39 (0.41, 14.00)	9.45 (0.96, 93.18)	
Failing Kidneys							0.418
No	2,348	Ref	0.73 (0.55, 0.97)	0.76 (0.58, 1.01)	0.71 (0.55, 0.92)	0.98 (0.74, 1.29)	
Yes	132	Ref	1.80 (0.74, 4.36)	1.22 (0.52, 2.87)	1.07 (0.43, 2.66)	1.84 (0.72, 4.65)	

Adjusted for gender, age, race, education level, ratio of family income to poverty rate, smoking, hypercholesterolemia, diabetes, cardiovascular disease, stroke, lung disease, failing kidneys, except the subgroup variable. HR, hazard ratio; CI, confidence interval; P inter, P interaction; Ref, reference.

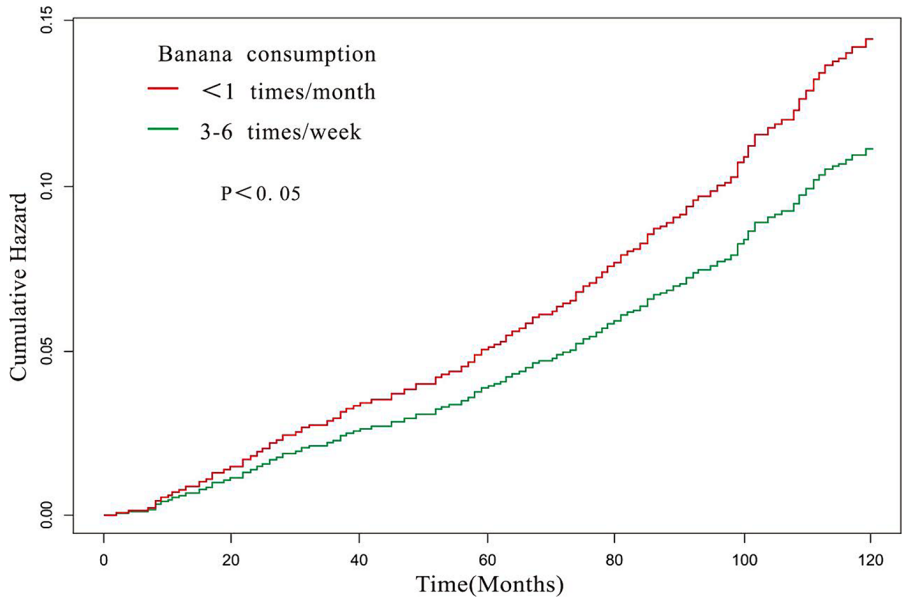

FIGURE 4
Time-mortality curve of the relationship between banana consumption and all-cause mortality. Adjusted for gender, age, race, education level, ratio of family income to poverty rate, smoking, hypercholesterolemia, diabetes, cardiovascular disease, stroke, lung disease, failing kidneys.

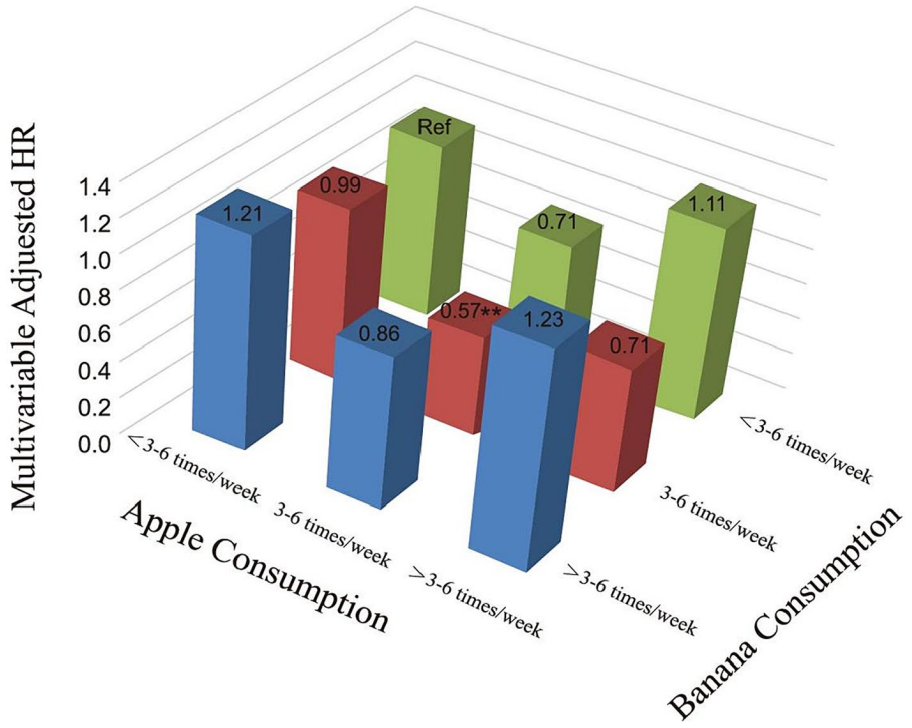

FIGURE 5
Three-dimensional histogram of relationship of combined consumption of apple and banana with the risk of all-cause mortality. Adjusted for gender, age, race, education level, ratio of family income to poverty rate, smoking, hypercholesterolemia, diabetes, cardiovascular disease, stroke, lung disease, failing kidneys, except the subgroup variable. HR, hazard ratio; Ref, reference. **, $p < 0.01$.

hypertensive patients. However, it is important to note that the conclusions of this study are specific to a particular population and cohort. Therefore, they should not be used to dismiss the health benefits of other fruits.

Strengths and weaknesses

An important strength of this study is that it examines the association between fruit consumption and all-cause mortality within a hypertensive population, thereby providing a unique contribution to existing literature that has primarily focused on the general population. Moreover, our study boasts a substantial and diverse sample size, encompassing participants from different regions of the United States, varying ethnic backgrounds, and diverse socioeconomic statuses. The selection of the NHANHS database was based on its reputation for providing high-quality data and its recognition within the field. However, the scope of our study is constrained as it solely focused on examining the effects of apple and banana consumption on all-cause mortality, without considering the associations with specific causes of mortality such as cardiovascular disease, cancer, or chronic conditions. The researchers assessed the fruit intake of participants, which may introduce random measurement errors due to variations in individual diets over time. Additionally, observational studies may be subject to bias. In our study, we adjusted for covariates such as education level, poverty rate, and smoking to account for potential confounding factors. Although we made diligent attempts to account for all potential confounding variables and mitigate the impact of covariates in our analysis, it is plausible that unidentified or unmeasured factors could have influenced our findings.

Conclusion

In summary, our study has revealed that the consumption of a suitable quantity of apples or bananas can effectively lower mortality rates among individuals diagnosed with hypertension. Furthermore, the synergistic effect of consuming both fruits may yield even more advantageous outcomes. These findings may contribute novel evidence to the existing body of knowledge on dietetics for hypertensive populations.

Data availability statement

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

Ethics statement

The studies involving humans were approved by the Ethics Review Board of the National Center for Health Statistics. 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

CS: Data curation, Formal analysis, Methodology, Writing – original draft. JL: Data curation, Formal analysis, Methodology, Writing – original draft. ZZ: Methodology, Writing – original draft. SR: Validation, Writing – original draft. YG: Writing – original draft. MZ: Validation, Writing – original draft. TL: Validation, Writing – original draft. LT: Validation, Writing – original draft. QY: Project administration, Supervision, Writing – review & editing. LC: Conceptualization, Project administration, Supervision, Writing – review & editing.

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Conflict of interest

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

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2024.1363574/full#supplementary-material

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Patient-centered nutrition education improved the eating behavior of persons with uncontrolled type 2 diabetes mellitus in North Ethiopia: a quasi-experimental study

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Background: Improving the clinical outcome of people with type 2 diabetes mellitus by modifying their eating behavior through nutrition education is an important element of diabetes self-management. Significant data from the literature supports this idea, however in the Ethiopian setting, there is a practice gap. Therefore, the purpose of this study was to assess how patient-centered nutrition education affected the eating behavior and clinical outcomes of people with uncontrolled type 2 diabetes mellitus.

Method: In this quasi-experimental trial, 178 people with uncontrolled type 2 diabetes were purposely assigned to the intervention (n = 89) or control (n = 89) arm. The intervention arm was given patient-centered nutrition education, whereas the control arm received the routine care. Eating behavior and clinical outcome indicators such as HbAc, lipid profile, anthropometric indices, and blood pressure were assessed in both groups at the start and completion of the intervention. All scale variables were tested for normality and log transformed when appropriate. The baseline characteristics of the intervention and control groups were compared using the t-test for continuous variables and the chi-square test for categorical variables. The effect of nutrition education was determined using a difference in differences (DID) approach. $P < 0.05$ was established as the criterion of significance.

Result: Food selection (DID = 15.84, $P < 0.001$), meal planning (DID = 31.11, $P < 0.001$), and calorie needs (DID = 37.65, $P < 0.001$) scores were statistically higher in the nutrition education arm. Furthermore, their overall eating behavior score (DID = 27.06, $P < 0.001$) was statistically greater than the controls. In terms of clinical outcomes, the overall picture reveals that the intervention did not outperform over the routine care. However, in comparison to the controls, the intervention arm showed clinically significant improvement in HbA1c (DID = −0.258, $P = 0.485$).

Conclusion: Patient-centered nutrition education has resulted in positive adjustments in the eating behavior of people with uncontrolled type 2 diabetes mellitus. Furthermore, it has shown a great potential for improving their glycemic control.

KEYWORDS

patient-centered, nutritional education, eating behavior, uncontrolled type 2 diabetes mellitus, Ethiopia

Background

Nearly entire diabetes care is accomplished by patients outside of a healthcare setting (1). Therefore, patient empowerment should be the main emphasis of initiatives meant to enhance diabetes care (2). The most important, yet complicated and difficult, of them is promoting and supporting adherence to a healthy diet (3). People with type 2 diabetes mellitus (T2DM) have a poor understanding of the role of nutrition in diabetes management (4). Since knowledge acquisition alone cannot result in behavioral change, even those who comprehend it have difficulty adapting their eating behavior to the new recommendation (5). As a result, unlike improvements in other facets of self-care, the involvement of people with T2DM in healthy eating is rather poor. Such a lack of awareness, and the resulting unhealthy eating behavior, leads to poor clinical prognosis and serious health implications (3).

Patient-centered nutrition education is a viable strategy to bridging the gap between nutrition information acquisition and eating behavior adjustment (6, 7). The teaching is adapted to the receivers' needs, values, and preferences (8), as well as their food literacy and numeracy (9). As a result, it promotes knowledge, perception, and behavior of healthy eating (10, 11). Indeed, data revealed that patient-centered education enhanced patients' satisfaction with their nutrition care (12) and helped them implement changes in eating behavior (13). However, implementation is difficult, and there is a considerable knowledge-to-practice gap (14).

Diabetes nutrition education services in general, and patient-centered approaches in particular, are scarce in Ethiopia (15–17). According to the American Diabetes Association, diabetic individuals should get healthy dietary pattern based nutritional counseling at diagnosis and as needed throughout their lives (18). However, actual information from most diabetes clinics shows that consultation periods are relatively short, leaving little or no opportunity for patient education. Furthermore, contrary to the ADA's guideline (18), most facilities do not include a dietician/nutritionist as a member of the diabetes care team, and the service is frequently provided by physicians or nurses with insufficient nutrition expertise (19–25). This type of teaching may not provide the diabetic with the knowledge, skills, and motivation needed to achieve optimal healthy eating behavior (24, 25). As a result, the goal of this study was to assess how patient-centered nutrition education guided by the revised Pender's Health Promotion Model (HPM) affected eating behavior and clinical outcomes in people with uncontrolled T2DM (HbA1c $\geq$ 7%).

Materials and methods

Study setting and participants: The study was conducted in two General Hospitals namely Mekelle general Hospital (intervention area) and Adigrat General Hospital (control area) in Tigray region, North Ethiopia. Study participants were persons with uncontrolled T2DM who had follow up at each hospital.

Study design: A quasi-experimental design with a non-equivalent control group and a pretest-posttest format was used to assess the effect of patient-centered nutrition education on eating behavior and clinical outcomes of people with uncontrolled T2DM.

Eligibility criteria

Inclusion criteria: We enrolled people with uncontrolled T2DM (HbA1c $\geq$ 7%), who were at least 18 years old, lived in the study area, could read Tigrigna (the local language), or who had a literate family member in the household, and owned a telephone (mobile or landline in the household).

Exclusion criteria: We excluded individuals with uncontrolled T2DM who had documented cognitive impairment, pregnant or nursing women, those who did not reside in the study area during the study period, and those who had changed medications in the most recent follow-up.

Sample size: The sample size was determined by placing the margin of error at 0.05, the power at 95%, and the intervention to control ratio at 1:1. The goal of the intervention was to effect a net reduction in HbA1c of 0.25 from the baseline (26). Assuming 15% attrition, there were 89 participants in each arm of the trial. The following formula was used to calculate the sample size:

$$n = \frac{2(S^2)(z_{\alpha/2} + z_{\beta})^2}{(\Delta\mu)^2}$$

Where n is the sample size in each group; $Z_{\alpha/2}$, margin of error; Z_{β}, the power; $\Delta\mu$, the mean difference between the intervention and comparison groups, and S, the standard deviation from previous study.

Sampling technique: The two hospitals were randomly assigned to one of two groups: control or intervention. Following that, the experiment was available to anyone with uncontrolled T2DM who had been identified from the intervention hospital in a previous study and met the inclusion criteria. In the previous study, 324 patients from both institutions were classified as having uncontrolled T2DM. 250 of them volunteered to take part in the

current study. Based on the inclusion criteria, obtaining a matching participant from the control group, and the calculated sample size, 89 persons were chosen from the intervention hospital to participate in the trial. An equal number of participants were picked from the control area to meet the 1:1 ratio, bringing the total sample size to 178.

Outcomes: Changes in eating behavior and HbA1c were the primary outcomes of the study. Changes in serum lipid profile, anthropometric indices, blood pressure and atherogenic index of the plasma were secondary outcomes.

Hypothesis: We hypothesized that a patient-centered NE intervention tailored to the participants' needs, values, and preferences would result in significant improvements in the outcomes under investigation at 3 months.

Intervention: The intervention group received two patient-centered nutrition education sessions over the course of 3 months, separated by 1-month intervals. The education was delivered in a mixed approach. The initial education session lasted 30 min and was tailored to each participant. This was offered at the time of enrollment of the participants into the intervention. The content of the education was basic information about diabetes, its symptoms and classification; complications associated with T2DM and an introduction to diabetes self- management (DSM) modalities. In addition individual nutrition related concerns were discussed. It was given by the principal investigator, who is a PhD student in Human Nutrition, together with their physician, who was an internist. A month after the first session, a second group-based nutrition education session was offered by the principal investigator. This session took 120 min with a 10-min health break in the middle. Families and caregivers of participants' were encouraged to attend, but only few have done so. Discussions regarding the contents of healthy diet (Choosing whole foods over highly processed ones, emphasizing use of non-starchy vegetables, fruits, minimizing refined grains, and avoiding added sugars, sugar-sweetened beverages, and trans fats); components of healthy eating (appropriate food selection, meal planning and identifying calorie needs); the objectives of healthy eating behavior (maintaining a healthy weight, acquiring nutritional requirements, achieving glycemic targets and other metabolic goals, and avoiding or reducing the progression of complications); and the methods for implementing healthy eating behavior were all included in the education. Planning meals and controlling portions were taught using the plate approach. A brochure with a brief summary of the second educational session was also distributed as a take-home guide for healthy eating.

With the contents specifically targeted to the participants' eating behavior determinants discovered in a prior qualitative study, notably dietary knowledge, cost and availability of health foods, and social support, the patient-centered nutrition education was informed by the behavior-specific constructs of Pender's HPM. The importance of healthy diet for all family members, regardless of their diabetes status, and meal planning on a limited budget were emphasized. The content was presented through Power Point presentations, discussions, and demonstrations. To help the subjects visualize portion sizes, the session used household measurements and food photographs. Participants' relevant positive deviant eating behaviors were also deliberated. The PI also got participant phone numbers to facilitate follow-up. Participants were phoned to remind them to attend the second nutrition education session and to encourage them to follow the healthy eating guide.

Compliance: Monitoring participant attendance at training sessions and keeping track of who received the two-page pamphlet summarizing the training were two ways to gauge compliance with the intervention. Additionally, repeated phone calls were made to the participants to motivate them to follow the instructions for eating healthy.

Data collection instruments and measures

Measurements were taken at the start and end of the trial. The baseline data were gathered prior to the intervention. Endline data were gathered right away following the closure of the intervention. The information collected, the tools utilized and the measurement techniques applied in both surveys were the same. Only at the baseline were demographic, socioeconomic, comorbidity status, and other pertinent clinical histories gathered.

A structured questionnaire created by the study team was used to gather demographic and clinical data (**Supplementary Tables 1**, **2**). A Demographic Health Survey (DHS) instrument was used to gather household socioeconomic data (27) (**Supplementary Table 3**). The WHO Stepwise Approach (STEPS) instrument (28) and the Global Physical Activity Questionnaire (GPAQ) (29) provided the framework for the collection of anthropometric and physical activity data, respectively. The Charlson's Comorbidity Index chart (30) was used to retrieve comorbidity information from their medical record. The Pentra C 400 clinical chemistry analyzer was used to do biochemical analysis in accordance with standard operating procedures (SOPs). While Humameter A1c was utilized to measure the HbA1c level.

Data on eating behavior was collected using a tool developed by Bhutanese investigators and customized to the setting by the research team (31, 32) (**Supplementary Table 4**). The Bhutanese tool had 19 Likert-type items. Based on the rigorous psychometric evaluation, 14 of the 19 items were validated for assessing the eating behavior of the participants in our setting. Of these, five items were used to assess the food selection dimension of the eating behavior. Six items were utilized to assess the meal planning dimension and the remaining three items were for calorie needs recognition dimension. Likert-type items in each dimension had four response anchors: strongly disagree, disagree, agree and strongly agree. They were given equal weight and allotted equidistant points that range from 1 for strongly disagree to 4 for strongly agree.

Each eating behavior dimension's Likert-type item scores were added up to create Likert-scale scores. For ease of comparison with studies that used different numbers of Likert-items or responses, the raw scores were converted to percentage of scale to maximum score (%SM) (33). The percent SM range was set to 0 to 100 because the lowest possible score for our Likert-type item was one. An SM cutoff score of 66.7% was used to define participant eating behavior in each dimension as healthy or unhealthy. Participants with % SM $\geq$ 66.7 were deemed to practice healthy eating, whereas those with % SM $<$ 66.7 were assumed to practice unhealthy eating. Ranks obtained in the three dimensions were aggregated to assess overall eating behavior. Our earlier article (32) provides a more detailed discussion of the tools and measurement methods.

Statistical analysis

Data were twice entered into Epidata 3.1 (Xunta de Galicia, Spain & PAHO, USA), and then exported to Stata version 14SE for cleaning and analyses. The latent variable that best accounts for the socioeconomic variation among the participants was found using Principal Component Analysis (PCA). The relative socioeconomic status of the subjects was then determined based on their scores in the discovered latent variable. Normality was checked for all scale variables and log transformed when relevant. For continuous variables, unless otherwise stated, data were reported as means +/- SD, and for categorical variables, absolute frequencies and percentages were used. To predict mortality risk, an age-adjusted Charlson's Comorbidity Index (CCI) was generated.

Baseline characteristics between intervention and control groups were compared using the *t*-test for continuous and chi-square test for categorical variables. Difference in differences (DID) analysis was carried out to test superiority of the patient-centered nutrition education package over the routine care with regard to improving eating behavior and clinical outcomes. Baseline variables (HDL & HDL/TC) demonstrating significant difference between the intervention and control groups were excluded from the DID analysis. The level of significance for all tests was set at $P < 0.05$.

Ethical approval

The project (IHRPGD/467/2018) was reviewed and approved by the Institutional Review Board (IRB) of the Institute of Health at Jimma University. Health authorities at the regional and facility

TABLE 1 Comparison on socio-demographic, economic and clinical characteristics of study participants.

Characteristic		Study group		Mean diff.	X^2(df)	Significance (p.value)
		Intervention	Control			
Mean age		54.36(±9.31)*	55.64(±10.59)*	−1.271		0.41
Sex	Male	36	40			
	Female	49	45		0.381(1)	0.537
Marital status	Single	10	13			
	Married	48	47			
	Divorced	6	7		0.710(3)	0.871
	Widowed	21	18			
Educational status	Illiterate	28	36			
	Able to read and write	13	12			
	1° level	10	14		4.707(4)	0.319
	2° level	13	6			
	College and above	21	17			
Economic status	Poorer	13	18			
	Poor	14	17			
	Average	13	19		1.312(4)	0.859
	Wealthy	17	15			
	Wealthiest	15	16			
Antidiabetic drug	Metformin	15	18			
	Glibenclamide	12	5			
	Metformin and glibenclamide	38	50		6.791(3)	0.079
	Insulin	20	12			
Treatment adherence	High	74	74			
	Moderate	11	10		1.048(2)	0.592
	Low	0	1			
Physical activity status	≥600 MET-min/week	57	63			
	<600 MET-min/week	11	9		1.033(2)	0.597
	Sedentary	17	13			
Mean duration of DM (years)		6.98(±5.52)*	6.72(±5.28)*	0.257		0.756
Mean CCI		2.56(±1.22)*	2.44(±1.19)*	0.124		0.503

X^2 – chi-square, df, degree of freedom; CCI, Charlson's Comorbidity Index, *- mean.

levels were informed of the study's purpose; as a result, written authorization to commence was obtained. Potential participants were given information about the study, including how the data collected would be used. They received a briefing on the process for gathering the data and assurances that there would be no costs or risks involved. Furthermore, the confidentiality of the data and the freedom to withdraw from the study at any time without penalty were assured. Inclusion in the intervention or comparison arm was limited to participants who gave a written informed consent. Participants in the control arm were also informed, for ethical reasons, of the significance of physical activity for glycemic control.

Results

Subjects and baseline characteristics

170 of the initial 178 participants had finished the research and were taken into account in the final analysis. Four intervention group participants dropped out for personal reasons; three skipped the group-based nutrition education session and the rest one participant failed to pick up the brochure for a healthy eating guide. Likewise, four members of the control group were unable to participate in the endline survey and were consequently omitted from the final analysis. For the intervention arm, the average length of time with T2DM was 6.98 (±5.52) years, whereas for the control arm, it was 6.72 (±5.28) years. Their mean ages were 55.64 (±10.59) years for the control arms and 54.36 (±9.31) years for the intervention. For the intervention, the proportion of males and females was 42.4% and 57.6%, but for the control arms, it was 47.1% and 52.9%, Table 1. The baseline characteristics of the intervention and control group did not significantly differ from one another, as shown in Table 2. Furthermore, none of the baseline variables assessed indicated that the eight dropouts were different from the rest of the group.

Table 3 summarizes the changes in the eating behavior dimensions from pre-intervention to post-intervention and compares the differences between the two groups. For any of the variables at the baseline, no differences between the two groups were found to be statistically significant. However, when the intervention was given, the intervention group showed statistically significant improvements. While the scores of the control group showed a non-significant decline. In terms of the difference in differences (DID) analysis between the two arms, the study found that the intervention arm's overall eating behavior changed by 27 percentage points when compared to the controls (DID = 0.27, $P < 0.000$). The overall eating behavior in the intervention arm improved by 21 percentage points, while it was declining by roughly 6 percentage points in the control arm. The mean changes between the two groups were also found to differ in each of the eating behavior dimensions, with statistically significant differences being noted.

Table 4 summarizes the changes in the clinical outcome indicator variables. Again, the two groups showed no statistically significant differences with regard to most of their baseline variables except for HDL and TC/HDL (data not shown). When compared to the control group, the mean HDL value in the intervention group was considerably higher (40.65 ± 10.96 vs. 36.83 ± 11.12, $P = 0.036$). In contrast, the mean TC/HDL in the intervention arm was considerably lower than in the control arm (4.58 ± 1.26 vs. 5.35 ± 1.61, $P = 0.000$). No clinical outcomes were significantly varied between the two arms as a result of the intervention. However, the intervention arm remarked within-group statistically significant reductions in HbA1c (delta $X = -0.49$, $p < 0.001$), as was seen for total cholesterol in both arms (C: −13.655, $P = 0.004$, I: −21.100, $P < 0.001$). In contrast, statistically noteworthy increments in LDL cholesterol (C; 21.51, $p < 0.001$, I; 13.33, $P = 0.002$) were evident among participants in either arm.

TABLE 2 Comparison of baseline clinical, biochemical and anthropometric variables.

Variable	Comparison X ± SD	Intervention X ± SD	Mean difference	P.value
HbA1c (%)	9.324 (1.704)	9.206 (1.653)	−0.118	0.652
Total Cholesterol (mg/dl)	185.851 (45.79)	178.423 (42.86)	−7.427	0.275
LDL Cholesterol(mg/dl)	98.013 (31.65)	94.541 (29.27)	−3.472	0.515
HDL Cholesterol (mg/dl)	36.829 (11.12)	40.654 (10.96)	3.825	0.036
Triglyceride (mg/dl)	156.932 (89.10)	143,081 (82.21)	−13.851	0.277
TC to HDL ratio	5.349 (1.61)	4.581 (1.26)	−0.769	0.000
Atherogenic index	0.585 (0.304)	0.494 (0.310)	−0.091	0.053
Waist circumference (cm)	87.624 (12.31)	90.612 (11.65)	2.988	0.096
BMI (kg/m^2)	22.843 (3.65)	22.829 (3.67)	−0.015	0.979
Waist to hip ratio	0.899 (0.11)	0.922 (0.08)	0.024	0.244
Waist to height ratio	0.533 (0.08)	0.553 (0.07)	0.020	0.063
Systolic blood pressure (mmHg)	128.75 (18.23)	127.14 (18.56)	−1.612	0.564
Diastolic blood pressure (mmHg)	81.19 (10.76)	80.28 (11.39)	−0.906	0.587

X ± SD-mean ± standard deviation.

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TABLE 3 Comparison of mean values of eating behavior dimensions between the intervention and comparison group.

Characteristic	Unstandardized mean scores								Standardized mean scores (%SM)							
	Comparison			Intervention			DID	P.value	Comparison			Intervention			DID	P.value
	Baseline	Endline	Difference	Baseline	Endline	Difference			Baseline	Endline	Difference	Baseline	Endline	Difference		
Food selection	13.65	13.75	0.1	13.60	16.08	2.48	2.38	0.00	57.65	58.35	0.7	57.33	73.88	16.55	15.84	0.00
Meal planning	11.12	9.39	−1.73	11.36	15.24	3.88	5.6	0.00	28.43	18.82	−9.61	29.80	51.31	21.51	31.11	0.00
Calorie recognition	5.27	4.22	−1.05	5.04	7.38	2.34	3.39	0.00	25.23	13.59	−11.6	22.61	48.63	26.02	37.65	0.00
Overall eating	30.04	27.36	−2.68	30	38.69	8.69	11.36	0.00	38.18	31.82	−6.36	38.10	58.80	20.7	27.06	0.00

Unstandardized mean scores denote the raw mean scores for each eating behavior dimension and the overall eating behavior; standardized mean scores denote that the means are transformed to a percentage of the scale to the maximum score (%SM).

Discussion

The study demonstrated that patient-centered nutrition education informed by Pender's Health Promotion Model behavior-specific constructs promotes healthy eating behavior. However, there were no statistically supported changes in clinical outcomes, with the exception of within-group substantial reductions in HbA1c and total cholesterol.

Adoption and maintenance of healthy eating is a key strategy to improve glycemic control, minimize risk of complications and improve health of persons with diabetes (34). Importantly, people's eating behaviors are influenced, among other things, by their perceptions and knowledge of a healthy diet (35). Therefore, in order to successfully promote and support healthy eating, nutrition education that communicates sufficient knowledge and encourages behavior modification is essential (36). Confirming this concept, participants in the intervention arm made significant improvements in their overall eating behavior compared to the control arm in the present study. Additionally, the intervention arm considerably outperformed the control arm across all dimensions of eating behavior. Similar to this study, a number of randomized controlled trials and systematic reviews have also noted the link between nutrition education and better eating behavior (37–40).

The principal favorable outcome anticipated as a result of improved eating behavior is better glycemic control (41, 42). This conclusion was supported by the UK prospective diabetes research (43), which found that after a 3-month dietary intervention, newly enrolled diabetic patients' HbA1c levels significantly reduced (from 9.1 to 7.2%) (43). Additionally, a number of cohort and randomized control trials have shown how nutrition education can help people with glycemic control (37, 44–47). However, despite being remarkable, the reduction in HbA1c as a result of implementing patient-centered nutrition education in the current trial did not reach statistical significance. Other similar studies (8, 48) also reported encouraging improvements in HbA1c levels that did not achieve statistical significance.

Although the difference in HbA1c levels between the two arms was statistically small, the finding was functionally important. According to the literature, a 0.3 to 0.5 drop in HbA1c value is considered clinically significant (49, 50). In this study, the 3-month nutrition education lowered the mean HbA1c within the intervention arm by roughly 0.5%, which was well-matched to the literature report. As a result, despite its statistical insignificance, the intervention could be clinically relevant in lowering the risk of diabetes-related complications. According to the UK Prospective Diabetes Study (UKPDS), a 1% decrease in HbA1c reduces microvascular complications by 37% and diabetes-related mortality by 21% (51). If risk reduction is proportional to HbA1c reduction, then the current study would reduce the risk of microvascular complications by roughly 19% and fatalities by 11%.

In addition to a higher HbA1c, T2DM is linked to significant alterations in plasma lipid and its components. In persons with uncontrolled T2DM, increases in LDL, TC, TG, and a decrease in HDL are frequent conditions that lead to Coronary Heart Disease (CHD) (52). Besides, increasing blood pressure and unfavorably changing body composition indices are extremely evident in further escalating the CHD risk (53). Unlike pharmacologic treatment, dietary intervention is capable of avoiding all of these

TABLE 4 Comparison of mean values of anthropometric, clinical, and biochemical variables between the intervention and comparison group.

Variable	Comparison				Intervention				DID	P.value
	Baseline	Endline	Diff	P.value	Baseline	Endline	Diff	P.value		
HbA1c	9.324	9.087	−0.237	0.080	9.206	8.712	−0.494	0.000	−0.258	0.485
TC	185.851	172.195	−13.655	0.004	178.423	157.322	−21.100	0.000	−7.445	0.438
LDL-C	98.013	119.519	21.506	0.000	94.541	107.872	13.330	0.002	−8.176	0.279
Triglyceride	156.932	144.789	−12.142	0.105	143.081	128.286	−14.795	0.122	−2.653	0.883
AIP	0.585	0.495	−0.090	0.001	0.494	0.427	−0.067	0.072	0.023	0.733
WC	87.624	88.459	0.835	0.389	90.612	90.753	0.141	0.824	−0.694	0.784
BMI	22.843	22.629	−0.214	0.268	22.829	22.653	−0.176	0.439	0.038	0.960
WHtR	0.533	0.540	0.007	0.280	0.553	0.556	0.003	0.549	−0.004	0.799
Systolic BP	128.75	122.47	−6.282	0.003	127.14	127.07	−0.071	0.971	6.212	0.117
Diastolic BP	81.19	79.06	−2.129	0.141	80.28	80.35	0.071	0.954	2.200	0.351

Unstandardized mean scores denote the raw mean scores for each anthropometric, clinical and biochemical variables; standardized mean scores denote that the means are transformed to a percentage of the scale to the maximum score (%SM).

CHD risk factors and is regarded as a cornerstone of diabetes control (54). Various studies supporting this concept found that dietary education effectively improved serum lipids, systolic and diastolic blood pressure, BMI, and waist circumference (47, 52, 55, 56). In the current study, however, providing nutrition education for 3 months had no effect on any of the previously listed clinical variables. Consistent with this conclusion, multiple randomized control trials also failed to establish the effectiveness of nutrition education in changing lipid profile, blood pressure, and anthropometric indices (48, 57, 58). Though further research is needed to determine the exact reasons, differences in educational content, delivery method, length, and frequency of intervention may explain this disparity.

Favorable reductions in HbA1c are likely to succeed tangible changes in the participants' eating behavior. Though a series of assessments were not done to determine the exact time required to adopt a healthy eating behavior, it is implied that a significant amount of time will elapse before the desired behavior alteration is achieved. As a result, the remaining time would be insufficient for biochemical changes to occur, limiting the achievement of significant reductions in HbA1c within the allocated time frame. This is demonstrated by a clinically significant reduction in HbA1c in the intervention arm, albeit not substantially superior to the control. This explanation also applies to the other clinical outcomes studied, as their improvement is thought to be dependent on suitable reductions in HbA1c. Further increase in LDL cholesterol during the course of the trial in both groups supports our view, as it demonstrates the inadequacy of the achieved glycemic reduction in triggering hormonal changes that reverse the lipogenesis process occurring in the liver. However, the reduction in atherogenic index of plasma (AIP) in both arms is noteworthy, which could be attributed to regulated fat consumption and/or adequate physical exercise.

Strengths and limitations

The nutrition education package in this study is specifically designed to meet the needs and preferences of the participants, which is its main strength. As a limitation, the participants' self-reported data were used to assess the eating behavior, and objective biomarkers of food consumption were not used to confirm it. Thus, the chance of social desirability bias is not completely ignored, so care must be taken while interpreting it. However, as the intervention package is tailored to the participants' situation, the observed behavior changes are more likely to occur. In contrast, the short intervention period appears to unacceptably shorten the time between behavior alteration and subsequent biochemical changes. Thus, despite the fact that it appears likely that the intervention package will enhance the participants' glycemic control, this conclusion is precluded by the issue of time.

Conclusion

Patients with uncontrolled T2DM who received the patient-centered nutrition education intervention in this trial reported significant improvements in both specific eating behavior dimensions and overall eating behavior. In addition, the provided intervention showed a promising potential to lower the individuals' HbA1c levels. Throughout the course of the trial, some of the secondary outcomes exhibited further derangement. This is likely explained by the fact that the intervention period ended before the beneficial metabolic effects of eating behavior change were ensued. Therefore, the time for measuring such clinical outcome indicators in future trials needs to be carefully considered. A patient center nutrition education initiative at the hospital level, with sufficient follow-up and training for health professionals to enhance their knowledge and skills, is advised to improve the eating behavior of persons with T2DM.

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 Institutional Review Board of Jimma University, Jimma, Ethiopia. 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

HG: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review and editing. GA: Funding acquisition, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – review and editing. AW: Methodology, Supervision, Validation, Visualization, Writing – review and editing. SB: Data curation, Investigation, Methodology, Supervision, Writing – review and editing. MA: Methodology, Supervision, Validation, Visualization, Writing – review and editing. AB: Methodology, Supervision, Validation, Visualization, Writing – review and editing. TL: Methodology, Supervision, Validation, Visualization, Writing – review and editing. TN: Conceptualization, Methodology, Supervision, Validation, Visualization, Writing – review and editing.

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Conflict of interest

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

Publisher's note

Supplementary material

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Associations of healthy eating index-2015 with osteoporosis and low bone mass density in postmenopausal women: a population-based study from NHANES 2007–2018

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Purpose: The current study aimed to explore the associations of diet quality assessed by healthy eating index-2015 (HEI-2015) with risks of osteoporosis and low bone mineral density (BMD) among American postmenopausal women aged 50 years and older.

Methods: Postmenopausal women aged 50 years and older in the National Health and Nutrition Examination Survey from 2007 through 2018 were included in the final sample. Analysis of variance and Rao-Scott adjusted chi-square tests were used to compare the characteristics across tertiles of HEI-2015. Univariate and multivariate weighted logistic regression models were employed to explore the associations of HEI-2015 tertiles and continuous HEI-2015 with the risks of osteoporosis and low BMD. Nonlinear dose-response associations were evaluated using weighted restricted cubic spline analyses, and the contributions of various HEI-2015 components were assessed using weighted quantile sum regression models.

Results: The final sample included 3,421 postmenopausal women aged 50 years and older representative for approximately 28.38 million non-institutionalized U.S. postmenopausal women. Osteoporosis prevalence decreased with HEI-2015 tertiles while the prevalence of low BMD showed no significant decrease. Compared with postmenopausal women in the first tertile of HEI-2015, those with the second (OR: 0.57, 95%CI: 0.38–0.84) and third (OR: 0.48, 95%CI: 0.29–0.78) HEI-2015 tertiles were associated with reduced osteoporosis risk after multivariate adjustments, but no significant association of HEI-2015 with the risk of BMD was identified. Furthermore, similar effects were confirmed in the sensitivity analyses and subgroup analyses and interaction effects. Moreover, significant nonlinear associations were observed between HEI-2015 with osteoporosis risk, and total vegetables, refined grains and greens and beans demonstrated the strongest protective effect among HEI-2015 components against osteoporosis.

Conclusions: This study strongly suggests the significant negative associations of HEI-2015 with osteoporosis risk in American postmenopausal women. These

findings highlight the importance of adherence to the dietary guidelines for Americans in reducing the risk of osteoporosis.

KEYWORDS

diet quality, HEI-2015, osteoporosis, bone mineral density, postmenopausal women

Introduction

Osteoporosis, a systemic skeletal disease characterized by reduced bone mineral density (BMD) and degradation of bone microstructure, has emerged as a prominent public health concern with the global prevalence being 19.7% (1, 2). Consequently, it leads to increased bone fragility and susceptibility to fractures, resulting in approximately an anual cost of 17.9 billion dollars and 4 billion pounds in the USA and UK of osteoporosis-related fracture (3). According to the International Osteoporosis Federation, 10.2 and 43.4 million adults aged 50 years and older were estimated to have osteoporosis and low BMD in the United States in 2010, and the prevalence were 10.3% and 43.9% (4). These figures highlight the significant burden of osteoporosis and low BMD in the US population, particularly among older adults. Furthermore, the significant correlation between the prevalence of osteoporosis and increasing age were approved by numerous studies. Moreover, the global society is currently experiencing a rapid shift in its age structure, with populations becoming increasingly dominated by older individuals. As a consequence, the prevalence of osteoporosis is expected to rise predictably in the coming years, in which managements of osteoporosis is urgently need to address this public health issue effectively.

Postmenopausal women are particularly susceptible to low BMD and osteoporosis due to the combination of age and hormonal changes. Specifically, estrogen plays a crucial role in maintaining BMD and it decreases significantly during menopause. As a result, the prevalence of osteoporosis in postmenopausal women is notably elevated to be about 40% in Caucasia while it varied between 15% and 33% in Brazil, depending on the methodology employed and the use of bone densitometry data or self-reporting by participants (5, 6). Therefore, the management of postmenopausal osteoporosis is indeed a pressing need. While exercise and medications play important roles in its treatment, dietary implementation is also recognized as a valuable measure for preventing and managing osteoporosis (7–15).

In addition to calcium and vitamin D, multiple studies have evaluated the influence of dietary nutrients intake such as potassium, vitamin K, vitamin C and total protein intake on osteoporosis (16–25). Beyond individual nutrients intake, the overall dietary pattern and quality such as dietary total antioxidant capacity have gained attention as a comprehensive approach to nutrition (26). However, studies specifically focusing on diet pattern and quality in relation to osteoporosis are relatively limited, with much of the research centered around the benefits of the Mediterranean diet and dietary approaches to stop hypertension (DASH) (27–30). Furthermore, it is important to note that studies examining diet pattern and quality vary in terms of measurement methods and target populations, resulting in heterogeneity in the results across different studies.

The healthy eating index-2015 (HEI-2015), a measure to assess the degree of individual food intake align with Dietary Guidelines of Americans (DGA), is adopted in plenty of studies to reflect diet quality and it is of great construct validity, reliability, and criterion validity (31, 32). To the best of our knowledge, our study is the first to explore the correlation of diet quality assessed by HEI-2015 and osteoporosis risk in postmenopausal women. With data from 2007 to 2018 National Health and Nutrition Examination Survey (NHANES), we aimed to investigate the associations of HEI-2015 with the risks of low BMD and osteoporosis among postmenopausal women aged 50 years and older. By examining these associations, we can provide valuable insights into the role of diet quality in preventing osteoporosis and help develop comprehensive dietary guidelines for promoting bone health in postmenopausal women.

Methods

Study population

NHANES, conducted by the National Center for Health Statistics of the Centers for Disease Control and Prevention, is a consecutive and population-based study carried out every 2 years to evaluate the nutrition and health status of the U.S. non-institutionalized population. NHANES encompasses a wide range of data, including demographics, dietary, examination, laboratory and questionnaire data, providing detailed information about demographics characteristics, socioeconomic status, physiological measurements, biochemical indicators and standardized questionnaires about health in various aspects. To ensure the reliability and representativeness of the data, NHANES implements a complex, multistage, probability sampling design, as well as oversampling of specific subpopulations. Additionally, the compensation provided to participants helps to ensure the collection of reliable and high-quality data.

In the current study, we included 7,171 postmenopausal women aged 50 years and older in 6 cycles from NHANES 2007–2008 to 2017–2018. Menopausal status was defined based on the self-reported reproductive health questionnaire. Postmenopausal women were limited to participants who answered "no" to the question "Have you had at least one menstrual period in the past 12 months?"and subsequently answered "hysterectomy" or "menopause/change of life" to the question "What is the reason that you have not had a period in the past 12 months?". Details of the current study sampling, and exclusion criteria are described in Figure 1. A total of 2,605 adults without bone mineral density examination and 505 individuals without complete dietary recall data were excluded from the study, and participants whose total energy intake >6,000 or <500 kcal per day ($n = 23$) were excluded

to eliminate the influences of extreme individuals. Additionally, the study excluded adults without information on education ($n = 6$), family income ($n = 380$) and marital status ($n = 1$). After excluding participants with missing values of serum calcium ($n = 152$), vitamin D ($n = 64$) and body mass index (BMI) as well as without detailed information on cardiovascular disease ($n = 1$), cancer ($n = 3$) and chronic kidney disease ($n = 1$), the final sample included 3,421 postmenopausal women with complete data for analysis in the study.

Outcome ascertainment

Participants underwent BMD examinations by dual-energy X-ray absorptiometry in mobile examination center by trained and certified radiology technologists, in which pregnant females, participants with self-reported history of radiographic contrast material in the past 7 days or with measured weight over 450 pounds met the exclusion criteria from the DXA examination. Detailed descriptions are provided in the DXA examination protocol documented in the Body Composition Procedures Manual. Low BMD and osteoporosis were defined on the basis of the total femur (TF), femoral neck (FN), and lumbar spine (LS) BMD measurements used in previous studies (33). The mean BMD values of female participants aged between 20 and 29 years old was used as the reference values. Individuals with any BMD value <2.5 standard deviations below the reference value were considered as osteoporosis, while individuals with any BMD value <1 standard deviations below the reference value were considered was low BMD (34, 35). Further details of female participants aged between 20 and 29 years old are listed in Supplementary Table 1.

Exposures

The HEI-2015 is established to assess diet quality, specifically the degree to which a set of foods aligns with the 2015–2020 DGA. HEI-2015 has been developed from the HEI-2010 by replacing empty calories with saturated fat and added sugar, with the result being 13 components (31). Although the most recent edition of DGA (2020–2025) has been published and corresponding HEI-2020 has been developed, the 13 components and scoring standards of the HEI-2020 fully align with the HEI-2015 and it was renamed just to clarify the consistency of 2020–2025 DGA (36). HEI-2015 is a density-based index specifically based on dietary nutrients intake per 1,000 kcal rather than absolute amount, and the total score range from 0 to 100 in which higher score indicate higher adherence to 2015–2020 DGA and higher diet quality. Nutrients intakes and alcohol consumption were calculated with the mean of two 24-h dietary recalls and then HEI-2015 were obtained by corresponding scoring standards, in which a face-to-face interview in the first day and a follow-up interview 3–10 days later by telephone were conducted. For subsequent statistical analyses, HEI-2015 was categorized into three groups with tertiles and the lowest tertile was set as the reference group.

Assessment of covariates

Various demographic variables were taken into consideration in current study, including age group (middle-aged, 50–64 years; older, ≥65 years), race (non-Hispanic White, non-Hispanic Black, Mexican Americans, and other races), education level (less than high school degree, high school degree, more than high school degree), family income level (measured as the ratio of family income to poverty (PIR), low family income: PIR ≤ 1.3, medium family income: 1.3 < PIR < 3.5, high family income: PIR ≥ 3.5), marital status (married or living with partner; divorced, separated, or widowed; never married). In additional, lifestyle factors such as BMI (normal or low body weight: <25, overweight: 25–29.9, obese: ≥30), serum cotinine levels (low: <1, medium: 1–10, high: ≥10), alcohol consumption (nondrinker: = 0, moderate drinker: 0–30 g/day for men and 0–15 g/day for women, heavy drinker: ≥ 30 g/day for men and ≥ 15 g/day for women), and leisure time physical activity (LTPA, calculated as twice the duration of vigorous physical activity plus the duration of moderate physical activity) were adjusted (37–40). Furthermore, total energy intake (expressed as kilocalorie) was adjusted for as the components of HEI-2015 were density-based rather than absolute dietary nutrients intake, and serum calcium and vitamin D were also taken into account. A series of chronic non-communicable disease including hypertension, cardiovascular diseases (CVD), diabetes, chronic kidney disease (CKD) and cancer were included on account of the associations with BMD. Hypertension was defined as average systolic pressure ≥ 140 mm Hg and/or diastolic pressure ≥ 90 mm Hg in 3 tests or self-reported hypertension. CVD was defined as self-reported diagnosis of congestive heart failure, coronary heart disease, angina, myocardial infarction or stroke by a professional doctor. Diabetes was defined as fasting plasma glucose ≥ 7.0 mmol/L, 2-h plasma glucose ≥ 11.0 mmol/L, hemoglobin A1c ≥ 6.5% or self-reported diabetes by a professional doctor. CKD was defined as an estimated glomerular filtration rate < 75 with the CKD-Epidemiology Collaboration (EPI) equation (41). Cancer was defined as self-reported cancer or a malignancy by a professional doctor or other health professional.

Statistical analysis

According to analytic guidelines in NHANES, dietary two-day sample weight, clustering, and stratification were taken into account. Moreover, dietary two-day sample weight divided by 6 was utilized to make the final sample representative of the national non-institutionalized population as the data of 6 consecutive cycles were combined in our analyses.

Statistical descriptions were presented by continuous variables expressed as weighted means (standard deviations), and categorical variables expressed with numbers (weighted percentages). Analyses of variance and Rao-Scott adjusted chi-square tests were used to compare the characteristics between adults across different HEI-2015 tertiles. Univariate and multivariate weighted logistic regression models were employed to explore the associations of HEI-2015 with low BMD and osteoporosis in the general population, in which model 1 was unadjusted, model 2 was adjusted

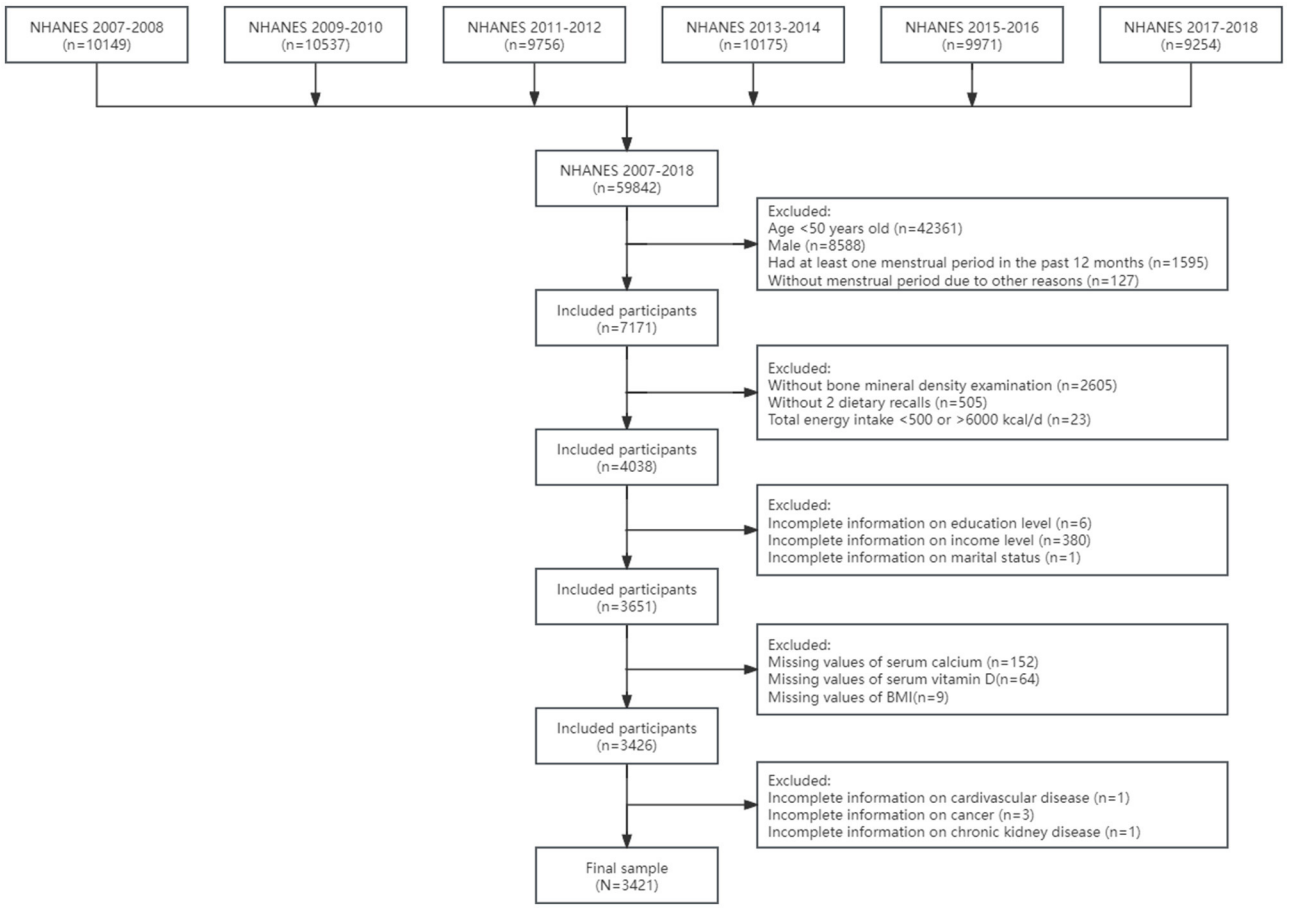

FIGURE 1
The flowchart of sample design. BMI, body mass index; NHANES, National Health and Nutrition Examination Survey.

for demographics variables (Age group, race, education level, income level, marital status) while model 3 was the fully adjusted model additionally adjusted for BMI status, serum cotinine level, alcohol consumption, LTPA, serum calcium and vitamin D and comorbidity (hypertension, CVD, diabetes, CKD and cancer) based on model 2. Moreover, trend tests (p for trend) were performed by entering the tertile-categorical HEI-2015 as a continuous variable and rerunning the corresponding regression models. Three sensitivity analyses were further conducted to validate the robustness of our results: (1) HEI-2015 was categorized into quartiles but not tertiles; (2) the definition of low BMD and osteoporosis was revised to be based on femoral neck and lumber spine BMD while total femur BMD was not considered; (3) we excluded participants who had previously taken anti-osteoporotic drugs to eliminate the influence. Stratified analyses were conducted to investigate whether the associations differ by demographic variables (age group, race, education level, income level and marital status) and interaction effects were tested. Weighted restricted cubic splines (RCS) were utilized to examine the nonlinear correlations of HEI-2015 with low BMD and osteoporosis, with three knots located at the 25th, 50th, and 75th percentiles of the distributions. Weighted quantile sum (WQS) regression models were employed to assess the contributions of various components to reducing the osteoporosis risk. The individual weight for each component in the HEI-2015 was estimated using quartiles (q=4) through bootstrap sampling ($n = 100$), where the data were randomly split into the training set (90%) and the validation set (10%).

All other statistical analyses were performed in Stata software (version 17.0, StataCorp LLC) except for analyses of variance and WQS in R software (version 4.2.2). All statistical tests were two-sided, and significance was considered at $\alpha = 0.05$.

Results

Characteristics

Characteristics of postmenopausal women grouped by tertiles of HEI-2015 were presented in Table 1. The final sample included 3,421 participants representative for 28.38 million non-institutionalized postmenopausal women (mean [SD] HEI-2015, 57.72 [13.00]; mean [SD] age, 62.63 [8.85]; 1,731 [weighted 75.5%] non-Hispanic White). Meanwhile, the prevalence of low BMD and osteoporosis are 65.8% and 10.2%, respectively.

In comparison to the lowest HEI-2015 tertile, adults in higher tertiles were more likely to be non-Hispanic White, married or

TABLE 1 The characteristics by tertiles of the HEI-2015.

Characteristics	Tertile 1 (≤51.82) (*n* = 1,175)	Tertile 2 (51.82–63.45) (*n* = 1,072)	Tertile 3 (>63.45) (*n* = 1,174)	Overall (*N* = 3,421)	*P* value
Age group (n/%)					0.0846
Middle-aged (50–64 y)	729 (67.7%)	591 (62.8%)	619 (60.4%)	1,939 (63.6%)	
Older (≥65 y)	446 (32.3%)	481 (37.2%)	555 (39.6%)	1,482 (36.4%)	
Race (n/%)					0.0041
Non-Hispanic White	600 (73.4%)	563 (78.4%)	568 (74.6%)	1,731 (75.5%)	
Non-Hispanic Black	275 (11.7%)	199 (7.9%)	190 (7.5%)	664 (9.0%)	
Mexican Americans	147 (5.1%)	126 (4.5%)	142 (4.5%)	415 (4.7%)	
Other races	153 (9.7%)	184 (9.2%)	274 (13.5%)	611 (10.8%)	
Education level (n/%)					<0.0001
<High school	292 (16.4%)	235 (13.0%)	229 (11.9%)	756 (13.8%)	
High school	361 (34.8%)	257 (24.8%)	250 (18.9%)	868 (26.2%)	
>High school	522 (48.8 %)	580 (62.1%)	695 (69.2%)	1,797 (60.0%)	
Family income level (n/%)					0.0005
Low	379 (21.7%)	276 (15.5%)	279 (14.2%)	934 (17.1%)	
Medium	488 (38.8%)	427 (33.1%)	439 (34.4%)	1,354 (35.4%)	
High	308 (39.5%)	369 (51.5%)	456 (51.4%)	1,133 (47.5%)	
Marital Status (n/%)					0.0010
Married or living with partner	558 (53.5%)	601 (66.8%)	631 (62.3%)	1,790 (60.9%)	
Divorced, separated, or widowed	533 (40.7%)	401 (29.6%)	472 (32.4%)	1,406 (34.2%)	
Never married	84 (5.8%)	70 (3.6%)	71 (5.3%)	225 (4.9%)	
BMI status (n/%)					<0.0001
Normal or low body weight	251 (23.6%)	286 (26.4%)	358 (36.6%)	895 (28.9%)	
Overweight	350 (27.8%)	367 (35.1%)	425 (33.7%)	1,142 (32.2%)	
Obese	574 (48.6%)	419 (38.5%)	391 (29.7%)	1,384 (38.9%)	
Serum cotinine (n/%)					<0.0001
Low (<1)	816 (70.9%)	894 (81.7%)	1,079 (91.4%)	2,789 (81.3%)	
Medium (1–10)	34 (1.9%)	20 (2.3%)	18 (1.4%)	72 (1.8%)	
High (≥10)	325 (27.2%)	158 (16.0%)	77 (7.3%)	560 (16.8%)	
Alcohol consumption (n/%)					0.0003
Nondrinker	971 (80.0%)	815 (72.1%)	880 (65.3%)	2,666 (72.5%)	
Moderate drinker	115 (10.3%)	128 (12.0%)	166 (18.2%)	409 (13.5%)	
Heavy drinker	89 (9.7%)	129 (15.9%)	128 (16.6%)	346 (14.1%)	
Hypertension (n/%)	860 (67.7%)	740 (61.6%)	775 (59.3%)	2,375 (62.9%)	0.0720
CVD (n/%)	198 (14.3%)	159 (14.6%)	128 (9.5%)	485 (12.8%)	0.0230
Diabetes (n/%)	310 (21.1%)	280 (20.0%)	265 (16.6%)	855 (19.2%)	0.1659
CKD (n/%)	367 (29.4%)	341 (31.9%)	381 (32.8%)	1,089 (31.3%)	0.5879
Cancer (n/%)	180 (15.4%)	183 (18.3%)	185 (18.0%)	548 (17.2%)	0.3957
Low BMD (n/%)	770 (65.8%)	734 (65.8%)	786 (65.9%)	2,290 (65.8%)	0.9984
Osteoporosis (n/%)	138 (13.5%)	125 (8.7%)	120 (8.4%)	383 (10.2%)	0.0176
Serum calcium (mg/dL), Mean (SD)	9.44 (0.39)	9.47 (0.36)	9.48 (0.40)	9.46 (0.38)	0.149

(Continued)

TABLE 1 (Continued)

Characteristics	Tertile 1 (≤51.82) (*n* = 1,175)	Tertile 2 (51.82–63.45) (*n* = 1,072)	Tertile 3 (>63.45) (*n* = 1,174)	Overall (*N* = 3,421)	*P* value
Serum vitamin D (nmol/L), Mean (SD)	75.28 (34.20)	81.12 (32.32)	85.91 (34.82)	80.77 (34.07)	<0.001
Total energy intake (kcal), Mean (SD)	1,744.45 (621.88)	1,771.99 (595.99)	1,673.97 (527.78)	1,730.10 (584.48)	0.086
LTPA (min/wk), Mean (SD)	82.56 (190.97)	140.71 (252.49)	167.80 (272.39)	130.40 (243.70)	<0.001

BMD, bone mineral density; CKD, chronic kidney disease; CVD, cardiovascular disease; LTPA, leisure time physical activity.

living with partner, normal or low body weight, and less likely to be non-drinker and comorbid with CVD and osteoporosis. Moreover, adults in higher tertiles had higher education level, family income level, LTPA, and serum vitamin D and lower serum cotinine. Nevertheless, no significant differences in low BMD prevalence across groups of HEI-2015 tertiles were observed.

Associations of HEI-2015 with low BMD and osteoporosis

As described in Table 2, stepped weighted logistic regression models revealed the negative associations of continuous HEI-2015 and HEI-2015 tertiles with osteoporosis risk in 3 models, but no significant relationship between HEI-2015 and low BMD was observed, neither continuous HEI-2015 nor HEI-2015 tertiles. Compared with the lowest HEI-2015 tertile, the second (OR: 0.57, 95%CI: 0.38–0.84) and the third (OR: 0.48, 95%CI: 0.29–0.78) tertiles were associated with lower risks of osteoporosis in the fully adjusted model. Additionally, there were significant trends observed across the HEI-2015 tertiles. Moreover, all three sensitivity analyses demonstrated similar correlations and trends as shown in Table 3, suggesting the strong and consistent associations between continuous HEI-2015, HEI-2015 tertiles, and the risk of osteoporosis.

Subgroup analyses and interaction effects of the associations of HEI-2015 with low BMD and osteoporosis

Tables 4, 5 exhibit the associations between HEI-2015 and low BMD with osteoporosis in demographic subpopulations in the fully adjusted models. The relationship between HEI-2015 and the risk of low BMD was not observed in all subpopulations except for older adults in which the trends were also observed. Furthermore, the study did not identify any interactions between demographic variables and HEI-2015 in relation to the risk of low BMD. Nevertheless, the correlations between HEI-2015 and the risk of osteoporosis were identified in various subgroups including all age groups, non-Hispanic White participants, individuals with less than and more than a high school education, high family income level and divorced, separated, or widowed postmenopausal women. Moreover, the trends were also identified to be significant. In addition, significant interaction effects of income ($P = 0.0210$) were shown, suggesting that the correlation was only identified to be significant in high family income subgroups.

Nonlinear associations of HEI-2015 with low BMD and osteoporosis

Weighted RCS were conducted to assess the nonlinear associations of HEI-2015 with the risks of low BMD and osteoporosis in the fully adjusted model, the results of which were displayed in Figure 2. Significant negative non-linear association of HEI-2015 and osteoporosis risk ($P = 0.0112$) was observed in Figure 2B while no significant relationship between HEI-2015 and the risk of low BMD ($P = 0.7130$) was demonstrated in Figure 2A. The results suggest that as HEI-2015 increase, osteoporosis risk decrease in a nonlinear manner.

Mixed effect of HEI-2015 on osteoporosis

WQS regression models were employed and the results were shown in Figure 3 to assess the impact of various components on reducing the risk of osteoporosis. In the fully adjusted model, the WQS index of HEI-2015 (OR: 0.16, 95%CI: 0.06–0.45) demonstrated the significant association with decreased risk of osteoporosis. Specifically, total vegetables (26.00%), refined grains (10.64%) and greens and beans (8.80%) were identified as the most weighted components, indicating that these three components contributed the most to reducing the osteoporosis risk.

The fully adjusted model was exclusively employed in the WQS model, encompassing adjustments for demographics data, BMI status, smoking status, alcohol consumption, LTPA, total energy intake, serum calcium and vitamin D levels, and comorbidities.

Discussions

Based on data from 6 cycles of the large cross-sectional survey, we found that diet quality assessed by HEI-2015 was negatively associated with osteoporosis risk in postmenopausal women aged 50 years and older while no significant association between HEI-2015 and risk of low BMD was identified. Moreover, these results were consistent across three sensitivity analyses, suggesting the robustness of our results. In addition, subgroup analyses and interaction effects demonstrated the stability of the

TABLE 2 The associations of HEI-2015 with low BMD and osteoporosis.

HEI-2015	Low BMD			Osteoporosis		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
Continuous	1.002 (0.994,1.011)	1.002 (0.993,1.011)	0.998 (0.988,1.007)	0.982 (0.968,0.996)	0.981 (0.966,0.996)	0.977 (0.961,0.992)
T1	ref	ref	ref	ref	ref	ref
T2	1.00 (0.75,1.34)	0.98 (0.73,1.33)	0.97 (0.71,1.33)	0.61 (0.42,0.90)	0.61 (0.42,0.89)	0.57 (0.38,0.84)
T3	1.00 (0.77,1.32)	0.96 (0.72,1.27)	0.86 (0.64,1.15)	0.59 (0.37,0.93)	0.54 (0.34,0.86)	0.48 (0.29,0.78)
P trend	0.972	0.762	0.298	0.021	0.010	0.004

BMD, bone mineral density.
Model 1 was unadjusted.
Model 2 was adjusted for demographics data.
Model 3 was the fully adjusted model adjusted for demographics data, BMI status, smoking status, alcohol consumption, LTPA, total energy intake, serum calcium and vitamin D, and comorbidity.

TABLE 3 The sensitivity analyses of associations of HEI-2015 with low BMD and osteoporosis.

HEI-2015	Low BMD			Osteoporosis		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
Sensitivity analysis 1 (HEI-2015 categorized into quartiles)						
Continuous	1.002 (0.994,1.011)	1.002 (0.993,1.011)	0.998 (0.988,1.007)	0.982 (0.968,0.996)	0.981 (0.966,0.996)	0.977 (0.961,0.992)
Q1	ref	ref	ref	ref	ref	ref
Q2	1.03 (0.75,1.42)	1.09 (0.77,1.53)	1.09 (0.76,1.57)	0.85 (0.56,1.28)	0.89 (0.59,1.35)	0.88 (0.57,1.37)
Q3	1.11 (0.75,1.65)	1.10 (0.74,1.63)	1.01 (0.67,1.52)	0.69 (0.44,1.10)	0.68 (0.40,1.15)	0.61 (0.38,0.99)
Q4	1.04 (0.76,1.43)	1.06 (0.77,1.45)	0.93 (0.66,1.30)	0.61 (0.37,1.01)	0.61 (0.37,1.01)	0.54 (0.31,0.92)
P trend	0.712	0.754	0.577	0.047	0.047	0.015
Sensitivity analysis 2 (The definition of low BMD and osteoporosis based on femoral neck and lumber spine)						
Continuous	1.003 (0.994,1.011)	1.002 (0.993,1.011)	0.997 (0.988,1.007)	0.978 (0.964,0.992)	0.976 (0.961,0.992)	0.971 (0.956,0.987)
T1	ref	ref	ref	ref	ref	ref
T2	0.99 (0.74,1.33)	0.98 (0.72,1.32)	0.96 (0.71,1.31)	0.61 (0.41,0.91)	0.61 (0.41,0.90)	0.56 (0.37,0.84)
T3	1.01 (0.76,1.35)	0.96 (0.71,1.29)	0.85 (0.63,1.16)	0.41 (0.31,0.83)	0.47 (0.28,0.78)	0.41 (0.24,0.68)
P trend	0.928	0.780	0.302	0.006	0.003	0.001
Sensitivity analysis 3 (Excluded participants who had previously taken anti-osteoporotic drugs)						
Continuous	1.001 (0.992,1.010)	1.001 (0.991,1.011)	0.996 (0.986,1.006)	0.986 (0.972,0.999)	0.986 (0.972,0.999)	0.981 (0.966,0.996)
T1	ref	ref	ref	ref	ref	ref
T2	0.94 (0.68,1.28)	0.93 (0.68,1.29)	0.91 (0.65,1.27)	0.62 (0.41,0.91)	0.63 (0.42,0.95)	0.58 (0.38,0.87)
T3	0.94 (0.71,1.24)	0.90 (0.67,1.21)	0.80 (0.58,1.09)	0.60 (0.37,0.96)	0.56 (0.35,0.90)	0.49 (0.30,0.80)
P trend	0.663	0.483	0.145	0.032	0.019	0.006

BMD, bone mineral density.
Model 1 was unadjusted.
Model 2 was adjusted for demographics data.
Model 3 was the fully adjusted model adjusted for demographics data, BMI status, smoking status, alcohol consumption, LTPA, total energy intake, serum calcium and vitamin D, and comorbidity.

associations in various demographic subgroups, with a particularly pronounced effect observed in participants with high family income. Furthermore, weighted RCS indicated the existence of non-linear association of HEI-2015 and osteoporosis risk, suggesting the osteoporosis risk decrease with HEI-2015 in a non-linear manner. Finally, we determined the contributions of different components of HEI-2015 to reducing the risk of osteoporosis with WQS. We found that total vegetables, refined grains, and greens and beans had the highest percentages of contribution, amounting to 26.00%, 10.64%, and 8.80% respectively. These findings suggest that focusing on these specific components of the diet may be particularly beneficial in reducing the risk of osteoporosis.

Apart from nutrients intake and food groups, recent studies have emphasized the importance of evaluating overall dietary patterns on osteoporosis and BMD and found the beneficial effect, since it takes into account the overall combination and balance

TABLE 4 The relationship between HEI-2015 and low BMD in demographic subgroups.

Characteristics	T1	T2	T3	*P* for interaction	*P* for trend
Age group (n/%)				0.5013	
Middle-aged adults (50–64 y)	Ref	1.04 (0.73,1.49)	1.00 (0.71,1.40)		0.977
Older adults (≥65 y)	Ref	0.78 (0.45,1.37)	0.56 (0.32,0.98)		0.038
Race (n/%)				0.3546	
Non-Hispanic White	Ref	0.94 (0.62,1.41)	0.83 (0.56,1.41)		0.354
Non-Hispanic Black	Ref	0.80 (0.48,1.33)	1.01 (0.59,1.75)		0.973
Mexican Americans	Ref	0.80 (0.38,1.67)	1.00 (0.51,1.94)		0.923
Other races	Ref	1.61 (0.69,3.73)	0.56 (0.29,1.08)		0.064
Education level (n/%)				0.9315	
<High school	Ref	0.80 (0.43,1.46)	0.94 (0.50,1.77)		0.817
High school	Ref	1.16 (0.63,2.13)	0.98 (0.53,1.80)		0.955
>High school	Ref	0.94 (0.59,1.49)	0.80 (0.51,1.26)		0.313
Family income level (n/%)				0.7785	
Low	Ref	0.86 (0.47,1.57)	0.71 (0.44,1.15)		0.162
Medium	Ref	0.96 (0.55,1.67)	1.05 (0.62,1.79)		0.863
High	Ref	0.93 (0.56,1.57)	0.75 (0.47,1.20)		0.204
Marital status (n/%)				0.5044	
Married or living with partner	Ref	0.89 (0.57,1.39)	0.79 (0.53,1.17)		0.224
Divorced, separated, or widowed	Ref	0.99 (0.55,1.77)	1.01 (0.60,1.70)		0.976
Never married	Ref	1.33 (0.42,4.17)	0.53 (90.15,1.91)		0.369

All models were fully adjusted for demographics data, BMI status, smoking status, alcohol consumption, LTPA, total energy intake, serum calcium and vitamin D, and comorbidity.

of foods consumed and nutrients intake, and have a broader and more comprehensive approach to nutrition. For instance, a Southern Spain study found the significant linear trends between the Mediterranean diet score and BMD, indicating the benefits of a varied diet based on Mediterranean diet patterns may be beneficial in the prevention of osteoporosis in postmenopausal women (27). Another study involving 418 healthy volunteers concluded that higher adherence to the Mediterranean diet was associated with higher T-score indicating better bone health status (28). Furthermore, a meta-analysis consisting of 6 cohorts, 6 cross-sectional and 1 case-control studies identified the higher BMD in participants with higher adherence to the Mediterranean diet (29). Similarly, higher DASH score was found to be associated with lower risk of osteoporosis at lumbar spine, but no significant relationship between DASH score and risk of osteoporosis at femoral neck was observed (30). Moreover, the Boston Puerto Rican osteoporosis study found that DASH was more positively associated with BMD than alternative HEI or Mediterranean diet score in postmenopausal women without estrogen (42).

HEI-2015, a measure to assess the degree of individual food intake align with DGA, was adopted in the current study to reflect diet quality. A similar study focusing on middle-aged and older Americans has evaluated the association between HEI-2015 total and component food scores with osteoporosis, and they found the significant negative association, similar to our study (43). In comparison with that study, we further extended the analyses and explored the associations in postmenopausal women and adjusted for various confounding factors including demographics variables, lifestyle factors, dietary and serum nutrition status, and comorbidities. In addition, we conducted sensitivity analyses, subgroup analyses, interaction effect, RCS and WQS models. Considering the robustness of the results, the dose-response relationships, and the contributions of various components, our study provides important insights into the associations of HEI-2015 and osteoporosis in postmenopausal women.

The results of RCS models revealed the significant association of HEI-2015 and osteoporosis risk in a non-linear manner. Specifically, the dose-response curves indicated a steep relationship between HEI-2015 and osteoporosis risk when the HEI-2015 score was relatively low. However, as the HEI-2015 score increased to higher levels, the relationship tended to become smoother. It cannot be denied that the improvements in diet quality may have a substantial impact on reducing the risk of osteoporosis especially HEI-2015 is at a poor or low level, and this finding suggests that improving diet quality from a poor or low level to a moderate level may have a more pronounced effect on reducing the risk of osteoporosis.

In addition, WQS displayed that total vegetables, refined grains, and greens and beans contributed the most on reducing the osteoporosis risk. Higher vegetables intake was found to be associated with lower osteoporosis risk in a cross-sectional study, and a meta-analysis concluded that higher vegetable-based diet

TABLE 5 The relationship between HEI-2015 and osteoporosis in demographic subgroups.

Characteristics	T1	T2	T3	*P* for interaction	*P* for trend
Age group (n/%)				0.3447	
Middle-aged adults (50–64 y)	Ref	0.57 (0.29,1.13)	0.35 (0.14,0.83)		0.020
Older adults (≥65 y)	Ref	0.56 (0.34,0.91)	0.54 (0.32,0.93)		0.033
Race (n/%)				0.7028	
Non-Hispanic White	Ref	0.54 (0.33,0.90)	0.42 (0.23,0.77)		0.006
Non-Hispanic Black	Ref	0.87 (0.26,2.93)	0.85 (0.32,2.30)		0.753
Mexican Americans	Ref	0.54 (0.26,1.13)	0.71 (0.25,2.00)		0.507
Other races	Ref	0.82 (0.25,2.05)	0.56 (0.23,1.39)		0.207
Education level (n/%)				0.1092	
<High school	Ref	0.79 (0.40,1.58)	0.30 (0.11,0.82)		0.015
High school	Ref	1.04 (0.50,2.16)	0.98 (0.46,2.08)		0.971
>High school	Ref	0.40 (0.21,0.77)	0.38 (0.19,0.76)		0.011
Family income level (n/%)				0.0210	
Low	Ref	0.98 (0.52,1.85)	0.71 (0.36,1.43)		0.365
Medium	Ref	0.94 (0.54,1.64)	0.63 (0.31,1.27)		0.188
High	Ref	0.22 (0.10,0.48)	0.26 (0.13,0.53)		0.001
Marital status (n/%)				0.7524	
Married or living with partner	Ref	0.61 (0.35,1.08)	0.59 (0.33,1.06)		0.081
Divorced, separated, or widowed	Ref	0.52 (0.28,0.99)	0.42 (0.21,0.83)		0.013
Never married	Ref	1.02 (0.30,1.47)	0.28 (0.05,1.65)		0.155

All models were fully adjusted for demographics data, BMI status, smoking status, alcohol consumption, LTPA, total energy intake, serum calcium and vitamin D, and comorbidity.

intake was related with reduced osteoporosis risk (44). However, the results in a meta-analysis displayed the significant negative association of vegetable intake and postmenopausal women in case-control studies but not in cross-sectional studies, indicating the heterogeneity of results and encouraging more high-quality studies such as randomized controlled trials to explore the relationships (45). Furthermore, a two-sample Mendelian randomization study found the causal relationship between servings of raw vegetables per day and osteoporosis, providing strong literature evidence (46). The protective effect of vegetables against osteoporosis may be attributed to their rich content of vitamins and minerals like vitamin C, which have been described earlier to be negatively correlated with osteoporosis.

In addition, the similar article also found that the negative association of beans consumption and osteoporosis risk, and a study involving 1,433 Korean postmenopausal women also found the preventive effect of higher beans intake on osteoporosis (47). Furthermore, the experiment in a rat model of osteoporosis found that consumption of yellow and black soybeans, and sword beans had a definite protective effect on inhibiting bone turnover and preventing bone resorption, thus leading to less bone loss and higher BMD (48). Specifically, researchers speculated that isoflavones and phytochemicals in these beans build the defense against osteoporosis. For instance, soy isoflavones as phytoestrogens exerted estrogen-like effect and were believed to decrease bone resorption marker urine deoxypyridinoline, inhibiting bone resorption and increasing lumbar spine BMD (49, 50). Meanwhile, beans are a good source of plant protein and proteins intake is positively associated with BMD and negatively related with osteoporosis regardless of protein source (51–53). Our results additionally demonstrated the beneficial effect of higher refined-grains score and lower refined-grains intake, and this may be attributed to the fact that refined grains are known to contain fewer vitamins, minerals, and phytosterols that are important for bone health and protection against osteoporosis (54). Furthermore, refined grains were found to decrease BMD by modulating osteoprotegerin and receptor activator of nuclear factor kappa B (NF-κB) in male rats (55).

Apart from the direct positive effect of estrogen deficiency on postmenopausal osteoporosis, oxidative stress, inflammation and immune cell alterations have been acknowledged to contribute to the pathogenesis of postmenopausal osteoporosis, in which healthy diet may play an important role in attenuating the development. Excessive reactive oxygen species production due to estrogen insufficiency not only disrupts the formation and functionality of osteoblasts, but also negatively affects their activity, viability, proliferation, and apoptosis (56–60). This leads to a reduction in osteoblastic number and functionality with consequent beginning and development of osteoporotic processes, resulting in the altered bone architecture and bone loss that characterize osteoporosis.

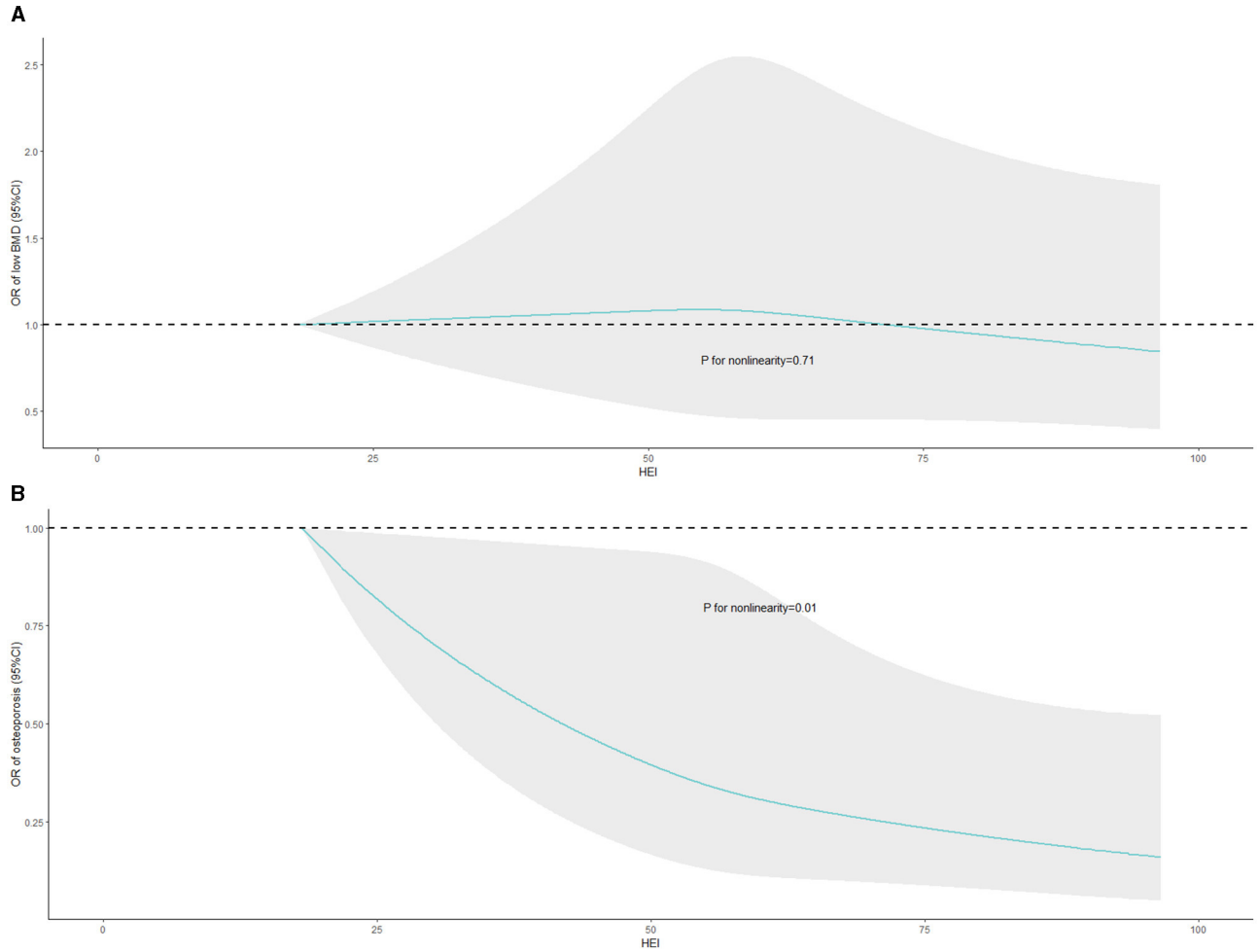

FIGURE 2
Nonlinear associations of HEI-2015 with the risks of low BMD and osteoporosis with weighted RCS. BMD, bone mineral density; HEI-2015, healthy eating index-2015; RCS, restricted cubic splines. The fully adjusted model was exclusively employed in the WQS model, encompassing adjustments for demographics data, BMI status, smoking status, alcohol consumption, LTPA, total energy intake, serum calcium and vitamin D levels, and comorbidities.

Postmenopausal women often exhibit a chronic low-grade inflammatory state with changes in cytokine expression and immune cell profile (61). Specifically, Estrogen deficiency activates the nucleotide-binding oligomerization domainlike receptor family pyrin domain-containing 3 (NLRP3) inflammasome expressed in osteoblasts and involved in immune innate response and inflammation, the abnormal activation of which plays an important role in the development of osteoporosis (62). Additionally, tissue necrosis factors α (TNF-α) was found to promote osteoblast apoptosis and indirectly stimulate osteoclastogenesis via B cell-produced receptor-activator of NF-κB ligand (RANKL), leading to bone loss during postmenopausal osteoporosis (63, 64). Interestingly, the gut-bone axis has emerged as a novel approach for the prevention and treatment of postmenopausal osteoporosis (65). Beneficial gut microbiota stimulates bone formation and inhibit bone resorption, making probiotic treatment a potential avenue for managing postmenopausal osteoporosis (66, 67). For instance, Prevotella was suggested to serve as a therapeutic agent or target for osteoporosis treatment since the proportion of Prevotella was identified lower in postmenopausal osteoporosis patients, and transplantation of Prevotella into ovariectomized mice helps in preventing bone loss (68).

The major strength of this study is the use of a large, nationally representative U.S. survey and the combination of data in 6 cycles, increasing the sample size and enhacing the generalizability of our results. Further, the adoptions of sensitivity analyses, subgroup analyses and interaction effects enhance the robustness and credibility of our results. Finally, weighted RCS and WQS models provided a more intuitive and comprehensive understanding of the dose-response relationships and contributions of various components. Nevertheless, it is undeniable that our study also has some limitations. Firstly, no causality but only associations could be inferred from this study as a result of the nature of cross-sectional studies. Secondly, some covariates were based on self-report but not medical records or medication, which may introduce potential bias and affect the reliability of the data. Finally, the effect of estrogen as the crucial determinant was

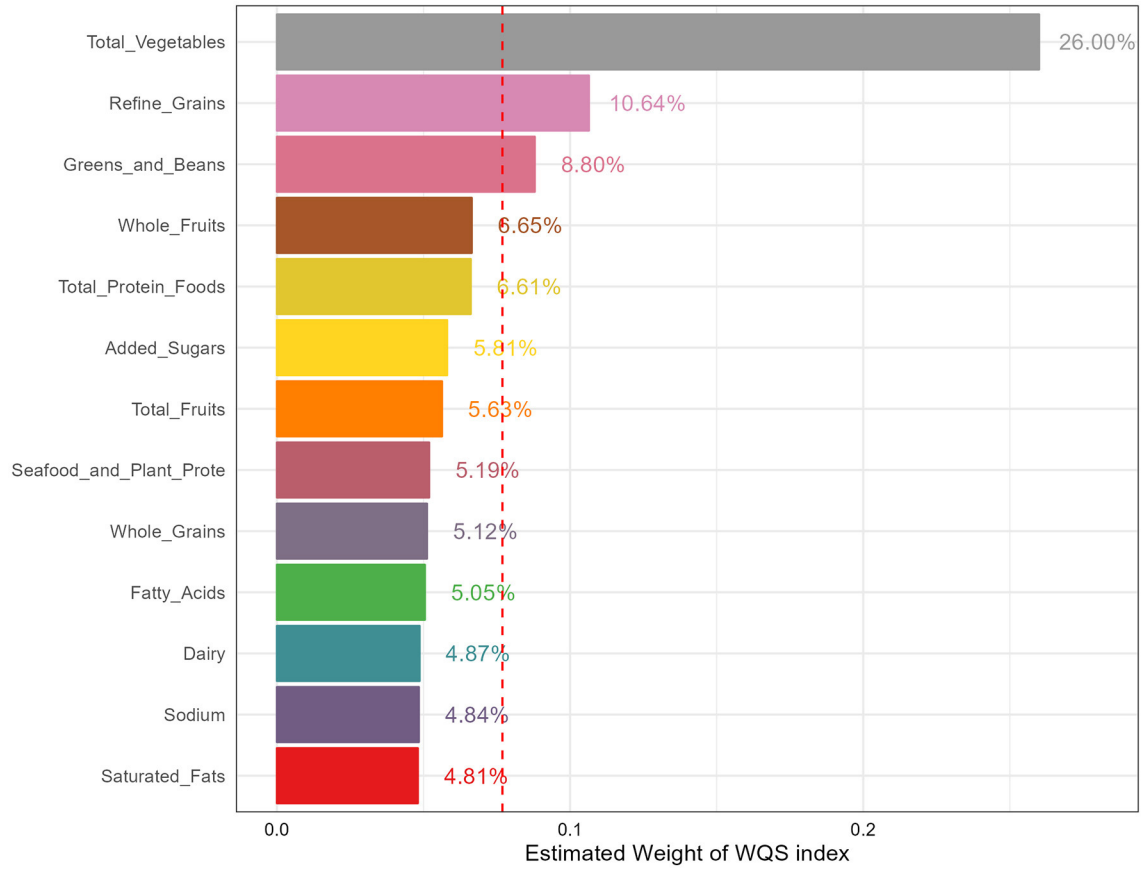

FIGURE 3
The estimated weight of various components in HEI-2015. HEI-2015, healthy eating index-2015; WQS, weighted quantile sum.

unavailable in the participants, which leave out the effect of sex hormones.

Conclusions

Among a nationally representative sample of U.S. postmenopausal women, we found the robust and negative associations of diet quality assessed by HEI-2015 and osteoporosis risk, but no significant association of low BMD was identified. Furthermore, the non-linear dose-response relationships remained stable in various sensitivity analyses and demographic subgroups, in which total vegetables, refined grains, and greens and beans contributed the most. By highlighting the relationships, we aim to emphasize the importance of adherence to dietary guidelines for Americans that can help reduce the osteoporosis risk.

Data availability statement

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

Author contributions

KW: Writing—original draft, Visualization, Validation, Supervision, Software, Methodology, Formal analysis, Data curation. JW: Writing—review & editing, Methodology. MD: Writing—review & editing, Methodology. FT: Writing—review & editing. QL: Writing—review & editing. XL: Writing—review & editing. FX: Writing—review & editing, Project administration.

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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.2024.1388647/full#supplementary-material

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Comparison of Dutch healthy eating and healthy eating indexes and anthropometry in patients with major depression with health subjects: a case-control study

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Background: Diseases and disorders related to mental health are spreading like other chronic diseases all around the world. Considering the role of food in the prevention and treatment of these disorders, including major depression, investigating the relationship between different food patterns and this disorder is of particular importance. The aim of this study was to compare Dutch healthy eating and healthy eating indexes and anthropometry in patients with major depression with healthy individuals.

Methods: In this case-control study, the final analysis was performed on 67 men and 111 women with an age range of 20–30 years. Height (cm), weight (kg), food frequency questionnaire (FFQ), physical activity (MET-min/week), demographic and PHQ-9 questionnaires were taken from all participants. In the following, all the food ingredients and their components were extracted and used to calculate HEI-2015 and DHD. Statistical analysis was performed using SPSS software with independent *t*-test, logistic regression and chi-square.

Results: It was found that people with major depression in this study were mostly women and occupied. The average HEI-2015 in healthy people and those with major depression was 58 and 54.3, respectively. Also, the average DHD in these people was 60.5 and 55, respectively. HEI-2015 and DHD had a significant negative correlation with depression score ($r = -0.16$, p-value $= 0.03$) ($r = -0.19$, p-value $= 0.01$). Also, in the logistic regression model, before and even after adjusting confounders, HEI-2015 and DHD had a reduced odds ratio in people suffering from major depression. The two groups did not differ significantly in terms of the average factors of height, weight and body mass index (BMI).

Conclusion: It seems that HEI2015 and DHD have a significant relationship in reducing major depression. However, due to the small number of studies in this regard, especially in the field of DHD, the need for more studies seems necessary.

KEYWORDS

major depression, Dutch Healthy Diet Index, healthy eating index 2015, PHQ-9, HEI

1 Introduction

Depressive disorders are one of the most important problems and concerns in the world (1). According to the World Health Organization, the second main cause of illness-related costs in 2020 was depression. In general, depressive disorders have affected about 350 million people of different ages (2). In some studies, the prevalence of depression in Iran has been stated as 8.2–43.3%, depending on the target groups studied, and a major part of this difference is related to age and the type of method used to measure depression (3, 4). Many factors are involved in depression. One of these factors is gender. As it has been stated that its prevalence in women is 2 times that of men (5). Another risk factor is the family history of depression, and it is actually a type of genetic risk factor (6). Another risk factor is alcohol and nicotine abuse (7, 8). Chronic diseases are another risk factor. It has been suggested that diseases such as diabetes, cardiovascular disease, infertility and some other diseases can be related to depression (9, 10). Age is another risk factor, and the highest prevalence of depression has been reported between 60 and 64 years and related to chronic diseases (11). Some other risk factors include marital status (12), bad events in life (13), low income (14), low education level (6), weight gain and obesity (15), and food intake (16).

Today, with the progress of various sciences, especially molecular sciences, the relationship of many non-infectious diseases with diet has been noticed. Diet is considered as a factor of prevention and even treatment of diseases. The relationship between food intake and depression has been investigated from different aspects. Some studies have investigated macronutrient and micronutrient intake in depression. For example, a prospective study with a follow-up of 8.5 years compared people with insufficient intake of more than four micronutrients compared to those with low intake of one micronutrient and its relationship with depression. It was found that people with insufficient intake of more than four micronutrients are more likely to suffer from depression by 37% (17). In a cross-sectional study, it was shown that a decrease in the intake of legumes, fruits and vegetables and an increase in the intake of sweets and refined sugars were associated with an increased risk of depression (18). Over time, by the creation of the opinion that people always receive a total of food and nutrients and these substances can have synergistic or reducing effects on each other, conducting studies in the form of food patterns became popular. One of the types of food patterns is the healthy eating index (HEI). Various studies have investigated the relationship between healthy eating index and depression. A case-control study in Iran obtained five dietary patterns using factor analysis. The results showed that following the HEI from the factor analysis was associated with a 39% reduction in depression (19). Also, in another cross-sectional study conducted in soldiers, it was shown that those who received the highest HEI-2010 had an 80% reduction in depression (20). Another study was conducted on overweight and obese women. In this study, in the final model and after adjusting for obesity, age, education, marital status, and caloric intake, HEI was not associated with depression (21).

Another dietary pattern that has been investigated is known as the Dutch Healthy Diet Index (DHD-Index). This dietary pattern was designed in 2012 based on the 2006 Dutch Healthy Diet Guidelines. This profile has 10 components including physical activity, vegetables, fruits and juices, fiber, fish, saturated and trans fatty acids, acidic foods and drinks, sodium and alcohol. Van lee and colleagues believe that individuals with high adherence to this pattern will have both high intakes of vitamins and minerals and a high nutrient density diet (16). The index was revised in 2015 and its components were changed to 15 components. These 15 components are vegetables, fruits, whole grains, legumes, nuts, dairy products, fish, tea, fat and oils, coffee, red meat, processed meat, sweetened beverages and juices, alcohol and salt (22). Studies that have examined the relationship between DHD-Index and depression are limited. One of these studies is a prospective study that stated that in the crude model, DHD-index and DASH were associated with a reduction in the risk of depression. After adjusting for socioeconomic factors, lifestyle and cardiovascular factors, only DHD-index was associated with a 17% reduction in depression (23). Also, a cross-sectional study in diabetic patients showed that in the entire diabetic population, the highest quartile of receiving DHD is associated with a reduction in the risk of depression (24). While the DHD-Index was established using Dutch dietary standards, its core principles apply to a wide range of populations around the world. The index highlights foods and dietary behaviors that are universally acknowledged to be beneficial for health, such as eating fruits, vegetables, and whole grains and avoiding excessive saturated fats and sugar (16). As a result, the DHD-Index can be an effective tool for evaluating dietary patterns and their connections with health outcomes across groups, and it provides a standardized framework for assessing adherence to these key dietary principles across different cultural contexts, including Iran.

The greatest incidence of depression is seen in the 20–30 age group in Iranian population (25). The results of existing studies on the relationship between HEI2015, BMI and DHD with depression are contradictory and, in some studies, a significant relationship has been observed, while in others no relationship has been observed. On the other hand, the number of studies in some fields is insufficient and the need for more studies is felt. Therefore, we decided to compare Dutch healthy eating and healthy eating indexes and anthropometry in patients with major depression ranging from 20 to 30 years old with healthy people.

2 Materials and methods

2.1 Study population

This research was conducted in Mehregan Hospital, Tehran, and participants were 178 totally (including 67 men and 111 women) with age of 20–30 years from the main centers for mental disorders [All 105 patients consumed antidepressant and in questionnaire (PHQ-9), it was definitely determined that all healthy people did not have depression and tendency to it]. Sampling method was simple and available. All people who had the conditions to enter the study and were willing to cooperate were included in the project. The exclusion criteria were: The presence of diseases affecting reception such as tumors, and kidney problems, following weight loss diets, taking drugs that affect appetite, and completing <70% of questions or refusing to continue questioning. In order to keep all information confidential, people were asked not to write their name and surname on the information

sheet, and personal information (name and surname and contact number) were collected in a separate notebook using only a code and note. This research was reviewed by the medical ethics committee of Islamic Azad University and approved under the code of ethics IR.IAU.SRB.REC.1401.151.

2.2 Anthropometric measurements

Anthropometric indices, including height and weight, were measured according to a standard protocol. Weight was measured and recorded with minimal clothing and without shoes using a scale with an accuracy of 100 grams. The height of people was measured using a tape measure while standing next to the wall without shoes while the shoulders were in normal conditions with an accuracy of 0.1 cm. The body mass index (BMI) of the subjects was calculated by dividing the weight by the square of the height (kg/m^2) of each person.

2.3 Dietary assessments

Nutritional information of people was collected face-to-face using a valid and reliable 147-item food frequency questionnaire (FFQ) (25, 26). People were asked to state their consumption of each of the 147 food items in the questionnaire in terms of day, week, month, and year. Finally, these amounts were converted into daily intakes in grams. A combination of the American food table was used to extract all the micro and macro nutrients available for each person (27). For mixed foods (such as pizza) the nutrients were calculated based on the sum of the nutrients of the food items that make up that food.

2.4 Calculation of HEI-2015

The calculation of this index was done in such a way that the data of the people were entered into the software and the macronutrients and micronutrients received by all the people participating in the study were calculated. HEI scoring was done based on previous studies (28).

2.5 Calculation of DHD-index

Ten components are required to calculate this index. Each of the components is scored from 0 to 10 and finally, with the sum of all components, the score range of this index is from 0 to 100 points. The components include physical activity, vegetables, fruits and juices, fiber, fish (even capsules containing fish oil), saturated fatty acids, trans fatty acids, acidic foods and drinks, sodium and alcohol (16).

2.6 Measuring depression

Major depression was measured in all subjects based on the PHQ-9 questionnaire. This questionnaire was designed and validated in 2001 by Robert Kroenke and his colleagues at Columbia University (29). The validity and reliability of this questionnaire has also been measured in Iran (30, 31). This questionnaire contains nine questions with a Likert scale. Answers to these questions are scored from 0 (in everything) to 3 (almost every day). Finally, each person received 0 to 27 points. A score above 20 was classified as severe depression, a score of 15–19 as moderately severe depression, a score of 10–14 as moderate depression, a score of 5–9 as mild depression, and a score of 0–4 as no depression.

2.7 Sample size

The sample size in the present study includes people living in Tehran. People were randomly selected. The sample size was calculated using G-power software version 3.1.9.7 (32) with settings for Linear Bivariate Regression studies and Correlation studies: Bivariate model as follows, and the highest number calculated in the above two cases is equal to 166 people. It is that by taking into account 20% probability of spillage, a total of 188 people were considered as a sample, who were randomly selected from among the volunteers who filled out the questionnaires. Finally, 80 people have been considered for each group, and considering the 10% reduction, 90 people have been considered for each group.

2.8 Statistical analysis

All data were analyzed using SPSS version 26. In the present study, correlation between DHD, HEI and major depression indexes was investigated. Shapiro-Wilk test and histogram curve were used to check the normality of the variables, and Chi-square test was used to determine the relationship between qualitative independent variables. Pearson's correlation was used to examine the relationship between quantitative variables. *T*-test was used to compare the data. Also, logistic regression was used in order to measure correlation and adjusting confounders. *P*-value <0.05 was considered as significant.

3 Result

Determination and comparison of demographic characteristics, HEI, DHD, and anthropometric measurements between healthy people and patients with major depression.

One hundred and eighty-eight people were examined. A number of people were excluded from the study due to the defects of the questionnaires and non-cooperation, and thus, the final analyzes were performed on 178 people. In chi-square analysis, it was found that healthy people and people with depression in terms of gender ($P = 0.04$), employment status ($P = 0.019$), family history of depression ($P = 0.02$) and history of depression ($P = 0.001$) had a significant difference with each other. A higher percentage of depression was observed in the working group compared to students or unemployed people; However, in the comparison of the two groups, no difference was observed in terms of marital status, education, smoking, alcohol consumption, special diet, or omega-3 consumption (Table 1). In the *t*-test analysis, it was found

that healthy people have a higher average HEI index than the depressed group. This difference was statistically significant ($P = 0.004$) (Table 1). More than that, the average DHD index in healthy and sick people was 60.5 and 55.0, respectively, and this difference was statistically significant ($P = 0.004$) (Table 1). Plus, the two groups were not significantly different in terms of weight, height and BMI. The average BMI in the healthy and depressed groups was calculated as 25.4 and 24.6 kg/m^2, respectively (Table 1).

3.1 Determining the relationship between HEI and DHD index and depression score

In Pearson's correlation, it was found that there is a negative but very weak correlation and a significant relationship between HEI and depression score ($P = 0.03$, $r = 0.16$). Also, there was a negative but very weak correlation and a significant relationship between DHD index and depression score ($P = 0.01$, $r = -0.19$).

3.2 Determining the relationship between HEI and the incidence of major depression

Logistic regression was used to investigate the relationship between following HEI and the occurrence of major depression. In the crude models, model 1 and also model 2, the increase in compliance with HEI was related to the decrease in the risk of major depression (Table 2).

3.3 Determining the relationship between DHD and major depression

Logistic regression was used to investigate the relationship between following DHD and the occurrence of major depression. In the crude models, model 1 as well as model 2, the increase in compliance with DHD was related to the decrease in the risk of major depression (Table 3).

4 Discussion

In this study, it was found that healthy and depressed people had significant differences with each other in terms of gender, employment status, family history of depression, and history of depression. The results of the present study are in line with the results of some studies, such as a cross-sectional study conducted on 554 people which showed that the depression score differed significantly according to gender, and it was significantly higher in women aged 16–23 years and in women aged 60–89 years was significantly lower than men of the same age (33). Also, in the study of Ma et al., women constituted a higher percentage of depressed people (34). Also, Kuczmarski et al. showed in their study that women have a significantly higher depression score than men (35). Of course, the current results are in contrast with the results of some other studies, including Exebio and his colleagues. They observed that the depression score was higher in women, although it was not significant (36). In the present study, working people had the most depression, while in Suchomlinov's study, retired people had a significantly higher depression score than students and working people. Also, in the study of Lee et al., who compared working people, people who never had a job, retired people, and unemployed people, they observed that unemployed and retired people have more depression (37). The HEI profile was linked to a lower incidence of serious depression in logistic regression. Confounding factor correction did not change the significance of this connection. The present study's findings are consistent with those of other research, such as a study conducted by Lanuza et al. on 2031 adults over 60 years of age, which found that a 72% lower incidence of serious depression was connected with those who consumed the healthiest foods (38). Additionally, Sánchez-Villegas et al. found that those in the fifth quintile of HEI-2010 had a 23% lower incidence of depression than those in the first quintile in a prospective analysis with a 10-year follow-up of 15,093 participants. These correlations held true even after controlling for age, gender, BMI, smoking, physical activity, and energy consumption (39). Furthermore, Nouri and colleagues found that the only healthy eating patterns linked to a 39% lower risk of major depression were those that were consistent with marital status, education, family history of depression, occupation, smoking, sleep patterns during the day and at night, income, and food security in 510 healthy and depressed individuals aged 19–65 (19).

Studying the correlation of the Healthy Eating Index (HEI) in the Iranian population not only provides insights into dietary patterns and their impact on physical health but also sheds light on its relationship with mental health outcomes, particularly major depression. Several research studies have investigated this correlation, highlighting the importance of dietary quality in mental wellbeing. For instance, studies by Khakpouri et al. explored the association between HEI and cardiovascular risk factors in Iranian adults, revealing a significant inverse relationship between HEI scores and markers of cardiovascular disease, which are often comorbid with depression (40). Furthermore, investigations by Saneei et al. (41) assessed the HEI in relation to metabolic syndrome and diabetes risk in the Iranian population, conditions that have been linked to an increased risk of depression (42). Moreover, Chegini et al. examined the relationship between HEI and mental health outcomes among Iranian older adults, suggesting that adherence to a higher HEI was associated with a reduced risk of major depression (43). Overall, these studies collectively underscore the significance of the Healthy Eating Index as a valuable tool for assessing dietary quality and its impact on various health outcomes, including major depression, in the Iranian population.

In this study, it was found that healthy subjects have a higher average HEI index than the depressed group. Many existing studies refrained from expressing the average of this profile between healthy people and those suffering from major depression and expressed it in the tertiles of receiving food patterns or types of profiles under investigation, or expressed it in general in the entire population (20, 38, 42). And this made it difficult to draw conclusions in this hypothesis.

The Dutch Dietary Guidelines place a strong emphasis on the consumption of fruits, vegetables, whole grains, fish, nuts, and legumes, while restricting the intake of processed meats,

TABLE 1 Determination and comparison of demographic characteristics between healthy people and patients with major depression.

		Healthy participants $n = 73$ (%)	Participants with depression $n = 105$ (%)	p-value*
Gender	Man	34 (46.6)	33 (31.4)	
	Woman	39 (53.4)	72 (68.6)	
Marital status	Single	31 (42.5)	59 (56.2)	
	Married	41 (56.2)	43 (41)	
	Divorced	1 (1.3)	3 (2.8)	
Education	High school	0 (0)	5 (4.8)	0.14
	Diploma and associate	5 (6.8)	9 (8.6)	
	Bachelor	30 (41.1)	53 (50.5)	
	Master	31 (42.5)	31 (29.5)	
	PhD	7 (9.6)	7 (6.6)	
Occupation	Unemployed	2 (2.7)	10 (9.5)	0.01
	student	15 (20.5)	35 (33.3)	
	employed	56 (76.8)	60 (57.2)	
Smoking	No	62 (84.9)	88 (83.8)	0.84
	Yes	11 (15.1)	17 (16.2)	
Drinking alcohol	No	62 (84.9)	90 (85.7)	0.14
	Less than half a glass per week	4 (5.5)	9 (8.6)	
	Half to 1.5 glasses per week	5 (6.8)	1 (1.0)	
	More than 1.5 glasses per week	2 (2.8)	5 (4.7)	
Omega-3	No	62 (84.9)	91 (86.7)	0.74
	Yes	11 (15.1)	14 (13.3)	
Being on a diet	No	66 (90.4)	90 (85.7)	0.34
	Yes	7 (9.6)	15 (14.3)	
Family history of depression	No	60 (82.2)	70 (66.7)	0.02
	Yes	13 (17.8)	35 (33.3)	
History of depression	No	70 (95.9)	73 (69.5)	0.001
	Yes	3 (4.1)	32 (30.5)	
HEI (achieved score)		58.0 ± 8.0	54.3 ± 8.6	**0.004**
DHD (achieved score)		60.5 ± 7.4	55.0 ± 7.8	**0.007**
Weight (kg)		169 ± 9.9	167.6 ± 8.8	0.35
Height (cm)		73.2 ± 17.2	69.5 ± 15.4	0.16
BMI (kg/m^2)		24.6 ± 4.2	24.6 ± 4.2	0.22

*Obtained from chi-square and independent t-test.
HEI, Healthy Eating Index; DHD, Dutch Healthy Diet; BMI, Body Mass Index. p-value less than 0.05 is considered to be statistically significant.

sugar-filled beverages, and harmful fats. This is measured by the DHD-index. The association between major depression risk reduction and DHD-index adherence has been explained by a number of different processes. First and foremost, the DHD-index encourages a healthy diet rich in vital nutrients, such as vitamins, minerals, and omega-3 fatty acids, all of which are proven to be important for neurotransmitter activity and brain health (23). Furthermore, following the DHD-index is frequently linked to better lifestyle choices, such consistent exercise and abstaining from alcohol, both of which enhance mental health results. The negative link between major depressive disorder incidence and DHD-index adherence has been strongly supported by recent epidemiological studies, underscoring the role that dietary patterns play in promoting mental health (44).

In this study, it was found that the average DHD index in healthy people is significantly higher than that of people with depression. Our results are consistent with the only available study. Gianfredi et al., who studied 2,646 people in a cohort study, showed

that the average DHD in healthy subjects was higher than in subjects with depression (84.5 vs. 79.6) and this difference was significant (23).

In this study, it was found that the two groups were not significantly different in terms of weight, height and BMI. The average BMI in this study was 25. Our results are in line with Suchomlinov et al. study which observed that there was a negative and significant correlation between height and depression score, although this relationship disappeared after adjusting for gender. Also, this negative relationship was significant only in students. No correlation was observed between BMI and depression score. BMI was not significantly different between the two groups (33). Also, in a study on 13,975 people, Ma and his colleagues observed that BMI values and waist-to-height ratio in people with depression compared to healthy people were 30.3 vs. 28.7 kg/m^2 and 61.5 vs. 58.8, respectively and it was non-significant. However, in the regression models and in the final adjusted model (for age, sex, race, educational status, marital status, smoking, and alcohol consumption), underweight and obese individuals were associated with 79 and 55% odds of developing depression compared to individuals with normal BMI. But such a relationship was not observed in overweight people (34). Also, in a cross-sectional study, Hadi et al. investigated the relationship between abdominal volume profile as a predictor of the relationship between depression, anxiety and obesity. In this study, 307 overweight and obese people were investigated. The average BMI in healthy and depressed people was 32.5 vs. 33.5, which was not significant (45). Although our results are in conflict with the results of some studies, including Khan et al., in a study on 60 Pakistani people aged 18–60 years, they reported that the average BMI in healthy people and those with major depression was 0.22 vs. 24.6, respectively, and it was significant. However, the average height and weight between the two groups was not significant (46). The most important reason for the contradiction between the present study and other studies is the sample size and the age range of people.

In logistic regression, HEI index was found to be associated with reduced risk of major depression. This relationship remained significant after adjusting for confounding factors. The results of the present study are in line with the results of some studies, including Lanuza et al. in a study on 2031 people over 60 years of age. They observed that people with the healthiest food intake were associated with a 72% reduction in the risk of major depression (38). Also, in a prospective study with 10-year follow-up of 15,093 people, Sánchez-Villegas et al. observed that people in the fifth quintile of HEI-2010 had a 23% reduced risk of depression compared to people in the first quintile. After adjusting for age, sex, BMI, smoking, physical activity and energy intake, these relationships remained significant (39). Also, in a study of 1,118 men and women aged 30–64, Kuczmarski et al. observed that HEI was inversely associated with depressive symptoms. For every one unit increase in HEI score, the chance of depression symptoms decreased by 0.98. In the linear regression model, after adjusting for gender, age and income, significant relationships remained (35).

In logistic regression, it was found that DHD index was associated with a reduced risk of major depression. This relationship remained significant even after adjustment for confounding factors. Studies examining the relationship between DHD and major depression are very limited. The findings of the present study are consistent with the findings of existing studies. Including Gianfredi et al. in a prospective study they conducted on 2,646 Dutch men and women in 2021 observed that in the primary model DHD is associated with a reduced risk of depression. Also, after adjusting for socioeconomic factors, lifestyle and cardiovascular factors, only DHD-index was associated with a 17% reduction in depression (23). Also, in a study published in 2020, Vogtschmidt et al. examined the relationship between DHD and depressive symptoms in healthy and diabetic individuals. In the results, it was found that in the entire diabetic population, the highest quartile of receiving DHD was associated with a reduction in the risk of depression (24).

The strength of this study is the comparison of HEI and DHD index for the first time, and the inevitable weakness of this study is the possibility of errors in filling out the questionnaires by people suffering from depression and mental problems. In our study, we focused on depression, but these people may also have other disorders that may influence the results in terms of nutrition and appetite, as well as how they respond to FFQ.

TABLE 2 Determining the relationship between HEI and the incidence of major depression.

	CI (%)	*P*-value*
Crude model	0.94 (0.91–0.97)	**0.005**
Model 1	0.95 (0.92–0.99)	**0.01**
Model 2	0.95 (0.92–0.99)	**0.02**

*Obtained from logistic regression.
Model 1: adjustment for gender, occupation, family history and history of depression.
Model 2: Model 1 with the addition of kilocalories and physical activity. *p*-value less than 0.05 is considered to be statistically significant.

TABLE 3 Determining the relationship between DHD and the incidence of major depression.

	CI (%)	P-value*
Crude model	0.95 (0.91–0.98)	**0.009**
Model 1	0.94 (0.90–0.98)	**0.01**
Model 2	0.94 (0.90–0.99)	**0.03**

*Obtained from logistic regression.
Model 1: adjustment for gender, occupation, family history and history of depression.
Model 2: Model 1 with the addition of kilocalories and physical activity. *p*-value less than 0.05 is considered to be statistically significant.

5 Conclusion

The results of this study showed that people with higher HEI and DHD indexes have lower depression scores. According to these results and the findings of previous studies, it seems that food observances and abstinences, alcohol consumption and reduced physical activity can be an important factor in causing depression. Although more complete and comprehensive studies are needed in this field. We suggest that prospective research be conducted in nutrition and psychology. Each group collects the necessary data, and in the end, collaborative and extensive investigations are conducted on the association between intakes and dietary patterns and depression, stress, and anxiety. Health clinics and schools appear to be the greatest places to project this duty.

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

This research was reviewed by the Medical Ethics Committee of Islamic Azad University and approved under the code of ethics IR.IAU.SRB.REC.1401.151. 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. 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

MT: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing—original draft, Writing—review & editing. AM: Investigation, Supervision, Validation, Writing—review & editing. AD: Validation, Writing—review & editing.

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Conflict of interest

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

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Association between composite dietary antioxidant index and kidney stone prevalence in adults: data from National Health and Nutrition Examination Survey (NHANES, 2007–2018)

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Background: The high prevalence of kidney stones in adults worldwide has prompted research into potential interventions, one of which involves exploring the consumption of antioxidants that may confer protective effects. However, the relationship between the composite dietary antioxidant index (CDAI), a crucial measure used to assess an individual's overall antioxidant capacity from daily dietary intake, and kidney stones remains unclear. Therefore, we conducted cross-sectional analysis to examine the association between CDAI and kidney stone prevalence.

Methods: The analysis was conducted utilizing data from the National Health and Nutrition Examination Survey (NHANES) from 2007 to 2018. Antioxidant intake was derived from two 24-h dietary recalls surveys, while CDAI, a comprehensive measure that includes antioxidants like vitamins A, C, and E, zinc, selenium, and carotenoids, was calculated. Multivariate logistic regression and restricted cubic spline (RCS) regression were utilized to examine the association between CDAI and the prevalence of kidney stones.

Results: The study included a total of 28,516 participants, with 2,748 individuals having a history of kidney stones. The median of CDAI was −0.01 (−2.02, 2.37). Individuals in the fourth quartile of CDAI exhibited a significantly lower prevalence of kidney stones compared to those in the first quartile (Odds Ratio [OR] = 0.769 [0.633–0.935]), even after adjusting for potential confounding factors (including age, sex, race, education level, poverty income ratio, smoking status, drinking status, body mass index (BMI), energy intake levels, physical activity level, serum calcium concentration, estimated glomerular filtration rate (eGFR), hypertension, diabetes and supplement use). The RCS analysis revealed a non-linear relationship between CDAI and kidney stone prevalence, with inflection points identified at 0.06 (p for non-linearity = 0.039). Subgroup analysis demonstrated consistent CDAI-kidney stone prevalence associations across all subsets. Furthermore, a significant inverse correlation was observed between CDAI and inflammatory markers.

Conclusion: This study provides evidence supporting a reciprocal correlation between adult dietary antioxidant intake, as measured by CDAI, and kidney stone prevalence. These findings emphasize the potential benefits of consuming dietary antioxidants in lowering the risk of kidney stone formation.

KEYWORDS

kidney stone, dietary antioxidants, composite dietary antioxidant index (CDAI), cross-sectional analysis, NHANES

1 Introduction

Formation of kidney stones results from the abnormal accumulation of crystalline substances, including calcium, oxalic acid, uric acid, and cystine, within the renal calyces and pelvis system (1). Over the past few years, there has been a notable rise in the occurrence of kidney stones, presenting a major issue for public health (2). It is estimated that approximately 11% of the population in the United States will experience kidney stones during their lifetimes (3). These stones cause severe pain and discomfort, significantly impacting the quality of life for individuals affected (4). Furthermore, kidney stones can result in complications such as urinary flow obstruction, urinary tract infections, and in some cases, even renal damage (5, 6). The process is intricate and multifaceted, with dietary factors, particularly food choices, implicated in their formation (7). Notably, extensive attention has been dedicated to investigating the potential protective properties exhibited by dietary antioxidant compounds against the development of kidney stones (8).

Various approaches, including lifestyle modification, physical activity, and particularly nutritional interventions, have been proposed in numerous studies for the prevention and treatment of various chronic diseases such as renal dysfunction (9–11). Antioxidants are essential for neutralizing the harmful impacts of reactive oxygen species (ROS) produced in normal cellular activities (12). Imbalance between ROS generation and the body's antioxidant capacity has been associated with various clinical conditions, including kidney stone formation (13). By reducing ROS levels, antioxidants have the potential to protect tubular cells from damage, thereby impeding mineral and crystal accumulation and ultimately preventing kidney stone formation (14). Dietary antioxidant compounds, such as β-carotene and β-cryptoxanthin, hold promise for the prevention of kidney stones (8). However, there is a significant association between total and supplemental vitamin C intake and an increased risk of kidney stones in men (15). Some dietary antioxidants, including retinol, β-carotene, vitamins B6, C, and E, and lycopene, were not observed to be associated with kidney stone risk in another study (16). These inconsistent outcomes regarding individual dietary antioxidants necessitate further investigations or comprehensive indicators to establish a definitive correlation between dietary antioxidants and susceptibility to kidney stones.

In this context, the Composite Dietary Antioxidant Index (CDAI) plays a significant role as a comprehensive measure of total antioxidant consumption (17). By encompassing both micronutrients (e.g., vitamins A, C, and E) and non-vitamin antioxidants (e.g., zinc, selenium and carotenoids), the CDAI measures antioxidant consumption from various food sources and consolidates them into a single score. Adequate intake of antioxidants, as measured by CDAI, has been linked to a lower likelihood of developing chronic illnesses like heart disease, cancer, hypertension, osteoarthritis and osteoporosis (18–22). Nevertheless, there is no research that has proven a connection between CDAI and the occurrence of kidney stones.

To explore the correlation between CDAIs and the occurrence of kidney stones in a diverse population, we carefully examined dietary antioxidant data from the 2007–2018 National Health and Nutrition Examination Survey (NHANES). Through exhaustive and rigorous analysis, our aim is to provide valuable insights into the role of dietary antioxidants in kidney stone pathogenesis and potentially discover innovative strategies for prevention and management of this condition.

2 Materials and methods

2.1 Study population

The NHANES initiative, overseen by the Centers for Disease Control and Prevention (CDC) in the United States, aims to assess the health, diet, and general welfare of individuals (23). NHANES collects data from a nationally representative sample of individuals through surveys, medical examinations, and laboratory tests. This comprehensive survey covers various domains, including chronic and infectious diseases, obesity, diabetes, cardiovascular health, nutrition, environmental exposures, and oral health. Approval for the research protocols was granted by the National Center for Health Statistics (NCHS) Research Ethics Review Board, with all participants giving informed consent.

In our research, a grand total of 59,842 people took part in the NHANES project from 2007 to 2018. We excluded 25,073 individuals below the age of 20 and those lacking information on kidney stones. Additionally, 3,980 individuals without the necessary data for calculating CDAI, 345 pregnant individuals, and 1,928 individuals with extreme energy intakes were also excluded. As a result, our analysis included a final sample size of 28,516 participants (Figure 1).

2.2 Assessment of CDAI and kidney stones

The CDAI considers the consumption of diet antioxidants, including vitamins A, C, and E, zinc, selenium, and carotenoids. To calculate the CDAI, we exercised a modified version of the CDAI protocol developed by Wright et al. (24). In short, the standardized values for each antioxidant were obtained by subtracting mean and dividing by their standard deviation. Then, we calculated the CDAI by

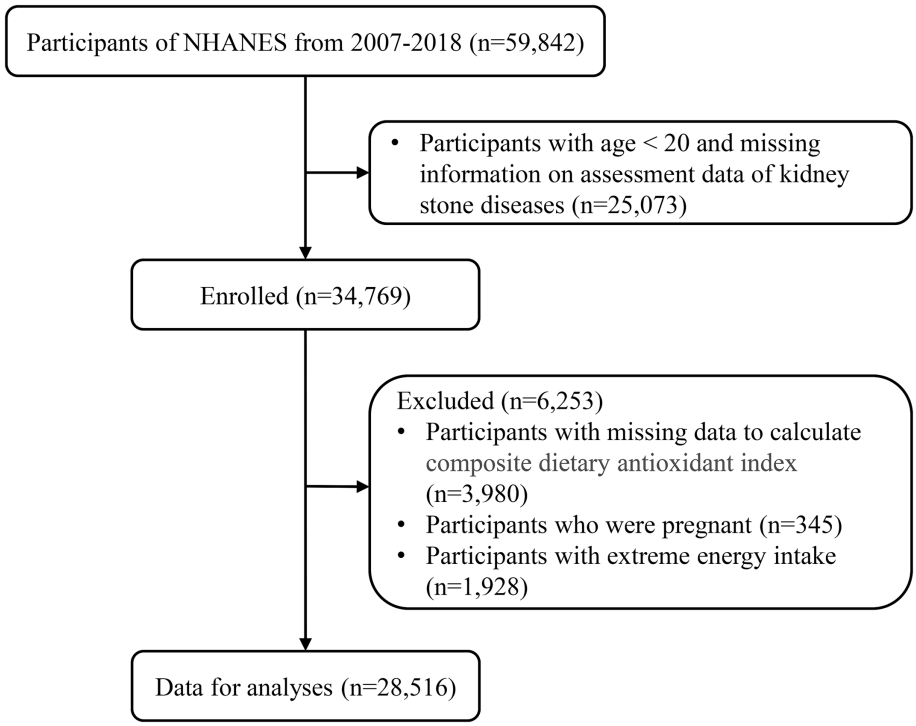

FIGURE 1
Flowchart of the study.

adding standardized values of all six antioxidants. A greater rating signifies a higher consumption of diet antioxidants. The average of two 24-h recall interviews was used to collect information on dietary antioxidants. To ensure data accuracy and reliability, individuals with abnormal total energy intake (>4,200 or < 800 kcal/day in males; >3,500 or < 500 kcal/day in females) were excluded (25). Participants were categorized as having kidney stones if they affirming the following question: Has a doctor or other health professional ever told you that you have kidney stones? (26).

$$CDAI = \sum_{i=1}^{n=6} \left(Individual\ Intake - Mean \right) / SD$$

2.3 Covariates

To mitigate potential confounding bias in our analyses, we selected covariates based on clinical expertise and previous research (27). The NHANES datasets provided information, including age (years), sex (male or female), race/ethnicity (Mexican American, other Hispanic, non-Hispanic White, non-Hispanic Black, or other), education level (below high school, high school, or above high school), total energy intake (kcal/day), serum calcium (mmol/L), estimated glomerular filtration rate (eGFR; ml/min/1.73 m2), and supplement use (%). Poverty Income Ratio (PIR) was determined by dividing an individual's income by the poverty threshold and then classified into one of three brackets (1.0, 1.1–3.0, or > 3.0) (28). Smoking status was categorized as never smokers (<100 cigarettes), current smokers (>100 cigarettes), and former smokers (>100 cigarettes and having quit smoking) (29). Participants were categorized based on their drinking habits as nondrinkers, low-to-moderate drinkers (men <2 drinks/day; women <1 drinks/day), or heavy drinkers (29). Physical activity was classified as inactive (no leisure-time physical activity), insufficiently active (moderate activity 1–5 times per week with metabolic equivalents [MET] 3–6 or vigorous activity 1–3 times per week with MET >6), and active (individuals engaging in more moderate or vigorous activity than mentioned above) (30). Body mass index (BMI) was used to assess weight status, categorizing individuals as normal weight (<25.0 kg/m2), overweight(25.0–29.9 kg/m2), or obese (>29.9 kg/m2) (31). The frequency of hypertension and diabetes was determined based on self-reported questionnaires.

2.4 Statistical analysis

Baseline characteristics were presented as means with standard errors (SEs), medians with interquartile ranges (IQRs), or numbers with percentages. The Student's t-test or Mann–Whitney U test were used to compare continuous variables, while the chi-square test was used to compare categorical variables. The relationship between CDAI and kidney stones prevalence was explored using multifactorial logistic regression. The potential nonlinear association was assessed using a restricted cubic spline (RCS) model with three knots placed at the 10th, 50th, and 90th percentiles of CDAI (32, 33). The median was set as the reference value. Additionally, stratified analyses were conducted to investigate factors that might influence the connection between CDAI and kidney stone prevalence. Finally, the multiple linear regression relationship between CDAI quartiles and inflammation indicators was determined. R (version 4.2.0) was used for all analyses, with statistical significance defined as *p*-values

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TABLE 1 Baseline characteristics of the general adult population in NHANES 2007–2018.

Characteristics	Total (*n* = 28,516)	Kidney stones		*p* value
		No (*n* = 25,768)	Yes (*n* = 2,748)	
Age, years	48.06 (0.24)	47.39 (0.25)	54.06 (0.34)	<0.001
Sex, %				<0.001
Female	14,820 (51.97)	13,589 (53.17)	1,231 (45.98)	
Male	13,696 (48.03)	12,179 (46.83)	1,517 (54.02)	
Race/ethnicity, %				<0.001
Mexican American	4,252 (14.91)	3,900 (8.54)	352 (5.87)	
Other Hispanic	2,965 (10.4)	2,652 (5.75)	313 (5.09)	
Non-Hispanic White	11,988 (42.04)	10,479 (66.38)	1,509 (77.37)	
Non-Hispanic Black	6,018 (21.1)	5,664 (11.44)	354 (5.61)	
Other race	3,293 (11.55)	3,073 (7.88)	220 (6.06)	
Education level, %				0.950
Below high school	6,859 (24.05)	6,178 (15.32)	681 (15.37)	
High school	6,500 (22.79)	5,881 (23.02)	619 (22.74)	
Above high school	15,157 (53.15)	13,709 (61.66)	1,448 (61.89)	
Family PIR, %				0.020
≤1.0	6,120 (21.46)	5,562 (14.61)	558 (12.20)	
1.1–3.0	12,029 (42.18)	10,841 (35.83)	1,188 (36.32)	
>3.0	10,367 (36.36)	9,365 (49.56)	1,002 (51.48)	
Smoking status, %				<0.001
Never smoker	15,953 (55.94)	14,602 (56.80)	1,351 (50.57)	
Former smoker	6,953 (24.38)	6,096 (24.34)	857 (30.43)	
Current smoker	5,610 (19.67)	5,070 (18.86)	540 (19.00)	
Drinking status, %				0.001
Nondrinker	6,516 (22.85)	5,852 (17.84)	664 (19.87)	
Low-to-moderate drinker	19,795 (69.42)	17,867 (72.61)	1928 (73.34)	
Heavy drinker	2,205 (7.73)	2049 (9.55)	156 (6.78)	
Body mass index, %				<0.001
<25.0 kg/m2	7,986 (28.01)	7,464 (30.20)	522 (19.36)	
25.0–29.9 kg/m2	9,403 (32.97)	8,467 (32.93)	936 (32.59)	
>29.9 kg/m2	11,127 (39.02)	9,837 (36.87)	1,290 (48.06)	
Physical activity, %				<0.001
Inactive	7,670 (26.9)	6,769 (21.67)	901 (28.03)	
Insufficiently active	8,943 (31.36)	8,133 (32.37)	810 (30.07)	
Active	11,903 (41.74)	10,866 (45.96)	1,037 (41.90)	
Total energy intakes, kcal/day				0.370
Quartile 1	7,135 (25.02)	6,443 (21.82)	692 (21.47)	
Quartile 2	7,134 (25.02)	6,430 (24.42)	704 (24.84)	
Quartile 3	7,120 (24.97)	6,424 (25.85)	696 (27.62)	
Quartile 4	7,127 (24.99)	6,471 (27.91)	656 (26.06)	
Serum calcium, mmol/L	2.35 (0.00)	2.35 (0.00)	2.34 (0.00)	0.070
eGFR, ml/min/1.73 m2	93.83 (0.32)	94.58 (0.33)	87.13 (0.50)	<0.001
Self-reported hypertension, %				<0.001
No	17,932 (62.88)	16,588 (69.08)	1,344 (52.54)	

(Continued)

TABLE 1 (Continued)

Characteristics	Total (n = 28,516)	Kidney stones		p value
		No (n = 25,768)	Yes (n = 2,748)	
Yes	10,584 (37.12)	9,180 (30.92)	1,404 (47.46)	
Self-reported diabetes, %				<0.001
No	24,625 (86.36)	22,512 (90.87)	2,113 (81.02)	
Yes	3,891 (13.64)	3,256 (9.13)	635 (18.98)	
Supplement use, %				0.010
No	13,977 (49.01)	12,729 (46.16)	1,248 (42.91)	
Yes	14,539 (50.99)	13,039 (53.84)	1,500 (57.09)	
CDAI	0.55 (0.05)	0.59 (0.05)	0.26 (0.10)	0.002

PIR, poverty income ratio; eGFR, estimated glomerular filtration rate; CDAI, composite dietary antioxidant index. Normally distributed continuous variables are described as means ± SEs, and continuous variables without a normal distribution are presented as medians [interquartile ranges]. Sampling weights were applied for calculation of demographic descriptive statistics; N reflect the study sample while percentages reflect the survey-weighted data.

below 0.05. To ensure reliable national estimates, data analysis considered the primary sampling units, sample weights, and strata, following the guidelines provided by the National Center for Health Statistics.

3 Results

3.1 Baseline characteristics of the participants

The characteristics of participants in the 2007–2018 NHANES are detailed in Table 1. This research included 28,516 people, 2,748 of whom had previous experience of kidney stones. The sample consisted of 48.03% male individuals and 42.04% non-Hispanic White participants. Significant differences were observed in all baseline variables when comparing individuals with and without kidney stones, except for education level, total energy intake, and serum calcium ($p > 0.05$). Patients with kidney stones were higher proportions of older males, non-Hispanic white participants, former smokers, low-to-moderate drinkers, and physically inactive individuals ($p < 0.01$). Additionally, they had a higher prevalence of metabolic disorders including obesity, hypertension and diabetes ($p < 0.01$). We performed an analysis of baseline characteristics of the general adult population based on CDAI quartiles (Supplementary Table 1). Participants in the highest quartile of the CDAI were more likely to be females, better educated adults, better off families, nonsmokers, low-to-moderate drinkers, normal weight and physically active individuals, as well as non-hypertensive and non-diabetic individuals ($p < 0.05$).

3.2 Distribution and concentration of CDAI in adults individuals with kidney stones

The distribution and concentration of CDAI in adult patients with kidney stones are shown in Table 2, and the median of CDAI was −0.01(−2.02, 2.37). In this study participants, the average daily consumption of vitamins A, C, and E, zinc, selenium, and carotenoids was 490 (276, 490) μg/day, 50.7 (20.90, 109.40) mg/day, 7.00 (4.57, 10.48) mg/day, 9.84 (6.87, 13.92) mg/day, 101.30 (71.40, 139.00) μg/day, and 5335.00 (2049.00, 12025.00) μg/day, respectively.

3.3 Association between CDAI and kidney stones

We utilized CDAI as a continuous variable and four categorical factors to explore the relationship between CDAI and kidney stone prevalence. By analysis of the continuous independent variable, higher continuous CDAI was substantially linked with reduced kidney stone prevalence in all models (Table 3). In the crude model, a statistically significant inverse correlation between CDAI and kidney stone prevalence was reported in the categorical independent variable analysis. This connection remained even after additional modifications for age, sex, and ethnicity. In model 2, it was discovered that people in the highest quarter of CDAI had a 23.1% reduced likelihood of kidney stones compared to those in the lowest quarter (OR = 0.769 [0.633–0.935], $p_{trend} = 0.003$). The results were similar even when subjects with cancer, thyroid disease, fatty liver, stroke, end-stage renal disease, and taking corticosteroid medications were excluded (Supplementary Tables 2–4). Additionally, the correlation between CDAI and kidney stones was examined in more detail through the use of RCS (Figure 2). A non-linear and negative correlation was found between CDAI and the occurrence of kidney stones, with inflection points at 0.06 (p for non-linearity = 0.039).

3.4 Association between the components of CDAI and kidney stones

The correlation between individual elements of the CDAI and occurrence of kidney stones was analyzed (Table 4). Lower prevalence of kidney stones was linked to the fourth quartile of vitamin C (OR = 0.777 [0.648–0.932], $p_{trend} = 0.008$), zinc (OR = 0.841 [0.712–0.992], $p_{trend} = 0.006$), and selenium (OR = 0.772 [0.652–0.914], $p_{trend} = 0.002$). RCS was used to explore the dose–response association between each antioxidant micronutrient and kidney stones (Supplementary Figure 1).

TABLE 2 Distributions and concentrations of composite dietary antioxidant index (CDAI) among adults in NHANES 2007–2018.

	Mean	5th	25th	50th	75th	95th
CDAI	0.55	−4.23	−2.02	−0.01	2.37	7.17
Vitamins A, μg/day	620.63	89.00	276.00	490.00	796.00	1525.00
Vitamins C, mg/day	79.19	4.30	20.90	50.70	109.40	241.30
Vitamins E, mg/day	8.44	2.19	4.57	7.00	10.48	19.21
Zinc, mg/day	11.14	3.81	6.87	9.84	13.92	22.15
Selenium, μg/day	110.47	39.50	71.40	101.30	139.00	209.40
Carotenoid, μg/day	9299.45	341.00	2049.00	5335.00	12025.00	31193.00

5^{th}, 5th percentile; 25^{th}, 25th percentile; 50^{th}, 50th percentile; 75^{th}, 75th percentile; 95^{th}, 95th percentile.

TABLE 3 ORs (95% CIs) of the prevalence of kidney stone according to quartiles of composite dietary antioxidant index (CDAI) among adults in NHANES 2007–2018.

	Crude	Model 1	Model 2
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Continuous CDAI	0.976 (0.960–0.992)	0.973 (0.956–0.990)	0.973 (0.953–0.993)
P value	0.005	0.002	0.009
Quartiles of CDAI			
Quartile 1	1 [Reference]	1 [Reference]	1 [Reference]
Quartile 2	1.023 (0.872–1.200)	0.964 (0.815–1.140)	0.929 (0.774–1.116)
Quartile 3	0.899 (0.757–1.068)	0.849 (0.710–1.014)	0.825 (0.681–0.999)
Quartile 4	0.831 (0.701–0.986)	0.787 (0.658–0.941)	0.769 (0.633–0.935)
P for trend	0.009	0.003	0.003

OR, odds ratio; CI, confidence interval; Model 1 was adjusted for age (continuous), sex (male or female), and race (Mexican American, Other Hispanic, Non-Hispanic White, Non-Hispanic Black or Other); Model 2 was adjusted for Model 1 plus education level (below high school, high school, or above high school), family income-to-poverty ratio (≤1.0, 1.1–3.0, or > 3.0), smoking status (never smoker, former smoker, or current smoker), drinking status (nondrinker, low-to-moderate drinker, or heavy drinker), BMI (<25.0, 25.0–29.9, or > 29.9), energy intake levels (in quartiles), physical activity (inactive, insufficiently active, or active), serum calcium (continuous), eGFR (continuous), hypertension (yes or no), diabetes (yes or no), and supplement use (yes or no).

3.5 Stratified analysis

Subgroup analyses were performed according to age, gender, ethnicity, smoking and alcohol habits, level of physical activity, body mass index, use of supplements, and eGFR (Table 5). RCS was employed to assess the concordance between CDAI and the risk of kidney stones in stratifying alcohol consumption and age (Supplementary Figure 2). Consistency in the relationship between CDAI and incidence of kidney stones was observed in all subcategories. The initial model was adjusted for total water intake, dietary calcium intake, serum phosphate and vitamin D levels, as well as various dietary factors and nutrient biomarkers. Notably, the final regression analysis yielded consistent results without significant changes, reaffirming the robustness of our findings (Table 6).

3.6 Association between CDAI and inflammatory markers

In addition, we examined the relationship between CDAI quartiles and inflammatory markers (Table 7). Interestingly, a significant negative correlation was observed between a high CDAI quartile and inflammatory markers (such as alkaline phosphatase [ALP], white blood cell count [WBC], neutrophil count [NEU], monocyte count [MON], and red blood cell distribution width [RDW]; $p < 0.05$).

4 Discussion

In this cross-sectional study, we included 28,516 individuals to analyze the potential link between CDAI and kidney stone prevalence. After controlling for all confounding factors, an inverse correlation between CDAI and kidney stone prevalence was discovered. A decrease in the occurrence of kidney stones was associated with the highest quartile of CDAI (OR = 0.769 [0.633–0.935], $p_{trend} = 0.003$). We discovered a non-linear and negative relationship between CDAI and kidney stone, with inflection points of 0.06. Furthermore, the stratified analysis did not reveal any variables that had a significant impact on the outcomes.

The CDAI is a novel index that quantifies the overall dietary antioxidant capacity based on the consumption of various antioxidants (17). Several studies have investigated the relation between CDAI and conditions such as hypertension, cancer, and depression (19, 21, 34). These studies indicate that increased CDAI scores are linked to a lower likelihood of specific diseases. For example, a study discovered that a higher CDAI score was associated with a reduced risk of mortality due to cardiovascular disease (18). Another study revealed that individuals with elevated

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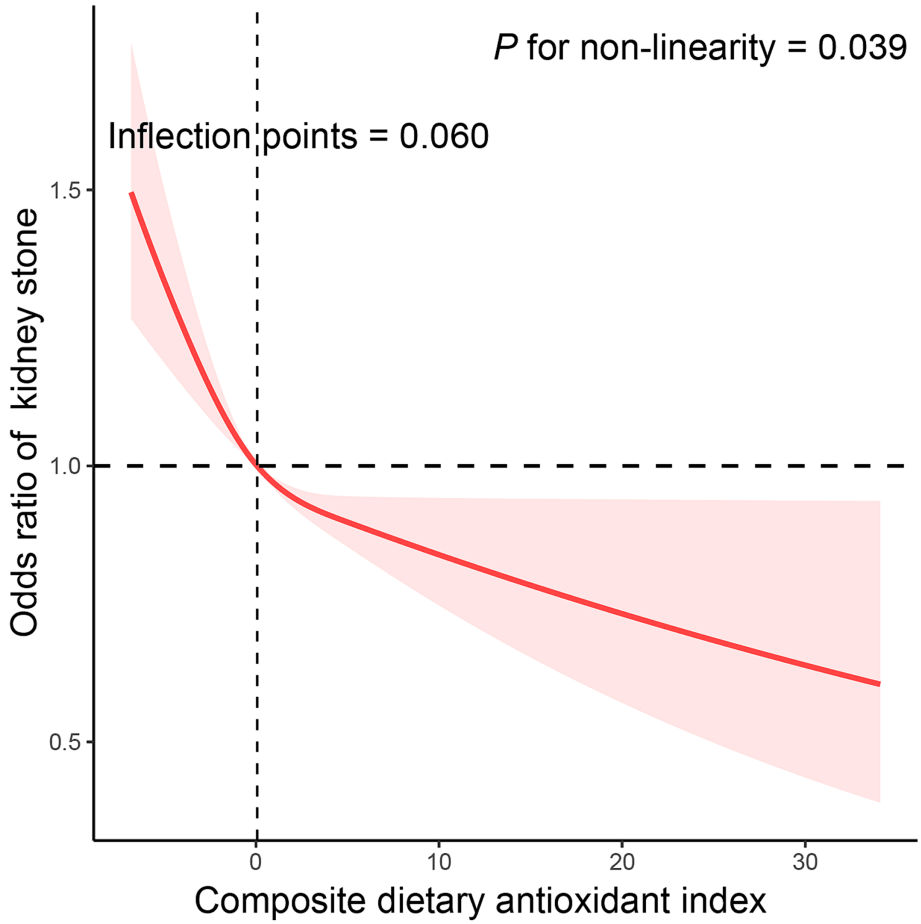

FIGURE 2
The exposure-response association of the composite dietary antioxidant index (CDAI) with the prevalence of kidney stone by restricted cubic spline (RCS). Model was adjusted for age (continuous), sex (male or female), race (Mexican American, Other Hispanic, Non-Hispanic White, Non-Hispanic Black or Other), education level (below high school, high school, or above high school), family income-to-poverty ratio (≤1.0, 1.1–3.0, or > 3.0), smoking status (never smoker, former smoker, or current smoker), drinking status (nondrinker, low-to-moderate drinker, or heavy drinker), BMI (<25.0, 25.0–29.9, or > 29.9), energy intake levels (in quartiles), physical activity (inactive, insufficiently active, or active), serum calcium (continuous), eGFR (continuous), hypertension (yes or no), diabetes (yes or no), and supplement use (yes or no).

TABLE 4 ORs (95% CIs) of the prevalence of kidney stone according to quartiles of dietary antioxidant micronutrients among adults in NHANES 2007–2018.

	Quartiles of dietary antioxidant micronutrients				
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*p* trend
Vitamins A	1 [Reference]	0.939 (0.777–1.133)	0.917 (0.744–1.131)	0.920 (0.761–1.113)	0.444
Vitamins C	1 [Reference]	0.925(0.782–1.094)	0.878 (0.723–1.066)	0.777 (0.648–0.932)	0.008
Vitamins E	1 [Reference]	1.069 (0.906–1.261)	0.857 (0.712–1.032)	0.994 (0.843–1.172)	0.740
Zinc	1 [Reference]	1.090 (0.956–1.243)	0.913 (0.783–1.065)	0.841 (0.712–0.992)	0.006
Selenium	1 [Reference]	0.940 (0.822–1.075)	0.877 (0.757–1.016)	0.772 (0.652–0.914)	0.002
Carotenoid	1 [Reference]	0.928 (0.777–1.109)	0.941 (0.789–1.122)	0.852 (0.696–1.044)	0.142

OR, odds ratio; CI, confidence interval; Model was adjusted for age (continuous), sex (male or female), race (Mexican American, Other Hispanic, Non-Hispanic White, Non-Hispanic Black or Other), education level (below high school, high school, or above high school), family income-to-poverty ratio (≤1.0, 1.1–3.0, or > 3.0), smoking status (never smoker, former smoker, or current smoker), drinking status (nondrinker, low-to-moderate drinker, or heavy drinker), BMI (<25.0, 25.0–29.9, or > 29.9), energy intake levels (in quartiles), physical activity (inactive, insufficiently active, or active), serum calcium (continuous), eGFR (continuous), hypertension (yes or no), diabetes (yes or no), and supplement use (yes or no).

CDAI scores had a decreased risk of developing colorectal cancer (35). This pilot investigation aims to explore the relationship between CDAI and kidney stone. The results of our study show a strong association between elevated CDAI scores and a reduced incidence of kidney stones, even after accounting for all potential influencing factors.

TABLE 5 Stratified analyses of the associations between quartiles of composite dietary antioxidant index (CDAI) and the prevalence of kidney stone in NHANES 2007–2018.

Subgroups	N	Quartiles of CDAI				*p*-interaction
		Quartile 1	Quartile 2	Quartile 3	Quartile 4	
Age, years						
20–39	9,102	1 [Reference]	0.881(0.642–1.210)	0.677(0.463–0.989)	0.760(0.529–1.090)	0.067
40–59	9,434	1 [Reference]	0.937(0.689–1.274)	0.729(0.531–0.999)	0.638(0.448–0.908)	
≥ 60	9,980	1 [Reference]	0.993(0.765–1.289)	1.088(0.802–1.477)	0.994(0.713–1.386)	
Sex, %						
Female	14,820	1 [Reference]	0.952(0.733–1.237)	0.727(0.561–0.943)	0.787(0.582–1.063)	0.252
Male	13,696	1 [Reference]	0.920(0.725–1.167)	0.915(0.701–1.195)	0.767(0.575–1.022)	
Race, %						
Non-Hispanic White	11,988	1 [Reference]	0.679(0.515–0.895)	0.623(0.447–0.869)	0.727(0.490–1.079)	0.125
Non-Hispanic Black	6,018	1 [Reference]	1.033(0.824–1.295)	0.908(0.708–1.165)	0.801(0.617–1.041)	
Other	10,510	1 [Reference]	0.736(0.526–1.029)	0.684(0.491–0.952)	0.762(0.502–1.156)	
Smoking status, %						
Never smoker	15,953	1 [Reference]	0.936(0.720–1.216)	0.835(0.620–1.124)	0.721(0.538–0.967)	
Former smoker	6,953	1 [Reference]	0.954(0.705–1.290)	0.839(0.623–1.130)	0.854(0.622–1.174)	0.993
Current smoker	5,610	1 [Reference]	0.921(0.585–1.449)	0.818(0.568–1.178)	0.830(0.518–1.330)	
Drinking status, %						
Nondrinker	6,516	1 [Reference]	1.137(0.811–1.594)	0.976(0.692–1.375)	1.018(0.657–1.578)	
Low-to-moderate drinker	19,795	1 [Reference]	0.886(0.734–1.070)	0.775(0.634–0.949)	0.693(0.564–0.852)	0.388
Heavy drinker	2,205	1 [Reference]	0.762(0.381–1.523)	0.897(0.455–1.770)	0.910(0.456–1.815)	
Physical activity, %						
Inactive	7,670	1 [Reference]	1.036(0.800–1.340)	0.895(0.655–1.223)	0.900(0.658–1.231)	
Insufficiently active	8,943	1 [Reference]	0.807(0.597–1.092)	0.816(0.596–1.119)	0.722(0.487–1.072)	0.625
Active	11,903	1 [Reference]	0.952(0.729–1.243)	0.777(0.574–1.053)	0.737(0.552–0.984)	
Body mass index, %						
<25.0 kg/m2	7,986	1 [Reference]	0.982(0.671–1.437)	1.190(0.769–1.843)	1.026(0.670–1.572)	
25.0–29.9 kg/m2	9,403	1 [Reference]	1.098(0.835–1.444)	0.871(0.634–1.196)	0.735(0.517–1.045)	0.328
>29.9 kg/m2	11,127	1 [Reference]	0.806(0.623–1.043)	0.673(0.520–0.871)	0.714(0.561–0.910)	
Supplement use, %						
No	13,977	1 [Reference]	0.937(0.724–1.213)	0.801(0.626–1.025)	0.712(0.548–0.925)	0.799
Yes	14,539	1 [Reference]	0.915(0.719–1.164)	0.848(0.647–1.113)	0.810(0.630–1.042)	
eGFR, ml/min/1.73 m2						
<90	11,737	1 [Reference]	0.971(0.773–1.219)	0.897(0.679–1.184)	0.872(0.642–1.184)	0.452
≥ 90	16,779	1 [Reference]	0.898(0.676–1.193)	0.762(0.576–1.007)	0.674(0.511–0.888)	

Analyses were adjusted for covariates age (continuous), sex (male or female), race (Mexican American, Other Hispanic, Non-Hispanic White, Non-Hispanic Black or Other), education level (below high school, high school, or above high school), family income-to-poverty ratio (≤1.0, 1.1–3.0, or > 3.0), smoking status (never smoker, former smoker, or current smoker), drinking status (nondrinker, low-to-moderate drinker, or heavy drinker), BMI (<25.0, 25.0–29.9, or > 29.9), energy intake levels (in quartiles), physical activity (inactive, insufficiently active, or active), serum calcium (continuous), eGFR (continuous), hypertension (yes or no), diabetes (yes or no), and supplement use (yes or no) when they were not the strata variables.

Dietary antioxidants are compounds designed to shield cells and tissues from the detrimental impacts of free radicals (36). A growing body of evidence indicates a link between consuming antioxidants and reducing the risk of chronic illnesses like heart disease, stroke, Alzheimer's, and cancer (37–40). Antioxidants can minimize the risk of certain diseases by neutralizing free radicals, which are recognized for causing damage to blood vessels, DNA, and other cellular components (41). Studies have investigated the association between individual antioxidant micronutrients and kidney stones. Selenium, an essential trace element for the human body, enhances antioxidative capacity, scavenges free radicals, reduces oxidative damage caused by reactive oxygen species to the kidneys, and inhibits oxalate synthesis (42). A cross-sectional study utilizing NHANES data discovered a negative correlation between serum selenium levels and the risk of kidney stones (43). Another study demonstrated an inverse relationship between dietary selenium intake and kidney stone risk, particularly

TABLE 6 ORs (95% CIs) of the prevalence of kidney stone according to quartiles of composite dietary antioxidant index (CDAI) among adults with further adjustment of dietary factors and nutrient biomarkers in NHANES 2007–2018.

	Quartiles of CDAI				*p* trend
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	
Model + total water intake	1 [Reference]	0.93 (0.77–1.11)	0.82 (0.68–1.00)	0.76 (0.63–0.92)	0.002
Model + dietary calcium intake	1 [Reference]	0.94 (0.79–1.13)	0.85 (0.70–1.04)	0.81 (0.66–0.99)	0.019
Model + dietary vitamin D intake	1 [Reference]	0.96 (0.80–1.15)	0.86 (0.71–1.05)	0.82 (0.66–0.99)	0.023
Model + serum phosphate	1 [Reference]	0.93 (0.78–1.12)	0.84 (0.69–1.01)	0.78 (0.64–0.95)	0.004
Model + serum vitamin D	1 [Reference]	0.93 (0.77–1.12)	0.82 (0.68–1.00)	0.77 (0.63–0.94)	0.003
Model + dietary factors*	1 [Reference]	0.96 (0.80–1.14)	0.87 (0.71–1.05)	0.82 (0.67–0.99)	0.029
Model + nutrient biomarkers†	1 [Reference]	0.93 (0.78–1.12)	0.83 (0.69–1.01)	0.77 (0.64–0.94)	0.003

Model was adjusted for age (continuous), sex (male or female), race (Mexican American, Other Hispanic, Non-Hispanic White, Non-Hispanic Black or Other), education level (below high school, high school, or above high school), family income-to-poverty ratio (≤1.0, 1.1–3.0, or > 3.0), smoking status (never smoker, former smoker, or current smoker), drinking status (nondrinker, low-to-moderate drinker, or heavy drinker), BMI (<25.0, 25.0–29.9, or > 29.9), energy intake levels (in quartiles), physical activity (inactive, insufficiently active, or active), serum calcium (continuous), eGFR (continuous), hypertension (yes or no), diabetes (yes or no), and supplement use (yes or no). *Further adjusted for Model + total water intake, and dietary factors (dietary calcium intake [in quartiles], and dietary vitamin D intake [in quartiles]). †Further adjusted for Model + total water intake, and nutrient biomarkers (serum phosphate [continuous] and serum vitamin D [in quartiles]).

TABLE 7 Multiple linear regression associations of quartiles of composite dietary antioxidant index (CDAI) with inflammatory markers in adults.

	Quartiles of CDAI				
	β	*β* (95% CI)	*β* (95% CI)	*β* (95% CI)	*p* trend
ALP	0 [Reference]	−0.024 (−0.039, −0.010)	−0.040 (−0.053, −0.026)	−0.051 (−0.067, −0.034)	<0.001
WBC	0 [Reference]	−0.004 (−0.018, 0.009)	−0.016 (−0.031, −0.001)	−0.024 (−0.040, −0.009)	0.002
NEU	0 [Reference]	−0.010 (−0.028, 0.008)	−0.022 (−0.042, −0.001)	−0.027 (−0.048, −0.007)	0.008
MON	0 [Reference]	0.001 (−0.015, 0.017)	−0.011 (−0.027, 0.004)	−0.016 (−0.033, 0.002)	0.039
RDW	0 [Reference]	−0.085 (−0.140, −0.031)	−0.114 (−0.178, −0.049)	−0.136 (−0.194, −0.078)	<0.001

CI, confidence interval; ALP, alkaline phosphatase; WBC, white blood cell count; NEU, neutrophil count; MON, monocyte count; RDW, red blood Cell distribution width.

among young men (<50 years) and overweight or obese individuals (BMI ≥ 25.0) (44). Zinc is a crucial component of antioxidant mitochondrial metalloenzymes that exerts its antioxidative effects through binding with metallothionein (45). Additionally, zinc can protect against kidney stones by inhibiting calcium phosphate (CaP) crystallization (46). Studies have indicated that both dietary zinc intake and serum zinc levels are inversely associated with kidney stone prevalence in adults (47). However, a separate study revealed a positive correlation between higher dietary zinc intake and an elevated susceptibility to kidney stone disease (48). The relationship and mechanism between vitamin C intake and kidney stone prevalence remains unclear. On one hand, as a potent antioxidant, vitamin C has the ability to scavenge free radicals and reduce calcium oxalate (CaOx) crystal formation. On the other hand, high vitamin C intake is considered a risk factor for kidney stone formation due to potential increases in urinary oxalate excretion (49). A Prospective cohort analysis revealed that both total vitamin C intake and supplementation were significantly associated with an increased risk of kidney stones in men, while dietary vitamin C intake showed no such association (15). Another study found no significant associations between retinol, β-carotene, vitamins B6, C and E, lycopene and the risk of kidney stones (16). However, when considering the co-existence of vitamin C with other vitamins, contradictory findings were obtained. The combination of vitamin E and vitamin C was reported to effectively reduce urinary calcium oxalate crystals (50). Co-exposure to multivitamins containing vitamin C was found to decrease the risk of kidney stones (51). Although our study also confirmed the protective effects of vitamin C, zinc and selenium on kidney stones, we acknowledge that there are biochemical interactions among antioxidant nutrients which make it challenging to explore and explain their associations with kidney stones using individual components alone (24). Therefore, employing the CDAI as a metric to assess overall antioxidant levels in the diet represents a logical and desirable approach for investigating the association with kidney stone risk.

The outcomes of our study align with prior research demonstrating the protective role of antioxidants against kidney stones (8). Antioxidants can mitigate the risk of kidney stone formation through various mechanisms. These compounds neutralize harmful free radicals in the body, thereby limiting oxidative stress and inflammation, which are recognized as triggers for kidney stone development (52). Elevated peroxidation and diminished thiol levels have the potential to heighten oxalate binding activity, causing harm to renal tubular cells and facilitating nucleation, crystal adhesion, and stone aggregation (14). Similarly, oxidative stress impacts various kidney structures, leading to glomeruli, tubules, and renal vessels, prompting the infiltration of inflammatory cells and the recruitment of proinflammatory cytokines (tumor necrosis factor alpha, TNFα) and transcription factors (nuclear factor kappa, NF-κB).This cascade ultimately leads to an inflammatory phase and subsequent fibrosis that impairs renal function (53). By reducing oxidative stress, antioxidants may help prevent the accumulation of minerals and crystals contributing to stone formation. Antioxidants also have the potential

to reduce the body's production of ROS, which are unstable molecules capable of damaging cells and leading to kidney stones (54). Furthermore, antioxidants can bind with ROS, neutralizing their harmful effects on cells and averting damage. Additionally, antioxidants can stimulate the synthesis of protective substances within the body, such as glutathione, safeguarding cells against ROS-induced harm (55). Moreover, antioxidants can enhance renal health by promoting urine excretion and improving kidney function (56). Collectively, these mechanisms hold promise for minimizing the likelihood of kidney stone occurrence.

In our stratified analysis, we observed a beneficial effect of low-to-moderate alcohol consumption compared to non-alcohol and heavy alcohol consumption on the risk of kidney stones. However, the P for interaction was not statistically significant, indicating that the impact of CDAI on kidney stone risk was not influenced by alcohol intake. Alcohol is known to increase the risk of stones by promoting the formation of uric acid metabolites and causing oxidative stress damage to kidney tissue (57). Nevertheless, the prevailing viewpoint suggests that alcohol can dilute metabolites in blood and urine, inhibit vasopressin secretion, and have a diuretic effect to prevent stone formation (58). A prospective population-based cohort study demonstrated a linear decrease in the risk for kidney stones with increasing alcohol intake; each 200 mL/d increment in alcohol consumption had a hazard ratio (HR) of 0.85 (95% Confidence Interval [CI]: 0.82–0.88) (59). However, excessive alcohol consumption should not be encouraged as it may lead to uncontrolled metabolism and negate the beneficial effects of moderate drinking on cardiovascular health (60). Compared to non-drinkers, individuals consuming 30.0–59.9 g of pure alcohol per day had a reduced risk of kidney stones (HR = 0.79, 95% CI: 0.72–0.87); however, there was no further decrease in risk with higher levels of alcohol consumption (58). Therefore, moderate alcohol consumption may potentially exert a beneficial impact on reducing the risk of kidney stones through a better balance between diuresis and oxidative stress.

As the concentration of oxidative products (including proteins, DNA, and lipids) increases with age, antioxidants can mitigate ROS production and aid in the prevention of age-related diseases such as cardiovascular disease, certain types of cancer, and neurodegenerative diseases (61, 62). However, this does not imply that the elderly derive greater protective benefits against kidney stones from a higher CDAI. Previous studies have demonstrated an inverse association between serum selenium levels and the risk of kidney stone history in the general population. Nevertheless, after conducting age-stratified analysis, only higher serum selenium levels remained significantly negatively associated with kidney stone risk in individuals aged 40–59 years; no significant benefit was observed for those over 60 years old (43). This is consistent with the results of our study. The metabolism of several dietary factors may undergo changes with advancing age，and the relationship between diet and kidney stones may differ among older adults (63). On one hand, intestinal absorption of nutrients that influence stone formation (e.g., calcium) may be diminished in older individuals (64), potentially rendering some antioxidants less effective at inhibiting CaOx crystal formation. On the other hand, aging affects gastrointestinal nutrient absorption function while making older adults particularly susceptible to malnutrition and dysphagia-related issues (65). Consequently, dietary antioxidants might not be fully absorbed or effectively utilized by elderly individuals.

While our study highlights the potential benefits of dietary antioxidants in reducing kidney stone prevalence, it is crucial to note that relying solely on supplements or isolated nutrients is not recommended. A well-balanced diet rich in fruits and vegetables naturally provides a diverse range of antioxidants and other essential nutrients contributing to overall health (66). Additionally, lifestyle factors such as hydration, physical activity, and genetics also play significant roles in kidney stone formation (67). Exploring their interactions with dietary antioxidants should be a focus of future research.

The study demonstrates notable strengths that bolster the robustness and relevance of its findings. A key strength lies in the extensive participant pool drawn from the 2007–2018 NHANES dataset, enhancing both statistical power and the generalizability of conclusions. This wealth of data provides comprehensive insights into the investigated relationship. Additionally, an innovative perspective is introduced by employing CDAI as a novel tool to assess dietary antioxidant intake. This index uniquely considers essential antioxidants, including vitamins A, C, and E, zinc, selenium, and carotenoids, thereby offering a more comprehensive and representative assessment of individuals' antioxidant consumption patterns. This analytical approach significantly enhances the precision and depth of the investigation.

Acknowledging the study's design limitations is essential. Firstly, the cross-sectional nature of the study poses a constraint on establishing causality, necessitating further longitudinal studies or interventional trials to establish a more certain causal link. Secondly, evaluating dietary nutrient consumption is based on mean values obtained from two 24-h dietary recalls, which might not completely reflect the daily fluctuations in individuals' eating habits. Moreover, it is crucial to mention that the outcomes of this study specifically pertain to the population of the United States and cannot be extrapolated to others, thereby requiring further investigation. Lastly, the study's applicability might be constrained by inherent population-specific or regional factors. Variations in dietary practices, genetic predispositions, and cultural norms could limit the generalizability of the findings beyond the study's specific participant pool and geographical context.

5 Conclusion

The current study reveals a negative correlation between CDAI and incidence of kidney stones in adults, suggesting that higher antioxidant consumption may potentially reduce the chances of kidney stone formation. Nevertheless, the inherent limitations of a cross-sectional design pose challenges in establishing a causal relationship. Therefore, there is a need for prospective research endeavors are warranted to delve deeper into the underlying mechanisms and provide a more comprehensive understanding of this phenomenon.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found at: Centers for Disease Control and Prevention (CDC), National Center for Health Statistics (NCHS), National Health and

Nutrition Examination Survey (NHANES) database, https://www.cdc.gov/nchs/nhanes/index.htm, NHANES 2007-2018.

Ethics statement

The studies involving humans were approved by the National Center for Health Statistics (NCHS) Research Ethics Review Board. The patients/participants provided their written informed consent to participate in this study. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

QD: Conceptualization, Writing – original draft, Writing – review & editing. HH: Data curation, Writing – original draft, Writing – review & editing. SZ: Data curation, Formal analysis, Writing – review & editing. YaW: Data curation, Formal analysis, Writing – review & editing. DL: Data curation, Funding acquisition, Writing – review & editing. LW: Formal analysis, Funding acquisition, Writing – review & editing. YS: Supervision, Writing – review & editing. YoW: Supervision, Writing – review & editing.

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Conflict of interest

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

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2024.1389714/full#supplementary-material

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The associations between dietary flavonoid intake and hyperlipidemia: data from the national health and nutrition examination survey 2007–2010 and 2017–2018

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Background: Hyperlipidemia is a worldwide health problem and a significant risk factor for cardiovascular diseases; therefore, it imposes a heavy burden on society and healthcare. It has been reported that flavonoids can increase energy expenditure and fat oxidation, be anti-inflammatory, and reduce lipid factor levels, which may reduce the risk of hyperlipidemia. However, the relationship between the prevalence of hyperlipidemia and dietary flavonoid intake in the population remains unclear.

Methods: This study included 8,940 adults from the 2007–2010 and 2017–2018 National Health and Nutrition Examination Surveys (NHANES). The relationship between dietary flavonoid intake and the prevalence of hyperlipidemia was analyzed using weighted logistic regression and weighted restricted cubic spline.

Results: We found an inverse relationship between subtotal catechins intake and hyperlipidemia prevalence in the third quartile [0.74 (0.56, 0.98), $p = 0.04$] compared with the first quartile. The prevalence of hyperlipidemia and total flavan-3-ol intake in the third quartile were inversely correlated [0.76 (0.59, 0.98), $p = 0.03$]. Total anthocyanin intake was inversely related to the prevalence of hyperlipidemia in the third quartile [0.77 (0.62, 0.95), $p = 0.02$] and the fourth quartile [0.77 (0.60, 0.98), $p = 0.04$]. The prevalence of hyperlipidemia was negatively correlated with total flavonols intake in the fourth quartile [0.75 (0.60, 0.94), $p = 0.02$]. Using restricted cubic splines analysis, we found that subtotal catechins intake and total flavan-3-ol intake had a nonlinear relationship with the prevalence of hyperlipidemia.

Conclusion: Our study may provide preliminary research evidence for personalizing improved dietary habits to reduce the prevalence of hyperlipidemia.

KEYWORDS

flavonoid, flavan-3-ol, anthocyanin, hyperlipidemia, NHANES

1 Introduction

Hyperlipidemia usually refers to an increase in plasma triglycerides or total cholesterol, including an increase in low-density lipoprotein cholesterol (LDL-C) and a decrease in high-density lipoprotein cholesterol. Hyperlipidemia is a risk factor for atherosclerotic cardiovascular disease (1, 2). In practice, controlling LDL-C levels is the primary goal of hyperlipidemia treatment to reduce the prevalence and mortality of cardiovascular diseases (3, 4). Management of hyperlipidemia includes lifestyle interventions and pharmacotherapy (5, 6). Common lifestyle interventions include reducing the intake of saturated fatty acids and cholesterol, exercising regularly, controlling weight, quitting smoking, limiting alcohol intake, and limiting salt intake (7–10). Lipid regulators include medications that lower cholesterol, those that lower triglycerides, and newer lipid-lowering drugs (11–13). With aggressive, comprehensive management, the prognosis of hyperlipidemia is good. Patients with hyperlipidemia have elevated levels of lipids in their blood, which can lead to atherosclerosis, which in turn causes the narrowing of the coronary arteries and reduces blood flow to the heart. Long-term myocardial ischemia can cause angina pectoris and myocardial infarction, leading to a decline in cardiac function, which may eventually lead to heart failure, which is a major risk factor for coronary heart disease (14, 15). Therefore, active prevention and treatment are of great significance to reduce the incidence of cardiovascular disease and improve the quality of life (16).

Flavonoids are a large and diverse group of bioactive polyphenolic compounds found in plants (17). Flavonoids can be divided into six subclasses based on their chemical structures, including anthocyanins, flavan-3-ols, flavanones, flavones, flavonols, and isoflavones (18). In recent years, numerous studies have applied flavonoids and their metabolites to prevent and treat many diseases, including cancer, obesity, diabetes mellitus, hypertension, hyperlipidemia, cardiovascular disease, and osteoporosis (19, 20). Also, various studies have shown that some of the different flavonoids found in foods and herbs have anti-inflammatory, antioxidant, glycemic profile, and liver enzyme improvement effects (21–23). Previous studies have found that flavonoids can increase energy consumption and fat oxidation (24, 25), promote fat phagocytosis, reduce lipid factor levels, inhibit lipid accumulation in the liver, reverse liver function abnormalities caused by lipid peroxidation (26), and regulate metabolism and gut flora (27, 28). Anthocyanins can reduce oxidized LDL-C levels (29). Flavonoids in grape derivatives can reduce plasma lipid levels. Drinking moderate amounts of red wine can reduce the oxidation of low-density lipoprotein and reduce endothelial toxicity caused by oxidized low-density lipoprotein molecules, thereby directly reducing the incidence of atherosclerotic disease (30). Catechin can increase energy consumption and fat oxidation (24). Marrein promotes fat autophagy by regulating the PI3K/AKT/mTOR pathway, thereby lowering lipids (26). These studies suggest that flavonoids have a protective role in developing hyperlipidemia.

Currently, no clinical studies report the relationship between dietary flavonoids and the prevalence of hyperlipidemia. Therefore, this study utilized publicly available data from the USDA Codex Flavonoid Value Database (flavonoid database, 2007–2010 and 2017–2018), Diet Facts in the United States (WWEIA), and NHANES to explore the relationship between flavonoid intake and the prevalence of hyperlipidemia in US adults aged ≥20 years.

2 Materials and methods

2.1 Study population

We collected data from the NHANES, a national population survey conducted by the National Center for Health Statistics (NCHS) in the US. It uses complex, multi-stage, and probability sampling techniques and is released on a 2-year cycle. It aims to investigate the nutritional and health status of the entire population in the United States (31). Information can be retrieved on the NHANES website.[1] The NCHS Ethics Review Board approved the NHANES study protocol, and each participant signed an informed consent form.

We collected 29,940 participants from the NHANES database in consecutive NHANES cycles 2007–2010 and 2017–2018. We excluded 5,786 participants with missing data on a hyperlipidemia diagnosis, 4,786 participants with missing data on flavonoid intake, 5,511 participants younger than 20 years of age, 463 participants with caloric intake greater than 4,200 calories, or Participants with caloric intake less than 700 calories, 153 participants. Pregnant participants and 1,462 cancer participants, for a total of 8,940 participants (Figure 1).

2.2 Assessment of flavonoid intakes

We collected data on dietary flavonoid intake from the USDA Survey of Food and Beverage Flavonoid Values Database ("flavonoid database"). This database provides intakes of compounds from foods and beverages from the USDA Dietary Study Food and Nutrient Database (32) and corresponding dietary data from WWEIA (33) and NHANES. The USDA Nutrient Data Laboratory measured the content (mg/100 g) of 29 flavonoids in each food/beverage. Dietary flavonoids include the following seven flavonoid classes and the total daily intake of all flavonoids (the sum of 29 flavonoids) calculated from all foods and beverages. This study collected dietary flavonoid intake data from the flavonoid database from 2007–2010 to 2017–2018. We defined dietary flavonoid intake as the average of 2 days for each flavonoid.

2.3 Assessment of hyperlipidemia

Hyperlipidemia was identified when any of the following criteria were met: triglycerides ≥150 mg/dL; total cholesterol ≥200 mg/dL; low-density lipoprotein ≥130 mg/dL; high-density lipoprotein ≤40 mg/dL (male); high-density lipoprotein ≤50 mg/dL (female); or utilization of antihyperlipidemic agents.

2.4 Assessment of covariates

We included the following covariates: age, race, education, Family income-poverty ratio (PIR), body mass index (BMI), smoking status, alcohol drinking, caloric intake, Protein, Carbohydrate, total fat, total saturated fatty acids (total sfat), total polyunsaturated fatty acids (total mfat), total monounsaturated fatty acids (total pfat), total cholesterol,

1 https://www.cdc.gov/nchs/nhanes/index.htm

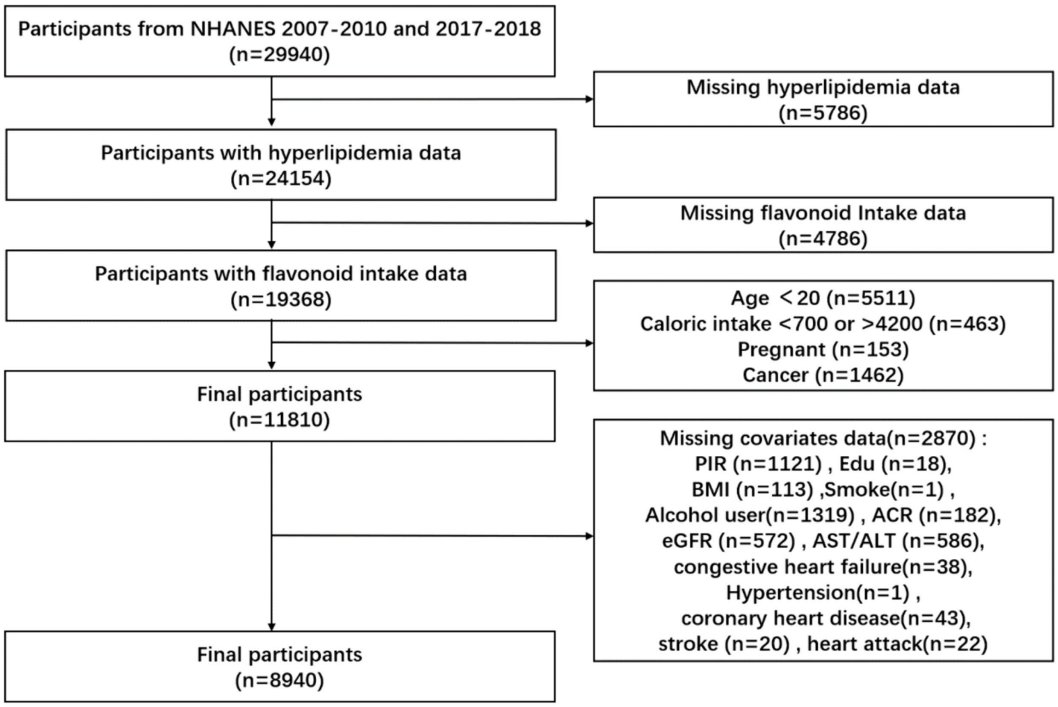

FIGURE 1
Flow chart of study participants.

vitamin D, vitamin E, AST/ALT, ACR, eGFR, lipid-lowering drugs, hypertension, diabetes, heart attack, stroke, and coronary heart disease.

Participants were divided into the following three groups according to age: <30 years, 30–59 years, and ≥60 years. Race was divided into non-Hispanic White, non-Hispanic Black, Mexican-American, and others. The family income-poverty ratio was classified as <1.5, 1.5–3.5, and > 3.5. Education level was categorized as less than high school, high school or equivalent, some college or AA degree, and college graduate or above. Smoking status was classified as never (smoked fewer than 100 cigarettes in life), former (smoked more than 100 cigarettes in life and smoke not at all now), now (smoked more than 100 cigarettes in life and smoked some days or every day). Alcohol drinking was classified as never (had <12 drinks in a lifetime); former (had ≥12 drinks in 1 year and did not drink last year, or did not drink last year but drank ≥12 drinks in a lifetime); Mild (defined as two drinks per day for men and one drink per day for women); moderate (defined as three drinks per day for men and two drinks per day for women, or binge drinking 2–4 days per day); heavy (defined as ≥ four drinks per day for men and ≥ three drinks per day for women, or binge drinking ≥5 days per day) (34).

Disease covariates in this study include hypertension, diabetes, heart attack, stroke, and coronary heart disease. Based on the questionnaire and physical examination results, participants were diagnosed with hypertension if they met one of the following three conditions: (1) the average systolic blood pressure ≥ 130 mmHg or the average diastolic blood pressure ≥ 80 mmHg; (2) the answer to the question "have you ever been told to take a prescription for hypertension" was "yes"; (3) the answer to the question "have you ever been told that you had high blood pressure" was "yes." All blood pressure determinations (systolic and diastolic) were taken at a mobile examination center. The following protocol calculated average blood pressure: The diastolic reading with zero was not used to calculate the diastolic average. If all diastolic readings were zero, then the average would be zero. If only one blood pressure reading was obtained, that reading is the average. If there was more than one blood pressure reading, the first reading was excluded from the average. The diagnostic criteria for diabetes were as follows: the doctor told the patient they have diabetes, HbA1c ≥ 6.5%; fasting glucose ≥7.0 mmol/L; random blood glucose ≥11.1 mmol/L; two-hour OGTT blood glucose ≥11.1 mmol/L; utilization of diabetes medication or insulin. DM: diabetes mellitus; IFG: impaired fasting glycemia (fasting glucose 6.1–7.0 mmol/L); IGT: Impaired Glucose Tolerance (two-hour OGTT blood glucose 7.8–11.1 mmol/L). Cardiovascular disease was diagnosed based on whether questionnaires and physical examination results were used, and cardiovascular disease was defined as heart attack, stroke, and coronary heart disease. The diagnostic criteria for heart attack: the answer to the question "Have you ever been told that you had a heart attack?" was "yes." The diagnostic criteria for stroke: the answer to the question "Have you ever been told that (the patient) had a stroke?" was "yes." The diagnostic criteria for coronary heart disease: the answer to the question "Have you ever been told that you had coronary heart disease?" was "yes."

2.5 Statistical analysis

All statistical analyses were performed using R software (version 4.1.3). Data preparation and statistical analysis were performed using the R packages "*NHANESR*" and "*survey*." In the analysis of baseline

information, continuous variables were expressed as weighted means ± standard deviations using one-way analysis of variance to compare differences between groups; categorical variables were expressed as frequencies and percentages and compared using the chi-square test. We used four weighted logistic regression models to examine the relationship between flavonoid consumption and hypertension prevalence. The crude model was unadjusted. Model 1 was adjusted for age, race, and sex. Model 2 was adjusted for age, race, sex, caloric intake, smoking status, alcohol drinking, and PIR. Model 3 was adjusted for age, race, sex, caloric intake, smoking status, alcohol drinking, education, PIR, protein, total fat, total sfat, total mfat, total pfat, total cholesterol, vitamin D, vitamin E, ACR, eGFR, AST/ALT, lipid-lowering drugs, hypertension, heart attack, stroke, coronary heart disease, and diabetes.

We used weighted restricted cubic splines from the "*rms*" package to evaluate potential nonlinear associations. Subgroup weighted logistic regression was used to analyze the effect of flavonoid intake on the prevalence of hyperlipidemia, stratified by age, race, sex, caloric intake, smoking status, alcohol drinking, education, PIR, protein, total fat, total sfat, total mfat, total pfat, total cholesterol, vitamin D, vitamin E, ACR, eGFR, AST/ALT, lipid-lowering drugs, hypertension, heart attack, stroke, coronary heart disease, and diabetes. Weighted logistic regression was used to calculate odds ratios and corresponding 95% confidence intervals. A significance level of $p < 0.05$ was used as the threshold for statistical significance. The P for interaction was based on the log-likelihood ratio test to assess the heterogeneity of the relationship between subgroups.

3 Results

3.1 Characteristics of participants

We included 8,940 participants. The baseline characteristics were grouped according to hyperlipidemia (Table 1). There were 6,520 patients with hyperlipidemia and 2,420 without. The average age of healthy participants was 38.89 (0.51) years, and that of participants with hyperlipidemia was 48.90 (0.37) years. Non-Hispanic white, Mexican-American participants and participants in less than high school and high school or equivalent were more likely to have hyperlipidemia than healthy participants. In terms of smoking status, more participants with hyperlipidemia were current or former smokers than healthy participants. Among participants with hyperlipidemia, the proportion of former or mild drinkers was higher than that of healthy participants. Participants with hyperlipidemia had a higher BMI, lower caloric intake, lower total pfat intake, and lower vitamin E intake than healthy participants. Hyperlipidemic participants had lower ACR, higher eGFR, and lower AST/ALT compared to healthy participants. Among 8,940 participants, 1753 participants took lipid-lowering medications and 7,187 participants did not take lipid-lowering medications (Supplementary Table 1). Among the 6,520 participants with hyperlipidemia, 1753 participants took lipid-lowering drugs and 4,767 participants did not take lipid-lowering drugs. In terms of comorbidities, participants with hyperlipidemia had higher rates of hypertension, diabetes, stroke, heart attack, and coronary heart disease than healthy participants. There were no significant differences in sex, PIR, protein, total fat, total sfat, total mfat, total cholesterol, and vitamin D between healthy participants and those with hyperlipidemia. However, the participants

TABLE 1 Characteristics of participants in the study.

Variable	Participants without hyperlipidemia	Participants with hyperlipidemia	*p*-value
N	2,420	6,520	
Age (years)			< 0.0001
20–39	2,998(44.86)	54 (4.00)	
40–59	2,664 (40.55)	503 (38.72)	
≥60	1,525 (14.59)	1,196 (57.28)	
Sex, N (%)			0.42
Female	1,228 (51.40)	3,410 (52.97)	
Male	1,192 (48.60)	3,110 (47.03)	
Race, N (%)			< 0.0001
Non-Hispanic White	1,009 (65.30)	3,114 (70.98)	
Non-Hispanic Black	595 (12.74)	1,130 (9.21)	
Mexican American	359 (7.86)	1,134 (8.56)	
Others	457 (14.10)	1,142 (11.25)	
Education, N (%)			< 0.0001
Less than high school	461 (11.35)	1,644 (15.44)	
High school or equivalent	508 (22.04)	1,579 (26.44)	
Some college or AA degree	782 (31.74)	1915 (30.82)	
College graduate or above	669 (34.87)	1,382 (27.31)	
Smoking status, N (%)			< 0.0001
Now	458 (16.67)	1,351 (19.75)	
Former	459 (20.71)	1,681 (24.94)	
Never	1,503 (62.62)	3,488 (55.31)	
Alcohol drinking, N (%)			< 0.0001
Former	248 (6.96)	1,026 (12.46)	
Heavy	609 (27.19)	1,314 (20.54)	
Mild	819 (36.11)	2,301 (39.31)	
Moderate	461 (19.91)	1,042 (18.15)	
Never	283 (9.84)	837 (9.54)	
PIR, N (%)			0.95
<1.5	805 (23.66)	2,331 (24.06)	
1.5–3.5	803 (30.10)	2,129 (30.19)	
>3.5	812 (46.24)	2060 (45.75)	
BMI (kg/m^2)	26.69 (0.20)	30.14 (0.13)	< 0.0001
Caloric intake (kcal)	2105.57 (19.50)	2055.48 (14.98)	0.03
Protein (g)	83.31 (0.97)	81.16 (0.70)	0.05
Carbohydrate (g)	249.07 (2.67)	244.59 (1.65)	0.13
Total fat (g)	80.78 (1.03)	79.70 (0.79)	0.4
Total sfat (g)	26.16 (0.38)	26.17 (0.28)	0.97
Total mfat (g)	28.64 (0.37)	28.45 (0.29)	0.68

(Continued)

TABLE 1 (Continued)

Variable	Participants without hyperlipidemia	Participants with hyperlipidemia	*p*-value
N	2,420	6,520	
Total pfat (g)	18.53 (0.28)	17.74 (0.22)	0.04
Total cholesterol (mg)	280.22 (4.07)	288.25 (4.20)	0.14
Vitamin D (mcg)	4.51 (0.10)	4.57 (0.08)	0.63
Vitamin E (mg)	8.83 (0.21)	7.97 (0.13)	< 0.001
ACR (mg/g)	18.03 (2.27)	31.55 (3.48)	0.01
eGFR (ml/min/1.73m^2)	102.41 (0.72)	93.01 (0.52)	< 0.0001
AST/ALT	1.19 (0.01)	1.07 (0.01)	< 0.0001
Lipid-lowering drugs, N (%)			< 0.0001
No	2,420 (100.00)	4,767 (76.55)	
Yes	0 (0.00)	1753 (23.45)	
Hypertension, N (%)			< 0.0001
No	1847 (80.75)	3,619 (60.49)	
Yes	573 (19.25)	2,901 (39.51)	
Stroke			< 0.0001
No	2,381 (98.74)	6,243 (96.81)	
Yes	39 (1.26)	277 (3.19)	
Heart attack, N (%)			< 0.0001
No	2,379 (98.92)	6,228 (96.56)	
Yes	41 (1.08)	292 (3.44)	
Coronary heart disease, N (%)			< 0.0001
No	2,395 (99.38)	6,219 (96.00)	
Yes	25 (0.62)	301 (4.00)	
Diabetes, N (%)			< 0.0001
No	2078 (90.27)	4,506 (75.24)	
DM	93 (2.96)	374 (5.53)	
IFG	188 (4.74)	1,390 (15.90)	
IGT	61 (2.03)	250 (3.33)	
Dietary intake of flavonoids (mg/day)			
Subtotal Catechins	67.31 (3.83)	82.10 (5.37)	0.02
Total Isoflavones	3.23 (0.36)	1.74 (0.22)	0.001
Total Anthocyanidins	14.46 (1.42)	14.35 (0.98)	0.94
Total Flavan-3-ols	151.81 (8.45)	184.18 (9.27)	0.002
Total Flavanones	12.69 (0.65)	12.20 (0.40)	0.43
Total Flavones	0.95 (0.04)	0.90 (0.03)	0.33
Total Flavonols	18.36 (0.36)	18.90 (0.42)	0.21
Total Sum of all 29 flavonoids	201.49 (8.99)	232.29 (9.57)	0.004

with hyperlipidemia had a higher intake of subtotal catechins, total flavan-3-ols, and total flavonoids. The specific content of participants' flavonoid dietary assessment is provided in Supplementary Table 2.

3.2 Associations between flavonoid intake and prevalence of hyperlipidemia

We analyzed weighted logistic regression to evaluate the potential association between flavonoid intake, and hyperlipidemia. Age, race, sex, caloric intake, smoking status, alcohol drinking, education, PIR, protein, total fat, total sfat, total mfat, total pfat, total cholesterol, vitamin D, vitamin E, ACR, eGFR, AST/ALT, lipid-lowering drugs, hypertension, heart attack, stroke, coronary heart disease, and diabetes were fully adjusted. We divided isoflavone intake into four groups based on flavonoid subclass intake; because more than 50% of participants did not report isoflavone intake, we divided isoflavone intake into two groups based on the median intake (Table 2).

In model 3, we observed that compared with the first quartile, there was an inverse relationship between subtotal catechins intake and the prevalence of hyperlipidemia in the third quartile [0.74 (0.56, 0.98), $p = 0.04$]. However, the p-value for the trend was insignificant ($p = 0.6$). Similarly, there was an inverse relationship between total flavan-3-ols intake and the prevalence of hyperlipidemia in the third quartile [0.76 (0.59, 0.98), $p = 0.03$], with a non-significant p-value for trend ($p = 0.83$). Compared with the first quartile, there was an inverse relationship between total anthocyanins intake and the prevalence of hyperlipidemia in the third [0.77 (0.62, 0.95), $p = 0.02$] and fourth quartiles [0.77 (0.60, 0.98), $p = 0.04$], the p-value for trend was significant ($p = 0.04$). Total flavonols intake in the fourth quartile [0.75 (0.60, 0.94), $p = 0.02$] was inversely related to the prevalence of hyperlipidemia, and the p-value for trend was significant ($p = 0.02$).

Because the p-value for a trend of the prevalence of hyperlipidemia and subtotal catechins intake and total flavan-3-ols intake were not significant, we considered a possible nonlinear relationship. We performed analyses using restricted cubic splines to explore whether there might be a nonlinear relationship between the prevalence of hyperlipidemia and subtotal catechins intake and total flavan-3-ols intake. There was a significant nonlinear relationship between the prevalence of hyperlipidemia and subtotal catechins intake (Figure 2A, $p = 0.0002$), total flavan-3-ols intake (Figure 2B, $p = 0.0006$), and total anthocyanidins (Figure 2C, $p = 0.0153$). In the above results, the nonlinear relationship between the prevalence of hyperlipidemia and subtotal catechins intake and total flavan-3-ols intake showed a U-shaped correlation. Through analysis, we observed that when the subtotal catechin intake was less than 25.36 mg/day, there was a significant negative linear relationship between the prevalence of hyperlipidemia and subtotal catechin intake. When the total flavan-3-ols intake is less than 41.09 mg/day, the prevalence of hyperlipidemia had a significant negative linear relationship with the total flavan-3-ols intake. However, the nonlinear relationship between the prevalence of hyperlipidemia and total flavones did not reach significance (Figure 2D).

3.3 Subgroup analysis

To assess the robustness of the association between flavonoid intake and hyperlipidemia， we performed subgroup analysis using weighted logistic regression to determine the subgroup interaction effect between flavonoid intake and the prevalence of hyperlipidemia. Stratified analyses were adjusted for age, sex, race, education, smoking status, alcohol drinking, PIR, caloric intake, hypertension, heart attack, stroke, coronary heart disease, diabetes, and other variables.

After analysis, we found that the interaction between the prevalence of hyperlipidemia and subtotal catechins intake (Table 3, p for interaction = 0.005) was significant when stratified by sex. However, when stratified by other variables, the relationship between the prevalence of hyperlipidemia and subtotal catechins intake was not statistically significant. This finding showed that age, race, education, smoking status, alcohol drinking, PIR, caloric intake, hypertension, heart attack, stroke, coronary heart disease, diabetes, and other variables did not significantly affect the relationship between the prevalence of hyperlipidemia and subtotal catechins intake (p for interaction >0.05). The interaction between the prevalence of hyperlipidemia and total flavan-3-ols intake was significant when stratified by sex (Supplementary Table 3, p for interaction = 0.01) and heart attack (Supplementary Table 3, p for interaction = 0.02). However, age, sex, race, education, smoking status, alcohol drinking, PIR, caloric intake, hypertension, heart attack, stroke, coronary heart disease, diabetes, and other variables did not significantly affect the relationship between the prevalence of hyperlipidemia and total anthocyanidin intake (Supplementary Table 4, p for interaction > 0.05). There was no significant interaction between hyperlipidemia prevalence and total flavonols intake when stratified by age, sex, race, education, smoking status, alcohol drinking, PIR, caloric intake, hypertension, heart attack, stroke, coronary heart disease, diabetes, and other variables (Supplementary Table 5, p for interaction >0.05).

There was an interaction between the prevalence of hyperlipidemia and flavonoid intake in sex stratification. We used restricted cubic splines analysis to evaluate the association between flavonoid intake and the prevalence of hyperlipidemia in sex stratification. The nonlinear associations between hyperlipidemia prevalence and subtotal catechins intake (Figure 3A, $p = 0.0001$) and total flavan-3-ols intake (Figure 3B, $p = 0.0002$) were significant among female participants.

4 Discussion

This was the first study to explore the relationship between dietary flavonoid intake and hyperlipidemia in US adults. This study analyzed the relationship between dietary flavonoid intake and hyperlipidemia using NHANES 2007–2010 and 2017–2018 data. The results demonstrated that moderate intake of dietary flavonoids can reduce the prevalence of hyperlipidemia. In model 3, we observed that compared with the first quartile, there was an inverse relationship between subtotal catechins intake and the prevalence of hyperlipidemia in the third quartile [0.74 (0.56, 0.98), $p = 0.04$]. However, the p-value for the trend was insignificant ($p = 0.6$). Similarly, there was an inverse relationship between total flavan-3-ols intake and the prevalence of hyperlipidemia in the third quartile [0.76 (0.59, 0.98), $p = 0.03$], with a non-significant p-value for trend ($p = 0.83$). Compared with the first quartile, there was an inverse relationship between total anthocyanins intake and the prevalence of hyperlipidemia in the third [0.77 (0.62, 0.95), $p = 0.02$] and fourth quartiles [0.77 (0.60, 0.98), $p = 0.04$], the p-value for trend was significant ($p = 0.04$). Total flavonols intake in the fourth quartile [0.75 (0.60, 0.94), $p = 0.02$] was inversely related to the prevalence of hyperlipidemia, and the p-value for trend was significant ($p = 0.02$). In comparison to the first quartile, we discovered that the third quartile showed an inverse connection between the prevalence of hyperlipidemia and subtotal catechin intake [0.74 (0.56, 0.98), $p = 0.04$]. There was an inverse relationship between total flavan-3-ols intake in the third quartile [0.76 (0.59, 0.98), $p = 0.02$] and the prevalence of hyperlipidemia. Total anthocyanin intake was inversely related to the prevalence of hyperlipidemia in the third quartile [0.77 (0.62, 0.95), $p = 0.02$] and the fourth quartile [0.77 (0.60, 0.98), $p = 0.04$]. Total flavonols intake in the fourth quartile [0.75 (0.60, 0.94), $p = 0.02$] was inversely related to the prevalence of hyperlipidemia. Through restricted cubic splines analysis, we found that subtotal catechins intake and total flavan-3-ols intake had a nonlinear relationship with the prevalence of hyperlipidemia.

Hyperlipidemia is a major risk factor for cardiovascular diseases. Therefore, improving hyperlipidemia is important for cardiovascular diseases. Flavonoids play a crucial role in lipid metabolism (35, 36). Green tea, black rice, blueberries, mulberries, and raspberries are rich in flavonoids. Green tea protects against hyperlipidemia (37, 38), and the catechins in green tea are essential for health promotion by reducing body weight, decreasing the accumulation of hepatic lipid droplets, preventing hepatic fat accumulation, and significantly lowering serum TC and LDL cholesterol concentrations (39–42). (−)-Epicatechin in subtotal catechins, a natural flavanol monomer found in cocoa, green tea, and various other plant foods, improved blood lipid levels in hyperlipidemic rats, reduced lipid peroxidation, inhibited pro-inflammatory cytokines, and lowered serum AST and ALT, protecting the liver from excessive fat accumulation (43). However, the low bioavailability of catechins limits their therapeutic potential. The addition of lemon juice increased plasma catechin levels significantly (44). Catechins and their derivatives epigallocatechin-3-gallate and (−) -epigallocatechin promoted cholesterol reduction by inhibiting the synthesis of hydroxy-3-methylglutaryl-CoA reductase (45).

Anthocyanins are common in the diet for their protective effects against hyperlipidemia (46). In a double-blind, randomized, placebo-controlled trial, 122 hypercholesterolemic subjects were randomized into two groups, taking either 160 mg of anthocyanins or a placebo twice daily for 24 weeks. Anthocyanin supplementation significantly increased HDL cholesterol, decreased LDL cholesterol concentrations, and increased paraoxonase 1 activity and cholesterol efflux capacity (47). Two randomized, double-blind studies showed that anthocyanins can reduce the inflammatory response in patients with hypercholesterolemia (48, 49). Dietary black rice anthocyanins may prevent obesity-associated hyperlipidemia, hepatic steatosis, and insulin resistance by influencing the gut microbiota and lipid metabolism (50). Blueberries are rich in bioactive anthocyanins with antioxidant properties. Intervention with blueberry anthocyanin extract in streptozotocin-induced diabetic mice reduced body weight, increased AMPK activity, and lowered blood and urine glucose, triglyceride, and total cholesterol levels (51). AMPK can lower blood lipids by inhibiting lipid synthesis of effectors and promoting the activity of HSL in lipolysis (52), suggesting that blueberry anthocyanins may improve hyperlipidemia by activating the AMPK signaling pathway. Mulberry anthocyanins have a hypolipidemic effect by activating AMPK phosphorylation, inhibiting lipid biosynthesis, and stimulating lipolysis (53). Raspberry anthocyanins may alleviate oxidative stress and regulate lipid metabolism (54). Total flavones include apigenin and luteolin. Apigenin lowers blood lipid levels (55), reduces lipid accumulation in adipocytes, and promotes browning of white adipocytes through autophagy inhibition, thereby ameliorating abnormalities in lipid metabolism (56). Luteolin improves lipid levels and hepatic steatosis (57, 58). T These studies have demonstrated the

TABLE 2 Associations between flavonoid intake and hyperlipidemia.

Flavonoid intake	Q1	Q2		Q3		Q4		
		OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value	*p* for trend
Total Sum of all 29 flavonoids(mg/day)	≤25.15	25.15–65.16		65.16–229.68		≥229.28		
Crude model	ref	0.80 (0.66,0.98)	0.03	0.90 (0.75,1.08)	0.24	0.85 (0.70,1.02)	0.08	0.42
Model 1	ref	0.70 (0.57,0.86)	0.001	0.71 (0.58,0.87)	0.002	0.69 (0.57,0.83)	<0.001	0.03
Model 2	ref	0.74 (0.61,0.90)	0.004	0.76 (0.62,0.93)	0.01	0.72 (0.60,0.85)	<0.001	0.04
Model 3	ref	0.83 (0.63,1.12)	0.07	0.82 (0.64,1.04)	0.09	0.86 (0.62,1.14)	0.12	0.18
Subtotal Catechins (mg/day)	≤4.96	4.96–14.80		14.80–68.86		≥68.86		
Crude model	ref	0.96 (0.76,1.22)	0.75	0.79 (0.62,1.00)	0.05	0.97 (0.80,1.19)	0.79	0.56
Model 1	ref	0.87 (0.67,1.11)	0.26	0.65 (0.50,0.84)	0.002	0.80 (0.64,0.99)	0.04	0.36
Model 2	ref	0.89 (0.69,1.14)	0.34	0.67 (0.52,0.88)	0.004	0.82 (0.66,1.01)	0.06	0.44
Model 3	ref	0.92 (0.70,1.22)	0.55	0.74 (0.56,0.98)	0.04	0.86 (0.68,1.09)	0.19	0.6
Total Isoflavones (mg/day)	≤0.01	0.01–366.18						
Crude model	ref	0.85 (0.73,0.99)	0.03					
Model 1	ref	0.86 (0.74,1.02)	0.08					
Model 2	ref	0.89 (0.76,1.05)	0.16					
Model 3	ref	0.99 (0.81,1.20)	0.87					
Total Anthocyanidins (mg/day)	≤0.14	0.14–2.05		2.05–11.20		≥11.20		
Crude model	ref	1.13 (0.89,1.42)	0.30	0.85 (0.71,1.04)	0.11	0.90 (0.73,1.11)	0.30	0.15
Model 1	ref	0.98 (0.78,1.24)	0.86	0.69 (0.57,0.84)	<0.001	0.63 (0.51,0.80)	<0.001	<0.001
Model 2	ref	1.00 (0.79,1.27)	0.99	0.72 (0.59,0.89)	0.003	0.69 (0.54,0.87)	0.003	0.002
Model 3	ref	1.04 (0.80,1.34)	0.76	0.77 (0.62,0.95)	0.02	0.77 (0.60,0.98)	0.04	0.04
Total Flavan-3-ols (mg/day)	≤5.04	5.04–15.55		15.55–165.22		≥165.22		
Crude model	ref	0.93 (0.74,1.18)	0.56	0.84 (0.68,1.03)	0.09	0.94 (0.76,1.17)	0.57	0.83
Model 1	ref	0.83 (0.64,1.07)	0.15	0.67 (0.53,0.85)	0.001	0.79 (0.63,0.99)	0.04	0.51
Model 2	ref	0.85 (0.66,1.09)	0.20	0.70 (0.56,0.88)	0.004	0.81 (0.65,1.01)	0.06	0.56
Model 3	ref	0.89 (0.68,1.17)	0.37	0.76 (0.59,0.98)	0.03	0.86 (0.67,1.12)	0.24	0.83
Total Flavanones (mg/day)	≤0.07	0.0–0.70		0.70–19.21		≥19.21		
Crude model	ref	0.89 (0.74,1.07)	0.21	0.95 (0.77,1.18)	0.65	0.92 (0.75,1.13)	0.41	0.66
Model 1	ref	0.83 (0.68,1.02)	0.08	0.84 (0.66,1.06)	0.14	0.77 (0.61,0.97)	0.03	0.05
Model 2	ref	0.87 (0.70,1.08)	0.21	0.90 (0.70,1.16)	0.40	0.82 (0.64,1.05)	0.10	0.12
Model 3	ref	0.89 (0.69,1.14)	0.31	0.95 (0.72,1.25)	0.68	0.84 (0.64,1.10)	0.19	0.17
Total Flavones (mg/day)	≤0.19	0.19–0.53		0.53–1.09		≥1.09		
Crude model	ref	0.92 (0.75,1.14)	0.45	0.94 (0.76,1.16)	0.53	0.83 (0.67,1.02)	0.08	0.11
Model 1	ref	0.86 (0.70,1.05)	0.14	0.80 (0.65,0.99)	0.04	0.67 (0.54,0.85)	0.001	0.002
Model 2	ref	0.88 (0.71,1.10)	0.25	0.84 (0.68,1.05)	0.12	0.72 (0.57,0.91)	0.01	0.01
Model 3	ref	0.85 (0.66,1.08)	0.16	0.83 (0.65,1.06)	0.13	0.79 (0.61,1.03)	0.08	0.13
Total Flavonols (mg/day)	≤7.17	7.17–13.09		13.09–22.74		≥22.74		
Crude model	ref	0.86 (0.72,1.01)	0.07	0.89 (0.73,1.08)	0.23	0.84 (0.68,1.03)	0.10	0.19
Model 1	ref	0.79 (0.66,0.95)	0.01	0.78 (0.64,0.96)	0.02	0.70 (0.57,0.85)	<0.001	0.003
Model 2	ref	0.81 (0.68,0.97)	0.02	0.81 (0.67,0.99)	0.04	0.71 (0.58,0.88)	0.002	0.01
Model 3	ref	0.87 (0.72,1.04)	0.12	0.85 (0.68,1.07)	0.15	0.75 (0.60,0.94)	0.02	0.02

Crude model: unadjusted. Model 1: adjusted by age, race, and sex. Model 2: adjusted by age, race, sex, caloric intake, smoking status, alcohol drinking, education, PIR. Model 3: adjusted by age, race, sex, caloric intake, smoking status, alcohol drinking, education, PIR, protein, total fat, total sfat, total mfat, total pfat, total cholesterol, vitamin D, vitamin E, ACR, eGFR, AST/ALT, lipid-lowering drugs, hypertension, heart attack, stroke, coronary heart disease, and diabetes.

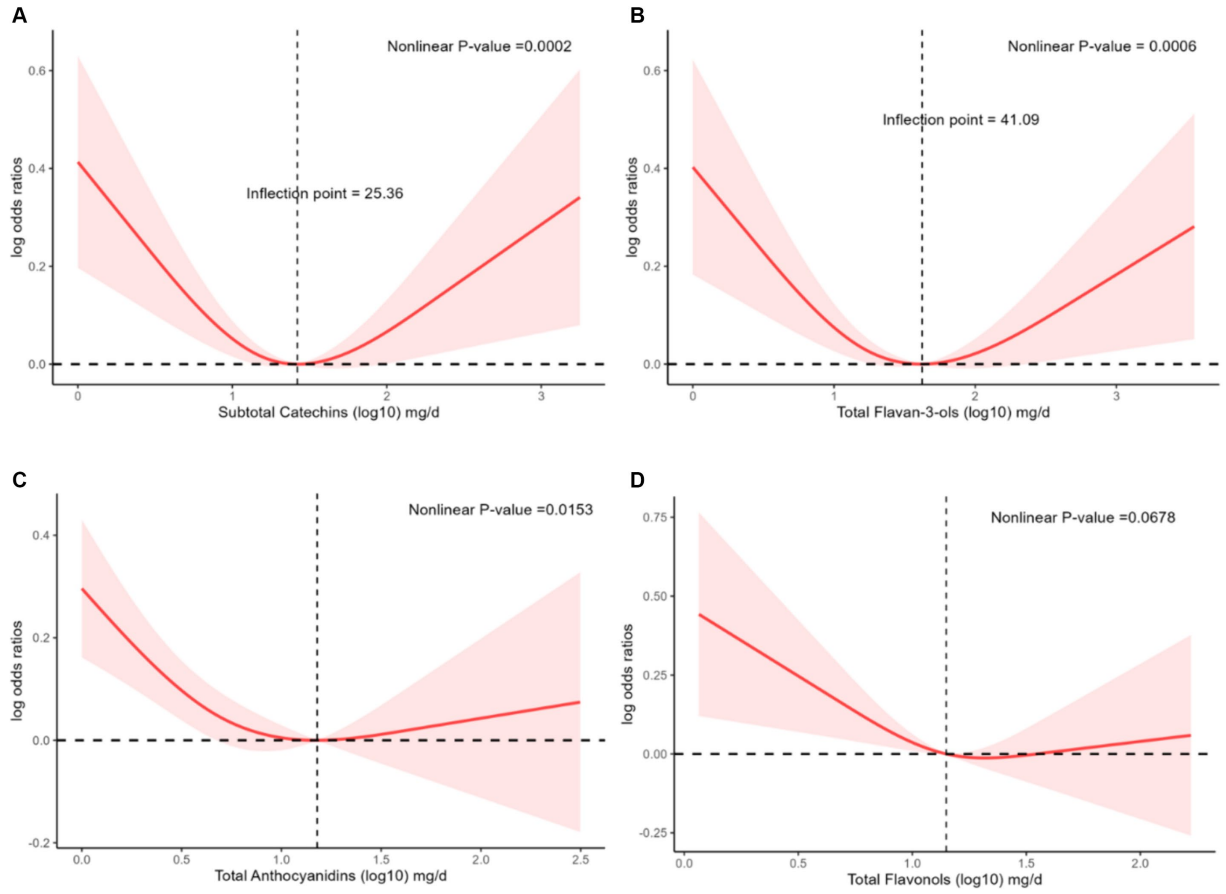

FIGURE 2
The association of flavonoid intake with prevalence of hyperlipidemia by restricted cubic splines. The y axis stands for the Log odds ratio of hyperlipidemia, and the X-axis stands for the log10 transformed intake of subtotal catechins **(A)**, total flavan-3-ols **(B)**, total anthocyanidins **(C)**, and total flavonols **(D)**. Models by restricted cubic splines were adjusted for age, race, sex, caloric intake, education, smoking status, alcohol drinking, PIR, protein, total fat, total sfat, total mfat, total pfat, total cholesterol, vitamin D, vitamin E, ACR, eGFR, AST/ALT, lipid-lowering drugs, hypertension, heart attack, stroke, coronary heart disease, and diabetes.

ability of flavonoids to regulate lipid metabolism and have a protective effect against hyperlipidemia.

When we analyzed the subgroups, we found that gender influenced the relationship between flavonoid intake and the prevalence of hyperlipidemia, with different trends in the prevalence of hyperlipidemia in women and men as flavonoid intake increased. In women, there was a statistically significant nonlinear correlation between the prevalence of hyperlipidemia and subtotal catechins intake (Figure 3A, $p = 0.0001$) and total flavan-3-ols intake (Figure 3B, $p = 0.0002$). However, the prevalence of hyperlipidemia in women showed a U-shaped curve with increasing flavonoid intake, which was different from the trend observed in men. This finding may be related to flavonoids being phytoestrogens, and there is a relationship between estrogen and lipid levels (59–61). Previous studies found that ApoC3 has a vital role in the lipoprotein lipase-mediated hydrolysis of triglyceride-rich lipoproteins, and knockdown of the ApoC3 gene significantly lowered triglyceride levels and elevated HDL cholesterol levels in hypertriglyceridemic patients (62). Estrogen inhibits ApoC3 expression, thereby reducing triglyceride levels (63). Unfortunately, no large-scale clinical studies are exploring the effect of sex on the prevalence of hyperlipidemia and flavonoids, and it is expected that large-scale prospective studies will be conducted in the future.

This study showed that among participants with hyperlipidemia, 57.28% were over 60 years old, and the average age of participants with hyperlipidemia was older than that of participants without hyperlipidemia, [48.90(0.37) vs. 38.89(0.51), $p < 0.0001$]. Among participants with hyperlipidemia, non-Hispanic White and Mexican Americans accounted for the largest proportions, 70.98, and 8.56%, respectively. However, in subgroup analysis, different races and age groups did not affect the relationship between flavonoids and hyperlipidemia prevalence (Table 3; Supplementary Tables 3–5, p for interaction >0.05).

The results of this study showed that among participants with hyperlipidemia, the proportion of former drinkers and moderate drinkers was large, accounting for 12.46 and 39.31%, respectively. The proportion of current smokers and former smokers is large, 19.25 and 24.94%, respectively. However, in subgroup analysis, alcohol drinking and smoking status had no significant impact on the relationship between the prevalence of hyperlipidemia and anthocyanin intake (Table 3; Supplementary Tables 3–5, p for interaction >0.05). It has been reported that alcohol consumption can increase plasma triglyceride levels and cause abnormalities in lipid metabolism, leading to hyperlipidemia (64–66). Studies have found that smoking increases total blood cholesterol levels and lowers beneficial high-density lipoprotein

TABLE 3 Subgroup analysis between hyperlipidemia and subtotal Catechins.

Variables	Q1	Q2		Q3		Q4			
		OR (95%CI)	*p* value	OR (95%CI)	*p* value	OR (95%CI)	*p* value	*p* for trend	*p* for interaction
Age									0.92
20–39	ref	0.93 (0.67,1.28)	0.65	0.85 (0.59,1.23)	0.39	0.97 (0.69,1.35)	0.83	0.87	
40–59	ref	1.00 (0.64,1.56)	0.99	0.67 (0.46,1.00)	0.05	0.82 (0.62,1.10)	0.18	0.46	
≥60	ref	0.90 (0.52,1.54)	0.69	0.68 (0.35,1.30)	0.23	0.80 (0.44,1.44)	0.44	0.75	
Race									0.51
Non-Hispanic White	ref	1.00 (0.69,1.46)	0.99	0.79 (0.55,1.12)	0.17	0.98 (0.73,1.30)	0.87	0.7	
Non-Hispanic Black	ref	1.13 (0.78,1.65)	0.50	1.33 (0.93,1.90)	0.12	1.33 (0.97,1.83)	0.07	0.12	
Mexican American	ref	0.75 (0.43,1.31)	0.30	0.83 (0.50,1.40)	0.48	0.72 (0.42,1.23)	0.22	0.41	
Others	ref	1.26 (0.75,2.14)	0.38	1.06 (0.61,1.84)	0.82	1.23 (0.74,2.03)	0.42	0.62	
Sex									0.005
Female	ref	0.83 (0.59,1.18)	0.30	0.84 (0.64,1.11)	0.22	1.20 (0.91,1.58)	0.20	0.01	
Male	ref	1.31 (0.98,1.76)	0.07	0.93 (0.64,1.34)	0.69	0.91 (0.71,1.17)	0.46	0.1	
Education									0.15
Less than high school	ref	0.85 (0.53,1.35)	0.47	1.21 (0.77,1.91)	0.40	1.10 (0.75,1.61)	0.64	0.52	
High school or equivalent	ref	0.90 (0.56,1.46)	0.67	0.55 (0.31,0.98)	0.04	1.10 (0.68,1.78)	0.68	0.24	
Some college or AA degree	ref	1.35 (0.96,1.92)	0.09	1.27 (0.95,1.70)	0.10	1.31 (0.93,1.85)	0.12	0.44	
College graduate or above	ref	1.02 (0.63,1.66)	0.92	0.86 (0.54,1.36)	0.51	0.97 (0.59,1.59)	0.90	0.93	
Smoking status									0.12
Never	ref	0.98 (0.77,1.24)	0.84	0.91 (0.70,1.20)	0.51	1.05 (0.83,1.32)	0.69	0.47	
Former	ref	1.82 (1.08,3.05)	0.03	1.22 (0.84,1.78)	0.28	1.32 (0.88,1.98)	0.18	0.92	
Now	ref	0.81 (0.50,1.31)	0.37	0.69 (0.43,1.11)	0.12	1.10 (0.72,1.68)	0.64	0.22	
Alcohol drinking									0.73
Former	ref	0.84 (0.41,1.69)	0.61	0.62 (0.31,1.24)	0.17	0.75 (0.41,1.36)	0.33	0.54	
Heavy	ref	1.03 (0.71,1.49)	0.87	0.89 (0.58,1.35)	0.57	1.09 (0.74,1.62)	0.64	0.58	
Moderate	ref	1.10 (0.68,1.78)	0.70	0.87 (0.57,1.34)	0.53	1.07 (0.61,1.88)	0.81	0.77	
Mild	ref	1.17 (0.85,1.61)	0.33	0.96 (0.70,1.33)	0.82	0.96 (0.69,1.33)	0.81	0.52	
Never	ref	0.83 (0.47,1.47)	0.51	0.83 (0.48,1.41)	0.48	1.53 (0.89,2.62)	0.12	0.03	
PIR									0.69
<1.5	ref	0.91 (0.64,1.28)	0.57	0.90 (0.62,1.30)	0.56	1.18 (0.85,1.65)	0.31	0.1	
1.5–3.5	ref	1.14 (0.85,1.53)	0.38	0.81 (0.55,1.18)	0.27	1.11 (0.78,1.57)	0.55	0.49	
>3.5	ref	1.06 (0.73,1.52)	0.77	0.93 (0.63,1.35)	0.69	0.98 (0.74,1.31)	0.91	0.9	
Caloric intake									0.23
<1913	ref	0.96 (0.66,1.40)	0.82	1.05 (0.75,1.47)	0.77	1.09 (0.81,1.46)	0.58	0.47	
≥1913	ref	1.15 (0.88,1.51)	0.29	0.83 (0.61,1.12)	0.22	1.08 (0.81,1.43)	0.61	0.48	
Hypertension									0.33
No	ref	0.97 (0.75,1.27)	0.85	0.81 (0.62,1.06)	0.12	0.98 (0.77,1.26)	0.90	0.6	

(Continued)

TABLE 3 (Continued)

Variables	Q1	Q2		Q3		Q4			
		OR (95%CI)	*p* value	OR (95%CI)	*p* value	OR (95%CI)	*p* value	*p* for trend	*p* for interaction
Yes	ref	1.29 (0.80,2.07)	0.28	1.12 (0.69,1.81)	0.65	1.34 (0.98,1.82)	0.07	0.18	
Heart attack									0.18
No	ref	1.03 (0.81,1.33)	0.79	0.90 (0.71,1.14)	0.37	1.06 (0.88,1.28)	0.53	0.32	
Yes	ref	1.76 (0.47,6.51)	0.39	0.40 (0.09,1.87)	0.24	0.68 (0.25,1.84)	0.44	0.45	
Stroke									0.2
No	ref	1.04 (0.82,1.33)	0.72	0.89 (0.70,1.12)	0.31	1.08 (0.90,1.29)	0.42	0.24	
Yes	ref	0.86 (0.22,3.39)	0.82	1.28 (0.35,4.72)	0.70	0.44 (0.09,2.07)	0.29	0.17	
Coronary heart disease									0.1
No	ref	1.02 (0.80,1.32)	0.85	0.88 (0.69,1.12)	0.29	1.06 (0.87,1.27)	0.57	0.29	
Yes	ref	2.60 (0.59,11.53)	0.20	2.86 (0.47,17.52)	0.25	0.84 (0.19, 3.71)	0.81	0.25	
Diabetes									0.18
No	ref	1.04 (0.81,1.35)	0.74	0.85 (0.66,1.08)	0.18	1.05 (0.84,1.31)	0.68	0.41	
DM	ref	1.41 (0.77,2.59)	0.25	2.07 (1.09,3.94)	0.03	1.05 (0.60,1.81)	0.87	0.41	
IFG	ref	0.76 (0.35,1.65)	0.48	1.24 (0.51,3.04)	0.62	1.13 (0.37,3.49)	0.82	0.69	
IGT	ref	0.83 (0.27,2.59)	0.74	0.50 (0.14,1.82)	0.28	1.46 (0.51,4.14)	0.46	0.22	

The subgroup analyses were adjusted for all covariates except the stratification variable itself.

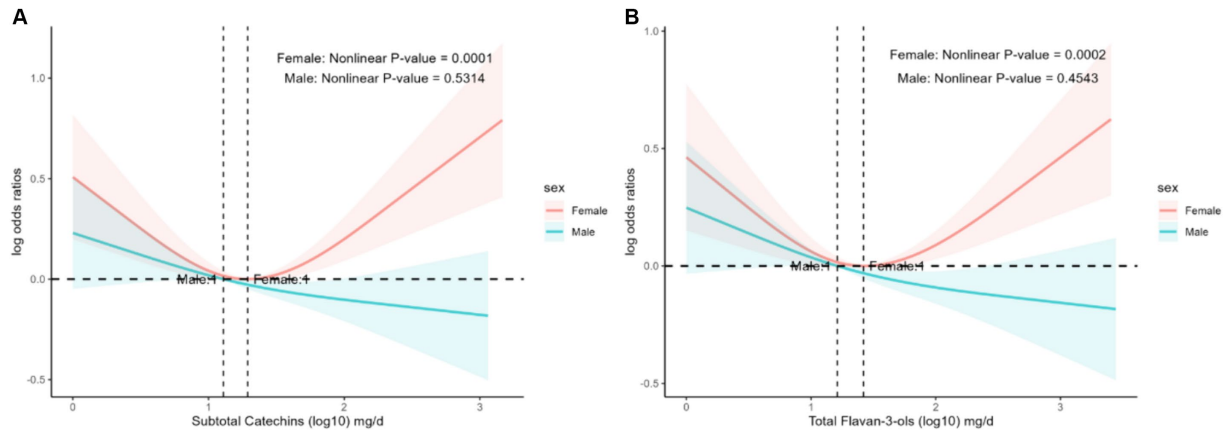

FIGURE 3
The association of flavonoid intake with prevalence of hyperlipidemia on sex by restricted cubic splines. The y-axis stands for the Log odds ratio of hyperlipidemia, and the X-axis stands for the log10 transformed intake of subtotal catechins **(A)** and total flavan-3-ols **(B)**. Models by restricted cubic splines were adjusted for age, race, caloric intake, smoking status, alcohol drinking, education, PIR, protein, total fat, total sfat, total mfat, total pfat, total cholesterol, vitamin D, vitamin E, ACR, eGFR, AST/ALT, lipid-lowering drugs, hypertension, heart attack, stroke, coronary heart disease, and diabetes.

(HDL) levels (67, 68). Therefore, smoking cessation and moderate alcohol consumption are crucial in the management of hyperlipidemia.

Our study had several strengths. First, to our knowledge, this was the first study to explore the relationship between dietary flavonoid intake and hyperlipidemia in US adults. Second, we explored the nonlinear relationship between dietary flavonoid intake and hyperlipidemia compared with previous studies. Third, our study showed consistent results from curve fitting and piecewise linear regression, indicating that the results were stable and reliable. Finally, we conducted a subgroup analysis and found that dietary flavonoid intake trends and hyperlipidemia prevalence were different in different genders. However, our study also had several limitations. This study was a cross-sectional study that cannot draw causal inferences. Dietary flavonoid intake was calculated based on 24-h dietary recall, which may be subject to recall bias. We look forward to future prospective studies with large samples and different genders.

5 Conclusion

Our study demonstrated that specific intakes of flavonoids were inversely associated with the risk of hyperlipidemia. We observed an inverse association between the risk of hyperlipidemia and moderate intake of subtotal catechins, flavan-3-ols, total anthocyanins, and total flavones. Our findings may provide valuable information for customized nutritional interventions to manage hyperlipidemia.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found at: All NHANES data for this study are publicly available and can be found at: https://wwwn.cdc.gov/nchs/nhanes.

Ethics statement

The studies involving humans were approved by Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of the National Center for Health Statistics (protocol #2005–06, #2011–17, #2018–01). 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

YW: Writing – review & editing, Writing – original draft, Validation, Project administration, Methodology, Conceptualization. DM: Writing – original draft, Formal analysis, Data curation. LY: Writing – review & editing, Data curation. WT: Writing – review & editing, Investigation. TW: Writing – review & editing, Software. XC: Writing – review & editing, Visualization. QS: Writing – review & editing, Supervision, Project administration. HX: Writing – review & editing, Supervision, Resources, Funding acquisition.

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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.2024.1374970/full#supplementary-material

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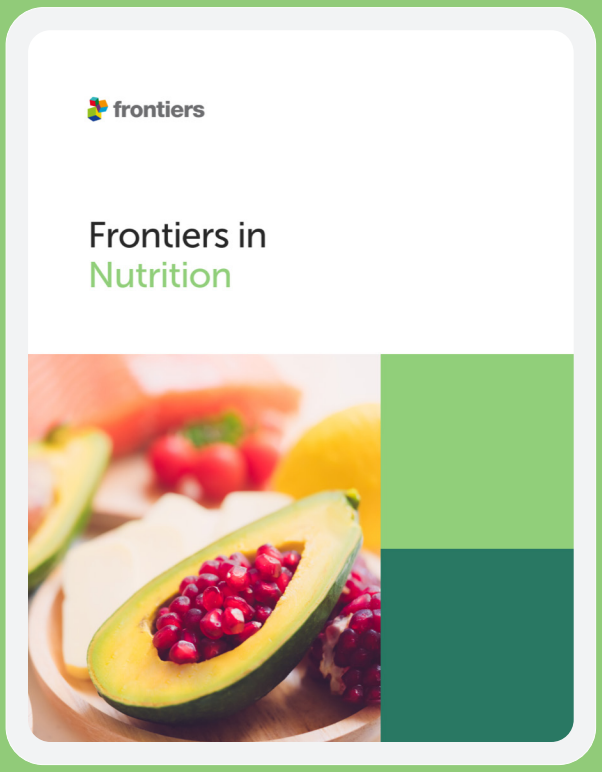

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