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Nutrition in the prevention and treatment of cardiovascular diseases

Edited by
Zhendong Liu, Changwei Li and Jichun Chen

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Nutrition in the prevention and treatment of cardiovascular diseases

Topic editors

Zhendong Liu — Shandong First Medical University, China

Changwei Li — Tulane University School of Public Health and Tropical Medicine, United States

Jichun Chen — Fuwai Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, China

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EDITED BY
Zhendong Liu,
Shandong First Medical University, China

REVIEWED BY
Fu-Zong Wu,
Kaohsiung Veterans General Hospital, Taiwan
Roberto Scicali,
University of Catania, Italy

*CORRESPONDENCE
Mei Xue
✉ meiar@126.com

†These authors have contributed equally to this work

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Association between visceral obesity and 10-year risk of first atherosclerotic cardiovascular diseases events among American adults: National Health and Nutrition Examination Survey

Liying Zheng[1,2†], Aochuan Sun[2,3†], Senfu Han[1,2], Rongming Qi[2,3], Rumeng Wang[1,2], Xiao Gong[1,2] and Mei Xue[1,2*]

[1]National Clinical Research Center for Chinese Medicine Cardiology, Xiyuan Hospital, China Academy of Chinese Medical Sciences, Beijing, China, [2]Xiyuan Hospital, China Academy of Chinese Medical Sciences, Beijing, China, [3]Graduate School, Beijing University of Chinese Medicine, Beijing, China

Background: In the United States, the relationship between visceral obesity and the risk of developing atherosclerosis cardiovascular disease (ASCVD) for the first time in 10 years is unclear.

Methods: Data for this cross-sectional study came from the National Health and Nutrition Examination Survey (NHANES) from 2011 to 2020. We collected variable information related to 10-year ASCVD risk and visceral obesity reliable indicators [Visceral obesity index (VAI) and Lipid accumulation product (LAP)]. And we used multiple logistic regression to analyze the correlation of visceral obesity indicators (VAI and LAP) with 10-year ASCVD risk. In addition, we assessed the linear relationship between VAI or LAP and 10-year ASCVD risk by smoothing curve fitting. Finally, we conducted subgroup analysis and sensitivity analysis after excluding participants with extreme VAI and LAP values to ensure that we obtained accurate and reliable results.

Results: Our study included a total of 1,547 participants (mean age: 56.5 ± 10.1, 60% of males). The results of the multiple logistic regression showed that compared with participants with the lowest VAI in the 1st Quartile (≤0.79), the adjusted OR values for VAI and elevated 10-year ASCVD risk in Q3 (1.30–2.14), and Q4 (≥2.15) were 2.58 (95% CI: 1.24–5.36, $P = 0.011$), 15.14 (95% CI: 6.93–33.05, $P < 0.001$), respectively. Compared with participants with the lowest LAP in the 1st Quartile (≤28.29), the adjusted OR values for VAI and elevated 10-year ASCVD risk in Q3 (46.52–77.00), and Q4 (≥77.01) were 4.63 (95% CI: 2.18–9.82, $P < 0.001$), 16.94 (95% CI: 6.74–42.57, $P < 0.001$), respectively. Stratified analysis showed that the association between VAI or LAP and the first ASCVD event was more pronounced in males.

Conclusion: Higher VAI or LAP scores are significantly associated with elevated 10-year ASCVD risk in adults aged 40 to 79 in the USA, which suggested that monitoring visceral obesity is crucial to reduce the risk of a first ASCVD event.

KEYWORDS

atherosclerotic cardiovascular disease, visceral obesity, visceral obesity index, lipid accumulation product, NHANES

1. Introduction

Despite encouraging achievements in the prevention, diagnosis, and treatment of ASCVD in recent years, ASCVD remains a leading cause of disability and premature death worldwide (1, 2). Due to the fact that most patients with early-onset ASCVD have modifiable risk factors before onset (3), exploring risk-related indicators for ASCVD and conducting early intervention is of paramount importance in reducing ASCVD mortality and alleviating the healthcare burden.

Obesity is a key risk factor for ASCVD (4–6), and the dramatic increase in obesity prevalence in recent years has undermined the gains made in controlling ASCVD risk factors and advancing medical technology (7). Body Mass Index (BMI) is a widely recognized standard for measuring obesity (8, 9). However, BMI can not distinguish between lean fat and whole fat, nor does it reflect the distribution of abdominal fat and body fat, and therefore it has some limitations in estimating the risk of ASCVD (10–12). Epidemiological findings suggested that visceral fat measured by imaging techniques such as CT or MRI is an independent risk factor for cardiovascular metabolic diseases and death (13). And there is evidence that ectopic fat deposition may be related to atherosclerosis and the increased risk of cardiometabolic (14). However, using techniques such as CT or MRI to measure ectopic fat deposition is expensive and limited by the detection instrument (15, 16). Therefore, several simple clinical tools have been developed to assess changes in visceral fat and ectopic fat deposition, of which VAI and LAP have been widely accepted and used clinically as two reliable indicators for assessing visceral obesity. VAI is a simple and reliable indicator of visceral adiposity dysfunction that reflects cardiometabolic risk, and is calculated by anthropometric parameters [waist circumference (WC) and BMI] and lipid measurement parameters [triglycerides (TG) and high-density lipoprotein cholesterol (HDL-C)] (17–19). LAP is an index of lipid hyperaccumulation based on WC and TG, and is considered to be a good continuous indicator to describe visceral obesity (20–22).

To our knowledge, few studies have been conducted on the association between visceral obesity and 10-year ASCVD risk, and the relationship between the two remains controversial. Therefore, we analyzed the association of VAI and LAP with 10-year ASCVD risk through a cross-sectional study to provide a scientific basis for clinical application.

2. Materials and methods

2.1. Study design and population

The National Health and Nutrition Examination Survey (NHANES) aims to assess and track the health and nutritional status of the non-institutionalized population in the United States through comprehensive health-related studies. A face-to-face interview is conducted at the individual's home to obtain information on demographics and medical history. Data from examinations, which include physiological, laboratory, and anthropometric data, were collected at the Mobile Examination Center (MEC). The NHANES protocol obtained approval from the National Center for Health Statistics ethics review committee and received written informed consent from all participants (23). For this cross-sectional study, we merged the NHANES data from 2011 to 2012, 2013–2014, 2015–2016, and 2017–2020. Participants included in this study had to meet the following criteria: (1) age between 40 and 79 years old, (2) no existing diagnosis of ASCVD, (3) HDL-C between 20 and 100 mg/dl, (4) total cholesterol (TC) between 130 and 320 mg/dl, and (5) systolic blood pressure (SBP) between 90 and 200 mmHg.

2.2. Measurement of VAI and LAP

The VAI and LAP was used as exposure variable and was calculated using gender-specific equations, as detailed below. VAI: male $[WC/39.68 + (1.88 \times BMI)] \times (TG/1.03) \times (1.31/HDL\text{-}C)$; female $[WC/36.58 + 1.89 \times (BMI)] \times (TG/0.81) \times (1.52/HDL\text{-}C)$ (24). LAP: male $[WC - 65] \times TG$; female $[WC - 58] \times TG$ (25). TG (mmol/L) was measured using the Wahlefeld method and HDL-C (mmol/L) was measured using the magnesium sulfate/glucan method. The calculation method for BMI is to divide weight (kilograms, kg) by height (meters, m) squared (kg/m^2). WC (cm) was measured with an accuracy of millimeters using electronic sports measurements.

2.3. ASCVD risk definition and assessment

The Pooled Cohort Equations (PCE) were implemented in 2013 by the American College of Cardiology/American Heart Association (ACC/AHA) as a tool for estimating the likelihood of developing ASCVD over ten years. This risk prediction model specifically caters to individuals aged 40–79 who are non-Hispanic white. This risk assessment equation includes characteristics such as age, gender, race, SBP, diastolic blood pressure (DBP), TC, HDL-C, low-density lipoprotein cholesterol (LDL-C), smoking status, hypertension treatment, statin use, and aspirin therapy. The 10-year risk of a first hard ASCVD event can be estimated by https://tools.acc.org/ASCVD-Risk-Estimator-Plus/#!/calculate/estimate/. Participants who scored ≥7.5% were classified as having an elevated 10-year ASCVD risk, whereas those who scored <7.5% were identified as low-risk individuals (26).

2.4. Statistical analysis

Continuous variables with normal distribution were expressed as mean ± standard deviation (SD), while those with skewed distribution were expressed as the median [interquartile range, (IQR)]. Categorical variables were presented as frequencies (%). The baseline characteristics of different 10-year ASCVD risk groups were compared using One-Way ANOVA when the data were normally distributed, Kruskal-Wallis H when the

distribution was skewed, and the chi-square test for categorical variables analysis. We used logistic regression to investigate the association between VAI and LAP with 10-year ASCVD risk (odds ratios [OR] and 95% confidence interval [CI]). Both non-adjusted and multivariate adjusted models were utilized in this study. Model 1 included adjustments for age, gender, and race. Model 2 was adjusted for sociodemographic characteristics such as age, gender, race, education level, marital status, PIR, smoking status, and BMI. Model 3 encompassed full adjustments, including sociodemographic characteristics, blood pressure measurements (SBP and DBP), TC, LDL-C, diabetes, statin use, and aspirin therapy.

Furthermore, we employed a smoothed curve fitting approach to evaluate the linear association between VAI or LAP and 10-year ASCVD risk. To ensure the accuracy of the findings from this study, multivariate logistic regression models were used for subgroup analysis. Possible variations in the relationship between VAI or LAP and 10-year ASCVD risk were examined, including gender, race, diabetes, statin use, and aspirin therapy. The interaction between subgroups was assessed using the likelihood ratio test. Moreover, participants with extreme VAI and LAP outside the mean ± 3 SD were excluded, for sensitivity analyses. All statistical analyses were conducted utilizing R version 3.3.2 (The R Foundation, http://www.R-project.org) and Free Statistics software version 1.7). A two-sided P value <0.05 was regarded as having statistical significance.

3. Results

3.1. Study population

This study included 45,462 prospective participants from NHANES (2011–2020), of which 3,468 adults (40–79 years) who met the inclusion criteria completed interviews and were subjected to MEC screening. Participants with missing data for age, gender, race, SBP, DBP, TC, HDL-C, LDL-C, diabetes, smoking status, hypertension treatment, statin, and aspirin therapy were excluded ($n = 1{,}147$). After excluding participants with incomplete covariate data ($n = 774$), a total of 1,547 participants were enrolled in this cross-sectional study. The flowchart of population screening is shown in **Figure 1**.

3.2. Characteristics of participants

The mean participants' age was 56.5 ± 10.1 years, and 928 (60.0%) were men. The mean baseline VAI and LAP were 1.73 ± 1.3 and 58.5 ± 42.3. There were 803 (51.9%) participants with elevated 10-year ASCVD risk. **Table 1** presents the baseline characteristics of study participants based on their 10-year ASCVD risk profile. There were obvious differences in age, gender, race, educational level, PIR, smoking status, SBP, DBP, diabetes status, statin use, and aspirin therapy between the two groups ($P < 0.05$). Marital status, BMI, TC, and LDL-C were comparable between the two groups ($P > 0.05$).

3.3. Association of VAI and LAP with 10-year ASCVD risk

The univariate analysis demonstrated that age, gender, race, education level, marital status, PIR, smoking status, SBP, DBP, diabetes status, statin use, and aspirin therapy were associated with elevated 10-year ASCVD risk (**Supplementary Table S1**).

The results of multifactor logistic regression analysis showed that after adjustment in multivariable analyses, VAI and LAP were significantly associated with elevated 10-year ASCVD risk. When VAI was assessed as a continuous variable, the adjusted OR was 3.46 (95% CI: 2.65–4.52) for elevated 10-year ASCVD risk in the full variables adjusted model (model 3). There was a significant positive correlation between VAI and elevated 10-year ASCVD risk after adjusting for all variables, when VAI was analyzed using quartiles. In model 3, compared with participants with the lowest VAI in the 1st Quartile (≤0.79), the adjusted OR values for VAI and elevated 10-year ASCVD risk in Q2 (0.79–1.29), Q3 (1.30–2.14), and Q4 (≥2.15) were 1.50 (95% CI: 0.75–3.00, $P = 0.254$), 2.58 (95% CI: 1.24–5.36, $P = 0.011$), 15.14 (95% CI: 6.93–33.05, $P < 0.001$), respectively (**Table 2**). When LAP was assessed as a continuous variable, the adjusted OR was 1.04 (95% CI: 1.03–1.05) for elevated 10-year ASCVD risk in model 3. When LAP was analyzed using quartiles, compared with participants with the lowest LAP in the 1st Quartile (≤28.29), the adjusted OR values for VAI and elevated 10-year ASCVD risk in Q2 (28.31–46.44), Q3 (46.52–77.00), and Q4 (≥77.01) were 3.00 (95% CI: 1.49–6.00, $P = 0.254$), 4.63 (95% CI: 2.18–9.82, $P < 0.001$), 16.94 (95% CI: 6.74–42.57, $P < 0.001$), respectively, in model 3 (**Table 2**). All of the models were statistically significant (**Table 2**, P for trend <0.05).

In addition, we used generalized additive models and smoothed curve fittings to assess the links between VAI or LAP and elevated 10-year ASCVD risk (**Figure 2**). There was a linear relationship of elevated 10-year ASCVD risk with VAI and LAP (P for non-linearity >0.05), which indicated that 10-year ASCVD risk increased with VAI and LAP.

3.4. Stratified analyses based on additional variables

Stratified analyses were conducted in various subgroups to examine the potential modification effect of VAI and LAP on the relationship with elevated 10-year ASCVD risk (**Figure 3**). No significant interactions were found in any of the subgroups after stratification by race, diabetes status, statin use, and aspirin therapy (P for interaction >0.05). After stratifying by gender, significant interactions were observed in both VAI and LAP groups (P for interaction <0.05).

3.5. Sensitivity analysis

After excluding participants with extreme VAI and LAP, 1,490 and 1,487 participants were remaining, respectively, and the

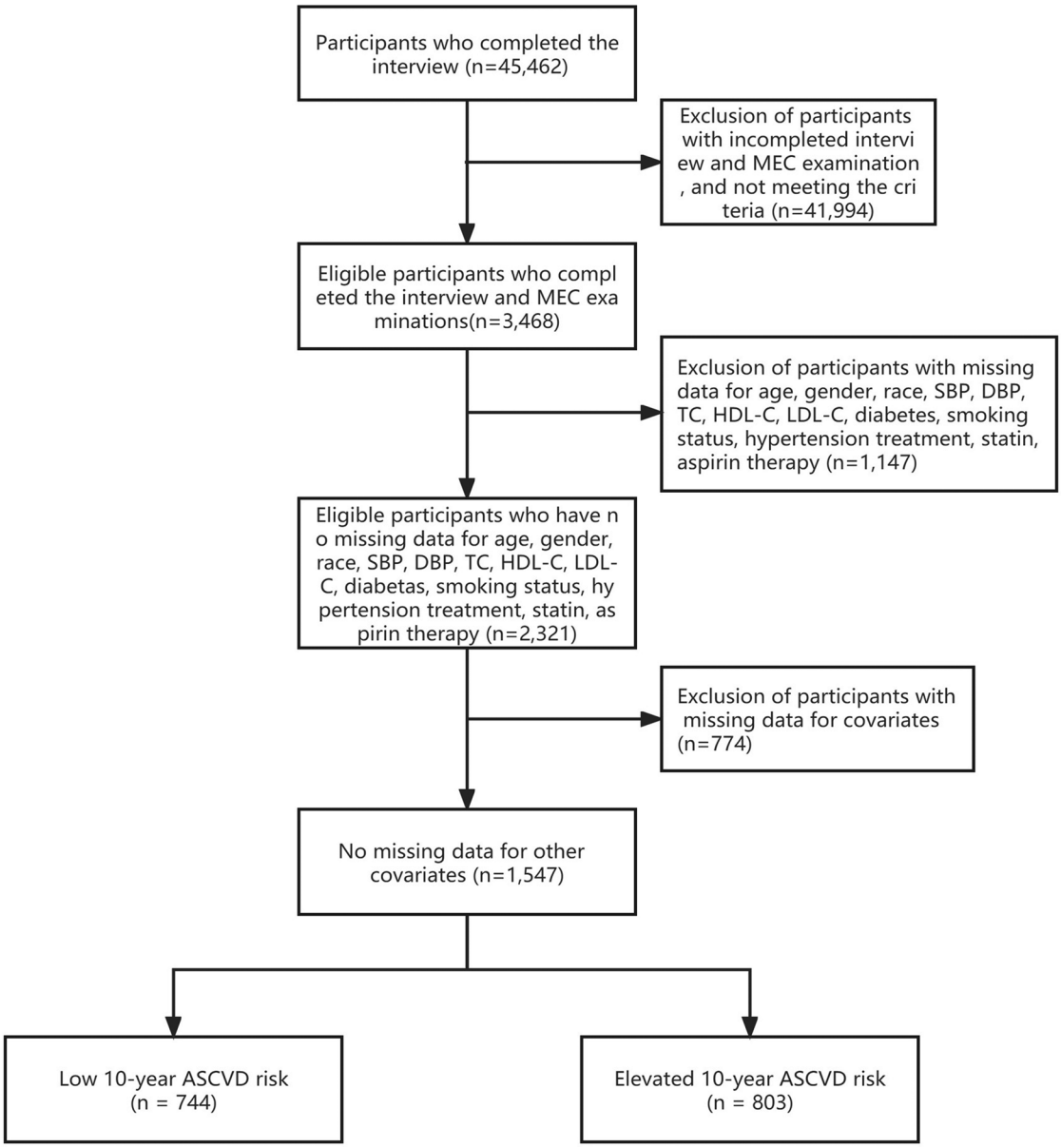

FIGURE 1
Flowchart of study population screening.

association between elevated 10-year ASCVD risk with VAI and LAP remained stable. When VAI or LAP was assessed as a continuous variable, in the fully adjusted models, the adjusted OR for a 10-year ASCVD risk increase was 3.04 (95% CI: 2.24–4.12, $P < 0.001$) and 1.03 (95% CI: 1.02–1.04, $P < 0.001$), respectively (**Supplementary Table S2**).

4. Discussion

This is a large cross-sectional study of American adults aged 40–79 years using NHANES data from 2011 to 2020. And the results of the study showed that VAI or LAP, whether as a continuous or categorical variable, was positively and linearly associated with elevated 10-year ASCVD risk when adjusted for potential confounding factors. The relationship between 10-year ASCVD risk with VAI and LAP remained robust after stratified and sensitivity analyses were performed. Interestingly, the stratified analysis also showed that this relationship was more pronounced among men.

It is well known that atherosclerosis is strongly associated with the risk of cardiovascular mortality worldwide (27, 28). Visceral obesity is strongly associated with increased atherosclerotic burden and is an emerging risk factor for CVD (13). And there is research showing that visceral obesity is significantly associated with the risk of recurrent ASCVD after myocardial infarction, residual cardiovascular risk, and CVD mortality (29). What's more a study on the South American population found that

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TABLE 1 Baseline characteristic of participants.

Variables	Total	Low 10-year ASCVD risk ($n = 744$)	Elevated 10-year ASCVD risk ($n = 803$)	*P*-value
Age, (years)	56.5 ± 10.1	50.0 ± 6.8	62.5 ± 8.9	<0.001
Gender, *n* (%)				<0.001
Male	928 (60.0)	327 (44)	601 (74.8)	
Female	619 (40.0)	417 (56)	202 (25.2)	
Race, *n* (%)				<0.001
White	685 (44.3)	372 (50)	313 (39)	
African American	352 (22.8)	118 (15.9)	234 (29.1)	
Other	510 (33.0)	254 (34.1)	256 (31.9)	
Education level, *n* (%)				<0.001
Did not graduate from high school	329 (21.3)	122 (16.4)	207 (25.8)	
Graduated from high school	379 (24.5)	176 (23.7)	203 (25.3)	
College education or above	839 (54.2)	446 (59.9)	393 (48.9)	
Marital status, *n* (%)				0.147
Married/Living with Partner	967 (62.5)	465 (62.5)	502 (62.5)	
Widowed/Divorced/Separated	423 (27.3)	193 (25.9)	230 (28.6)	
Never married	157 (10.1)	86 (11.6)	71 (8.8)	
PIR	2.6 ± 1.6	2.7 ± 1.7	2.4 ± 1.6	<0.001
Smoking status, *n* (%)				<0.001
Current	594 (38.4)	247 (33.2)	347 (43.2)	
Former	283 (18.3)	135 (18.1)	148 (18.4)	
Never	670 (43.3)	362 (48.7)	308 (38.4)	
BMI, (kg/m^2)	29.8 ± 6.7	30.0 ± 7.1	29.7 ± 6.4	0.414
SBP, (mmHg)	127.6 ± 16.8	120.5 ± 13.2	134.1 ± 17.2	<0.001
DBP, (mmHg)	75.1 ± 9.5	74.5 ± 8.8	75.7 ± 10.0	0.015
TC, (mg/dl)	196.6 ± 33.1	197.8 ± 32.6	195.5 ± 33.6	0.182
LDL-C, (mg/dl)	118.9 ± 28.9	119.4 ± 27.8	118.5 ± 29.9	0.519
Diabetes, *n* (%)				<0.001
Yes	257 (16.6)	51 (6.9)	206 (25.7)	
Statin use, *n* (%)				<0.001
Yes	363 (23.5)	122 (16.4)	241 (30)	
Aspirin therapy, *n* (%)				<0.001
Yes	432 (27.9)	121 (16.3)	311 (38.7)	
VAI	1.7 ± 1.3	1.5 ± 1.1	1.9 ± 1.4	<0.001
LAP	58.5 ± 42.3	54.3 ± 40.0	62.4 ± 44.0	<0.001

Data were mean ± SD or median (IQR) for skewed variables or numbers (proportions) for categorical variables.
PIR, ratio of family income to poverty; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; LDL-C, low density lipoprotein cholesterol; VAI, visceral obesity index; LAP, lipid accumulation product.

TABLE 2 Multivariable-adjust ORs and 95% CI of the VAI and LAP quartiles associated with elevated 10-year ASCVD risk.

Variable	Unadjusted		Model 1		Model 2		Model 3	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
VAI	1.25 (1.15 – 1.36)	<0.001	1.95 (1.71 – 2.22)	<0.001	2.25 (1.91 – 2.65)	<0.001	3.46 (2.65 – 4.52)	<0.001
1st Quartile (≤0.79)	1 (Ref)		1 (Ref)		1 (Ref)		1 (Ref)	
2st Quartile (0.79–1.29)	1.35 (1.02 – 1.80)	0.036	1.45 (0.94 – 2.25)	0.095	1.54 (0.92 – 2.59)	0.103	1.50 (0.75 – 3.00)	0.254
3st Quartile (1.30–2.14)	1.70 (1.28 – 2.27)	<0.001	2.64 (1.70 – 4.10)	<0.001	2.73 (1.60 – 4.65)	<0.001	2.58 (1.24 – 5.36)	0.011
4st Quartile (≥2.15)	2.06 (1.54 – 2.74)	<0.001	6.98 (4.41 – 11.05)	<0.001	8.52 (4.90 – 14.81)	<0.001	15.14 (6.93 – 33.05)	<0.001
P for trend		<0.001		<0.001		<0.001		<0.001
LAP	1.01 (1.00 – 1.01)	<0.001	1.02 (1.01 – 1.02)	<0.001	1.02 (1.02 – 1.03)	<0.001	1.04 (1.03 – 1.05)	<0.001
1st Quartile (≤28.29)	1 (Ref)		1 (Ref)		1 (Ref)		1 (Ref)	
2st Quartile (28.31–46.44)	1.30 (0.98 – 1.73)	0.067	1.88 (1.22 – 2.90)	0.004	2.37 (1.40 – 4.00)	0.001	3.00 (1.49 – 6.00)	0.254
3st Quartile (46.52–77.00)	1.72 (1.29 – 2.28)	<0.001	2.60 (1.69 – 4.00)	<0.001	3.83 (2.19 – 6.69)	<0.001	4.63 (2.18 – 9.82)	<0.001
4st Quartile (≥77.01)	1.68 (1.27 – 2.23)	<0.001	4.99 (3.21 – 7.76)	<0.001	8.12 (4.38 – 15.05)	<0.001	16.94 (6.74 – 42.57)	<0.001
P for trend		<0.001		<0.001		<0.001		<0.001

Model 1 adjust for Age, Gender, Race.
Model 2 adjust for Model 1 + Education level, Marital status, PIR, Smoking status, BMI.
Model 3 adjust for Model 1 + Model 2 + SBP, DBP, TC, LDL-C, Diabetes, Statin use, Aspirin therapy.
Ref, reference; PIR, ratio of family income to poverty; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; LDL-C, low density lipoprotein cholesterol; VAI, visceral obesity index; LAP, lipid accumulation product.

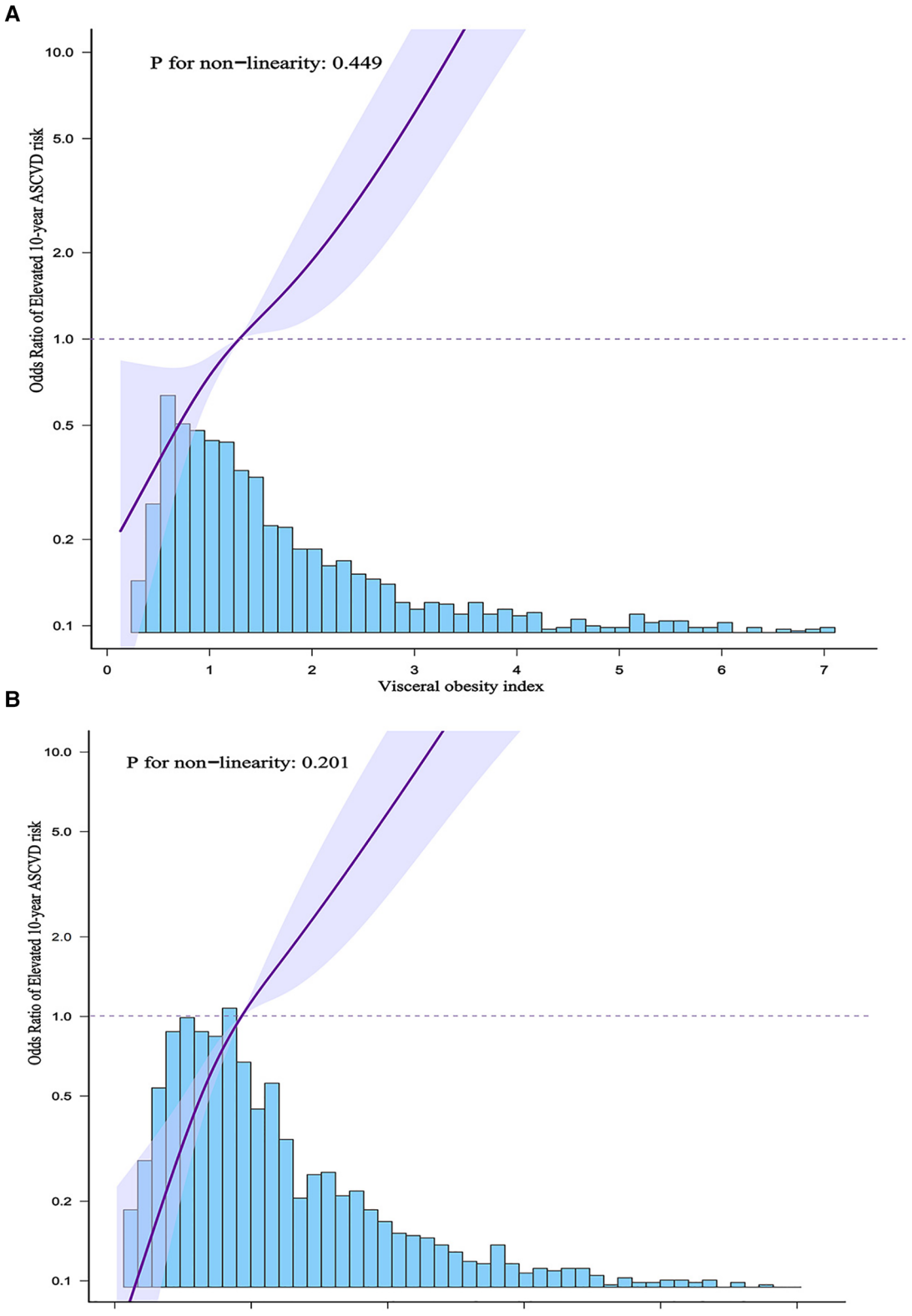

FIGURE 2
(**A**) Shows the association between VAI and elevated 10-year ASCVD risk. (**B**) Shows the association between LAP and elevated 10-year ASCVD risk. The solid purple line indicates the estimated or predicted value, the shaded area around the solid purple line indicates the 95% confidence interval, and the blue bar provides information on the sample size.

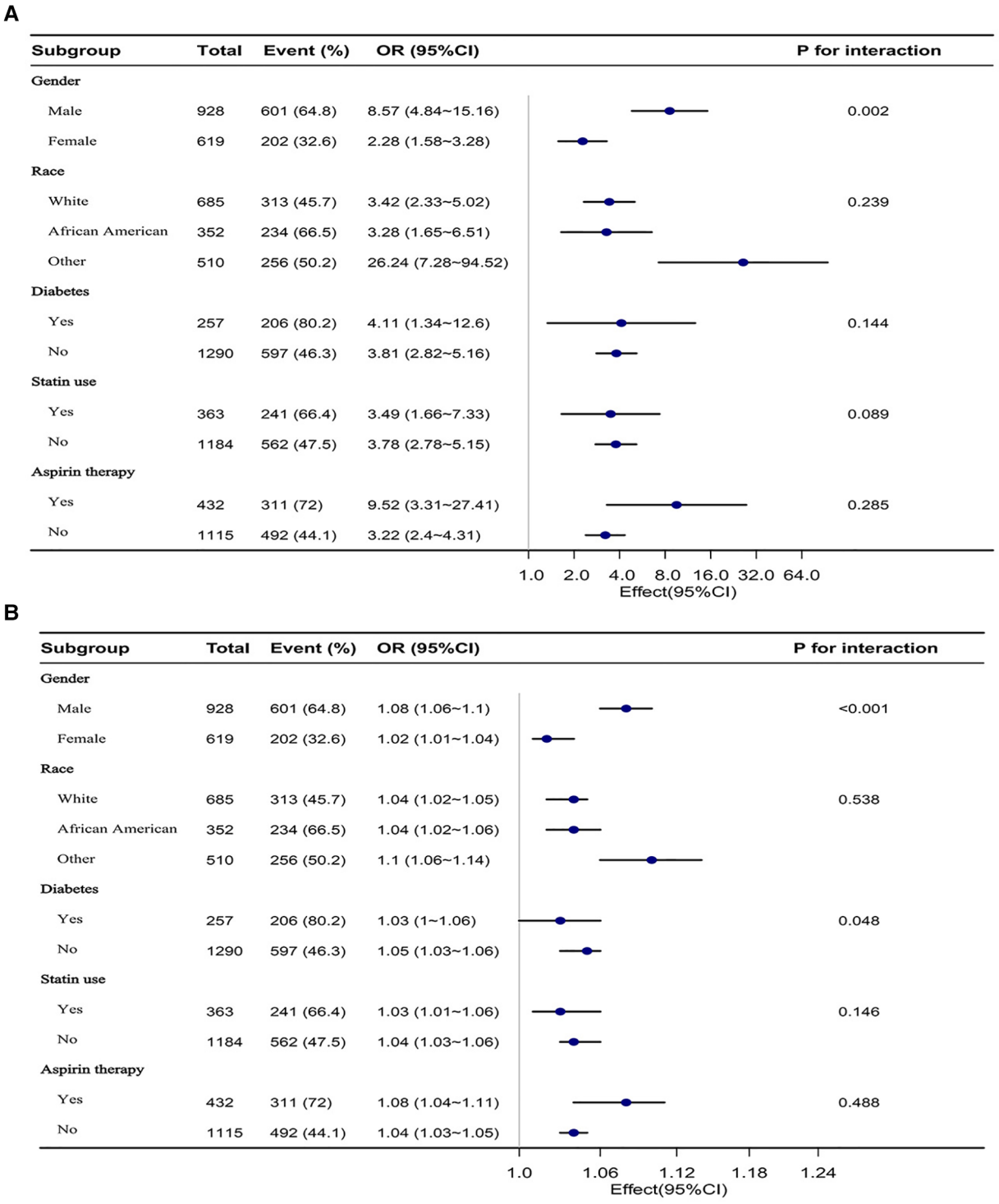

FIGURE 3
(A) Is a forest plot of the subgroup analysis of VAI and elevated 10-year ASCVD risk. (B) Is a forest plot of the subgroup analysis of LAP and elevated 10-year ASCVD risk. Each subgroup was adjusted for all other variables except the grouping factor itself.

visceral obesity accounts for 15.4% of the 12 modifiable risk factors for CVD, ranking second. And its contribution to CVD mortality is 9.7% (30). ASCVD, recurrent cardiovascular events, and residual CVD risks impose a heavy burden on human health and the development of the economy and society. Therefore, paying attention to visceral obesity is crucial for reducing the burden of atherosclerosis. CT, MRI and other imaging methods are the gold standard for detecting visceral obesity, providing a visual display of the thickness and area of visceral fat. However, due to the high cost, time-consuming nature, and the need for professional operators, these imaging examinations are not suitable for large-scale surveys of the general population in

clinical settings (31–33). VAI and LAP are considered sensitive and reliable indicators for assessing visceral obesity, especially VAI has been proven to be highly correlated with visceral fat measured through gold standard methods (17, 22). Its advantages of high safety, easy operation, and low cost make it replace complex imaging methods and become an alternative indicator for evaluating visceral obesity. Amato et al. showed for the first time in a retrospective study of Alkam metabolic syndrome (AlkaMeSy) that an increase in VAI was independently associated with increased cardiovascular and cerebrovascular events (18). Subsequent studies suggested that VAI was independently associated with coronary atherosclerosis and could assess cardiometabolic risk, ASCVD risk, and CVD mortality (34–38). However, the relationship between VAI and 10-year ASCVD risk remains controversial. In a prospective cohort study conducted in Europe, Koulii et al. found that VAI was independently associated with a 10-year risk of CVD, especially in males, and its relevance was not affected by potential confounding factors such as lifestyle factors (39). On the contrary, Aysegul et al. conducted a prospective cohort study on 55 postmenopausal women and found that there was no significant association between VAI and 10-year CVD risk (40). Our research on American adults aged 40–79 shows that there is a significant correlation between AVI and the 10-year ASCVD risk, and this relationship is more pronounced in males, which is similar to the findings of Koulii et al. This gender difference may be due to the fact that men and women differ greatly in body fat distribution, with men being more prone to visceral fat accumulation than women (41, 42). And a study showed that the measurement of visceral fat tissue in men using CT scans is twice as high as that in premenopausal women, and postmenopausal women also have lower accumulation of visceral fat tissue. As a result, women have lower risk of cardiovascular metabolic disorders (43, 44). In addition, hormones have a great impact on fat distribution patterns. Research has shown that androgens can promote the accumulation of visceral fat, while estrogens have less impact on the accumulation of visceral fat (43). Therefore, the VAI in males may be relatively higher than in females, with a greater increase in 10-year ASCVD risk. However, whether there are gender differences in the association between VAI and 10-year ASCVD risk still requires further validation through large-scale clinical studies. In 2005, Henry Kahn et al. based on the cross-sectional study of the NHANES III first proposed the LAP index and pointed out that compared with BMI, LAP had a better correlation with key risk factors for CVD (such as heart rate and blood lipids, as well as uric acid circulation levels), and may better predict the incidence of CVD (22). Subsequent studies have shown that LAP was associated with atherosclerosis in elderly and menopausal women, and can independently predict the risk of cardiovascular events in women with polycystic ovary syndrome (PCOS) as well as in participants with normal BMI (35, 44–46). Ioachimescu et al. found that LAP, rather than BMI, can predict the mortality of non-diabetes patients with high CVD risk, which suggested that LAP may be a useful tool for risk stratification of obesity-related adverse consequences in clinical practice (47). Li et al.'s cross-sectional study conducted in China showed that the alternative indicators of visceral obesity, VAI and LAP, may be related to the risk of intracranial Atherosclerosis stenosis (ICAS) in women ≥40 years (48). Kyrou et al. found that LAP was independently related to the long-term incidence of CVD in a prospective study of the Greek population (49), which was similar to our research findings. However, unlike the findings of Huang et al. in 3,143 Taiwanese adults, our study did not find any differences in the association strength between VAI and LAP with 10-year ASCVD risk, which may be due to ethnic differences in the study population (50).

The mechanism by which central obesity indicators (VAI and LAP) are associated with 10-year ASCVD risk is still unclear. There are several possible explanations for the research results. Firstly, the study indicates that abnormal distribution and accumulation of adipose tissue are fundamental causes of atherosclerosis, and VAI and LAP are representative indices for assessing adipose distribution and accumulation (35). Secondly, the characteristic of visceral obesity is an increased deposition of visceral and ectopic fat, which is associated with insulin resistance (51), elevated blood pressure (52), dyslipidemia (53), and inflammation (54), all of which are closely related to ASCVD risk. Visceral adipose tissue can increase basal fat breakdown, release free fatty acids (FFA), and specific cytokines secreted by visceral adipocytes, such as leptin and adiponectin, which can increase insulin resistance (55–57). In addition, inflammatory cytokines (tumor necrosis factor-alpha and interleukin-6) released by macrophages accumulated in visceral adipose tissue can weaken insulin sensitivity and thus promote insulin resistance (58). In insulin resistance, co-causative factors including glucotoxicity, lipotoxicity, and inflammation selectively impair PI3K-dependent insulin signaling pathways, thereby inducing the atherogenic process and leading to the occurrence of ASCVD (59). Hypertension is a recognized risk factor for ASCVD. Visceral adiposity patients have increased insulin and leptin which promotes sympathetic nervous system (SNS) activity (60–62). The SNS stimulates renin release and the production of angiotensin II, which increases the activity of the Renin-Angiotensin-Aldosterone System (RAAS) and therefore raises blood pressure (63, 64). In addition, visceral obesity causes the kidneys to reabsorb sodium through the SNS, hormones (aldosterone and insulin), and renal vasculature (angiotensin II). The increase in sodium also contributes to higher blood pressure to maintain sodium balance and volume homeostasis (65, 66). Dyslipidemia is highly associated with ASCVD risk. Abnormal lipid metabolism causes the blood to be in a highly cohesive state, the blood viscosity increases, and promotes the formation of atherosclerotic plaque (67). Insulin resistance, abnormal metabolism of fat factors [pro-inflammatory adipokines (leptin, resistin, TNF-α), anti-inflammatory adipokine (adiponectin), specific adipokine Sfrp5], and vitamin D deficiency are all possible causes of abnormal blood lipids in visceral obese individuals (53). In addition, excessive production of very low-density lipoprotein (VLDL) by the liver and reduced breakdown of triglycerides (TG) during lipid metabolism circulation, damaged peripheral FFA uptake, increased FFA from

adipocytes to the liver and other tissues, and the formation of small dense LDL as well as damage to the ASP/C3adesArg pathway are also possible mechanisms of obesity-induced abnormal blood lipids (68). Inflammation is a key link in the occurrence and development of ASCVD. When there is excessive visceral fat, subcutaneous enlarged adipocytes secrete pro-inflammatory cytokines such as IL-6, reducing the secretion of possible anti-inflammatory and insulin sensitized cytokines adiponectin, and prone to cell apoptosis, leading to macrophage invasion (69–71). Macrophages infiltrate into enlarged adipocytes, further leading to an increase in the production of inflammatory cytokines such as tumor necrosis factor-alpha and interleukin-6, a decrease in the production of protective adipokine adiponectin, and harmful cross-talk between macrophages and enlarged adipocytes resulting in the production of detrimental secreted products (13, 72).

To our knowledge, this is the first exploration of the relationship between VAI and LAP with 10-year risk of first ASCVD events in US adults. However, there also are some limitations in our study. Firstly, although regression models, subgroup analysis, and sensitivity analysis are used, residual confounding effects of unmeasured or unknown factors cannot be completely excluded. Secondly, the current research results are based on a survey of adults aged 40–79 in the United States, and further research is still needed to determine whether the results of this study are applicable to other populations. In addition, although one of the indicators of visceral obesity, VAI, is a composite calculated from BMI, WC, TG and HDL-C. However, it has a similar parameter to the ASCVD, and some validation bias may exist even though the primary results did not change after adjusting for the similar parameter. Finally, the cross-sectional study can only explore the correlation, and can not further draw causal inferences, thus future longitudinal studies or randomized controlled trials are needed for further validation.

5. Conclusion

In conclusion, in American adults, especially males, VAI or LAP score is positively correlated with 10-year risk of first ASCVD events. Our research indicates that doctors should assess the degree of visceral obesity to identify individuals at high risk for ASCVD.

Data availability statement

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

Ethics statement

The studies involving humans were approved by the National Center for Health Statistics 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

MX, LZ, and AS designed the study and extracted the relevant data. SH and RQ collated and cleaned the data. RW and XG examined the cleaned data. LZ and AS analyzed the data and wrote the original manuscript. MX reviewed and revised the manuscript. LZ and AS contributed equally to the study. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2023.1249401/full#supplementary-material

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EDITED BY
Changwei Li,
Tulane University School of Public Health and Tropical Medicine, United States

REVIEWED BY
Chengxue Zhong,
Boehringer Ingelheim, United States
Ruiyuan Zhang,
Tulane University, United States

*CORRESPONDENCE
Jie Feng
✉ 4010009@csu.edu.cn

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Comparison of seven surrogate insulin resistance indexes for predicting the prevalence of carotid atherosclerosis in normal-weight individuals

Zeyu Liu[1], Bi Deng[1], Qin Huang[2], Ruxin Tu[1], Fang Yu[1], Jian Xia[1,3,4] and Jie Feng[1,3,4]*

[1]Department of Neurology, Xiangya Hospital, Central South University, Changsha, Hunan, China, [2]Department of Neurology, Peking University People's Hospital, Beijing, China, [3]Clinical Research Center for Cerebrovascular Disease of Hunan Province, Central South University, Changsha, Hunan, China, [4]National Clinical Research Center for Geriatric Disorders, Xiangya Hospital, Central South University, Changsha, Hunan, China

Introduction: The aim of this study was to assess the correlation between surrogate insulin resistance (IR) indexes and carotid atherosclerosis (CA) in normal-weight populations, as well as compared their ability to predict CA.

Method: A total of 26,795 middle-aged and older adult individuals with normal body weights were included. Triglyceride-glucose index (TyG), TyG-body mass index, TyG-waist circumference (TyG-WC), TyG-waist-to-height ratio (TyG-WHtR), visceral adiposity index, Chinese VAI (CVAI) and lipid accumulation product (LAP) were determined using established formulas. The associations between these surrogate indexes and CA were assessed using logistic regression models and restricted cubic spline (RCS) analysis. Receiver operating characteristic curves were utilized to compare the performance of these indexes for predicting CA.

Result: The levels of all seven surrogate indexes of IR were significantly higher in normal-weight individuals with CA than in those without CA ($p < 0.001$). In the full-adjusted model, only CVAI, TyG-WC, TyG-WHtR and LAP were significantly associated with CA, with the adjusted odds ratios (95% CI) of CA being 1.25 (1.20–1.30), 1.18 (1.14–1.23), 1.20 (1.16–1.25) and 1.25 (1.18–1.32) for each one standard deviation increase in CVAI, TyG-WC, TyG-WHtR and LAP, respectively. RCS analysis revealed a significant increase in the prevalence of CA among normal-weight individuals with CVAI >89.83, LAP >28.91, TyG-WHtR >4.42 and TyG-WC >704.93. The area under the curve for CVAI was significantly greater than for other indexes ($p < 0.001$).

Conclusion: CVAI, TyG-WC, TyG-WHtR and LAP were independently associated with the prevalence of CA. Specifically, CVAI may be the most appropriate predictor of CA in normal-weight individuals.

KEYWORDS

surrogate insulin resistance indexes, carotid atherosclerosis, carotid intima-media thickness, carotid plaque, carotid stenosis, normal-weight individuals

1. Introduction

Cardiovascular diseases (CVDs), particularly ischemic heart disease and stroke, remain the leading cause of mortality and a significant contributor to disability globally (1). According to the World Health Organization report from 2019, around 17.9 million deaths were attributed to CVDs, which corresponded to 31% of all the global mortality rate (2). Atherosclerosis, the primary etiology of CVD, poses a significant public health challenge owing to its asymptomatic nature over long terms, unfavorable prognosis, and reduced life expectancy (3, 4). Carotid atherosclerosis (CA), which encompasses increased carotid intima-media thickness (CIMT), plaque and stenosis, is widely recognized as a crucial indicator of generalized atherosclerosis and a predictor of cardiovascular disease events (5–8). Early detection of CA through regular non-invasive ultrasonography is advantageous in implementing proactive measures to prevent or manage CVD before its progression (9). Given the significant and escalating burden of CVD, it is imperative to promptly detect CA in the general population, identify promising biomarkers for early detection and implement preventive measures.

Recent accumulating evidence suggests that obesity, as measured by body mass index (BMI), is strongly associated with an increased risk of developing CA (10, 11). However, a significant number of individuals with normal weight but metabolic abnormalities also exhibit a cluster of metabolic risk factors as well as an elevated risk for carotid artery disease (12, 13). Furthermore, individuals with a normal weight, as determined by BMI, frequently perceive themselves as being in good health. Consequently, it is less probable that individuals with normal weight will undergo clinical screening and early intervention for CA compared to those who are obese. Therefore, timely detection of CA in individuals with normal body weight is imperative.

Insulin resistance (IR), defined as the attenuation of insulin responsiveness in tissues, not only expedites the advancement of atherosclerosis but also serves as a primary characteristic of metabolically obese normal-weight individuals (14). This implies that determining the degree of IR might be advantageous in predicting the likelihood of developing CA. The homeostatic model assessment of insulin resistance (HOMA-IR) has traditionally been employed to quantify insulin resistance; however, there has been no consensus regarding the association of HOMA-IR scores with the risk of CA (15–17). Furthermore, HOMA-IR is substantially limited in clinical practice by the need to measure insulin levels. The demand for a dependable and cost-effective indicator of IR has prompted the creation of innovative surrogate indexes, including triglyceride-glucose index (TyG) (18, 19), TyG-BMI (20), TyG-waist circumference (TyG-WC) (21), TyG-waist-to-height ratio (TyG-WHtR) (22), Chinese visceral adiposity index (CVAI) (23), visceral adiposity index (VAI) (24) and lipid accumulation product (LAP) (18), which are effective in assessing IR status. Reportedly, a few studies have evaluated the association between these partially surrogate IR indexes and atherosclerosis (25–29). However, many of these studies had small sample sizes and did not specifically target individuals with a normal weight, a population that has been understudied and often overlooked in early screening for CA. Furthermore, it remains ambiguous as to which indexes hold greater predictive value for CA.

Despite considerable research on the surrogate indexes of IR, no studies have investigated their relationship with CA prevalence in normal-weight individuals. Accordingly, the present large, cross-sectional study enrolled 26,795 community residents with normal weight to explore the relationship between surrogate IR indexes and CA. In addition, the study identified the index with the most predictive ability for IR in a normal-weight population.

2. Materials and methods

2.1. Study participants

During the period of 2017–2020, the participants were recruited from the China Stroke High-risk Population Screening and Intervention Program (CSHPSIP) in Hunan province, China (30). The CSHPSIP enrolled community-dwelling adults who met the following criteria: (1) aged >40 years, (2) resided in the community for >6 months, and (3) provided informed consent (31). The Institutional Review Board at Capital Medical University Xuanwu Hospital reviewed and approved the protocol for the CSHPSIP program, and this study was conducted in accordance with the research protocol of CSHPSIP.

A total of 26 communities, comprising 13 urban and 13 rural areas, were selected in proportion to local population size and community numbers. Between January 2017 and December 2020, face-to-face surveys were conducted among 133,489 individuals, with 53,222 participants receiving carotid ultrasound examinations in accordance with the screening protocol. The present cross-sectional investigation excluded participants who exhibited abnormal weight, as defined by the World Health Organization standards, including those with a BMI $\geq$ 25 (n = 22,354) or BMI < 18.5 (n = 1,355), as well as individuals with incomplete laboratory assay results (n = 2,714) and missing data on waist circumference (WC) (n = 4). Ultimately, the final analysis included a total of 26,795 normal-weight individuals (Figure 1).

2.2. Data collection

A face-to-face interviewer-administered questionnaire was conducted by trained medical staff to gather data on medical, socio-demographic, and lifestyle-related variables. The demographic information collected included age, sex, education level (categorized as "primary school or below," "middle school," and "high school or above"), living status, and lifestyle risk factors such as tobacco use, alcohol consumption, and physical activity. Additionally, medical history pertaining to hypertension, diabetes mellitus, cerebrovascular diseases, and heart diseases was obtained. Physical inactivity refers to the absence of moderate-to-vigorous physical activity for >150 min/week or vigorous-intensity physical activity for >75 min/week (31). Diabetes was defined as a fasting plasma glucose level of $\geq$7.0 mmol/L, a previous diagnosis of diabetes mellitus, or the use of antidiabetic medication or insulin (32). Hypertension was defined as a blood pressure of $\geq$140/90 mmHg, a history of hypertension, or the use of antihypertensive medication (32). Dyslipidemia was defined as serum total cholesterol (TC) concentration $\geq$ 6.22 mmol/L, and/or low-density lipoprotein cholesterol (LDL-C) concentration $\geq$ 4.14 mmol/L, and/or TG concentration $\geq$ 2.26 mmol/L, and/or HDL-C concentration < 1.04 mmol/L, or previous history of

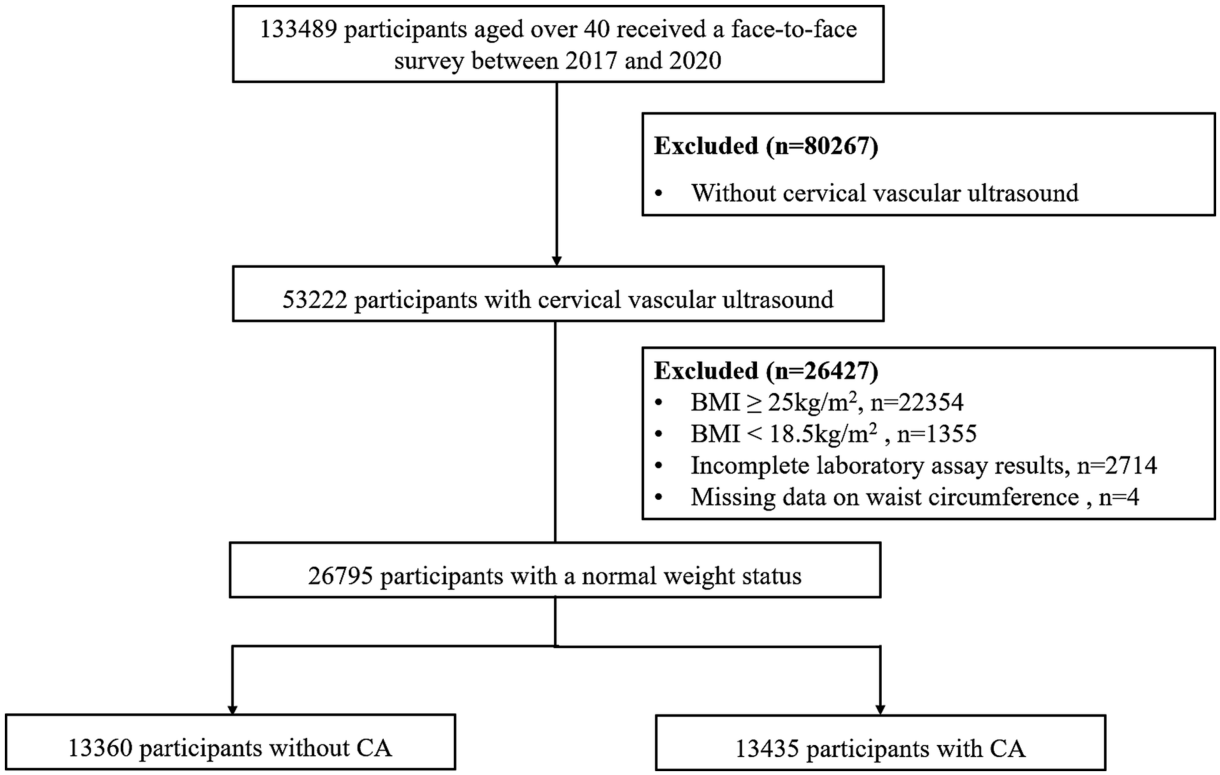

FIGURE 1
The process of study participants selection.

hyperlipidemia (32). The height, weight, and WC were measured twice by a qualified nurse or physician and the results were averaged. BMI was calculated as body mass (in kilograms) divided by the square of height (in meters). Additionally, venous blood samples were collected after an 8 h fast, and laboratory parameters, including fasting blood glucose (FBG), TC, TG, LDL-C, and HDL-C, were analyzed. The seven surrogate indexes of IR were calculated using established formulas, as detailed in Supplementary Table S1.

2.3. Definition of carotid atherosclerosis

Two proficient ultrasound technologists, who were unaware of the patient's clinical information, performed carotid ultrasonography examinations in a skilled and autonomous manner. The participants' bilateral carotid arteries were scanned in the supine position with the neck in a hyperextended position. The measurement of CIMT was conducted at three distinct locations on the far wall of a 1 cm-long segment of the common carotid artery, situated in close proximity to the carotid bulb. An increased CIMT was defined as a range of 1.0 to 1.5 mm, which is in line with previous research (28). Carotid plaques were identified as having an intima-media thickness exceeding 1.5 mm or protruding into the lumen by 50% more than the surrounding intima-media thickness (28). Carotid stenosis was defined as the occlusion or more than 50% stenosis of at least one common carotid or internal carotid artery (28). Participants exhibiting increased CIMT, plaques, or carotid stenosis were diagnosed with CA.

2.4. Statistical analysis

This study utilized counts (proportions) to present categorical variables and medians (interquartile ranges) for non-normally distributed data to present continuous variables. To compare the baseline characteristics of participants without CA to those with CA, the Mann–Whitney test was used for continuous variables and the chi-square test for categorical variables. Three logistic models were employed to evaluate the association between surrogate indexes of IR and CA, such as increased CIMT, carotid plaques, or stenosis. These models consisted of an unadjusted crude model (Model 1), a model adjusted for demographic factors including age, sex, education level, and living status (Model 2), and a model further adjusted for lifestyle factors such as current smoking, alcohol consumption, physical inactivity, medical history of hypertension, diabetes, cerebrovascular disease and heart disease, as well as biochemical markers and anthropometric measurements including FBG, TC, TG, LDL-C, HDL-C, and BMI (Model 3).The variables included in the models all satisfied the criteria of tolerance values greater than 0.1 and variance inflation factor less than 10. *p* for trends was calculated using quartiles of surrogate IR indexes as the ordinal variable. Additionally, surrogate IR indexes were analyzed as continuous variables to investigate the dose–response relationship between a per standard deviation (SD) increase and CA, increased CIMT, carotid plaque, or stenosis. Additional subgroup analyses were conducted to explore the correlation between a per SD increase in CVAI, TyG-WC, TyG-WHtR, or LAP, and CA in diverse subgroups stratified by age (40–49, 50–59, 60–69, and ≥ 70 years), sex (male, female), diabetes (yes, no), and

hypertension (yes, no). Additionally, a restricted cubic spline analysis was employed to investigate potential nonlinear associations and visualize the dose–response relationship between surrogate indexes and CA. The study also employed the receiver operator characteristic curve to evaluate the predictive ability of various indexes, including TyG, TyG-BMI, TyG-WC, TyG-WHtR, CVAI, VAI, and LAP, for identifying CA, increased CIMT, carotid plaque, or stenosis. *Z*-tests were utilized to investigate the disparities in area under the curve (AUC) values.

All seven surrogate indexes were calculated based on triglyceride values, thereby raising concerns about potential bias arising from the utilization of anti-dyslipidemia medications. However, medication information for participants in this study was largely missing. Therefore, a sensitivity analysis was conducted by excluding all patients with dyslipidemia from the analyses to assess bias. In the participants without dyslipidemia, we evaluate the predictive capacity of different indexes again and additionally investigate the association between CA and the following measures: TyG-WC, TyG-WHtR, CVAI, and LAP. Detailed results can be found in Supplementary Tables S2, S8.

SPSS version 25.0 (IBM SPSS, Armonk, NY, United States) and R version 4.2.3 (R Development Core Team, Vienna, Austria) were used for all statistical analyses. A two-tailed p-value of <0.05 was considered to indicate statistical significance.

3. Results

3.1. Baseline characteristics

The baseline characteristics of eligible study participants are indicated in Table 1. Of 26,795 normal-weight individuals, 13,435 (50.1%) had CA. The individuals with and without CA had significant differences with regard to age; sex; educational level; living status; smoking and alcohol consumption habits; physical activity levels; history of hypertension, diabetes, cerebrovascular disease and heart disease, as well as baseline serum levels of FBG, TG, TC, LDL-C and HDL-C. Notably, individuals with CA exhibited significantly higher median levels of all surrogate IR indexes (TyG, TyG-BMI, TyG-WC, TyG-WHtR, CVAI, VAI, and LAP) than those without CA.

3.2. Association of surrogate IR indexes with CA

Figure 2 illustrates the relationship between different quartiles of surrogate IR indexes and the prevalence of CA. Briefly, as the levels of surrogate IR indexes increased, the prevalence of CA increased as well (p for trend <0.05).

Table 2 shows odds ratios (ORs) and 95% confidence intervals (CIs) of CA by different quartiles of TyG, TyG-BMI, TyG-WC, TyG-WHtR, CVAI, VAI, and LAP. After adjusting for confounding factors, the ORs (95% CIs) for CA as assessed using CVAI were 1.25 (1.15–1.36), 1.47 (1.34–1.61), and 1.69 (1.51–1.88) in quartiles 2, 3 and 4 respectively, compared with those in quartile 1. Similar findings were observed for TyG-WC, TyG-WHtR, and LAP. Furthermore, sensitivity analyses are provided in the Supplementary Table S2, which did not change results above significantly.

However, the fully adjusted model revealed significant associations between CA and the fourth quartile of VAI, whereas no such associations were observed for the second and third quartiles. No significant positive correlation was observed between TyG or TyG-BMI and the prevalence of CA among normal-weight individuals. Moreover, the correlation between the surrogate IR indexes and different types of CA suggested that only individuals in the highest quartiles of CVAI or TyG-WHtR exhibited a significantly elevated prevalence for all subtypes of CA (including increased CIMT, plaque and stenosis). Detailed results can be seen in Supplementary Tables S3–S5.

The prevalence of CA by per-SD increase of surrogate IR indexes is illustrated in Figure 3. With each additional SD increase in TyG-WC, TyG-WHtR, CVAI, and LAP, the likelihood of CA increased by 18, 20, 25, and 25%, respectively. Similar results were observed for the prevalence of increased CIMT, carotid plaque and carotid stenosis.

Multivariable restricted cubic spline analysis indicated a significantly elevated rate of CA at higher levels of CVAI, LAP, TyG-WHtR and TyG-WC (Figure 4). Specifically, an appreciable increase was noted in the prevalence of CA among individuals with certain anthropometric indexes such as CVAI >89.83, LAP >28.91, TyG-WHtR >4.42 and TyG-WC >704.93.

3.3. Subgroup analyses for the association between surrogate IR indexes and CA prevalence

Table 3 and Supplementary Table S6 display the findings of subgroup analyses that investigate the correlation between CVAI, TyG-WC, TyG-WHtR, and LAP with the prevalence of CA. The relationship between elevated CVAI, TyG-WC, TyG-WHtR, or LAP (per 1 SD) and the prevalence of CA among individuals with normal weight remained consistent across various subgroups. However, a more pronounced association between CVAI, TyG-WC, TyG-WHtR, or LAP and the increased prevalence of CA was observed among females and those aged between 40 and 49 years old.

3.4. Predictive performance of surrogate IR indexes for CA

Figure 5 and Supplementary Table S7 demonstrate the predictive performance of seven surrogate indexes for CA. CVAI exhibited the largest AUC of 0.638 ($p < 0.001$). Moreover, the optimal CVAI value for detecting CA in normal-weight individuals was 86.69, with a sensitivity of 0.631 and specificity of 0.583. Furthermore, CVAI exhibited superior accuracy in predicting all assessed subtypes of CA, including increased CIMT, carotid plaque and carotid stenosis (all $p < 0.001$). The results of the sensitivity analyses, which did not significantly change the results, are provided in the Supplementary Table S8.

4. Discussion

Using data from CSHPSIP, this large-scale, cross-sectional study demonstrated a significant correlation between the prevalence of CA

TABLE 1 Baseline characteristics of study participants with and without CA.

Characteristics	Total (26795)	Non-CA (13360)	CA (13435)	*p* value
Age, years	62 (52–69)	55 (49–65)	66 (58–72)	<0.001
40–49	4,603 (17.2)	3,878 (29.0)	725 (5.4)	<0.001
50–59	7,647 (28.5)	4,612 (34.5)	3,035 (22.6)	
60–69	7,896 (29.5)	2,857 (21.4)	5,039 (37.5)	
≥70	6,649 (24.8)	2013 (15.1)	4,636 (34.5)	
Male, *N* (%)	11,642 (43.4)	5,307 (39.7)	6,335 (47.2)	<0.001
Education, *N* (%)				<0.001
Primary school or below	10,541 (39.3)	4,588 (34.3)	5,953 (44.3)	
Middle school	8,637 (32.2)	4,607 (34.5)	4,030 (30.0)	
High school or above	7,617 (28.4)	4,165 (31.2)	3,452 (25.7)	
Live alone, *N* (%)	1,315 (4.9)	511 (3.8)	804 (6.0)	<0.001
Current smoking, *N* (%)	6,935 (25.9)	2,993 (22.4)	3,942 (29.3)	<0.001
Alcohol consumption, *N* (%)	4,549 (17.0)	2,101 (15.7)	2,448 (18.2)	<0.001
Physical inactivity, *N* (%)	9,971 (37.2)	4,861 (36.4)	5,110 (38.0)	0.003
Hypertension, *N* (%)	13,808 (51.5)	5,419 (40.6)	8,389 (62.4)	<0.001
Diabetes, *N* (%)	7,403 (27.6)	3,078 (23.0)	4,325 (32.2)	<0.001
Cerebrovascular disease, *N* (%)	1,331 (5.0)	318 (2.4)	1,013 (7.5)	<0.001
Heart disease, *N* (%)	1,303 (4.9)	350 (2.6)	953 (7.1)	<0.001
Increased CIMT	10,489 (39.1)		10,489 (78.1)	
Carotid plaques	10,081 (37.6)		10,081 (75.0)	
Carotid stenosis	316 (1.2)		316 (2.4)	
FBG, mmol/L	5.19 (4.50–6.20)	5.10 (4.50–6.00)	5.20 (4.57–6.50)	<0.001
TG, mmol/L	1.50 (1.07–2.16)	1.50 (1.06–2.14)	1.50 (1.08–2.18)	0.027
TC, mmol/L	4.80 (4.10–5.55)	4.78 (4.10–5.49)	4.83 (4.11–5.60)	<0.001
LDL-C, mmol/L	2.60 (2.04–3.25)	2.57 (2.03–3.19)	2.64 (2.05–3.30)	<0.001
HDL-C, mmol/L	1.36 (1.13–1.65)	1.38 (1.14–1.68)	1.35 (1.12–1.62)	<0.001
BMI, kg/m^2	22.70 (21.30–23.83)	22.72 (21.34–23.83)	22.68 (21.25–23.83)	0.053
WC, cm	80.0 (75.0–85.0)	80.0 (75.0–84.0)	80.0 (76.0–85.0)	<0.001
Surrogate IR indexes				
TyG	8.78 (8.37–9.21)	8.76 (8.35–9.18)	8.79 (8.39–9.24)	<0.001
TyG-BMI	198.48 (183.10–213.32)	198.08 (182.93–212.64)	198.99 (183.26–214.04)	0.005
TyG-WC	702.48 (647.03–761.47)	693.34 (637.77–750.79)	711.44 (655.89–771.18)	<0.001
TyG-WHtR	4.42 (4.07–4.80)	4.35 (4.01–4.71)	4.49 (4.14–4.87)	<0.001
VAI	1.73 (1.09–2.82)	1.71 (1.08–2.75)	1.76 (1.10–2.88)	<0.001
CVAI	88.56 (68.06–109.05)	80.79 (61.15–100.99)	95.99 (76.43–115.30)	<0.001
LAP	27.80 (17.08–44.52)	26.65 (16.40–42.60)	28.80 (17.86–46.25)	<0.001

CA, carotid atherosclerosis; CIMT, carotid intima-media thickness; FBG, fasting blood glucose; TG, triglyceride; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; BMI, body mass index; WC, waist circumferences; TyG, triglyceride-glucose index; WHtR, waist-to-height-ratio; VAI, the visceral adiposity index; CVAI, the Chinese visceral adiposity index; LAP, lipid accumulation product.

and TyG-WC, TyG-WHtR, CVAI, and LAP in normal-weight adults. However, no significant association was observed between the prevalence of CA and TyG, TyG-BMI or VAI. Furthermore, among all the indexes, CVAI exhibited superior predictive ability for determining CA, increased CIMT, plaque and stenosis.

Research suggests that atherosclerosis is characterized by an initial, extended asymptomatic phase, which can commence as early as adolescence or even childhood (33). Given the increasing burden of CVD, it is crucial to conduct early screening and timely interventions for atherosclerosis for reducing the incidence of CVD. Furthermore, it is less likely that the normal-weight population will undergo clinical screening and early intervention for CA compared with the obese population. However, the present study found that the prevalence of CA was as high as 50.1% in

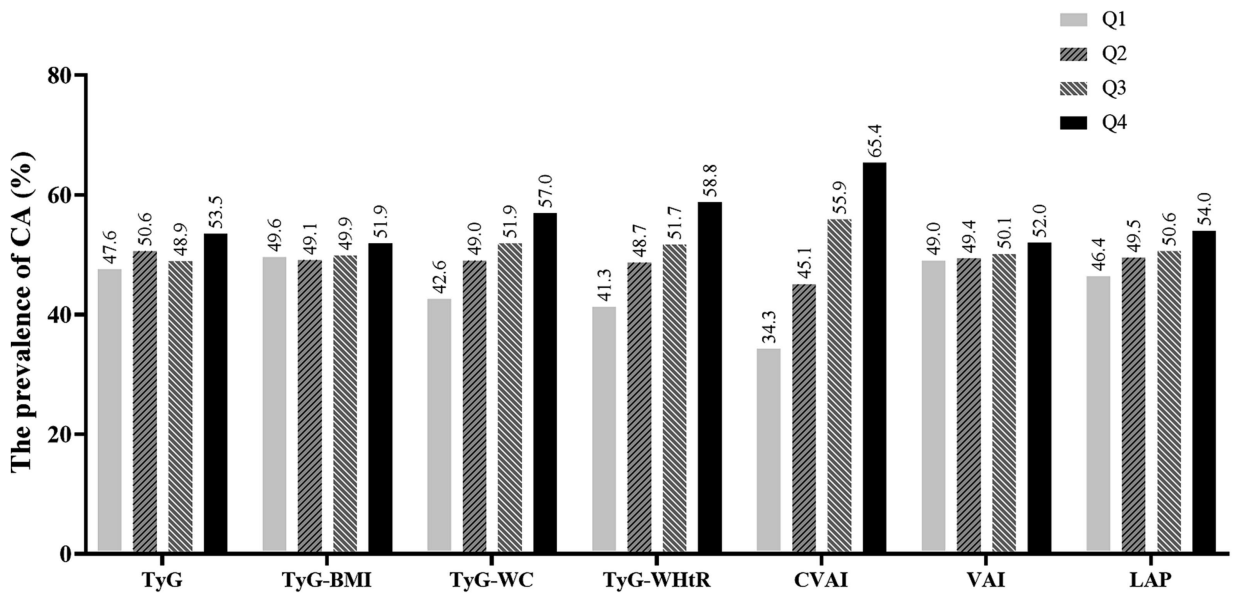

FIGURE 2
The prevalence of CA for quartiles of seven surrogate IR indexes. CA, carotid atherosclerosis; TyG, triglyceride-glucose index; TyG-BMI, TyG-body mass index; TyG-WC, TyG-waist circumference; TyG-WHtR, TyG-waist-to-height ratio; VAI, the visceral adiposity index; CVAI, the Chinese visceral adiposity index; LAP, lipid accumulation product.

TABLE 2 Odds ratio of CA by quartiles of surrogate IR indexes.

Variants	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*p* for trend
TyG					
Model 1	Reference	1.13 (1.06–1.21)	1.05 (0.98–1.13)	1.27 (1.19–1.36)	<0.001
Model 2	Reference	1.07 (0.99–1.15)	0.99 (0.92–1.07)	1.18 (1.09–1.27)	0.001
Model 3	Reference	1.01 (0.94–1.09)	0.89 (0.82–0.97)	1.01 (0.90–1.12)	0.228
TyG-BMI					
Model 1	Reference	0.98 (0.92–1.05)	1.01 (0.95–1.08)	1.10 (1.03–1.17)	0.004
Model 2	Reference	1.02 (0.94–1.10)	1.03 (0.95–1.11)	1.14 (1.05–1.22)	0.001
Model 3	Reference	0.99 (0.90–1.08)	0.97 (0.86–1.08)	1.03 (0.88–1.19)	0.830
TyG-WC					
Model 1	Reference	1.30 (1.21–1.39)	1.45 (1.36–1.55)	1.79 (1.67–1.91)	<0.001
Model 2	Reference	1.15 (1.07–1.24)	1.22 (1.13–1.32)	1.44 (1.34–1.56)	<0.001
Model 3	Reference	1.14 (1.05–1.23)	1.20 (1.11–1.31)	1.44 (1.31–1.58)	<0.001
TyG-WHtR					
Model 1	Reference	1.35 (1.26–1.45)	1.52 (1.42–1.63)	2.03 (1.89–2.17)	<0.001
Model 2	Reference	1.22 (1.13–1.31)	1.26 (1.17–1.35)	1.54 (1.43–1.66)	<0.001
Model 3	Reference	1.21 (1.12–1.31)	1.27 (1.17–1.38)	1.60 (1.45–1.77)	<0.001
CVAI					
Model 1	Reference	1.57 (1.47–1.69)	2.43 (2.27–2.60)	3.62 (3.37–3.89)	<0.001
Model 2	Reference	1.24 (1.15–1.34)	1.45 (1.34–1.57)	1.63 (1.50–1.77)	<0.001
Model 3	Reference	1.25 (1.15–1.36)	1.47 (1.34–1.61)	1.69 (1.51–1.88)	<0.001
VAI					
Model 1	Reference	1.02 (0.95–1.09)	1.05 (0.98–1.12)	1.13 (1.05–1.21)	<0.001
Model 2	Reference	1.10 (1.02–1.18)	1.15 (1.07–1.24)	1.26 (1.17–1.36)	<0.001
Model 3	Reference	1.02 (0.94–1.10)	1.03 (0.94–1.13)	1.13 (1.01–1.27)	0.061
LAP					
Model 1	Reference	1.13 (1.06–1.21)	1.19 (1.11–1.27)	1.36 (1.27–1.45)	<0.001
Model 2	Reference	1.14 (1.06–1.23)	1.17 (1.09–1.26)	1.37 (1.27–1.48)	<0.001
Model 3	Reference	1.13 (1.04–1.22)	1.16 (1.07–1.26)	1.43 (1.30–1.59)	<0.001

Model 1: Unadjusted. Model 2: Adjusted for age, sex, living status, and education level. Model 3: Adjusted for age, sex, living status, education level, current smoking, alcohol consumption, physical inactivity, hypertension, diabetes, cerebrovascular diseases, heart disease, FBG, TC, TG, LDL-C, HDL-C, and BMI.

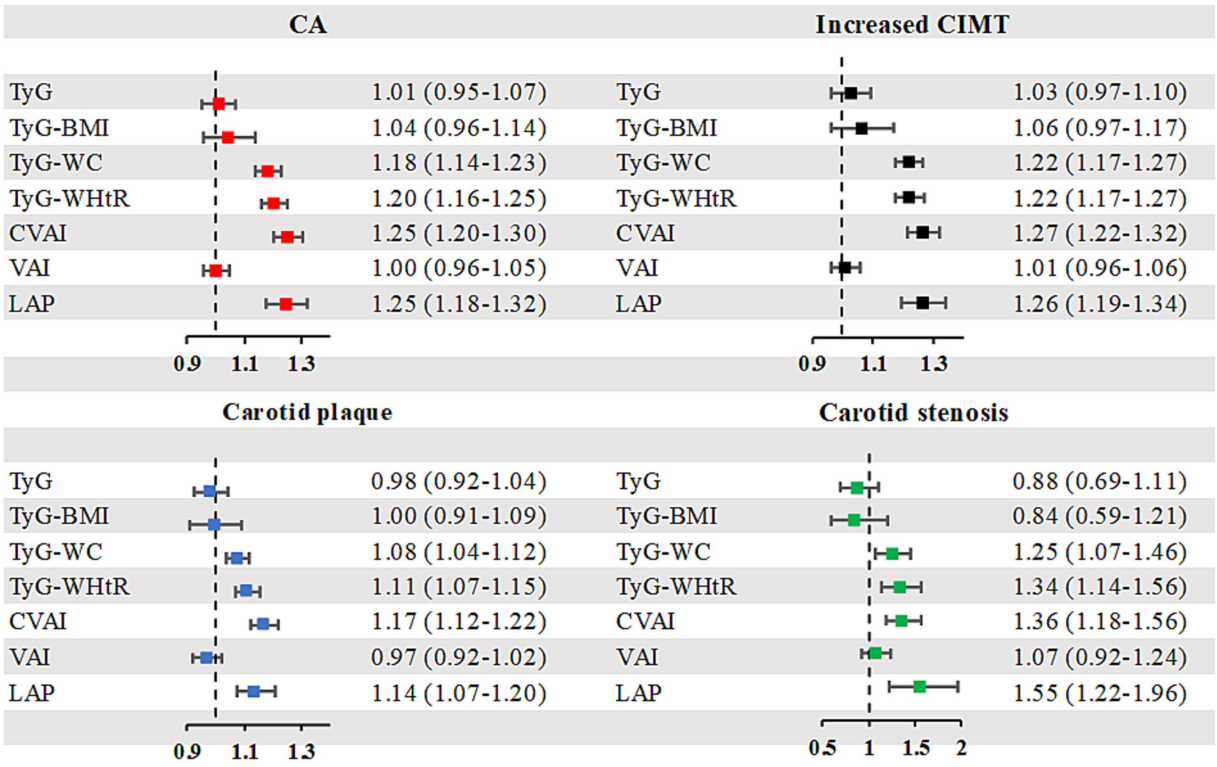

FIGURE 3
Risk of CA by a per SD increase of surrogate IR indexes. CA, carotid atherosclerosis; CIMT, carotid intima-media thickness; SD, standard deviation; TyG, triglyceride-glucose index; TyG-BMI, TyG-body mass index; TyG-WC, TyG-waist circumference; TyG-WHtR, TyG-waist-to-height ratio; VAI, the visceral adiposity index; CVAI, the Chinese visceral adiposity index; LAP, lipid accumulation product.

normal-weight individuals. This indicates that it is imperative to incorporate carotid ultrasound into routine annual physical examinations even for individuals with normal body weight.

IR is a robust predictor of atherosclerotic CVD, as it plays a pivotal role in the initiation and progression of atherosclerosis via complex pathophysiological processes such as endothelial injury, activation of the inflammatory response and oxidative stress (34). Many observational studies have shown that over 30% of individuals with a normal body weight exhibit metabolic abnormalities, such as abdominal adiposity and insulin resistance, similar to those typically seen in overweight or obese individuals (known as the "MONW" phenotype) (35, 36). Furthermore, Asian populations who are metabolically obese but have normal weight are at an elevated risk of developing CA compared with metabolically normal but obese or normal-weight individuals (12). However, there is a dearth of metabolic indicators to determine the onset of CA in individuals with normal body weight. To the best of our knowledge, the present study is the first to enroll 26,795 normal-weight individuals and to demonstrate that CVAI is the most effective surrogate index for predicting CA. Moreover, CVAI can be used as a reliable and easily quantifiable measure to identify high-risk populations and implement primary prevention strategies against atherosclerosis.

CVAI is indicative of the distribution of abdominal fat and dyslipidemia and is linked to insulin resistance, abnormal glucose metabolism and an elevated risk of CVD in adults (23, 37, 38). In a cohort study of 3,640 Chinese individuals from CHARLS, CVAI exhibited a higher predictive ability for metabolic syndrome in females than the other six surrogate indexes examined in our study (39). Another study enrolling 1,452 Chinese adults similarly demonstrated that CVAI had a superior predictive ability for identifying metabolic syndrome (40). In certain studies, the correlation between CVAI and CA has also been examined. A study based on 4,075 workers from a steel company has revealed that an increased CVAI is a predictive indicator of increased CIMT (29). However, it should be noted that steelworkers are more overweight and obese than the general population owing to occupational factors such as shift work, noise exposure and occupational stress (29). As such, the findings may not be generalizable to individuals within the normal-weight range. Furthermore, a retrospective study in Taiwan Province revealed a positive correlation between CVAI and the prevalence of CA (41). In addition, the study by Hu et al. observed a significant association between CVAI and the risk of carotid plaque (42). However, these studies did not include participants with normal weight; thus, the results may not be generalizable to the Chinese population with normal weight. Compared with previous studies, the present study specifically examined individuals with normal weight and identified a non-linear, positive association between CVAI and CA, thereby addressing gaps in our understanding of the relationship between CVAI and CA occurrence among normal-weight individuals. Notably, when CVAI exceeds 89.83, the prevalence of CA increases significantly. Therefore, for adults with normal weight, it is recommended to undergo further carotid ultrasound examination when their CVAI exceeds 89.83.

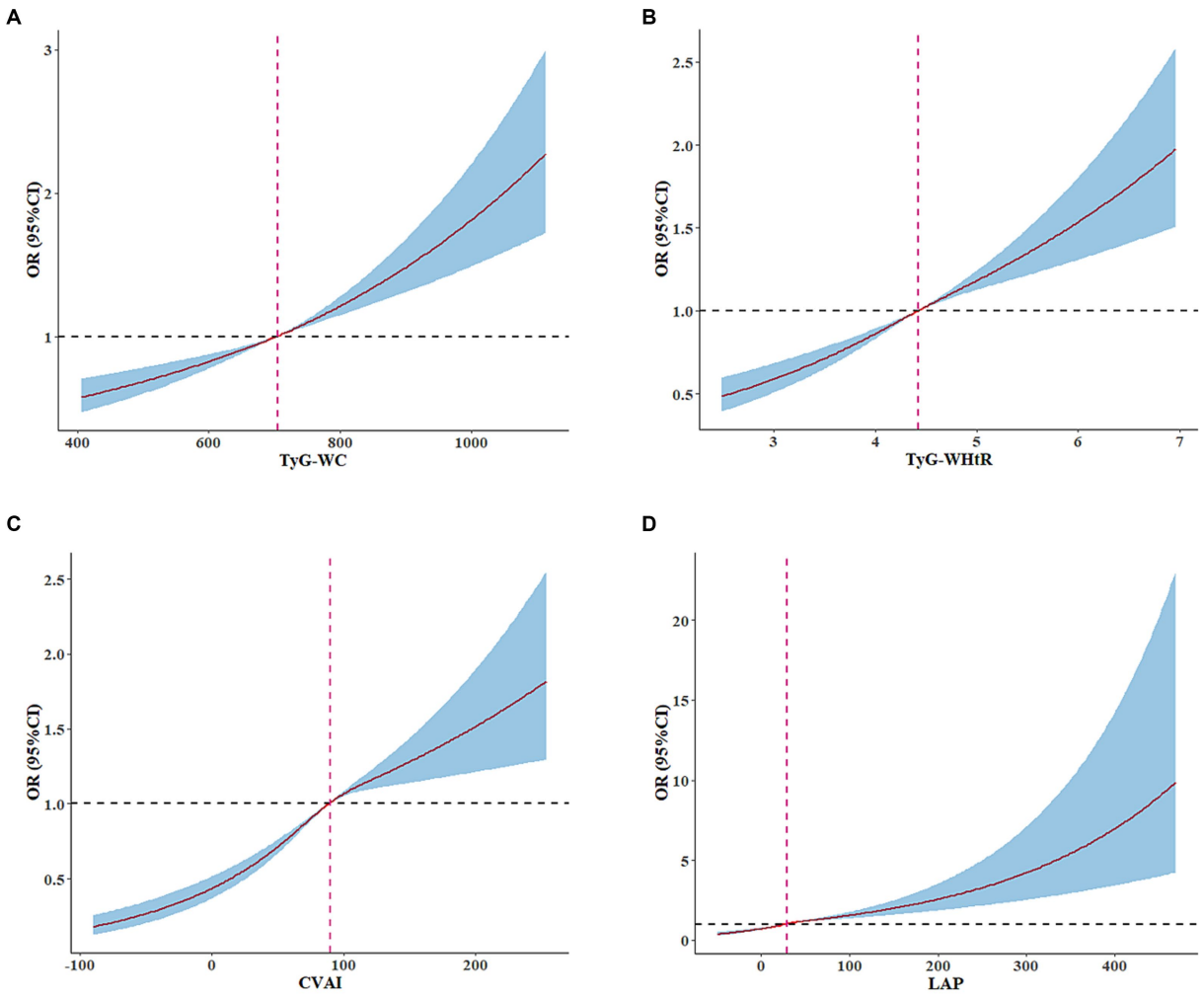

FIGURE 4
Adjusted cubic spline model of the relationship between TyG-WC, TyG-WHtR, CVAI, LAP, and CA risk. RCS analysis revealed a significant increase in the prevalence of CA among normal-weight individuals with CVAI >89.83, LAP >28.91, TyG-WHtR >4.42 and TyG-WC >704.93. Adjusted for age, sex, living status, education level, current smoking, alcohol consumption, physical inactivity, hypertension, diabetes, cerebrovascular disease, heart disease, FBG, TC, TG, LDL-C, HDL-C, and BMI.

The LAP index, a measure of obesity that is based on WC and fasting TG level, is used for determining the burden of coronary atherosclerotic plaques and the risk of CVD (43, 44). To date, only one study has indicated a correlation between LAP and carotid plaque; however, its small sample size and exclusive focus on acromegalic populations limits the generalizability of the findings (27). The present study revealed a significant correlation between an increase of one SD in LAP and the development of atherosclerotic phenotype, particularly stenosis, among individuals with normal BMI. However, further research is necessary to validate the applicability of these findings to individuals who are either obese or underweight.

The TyG index serves as a practical surrogate for IR and exhibits superior performance compared with the traditional HOMA-IR (45). However, there has been no consensus regarding the correlation between elevated TyG and an increased prevalence of CA. In respective studies, Irace et al. and Li et al. demonstrated a significant correlation between the TyG index and CA (15, 46). However, Zhao et al. failed to establish any association between the TyG index and increased CIMT or carotid plaque (47). Irrespective, detailed analyses of different types of CA or subgroups of participants with normal weight were not conducted in these studies. Li et al. revealed that overweight individuals in the fourth quartile of TyG were at a higher risk for developing CA, increased CIMT, plaque formation and stenosis than those in the first quartile (28). Nevertheless, there were no notable correlations between either carotid plaques or stenosis with regard to individuals with normal BMI in the second to fourth quarters of the TyG index (28). The current investigation additionally revealed no significant correlation of TyG with CA, increased CIMT, plaque, and stenosis. These findings suggest that TyG may not be a dependable indicator for evaluating CA, particularly in individuals with normal BMI.

TyG index-related parameters are composite indicators that incorporate the TyG index with BMI, WC, and WHtR, as initially proposed by Er et al. (20). As mounting evidence suggests a close association between visceral adiposity and IR, the combination of visceral adiposity and TyG may offer a greater potential for identifying IR than TyG alone (20–22). Similarly, although the current study revealed no significant correlation between TyG and increased prevalence of CA among normal-weight participants, a noteworthy

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TABLE 3 Subgroup analyses for the association between a per SD increase of CVAI, TyG-WC, TyG-WHtR, or LAP, and CA.

	CVAI	TyG-WC	TyG-WHtR	LAP
Age, years				
40–49	1.36 (1.19–1.54)	1.28 (1.14–1.43)	1.35 (1.20–1.52)	1.42 (1.18–1.70)
50–59	1.27 (1.18–1.38)	1.21 (1.13–1.29)	1.23 (1.15–1.32)	1.17 (1.07–1.28)
60–69	1.23 (1.14–1.32)	1.15 (1.08–1.23)	1.16 (1.08–1.24)	1.23 (1.12–1.37)
≥70	1.18 (1.09–1.27)	1.14 (1.06–1.23)	1.16 (1.08–1.25)	1.29 (1.15–1.45)
Sex				
Female	1.80 (1.61–2.01)	1.22 (1.16–1.28)	1.21 (1.15–1.28)	1.28 (1.18–1.39)
Male	1.15 (1.10–1.20)	1.13 (1.07–1.19)	1.15 (1.09–1.22)	1.21 (1.12–1.31)
Hypertension				
Yes	1.25 (1.18–1.32)	1.18 (1.13–1.25)	1.19 (1.14–1.26)	1.20 (1.12–1.29)
No	1.23 (1.16–1.31)	1.17 (1.11–1.24)	1.20 (1.14–1.27)	1.33 (1.21–1.46)
Diabetes				
Yes	1.26 (1.16–1.36)	1.18 (1.10–1.26)	1.18 (1.10–1.26)	1.25 (1.14–1.37)
No	1.26 (1.20–1.32)	1.22 (1.16–1.28)	1.25 (1.19–1.31)	1.24 (1.15–1.33)

Adjusted for age, sex, living status, education level, current smoking, alcohol consumption, physical inactivity, hypertension, diabetes, cerebrovascular diseases, heart disease, FBG, TC, TG, LDL-C, HDL-C, and BMI.

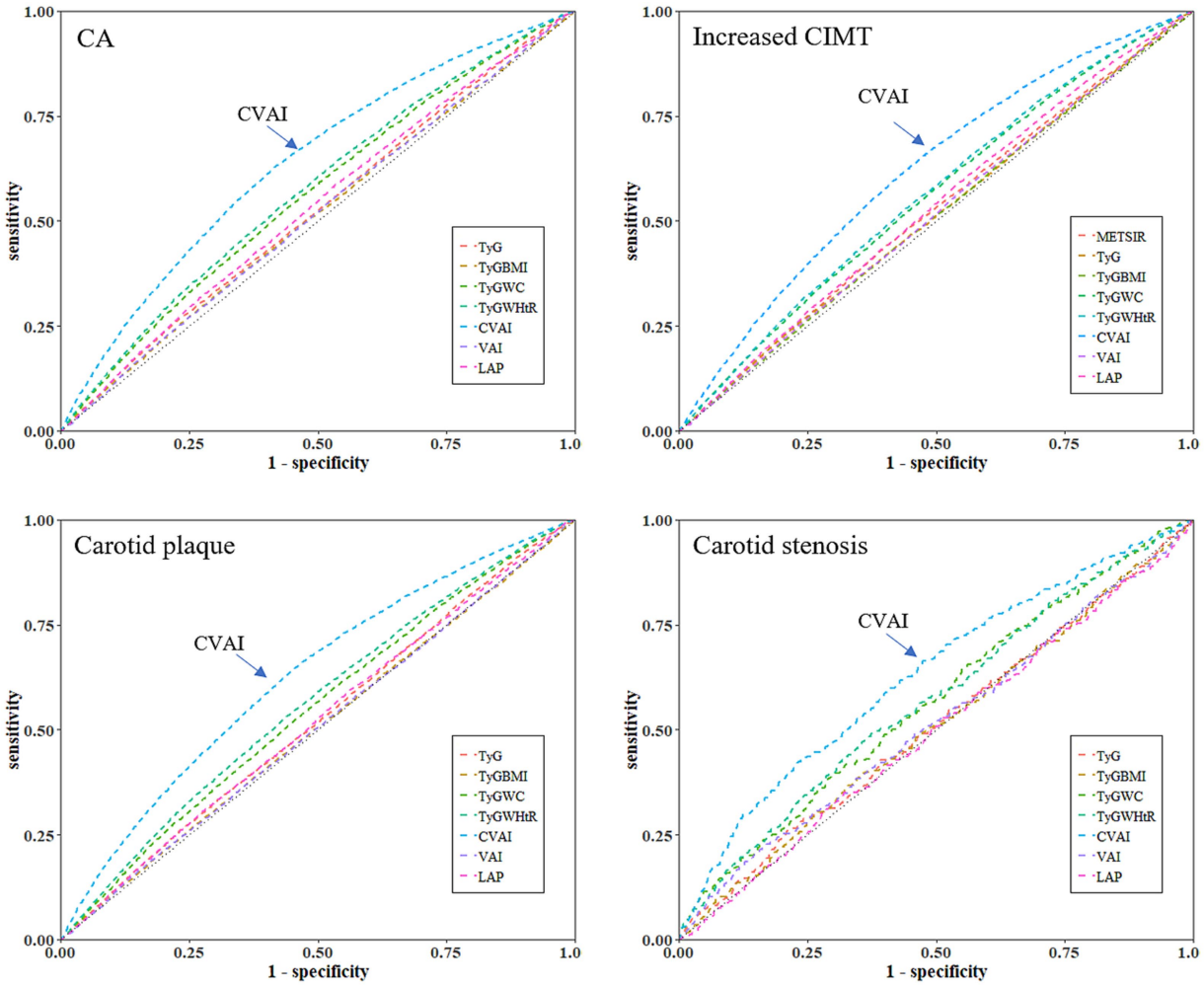

FIGURE 5
Receiver operating characteristic curves of seven surrogate indexes for predicting CA, increased CIMT, carotid plaque or stenosis. CA, carotid atherosclerosis; CIMT, carotid intima-media thickness; TyG, triglyceride-glucose index; TyG-BMI, TyG-body mass index; TyG-WC, TyG-waist circumference; TyG-WHtR, TyG-waist-to-height ratio; VAI, the visceral adiposity index; CVAI, the Chinese visceral adiposity index; LAP, lipid accumulation product.

association was observed when combined with a composite measure of visceral adiposity (including WC and WHtR).

The association between VAI and atherosclerosis has yielded inconsistent findings in prior research studies. Several studies, despite their relatively small sample sizes, demonstrated a significant correlation between VAI and CA in the general population (25, 26). Xu et al. enrolled 3,363 older adult Chinese individuals and demonstrated that increased VAI was not linked with CA risk (48). Similarly, a cross-sectional study involving 788 Spanish patients did not reveal any correlation between VAI and CA risk (49).The sample size in this study was higher than that reported previously, leading to more robust findings. However, there was no significant correlation between an increase in per VAI SD and an elevated prevalence of CA among individuals with normal weight. This suggests that VAI may not be an effective predictor of CA.

The subgroup analysis conducted in this study demonstrated that the impact of CVAI, TyG-WC, TyG-WHtR, and LAP on the prevalence of CA was notably more significant among females and individuals aged between 40 and 49 years. This finding may be attributed to the heightened risk of atherosclerotic complications during the menopausal transition period for females, as previously suggested in literature (50). The decrease in estrogen secretion during peri-menopause and menopause is known to result in the accumulation of central adiposity and insulin resistance (51). In the context of insulin resistance, the absence of estrogen's safeguarding impact on endothelial function increases the vulnerability to atherosclerosis. To substantiate this conjecture, additional external validation in more representative populations is imperative.

While benefiting from the well-established cohort and its relatively large size, this study is subject to certain limitations. First, certain confounding factors such as dietary habits and postmenopausal status were not considered in this investigation, which may have affected study results. Second, the study could not determine causality between surrogate IR indexes and CA due to its cross-sectional design. Finally, the present findings should be cautiously generalized to other populations, as the study only included Chinese middle-aged and older adult participants with normal weight.

5. Conclusion

Our study has provided evidence suggesting that CVAI, TyG-WC, TyG-WHtR, and LAP are potential predictors of CA in middle-aged and older adult individuals who have normal weight. Specifically, CVAI may be the most appropriate index for predicting CA in a normal-weight 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 reviewed and approved by Xiangya Hospital Ethics Committee. The protocol and informed consent for the study of the China Stroke High-risk Population Screening and Intervention Program were reviewed and approved by the Institutional Review Board at the Capital Medical University Xuanwu Hospital early. 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

ZL and JX: conceptualization. JF: data curation, resources, and writing – review and editing. ZL: formal analysis and writing – original draft. RT: investigation. ZL, BD, and QH: methodology. JX: project administration. BD, QH, and FY: software. RT, FY, and JF: validation. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.1241523/full#supplementary-material

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EDITED BY
Zhendong Liu,
Shandong First Medical University, China

REVIEWED BY
Jin-Yu Sun,
Nanjing Medical University, China
Lukasz Pietrzykowski,
Nicolaus Copernicus University in Toruń, Poland
Monika Bronkowska,
Opole University, Poland

*CORRESPONDENCE
Jacek Smereka
jacek.smereka@umw.edu.pl

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Sex-related differences in the impact of nutritional status on length of hospital stay in atrial fibrillation: a retrospective cohort study

Adrian Kwaśny[1], Katarzyna Łokieć[2], Bartosz Uchmanowicz[3], Agnieszka Młynarska[4], Jacek Smereka[5]* and Michał Czapla[5,6,7]

[1]Institute of Dietetics, The Academy of Business and Health Science, Lodz, Poland, [2]Department of Propaedeutic of Civilization Diseases, Medical University of Lodz, Lodz, Poland, [3]Department of Nursing and Obstetrics, Faculty of Health Sciences, Wroclaw Medical University, Wroclaw, Poland, [4]Department Gerontology and Geriatric Nursing, School of Health Sciences, Medical University of Silesia, Katowice, Poland, [5]Department of Emergency Medical Service, Wroclaw Medical University, Wroclaw, Poland, [6]Group of Research in Care (GRUPAC), Faculty of Health Sciences, University of La Rioja, Logroño, Spain, [7]Institute of Heart Diseases, University Hospital, Wroclaw, Poland

Background: Nutritional status is related to the length of hospitalization of patients with atrial fibrillation (AF). The aim of this study is to assess the prognostic impact of nutritional status and body mass index on length of hospital stay (LOHS) among patients with AF relative to their sex.

Methods: A retrospective analysis of the medical records of 1,342 patients admitted urgently with a diagnosis of AF (ICD10: I48) to the Cardiology Department (University Hospital in Wroclaw, Poland) between January 2017 and June 2021.

Results: In the study group, women were significantly older than men (72.94 $\pm$ 9.56 vs. 65.11 $\pm$ 12.68, $p < 0.001$). In an unadjusted linear regression model, malnutrition risk was a significant independent predictor of prolonged hospitalization in men (B = 1.95, $p = 0.003$) but not in women. In the age-adjusted linear regression model, malnutrition risk was a significant independent predictor of prolonged hospitalization in men (B = 1.843, $p = 0.005$) but not in women. In the model adjusted for age and comorbidities, malnutrition risk was a significant independent predictor of prolonged hospitalization in men only (B = 1.285, $p = 0.043$). In none of the models was BMI score a predictor of LOHS in either sex.

Conclusion: The risk of malnutrition directly predicts the length of hospital stays in men but not women. The study did not find a relationship between body mass index and length of hospital stay in both women and men.

KEYWORDS

nutritional status, obesity, malnutrition, sex difference, body mass index, atrial fibrillation

1. Introduction

Atrial fibrillation (AF) is estimated to affect about 2–4% of the adult population, and the incidence is projected to continue to increase up to 4-fold by 2050 (1–3). Both malnutrition and overweight and obesity are challenges to modern public health in developed and developing countries (4). Excess body weight is associated with high

cardiovascular risk, risk of prolonged hospitalization and mortality (5–7). Despite knowledge on the subject, malnutrition remains one of the most common causes of death in developing countries. In 70% of cases, nutritional deterioration occurs during hospitalization (8, 9). Several publications indicate an association between AF incidence and overweight and obesity. Studies show a relationship between AF risk and body weight; overweight and underweight were associated with higher arrhythmia events during the follow-up period. It was confirmed that body mass index (BMI), waist circumference, hip circumference and body surface area, among others, were independent predictors of atrial fibrillation (10–12). Thacker et al. observed that higher BMI was an independent factor in arrhythmia progression from paroxysmal or persistent AF to fixed AF, in contrast to other factors (13). Also, a higher BMI score is an independent factor in the progression of arrhythmias from paroxysmal to sustained atrial fibrillation, in contrast to other cardiovascular risk factors (14). Pathak et al. showed that a 10% weight loss in obese patients resulted in a sixfold greater likelihood of maintaining sinus rhythm than patients with no change in body weight values (15). Although some researchers have described a phenomenon occurring among AF patients called the "obesity paradox" concerning deaths from all causes and those from cardiovascular causes, there is an inverse relationship between overweight/obesity and better cardiovascular prognosis at long-term follow-up (16, 17). There are studies showing gender differences in AF (18, 19). However, data on the relationship between nutritional status, gender and length of hospitalization in AF are scarce. This thread has not been sufficiently explored, justifying the need for such observations.

The aim of this study is to assess the prognostic impact of NRS-2002 and body mass index on length of hospital stay (LOHS) among patients with AF relative to their sex.

2. Materials and methods

2.1. Study design and setting

A retrospective analysis of the medical records of 1,342 patients admitted urgently with a diagnosis of AF (ICD10: I48) to the Cardiology Department (Institute of Heart Diseases, University Hospital in Wroclaw, Poland) between January 2017 and June 2021 was conducted.

2.2. Study population and data

Medical records of all patients who met the following inclusion criteria were included in the analysis: emergency admission to the cardiology department for AF (primary reason for hospital admission), BMI and Nutritional Risk Screening 2002 (NRS-2002) score noted in medical records at the time of admission, age ≥18 years old. Finally, data from 1,342 patients were analyzed, such as NRS-2002 score, Body Mass Index (BMI) score, comorbidities: heart failure (HF), chronic kidney disease (CKD), arterial hypertension (HT), diabetes mellitus (DM), thyroid disease (TD), history of cerebral stroke; acute coronary syndrome (ACS) and length of hospital stay (LOHS). Comorbidities and past medical conditions have been recorded by a doctor in the patient's medical record when the patient is admitted to the hospital.

2.3. Tools for assessing nutritional status

Risk of malnutrition was assessed using the screening tools NRS-2002 (20). This tool assesses impaired nutritional status (0–3 points) and severity of disease (0–3 points). If the patient's age ≥70 years, the patient receives 1 point more. The risk of malnutrition was found when the patient received ≥3 points (20). The WHO criteria for indicating nutritional status are used to classify patients as obese (BMI ≥ 30), pre-obese (BMI 25–29.9), normal body weight (BMI 18.5–24.9), and underweight (BMI < 18.5) (21). Both the NRS-2002 and the BMI score were assessed and recorded in the patient's medical record by the physician at the time of admission to the hospital.

2.4. Ethical considerations

The study was conducted following the principles of the Declaration of Helsinki and approved by the independent Bioethics Committee of Wroclaw Medical University, protocol no. KB-837/2022. The study followed the STROBE guidelines (Strengthening the Reporting of Observational Studies in Epidemiology).

2.5. Statistical analysis

Distributions of quantitative variables were summarized with mean, standard deviation, median and quartiles. In contrast, distributions of qualitative variables were summarized with the number and percent of occurrence for each value. Chi-squared test (with Yates' correction for 2 × 2 tables) was used to compare qualitative variables among groups. In the case of low values in contingency tables, Fisher's exact test was used instead. Mann–Whitney test was used to compare quantitative variables between two groups. Logistic regression was used to analyze the impact of quantitative variables on dichotomous outcomes. All clinical variables recorded in medical records at hospital admission were used to construct a multivariate model. Odds ratios (OR) with 95% confidence intervals were shown. The significance level for all statistical tests was set to 0.05. R 4.2.2. was used for computations.

3. Results

3.1. Comparison of patient characteristics by sex

All 1,342 patients were included in the analysis. In the first step, a comparison was made concerning gender. A comparison of the groups by gender is shown in Table 1. Women were significantly older than men (72.94 ± 9.56 vs. 65.11 ± 12.68, $p < 0.001$). Women were also significantly more likely than men to suffer from CKD, thyroid disease

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TABLE 1 Comparison of patient characteristics by sex.

Parameter		Female (*N* = 568)	Male (*N* = 774)	Total (*N* = 1,342)	*p*
Age [years]	Mean (SD)	72.94 (9.56)	65.11 (12.98)	68.42 (12.28)	<0.001*
	Median (quartiles)	72 (68–80)	67 (59–73)	70 (63–76)	
	Range	31–94	19–95	19–95	
Type of AF	Paroxysmal	236 (41.55%)	281 (36.30%)	517 (38.52%)	0.04*
	Persistent	227 (39.96%)	363 (46.90%)	590 (43.96%)	
	Permanent	105 (18.49%)	130 (16.80%)	235 (17.51%)	
HF	No	449 (79.05%)	639 (82.56%)	1,088 (81.07%)	0.121
	Yes	119 (20.95%)	135 (17.44%)	254 (18.93%)	
DM	No	449 (79.05%)	613 (79.20%)	1,062 (79.14%)	1
	Yes	119 (20.95%)	161 (20.80%)	280 (20.86%)	
CKD	No	474 (83.45%)	688 (88.89%)	1,162 (86.59%)	0.005*
	Yes	94 (16.55%)	86 (11.11%)	180 (13.41%)	
CS	No	491 (86.44%)	697 (90.05%)	1,188 (88.52%)	0.05*
	Yes	77 (13.56%)	77 (9.95%)	154 (11.48%)	
HT	No	233 (41.02%)	346 (44.70%)	579 (43.14%)	0.197
	Yes	335 (58.98%)	428 (55.30%)	763 (56.86%)	
ACS	No	502 (88.38%)	699 (90.31%)	1,201 (89.49%)	0.294
	Yes	66 (11.62%)	75 (9.69%)	141 (10.51%)	
TD	No	411 (72.36%)	682 (88.11%)	1,093 (81.45%)	<0.001*
	Yes	157 (27.64%)	92 (11.89%)	249 (18.55%)	
BMI	18.5–24.9	154 (27.11%)	182 (23.51%)	336 (25.04%)	0.124
	<18.5	2 (0.35%)	3 (0.39%)	5 (0.37%)	
	25.0–29.9	193 (33.98%)	310 (40.05%)	503 (37.48%)	
	≥30	219 (38.56%)	279 (36.05%)	498 (37.11%)	
NRS-2002	<3	460 (80.99%)	652 (84.24%)	1,112 (82.86%)	<0.001*
	≥3	63 (11.09%)	30 (3.88%)	93 (6.93%)	
	Unknown	45 (7.92%)	92 (11.89%)	137 (10.21%)	
LOHS [days]	Mean (SD)	4.41 (3.16)	4.31 (3.42)	4.35 (3.31)	0.234
	Median (quartiles)	4 (3–6)	3 (2–5)	3 (2–5.75)	
	Range	1–26	1–34	1–34	
BMI [kg/m^2]	Mean (SD)	28.95 (5.55)	28.67 (4.58)	28.79 (5.01)	0.654
	Median (quartiles)	28.3 (24.6–32.8)	28.1 (25.2–31.6)	28.3 (25–32)	
	Range	18.5–48.9	18.5–56.8	18.5–56.8	

p – qualitative variables: chi-squared or Fisher's exact test. Quantitative variables: Mann–Whitney test. *Statistically significant ($p < 0.05$). *n*, number of participants; AF, atrial fibrillation; HF, heart failure; CKD, chronic kidney disease; HT, arterial hypertension; DM, diabetes mellitus; CS, cerebral stroke; ACS, acute coronary syndrome; TD, thyroid disease; BMI, body mass index; NRS-2002, Nutritional Risk Score; LOHS, length of hospital stay.

and stroke history. This group also had a higher risk of malnutrition (11.09% vs. 3.99%, $p < 0.001$).

3.2. Group comparison relative to obesity

Patients of each gender were divided into two groups according to WHO criteria: obese (BMI ≥ 30) and non-obese (BMI < 30). Women with obesity were significantly more likely to be younger and have DM compared to women in the non-obese group. Women with obesity were significantly less likely to have CKD, CS and less likely to have malnutrition risk, according to NRS-2002, compared to the obese group. Obese men were significantly younger than non-obese men. Obese men were less often at risk in malnutrition (Table 2).

3.3. Group comparison against malnutrition risk

Women at risk for malnutrition were significantly older. They also were more likely to have CKD and less likely to have HT and TD, and had a lower BMI compared to the group without malnutrition risk.

TABLE 2 Comparison of patient characteristics by absence or presence of obesity.

Parameter		Female (*N* = 568)			Male (*N* = 794)		
		Obese (*N* = 219)	Non-obese (*N* = 349)	*p*	Obese (*N* = 279)	Non-obese (*N* = 495)	*p*
Age [years]	Mean (SD)	70.13 (7.24)	74.7 (10.38)	<0.001*	63.78 (10.39)	65.85 (14.19)	0.001*
	Median (quartiles)	70 (66.5–74)	74 (68–83)		66 (58–70)	68 (60–74)	
	Range	46–91	31–94		35–93	19–95	
Type of AF	Paroxysmal	79 (36.07%)	157 (44.99%)	<0.001*	77 (27.60%)	204 (41.21%)	<0.001*
	Persistent	113 (51.60%)	114 (32.66%)		163 (58.42%)	200 (40.40%)	
	Permanent	27 (12.33%)	78 (22.35%)		39 (13.98%)	91 (18.38%)	
HF	No	167 (76.26%)	282 (80.80%)	0.234	220 (78.85%)	419 (84.65%)	0.052
	Yes	52 (23.74%)	67 (19.20%)		59 (21.15%)	76 (15.35%)	
DM	No	160 (73.06%)	289 (82.81%)	0.008*	213 (76.34%)	400 (80.81%)	0.169
	Yes	59 (26.94%)	60 (17.19%)		66 (23.66%)	95 (19.19%)	
CKD	No	193 (88.13%)	281 (80.52%)	0.024*	248 (88.89%)	440 (88.89%)	1
	Yes	26 (11.87%)	68 (19.48%)		31 (11.11%)	55 (11.11%)	
CS	No	200 (91.32%)	291 (83.38%)	0.01*	254 (91.04%)	443 (89.49%)	0.573
	Yes	19 (8.68%)	58 (16.62%)		25 (8.96%)	52 (10.51%)	
HT	No	79 (36.07%)	154 (44.13%)	0.07	117 (41.94%)	229 (46.26%)	0.277
	Yes	140 (63.93%)	195 (55.87%)		162 (58.06%)	266 (53.74%)	
ACS	No	197 (89.95%)	305 (87.39%)	0.428	250 (89.61%)	449 (90.71%)	0.711
	Yes	22 (10.05%)	44 (12.61%)		29 (10.39%)	46 (9.29%)	
TD	No	165 (75.34%)	246 (70.49%)	0.245	248 (88.89%)	434 (87.68%)	0.701
	Yes	54 (24.66%)	103 (29.51%)		31 (11.11%)	61 (12.32%)	
NRS-2002	<3	187 (85.39%)	273 (78.22%)	<0.001*	236 (84.59%)	416 (84.04%)	0.006*
	≥3	4 (1.83%)	59 (16.91%)		3 (1.08%)	27 (5.45%)	
LOHS [days]	Mean (SD)	4.25 (2.98)	4.52 (3.27)	0.527	4.13 (2.87)	4.41 (3.7)	0.953
	Median (quartiles)	4 (2.5–6)	4 (3–6)		3 (2–5)	3 (2–5)	
	Range	1–24	1–26		1–22	1–34	

p – qualitative variables: chi-squared or Fisher's exact test. Quantitative variables: Mann–Whitney test. *Statistically significant ($p < 0.05$). *n*, number of participants; AF, atrial fibrillation; HF, heart failure; CKD, chronic kidney disease; HT, arterial hypertension; DM, diabetes mellitus; CS, cerebral stroke; ACS, acute coronary syndrome; TD, thyroid disease; TG, triglycerides; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TC, total cholesterol; hsCRP, high-sensitivity C-reactive protein; K, potassium; Na, sodium; BMI, body mass index; NRS-2002, Nutritional Risk Score; LOHS, length of hospital stay.

Men at risk of malnutrition were less likely to have diseases such as DM and HT. Men in this group also lower BMIs than men at no malnutrition risk (Table 3).

3.4. Effect of BMI and NRS-2002 on LOHS – unadjusted and adjusted for age

For women, a multivariate linear regression model showed that none of the analyzed characteristics was a significant independent predictor of hospitalization length. However, for men, a significant independent predictor of prolonged hospitalization was the risk of malnutrition (B = 1.95; $p = 0.003$), which prolonged hospitalization by an average of almost 1.95 days (Table 4). In an age-adjusted linear regression model, this proved to be a significant independent predictor of LOHS in both women (B = 0.072, $p < 0.001$) and men (B = 0.035, $p = 0.001$). In addition, in men, the risk of malnutrition remained a significant independent predictor (B = 1.843, $p = 0.005$), which on average prolonged hospitalization by 1.843 days (Table 4).

3.5. Impact of BMI and NRS on length of hospitalization – adjusted for comorbidities

For female patients, a multivariate linear regression model showed that significant independent predictors of length of hospitalization are age (B = 0.075), persistent AF (B = 0.717), and HT (B = −0.751). In male patients, independent predictors of length of hospitalization are age (B = 0.029), persistent AF (B = −0.612), permanent AF (B = 1.217), history of stroke (B = −1.598), and HT (B = −0.979). Still, despite the addition of comorbidities to the model, the risk of malnutrition was a significant independent factor affecting the length of hospitalization (B = 1.285, $p = 0.043$) in men (Table 5).

TABLE 3 Group comparison concerning malnutrition risk.

Parameter		Female ($N = 523$)			Male ($N = 682$)		
		NRS ≥ 3 ($N = 63$)	NRS < 3 ($N = 460$)	p	NRS ≥ 3 ($N = 30$)	NRS < 3 ($N = 652$)	p
Age [years]	Mean (SD)	76.59 (10.78)	72.65 (9.52)	<0.001*	69.77 (17.39)	65.18 (12.89)	0.051
	Median (quartiles)	78 (72–84)	72 (67–80)		72.5 (64–83)	67 (59–73)	
	Range	31–92	33–94		26–95	19–95	
Type of AF	Paroxysmal	26 (41.27%)	194 (42.17%)	0.985	9 (30.00%)	240 (36.81%)	0.197
	Persistent	24 (38.10%)	175 (38.04%)		12 (40.00%)	300 (46.01%)	
	Permanent	13 (20.63%)	91 (19.78%)		9 (30.00%)	112 (17.18%)	
HF	No	50 (79.37%)	363 (78.91%)	1	26 (86.67%)	538 (82.52%)	0.733
	Yes	13 (20.63%)	97 (21.09%)		4 (13.33%)	114 (17.48%)	
DM	No	51 (80.95%)	369 (80.22%)	1	29 (96.67%)	514 (78.83%)	0.032*
	Yes	12 (19.05%)	91 (19.78%)		1 (3.33%)	138 (21.17%)	
CKD	No	43 (68.25%)	390 (84.78%)	0.002*	24 (80.00%)	577 (88.50%)	0.154
	Yes	20 (31.75%)	70 (15.22%)		6 (20.00%)	75 (11.50%)	
CS	No	53 (84.13%)	396 (86.09%)	0.821	27 (90.00%)	585 (89.72%)	1
	Yes	10 (15.87%)	64 (13.91%)		3 (10.00%)	67 (10.28%)	
HT	No	35 (55.56%)	184 (40.00%)	0.027*	23 (76.67%)	281 (43.10%)	0.001*
	Yes	28 (44.44%)	276 (60.00%)		7 (23.33%)	371 (56.90%)	
ACS	No	53 (84.13%)	408 (88.70%)	0.399	30 (100.00%)	582 (89.26%)	0.062
	Yes	10 (15.87%)	52 (11.30%)		0 (0.00%)	70 (10.74%)	
TD	No	53 (84.13%)	323 (70.22%)	0.031*	27 (90.00%)	571 (87.58%)	1
	Yes	10 (15.87%)	137 (29.78%)		3 (10.00%)	81 (12.42%)	
BMI	Underweight	2 (3.17%)	0 (0.00%)	<0.001*	0 (0.00%)	3 (0.46%)	<0.001*
	Normal	36 (57.14%)	116 (25.22%)		19 (63.33%)	152 (23.31%)	
	Overweight	21 (33.33%)	157 (34.13%)		8 (26.67%)	261 (40.03%)	
	Obesity	4 (6.35%)	187 (40.65%)		3 (10.00%)	236 (36.20%)	
LOHS [days]	Mean (SD)	4.48 (2.84)	4.5 (3.22)	0.802	6.4 (5.85)	4.33 (3.27)	0.051
	Median (quartiles)	4 (2–6.5)	4 (3–6)		4 (3–7)	3 (3–5)	
	Range	1–13	1–26		1–23	1–34	

p – qualitative variables: chi-squared or Fisher's exact test. Quantitative variables: Mann–Whitney test. *Statistically significant ($p < 0.05$). n, number of participants; AF, atrial fibrillation; HF, heart failure; CKD, chronic kidney disease; HT, arterial hypertension; DM, diabetes mellitus; CS, cerebral stroke; ACS, acute coronary syndrome; TD, thyroid disease; BMI, body mass index; NRS-2002, Nutritional Risk Score; LOHS, length of hospital stay.

4. Discussion

The impact of nutritional status on CVD is widely reported in the scientific literature. Its effects can range from the risk of cardiovascular events, presentation of symptoms, condition treatment methods, length of hospitalization and influence patient prognosis. The association of obesity with AF and the effect of weight reduction on its course is well known (22). It is also known that being underweight can be an independent risk factor for AF, and the association of BMI with AF risk takes a "U" shape (23). Scientific reports are also increasingly pointing out the gender differences present in atrial fibrillation (24). However, to the best of our knowledge, this study is one of the few to evaluate gender differences in the effect of nutritional status on the length of hospitalization in patients with AF, highlighting the complexity of this problem.

In the study, a multivariate linear regression model showed that malnutrition risk, as determined by the NRS-2002 scale, was a significant independent predictor of prolonged LOHS in men (B = 1.285, $p = 0.005$). No such effect was demonstrated in women. We also noted no effect of BMI score on LOHS for either sex. A study by Cheng et al. confirmed the impact of malnutrition on clinical outcomes, which showed that moderate to severe malnutrition is an independent predictor of adverse prognosis among older adult patients with non-valvular AF (25). The impact on LOHS was also evaluated in the work of Alturi et al., where it was shown that protein-calorie malnutrition in patients with AF could prolong hospital stay by 2.76 days (26). When comparing the groups in relation to the risk of malnutrition, statistically significant differences in the length of hospitalization in both men and women were not registered. However, the length of hospitalization is prolonged in the group of men with NRS ≥ 3 (6.4 vs. 4.33), which, although not statistically significant, may be clinically relevant and affect the total cost of treatment.

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TABLE 4 Effect of BMI and NRS-2002 on LOHS – unadjusted and adjusted for age.

Unadjusted model	Trait		B	95%CI		*p*
Female	BMI	18.5–24.9	ref.			
		<18.5	−1.976	−6.467	2.515	0.389
		25.0–29.9	0.203	−0.494	0.9	0.569
		≥30	−0.072	−0.776	0.632	0.841
	NRS-2002	<3	ref.			
		≥3	0.012	−0.871	0.894	0.98
Male	BMI	18.5–24.9	ref.			
		<18.5	−1.561	−5.468	2.346	0.434
		25.0–29.9	−0.318	−0.982	0.346	0.348
		≥30	−0.263	−0.947	0.42	0.45
	NRS-2002	<3	ref.			
		≥3	1.95	0.674	3.226	0.003*

Adjusted for age	Trait		B	95%CI		*p*
Female	BMI	18.5–24.9	ref.			
		<18.5	−0.59	−5.017	3.837	0.794
		25.0–29.9	0.167	−0.515	0.849	0.632
		≥30	0.228	−0.471	0.927	0.523
	NRS-2002	<3	ref.			
		≥3	−0.213	−1.081	0.656	0.631
	Age	[years]	0.072	0.043	0.1	<0.001*
Male	BMI	18.5–24.9	ref.			
		<18.5	−1.842	−5.722	2.037	0.352
		25.0–29.9	−0.218	−0.879	0.443	0.518
		≥30	−0.115	−0.798	0.568	0.742
	NRS-2002	<3	ref.			
		≥3	1.843	0.576	03.lis	0.005*
	Age	[years]	0.035	0.015	0.054	0.001*

B, unstandardized regression coefficient; *p*, multiple linear regression. *Statistically significant ($p < 0.05$). BMI, Body Mass Index; NRS-2002, Nutrition Risk Screening.

The risk of malnutrition can be studied using several different tools. Zhu et al. evaluated the effect of malnutrition assessed by the nutritional status score (CONUT score) and geriatric nutritional risk index (GNRI) on AF recurrence in patients after ablation procedures. They found that malnourished patients were more likely to experience AF recurrence (27). Malnutrition can also affect the increased risk of complications. Kim et al. showed that it increases the risk of complications in AF patients undergoing catheter ablation. The overall complication rate was more marked among malnourished women (7.1%) than malnourished men (3.7%) (28). Monitoring patients' nutritional status is essential to the medical care process, as it can deteriorate during a hospital stay (29). The assessment should be performed at the time of admission to the hospital and during hospitalization. This is because it has been shown that a drop in category on the Subjective Global Assessment (SGA) or significant weight loss during the first week of hospitalization may be associated with a greater likelihood of a longer hospital stay (30).

In our study, only males had malnutrition risk according to NRS-2002 as a significant independent predictor of LOHS. Although this hypothesis requires further research, it may be influenced by different body fat content relative to gender. It is indicated that with similar BMI, the body fat percentage in men is lower than in women (31). In our study, we also found no effect of BMI on LOHS in either sex, which seems to confirm the lack of reflection of body composition in the BMI parameter. This is because it does not consider body fat, muscle mass or water content but only the patient's weight-to-height ratio.

Researchers identify multiple determinants of prolonged hospital stay for patients with AF. Independent predictors of LOHS include acute coronary syndromes, acute decompensated heart failure, heart failure with reduced ejection fraction, and elevated NT-proBNP levels (32). Sex differences in AF are related to comorbidities, the influence of sex hormones, differences in electrophysiology, endothelial dysfunction, and pro-inflammatory signalling, among other factors (33). Researchers indicate that women with AF have a larger left atrial diameter, which affects their mortality (34), prolonged hospitalization time compared to men after ablation (35), and a higher risk of AF recurrence after radiofrequency catheter ablation (35). Women with AF also report poorer overall quality of life (36). Although in our

TABLE 5 Effect of BMI and NRS-2002 on LOHS in men and women – adjusted model.

	Trait		B	95%CI		*p*
Female	Age	[years]	0.075	0.045	0.105	<0.001*
	Type of AF	Paroxysmal	ref.			
		Persistent	0.717	0.119	1.315	0.019*
		Permanent	0.028	−0.753	0.808	0.945
	HF	No	ref.			
		Yes	0.434	−0.286	1.153	0.238
	DM	No	ref.			
		Yes	−0.043	−0.756	0.67	0.905
	CKD	No	ref.			
		Yes	−0.474	−1.266	0.317	0.241
	CS	No	ref.			
		Yes	−0.379	−1.213	0.456	0.374
	HT	No	ref.			
		Yes	−0.751	−1.357	−0.145	0.016*
	ACS	No	ref.			
		Yes	−0.692	−1.56	0.176	0.119
	TD	No	ref.			
		Yes	−0.154	−0.751	0.443	0.613
	BMI	18.5–24.9	ref.			
		<18.5	−0.917	−5.286	3.453	0.681
		25.0–29.9	0.047	−0.636	0.731	0.893
		≥30	0.004	−0.706	0.714	0.992
	NRS-2002	<3	ref.			
		≥3	−0.312	−1.183	0.559	0.483
Male	Age	[years]	0.029	0.008	0.05	0.007*
	Type of AF	Paroxysmal	ref.			
		Persistent	−0.612	−1.185	−0.039	0.037*
		Permanent	1.217	0.42	2.014	0.003*
	HF	No	ref.			
		Yes	0.383	−0.323	1.089	0.288
	DM	No	ref.			
		Yes	−0.63	−1.309	0.049	0.07
	CKD	No	ref.			
		Yes	0.764	−0.06	1.587	0.069
	CS	No	ref.			
		Yes	−1.598	−2.459	−0.737	<0.001*
	HT	No	ref.			
		Yes	−0.979	−1.544	−0.414	0.001*
	ACS	No	ref.			
		Yes	0.154	−0.722	1.03	0.731
	TD	No	ref.			
		Yes	−0.181	−0.935	0.573	0.638
	BMI	18.5–24.9	ref.			
		<18.5	−2.594	−6.37	1.182	0.179
		25.0–29.9	−0.001	−0.652	0.649	0.997
		≥30	0.138	−0.539	0.816	0.689
	NRS-2002	<3	ref.			
		≥3	1.285	0.042	2.529	0.043*

B, unstandardized regression coefficient; *p*, multiple linear regression. *Statistically significant ($p < 0.05$). *n*, number of participants; AF, atrial fibrillation; HF, heart failure; CKD, chronic kidney disease; HT, arterial hypertension; DM, diabetes mellitus; CS, cerebral stroke; ACS, acute coronary syndrome; TD, thyroid disease; BMI, body mass index; NRS-2002, Nutritional Risk Score.

study, BMI results were not a factor in the length of hospitalization, it should be noted that many authors show a positive association between the occurrence of AF and obesity, overweight and underweight (37–39). Also, in the study we conducted, there were no deaths; however, it is worth noting that increasingly researchers are pointing to gender differences in the incidence of mortality and the course of atrial fibrillation (40, 41). Renoux et al. showed that AF mortality was higher in males (10.0, 95% CI 9.8 to 10.1) than in females (8.5, 95% CI 8.3 to 8.6) (40). Our findings of gender differences in the effects of BMI and NRS on LOHS in patients with AF justify the need for further prospective studies in this area, highlighting the complexity of factors affecting the length of hospitalization.

4.1. Study limitation

This study had several limitations. The percentage of male patients at risk for malnutrition was low at 3.88%. In addition, due to the study's retrospective nature, among other factors, patients' body composition was not analyzed by electrical bioimpedance or anthropometric measurements were not taken. The patient's body composition was not assessed in the present study, only the NRS-2002 score and BMI. Anthropometric differences between genders may affect prognosis, which may have been a limitation of this study. Due to restrictions on access to patients' data under Polish law, the long-term survival of patients with AF could not be assessed.

5. Conclusion

The risk of malnutrition according to the NRS-2002 directly predicts the length of hospital stays in men but not women. The study did not find a relationship between body mass index and length of hospital stay in both women and men. Because the number of participants were at risk of malnutrition, these results should be interpreted within the context of each patient. Additional independent predictors of length of hospitalization for female patients independent predictors of length of hospitalization are age, persistent AF, hypertension and in male patient's age, persistent AF, permanent AF, history of stroke and hypertension. Undoubtedly, the impact of NRS-2002 and BMI results in patients hospitalized in the cardiology department due to atrial fibrillation relative to sex requires further investigation.

Data availability statement

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

Author contributions

AK and MC: conceptualization, methodology, validation, formal analysis, resources, writing-original draft preparation, and writing-review and editing. AK and KŁ: software. MC, BU, AM, KŁ, and JS: investigation. AK: data curation. AK and AM: visualization. MC: supervision. KŁ: project administration. JS: funding acquisition. All authors contributed to the article and approved the submitted version.

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There were no other contributors to the article than the authors. Certified English language services were provided.

Conflict of interest

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

Publisher's note

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EDITED BY
Zhendong Liu,
Shandong First Medical University, China

REVIEWED BY
Suman Kundu,
Vanderbilt University Medical Center, United States
Zonglin He,
Hong Kong University of Science and Technology, Hong Kong SAR, China

*CORRESPONDENCE
Enrique Hernández-Lemus
✉ ehernandez@inmegen.gob.mx
Guadalupe Gutiérrez-Esparza
✉ ggutierreze@conacyt.mx

†These authors share first authorship

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A machine learning approach to personalized predictors of dyslipidemia: a cohort study

Guadalupe Gutiérrez-Esparza[1,2*†], Tomas Pulido[2†], Mireya Martínez-García[3], Tania Ramírez-delReal[1,4], Lucero E. Groves-Miralrio[3], Manlio F. Márquez-Murillo[5], Luis M. Amezcua-Guerra[3], Gilberto Vargas-Alarcón[6] and Enrique Hernández-Lemus[7,8*]

[1]Researcher for Mexico CONAHCYT, National Council of Humanities, Sciences, and Technologies, Mexico City, Mexico, [2]Clinical Research, National Institute of Cardiology "Ignacio Chávez", Mexico City, Mexico, [3]Department of Immunology, National Institute of Cardiology "Ignacio Chávez", Mexico City, Mexico, [4]Center for Research in Geospatial Information Sciences, Aguascalientes, Mexico, [5]Department of Electrocardiology, National Institute of Cardiology "Ignacio Chávez", Mexico City, Mexico, [6]Department of Molecular Biology and Endocrinology, National Institute of Cardiology "Ignacio Chávez", Mexico City, Mexico, [7]Computational Genomics Division, National Institute of Genomic Medicine, Mexico City, Mexico, [8]Center for Complexity Sciences, Universidad Nacional Autónoma de México, Mexico City, Mexico

Introduction: Mexico ranks second in the global prevalence of obesity in the adult population, which increases the probability of developing dyslipidemia. Dyslipidemia is closely related to cardiovascular diseases, which are the leading cause of death in the country. Therefore, developing tools that facilitate the prediction of dyslipidemias is essential for prevention and early treatment.

Methods: In this study, we utilized a dataset from a Mexico City cohort consisting of 2,621 participants, men and women aged between 20 and 50 years, with and without some type of dyslipidemia. Our primary objective was to identify potential factors associated with different types of dyslipidemia in both men and women. Machine learning algorithms were employed to achieve this goal. To facilitate feature selection, we applied the Variable Importance Measures (VIM) of Random Forest (RF), XGBoost, and Gradient Boosting Machine (GBM). Additionally, to address class imbalance, we employed Synthetic Minority Over-sampling Technique (SMOTE) for dataset resampling. The dataset encompassed anthropometric measurements, biochemical tests, dietary intake, family health history, and other health parameters, including smoking habits, alcohol consumption, quality of sleep, and physical activity.

Results: Our results revealed that the VIM algorithm of RF yielded the most optimal subset of attributes, closely followed by GBM, achieving a balanced accuracy of up to 80%. The selection of the best subset of attributes was based on the comparative performance of classifiers, evaluated through balanced accuracy, sensitivity, and specificity metrics.

Discussion: The top five features contributing to an increased risk of various types of dyslipidemia were identified through the machine learning technique. These features include body mass index, elevated uric acid levels, age, sleep disorders, and anxiety. The findings of this study shed light on significant factors that play a role in dyslipidemia development, aiding in the early identification, prevention, and treatment of this condition.

KEYWORDS

hypertriglyceridemia, hypercholesterolemia, hypoalphalipoproteinemia, mixed hyperlipidemias, feature selection, machine learning, *Tlalpan 2020* cohort, Mexico City

1. Introduction

Dyslipidemia is a metabolic alteration characterized by elevated levels of cholesterol, triglycerides (TGs), and Low-Density Lipoprotein Cholesterol (LDL), as well as a decrease in High-Density Lipoprotein Cholesterol (HDL) levels. Worldwide, dyslipidemia presents as an exponential health problem with severe consequences and is considered one of the main risk factors for ischemic heart disease, cardiovascular disease, stroke, coronary heart disease, and type 2 diabetes mellitus (T2DM), which is the principal cause of death in adults in Mexico (1, 2). Pirillo et al. (3) have pointed out that ischemic heart disease reached a total of 3.78 million deaths in 2019, with high plasma LDL being the principal cause. These authors also reported between 0.61 and 2.73 million deaths due to ischemic stroke, a strongly associated condition. Similarly, there is a high variation in the number of deaths between countries, presumably due to regional differences and types of dyslipidemia. According to the same authors Pirillo et al. (3), low plasma HDL levels have been the most common type of dyslipidemia in Latin America since 2005, followed by hypertriglyceridemia and high plasma LDL levels.

According to the *National Cholesterol Education Program Adult Treatment Panel III (ATP III)* criteria, the classification of lipid profile dyslipidemias includes four types (see Table 1). Hypertriglyceridemia is a common lipid abnormality characterized by elevated triglyceride (TG) levels, often affecting individuals with visceral obesity, metabolic syndrome, and type 2 diabetes mellitus (T2DM) (4, 5). On the other hand, hypercholesterolemia is associated with high levels of LDL or CHOL and may also be present in individuals with a genetic disorder leading to elevated cholesterol levels (6). Hypoalphalipoproteinemia is frequently observed in people with coronary artery disease and is characterized by low levels of plasma high-density lipoproteins (HDL) (7). Finally, mixed hyperlipidemia, a genetic disorder involving higher cholesterol and triglyceride levels, contributes to the development of coronary artery disease.

In general terms, there are potential risk factors such as increased body mass index (BMI), an excessive dietary intake of saturated fat, and a sedentary lifestyle that contribute to developing a given type of dyslipidemia, a highly complex and heterogeneous set of conditions. This fact complicates the prognosis and diagnostics. In this regard, the widespread use of machine learning (ML) has allowed the application of computational intelligence tools as diagnostic tools for medical issues based on data acquired from analyzed patients. Therefore, such ML models (trained by medical guidance) have been successful in helping doctors to determine medical conditions with improved accuracy in a timely manner (8).

TABLE 1 Criteria for lipid profile dyslipidemias used in this study.

Dyslipidemia type	CHOL (mg/dL)	HDL (mg/dL)	TGs
Hypertriglyceridemia	<200		>150
Hypercholesterolemia	>200		<150
Hypoalphalipoproteinemia		<40	>150
Mixed hyperlipidemias	>200		>150

A study proposed by Cui et al. (9) uses ML to predict the risk of dyslipidemia in steelworkers by studying a set of standardized outcomes. They acquired the data by surveying anthropometric data, habits, personal status, and working details. Finally, they apply a Recurrent Neural Network (RNN) and Long Short-Term Memory (LSTM) algorithm, showing excellent performance in predicting dyslipidemia in steel and iron industry employees.

Machine learning has emerged as a valuable tool in predicting dyslipidemia and related conditions based on patient data. For instance, Cui et al. (9) used a recurrent neural network and LSTM algorithm to predict dyslipidemia in steelworkers, achieving excellent accuracy. Lee et al. (10) correlated facial characteristics with hypertriglyceridemia using Naive Bayes classifiers, while Pina et al. (11) showed that a neural network outperformed the Dutch lipid score in predicting dyslipidemia in specialized lipid clinics.

Hatmal et al. (12) used ten ML techniques to predict dyslipidemia with an accuracy of 0.75, considering CD36 protein levels, lipid profile, blood sugar, gender, and age. Similarly, Kim et al. (13) classified and predicted overweight/obesity, dyslipidemia, hypertension, and T2DM using a deep neural network model based on nutritional intake data from Korean citizens. For each disease risk, the accuracies achieved were 0.62496, 0.58654, 0.79958, and 0.80896, respectively.

Dyslipidemia is a complex and heterogeneous condition with potential risk factors such as increased BMI, excessive dietary intake of saturated fat, and a sedentary lifestyle. In this context, machine learning models trained on medical data have shown promising results in improving the diagnosis and prognosis of this condition.

However, recent research indicates that the impact of dyslipidemia on cardiovascular health can vary between men and women due to hormonal, genetic, and lifestyle differences. By analyzing gender-specific differences in dyslipidemia, we can identify unique risk profiles, treatment responses, and underlying mechanisms that may contribute to cardiovascular outcomes. Tailoring interventions based on gender-specific dyslipidemia patterns can lead to more targeted and effective therapies, ultimately improving cardiovascular health for both men and women. This approach also highlights the importance of recognizing and addressing gender-related disparities in dyslipidemia management to optimize patient outcomes and reduce the burden of cardiovascular diseases.

Historically, clinical trials are predominantly done in men, excluding women, even in studies with cells and mice (only male). A review studies the significant causes of diseases by bias in sex and gender. The authors express the influence of differences between sex and gender in genetics, implying affection in diagnosing and treating illnesses (14).

In this context, the present work provides a machine-learning approach to characterize the particularities of men and women with a given type of dyslipidemia (hypertriglyceridemia, hypercholesterolemia, hypoalphalipoproteinemia, as well as mixed hyperlipidemias), identifying the association with clinical factors, biochemical screening, family health history, dietary information, and additional risk factors in order to provide features that can be monitored by health authorities to decrease the risk of long-term complications caused by lipid abnormalities in the

study population. While dyslipidemia is a significant risk factor for serious diseases, we acknowledge that our analysis does not incorporate a specific time frame within which an individual might develop the disease. Instead, our study aims to elucidate the underlying risk factors associated with dyslipidemia, providing valuable insights into its etiology and contributing factors. The criteria used in this study to classify dyslipidemia types are shown in Table 1.

2. Materials and methods

2.1. Data

The present study investigates the cross-sectional association between various factors and cardiovascular health outcomes utilizing data collected from the baseline assessment of the *Tlalpan 2020* cohort (15), a longitudinal research project conducted by the National Institute of Cardiology (Instituto Nacional de Cardiología-Ignacio Chvez) in Mexico City.

The dataset used in this study consists of 2,621 participant records and 137 variables related to anthropometric measurements, clinical parameters, biochemical tests, family health history, physical activity, sleep disorders, smoking habits, alcohol consumption, psychological stress levels, and dietary information. The study identified four types of lipid disorders: 696 cases of hypertriglyceridemia (HTG), 402 cases of hypercholesterolemia (HPLC), 608 cases of hypoalphalipoproteinemia (HPLF), and 548 cases of mixed hyperlipidemia (MIX). Regarding data collection, it was carried out as follows:

- The anthropometric measurements, such as weight, height, and waist circumference (WC), were measured following the *International Society for the Advancement of Kinanthropometry* (16); the clinical parameters systolic (SBP) and diastolic blood pressure (DBP) were calculated considering three measures of each one, with a duration of the 3-min gap.
- In the case of the biochemical tests, the blood samples: fasting plasma glucose (FPG), TGs, HDL, LDL, CHOL, uric acid (URIC), and atherogenic index of plasma (AIP) were taken after 12 h of overnight fasting.
- The variables of family health history considered diseases the mother and father suffered, such as diabetes, obesity, hypertension, dyslipidemia, and heart attack.
- The physical activity was classified based on *International Physical Activity Questionnaire* (17) by METs (metabolic equivalents)-minutes/week into three categories low, moderate, and high.
- We used the *Medical Outcomes Study-Sleep 12-item scale* to determine sleep disorders (18, 19).
- Alcohol consumption was estimated by considering if the participant is a current drinker, the frequency, and the number of cups or beers consumed.
- To classify smoking practice, we consider if the participant is a current smoker, an ex-smoker, or if he/she has never smoked. Supplementary Tables 1–3—presents the variables mentioned in this section.
- Regarding dietary information we applied a software tool called *Evaluation of Nutritional Habits and Nutrient Consumption System* (20). This system analyzes the meals consumed by the participant during a day in the last year and calculates the amount of nutrients consumed. The variables corresponding to the *Evaluation of Nutritional Habits and Nutrient Consumption System* are shown in Supplementary Tables 1, 2.

2.2. Methods

This work utilized several statistical and data analytics methods. Figure 1 presents the general workflow of the model and describes the methodology used to classify participants with a given type of dyslipidemia and identify the risk factors. Dyslipidemia types were classified according to the ATP III criteria. The dataset was divided into two-thirds for training and the rest for testing. We must note that we applied the SMOTE technique to balance the class distribution in the training dataset.

To find the best subset of variables contributing to improving model performance, we used four methods for feature selection: VIM of RF, XGBoost, RPART, and SHAP. For this study, we applied RF to predict the type of dyslipidemia due to its high performance in diagnosing or predicting dyslipidemia and related diseases (21–23). We developed and evaluated RF performance by running 30 executions using different seeds for each one. To measure the effectiveness of the model, we utilized sensitivity (SENS), specificity (SPC), and balanced accuracy (B.ACC), metrics that have been used for imbalanced data learning assessment. Finally, we obtained the best-performing predictive model.

The dataset is divided by individuals distinguished by sex (male or female). To justify this division, we perform the correlation matrix with the characteristic variables in addition to the classifications. Figure 2A shows the correlation matrix for women, and Figure 2B shows it for men. The color variation for the correlation is not evident, which is why the subtraction of both is obtained; the result is shown in Figure 2C, where it is evident that there are characteristics that are more related to one gender than to another, in addition to the importance of the difference in the classification of the diagnosis.

2.2.1. Random forest

Random Forest, developed by Breiman et al. (24), is an ensemble machine learning algorithm composed of multiple tree-based estimators for solving classification and regression problems. To reduce over-fitting and improve predictions, this algorithm builds multiple tree-based estimators from training data samples using the Gini index. The Gini index measures the purity of the nodes and can be computed using the following equation:

$$G = \sum_{i=1}^{c} p(i) * [1 - p(i)] \quad (1)$$

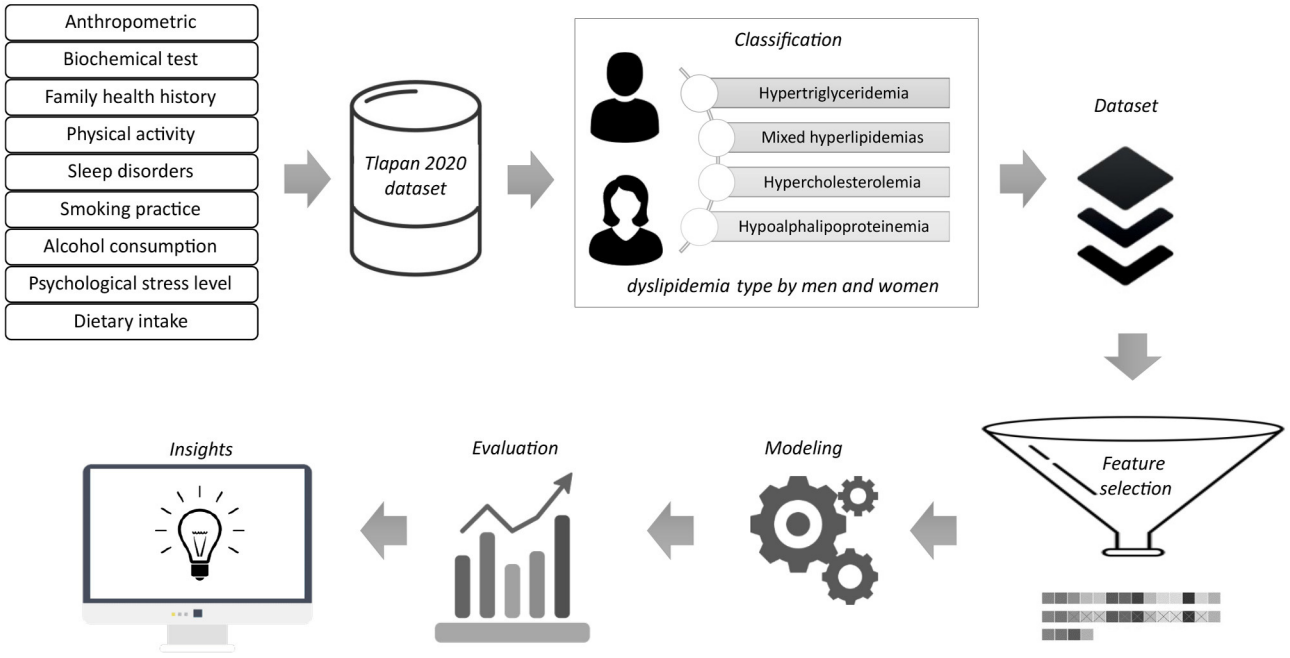

FIGURE 1
Prediction model.

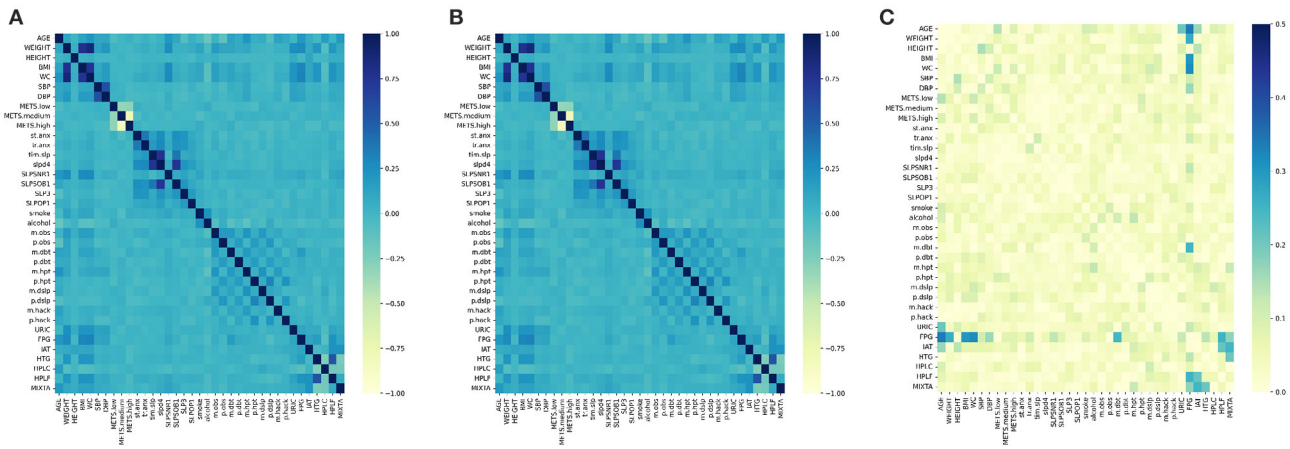

FIGURE 2
Correlation matrix. **(A)** Women. **(B)** Men. **(C)** Substraction.

where c is the number of classes and $p(i)$ is the proportion of samples that belong to class c.

In addition, this algorithm can be used for feature selection by calculating the importance score of variables using the permutation feature importance method.

2.2.2. XGBoost

Extreme Gradient Boosting (XGBoost), presented by Chen and Guestrin (25), is a high-performance ensemble machine learning algorithm that calculates the variable importance by providing a score for each feature.

2.2.3. GBM

GBM is an ensemble model introduced by Friedman et al. (26) that follows the principle of gradient boosting. It consists of a set of individual decision trees, called weak learners, that are trained sequentially to minimize the loss function of the simple models. This model can be computed using the following equation:

$$F(x_i) = \sum_{m=1}^{M} \nu h_m(x_i) \tag{2}$$

where y_i and x_i are weak learners, with $i \in (1, ..., n)$ and $i \in \mathbb{Z}^+$. The constant ν (shrinkage factor) is used to control the learning

rate, and $h_m(x_i)$ comes from a decision tree. GBM tries to fit $h_m(x)$ by minimizing the loss function:

$$\sum_{i=1}^{n} \left(y_i - F_m(x_i)\right) \tag{3}$$

2.2.4. Performance measures

To evaluate the performance of models and the different subsets of features, we used the following performance metrics: balanced accuracy (B.ACC), sensitivity (SENS), and specificity (SPC)

$$SENS = \frac{TP}{TP + FN} \tag{4}$$

$$SPC = \frac{TN}{FP + TN} \tag{5}$$

$$B.ACC = \frac{\left(\frac{TP}{(TP+FN)}\right) + \left(\frac{TN}{FP+TN}\right)}{2} \tag{6}$$

Where *P = Positive, N = Negative, TP = True Positive, FN = False Negative, TN = True Negative, and FP = False Positive*, respectively.

3. Experimental setup

We used a 32 GB RAM, 3.50 GHz, Intel Xeon® Dell® Workstation to perform all calculations. **R** v. 3.6.1 with `RStudio` and `Python` v. 3.10.7 were used as programming languages. Purposely, these resources are readily available for implementation in most hospital informatics settings.

4. Results

The problem of abnormal TG levels can develop based on different factors influencing individuals depending on their lifestyle. Moreover, LDL levels tend to be higher in men than in women until menopause. Hence, in this study, we initially separated the data by gender to obtain the most crucial care features according to the type of dyslipidemia. To identify the potential features by gender and type of dyslipidemia, we applied SMOTE as a resampling method due to class imbalance and three machine learning algorithms, namely VIM of RF, XGBoost, and GBM.

Once we obtained the results from the aforementioned algorithms, we considered displaying at least the top ten most important variables (ranked) that influence each type of dyslipidemia. Each result table shows a different subset of features for each gender and type of dyslipidemia by applying VIM of RF, XGBoost, and GBM.

The results obtained for hypertriglyceridemia are presented in Table 2, followed by the results for hypercholesterolemia in Table 3, as well as the essential variables for hypoalphalipoproteinemia, displayed in Table 4, and finally, the results for mixed hyperlipidemias in Table 5. Summarized general data from the total cohort is presented in Supplementary Table 4.

Subsequently, each algorithm generated subsets of variables, which were used to select the best features. To perform this feature selection process, we applied RF, which was optimized by *grid search method* (27) (resulting in varying *mtry* and *ntree* values for each gender and dyslipidemia type). We employed 10-fold cross-validation with ten repeats to evaluate the performance. Following this, we conducted 30 independent executions with different seeds to ensure robustness and approximate a normal distribution. This approach aligns with similar practices observed in relevant studies (28, 29). The evaluation was based on balanced accuracy, serving as the primary criterion for assessment.

To measure the performance of the RF model, the metrics B.ACC, SENS, and SPC were considered; likewise, it was necessary to apply SMOTE due to the unbalanced dataset. Table 6 shows each result of RF by using the different subset of variables obtained by VIM of RF, XGBoost, RPART, and SHAP, for men and women, as well as the respective parameter tuning and standard deviation (SD).

In the case of men with hypertriglyceridemia, the subset of features obtained by XGBoost achieved the best RF performance with a B.ACC of 82.77% and SD of 1.26. The top variables of this subset showed the influence of overweight, where the first three variables are related to it and *body mass index* (BMI), followed by *age*, *sleep disturbance* (SLPD4) and FYI (SLPSNR1), *anxiety as a trait* (TR.ANX), *smoking practice* (SMOKE), *somnolence* (SLP3), *alcohol consumption* (ALCOHOL), *soy oil consumption* (SOYAOIL), *glucose levels* (FPG), and *medical history of the mother with hypertension* (M.HPT).

Moreover, for women, the subset of variables obtained by VIM of RF achieved the best performance with a B.ACC of 82.50 and an SD of 1.08, where the principal variable was *uric acid levels* (URIC) [several studies (30, 31) have found an association between high uric acid and hypertriglyceridemia]. The other variables in this subset include *glucose levels* (FPG), *body mass index* (BMI), *Systolic blood pressure* (SBP), *weight*, *age*, *Diastolic blood pressure* (DBP), *Waist circumference* (WAIST), *sleep disturbance* (SLPD4), *somnolence* (SLP3), *height*, *snoring* (SLPSNR1), and *smoking practice* (SMOKE). All these variables are considered risk factors contributing to the development of hypertriglyceridemia (32, 33).

For hypercholesterolemia, the variables obtained by GBM achieved the best RF performance for men, with a B.ACC of 83.69% and an SD of 1.52. The principal variables found by this model denote a close relation between being overweight as represented by (WEIGHT, WC, AGE, and HEIGHT), *sleep disturbances* (SLPSNR1, SLP3, and SLPSOB1), *anxiety disorders* (TR.ANX), and habits such as *consumption of flavored soda* (FLAVSODA) and *smoking* (SMOKE).

In the case of women with hypercholesterolemia, the best performance was obtained by the subset generated by VIM or RF with a B.ACC of 79.74% and SD of 1.16, where the *anxiety disorders* (TR.ANX) and *uric acid levels* (URIC) were the principal variables, as well as frequently consuming some foods like *chicken liver* (LIVERSTK), *bread* (WHBREADSL), *oatmeal bowl* (OATMEAL), and *margarine* (MARGARIN), likewise, variables related to sleep disorders like the *time to fall asleep* (TIM.SLP) and *sleep short duration* (SLPOP1), followed by *low physical activity* (METS.low), *smoking* and *history of obese parents* (P.OBS).

TABLE 2 Features obtained for prediction of hypertriglyceridemia.

Random forest				Extreme gradient boosting				Gradient boosting machine			
MEN	RANK	WOMEN	RANK	MEN	RANK	WOMEN	RANK	MEN	RANK	WOMEN	RANK
SLPOP1	135.9878	BMI	62.7571	WEIGHT	178	URIC	153	WEIGHT	9.04658472	URIC	15.0950
WHBREADSL	69.1448	WC	47.4358	HEIGHT	149	FPG	128	WC	7.76540979	BMI	14.1867
ANIMALFT	58.8152	SLPSNR1	45.3041	WC	145	BMI	126	AGE	5.3379241	WC	12.6502
TR.ANX	57.88	P.HPT	43.3103	AGE	133	SBP	122	HEIGHT	5.26205646	FPG	11.6328
VEGSHORT	54.99	SLPSOB1	42.7748	SLPD4	122	WEIGHT	120	SLPD4	3.43920487	WEIGHT	6.2303
M.OBS	50.4908	URIC	40.5966	SLPSNR1	69	AGE	110	TR.ANX	2.63816295	SLPD4	5.4541
MAMEYSLC	46.891	WEIGHT	38.9927	TR.ANX	56	DBP	96	SLPSNR1	2.54049134	DBP	5.0677
BMIB	46.3552	COLASMD	38.5838	SMOKE	46	WC	96	SLP3	2.32463614	AGE	4.4456
BLCKCOFE	43.3054	FPG	38.0575	SLP3	44	SLPD4	94	FLAVSODA	2.12517177	SBP	4.1410
GREENBNS2	38.4609	WC	37.6175	ALCOHOL	37	SLP3	74	SMOKE	1.63174985	COLASMD	3.0547
MARGARIN	37.257	TR.ANX	36.8778	SOYAOIL	36	HEIGHT	70	OATMEAL1	1.55762621	ANIMALFT	2.2684
OATMEAL	36.9247	CORNCRLS	35.0434	FPG	29	SLPSNR1	47	SLPSOB1	1.55742209	M.OBS	1.9740
ALCOHOL	36.4578	DBP	34.0421	M.HPT	29	SMOKE	33				

TABLE 3 Features obtained for prediction of hypercholesterolemia.

Random forest				Extreme gradient boosting				Gradient boosting machine			
MEN	RANK	WOMEN	RANK	MEN	RANK	WOMEN	RANK	MEN	RANK	WOMEN	RANK
METS.LOW	18.1341	TR.ANX	18.8690	WEIGHT	120	URIC	160	WEIGHT	12.3907	AGE	9.56756769
SMOKE	18.0843	URIC	16.7090	AGE	103	FPG	127	AGE	7.9561	URIC	6.6324207
P.HPT	13.9113	LIVERSTK	16.6255	WC	86	BMI	124	WC	7.3735	SBP	6.53886356
MARGARIN	13.3063	WHBREADSL	14.9842	HEIGHT	68	SBP	119	HEIGHT	5.8700	BMI	5.9425091
TR.ANX	12.8586	TIM.SLP	14.8968	SLPD4	54	AGE	114	SLP3	4.4935	FPG	5.9132817
WC	12.4936	BMIB	13.9930	SLP3	50	DBP	104	SLPD4	3.6670	FLAVSODA	4.21043414
HEIGHT	11.9679	METS.low	12.1474	SLPSNR1	32	WEIGHT	99	SLPSNR1	3.3304	SLPSNR1	3.76874362
WEIGHT	11.4366	SLPOP1	11.4056	TR.ANX	30	SLPD4	73	SOYAOIL	2.1166	WEIGHT	3.59883532
OATMEAL2	11.0669	OATMEAL	11.3356	OATMEAL1	29	WC	65	OATMEAL1	2.1137	WC	3.38394044
HARDLQUR	10.2940	MARGARIN	11.1782	SMOKE	28	HEIGHT	61	ALCOHOL	2.0129	SLPD4	2.94644812
CHOCPWDR	8.9039	SMOKE	10.8057	WHBREADSL	25	SLP3	55	SMOKE	1.9512	HEIGHT	2.51790709
AGE	8.8006	WEIGHT	9.5272	SLPOP1	24	SLPSNR1	48	DIETCOLA	1.9308	DBP	2.49228445
URIC	8.5430	P.OBS	9.8361	SLP0B1	23	TR.ANX	28				

For men with hypoalphalipoproteinemia, the best subset of variables was presented by GBM with a B.ACC of 80.50% and SD of 1,29, being variables related to *overweight* the best qualified (WEIGHT, WC, and HEIGHT), as well as *age*, followed by indicators of sleep disorders like *sleep disturbance* (SLPD4), *snoring* (SLPSNR1) and *somnolence* (SLP3). Likewise, habits of *alcohol consumption* and *smoking*, *anxiety disorder*, *cream cheese consumption* (CRMCHSPOO) and elevated *uric acid levels* (URIC).

Similarly, the VIM of RF was the best subset of variables for women with hypoalphalipoproteinemia, with a B.ACC of 83.65% and SD of 1.22. In this case, the principal variable was elevated *uric acid levels*, followed by *snoring* (SLPSNR1) and variables closely related to *overweight* (BMI, WC, WEIGHT), as well as *glucose levels* (FPG) and *blood pressure levels* (SBP and DBP) denoted their presence as risk factors, finishing with the consumption of *alcohol* and *bread* (WHBREADSL), as well as *anxiety*.

Finally, the subset of variables obtained by VIM of RF got the best performance for men with mixed hyperlipidemia. In this case, the main variables were closely related to food consumption such as *atole without milk* (OATMEAL1), *oatmeal*

TABLE 4 Features obtained for prediction of hypoalphalipoproteinemia.

Random forest				Extreme Gradient Boosting				Gradient Boosting Machine			
MEN	RANK	WOMEN	RANK	MEN	RANK	WOMEN	RANK	MEN	RANK	WOMEN	RANK
MARGARIN	94.9750	URIC	45.6856	WEIGHT	143	URIC	145	WEIGHT	11.4121	URIC	20.7737
OATMEAL	62.1306	SLPSNR1	44.5059	HEIGHT	122	SBP	126	WC	10.1244	BMI	13.721
ALCOHOL	62.1098	BMI	39.4508	SLPD4	120	FPG	103	AGE	7.1326	FPG	13.348
BMI	47.3970	WC	38.4695	WC	119	DBP	101	HEIGHT	6.8948	SBP	9.7432
FPG	45.2968	FPG	30.7986	AGE	116	BMI	101	SLPD4	5.3522	WEIGHT	4.9799
SOYAOIL	43.7874	SLPSOB1	27.0383	SLP3	74	AGE	86	SLPSNR1	2.6590	WC	3.8663
TR.ANX	43.4292	WEIGHT	26.7650	SLPSNR1	73	WEIGHT	85	SLP3	2.5206	SLPD4	3.3011
HARDLQUR	42.4482	FPG	25.6375	SMOKE	43	SLPD4	70	ALCOHOL	2.2908	SLP3	3.0089
METS.low	41.2810	SBP	25.4510	P.DSLP	42	HEIGHT	70	SMOKE	2.2221	ALCOHOL	2.7355
DIETCOLA	40.1276	DBP	24.0586	TR.ANX	35	SLP3	59	TR.ANX	1.9325	WHBREADSL	2.4858
SLPOP1	38.4485	ALCOHOL	24.0578	URIC	34	WC	58	CRMCHSPOO	1.4264	ST.ANX	2.0462
LIVERSTK	36.6570	WHBREADSL	21.9719	SLPSOB1	30	SMOKE	35	URIC	1.3727	AGE	1.8986
M.OBS	32.6166	TR.ANX	21.3765			SLPSNR1	33				

TABLE 5 Features obtained for prediction of mixed hyperlipidemias.

Random forest				Extreme Gradient Boosting				Gradient Boosting Machine			
MEN	RANK	WOMEN	RANK	MEN	RANK	WOMEN	RANK	MEN	RANK	WOMEN	RANK
OATMEAL1	111.3498	BMI	54.9825	WEIGHT	134	URIC	127	WEIGHT	7.2914	AGE	15.636
OATMEAL	61.6553	AGE	47.9841	WC	119	SBP	123	OLIVEOIL	7.1260	FPG	14.1844
MARGARIN	46.1016	SLPSNR1	45.7455	AGE	116	BMI	121	WC	6.5050	URIC	13.2189
TABLEWIN	40.2253	FPG	40.0908	HEIGHT	110	DBP	117	HEIGHT	6.4946	BMI	9.0322
SAFFLOWR	38.8777	WC	37.5964	SLPD4	95	FPG	102	AGE	5.7541	HEIGHT	7.0715
HARDLQUR	36.1876	SLPSOB1	29.5068	SLP3	75	AGE	94	SLPD4	4.5321	SBP	6.3664
ALCOHOL	34.9600	URIC	28.1884	SLPSNR1	60	WC	87	PLUMS	3.7759	DBP	4.8929
BMI	34.4313	SMOKE	26.6538	SMOKE	36	WEIGHT	84	SLP3	2.7475	SLPD4	4.6317
P.DSLP	33.0949	HEIGHT	26.3499	SLPSOB1	30	HEIGHT	78	SAFFLOWR	2.2864	WC	2.6707
ZAPOTE	37.7836	TR.ANX	25.2881	ALCOHOL	29	SLPD4	71	SLPSNR1	1.8169	FLAVSODA	2.5535
CRMCHSPOO	28.5640	ALCOHOL	25.2773	M.HPT	28	SLP3	53	ALCOHOL	1.5273	METS.low	2.4744
AGE	28.1579	SBP	25.1633	SLPOP1	27	SLPSNR1	35	BUTTER	1.4225	CORNCRLS	2.0466
OLIVEOIL	27.9041	SUGRDRNK	22.7089	TR.ANX	26	TR.ANX	28				

bowl (OATMEAL), a *teaspoon of margarine* (MARGARIN), a *glass of table wine* (TABLEWIN), *safflower oil* (SAFFLOWR), *rum, brandy or tequila* (HARDLQUR), *zapote* (FREQ025), a *tablespoon of cream cheese* (FREQ005) and *olive oil* (OLIVEOIL), as well as, ALCOHOL, BMI, history of *a parent with dyslipidaemia* (P.DSLP), and *age*.

For women with mixed hyperlipidemia, the variables obtained by VIM of RF with the best-ranked factors were BMI, *age*, and *snoring*, followed by *glucose levels*, *waist circumference*, *sleep short duration*, *uric acid levels*, *smoking*, *height*, *anxiety*, *alcohol consumption*, *Systolic Blood Pressure*, and *a glass of flavored sugar water* (SUGRDRNK).

5. Discussion

In what follows, we will discuss the present analysis's expected and novel findings to contextualize the potential value of public health interventions.

In order to determine the significance of studying males and females separately, a significance analysis was conducted using the chi-squared test. The results indicated a strong relationship between gender and the prediction of dyslipidemia types and their critical factors.

The significant associations found for SEX in all dyslipidemias type further emphasize the importance of gender as a significant

TABLE 6 Results of random forest using different variable subsets.

Dyslipidemia	Sex	Parameters	Random forest			Extreme gradient boosting			Gradient boosting machine		
			BACC	Sensitivity	Specificity	BACC	Sensitivity	Specificity	BACC	Sensitivity	Specificity
HTG	MEN	mtry = 10	77.44%	85.98%	70.91%	**82.77%**	86.34%	79.20%	77.55%	83.00%	72.09%
		ntree = 200	1.7258	2.8453	2.2075	1.2692	2.1674	1.0794	1.4228	2.4354	1.5687
	WOMEN	mtry = 7	**82.50%**	87.57%	77.43%	73.38%	82.64%	64.12%	80.10%	80.67%	79.54%
		ntree = 500	1.0866	1.8336	1.0639	1.5623	1.9396	2.5682	1.5182	2.5473	1.1955
HPLC	MEN	mtry = 6	76.88%	95.18%	66.04%	72.56%	85.61%	59.51%	**83.69%**	87.91%	79.47%
		ntree = 200	2.6915	1.3835	3.8351	1.3663	2.3122	2.1522	1.5232	2.8082	1.2830
	WOMEN	mtry = 9	**79.74%**	87.45%	72.03%	75.94%	86.35%	65.52%	73.12%	79.84%	71.39%
		ntree = 200	1.1626	2.0079	1.6864	1.7560	2.7484	2.6783	2.0683	2.9511	2.6050
HPLF	MEN	mtry = 10	78.18%	86.77%	71.01%	80.09%	83.04%	77.15%	**80.50%**	83.68%	77.32%
		ntree = 300	1.6872	2.2423	2.2685	1.4658	2.3286	1.3990	1.2918	2.1942	1.3077
	WOMEN	mtry = 7	**83.65%**	87.55%	79.75%	72.95%	82.46%	63.45%	74.30%	87.48%	61.13%
		ntree = 800	1.2227	2.2218	1.5631	1.7576	2.2209	2.7013	1.5893	2.6710	2.5128
MIXED	MEN	mtry = 10	**83.71%**	94.58%	72.84%	73.98%	85.66%	63.30%	83.32%	84.64%	82.01%
		ntree = 200	1.1905	1.5817	2.0563	1.7822	2.4196	2.3847	1.5611	3.0704	1.4224
	WOMEN	mtry = 7	**81.70%**	90.85%	72.55%	76.00%	86.51%	65.49%	73.27%	77.54%	70.00%
		ntree = 100	1.3209	2.2095	1.7068	1.4999	2.2765	2.4131	1.9856	2.9964	3.2172

The bolded values correspond to the models with the highest balanced accuracy based on gender and type of dyslipidemia.

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factor influencing dyslipidemia prediction. Therefore, conducting separate analyses for males and females was crucial to gain a comprehensive understanding of the underlying factors associated with dyslipidemia in each gender group. The results of this significance analysis can be seen in the Supplementary Tables 5–8.

In the case of men with hypertriglyceridemia, several known associations arise. That is the case of *overweight* (34–37), *age* (38, 39), and *waist circumference* (40, 41). Additionally, we discovered a set of relatively new yet significant predictors whose relevance and mechanisms concerning hypertriglyceridemia in men are still to be determined, such as *anxiety*, *tomato sauce consumption*, and *history of hypertension in the mother*. Regarding the association between *anxiety* and hypertriglyceridemia, van Reedt Dortland and collaborators have identified a potential role of tricyclic antidepressant drugs (42). In contrast, other authors have identified an increased risk of hypertriglyceridemia in patients with psychiatric diseases without relation to specific pharmacological treatment (43).

The case of *tomato sauce consumption* presents some contradictory features. At the same time, some authors have described a protective role of processed tomato products to post-prandial oxidation and inflammation (both associated with dyslipidemias) in *healthy weight* subjects (44–46). In contrast, others have related processed foods (including tomato sauce) to hypertriglyceridemia (47, 48).

Since these studies differ in the methods and types of populations under investigation, differences may be explained by such disparate approaches. Hence definite associations need to be further studied with properly defined research methods.

No previous studies have directly linked *maternal hypertension history* to hypertriglyceridemia. Interestingly however, is the fact that there is an unusual prevalence of hypertriglyceridemia in small populations with known risk factors for pregnancy-associated high blood pressure (49–52), though, at this stage, an actual association is still to be further validated in more extensive population studies.

Similarly, in the case of women with hypertriglyceridemia, the best predictors were some known factors such as AIP (a prominent feature by construction) as well as *BMI*, *age*, and *cola drink consumption*. Other metabolic features appear, such as glucose and uric acid levels and also *raw tomato consumption*. Regarding the role of high fasting glucose levels in the presence of hypertriglyceridemia, reports have long been made, particularly by driving mechanisms of endogenous hypertriglyceridemia (35, 53, 54). The fact that *FPG* is a better predictor for hypertriglyceridemia in women than in men may be related to the effects of hormone (in particular, estrogen) metabolism in lipid and glucose processing biochemical pathways (55–57).

Elevated *uric acid levels* have been previously associated with hypertriglyceridemia, both in extensive cohort studies (31, 52, 58–60), population-based research (61–64), and biochemically-based analyses (65–69). Unlike processed tomato products, whose effects on hypertriglyceridemia are ambiguous (as previously discussed), *raw tomato consumption* has been acknowledged as a *protective factor* (44) against dyslipidemia in general and hypertriglyceridemia, in particular, (70–73).

Regarding men with hypercholesterolemia, some of the main predictors are (unsurprisingly) meat-based products with high lipid contents such as tacos *al pastor* (shepherd style), *carnitas*, and *longaniza* (74–76). There is evidence that consuming fatty meats, such as beef, pork, and lamb, may contribute to the development of hypercholesterolemia.

For instance, one study published in the American Journal of Clinical Nutrition found that a diet high in saturated fat, such as that found in fatty meats, was associated with an increase in LDL cholesterol that can, in turn, contribute to the development of cardiovascular disease (77). Another study published in the American Journal of Epidemiology found that individuals who consumed a diet high in red and processed meats had a higher risk of developing hypercholesterolemia than those who consumed a diet low in these types (78).

Aside from fatty meat products, other predictors are foods such as chocolate powder, cream cheese and anthropometrics such as weight and height (79, 80). Some evidence, for instance, suggests that chocolate consumption may be associated with a modest reduction in cholesterol levels, although the effect may be small and may depend on the type of chocolate and the individual.

Several studies published in the American Journal of Clinical Nutrition and the European Journal of Clinical Nutrition found that cocoa and chocolate intake was associated with a slight reduction in total cholesterol and low-density lipoprotein (LDL) cholesterol and that the effect of chocolate on cholesterol levels may be influenced by the type of chocolate consumed, with some studies suggesting that dark chocolate may have a more significant effect on cholesterol levels than milk chocolate (81–83). In contrast, another study recalls that these effects may come via activating flavonoid metabolism and anti-oxidant pathways (84).

In the case of women with hypercholesterolemia, there are well-known factors such as *age* (85, 86), *pork rind* (87, 88), *mayonnaise consumption* (89, 90), and *BMI* (91, 92). Other less-known predictors emerge from our study. Such is the case of *sleep disturbance*. Abnormal sleep conditions are gradually being recognized as relevant players in metabolic and cardiovascular diseases (93–95). However, it is noteworthy that most studies relating hypercholesterolemia with sleep disturbances center on the possible effects on sleep induced by drugs such as Pravastatin and Lovastatin (96–100).

The main predictors found for alphalipoproteinemia in men were *waist circumference* and *BMI* (101, 102), as well as conditions such as *anxiety* (103, 104), and *consumption of seafood* (105, 106) and *plums* (107). In contrast, in women, selected features were known metabolic state and anthropometric markers such as *AIP* (108), *glucose levels* (109, 110), *BMI* and *waist circumference* (101, 102), also *uric acid levels* (111, 112); consumption of high fat or high caloric foods like *pork meat*, *flavored soda*, *Oaxaca cheese*, and *bacon* (113). Interestingly *snoring* while sleeping was also a relevant predictor for alphalipoproteinemia in women. Though a direct association of snoring with female alphalipoproteinemia has not been reported, a population-based study has indeed associated self-reported snoring with dyslipidemia, high total cholesterol, and high low-density lipoprotein cholesterol in obese individuals in rural China (114).

Mixed hyperlipidemias in men were best predicted by: *AIP* (115, 116), *waist circumference*, *BMI* (117, 118), *age* (119), as well as *dried chile peppers consumption* (DRYCHILES) (120–122), as well

as drinking *whole milk* (MILKGLASS) (123, 124), *alcohol* (125–127), *sweet bread* (SWEETBRD) (128, 129), and *orange* (ORANGE) intake (130–132). In the case of women with mixed hyperlipidemias top predictive features were: *BMI* (117, 118), *age* (119), *snoring* (114), *glucose levels* (133, 134), *uric acid levels* (64), *smoking* (133), and *anxiety* (135), but also *alcohol* (125, 136) and *flavored sugar water* (BACONSLC) (137, 138) consumption.

6. Conclusions

By focusing on identifying risk factors without a time frame, our study lays the foundation for future investigations that could incorporate temporal aspects for predicting the onset of dyslipidemia or subsequent development of CVD. The findings from our research can serve as a basis for developing predictive models that integrate time-based parameters, enabling more accurate and clinically relevant disease prognosis and management.

In this work, the application of machine learning models in a cohort of Mexico City allowed the identification of subsets of attributes acting as risk factors associated with several types of dyslipidemias. Multi-feature diagnostics, i.e., the diagnosis based on different aspects, is considered essential to support healthcare providers as it allows early detection of patients at the most significant risk of developing a type of dyslipidemia, which supports the development of strategies for prevention, treatment, and prognosis the condition.

The separation by gender allowed the discovery of differences between subsets of risk factors associated with each type of dyslipidemia.

Even when we obtained high-performance models with this particular data and the support of SMOTE, it is possible to note that the best classifiers identified risk factors in men with hypercholesterolemia (with a B.ACC of 83.69%) and women with hypoalphalipoproteinemia (with a B.ACC of 83.65%). Therefore, the exploration of other ML models and the continuous update of the data set may not be ruled out in future work to improve the values of the metrics and predict the development of dyslipidemia types.

Data availability statement

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

Ethics statement

The studies involving humans were approved by Research Ethics Board for Biomedical Research in Humans by the National Institute of Cardiology Ignacio Chavez-Protocol approved with key 13-802. 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

GG-E designed computational strategy, implemented computing code and algorithmics, evaluated performance measures, co-supervised the project, and drafted the manuscript. TRP-Z guided the clinical approach and provided feedback to the modeling. TR-d implemented computing code and algorithmics and contributed to drafting the manuscript. MM-G performed clinical, sociomedical, and health policy research contributed to drafting the manuscript. LG-M supported data curation. MFM-M performed a clinical assessment. LMA-G contributed to clinical assessment. LMA-G, TRP-Z, and GV-A reviewed clinical results. EH-L devised the overall study strategy, co-supervised the project, performed the technical assessment, and revised and edited the manuscript. All authors read and approved the submitted version of the manuscript.

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Conflict of interest

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

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.1213926/full#supplementary-material

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EDITED BY
Zhendong Liu,
Shandong First Medical University, China

REVIEWED BY
Florencia Ceriani,
Universidad de la República, Uruguay
Federica Fogacci,
University of Bologna, Italy

*CORRESPONDENCE
André Moreira-Rosário
✉ andre.rosario@nms.unl.pt

†These authors have contributed equally to this work

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Empowerment-based nutrition interventions on blood pressure: a randomized comparative effectiveness trial

André Moreira-Rosário[1,2]*, Shámila Ismael[1,2,3], Inês Barreiros-Mota[1,3], Juliana Morais[1,2], Catarina Rodrigues[1,3], Inês Castela[1,2,3], Inês Curvelo Mendes[4], Maria Inês Soares[4], Luís Soares da Costa[4], Catarina Batista Oliveira[4], Tiago Henriques[4], Patrícia Pinto[4], Débora Pita[4], Catarina Marques de Oliveira[4], Janaína Maciel[4], Thaina Serafim[4], João Araújo[1,2], Júlio César Rocha[1,2], Diogo Pestana[1,2], Marta P. Silvestre[1,2], Cláudia Marques[1,2], Ana Faria[1,2,3], Jorge Polonia[5,6,7†] and Conceição Calhau[1,2†]

[1]NOVA Medical School, Faculdade de Ciências Médicas, NMS, FCM, Universidade Nova de Lisboa, Lisbon, Portugal, [2]CINTESIS@RISE, NOVA Medical School, Faculdade de Ciências Médicas, NMS, FCM, Universidade Nova de Lisboa, Lisbon, Portugal, [3]CHRC, NOVA Medical School, Faculdade de Ciências Médicas, NMS, FCM, Universidade Nova de Lisboa, Lisbon, Portugal, [4]CUF Academic and Research Medical Center, Lisbon, Portugal, [5]Department of Community Medicine, Information and Health Decision Sciences (MEDCIDS), Faculty of Medicine, University of Porto, Porto, Portugal, [6]CINTESIS@RISE, Faculty of Medicine, University of Porto, Porto, Portugal, [7]Hypertension and Cardiovascular Risk Unit, Unidade Local de Saúde Matosinhos, Matosinhos, Portugal

Introduction: Empowerment lifestyle programs are needed to reduce the risk of hypertension. Our study compared the effectiveness of two empowerment-based approaches toward blood pressure (BP) reduction: salt reduction-specific program vs. healthy lifestyle general program.

Methods: Three hundred and eleven adults (median age of 44 years, IQR 34–54 years) were randomly assigned to a salt reduction ($n = 147$) or a healthy lifestyle program ($n = 164$). The outcome measures were urinary sodium (Na^+) and potassium (K^+) excretion, systolic (SBP) and diastolic (DBP) blood pressure, weight, and waist circumference.

Results: There were no significant differences in primary and secondary outcomes between the two program groups. When comparing each program to baseline, the program focused on salt reduction was effective in lowering BP following a 12-week intervention with a mean change of −2.5 mm Hg in SBP (95% CI, −4.1 to −0.8) and − 2.7 mm Hg in DBP (95% CI, −3.8 to −1.5) in the intention-to-treat (ITT) analysis. In the complete-case (CC) analysis, the mean change was −2.1 mm Hg in SBP (95% CI, −3.7 to −0.5) and − 2.3 mm Hg in DBP (95% CI, −3.4 to −1.1). This effect increases in subjects with high-normal BP or hypertension [SBP − 7.9 mm Hg (95% CI, −12.5 to −3.3); DBP − 7.3 mm Hg (95% CI, −10.2 to −4.4)]. The healthy lifestyle group also exhibited BP improvements after 12 weeks; however, the changes were less pronounced compared to the salt reduction group and were observed only for DBP [mean change of −1.5 mm Hg (95% CI, −2.6 to −0.4) in ITT analysis and − 1.4 mm Hg (95% CI, −2.4 to −0.3) in CC analysis, relative to baseline]. Overall, improvements in Na^+/K^+ ratio, weight, and Mediterranean diet adherence resulted in clinically significant SBP decreases. Importantly, BP

reduction is attributed to improved dietary quality, rather than being solely linked to changes in the Na^+/K^+ ratio.

Conclusion: Salt-focused programs are effective public health tools mainly in managing individuals at high risk of hypertension. Nevertheless, in general, empowerment-based approaches are important strategies for lowering BP, by promoting health literacy that culminates in adherence to the Mediterranean diet and weight reduction.

KEYWORDS

cardiovascular diseases, hypertension, blood pressure, mediterranean diet, sodium/potassium ratio

1. Introduction

Changing unhealthy lifestyle behaviors can decrease the prevalence of individuals with high blood pressure (BP) and cardiovascular diseases (CVD), contributing greatly to the sustainability of healthcare systems worldwide (1, 2). Current guidelines for managing hypertension recommend the adoption of a healthy diet as an integral part of disease treatment, regardless of antihypertensive medication intake (2–4).

Several dietary approaches have been proposed to reduce BP, including the Dietary Approaches to Stop Hypertension (DASH), the low-salt diet, and the Mediterranean diet (5–9). Recent systematic reviews of randomized controlled trials (RCTs) showed that dietary approaches with low sodium (Na^+) and high potassium (K^+) intake, such as DASH and low-salt diets, are effective in lowering BP (6, 7, 10). DASH and low-salt diets promote the consumption of nutrients and food components with antihypertensive properties such as minerals (potassium, magnesium, and calcium), vitamins, phytochemicals, polyphenols, unsaturated fatty acids, and fiber (11). Otherwise, the Mediterranean diet places greater emphasis on food groups and meals, rather than isolated nutrients. It is characterized by its elevated consumption of plant-based foods, such as fruits, vegetables, legumes, and nuts, while relying on olive oil as the main fat source. The diet also includes a moderate intake of fish and poultry and a reduced intake of dairy products, red and processed meats, and whole-fat dairy products (12). The protective effect of the Mediterranean diet against CVD has also been extensively studied (13). When compared to the DASH diet, the Mediterranean diet has demonstrated greater effectiveness in reducing the risk of CVD, particularly within populations already accustomed to these dietary and lifestyle practices (14).

However, in the context of preventing and treating hypertension, dietary interventions are mostly assessed individually. Yet, recent systematic reviews exploring both the DASH and Mediterranean diets have revealed that the DASH diet shows the most convincing proof of its efficacy in lowering BP (7, 8). Significantly, despite these insights, there has been no randomized trial so far that directly compares how the DASH and Mediterranean diets differ in their effects on reducing BP.

Furthermore, some of these studies use controlled and specific feeding methods to make sure participants stick to the planned diets. This is verified through close monitoring of participants during on-site meals, along with inquiries about their consumption of study foods, and the collection of urine samples. Although it is important to acknowledge that while these controlled scenarios play a critical role in assessing efficacy, they may not precisely mirror how these findings would apply to the daily circumstances of the broader population.

In the realm of encouraging changes in behavior, empowerment-based methods have emerged as powerful triggers, giving citizens the freedom to steer their own choices toward healthier eating preferences (15–19). However, despite its clear importance in improving health and well-being, the concept of empowerment has unfortunately not been used enough in programs designed to promote healthy dietary habits (15, 16). According to the World Health Organization (WHO), health promotion is a process that empowers individuals to have more control over the decisions and actions that affect their well-being (20). This broad and multifaceted view of health encompasses social, economic, and environmental factors, all of which play crucial roles in shaping daily health conditions (20, 21).

Hence, the driver to improve public health centers on spreading health information grounded in evidence, raising awareness, and empowering people to integrate personalized and suitable health-conscious behaviors into their daily routines.

With this viewpoint in mind, we designed a randomized comparative trial to thoroughly examine the effectiveness of two empowerment-driven approaches. One of these strategies focused on reducing salt intake, echoing the principles of the DASH diet, while the other centered around fostering a holistic and all-encompassing healthy lifestyle regimen. This latter approach incorporated guidance aligned with the core principles of the Mediterranean dietary pattern.

These educational efforts were carefully designed to enhance participants' understanding of beneficial lifestyle practices. Moreover, the programs provided participants with practical resources to help them adopt new habits. This comprehensive toolkit encompassed strategies for embracing wholesome cooking practices and making well-informed choices when buying food. Essentially, our main goal was to determine which of these empowerment-focused methods would prove to be the more effective driver in nurturing health-oriented dietary habits and achieving reductions in BP across the broader population.

2. Materials and methods

2.1. Study design

This study is a multicenter, randomized, comparative effectiveness trial comparing the outcomes of two different 12-week

empowerment-based approaches to promote healthy habits in the general population. The trial was conducted between March 2019 (the first candidate screened for eligibility) and September 2019 (the end of the 12-week follow-up of the last participant), after obtaining approval from the Ethical Committee of the Hospital CUF on December 18, 2018, for the project. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and followed the Good Clinical Practice guidelines. All enrolled participants provided voluntary, written informed consent. The present study adhered to the CONSORT reporting guidelines (Supplementary Table S1) and was registered on the ClinicalTrials.gov database (NCT03830021).

2.2. Participants

The study enrolled adult participants aged 20 to 70, who were responsible for acquiring and preparing their own meals, normal or with hypertension. Medicated hypertense individuals were included if medication and diet was stable for at least 3 weeks before the study. Eligible participants had to be willing and able to comply with the study protocol and provide informed consent. Exclusion criteria included a history of cardiovascular disease (such as ischemic cardiovascular disease, stable or unstable angina, myocardial infarction, stroke, or symptomatic peripheral arteriosclerosis), liver or kidney diseases, or cancer. Participants were also excluded if they were pregnant or breastfeeding women, women planning to become pregnant within the study period, had a history of drug, alcohol, or other substance abuse, or had other factors that might limit their ability to cooperate during the study.

2.3. Recruitment

Participants were recruited from the Lisbon Metropolitan Area through public advertisements in online newspapers and social media. Participants underwent eligibility screening and assessment at the study centers, which included the Hospital CUF Descobertas and Hospital CUF Infante Santo. Eligible participants were randomly assigned to one of two intervention groups (in a 1:1 ratio) using a computer-generated allocation sequence. The allocation was concealed through sequentially numbered, opaque, sealed envelopes. The allocation sequence was generated by a statistician who was not involved in recruitment or intervention delivery, ensuring that the allocation process was objective and unbiased. To maintain participant masking, the interventions were administered on different schedules, and participants were kept unaware of their assigned interventions.

2.4. Interventions

2.4.1. Salt-reduction program

Participants randomized to the salt reduction program received a multi-component educational program for 12 weeks, consisting of three educational sessions that occurred during clinic visits (baseline, 4-week, and 8-week), five individual practical training sessions at the local supermarket, and 8 telephone counseling calls. During the initial educational session, participants received information regarding salt consumption, the health implications of excessive salt intake, and the foods they should avoid to reduce their salt intake. In the subsequent session, participants were educated on how to decipher food labels, make choices that have lower salt content within the same food group, and understand the significance of substituting salt with herbs and spices. In the final session, participants were enlightened about interpreting salt-related nutritional claims and the importance of meeting recommended fruit and vegetable intake. Additionally, the impact of potassium, calcium, and magnesium on BP was discussed, along with the identification of optimal dietary sources for these minerals. Following each session, participants were provided with an informational flyer covering the discussed topics. Participants in the salt reduction group benefitted from practical educational sessions conducted within supermarkets, facilitating the application of the acquired knowledge during the purchasing process. To further solidify the information transmitted during in-person education, telephone counseling calls were implemented between sessions.

2.4.2. Healthy lifestyle program

Participants randomized to the healthy lifestyle program received a 12-week educational program that consisted of three sessions during clinic visits (at baseline, 4-weeks, and 8-weeks) and 12 telephone counseling calls. The first session focused on the impact of the Mediterranean diet on health, with an emphasis on cardiovascular health. It included recommendations on the best food choices and foods to avoid as part of the principles of the Mediterranean food pattern. The second session addressed various lifestyle topics, such as the importance of hydration, how to increase water intake, physical activity, and sleep quality. The third session focused on the negative health impact of addictive habits, such as alcohol consumption and smoking, as well as healthy culinary methods. After each session, participants received a flyer summarizing the topics discussed. Furthermore, they received four telephone counseling calls after each face-to-face session to reinforce the information and clarify any questions or doubts.

2.5. Outcome assessment

We collected 24-h urine samples at baseline and after the 12-week intervention period to estimate Na^+ and K^+ excretion. Secondary outcome measures including office BP, anthropometric measurements, and additional covariates (namely adherence to the Mediterranean diet), were measured at baseline and during follow-up at 4, 8, and 12 weeks (Figure 1). Participants were instructed on how to collect 24-h urine samples. Na^+ and K^+ in the urine were measured using flame photometry, and creatinine was measured using an automated validated enzymatic method at an authorized Clinical Analysis Laboratory (Centro de Medicina Laboratorial Germano de Sousa). We assessed the adequacy of collection based on the expected normal range of creatinine excretion, as previously described by Brenner and Rector (22). Since a large proportion of urinary samples fell outside the expected creatinine ranges, indicating inadequate urine collections, we used Tanaka formulas to estimate 24-h urinary Na^+ and K^+ excretion (23). We estimated salt intake from 24-h urinary sodium excretion as 1 mEq/24 h $Na^+ = 0.058$ g per day salt. Office BP measurements were performed according to the guidelines of the European Society of Hypertension/European Society of

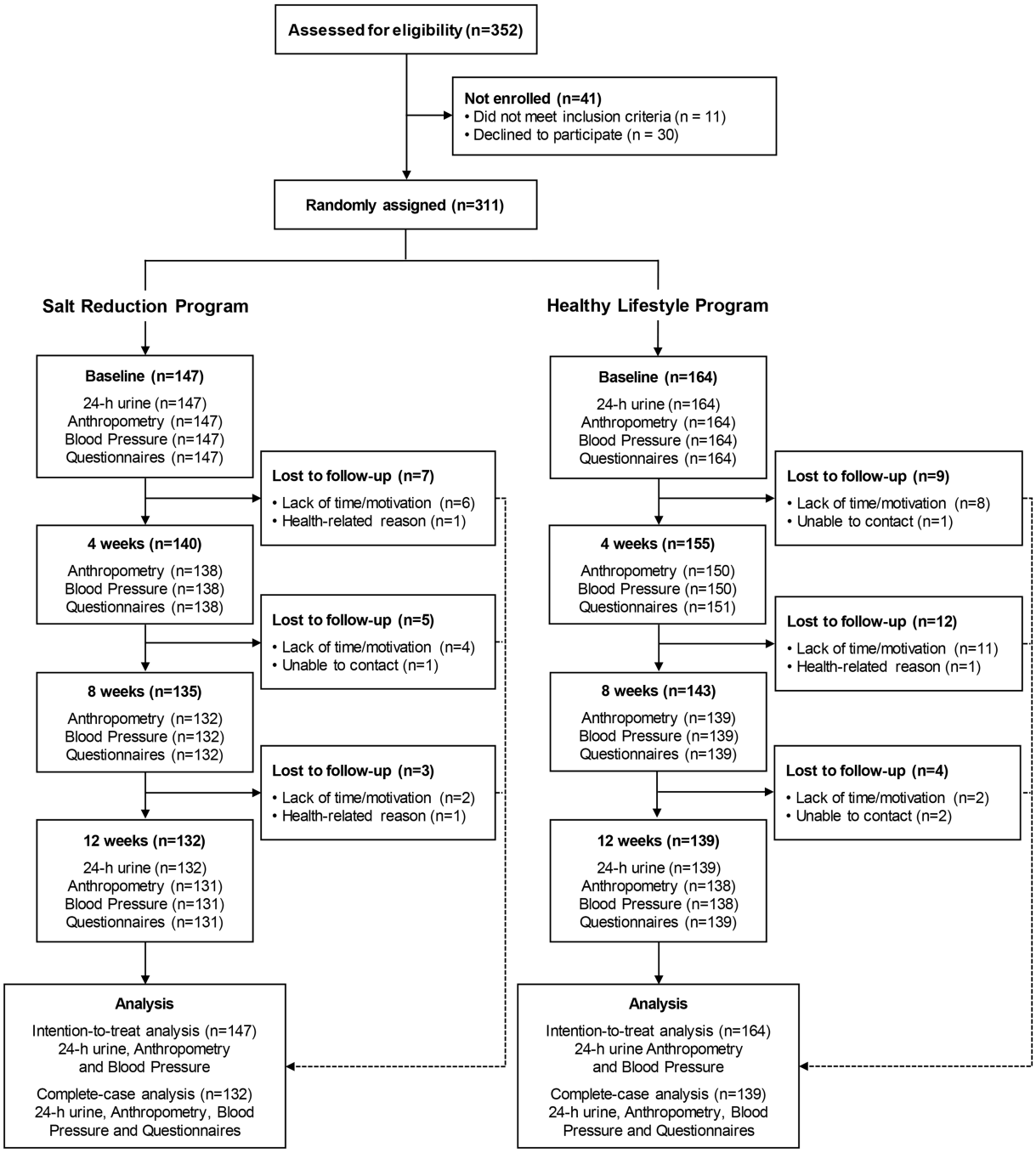

FIGURE 1
Flow diagram portraying the study design.

Cardiology (24), using Omron M7 (HEM-780-E) oscillometric automated BP monitoring devices. These devices were purposefully acquired for their first use in the trial. These devices have been rigorously validated and achieved an 'A/A' performance classification under the British Hypertension Society (BHS) and Association for the Advancement of Medical Instrumentation (AAMI) SP10 requirements (25). Anthropometric measurements were performed according to the Directorate-General for Portuguese Health protocol for body weight, height, and waist circumference (26). Trained nutritionists, following a standardized protocol and strict quality control procedures, conducted both the BP and anthropometric measurements, including body weight, height, and waist circumference, during face-to-face clinic visits at Hospital CUF Descobertas and Hospital CUF Infante Santo. Within our Standard Operating Procedures (SOP), we diligently considered the following key factors regarding BP measurements: 1. Controlled the temperature of the clinical cabinet, maintaining it between 18 and 22°C; 2. Instructed and controlled the participants, ensuring they refrained from smoking or consuming stimulants such as coffee at least 60 min before the visit; 3. Allowed the participants to rest briefly

before BP measurement; 4. Ensured that the participants positioned their supported measurement arm horizontally at the height of the heart during measurements; 5. Instructed the participants to place the sleeve of their shirt folded between the shoulder and the elbow, without exerting pressure on the arm and keeping their legs slightly open; 6. Enforced silence during BP measurements; 7. Conducted BP measurements in both arms during the recruitment visit, noting the arm with consistently higher pressure for subsequent visits; 8. At each appointment, BP was measured twice. If a significant discrepancy was observed between the initial measurements, a third measurement was taken into consideration. The questionnaire was used to collect relevant covariates, including socio-demographic and health information, dietary assessment, medication, smoking status, and protocol compliance. Adherence to the Mediterranean diet was evaluated using a previously validated 14-item questionnaire, known as the PREDIMED Mediterranean Diet Adherence Screener (MEDAS) (27). The MEDAS score was categorized as having the lowest adherence (score 0–5), average adherence (score 6–9), and highest adherence (score $\geq$ 10), as is commonly reported in the literature (28–30). The assessment of salt content in food purchased was not performed, as planned, due to a delay in the authorization from the grocery company.

2.6. Statistical analysis

The sample size calculation was based on the estimated difference in salt reduction between the two groups after 12 weeks. Assuming a salt reduction of 1 g/day and a standard deviation of 3.8 g/day (22), a sample size of 500 participants (250 per group) was calculated to provide 80% power at a 5% level of significance (two-sided) while taking into account a 10% dropout rate.

Descriptive statistics were reported as numbers and percentages for categorical variables and as mean and standard deviation for continuous variables, or median and interquartile ranges if the variable's distribution was skewed. Between-group differences at baseline were assessed using appropriate tests such as the independent sample t-test, Mann–Whitney U test, or chi-squared test.

The effect of the intervention on changes in BP, 24-h urinary excretion of Na^+ and K^+, and anthropometry measurements such as weight, BMI, and waist circumference were assessed using ANCOVA with treatment group as the predictor and study center, age, sex, baseline antihypertensive medications, baseline systolic BP value, participant program protocol compliance, and smoking status as covariates. Protocol compliance was evaluated based on adherence to the sessions aimed to improve health literacy, as our primary goal was to empower participants and then, assess the effectiveness of two programs for salt reduction. To quantify participants' adherence to the study protocol, we established a scoring system, and the score value was taken into consideration in the ANCOVA model. To manage missing data, multiple imputation was performed for intention-to-treat (ITT) analysis, using the chained equations approach with 5 imputed datasets and 10 iterations, and the results were pooled using Rubin's rule (31). Sensitivity analyses were carried out to assess the robustness of the multiple imputation method by comparing the distribution plots of recorded values with imputed values. All analyses were conducted using SPSS version 27 software (SPSS Inc., Chicago, IL, United States).

3. Results

3.1. Recruitment and baseline characteristics of the participants

From March 29 to June 4, 2019, a total of 352 candidates were screened for eligibility. After an initial assessment, 30 declined to participate and 11 did not meet the inclusion criteria. Thus, 311 participants were enrolled, comprising 224 women and 87 men with a median age of 44 years (IQR 34–54 years), who were randomly assigned to either a salt reduction-focused program ($n = 147$) or a healthy lifestyle program ($n = 164$; see Figure 1).

The study ended before the estimated 500 participants were recruited due to lower than anticipated recruitment rates. All participants contributed to baseline data and their characteristics are shown in Table 1, according to the intervention group. The proportion of women was higher in the healthy lifestyle group (78.0% vs. 65.3%, $p = 0.012$), but demographic and clinical characteristics were otherwise balanced across the groups. The healthy lifestyle group had a slightly higher proportion of participants who withdrew from the study (15.2% vs. 10.2%, $p = 0.185$); the lack of time or motivation was the most frequent reason for discontinuation in both groups. None of the participants reported adverse effects.

Most participants were white Europeans (92.6%), professionally active (81.0%), and had a university degree (74.9%). Additionally, over half were overweight or obese (61.4%) and had an average adherence to a Mediterranean diet (67.2%) at baseline. Two-thirds of the participants had a family history of hypertension, dyslipidemia, or CVD (66.9%), while almost one-fourth had dyslipidemia (26.0%). At study entry, 17.0% of participants reported having hypertension, and 22.5% were taking antihypertensive medication. At baseline, the mean systolic/diastolic BP was 116/76 (SD 15/10) mmHg, and the estimated mean 24-h urinary Na^+ excretion was 156.3 (SD 24.9) mmol/day.

The study's primary and secondary outcome measures are presented in Table 2. To evaluate the effectiveness of the interventions, both intention-to-treat (ITT) and complete-case (CC) analyses were conducted. The ITT analysis included all participants who were randomized and is considered the most reliable method of analysis, while the CC analysis only included participants who completed the study and may overestimate the intervention's effectiveness. By presenting results from both the ITT and CC analyses, we provide a more comprehensive understanding of the intervention's effectiveness, accounting for both ideal and real-world scenarios. This approach ensures that the study's findings are robust and applicable to clinical practice.

After the 12-week intervention, there were no significant differences observed between the salt reduction-focused and healthy lifestyle programs regarding predicted 24-h urinary Na^+ and K^+ excretion, as well as systolic and diastolic blood pressure (SBP and DBP), weight, and waist circumference. Nonetheless, the salt reduction program led to noteworthy enhancements in BP compared to baseline, with a mean change of −2.5 mm Hg in SBP (95% CI, −4.1 to −0.8) and − 2.7 mm Hg in DBP (95% CI, −3.8 to −1.5) in the intention-to-treat (ITT) analysis, while −2.1 mm Hg in SBP (95% CI, −3.7 to −0.5) and − 2.3 mm Hg in DBP (95% CI, −3.4 to −1.1) in the complete-case (CC) analysis. Notably, the healthy lifestyle group also exhibited BP improvements after 12 weeks; however, these were less pronounced compared to the salt reduction group and were observed

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TABLE 1 Baseline demographic and clinical characteristics of participants by randomized group.

Characteristic	Salt reduction program ($n = 147$)	Healthy lifestyle program ($n = 164$)	*P* value
Age, y	44 [34–52]	44 [35–55]	0.688
Sex, female	96 (65.3%)	128 (78.0%)	**0.012**
Ethnicity			
White/European	137 (93.2%)	151 (92.1%)	0.842
White/African or South American	6 (4.1%)	7 (4.3%)	
Black	1 (0.7%)	3 (1.8%)	
Mixed	3 (2.0%)	3 (1.8%)	
Weight, kg	75.6 (14.3)	74.5 (18.2)	0.570
BMI, kg/m^2	27.1 (4.7)	27.6 (6.0)	0.430
Overweight/Obese (≥25 BMI)	92 (62.6%)	99 (60.4)	0.688
Waist circumference, cm	85.7 (11.9)	85.0 (15.5)	0.649
Smoking status			
Current smoker	19 (12.9%)	23 (14.0%)	0.761
Former smoker	29 (19.7%)	37 (22.6%)	
Married or cohabiting	126 (85.7%)	132 (80.5%)	0.221
Professionally active	124 (84.4%)	128 (78.0%)	0.157
Education			
University	111 (75.5%)	122 (74.4%)	0.820
Secondary or lower	36 (24.5%)	42 (25.6%)	
Self-reported medical disorders			
Hypertension	25 (17.0%)	28 (17.1%)	0.988
Diabetes	4 (2.7%)	2 (1.2%)	0.336
Dyslipidemia	39 (26.5%)	42 (25.6%)	0.853
Hypothyroidism	3 (2.0%)	10 (6.1%)	0.074
Hyperthyroidism	1 (0.7%)	4 (2.4%)	0.218
Family history of hypertension, dyslipidemia, or CVD	99 (67.3%)	109 (66.5%)	0.869
MEDAS, score			
Low adherence (score ≤ 5)	26 (17.7%)	24 (14.6%)	0.511
Average adherence (score 6–9)	94 (63.9%)	115 (70.1%)	
High adherence (score ≥ 10)	27 (18.4%)	25 (15.2%)	
Office measurements			
Systolic blood pressure, mm Hg	116.1 (15.0)	115.4 (15.5)	0.670
Diastolic blood pressure, mm Hg	75.1 (9.9)	76.0 (9.1)	0.446
Heart rate, beats per minute	71.7 (11.0)	73.8 (10.2)	0.088
Urinary excretion (Tanaka prediction)			
Sodium, mmol/24 h	157.2 (26.3)	155.6 (23.8)	0.572
Potassium, mmol/24 h	48.6 (6.7)	47.9 (6.7)	0.384
Salt intake estimated, g/d	9.2 (1.5)	9.1 (1.4)	0.572
Antihypertensive medications	29 (19.7%)	41 (25.0%)	0.125

Data are number of participants (%), mean (standard deviation), and median (interquartile range). CVD, cardiovascular diseases; BMI, body mass index; BP, blood pressure. p values were calculated using independent samples t test, Mann–Whitney U test or chi-squared test as appropriate.

only for DBP [mean change of −1.5 mm Hg (95% CI, −2.6 to −0.4) in ITT analysis and − 1.4 mm Hg (95% CI, −2.4 to −0.3) in CC analysis, relative to baseline].

The reduction in BP within the groups may be attributed to the enhancement in predicted 24-h K^+ excretion after the 12-week intervention compared to baseline. This positive trend was observed in both groups during the ITT, with a mean change of 2.1 mmol/24 h (95% CI, 0.9 to 3.3) for the healthy lifestyle group and 1.4 mmol/24 h (95% CI, 0.1 to −2.6) for the salt reduction group. In the CC analysis, this improvement was relatively smaller, achieving statistical significance solely within the healthy lifestyle group at 1.9 mmol/24 h (95% CI, 0.6 to 3.2).

3.2. Impact of intervention on blood pressure

After 4 weeks, both the salt reduction and healthy lifestyle programs led to lower SBP compared to baseline: −1.7 mm Hg (95% CI, −3.1 to −0.3) for the salt reduction and − 1.5 mm Hg (95% CI, −2.8 to −0.2) for the healthy lifestyle. Importantly, the salt reduction group maintained lower SBP at 8 and 12 weeks, unlike the healthy lifestyle group (Figure 2A). Both groups showed DBP improvement after 12 weeks (Figure 2B). Moreover, there were no significant sex differences in BP outcomes (data not shown).

In participants with high-normal or hypertension (SBP ≥ 130 and/or DBP ≥ 85, mm Hg; $n = 32$ in the healthy lifestyle group and $n = 30$ in the salt reduction group), a subgroup analysis revealed significant BP reduction after 12 weeks within the salt reduction group: SBP decreased by −7.9 mm Hg (95% CI, −12.5 to −3.3), and DBP decreased by −7.3 mm Hg (95% CI, −10.2 to −4.4). Furthermore, notable differences between the groups were observed at week 8 in both SBP [−6.8 mm Hg (95% CI, −12.8 to −0.7), $p = 0.029$] and DBP [−4.6 mm Hg (95% CI, −8.6 to −0.6), $p = 0.025$]. Interestingly, a significant between-group difference in DBP was also evident at the end of the 12-week intervention [−4.4 mm Hg (95% CI, −8.7 to −0.2), $p = 0.041$], favoring the salt reduction program (Figures 2C,D).

3.3. Impact of Na^+/K^+ ratio on blood pressure

Participants were categorized into quintile groups (Q1 to Q5) based on changes in the 12-week Na^+/K^+ ratio relative to the baseline for each program. The quintile groups represent the range of changes from lowest to highest. The variations in BP across these quintile groups are shown in Figure 3.

While not reaching statistical significance, these findings suggest that a lower Na^+/K^+ ratio tends to correspond with a reduction in mean SBP variation. This reduction ranges from −1.9 mm Hg (95% CI, −5.1 to 1.4) to −4.8 mm Hg (95% CI, −8.7 to −0.6) for the salt reduction program, and from 0.6 mm Hg (95% CI, −2.8 to 3.9) to −2.6 mm Hg (95% CI, −6.2 to 0.9) for the healthy lifestyle program, when comparing the lowest (Q1) to the highest (Q5) quintiles. This observed tendency remains consistent even when considering participants with high-normal or hypertension at baseline, as illustrated in Figure 3C. Notably, within this subgroup, the slope is more pronounced in the salt reduction group, ranging from −2.1 mm

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TABLE 2 Mean difference in outcome measures after 12 weeks.

	Complete-case					Intention-to-treat				
	Salt reduction program ($n = 132$)		Healthy lifestyle program ($n = 139$)		*P* value between groups	Salt reduction program ($n = 147$)		Healthy lifestyle program ($n = 164$)		*P* value between groups
	n	Mean change from baseline (95% CI)	*n*	Mean change from baseline (95% CI)		*n*	Mean change from baseline (95% CI)	*n*	Mean change from baseline (95% CI)	
Office measurements										
Systolic blood pressure, mm Hg	131	−2.5 (−4.1, −0.8)*	138	−1.1 (−2.8, 0.5)	0.263	147	−2.1 (−3.7, −0.5)*	164	−0.7 (−2.3, 0.9)	0.237
Diastolic blood pressure, mm Hg	131	−2.7 (−3.8, −1.5)*	138	−1.4 (−2.4, −0.3)*	0.107	147	−2.3 (−3.4, −1.1)*	164	−1.5 (−2.6, −0.4)*	0.330
Heart rate, beats per minute	131	−2.1 (−3.7, −0.6)*	138	−1.6 (−3.1, −0.1)*	0.655	147	−1.8 (−3.3, −0.3)*	164	−1.6 (−3.1, −0.2)*	0.873
Urinary excretion (Tanaka prediction)										
Sodium, mmol/24 h	132	0.0 (−4.8, 4.8)	139	−1.1 (−5.8, 3.6)	0.754	147	0.1 (−4.4, 4.6)	164	−0.4 (−4.6, 3.9)	0.880
Potassium, mmol/24 h	132	1.1 (−0.3, 2.4)	139	1.9 (0.6, 3.2)*	0.413	147	1.4 (0.1, 2.6)*	164	2.1 (0.9, 3.3)*	0.400
Salt intake estimated, g/d	132	0.0 (−0.3, 0.3)	139	−0.1 (−0.3, 0.2)	0.754	147	0.0 (−0.3, 0.3)	164	0.0 (−0.3, 0.2)	0.880
Sodium/ potassium ratio	132	0.0 (−0.1, 0.1)	139	−0.1 (−0.2, 0.0)	0.321	147	0.0 (−0.1, 0.0)	164	−0.1 (−0.2, 0.0)	0.719
Weight, kg	131	−0.3 (−0.7, 0.0)	138	−0.3 (−0.7, 0.0)	0.965	147	−0.5 (−1.5, 0.4)	164	−0.3 (−1.2, 0.7)	0.698
BMI, kg/m^2	131	−0.1 (−0.2, 0.1)	138	−0.1 (−0.2, 0.1)	0.813	147	−0.2 (−0.6, 0.2)	164	−0.1 (−0.5, 0.3)	0.831
Waist circumference, cm	131	0.0 (−0.7, 0.7)	135	−0.3 (−1.0, 0.4)	0.539	147	−0.1 (−1.3, 1.0)	164	0.2 (−0.9, 1.3)	0.696

Values are mean (95% CI). ANCOVA models were adjusted for study center, age, sex, antihypertensive medications, baseline systolic blood pressure value, participant program protocol compliance and smoking status. *p value is statistically significant.

Hg (95% CI, −7.7 to 3.4) to −11.1 mm Hg (95% CI, −25.3 to 3.1), whereas the healthy lifestyle group displays a modest decrease from −1.0 mm Hg (95% CI, −12.0 to 9.9) to −3.6 mm Hg (95% CI, −9.7 to 2.6).

3.4. Impact of weight and adherence to the mediterranean diet on blood pressure

For each program, participants were divided into Q1 to Q5 quintile groups based on weight changes after 12 weeks compared to baseline (lowest to highest change). We then analyzed how changes in SBP and DBP related to these weight quintile groups (shown in Figures 4A,B). Results indicate that higher SBP reductions are linked with greater weight loss, particularly in the higher weight reduction quintiles (Figure 4A). Notably, participants in the highest weight change quintile (Q5) experienced a − 3.1 mm Hg reduction in SBP for both programs. However, this trend is more pronounced in the healthy lifestyle group (Figure 4A). Importantly, a significant difference in SBP is observed in the healthy lifestyle group when comparing Q1 and Q5 quintile groups [6.2 mm Hg (95% CI, 0.0 to 12.4), $p = 0.048$].

Adherence to the Mediterranean diet was assessed using a well-established 14-item questionnaire known as the Mediterranean Diet Adherence Screener (MEDAS). Based on MEDAS scores, there was a noteworthy increase in mean adherence to the Mediterranean diet within both groups after the 12-week period: 0.9 (0.6 to 1.2, $p = 0.001$) for the salt reduction program and 0.8 (0.5 to 1.1, $p = 0.001$) for the healthy lifestyle program (data not shown). These changes in score seemed to be driven by increased intake of specific dietary components, namely vegetables, fruits, fish or seafood, tree nuts, and dishes seasoned with sofrito (sofrito is a seasoning blend commonly used in Mediterranean cuisine, made with chopped onions, garlic, and other aromatic ingredients sautéed with olive oil). Simultaneously, there was a decrease in the consumption of red or processed meats, butter, cream, margarine, soda drinks, sweets, and confectionery (Supplementary Figure S1). Moreover, no differences between-group were observed in terms of the total MEDAS score or between specific dietary components (data not shown).

Subsequently, participants were categorized into quintile groups based on the extent of their changes in adherence to the Mediterranean diet following the 12-week follow-up in comparison to their baseline measurements (Figures 4C,D); the stratification was done for each

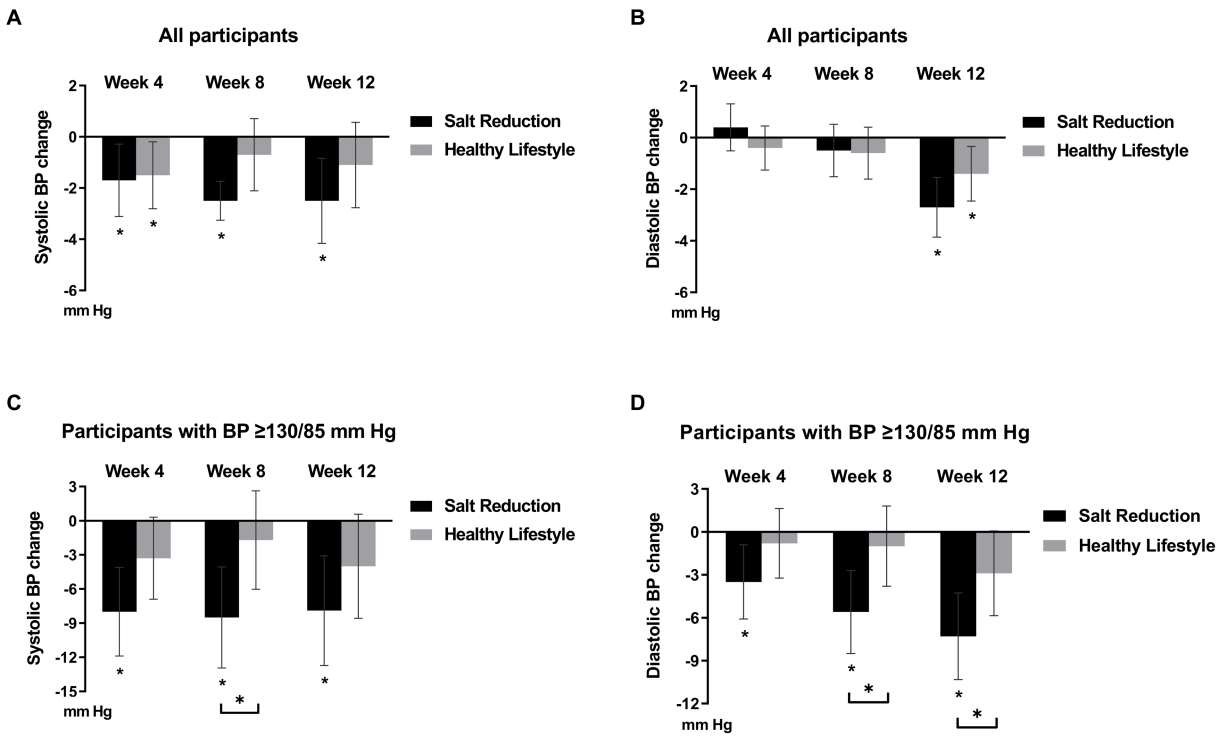

FIGURE 2
Change in office blood pressure (BP) from baseline to 4, 8 and 12 weeks in the complete-case population. All participants from salt reduction and healthy lifestyle groups were included in the analysis of systolic BP **(A)** and diastolic BP **(B)**. Subgroup analysis of participants with high-normal or hypertension at baseline (SBP ≥ 130 and/or DBP ≥ 85, mm Hg; $n = 32$ in the healthy lifestyle group and $n = 30$ in the salt reduction group) were also included in the analysis of systolic BP **(C)** and diastolic BP **(D)**. Data are presented as mean (95% CI), adjusted for study center, age, sex, antihypertensive medications, baseline systolic blood pressure value, participant program protocol compliance and smoking status (ANCOVA). *p value is statistically significant.

intervention program. This analysis demonstrates that participants who exhibited the most significant shift toward adherence to the Mediterranean diet experienced a modest yet noticeable reduction in SBP within both programs.

Furthermore, an investigation was undertaken to explore the relationship between Na+/K+ ratios and enhanced adherence to the Mediterranean diet (Supplementary Table S2). As anticipated, individuals with the highest adherence to the Mediterranean diet (MEDAS score ≥ 10) exhibited a notably lower mean Na^+/K^+ ratio, in comparison to both the average MEDAS score ($p = 0.031$) and the lowest adherence group ($p = 0.009$, Supplementary Table S2). This comparison suggests that the reduction in the Na^+/K^+ ratio is associated with adherence to the intervention programs, which, in turn, corresponds with adhering to the Mediterranean diet.

4. Discussion

In the broader effort to address the impact of high BP and CVD across populations, there is a pressing need to establish effective strategies for encouraging behavior changes (1, 2). However, implementing these strategies is challenging for healthcare professionals. Thus, we conducted a randomized trial to assess the impact of two distinct empowerment-focused approaches on dietary habits and BP, as endorsed by clinical nutrition experts. Our goal was to identify key factors in lifestyle adjustments that contribute to successful BP reduction. To achieve this, we compared a salt reduction program with a holistic healthy lifestyle approach.

Our findings revealed that both interventions were effective in reducing DBP after 12 weeks. However, only the intervention focused on salt reduction was significantly effective in decreasing SBP, with a substantial mean reduction of −2.5 mm Hg after 12 weeks compared to baseline. Furthermore, the salt reduction program was more effective at reducing BP in participants with high-normal or hypertension at baseline (SBP ≥ 130 and/or DBP ≥ 85, mm Hg; Figure 5). This highlights the notion that customizing recommendations to address specific public health concerns, such as hypertension, can lead to a more pronounced impact, especially within risk groups These results are in line with recent systematic reviews that emphasize the superior efficacy of both the DASH and low-salt diet in lowering BP when compared to the Mediterranean diet (6–8, 10). However, it is crucial to emphasize that while distinctions were noticeable, especially among participants with high-normal BP or hypertension, there were no statistically significant differences observed across all study participants.

The magnitude of our results in a short period is outstanding and consolidates the importance of diet and nutrition in the management of hypertension, independently of pharmacology. Because BP decrease is semilogarithmic associated with the incidence of cardiovascular outcomes, even a minor reduction has significant benefits (7). Undeniably, this improvement in BP is highly relevant since previous studies demonstrated that even a 2 mmHg reduction in SBP and DBP

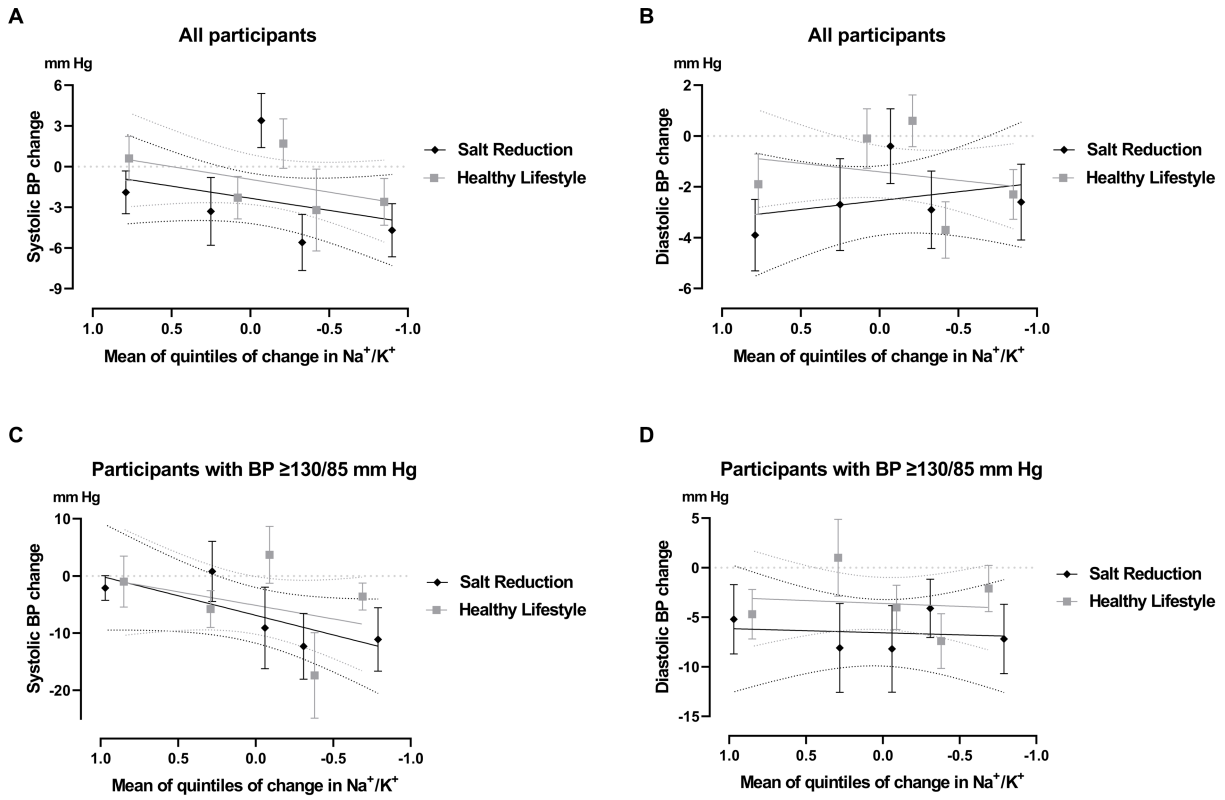

FIGURE 3
Change in office blood pressure (BP) stratified by mean quintiles of changes in Na^+/K^+ ratio, after 12-week follow-up. Complete-case participants from salt reduction and healthy lifestyle groups were included in the analysis of systolic BP **(A)** and diastolic BP **(B)**. Subgroup analysis of participants with high-normal or hypertension at baseline (SBP ≥ 130 and/or DBP ≥ 85, mm Hg) were also included in the analysis of systolic BP **(C)** and diastolic BP **(D)**. Data are presented as mean (SEM). Significance between Q1 to Q5 quintile subgroups was assessed by one-way analysis of variance (ANOVA) corrected with Bonferroni test for multiple comparisons. Differences in the same quintile between salt reduction and healthy lifestyle groups were assessed by independent t test.

is associated with 10% lower stroke-related mortality and with a 7% lower risk of coronary artery disease (6). Likewise, 2 mmHg reduction in SBP substantially reduced the risk of CVD (27 events for coronary heart disease, 24 events for stroke, and 41 events for heart failure per 100,000 person-years) (32).

Nevertheless, it was somewhat surprising that the interventions yielded no significant impact on Na^+ and K^+ concentrations. It is noteworthy to emphasize that our study design involved participants attending dietary educational sessions, resembling intervention studies focused on the Mediterranean diet (8), as opposed to the controlled feeding protocols seen in DASH trials (7). This suggests that the reduced BP is more likely a result of an overall improvement in dietary quality rather than changes in the Na^+/K^+ ratio, as previously emphasized (9).

Indeed, the observed decrease in BP in our study can be attributed to the intentional behavior changes adopted by participants over the 12-week intervention period. Specifically, participants increased their consumption of vegetables, fruits, fish, tree nuts and dishes seasoned with sofrito, while reducing their intake of processed meats, butter, margarine, and high-sugar products. Significantly, these dietary changes comprise beneficial food ingredients that could account for the observed decrease in BP. Notably, the presence of vitamins and flavonoids in vegetables and fruits might induce blood vessel relaxation, driven by their antioxidant and anti-inflammatory properties (33). Similarly, fish consumption, attributed to its long-chain n-3 polyunsaturated fatty acids, is associated with a moderate reduction in BP, possibly by enhancing vascular reactivity and endothelial function (34). The diverse range of nutrients in nuts, including polyunsaturated fatty acids, magnesium, and antioxidants, could potentially confer a favorable impact on BP (35). Importantly, the olive oil within sofrito is rich in bioactive phenolic compounds that may enhance endothelial function by increasing nitric oxide availability and triggering vasodilation (36).

Furthermore, these dietary modifications yielded improvements in various anthropometric measures, ultimately contributing to the reduction in BP. While variations in body measurements did not result in a significant mean difference, a noticeable trend toward weight reduction was apparent. It is worth noting that weight loss constitutes a significant lifestyle factor in the prevention and management of hypertension, often influenced by dietary choices and physical activity (37). Importantly, our clinical trial indicates that participants who achieved more substantial weight reduction within the highest quintiles also observed greater reductions in BP. Interestingly, the slope of this trend was more pronounced in the healthy lifestyle group. Nevertheless, both groups reduced −3.1 mm Hg SBP in the highest quintiles of weight change. These findings corroborate a recent systematic review and meta-analysis (11), indicating that larger variations in body weight are associated with a more pronounced

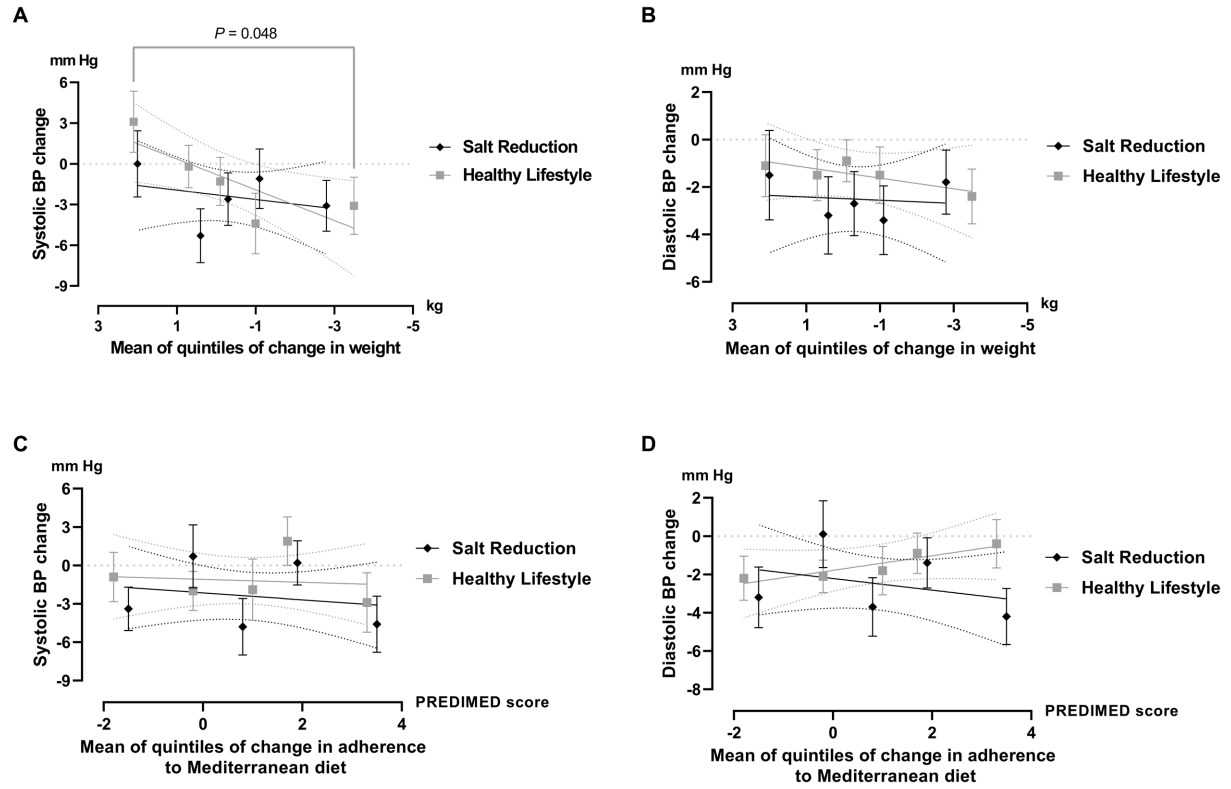

FIGURE 4
Change in office blood pressure (BP) stratified by mean quintiles of changes in weight **(A,B)** and adherence to Mediterranean diet **(C,D)**, after 12-week follow-up. Complete-case participants from salt reduction and healthy lifestyle groups were included in the analysis of systolic BP and diastolic BP. Data are presented as mean (SEM). Significance between Q1 to Q5 quintile subgroups was assessed by one-way analysis of variance (ANOVA) corrected with Bonferroni test for multiple comparisons. Differences in the same quintile between salt reduction and healthy lifestyle groups were assessed by independent t test.

impact on BP. Similarly, a comprehensive dose–response meta-analysis (38) revealed that each 1 kg of weight loss corresponds to an approximate 1 mmHg reduction in SBP.

As expected, participants who achieved the largest reductions in Na^+/K^+ ratio exhibited a trend toward lower SBP, especially among individuals with high-normal or hypertension at baseline, although the results did not attain statistical significance. Importantly, following the 12-week intervention, participants with the highest adherence to the Mediterranean diet exhibited a significantly lower mean Na^+/K^+ ratio. This was expected since increased urinary K^+ excretion is associated with a higher intake of vegetables and fruit, whole grains, low-fat dairy products, fish, and poultry, all endorsed in the Mediterranean diet. Likewise, lower excretion is associated with an unhealthy diet, including calorie-dense foods such as fast food and high-energy drinks. Furthermore, urinary K^+ measurement is correlated with surrogate outcomes, such as heart rate and BP, and is a predictor of both all-cause and cause-specific mortality in the general population (39).

According to current hypertension prevention guidelines, lifestyle changes such as a healthy diet are recommended for all patients as they can delay or complement ongoing treatment (40). Our study provides evidence and guidance to support the adoption of behavioral approaches in clinical settings as effective strategies to promote healthy habits. These approaches include improving population education through health information, awareness, and knowledge. Therefore, the proposed interventions are crucial as they facilitate long-term healthy behavioral changes, improve health outcomes, and counteract the growing prevalence of unhealthy diets.

The strengths of our study include a randomized design and a notably ample sample size. We employed an interdisciplinary empowerment-based approach by collaborating with a multidisciplinary team of 12 nutritionists operating within clinical and grocery shopping settings. Furthermore, we adopted a pragmatic approach, involving participants with hypertension and those using antihypertensive medications. Through this deliberate inclusion of individuals from this high-risk group, the applicability of the study findings to a broader population is enhanced, thereby increasing the generalizability of our findings. Lastly, we followed a standardized protocol and strict quality control procedures for clinical measurements and data collection, thus ensuring the accuracy and consistency of our data.

On the other hand, this trial presents several limitations that warrant acknowledgment. Firstly, differences in group retention were noted, with a lower attrition rate observed among participants in the salt reduction program compared to the holistic healthy lifestyle group. This divergence could be attributed to the comparatively reduced contact inherent to the healthy lifestyle program, potentially leading to a diminished level of motivation among these participants. This variance in follow-up could potentially introduce bias favoring the salt reduction group. However, intention-to-treat analyses

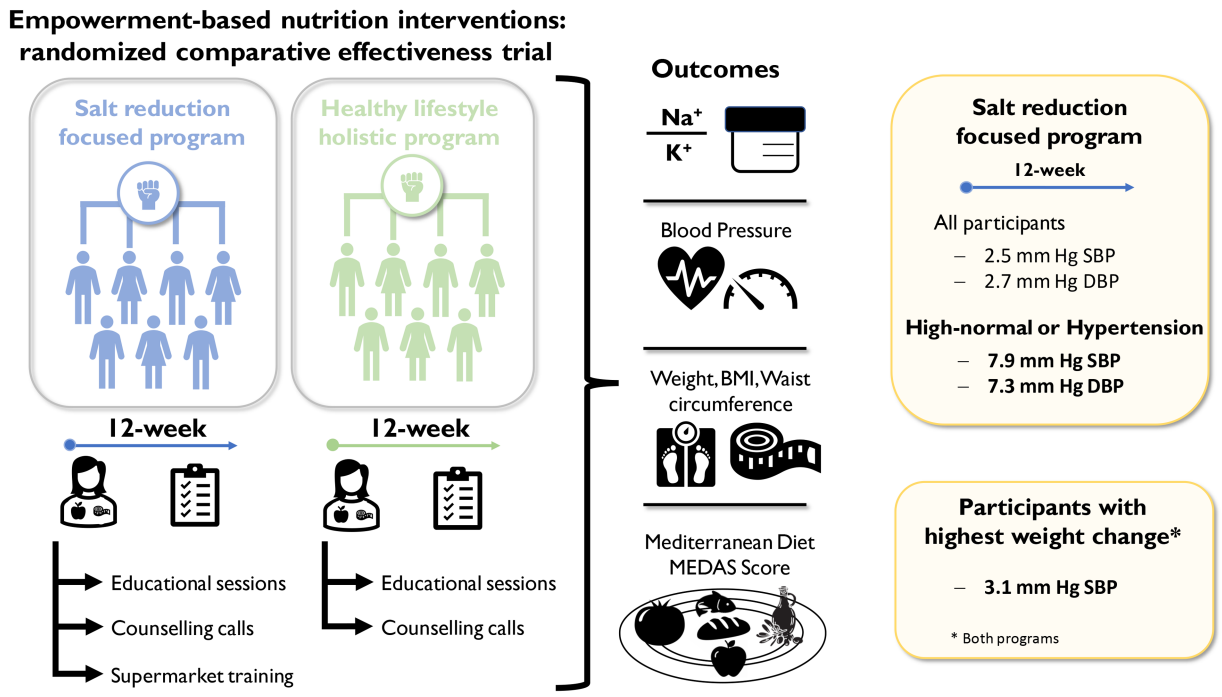

FIGURE 5
Schematic representation of the clinical trial design, showing the major characteristics of the intervention groups. The outcome variables are highlighted as well as the major findings.

employing multiple imputation methods, to address missing data, yielded outcomes consistent with the complete-case analysis. Secondly, there was an imbalance in the sex distribution, with a higher proportion of women in the healthy lifestyle group. Nonetheless, we addressed this disparity by incorporating sex and participant compliance as covariates in the analysis to mitigate potential confounding effects. Thirdly, the study concluded before attaining the intended sample size of 500 participants. Although the study still encompassed a relatively substantial sample size, the failure to reach the target number might have impacted the statistical power to discern differences in outcome assessments between the groups. Fourth, due to ethical considerations, the study lacked a no-intervention control group, and the design did not allow double-blinding. Fifth, it is worth noting that participants who volunteer for dietary trials generally exhibit a higher degree of motivation to adhere to a dietary program compared to the broader population. Furthermore, most participants were professionally active and had higher levels of education, potentially facilitating a greater assimilation of knowledge. Consequently, the outcomes of the programs may not be as effective in the general population.

5. Conclusion

This study shows that empowerment-based approaches, aimed at promoting healthy culinary habits and improved purchasing options, effectively lower BP in the short term. However, an intervention focused on educating participants about salt reduction was found to be more impactful in lowering both systolic and diastolic BP, particularly in those with high-normal or hypertensive BP. Moreover, approaches that promote adherence to the Mediterranean diet were associated with weight loss and a decrease in the Na^+/K^+ ratio, resulting in improved BP. Importantly, the decrease in BP primarily results from an overall improvement in dietary quality, rather than being solely attributed to changes in the Na^+/K^+ ratio. These findings highlight the importance of targeted lifestyle interventions and the potential benefits of a Mediterranean-style diet in BP management. Thus, the study results highlight the importance of promoting healthy lifestyle practices through empowerment, aiming to prevent the onset of hypertension and ameliorate advanced stages of elevated BP. This approach could contribute to reducing the risk of potential complications. Therefore, it is imperative to define new strategies that mirror a similar reduction program promoted by registered nutritionists and dietitians, which can provide the tools to the population for making healthier choices. This can contribute to reducing long-term health costs and improving the quality of life for the general population.

Data availability statement

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

Ethics statement

The studies involving humans were approved by Ethical Committee of the Hospital CUF. 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

AM-R: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Supervision, Validation, Visualization, Writing – original draft. SI: Data curation, Investigation, Writing – review & editing. IB-M: Data curation, Investigation, Writing – review & editing. JM: Data curation, Investigation, Writing – review & editing. CR: Data curation, Investigation, Writing – review & editing. IC: Data curation, Investigation, Writing – review & editing. IM: Data curation, Writing – review & editing. MIS: Data curation, Writing – review & editing. LC: Data curation, Writing – review & editing. CBO: Data curation, Writing – review & editing. TH: Data curation, Writing – review & editing. PP: Data curation, Writing – review & editing. DÉP: Data curation, Writing – review & editing. CMO: Data curation, Writing – review & editing. JM: Data curation, Writing – review & editing. TS: Data curation, Writing – review & editing. JA: Writing – review & editing. JR: Writing – review & editing. DIP: Writing – review & editing. MPS: Writing – review & editing. CM: Writing – review & editing. AF: Writing – review & editing. JP: Conceptualization, Formal analysis, Investigation, Supervision, Validation, Visualization, Writing – review & editing. CC: Conceptualization, Formal analysis, Funding acquisition, Investigation, Supervision, Validation, 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.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.1277355/full#supplementary-material

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EDITED BY
Zhendong Liu,
Shandong First Medical University, China

REVIEWED BY
Edna J. Nava-Gonzalez,
Autonomous University of Nuevo León, Mexico
Syeda Mehpara Farhat,
National University of Medical Sciences (NUMS), Pakistan

*CORRESPONDENCE
Qing Feng
✉ qingfeng@njmu.edu.cn
Anita Nyarkoa Walker
✉ walkeranita30@gmail.com

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Healthy eating habits and a prudent dietary pattern improve Nanjing international students' health-related quality of life

Anita Nyarkoa Walker[1]*, Makhala Mary Weeto[1], Christiana Babymay Priddy[1], Salimata Yakubu[1], Margaret Zaitoun[1], Qianfeng Chen[1], Bohan Li[1], Yucong Feng[1], Yuxia Zhong[1], Yuandie Zhang[1], Tao Wei[1], Solim Essomandan Clémence Bafei[2] and Qing Feng[1]*

[1]Department of Nutrition and Food Hygiene, Nanjing Medical University, Nanjing, Jiangsu, China, [2]Department of Epidemiology and Health Statistics, Nanjing Medical University, Nanjing, Jiangsu, China

Purpose: Low-quality dietary practices, such as fast food consumption and skipping meals, deteriorate the quality of life. However, the available studies on diet and health-related quality of life (HRQoL) used matrices not specific to nutrition. Moreover, how diet affects the HRQoL of international students in China is unknown. Therefore, using a cross-sectional study, the effect of dietary patterns and habits on the HRQoL of international students in Nanjing, China, was examined.

Methods: The researchers collected dietary data using a food frequency questionnaire (FFQ) from February to March 2022. Then, the Food Benefit Assessment (FBA) was used to access HRQoL. Finally, the effect of eating habits and dietary patterns on HRQoL was explored using multilinear regression.

Results: Approximately 454 responses were obtained, with the responses mostly from male subjects (56.4%) and those aged 26years and above (75.6%). The quality of life according to the food consumed was about average for all the constructs except for aesthetics and disease prevention, as 65.8% skipped meals, particularly breakfast (47.8%). Furthermore, three dietary patterns were identified: prudent, Western, and animal protein patterns. Consequently, by skipping breakfast, vitality (β=−2.362, p=0.04), wellbeing (β=−3.592, p=0.007), digestive comfort (β=−4.734, p=0.008), and disease prevention (β=−5.071, p=0.031) were all reduced. However, consuming at least three meals daily enhanced vitality (β=2.254, p=0.003) and disease prevention (β=4.441, p=0.019). Furthermore, aesthetics (β=4.456, p=0.05), physical appearance (β=5.927, p=0.003), and vitality (β=3.323, p=0.009) were also significantly increased by healthy dietary patterns. However, a more Westernized diet led to frequent snacking (β=−4.631, p=0.032), a decline in wellbeing (β=−5.370, p<0.001), and discomfort with digestion (β=−5.101, p=0.01). Finally, increased frequency of snacking (β=−6.036, p=0.012), a decrease in wellbeing (β=−4.494, p=0.004), digestive comfort (β=−9.940, p<0.001), physical appearance (β=−4.926, p=0.027), and disease prevention (β=−5.835, p=0.043) were all associated with an increase in animal protein patterns.

Conclusion: This research indicates that healthy eating habits and patterns positively impact international students' HRQoL. Therefore, the appropriate authorities should advise students to consume healthy foods regularly to improve their HRQoL.

KEYWORDS

dietary pattern, snacking, wellbeing, disease prevention, vitality, digestive comfort, aesthetic, meal skipping

1 Introduction

People of all ages, especially students, must preserve their health and quality of life through an active, healthy lifestyle, and a balanced diet (1). As a result, the world is working to enhance these factors that influence their health-related quality of life (HRQoL). HRQoL is a broad and multidimensional measure of an individual's perceived physical and mental health. It often includes self-perceptions of disease symptoms or health conditions, side effects, functional status across various living domains, and life quality and satisfaction (2–4). Self-perceived health-related quality of life indicates mortality (5, 6). In addition to being used among patients with irritable bowel syndrome (IBS), persistent constipation, fecal incontinence, diabetes, and cancer, researchers also use HRQoL in healthy individuals. It accurately predicts morbidity and mortality, unmet needs, and intervention outcomes (7–9). Due to its significance to health, improving HRQoL and identifying factors affecting it are current priorities for public health professionals (7, 8).

People's eating habits, including the manner of eating, the type of food eaten, and whom they eat with, are shaped by their social contacts and affect their HRQoL (10). Healthy dietary patterns consisting of more whole grains, vegetables, fruits, low- and non-fat dairy, and lean meat lower the risk of obesity, cardiovascular disease, and some malignancies and also improve QoL (11). For instance, the Mediterranean diet, which includes more fruits, vegetables, seafood, whole grains, olive oil, and other foods, is advantageous to health and improves HRQoL (12–14). Conversely, unhealthy dietary patterns, such as those high in fat, sugar, processed foods, and fewer fruits and vegetables, were linked to a decline in HRQoL (13, 15). Aside from dietary patterns, a person's quality of life is influenced by eating habits such as skipping meals, especially breakfast, eating late, irregular eating times, and overeating. For instance, regularly eating breakfast is linked to lower body mass index (BMI) (16), better levels of wellbeing (17), and higher levels of life quality (18), but missing meals lowers life quality (15).

Although HRQoL evaluation tools are crucial in nutrition research, most measures are not nutrition specific. For instance, the Short Form-36 (SF-36), the Weight Impact on Quality of Life Tool, the Irritable Bowel Syndrome Quality of Life Tool, and the Gastrointestinal Quality of Life Index questionnaire (19, 20) do not measure the direct effect of foods ingested on the quality of life of consumers. Therefore, it is essential to calculate the total impact of diet on HRQoL using a questionnaires specific for nutrition, such as the Food Benefit Assessment Questionnaire (FBA). The FBA questionnaire evaluates how participants who are healthy or overweight perceive the effects of their food intake. It describes how a person's health, vitality, sleep, and digestion are affected by their food (21).

International students have traveled from their country of origin to a host country for academic purposes. These students might experience a lower quality of life because they face issues such as negotiating the healthcare system, the pressures of learning a new language, and balancing financial concerns, social connectivity, and anxiety due to isolation from family and friends (22), all of which affect their health compared to their counterparts in their host countries. Additionally, compared to the native population, immigrants have a worse rate of HRQoL (23–25) due to prejudice, socioeconomic hardship, unfavorable working or studying conditions, and climate change, all potential causes of these disparities (26, 27).

The number of immigrant students in China has drastically expanded in recent years (28), suggesting differences in their HRQOL compared to host students. Furthermore, a prior study in Nanjing indicated that most international students consume mainly Western and meat-heavy diets, which increases non-communicable diseases and lowers quality of life. Nevertheless, as far as we are aware, no research has looked into the HRQoL of immigrant students in China. Therefore, what is the current status of their HRQoL, and how do their dietary patterns and habits influence this aspect of their life? It is expected that healthy nutritional habits and/or patterns will have a positive influence on HRQoL. To achieve this, the HRQoL, dietary patterns, and eating habits of international students in Nanjing were assessed. Then, the impact of dietary patterns and eating habits on HRQoL was investigated. The appropriate authorities can use the findings of this study to customize the actions required to raise the standard of living for international students in Nanjing.

2 Materials and methods

2.1 Study design, population, and sampling

Nanjing, the capital of Jiangsu province of the People's Republic of China, is the second-largest city in the East of China and hosts the majority of international students in the province. The researchers purposively recruited international students from universities in Nanjing through social media promotion of the study link from February 1 to March 31, 2022. The survey questionnaire was then pretested among 30 international students at Nanjing Medical University. The final version of the survey was hosted on the "Wenjuanxing" online platform,[1] designed for online questionnaires, voting, and comments. Thereafter, volunteers from the various schools shared the link to the survey with WeChat groups of international students. The survey allowed only one entry per participant with a specific WeChat account. There was no inducement to take part. Confidentiality was guaranteed as there was no collection of information about personal identity. The survey could be completed in 5–10 min. Participants consented to participate in the survey by selecting "agree to participate." Individuals who chose "disagree" automatically ended the questionnaire. The study protocol was exempted from review by the research and ethics committee of Nanjing

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Medical University because it did not collect biological samples or obtain confidential information. However, the ethical standards of the Declaration of Helsinki and its later amendments were adhered to.

2.2 Assessment of health-related quality of life

A self-administered Food Benefit Assessment Questionnaire (FBA) was used to assess the subjects' HRQoL (FBA) (21). The questionnaire has 41 items divided into seven categories: vitality (Ten items), digestive comfort (nine items), wellbeing (six items), disease prevention (six items), aesthetics (five items), snacking (two items), and physical appearance three items. A five-point Likert response scale ranging from 1 (never/certainly not) to 5 (always/certainly) was used to examine these domains. Respondents were asked to think about what they had eaten in the previous 2 weeks while answering the questions. The final scores for each dimension were determined as follows.

$$\text{Final score} = \frac{Raw\ score - Minimum\ score}{Maximum\ score - minimum\ score} \text{X}\,100$$

The raw score of a dimension is the mean of the items in the dimension.

Minimum score = 1 and Maximum score = 5.

The final score is determined based on a linear transformation of the mean score and ranges from 0 to 100.

Higher scores indicate a higher positive impact or satisfaction from the daily diet.

This survey tool has been approved and validated with high internal consistency. Cronbach's α for the various components are as follows: vitality (0.91), digestive comfort (0.89), disease prevention (0.88), wellbeing (0.87), aesthetics (0.82), physical appearance (0.79), and snacking (0.81) (21). The individual aspects of the various domains of this questionnaire can be found in Supplementary Table 1.

2.3 Assessment of dietary patterns using the food frequency questionnaire and principal component analysis

To gather the nutritional intake of international students in Nanjing, a modified version of a semi-quantitative food frequency questionnaire (FFQ) that has been validated and used among university students (28, 29) was used. The FFQ contained 56 food items in this survey. The following intake frequencies were used: >1 time daily, 1 time daily, 3–6 times per week, 1–2 times per week, 1–3 times per month, and never or rarely. The food items in the FFQ were arranged in a Likert format, with the frequency of consumption in the rows, the type of food, and the serving sizes in the columns. To minimize the errors in the diet data, an FFQ specific to and validated among university students was used (29). Furthermore, before data collection, the questionnaire was pretested among 30 international students from various countries to ensure that the food list covered most of the foods consumed by the students. We then converted the absolute consumption amounts into the daily portions consumed. For the dietary pattern analysis, we condensed the original 55 food items in the FFQ into nine food groups (28). The nine food groups were then input into a principal component analysis (PCA), and a varimax (orthogonal) rotation was performed to construct dietary patterns. The screen plot, parallel analysis, and component interpretability were used to determine the number of components to be retained (30). Each dietary pattern was interpreted using food groups with factor loadings ≥0.4.

2.4 Statistical analysis

The Statistical Package for Social Sciences (Version 26; SPSS Inc., Chicago, IL, United States) was used for statistical analysis. The description of the data was done using frequencies, percentages, and mean and standard deviations. Factor scores and eating patterns were found using principal component analysis. The multilinear regression model was employed to determine how their dietary patterns and eating habits affect their health-related quality of life, with a statistical significance level at a value of p <0.05. We controlled for confounders such as sex, age, and monthly expenditure. Resource identification initiative IBM SPSS Statistics (RRID: SCR_019096).

3 Results

3.1 General characteristics, eating habits, and HRQoL of the study population

The 454 respondents were primarily males (56.4%), within the age range of 26 years and above (75.6%), postgraduates or above (72.7%), and mostly from Africa (82.2%). The majority skipped meals (64.8%), particularly breakfast (47.8%), making them eat either once or twice a day (56.8%). As a result, according to the FBA, their quality of life was about average for all the constructs except for aesthetics and disease prevention (Table 1).

3.2 Food groups and factor loading for the three dietary patterns

According to Table 2, the principal component analysis identified three dietary patterns, i.e., traditional, Western, and animal protein. The prudent pattern explained 31.175% and was heavily loaded with vegetables, legumes, seeds and nuts, cereals and grains, eggs, and milk and its products. The variance explained by the Western pattern was 18.688%, with the fast food and drink loadings being high. On the other hand, the animal protein pattern explained approximately 17.856% of the variance and consisted of red meat and other animal products. The food groups of each pattern had factor loadings of >0.4.

From Figure 1, the third tertile of all the dietary patterns, Western (β = −6.036, p = 0.012), animal meat pattern (β = −4.631, p = 0.032), and even prudent dietary pattern (β = −3.395, 0.023) were all associated with an increased snacking behavior.

According to Figure 2, skipping meals (β = −3.566, p = 0.045) reduced the aesthetics of the students. However, having a prudent dietary pattern (β = 4.456, p = 0.05) improved one's aesthetics.

As shown in Figure 3, digestive comfort was a major problem among our respondents. In this study, skipping meals (β = −4.996, p = 0.003), such as breakfast (β = −4.734, p = 0.008), or both breakfast

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TABLE 1 Demographic characteristics of eating habits and health-related quality of life (HRQoL) of international university students in Nanjing ($n = 454$).

Variables		*N* (%) /mean (SD)
Sex		
	Male	256 (56.4)
	Female	198 (43.6)
Age		
	18–25	110 (24.2)
	26 and above	344 (75.8)
Education		
	Undergraduate and below	124 (27.3)
	Postgraduate and above	330 (72.7)
Program of study		
	Medical related	157 (34.6)
	Non-medical related	297 (65.4)
Weight status		
	Underweight	22 (4.9)
	Normal	190 (41.6)
	Overweight	156 (34.5)
	Obese	86 (19.0)
Monthly expenditure		
	Less than 1,000 RMB	99 (21.8)
	Between 1,000 and 3,000 RMB	229 (50.4)
	More than 3,000 RMB	126 (27.8)
Continent		
	Asia	72 (15.9)
	Africa	373 (82.2)
	Others	9 (2.0)
Do you skip meals in China?		
	Yes	294 (64.8)
	No	160 (35.2)
What type of meal do you skip?		
	I do not skip a meal	160 (35.2)
	Breakfast	217 (47.8)
	Lunch and supper	33 (7.3)
	Breakfast and lunch	44 (9.7)
How many times do you eat in a day?		
	Once/twice	258 (56.8)
	Thrice/more	196 (43.2)
Health-related quality of life		
	Snacking	51.83 (18.77)
	Vitality	57.65 (11.03)
	Wellbeing	56.34 (12.96)
	Physical appearance	61.71 (17.38)
	Aesthetics	73.40 (19.87)
	Digestive comfort	59.44 (17.50)
	Disease prevention	73.04 (22.50)

TABLE 2 Food groups used in the principal component analysis and the factor loadings of each dietary pattern of the 454 international students in Nanjing.

Food groups	Food items	Prudent pattern	Western pattern	Animal protein pattern
Vegetables	Spinach/other leafy vegetables, tomatoes, ginger/garlic, potato, onion, lady finger (okra), broccoli, brinjal, pumpkin, cabbage/cauliflower, chilly, bell pepper, and others	0.825	-	-
Legumes	Red beans, soybeans, and other beans	0.800	-	-
Seeds and nuts	Groundnuts, almonds, cashew nuts, currants/raisins, and others	0.699	-	-
Cereals and grains and their products	Maize, white flour, brown flour, instant noodles, white rice, brown rice, oats, porridge, bread/toast, biscuit/cake, and others	0.696	-	-
Fruits	Bananas, grapes, apples/pear, mango, orange, pineapple, strawberries, and others	0.682	-	-
Drinks	Tea, coffee, carbonated drinks, and others	-	0.845	-
Dairy product	Milk, cheese, milk powder, yogurt, and others	0.417	-	-
Fast foods	Chips, pizzas, burgers, sandwiches, and others	-	0.547	-
Eggs	Eggs	0.438		
Red meat	Mutton, beef, pork, and others	-	-	0.836
Other animal products	Chicken, fish, shrimp, and others	-	-	0.710
Variance explained		31.175%	18.688%	17.856%

[a]Food groups with absolute factor loadings of ≥0.400 are included in each dietary pattern. [b]Kaiser–Meyer–Olkin measure of sampling adequacy = 0.827. [c]p for Bartlett's test of sphericity < 0.001. [d]Rotation method: varimax orthogonal rotation.

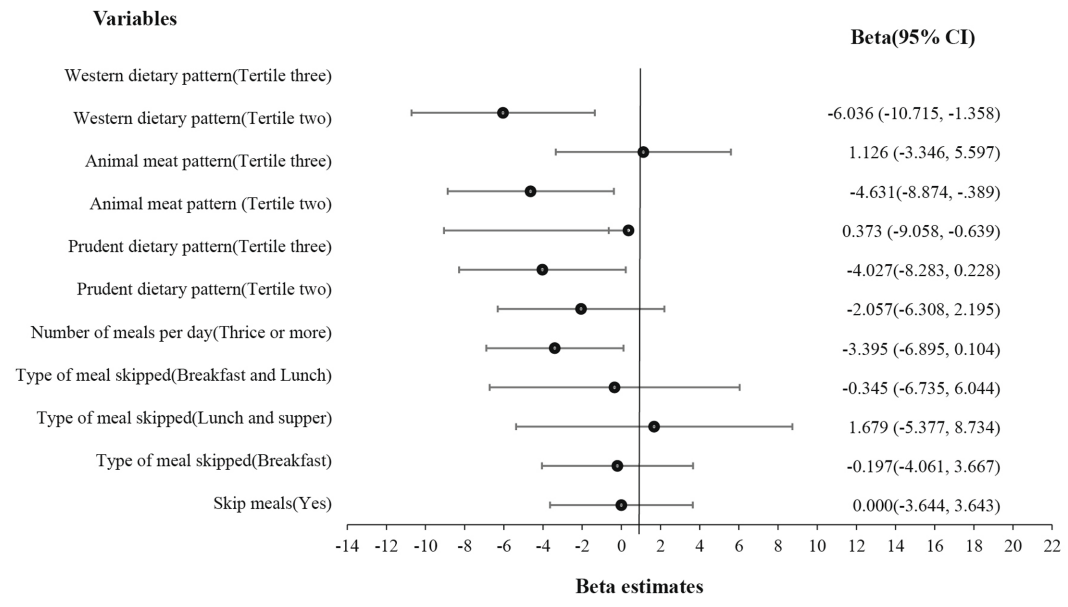

FIGURE 1
Effect of eating behavior and dietary patterns on snacking.

and lunch (β = −7.121, p = 0.015), all negatively affected their digestive comfort. Similarly, all three dietary patterns, namely, Western (β = −9.940, p < 0.001), animal meat pattern (β = −5.101, p = 0.01), and prudent dietary pattern (β = −4.244, p = 0.032), resulted in lower digestive comfort.

With reference to Figure 4, skipping meals (β = −4.996, p = 0.003), especially breakfast (β = −5.071, p = 0.031), and consuming a Western dietary pattern (β = −5.835, p = 0.043) negatively affected disease prevention, but having a prudent dietary pattern (β = 4.748, p = 0.03) increased one's ability to prevent diseases.

According to Figure 5, skipping meals (β = −4.107, p < 0.001) of any type, such as breakfast (β = −5.071, p = 0.031), breakfast and lunch (β = −4.425, p = 0.043), or even lunch and supper (β = −7.009, p = 0.004), reduced wellbeing. In addition, all the dietary patterns

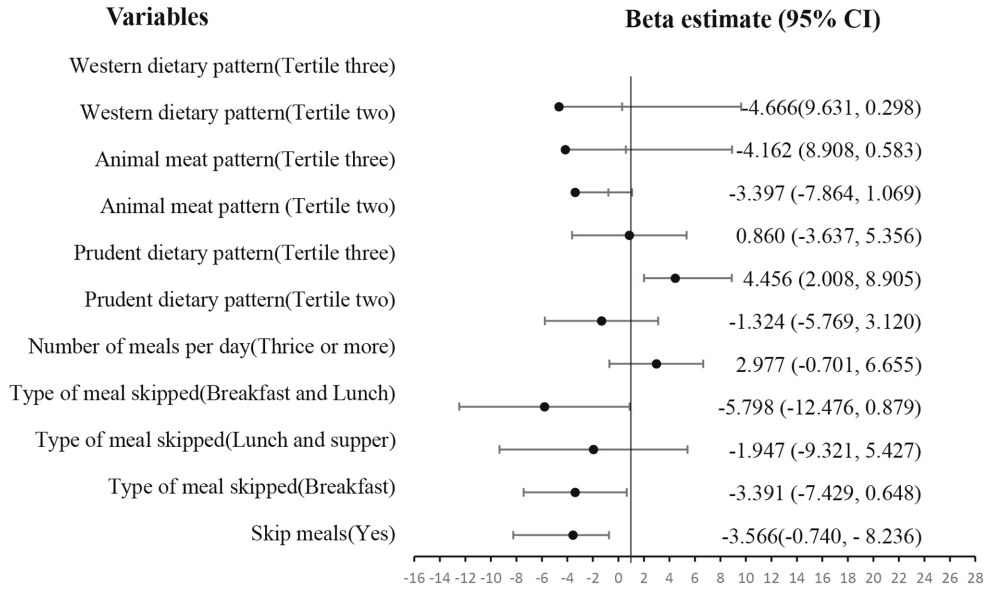

FIGURE 2
Effect of eating behavior and dietary patterns on aesthetics.

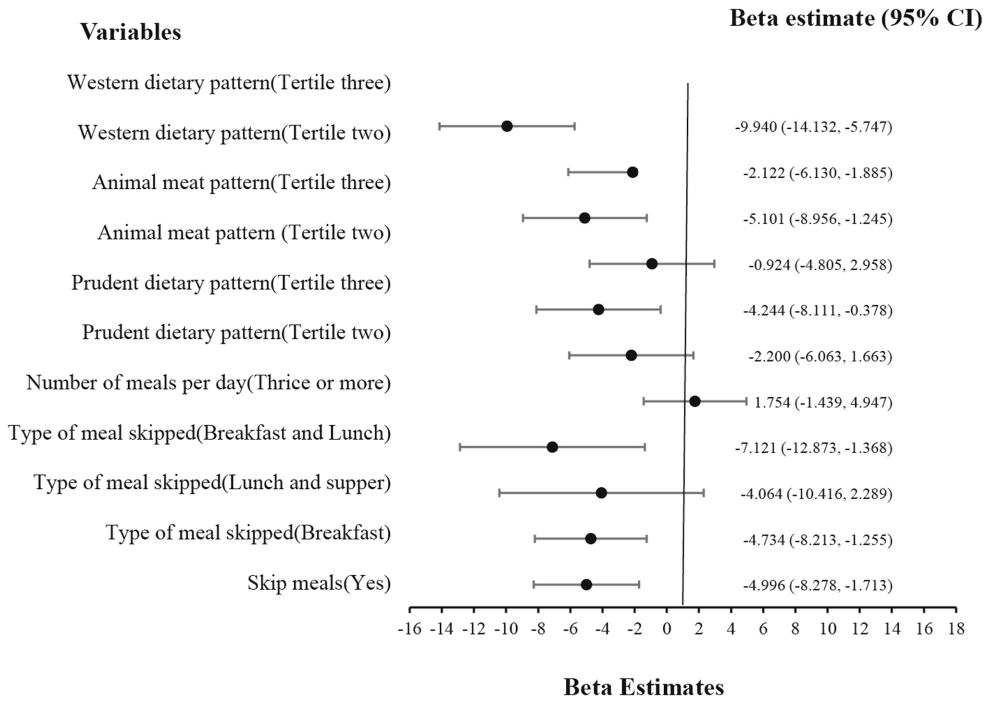

FIGURE 3
Effect of eating behavior and dietary patterns on digestive comfort.

such as prudent ($\beta = -1.835$, 0.04), animal meat ($\beta = -5.370$, $p < 0.001$), and Western ($\beta = -4.494$, $p = 0.004$) reduced their wellbeing.

The Western dietary pattern ($\beta = -4.926$, $p = 0.027$) reduced while the prudent dietary pattern ($\beta = 5.927$, $p = 0.003$) increased the student's perception of their physical appearance, as shown in Figure 6.

According to Figure 7, skipping meals ($\beta = -2.791$, $p = 0.01$), for example, breakfast ($\beta = -2.362$, $p = 0.04$) or both breakfast and lunch ($\beta = -4.441$, $p = 0.019$), reduced vitality. However, eating more than thrice a day ($\beta = 2.254$, $p = 0.003$) and practicing a prudent dietary pattern ($\beta = 3.323$, $p = 0.009$) increased their vitality.

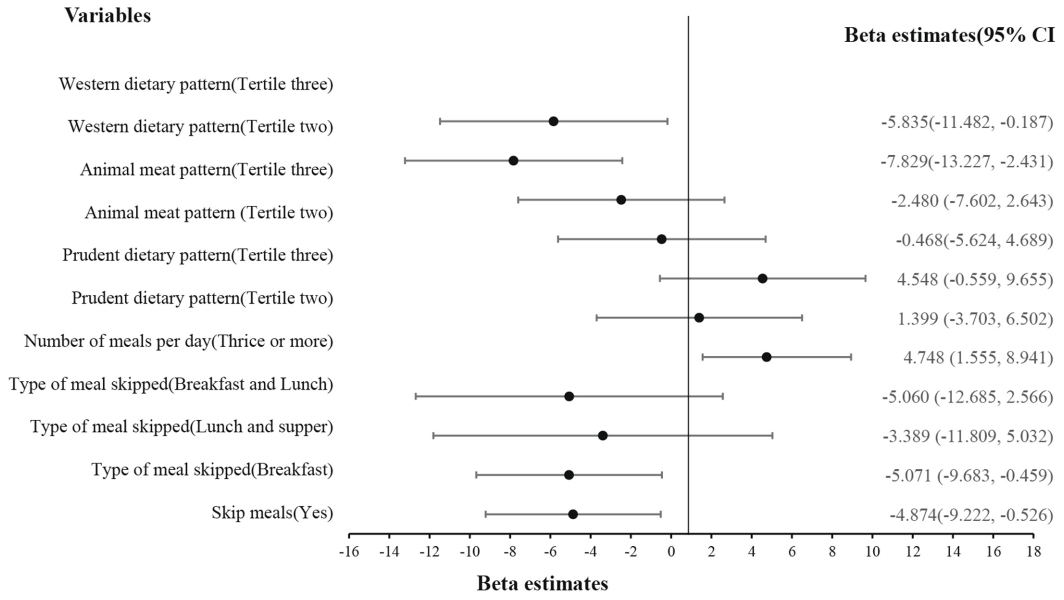

FIGURE 4
Effect of eating behavior and dietary patterns on disease prevention.

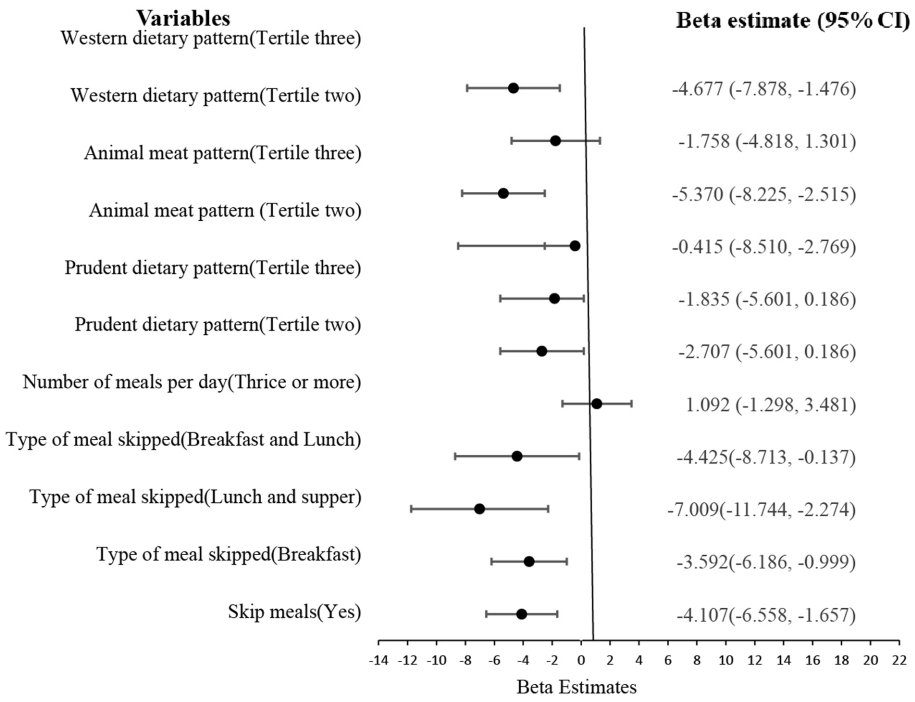

FIGURE 5
Effect of eating behavior and dietary patterns on wellbeing.

4 Discussion

In this cross-sectional study, 454 international students in Nanjing were investigated for their HRQoL, dietary patterns, and eating habits. Research has established that these three variables, namely, sex, age, and income, affect how an individual perceives their quality of life; hence, we controlled them to obtain the actual effect of diet and dietary behavior on their quality of life. For instance, female subjects, young adults, and individuals with high incomes have reported a better quality of life (31–33). This study found that, except for disease prevention and aesthetics, the students' QoL was about average. Three major dietary patterns were identified: healthy, Western, and animal protein. Finally, unhealthy eating patterns and skipping meals affect HRQoL

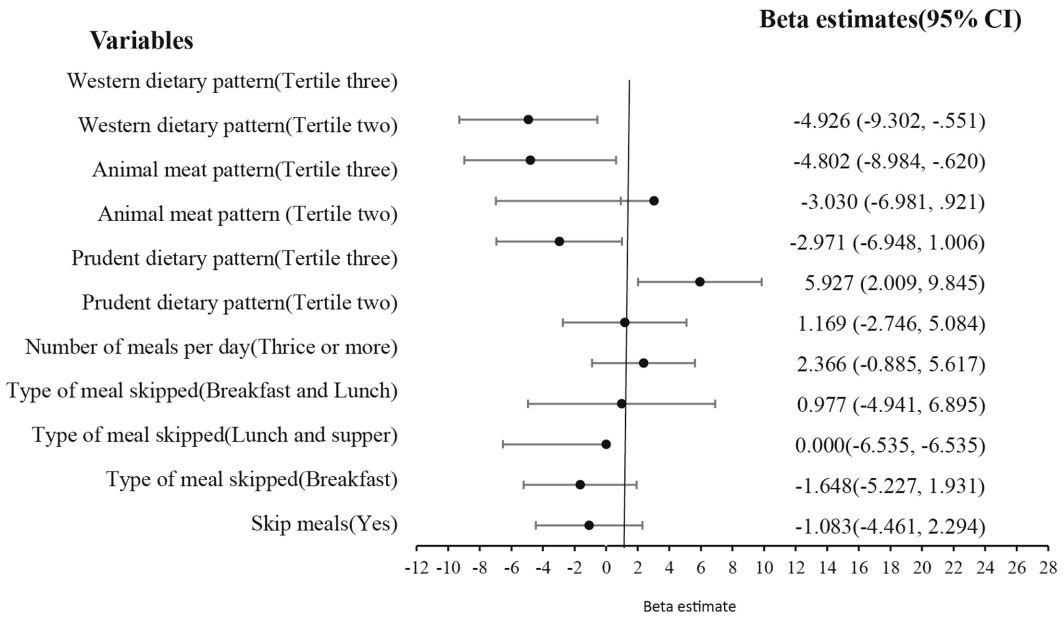

FIGURE 6
Effect of eating behavior and dietary patterns on physical appearance.

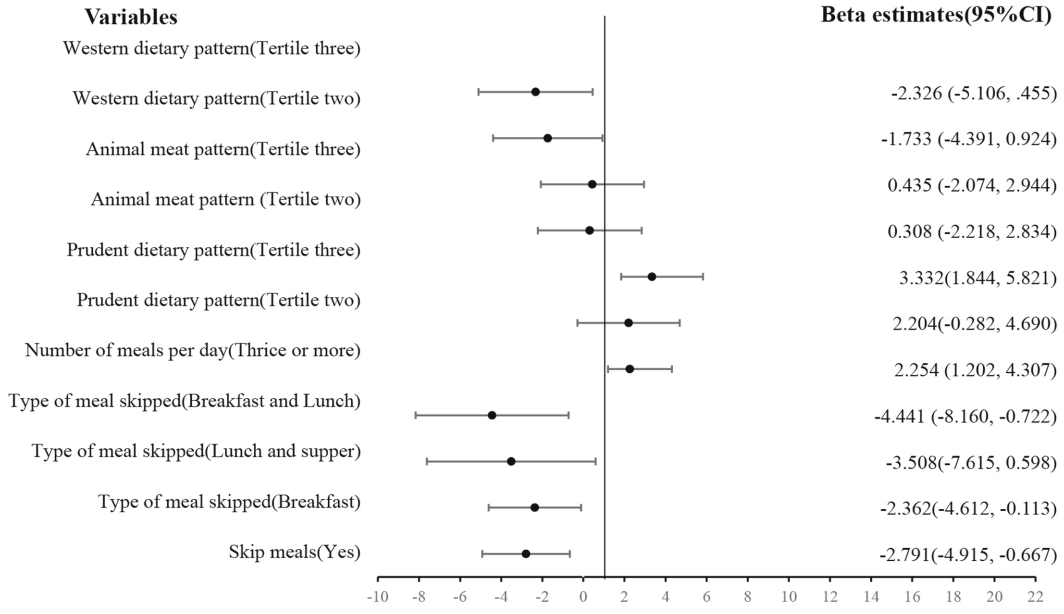

FIGURE 7
Effect of eating behavior and dietary patterns on vitality.

negatively, while healthy nutritional habits have a positive effect.

Unhealthy eating habits negatively influence vitality, wellbeing, digestive comfort, and disease prevention. Skipping breakfast and lunch was explicitly associated with lower vitality, wellbeing, and digestive comfort. In addition to vitamins A, C, and D, breakfast meals are also good sources of protein, dietary fiber, carbohydrates, fats, and cholesterol (34, 35). Maintenance and improvement of the gastrointestinal system, wellbeing, and vitality require maximum consumption of these nutrients. Hence, meal skippers will suffer poorer wellbeing, vitality, and digestive comfort due to being deficient in these essential nutrients.

Conversely, eating three meals daily can boost vitality and prevent disease. For instance, data from NHANES have shown an increasing meal frequency to reduce cardiovascular mortality (36). Moreover, cross-sectional data have also demonstrated a relationship between lower total and LDL cholesterol levels and more frequent eating (37). This implies that these people will have high vitality and can fend off diseases.

Similarly, healthy dietary patterns have a direct positive relationship with QoL. Accordingly, prudent eating patterns improve vitality, aesthetics, and physical appearance. For instance, similarly to our study, other researchers have established a positive association between vitality and nutritious meals high in natural, plant-based nutrients (38). Furthermore, improved aesthetics and physical appearance require foods rich in healthy nutrients. For example, maintaining good skin, nails, hair, and gums requires meals rich in eggs, seeds and nuts, whole grains, nutritious fats, proteins, dark leafy greens, and fruits (39). This explains why people who follow a healthy eating pattern think highly of their physique and aesthetics features.

Unsurprisingly, poor eating habits lowered QoL. First, a more Westernized diet decreased the wellbeing of the students. Western food consumption is associated with several ailments that affect people's QoL. Most foods contained in Western dietary patterns are rich in calories from fat, cholesterol, salt, and sugar but low in vitamins, minerals, and other nutrients (40) compared to healthy foods essential for a person's wellbeing. Second, a high animal protein pattern is associated with poor wellbeing, physical appearance, and disease prevention. Red meat in particular may increase the risk of various forms of long-term diseases when consumed in excess (41, 42). Chronic illnesses reduce how an individual perceives wellbeing and physical appearance. Similarly, those with chronic conditions may believe they have a low capacity for disease prevention.

Furthermore, inappropriate eating habits and skipping meals of the students had a detrimental impact on digestive comfort and snacking. For instance, those who skipped breakfast and those who followed Western and animal protein consumption patterns experienced less digestive comfort. Critical nutrients such as calcium, vitamins, fiber, and others can be found in breakfast foods such as yogurt, milk, and cereal (43). Hence, people who skip breakfast may experience digestive issues because they miss out on the microorganisms and fiber from milk, yogurt, and cereal consumption that aid digestion. Western foods are similarly high in fat, processed sugar, and fiber, leading to the loss of vital microbiomes required for digestion and disease prevention (44). Too much meat consumption also makes it less likely for someone to eat other meals consisting of whole grains, vegetables, and fruits. These may make them feel bloated and occasionally experience constipation due to poor digestion (45).

Moreover, the fatty parts of beef include significant amounts of the sulfur-containing amino acid methionine, which is broken down into offensive gas in the intestines as a result of malabsorption that contributes to indigestion (46). Last but not least, meat typically contains less fiber, an indigestible form of carbohydrate that helps the movement of fecal matter through the stomach and the intestine at a faster pace, aiding digestion and preventing constipation. The factors above could explain why depending on the animal protein pattern severely impacts intestinal comfort. In addition to the digestive function, which meat lacks, fibers also increase satiety by speeding up oral processing and requiring more effort to masticate. These two factors are related to fullness (47). Therefore, people who consume too much animal protein in their diet due to its low fiber content may have low satiety, feel hungry soon after eating, and be at increased risk of snacking between meals.

This study implies that decision-makers can use QoL matrices specific to nutrition to assess how a population's diet influences their wellbeing. Policymakers and school authorities responsible for international students can encourage international students to regularly consume foods rich in whole grains, nuts, vegetables, fruits, eggs, nuts, legumes, fish, and poultry without skipping meals to improve their quality of life.

The current study's strength is that it is the first to analyze students' QoL using the food benefit assessment questionnaire. This questionnaire is specific to the food they consume. Second, the FFQ used is student specific. It does, however, have some limitations. Since the sample size was limited to international students in Nanjing, the findings cannot be extended to include all international students in China. Second, recall bias could arise from the use of the FFQ. Third, comparing our results to previous studies was challenging because this was the first study to use the FBA to determine quality of life. Finally, the cross-sectional design of this investigation precluded the establishment of a causal relationship between the FBA components and dietary patterns and eating behaviors.

4.1 Conclusion

In conclusion, this research indicates that healthy eating practices and dietary patterns positively impact international students' HRQoL. For instance, consuming foods abundant in vegetables, fruits, eggs, nuts, legumes, fish, and poultry improves physical appearance, vitality, and aesthetics. Conversely, Western patterns of drinks, chips, pizza, burgers, and sandwiches, etc., lead to frequent snacking. Additionally, the animal protein patterns of mutton, beef, and pork, etc., are detrimental to wellbeing, physical appearance, and digestive health. Finally, skipping meals such as breakfast increases the problem of digestive discomfort and lowers wellbeing and disease prevention. Nonetheless, eating at least three times every day increases vitality and disease prevention.

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 requirement of ethical approval was waived by Nanjing Medical University, Nanjing, China, for studies involving humans. 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

AW, SY, MW, MZ, QC, BL, YF, YZho, YZha, TW, SB, and QF: study's conception and design. QF and AW: conceptualization. AW: methodology, software, and writing—original draft preparation. AW and SB: validation. AW and SY: formal analysis. MZ, MW, and SY:

investigation. SY: writing—review and editing. QF: supervision. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.1211218/full#supplementary-material

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EDITED BY
Zhendong Liu,
Shandong First Medical University, China

REVIEWED BY
Eduardo Gutiérrez-Abejón,
Universidad de Valladolid, Spain
Dian Novita Chandra,
University of Indonesia, Indonesia

*CORRESPONDENCE
Xiangyu Zhang
✉ xiangyuzhang@csu.edu.cn

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Association between plain water intake and risk of hypertension: longitudinal analyses from the China Health and Nutrition Survey

Shizhen Li, Xun Xiao and Xiangyu Zhang*

Department of Geriatrics, The Second Xiangya Hospital, Central South University, Changsha, Hunan, China

Objective: This study aimed to investigate the prospective association between plain water intake and the risk of hypertension based on a longitudinal cohort study in China.

Methods: Logistic regression analyses were performed to investigate the association between plain water intake and hypertension. Restricted cubic spline model was use to evaluate non-linear relationship between plain water intake and hypertension. Subgroup analyses and interaction tests were conducted based on age, gender, residence site, educational level and tea consumption.

Results: A total of 3,823 participants (46.5% male) with a mean age of 46.8 years from the China Health and Nutrition Survey (CHNS) were assessed and divided into 4 groups based on plain water intake. There was a decreasing trend of hypertension risk as plain water intake increased. Logistic regression analyses indicated that participants consuming plain water ≥6 cups/day (1 cup ≈ 240 mL) had significantly lower risk of hypertension compared to those consuming ≤1 cup/day, even after adjustments for covariates. Restricted cubic spline curve revealed that participants consuming about 6–8 cups/day were at lower risk for developing hypertension. In subgroup analyses, the results were generally consistent with the main findings in participants who aged less than 60 years, who were male, who attained higher education and who were low tea consumers.

Conclusion: Our findings suggested that there might be a favorable effect of plain water intake on preventing hypertension in a large cohort of Chinese adults from the general population. Drinking adequate amounts of plain water (about 6–8 cups/day) may reduce the risk of hypertension, particularly in the selected population. Further interventional studies are required to investigate the potential effect of increasing plain water intake on blood pressure regulation.

KEYWORDS

plain water intake, hydration, hypertension, longitudinal cohort, China Health and Nutrition Survey

1 Introduction

Hypertension represents an increasing global disease burden affecting nearly one third population worldwide (1). It is an important risk factor for incidence and mortality of cardiovascular disease. Despite the increasing prevalence, the proportions of awareness, treatment and control of hypertension are low (2). The etiology of hypertension is complex and involves environmental and pathophysiological factors, as well as genetic conditions (3). Hypertensive patients usually require both lifestyle and pharmacologic intervention. Healthy lifestyle interventions, including healthy diet, normal body weight, exercise training, and non-smoking, are recommended to prevent or control early stage of hypertension and proved to provide health benefits for hypertensive patients (4, 5).

Adequate plain water intake is essential for normal functioning of the human body (6). Recent evidence has demonstrated that maintaining appropriate hydration status is an integral part of healthy lifestyle behaviors for the prevention and management of metabolic diseases (7, 8). Observational studies also suggest that appropriate hydration status could decrease the risk of age-related diseases (9–12). Furthermore, plain water substituting for sugar-sweetened beverages was associated with lower risk of cardiovascular mortality in diabetic patients (13). However, there is no population-based evidence about the association between plain water intake and risk of hypertension. It remains unknown whether high water intake has a favorable effect on blood pressure control. In the present study, we aimed to investigate the association between plain water intake and the risk of hypertension during a follow-up period of 9-year in China Health and Nutrition Survey (CHNS) among Chinese adults.

2 Materials and methods

2.1 Study design and population selection

The CHNS is a population-based longitudinal survey with a multistage, random cluster design across nine provinces (including Jiangsu, Hubei, Hunan, Guangxi, Guizhou, Heilongjiang, Liaoning, Shandong, and Henan) in China. Based on the Qinling Mountains–Huaihe River Line, China is divided into North China and South China geographic areas (14). The nine provinces selected in the original CHNS are distributed in these two regions, Heilongjiang, Liaoning, Shandong and Henan in northern China; Jiangsu, Hubei, Hunan, Guangxi and Guizhou in southern China. All the analyses in this study were based on the data in the wave of 2006 and 2015. Further information on survey procedures and the rationale of the CHNS is in the cohort profile and available at the website.[1] The survey received ethical approval by the Institutional Review Board of the University of North Carolina at Chapel Hill, the National Institute for Nutrition and Food safety at China Center for Disease Control and Prevention, and the Human and Clinical Research Ethics Committee of the China-Japan Friendship Hospital. All participants signed the written informed consents. The detailed information of the CHNS has been published elsewhere (15).

A total of 11,741 participants in the wave of 2006 from CHNS were enrolled. The exclusion criteria of the present study included age less than 18 years old ($n = 1{,}950$), pregnancy ($n = 32$), missing data on plain water and beverage consumption ($n = 2{,}101$), and diagnosed with hypertension or missing data on hypertension ($n = 789$). 3,046 participants lost follow up in the wave of 2015, and 3,823 participants were finally included in the study. The procedure of population selection was depicted in Figure 1.

2.2 Assessment of plain water intake

A frequency questionnaire and the China food composition tables were used to collect daily water intake in the wave of 2006. The questions, "How often did you drink water during the past 30 days?" and "How many cups (1 cup ≈ 240 mL) did you drink per day?" were used for calculating the consumption of plain water.

2.3 Ascertainment of hypertension

Hypertension was identified by the questionnaire-based interview in two surveys in the wave of 2006 and 2015. The question involved in these questionnaires was to collect individual information about the history of hypertension: Has a doctor ever told you that you suffer from high blood pressure? Answering "yes" to the question was defined as having self-reported diagnosis of hypertension and identified with new-onset hypertension in the following survey in 2015.

2.4 Covariates

Demographic data and lifestyle information were obtained by the CHNS questionnaire and physical examination including age, gender, height, weight, beverage consumption, diabetes mellitus, myocardial infarction and stroke. Body mass index (BMI) was calculated as weight (kg)/ height^2 (m^2), and categorized as ≥24 or < 24 kg/m^2 group to evaluate potential effect of overweight/obesity. Smoking status was categorized as past or current smoker, and never. Urbanization was categorized as urban and rural residence. Education level was categorized as junior high school or below, and senior high school or above. Energy intake was calculated from 3-day dietary-recall Chinese food composition tables, and categorized as ≥2,147 or < 2,147 kcal/day group by the median value across participants. Beverage consumption contained alcohol, tea, coffee, soft drinks and sugared fruit drinks. Diabetes mellitus, myocardial infarction and stroke was derived from the questions "Has a doctor ever told you that you suffer from diabetes mellitus, myocardial infarction, or stroke?"

2.5 Analysis

Continuous variables are presented as mean (standard deviation) or median (interquartile range) according to the distribution; categorical variables are presented as frequency (percentage). The trend differences across groups were tested by regression analysis for continuous variables and Cochran-Armitage

1 http://www.cpc.unc.edu/projects/china/home.html

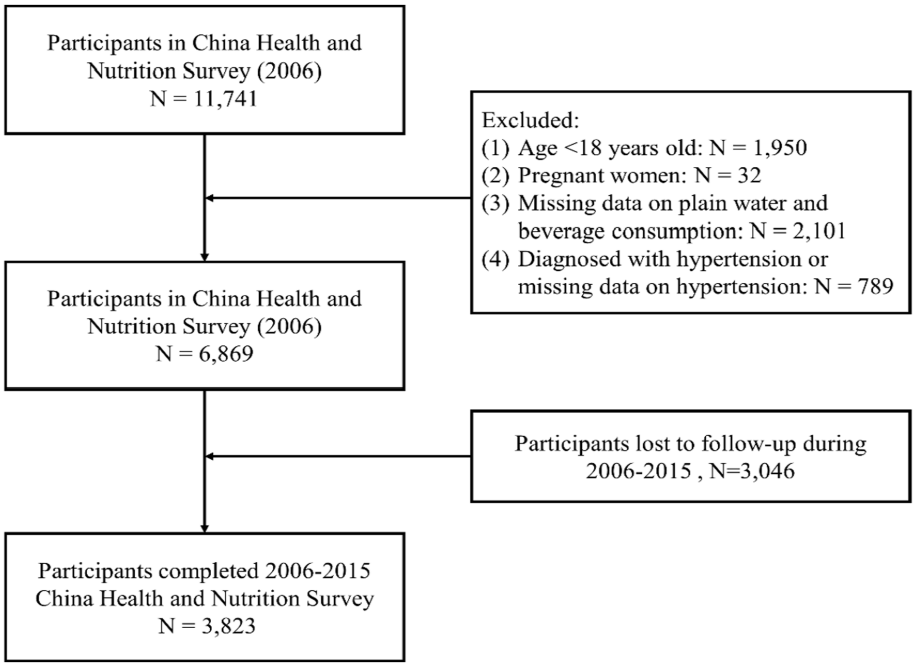

FIGURE 1
The flow diagram of participant selection.

tests for categorical variables. Multivariable logistic regression models were performed to explore whether plain water intake influenced onset risk of hypertension independently. Model 1 was only adjusted by age (≥ 60 or < 60 years), gender (male or female) and BMI (≥ 24 or < 24 kg/m^2). Model 2 was adjusted for factors from Model 1 plus residence site (urban or rural), geographical region (North China and South China), education level (junior high school or below, or senior high school or above), energy intake (≥ 2,147 or < 2,147 kcal/day), smoking status (former or current smoker, or non-smoker), alcohol consumption (yes or no), tea consumption (more than 4–5 times/week or less than 2–3 times/week), coffee consumption (yes or no), and soft drinks or sugared fruit drinks consumption (yes or no). Restricted cubic spline analysis was used to evaluate the dose–response relationship between plain water intake and hypertension. Subgroup analyses based on age, gender, residence site, educational levels and tea consumption were used to evaluate the relationship between plain water intake and hypertension in these subgroups and the potential interaction between plain water intake and these stratified variables. All analyses were performed with R version 4.1.3 (The R Foundation for Statistical Computing, Vienna, Austria). A two-tailed p value <0.05 was determined to be statistically significant.

3 Results

A total of 3,823 Chinese adults with a mean age of 46.8 years and 1777 (46.5%) men were finally included in this study. Participants were divided into four groups: ≤ 1 cup/day, 2–3 cups/day, 4–5 cups/day and ≥ 6 cups/day according to self-reported plain water intake. Demographic and clinical characteristics of all participants across four groups were displayed in Table 1. There was an increasing trend in the proportion of males and urban residence as plain water intake increased. Participants consuming more plain water tended to be younger and educated. The incidence of hypertension was decreased across water intake groups, but not observed in diabetes mellitus, myocardial infarction and stroke. Since plain water and tea intake accounted for the most part of daily fluid intake, participants consuming less plain water were likely to drink more tea. As for other beverages, it was relatively evenly distributed in different water intake groups.

To further explore the relationship between plain water intake and risk of hypertension, multivariate logistic regression analyses were conducted and summarized in Table 2. Taking the ≤ 1 cup/day group as reference, the unadjusted ORs (95% CIs) for 2–3 cups/day, 4–5 cups/day and ≥ 6 cups/day groups were 0.81 (0.64, 1.05), 0.78 (0.58, 1.04), and 0.59 (0.39, 0.89), respectively. There was a decreasing trend for hypertension risk across these groups. Moreover, the results remained similar after adjustments for corresponding covariates in both adjusted model 1 and model 2. As shown in Figure 2, there was no significant non-linear association (P-nonlinear >0.05) between plain water intake and hypertension displayed by restricted cubic spline curve. However, participants consuming about 6–8 cups/day were at lower risk for developing hypertension.

The results of stratified analyses were based on potential confounding factors including age, gender, residence site, educational level and tea intake (Figure 3). By stratifying age, there was only statistically significance of reduced risk of hypertension in ≥ 6 cups/day group in participants aged less than 60 years. Similarly, an inverse association with the risk of hypertension was found in participants who were male, who attained higher education and who consumed tea for less than 2–3 times/week. For participants living in urban residence,

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TABLE 1 Baseline characteristics of participants according to plain water intake.

Variables	Total	≤ 1 cup/day	2–3 cups/day	4–5 cups/day	≥ 6 cups/day	*p* for trend
Participants, *n* (%)	3,823 (100.0)	612 (16.0)	2009 (52.6)	888 (23.2)	314 (8.2)	
Age, years	46.8 (12.8)	48.6 (13.0)	46.9 (12.9)	45.7 (12.5)	45.9 (12.4)	<0.001
Men, *n* (%)	1777 (46.5)	259 (42.3)	935 (46.5)	417 (47.0)	166 (52.9)	0.006
BMI, kg/m^2	23.1 (3.2)	22.9 (3.2)	23.1 (3.3)	23.1 (3.1)	23.2 (3.3)	0.222
Residence site, *n* (%)						<0.001
Urban	1,044 (27.3)	109 (19.8)	520 (25.8)	301 (33.5)	114 (36.1)	
Rural	2,779 (72.7)	503 (80.2)	1,489 (74.2)	587 (66.5)	200 (63.9)	
Geographical region						0.895
North China	1,659 (43.4)	266 (43.5)	859 (42.8)	413 (46.5)	121 (38.5)	
South China	2,164 (56.6)	346 (56.5)	1,150 (57.2)	475 (53.5)	193 (61.5)	
Educational level, *n* (%)						<0.001
Junior high school or below	1,650 (43.2)	295 (48.2)	909 (45.2)	325 (36.6)	121 (38.5)	
Senior high school or above	2,173 (56.8)	317 (51.8)	1,100 (54.8)	563 (63.4)	193 (61.5)	
Energy intake, kcal/day	2,147 (1731, 2,603)	2,100 (1713, 2,577)	2,147 (1718, 2,639)	2,150 (1746, 2,538)	2,205 (1821, 2,592)	0.888
Former or current smoker, *n* (%)	1,182 (30.9)	186 (30.4)	623 (31.0)	266 (30.0)	107 (34.1)	0.534
Alcohol drinking, *n* (%)	1,263 (33.0)	182 (29.7)	684 (34.0)	286 (32.2)	111 (35.4)	0.249
Diabetes mellitus, *n* (%)	26 (0.7)	5 (0.8)	10 (0.5)	9 (1.0)	2 (0.6)	0.655
Myocardial infarction, *n* (%)	9 (0.2)	0 (0.0)	5 (0.2)	2 (0.2)	2 (0.6)	0.113
Stroke, *n* (%)	7 (0.2)	2 (0.3)	5 (0.2)	0 (0.0)	0 (0.0)	0.090
Hypertension, *n* (%)	530 (13.9)	101 (16.5)	278 (13.8)	118 (13.3)	33 (10.5)	0.015
Tea consumption, *n* (%)						<0.001
More than 4–5 times/week	757 (19.8)	187 (30.6)	426 (21.2)	112 (12.6)	32 (10.2)	
Less than 2–3 times/week	3,066 (80.2)	425 (69.4)	1,583 (78.8)	776 (87.4)	282 (89.8)	
Coffee consumption, *n* (%)						0.984
Yes	47 (1.2)	9 (1.5)	23 (1.1)	10 (1.1)	5 (1.6)	
No	3,776 (98.8)	603 (98.5)	1986 (98.9)	878 (98.9)	309 (98.4)	
Soft drinks or sugared fruit drinks consumption, *n* (%)						0.095
Yes	878 (23.0)	112 (18.3)	484 (24.1)	209 (23.5)	73 (23.2)	
No	2,945 (77.0)	500 (81.7)	1,525 (75.9)	679 (76.5)	241 (76.8)	

BMI, body mass index. Continuous variables are presented as mean (standard deviation) or median (interquartile range) according to the distribution; categorical variables are presented as frequency (percentage). The trend differences across groups were tested by regression analysis for continuous variates and Cochran-Armitage tests for categorical variates.

TABLE 2 Association between consumption of plain water intake and the risk of hypertension in the 9-year period cohort: CHNS 2006–2015.

	Crude model		Adjusted model 1		Adjusted mode 2	
Plain water intake	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value
≤ 1 cup/day	Reference		Reference		Reference	
2–3 cups/day	0.81 (0.64, 1.05)	0.101	0.82 (0.64, 1.07)	0.142	0.83 (0.64, 1.08)	0.156
4–5 cups/day	0.78 (0.58, 1.04)	0.084	0.79 (0.58, 1.07)	0.128	0.81 (0.59, 1.10)	0.177
≥ 6 cups/day	0.59 (0.39, 0.89)	0.015	0.60 (0.38, 0.91)	0.020	0.59 (0.37, 0.91)	0.021
P for trend	0.015		0.024		0.031	

OR, odds ratio; CI, confidence interval. Model 1, adjusted for age, gender, BMI. Model 2: adjusted for model 1 covariates plus urban residence, geographical region, educational level, energy intake, smoking status, alcohol consumption, and other beverages consumption.

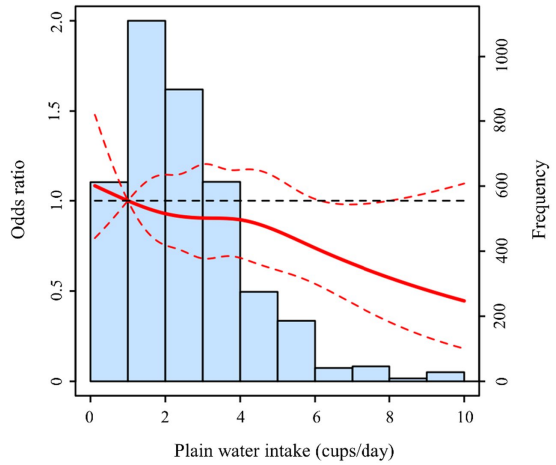

FIGURE 2
Non-linear association between plain water intake and hypertension risk in restricted cubic spline model. The red solid line represented OR, and the red dashed lines represented 95% CI. The model was adjusted by age, gender, BMI, residence, educational level, energy intake, smoking, alcohol consumption, and other beverages consumption.

there was a similar trend in ≥6 cups/day group but without significance. In subgroup analyses, no interaction effect was found among these variables which indicated the results were relatively robust.

4 Discussion

To the best of our knowledge, this study was the first to investigate the association between plain water intake and hypertension in a large-scale, nationwide sample cohort among Chinese adults. In the present study, we found an inverse trend between plain water intake and the risk of hypertension over a follow-up of 9 years. Multivariate logistic regression analyses suggested that participants consuming ≥6 cups/day plain water had significantly lower risk of hypertension than those consuming ≤1 cup/day. In addition, subgroup analyses also found similar relationship in participants who aged less than 60 years, who were male, who attained higher education and who consumed tea for less than 2–3 times/week.

In a recent study published in *British Medical Journal*, Ma et al. found that replacing sugar-sweetened beverages with plain water could lower all cause and cardiovascular mortality in adults with type 2 diabetes (13). Their results highlighted the potential role of plain water to prevent cardiovascular disease risk in diabetic patients. Accumulating evidence has demonstrated that adequate water intake may be favorable for glycemic homeostasis and other health outcomes (16–19). Based on the evidence, the present study investigated the prospective association between plain water intake and the risk of developing hypertension. Our findings supported an independent role of drinking plain water ≥6 cups/day on reducing risk of hypertension. However, the attenuating effect of water intake on hypertension risk was only observed in participants consuming about 6–8 cups per day in restricted cubic spline model. Of note, too few participants consumed more than 8 cups per day, which may undermine statistical power to attain significance. In subgroup analyses, similar results were observed in participants aged less than 60 years, but not in older adults. It implied that low water intake may predispose youngers to develop hypertension later compare to the older adult. Gender differences also exist in this setting where males consuming ≥6 cups/day plain water had lower risk of hypertension compared with those consuming ≤1 cup/day. Interestingly, education attainment had a modifiable effect on the association between plain water intake and hypertension. It can be explained that individuals with the increase of education levels pay more attention in healthy lifestyles and health care. Plain water and tea intake account for the most part of daily fluid intake in Chinese adults. To minimize the influence of tea intake, we divided all participants into high tea consumers (more than 4–5 times/week) and low tea consumers (less than 2–3 times/week), and the results were generally consistent with the main findings in low tea consumers. Targeted water intake interventions in these subgroups might be more effective for the prevention of hypertension.

Plain water intake can be influenced by multiple factors, including age, gender, comorbidities, physical activity and environment (20, 21). In the present study, water intake was strongly associated with age, gender, residence and educational level at baseline. There was an increasing trend in the proportion of males and urban residence as plain water intake increased. Participants consuming more plain water tended to be younger and educated. In line with reason, participants consuming more plain water were likely to drink less tea. Generally, high plain water consumers are known to differ from low plain water consumers in many ways and more inclined to engage in other health-conscious behaviors, which may skew the observed association between plain water intake and hypertension. The beneficial effect of drinking adequate plain water requires confirmation from rigorously designed interventional studies.

Currently, the mechanisms underlying the relationship between plain water intake and hypertension are still elusive. In experimental studies, two disease animal models under conditions of pathological loss of free water developed arterial hypertension, which may be partly attributed to cutaneous vasoconstriction for limiting epidermal water loss (22, 23). Likewise, low water intake induces other type of dehydration, and leads to relative hyperosmolar milieu interne (24). The raised plasma osmolarity could increase blood pressure, both acutely and chronically (25). This state may involve activation of arginine vasopressin pathway which plays a crucial role in water reservation and vasoconstriction (26). Furthermore, maintaining appropriate hydration status is associated with metabolic improvement, which may modulate blood pressure to some extent (27–29). Given that, drinking adequate water seems to be protective from hypertension.

There were several limitations in the study. First, it was an observational study among Chinese adult residents, which was unable to confirm causal relationship between plain water intake and hypertension, and the results may not be generalized to other populations. Second, it was unavailable to eliminate the effects of potential confounding factors, such as family-related factors and socioeconomic status due to the limited information in this retrospective study. Third, there was nearly a decade elapsed since the

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Subgroup		OR(95%CI)	P value	P for interaction
Age				0.223
≥60 years	≤ 1 cup/day	Reference		
	2–3 cups/day	0.70 (0.43-1.12)	0.133	
	4–5 cups/day	0.92 (0.51-1.68)	0.790	
	≥ 6 cups/day	0.89 (0.41-1.90)	0.757	
< 60 years	≤ 1 cup/day	Reference		
	2–3 cups/day	0.93 (0.67-1.29)	0.652	
	4–5 cups/day	0.83 (0.57-1.21)	0.334	
	≥ 6 cups/day	0.52 (0.29-0.92)	0.026	
Gender				0.807
Male	≤ 1 cup/day	Reference		
	2–3 cups/day	0.71 (0.47-1.07)	0.100	
	4–5 cups/day	0.76 (0.48-1.22)	0.262	
	≥ 6 cups/day	0.50 (0.26-0.95)	0.034	
Female	≤ 1 cup/day	Reference		
	2–3 cups/day	0.90 (0.63-1.28)	0.563	
	4–5 cups/day	0.82 (0.54-1.26)	0.375	
	≥ 6 cups/day	0.66 (0.35-1.26)	0.207	
Residence site				0.393
Urban	≤ 1 cup/day	Reference		
	2–3 cups/day	0.81 (0.44-1.47)	0.483	
	4–5 cups/day	0.75 (0.39-1.46)	0.400	
	≥ 6 cups/day	0.42 (0.16-1.09)	0.075	
Rural	≤ 1 cup/day	Reference		
	2–3 cups/day	0.83 (0.62-1.11)	0.216	
	4–5 cups/day	0.82 (0.57-1.19)	0.297	
	≥ 6 cups/day	0.71 (0.42-1.18)	0.185	
Educational level				0.197
Junior high school or below	≤ 1 cup/day	Reference		
	2–3 cups/day	0.82 (0.58-1.18)	0.290	
	4–5 cups/day	0.83 (0.53-1.30)	0.422	
	≥ 6 cups/day	0.93 (0.52-1.67)	0.809	
Senior high school or above	≤ 1 cup/day	Reference		
	2–3 cups/day	0.81 (0.55-1.21)	0.308	
	4–5 cups/day	0.78 (0.49-1.20)	0.248	
	≥ 6 cups/day	0.33 (0.16-0.70)	0.004	
Tea consumption				0.495
More than 4-5 times/week	≤ 1 cup/day	Reference		
	2–3 cups/day	0.94 (0.54-1.62)	0.819	
	4–5 cups/day	1.03 (0.50-2.14)	0.938	
	≥ 6 cups/day	0.92 (0.28-3.06)	0.892	
Less than 2-3 times/week	≤ 1 cup/day	Reference		
	2–3 cups/day	0.78 (0.57-1.06)	0.114	
	4–5 cups/day	0.73 (0.51-1.04)	0.083	
	≥ 6 cups/day	0.53 (0.33-0.87)	0.012	

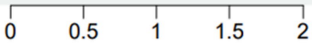

FIGURE 3
The association between plain water intake and hypertension in subgroups. Multivariate logistic analyses were performed in subgroups based on age (≥ 60 or < 60 years), gender (male or female), residence site (urban or rural), educational levels (junior high school or below, or senior high school or above) and tea consumption (more than 4–5 times/week or less than 2–3 times/week) after adjustments for covariates.

cut-off date of our study design, which might result in a potential bias due to this time gap. Long-term studies of healthy water intake interventions are needed to evaluate the potential effect of optimal hydration status on hypertension in the future.

5 Conclusion

In summary, our findings suggested that there might be a favorable effect of plain water intake on preventing hypertension in a large cohort of Chinese adults from the general population. Drinking adequate amounts of plain water (about 6–8 cups/day) may reduce the risk of hypertension, particularly in the selected population. Further interventional studies are required to investigate the potential effect of increasing plain water intake on blood pressure regulation.

Data availability statement

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

Ethics statement

The studies involving humans were approved by the Institutional Review Board of the University of North Carolina at Chapel Hill, the National Institute for Nutrition and Food safety at China Center for Disease Control and Prevention, and the Human and Clinical Research Ethics Committee of the China-Japan Friendship Hospital. 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

SL: Data curation, Formal analysis, Writing – original draft. XX: Visualization, Writing – original draft. XZ: Conceptualization, Funding acquisition, Writing – review & editing.

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Conflict of interest

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

Publisher's note

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EDITED BY
Zhendong Liu,
Shandong First Medical University, China

REVIEWED BY
Silvana Funghetto,
University of Brasilia, Brazil
Abbas Malandish,
Urmia University, Iran

*CORRESPONDENCE
Rafi Alnjadat
✉ rafi.alnjadat@bau.edu.jo

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Level of adherence to diet and physical activity among menopausal women and influencing factors in Jordan: a descriptive cross-sectional study

Rafi Alnjadat*, Eshraq Al Momani, Mohammad Etoom, Falastine Hamdan and Salwa Abu ALrub

Department of Applied Health Sciences, Al-Balqa Applied University, Al-Salt, Jordan

Background: During menopause, a woman's lifestyle may change significantly, which will have implications on her quality of life. Women will experience menopause for more than a third of their life; therefore, maintaining good health during this period is crucial. A healthy diet and physical activity can help women maintain their health during menopause. Hence, assessing adherence to a healthy diet and physical activity among menopausal women is important.

Purpose: This study aims to assess the degree of adherence to a healthy diet and physical activity of menopausal women in Jordan and determine the most influential factors.

Methods: A descriptive cross-sectional design was used in this study, and an online self-administered questionnaire was sent to 299 menopausal women selected through simple random sampling. A valid and reliable questionnaire was used to assess the menopausal women's adherence to a healthy diet and physical activity. The questionnaire consisted of 14 items covering two domains: 12 questions for the diet domain and two questions for the physical activity domain. Descriptive statistics were obtained, mean weight and body mass index (BMI) were calculated, and stepwise regression was conducted for the data analysis.

Results: The overall degree of adherence to a healthy diet and physical activity of the women was moderate (49.25, $SD = 7.17$). Most of the participants reported eating refined food items once a month or less ($n = 188$, 62.9%) and not exercising weekly ($n = 119$, 39.8%), and only a few reported eating refined food items at least once a day ($n = 5$, 1.7%) and exercising 5–6 times a week ($n = 15$, 5%). The regression analysis showed that age ($B = 0.145$, $p = 0.014$), having two children ($B = 0.123$, $p = 0.034$) and completing primary or secondary education ($B = 0.120$, $p = 0.038$) were statistically significant and the strongest predictors of adherence. The predictors accounted for 68% of the variance in adherence to a healthy diet and physical activity ($R^2 = 0.068$, F [343.54] = 7.123, $p = 0.000$).

Conclusion: The majority of the middle-aged menopausal women in this study showed moderate adherence to a healthy diet and physical activity. Age, having two children and completing primary or secondary education were associated with degree of adherence to a healthy diet and physical activity. Therefore, healthcare intervention, such as physical activity and dietary control programs, should target women in this age group and stage in life.

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KEYWORDS

diet, exercise, menopause, physical activity, women

Introduction

Menopause is a natural transitional period that affects around 1.5 million women annually (1). Menopause is defined as the permanent cessation of ovulation and reduction in estrogen and progesterone owing to diminished ovarian activity (2). The key diagnostic criterion for menopause is the absence of menstrual bleeding within a 12-month period (3). In reality, women spend one third of their life in menopause (4).

Menopause typically begins around the age of 40–60 years (5). The international average age of menopause is 51 years (6). Specifically, the average age of menopause is 51.3 years in European countries, 52.5 years in United States, 48.3 years in South American countries and 51.09 years in Asian countries (7). In Jordan, the average age of natural menopause is 48.5 ± 5.0 years (8). However, the age at menopause may be influenced by the age at menarche, the number of pregnancies, menstrual cycle irregularity, the use of hormonal therapy, the body mass index (BMI), physical activity, smoking, alcohol consumption, socioeconomic status and education level (9, 10).

Estrogen can influence endothelial functions, blood vessel tone and heart functions, as well as the lipid profile and inflammatory status (11). During menopause transition, women may experience troublesome symptoms such as sleep disorders, fluctuating moods, anxiety, fatigue, joint pain, sexual dysfunction, and heart palpitations (12). In addition, vaginal dryness, hot flashes and night sweats are the most frequently reported symptoms (10). Furthermore, the menopausal age is associated with various comorbidities and chronic diseases (13), such as obesity, cardiovascular disease, diabetes, chronic pulmonary disease, osteoporosis, mental illness, depression, dementia and premature death (14–16). Menopause was also reported to be a risk factor of metabolic syndrome (2). Therefore, the proper conditioning of menopausal women's bodies is important to alleviate symptoms and prevent chronic diseases (17). However, several studies found that regular exercise and food control can alleviate menopausal symptoms and enhance quality of life (18), and obesity and lack of physical activity are associated with decreased quality of life (19).

Certain structural changes that occur in the body during menopause cannot be ameliorated; however, behavior, and lifestyle, specifically, nutrition and physical activity, are among the factors that can be corrected, which can reduce the risk of comorbidities and chronic diseases (20). Adequate nutrition, along with lifestyle adjustment, can help women maintain their health during menopause (21). In addition, adherence to a healthy diet can reduce the risk of metabolic syndrome, heart disease, diabetes, and cancer (22). Similarly, adherence to physical activity may minimize the adverse effect of menopausal symptoms and improve mental health (23). Physical activity may also help reduce weight gain caused by menopause and aging, risk of heart disease and other physical and psychological symptoms, such as body discomfort, exhaustion, poor sleep, and depression (11, 12).

Conversely, insufficient diet and poor physical activity can lead to weight gain and obesity (24), which can increase risk of metabolic diseases and metabolic syndrome and decrease quality of life (6, 19). Therefore, women must maintain a healthy lifestyle, including engaging in exercise; eating low-calorie and low-sodium foods, food that contains appropriate amounts of calcium and vitamin D and fruits, vegetables and fish; and avoiding smoking (25).

Studies have yet to examine factors that can affect adherence to a healthy diet and physical activity among menopausal women in Jordan. Therefore, this study aims to:

I. Assess the degree of adherence to a healthy diet and physical activity of menopausal women in Jordan.
II. Determine the most influential factors affecting degree of adherence to a healthy diet and physical activity of menopausal women in Jordan.

Methods

Design and setting

A descriptive cross-sectional design using an online self-administrated questionnaire was employed in this study to assess the degree of adherence to a healthy diet and physical activity of menopausal women and determine the most influential factors. A sample of 299 menopausal women between the ages of 40 and 60 years were recruited from the northern region. The age range is compatible with the natural age of menopause of women in Jordan, regardless of their marital status, education level, income, and health insurance availability.

Participants

Probability random sampling through an online questionnaire was conducted to select the participants. The inclusion criteria were as follows: women who were able and willing to participate in the study, her ages are above 40 and less than 60, women who had their last menstrual period 12 months ago and women who could read Arabic. Women with a mental illness, who took medications affect mentality, who experienced artificial menopause owing to radiation, a hysterectomy or an oophorectomy, following a specialized diet were excluded from the research.

The sample size was calculated using a power analysis software based on the medium effect size, the 0.05 significance level and a power level of 0.8 and multiple regression for 15 predictors. Therefore, the sample size should be at least 139 participants (26). The oversampling was intended to overcome attrition or the problem of incomplete responses. Hence, the sample size was set to 167 women.

Google Forms was used for the data collection, and Excel was employed for the data extraction and recording. The participants were recruited via social media and email, that is, the link to the questionnaire was sent to the participants via social media, such as Facebook and WhatsApp. The questionnaire required around 10 min

to answer. However, to minimize the risk of response bias, the questionnaires were filled out electronically by participants in the study using a specified tablet.

Ethical considerations

Approval to collect data was obtained from the Institution Review Board of the Al-Balqa Applied University (number). An online consent form was obtained from each of the participants. The researchers explained the purpose of the study and the expected results and informed the participants that their participation was voluntary, and they had the right to refuse or withdraw from the study at any time without explanation and penalty. Furthermore, the researchers assured the participants that their responses would be confidential.

Measurement tool

The first part of the instrument collected the participants' demographic data [i.e., age, education level, employment status, place of residence, governorate, marital status, number of births, economic status, chronic disease, whether they smoked, what they smoked, whether they had undergone hormonal therapy, height, weight, and body mass index (BMI)].

The second part of the instrument, which was developed by Dubasi et al. (27), assessed the women's adherence to a healthy diet and exercise. The questionnaire consisted of 14 items covering two domains: 12 questions for the diet domain and two questions for the physical activity domain (27).

The responses were measured on a five-point Likert scale (1–5), and the participants with healthy dietary and physical activity habits received a high score, whereas those with poor dietary and physical activity habits received a low score. The score for each question was added to determine the final score (27).

In this study, the scoring system used intervals based on quartiles to determine the degree of adherence to a healthy diet and exercise. A total mean score percentage ranging from 0 to 33.99% indicated poor adherence, a score percentage ranging from 34 to 66.99% indicated moderate adherence and a score percentage of more than 66% indicated satisfactory adherence.

The questionnaire was a valid and reliable tool for assessing adherence to a healthy diet and exercise, the exploratory factor analysis result explained 69.07% of the variance and Cronbach's alpha was 0.94, which indicated an acceptable internal consistency (27). Furthermore, two qualified translators were recruited to translate the tool into Arabic, and two other qualified translators were recruited to back translated to English and approve the content and format.

A pilot study was conducted to check the readability and psychometric properties of the translated questionnaire. The pilot study involved 11 participants (their data were excluded from the final analysis). The Cronbach's alpha of the questionnaire was above 0.64.

Data analysis

Statistical Package for Social Sciences (SPSS; version 26) for Windows was used for the data analysis. Descriptive statistics (mean, standard deviation, and frequency) were used to describe and review the demographic data based on the level of the measurements. Inferential statistics through simple and general stepwise regression were used to identify the factors that may affect adherence to physical activity and a healthy diet among the menopausal women.

Results

Participants demographic characteristics

The questionnaire was distributed to 311 menopausal women, 299 of whom completed and returned the questionnaire; thus, the response rate was 96.1%. The mean age of the participants was 44.90 years ($SD = 7.71$), and most of the participants held a BSC degree and a postgraduate degree ($n = 153$, 51.2).

The majority of the participants was a housewife ($n = 155$, 51.8%), was married ($n = 247$, 82.6), lived in town ($n = 202$, 67.6), was from the Irbid Governorate ($n = 227$, 75.9), had three or more births ($n = 222$, 74.2), was a nonsmoker ($n = 257$, 86) and had never undergone hormonal therapy ($n = 235$, 84.6).

Most of the participants in this study were unemployed and expressed dissatisfaction with their monthly income, which ranged from JOD 400 to JOD 800. In addition, the majority of the study participants did not report any chronic disease ($n = 196$, 65.6). The height of the participants was $M = 1.61$ ($SD = 0.075$), their weight was $M = 75.2$ ($SD = 14.6$) and their body mass index (BMI) was $M = 28.9$ ($SD = 5.74$). Table 1 presents the detailed demographic characteristics of the participants.

Adherence to diet and exercise

The overall total mean score of the menopausal women for adherence to a healthy diet and physical activity was 49.25 ($SD = 7.17$). Specifically, the observed mean score for adherence to a healthy diet was 41.3 ($SD = 7.21$), and the observed mean score for adherence to exercise was 7.86 ($SD = 2.19$; Table 2).

Regarding the adherence to a healthy diet and exercise questionnaire items, more than half of the participants (188, 62.9%) reported eating refined food items once a month or less, 174 (58.2%) reported dining out less than once a month, 167 (55.9%) reported eating three meals a day and 160 (53.5%) reported eating ghee, butter, cream and mayonnaise once a month or less (Table 3).

Meanwhile, a few of the participants (30; 10%) reported eating salty snacks 3–6 times a week; 30 (10%) reported eating saturated fats 2–3 times a month; 29 (9.7%) reported eating sprouted pulses and green vegetables in every meal as their main diet; 28 (9.4%) reported consuming sugar in their coffee and tea 3–6 times a week; 18 (6%) reported eating fruits and a salad less than once a week; 17 (5.7%) reported drinking sweetened beverages 3–6 times a week; 16 (5.4%) reported eating fried food at least once a day; 11 (3.7%) reported eating ghee, butter, cream, and mayonnaise at least once a day and 3–6 times a week; 8 (2.7%) reported dining out more than three times a week; and 5 (1.7%) reported eating refined food items at least once a day.

In terms of exercise, most of the participants (119; 39.8%) reported not exercising weekly, and 146 (48.8%) reported participating

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TABLE 1 Participants demographic characteristics.

Variable	Frequency (*F*)	Percentage (%)	Mean	*SD*
Age			44.90	7.71
Educational level				
- Illiterate	6	2		
- Primary or secondary	79	26.4		
- Diploma	61	20.4		
- BSC and postgraduate	153	51.2		
Employment status				
- Employee	138	46.2		
- Housewife	155	51.8		
- Other	6	2		
Place of residence				
- Village	97	32.4		
- Town	202	67.6		
Governorate				
- Irbid	227	75.9		
- Ajlun	40	13.4		
- Jerash	26	8.7		
- Al Mafraq	6	2		
Marital status				
- Married	247	82.6		
- Single	14	4.7		
- Widow	17	5.7		
- Divorced	21	7		
Number of births				
- Nulliparous	26	8.7		
- One	22	7.4		
- Two	29	9.7		
- Three or more	222	74.2		
Economic status				
- Less than 400 JD	110	36.8		
- Between 400 and 800 JD	110	36.8		
- More than 800 JD	79	26.4		
Chronic disease				
- Yes	103	34.4		
- No	196	65.6		
Smoking				
- Yes	42	14		
- No	257	86		
Smoking type				
- Cigarettes	21	7.0		
- Bubbly	19	6.4		
- Electronic cigarettes	2	0.7		
Hormonal thereby				
- Yes, now	30	10		
- Yes, previously	16	5.4		
- No	235	84.6		

(Continued)

TABLE 1 (Continued)

Variable	Frequency (*F*)	Percentage (%)	Mean	*SD*
Height (M)			1.61	0.075
Weight (Kg)			75.22	14.61
Body mass index			28.96	5.747

$N = 299$.

TABLE 2 Level of adherence to diet and exercise.

	Number of items	Actual total score	Mean for observed total score	*SD*
Diet	12	12–60	41.3	7.21
Exercise	2	2–10	7.86	2.19
Total	14	14–70	49.25	7.17

$N = 299$.

in an exercise session that lasted less than 10 min. Few participants reported exercising 5–6 times a week (15; 5%), and 20 (6.7%) reported participating in an exercise session that lasted more than 40 min.

Factors predicting adherence to diet and physical activity

The results of the simple linear regression analysis revealed that age ($B = 0.206$, $p = 0.000$), completing primary or secondary education ($B = 0.146$, $p = 0.010$), having BSC and postgraduate degrees ($B = -0.148$, $p = 0.009$), having two children ($B = -0.167$, $p = 0.003$), smoking electronic cigarettes ($B = -0.119$, $p = 0.036$) and body mass index (BMI) ($B = 0.136$, $p = 0.019$) were significant predictors of adherence to a healthy diet and physical activity (Table 4). All the predictors with a $p < 0.25$ value were entered into another model for the stepwise regression analysis.

The results of the general stepwise regression revealed that age ($B = 0.145$, $p = 0.014$), having two children ($B = 0.123$, $p = 0.034$) and completing primary or secondary education ($B = 0.120$, $p = 0.038$) were statistically significant and the strongest predictors of adherence. The predictors accounted for 68% of the variance in adherence to a healthy diet and physical activity ($R^2 = 0.068$, F [343.54] = 7.123, $p = 0.000$; Table 5).

Result from general stepwise regression revealed that age ($B = 0.145$, $p = 0.014$), had two children ($B = 0.123$, $p = 0.034$), had a primary or secondary education ($B = 0.120$, $p = 0.038$), are statistically significant and strongest and predictors. These predictors account for 68% variance in adherence to diet and physical activity ($R^2 = 0.068$, F (343.54) = 7.123, $p = 0.000$; Table 5).

Discussion

This study aims to assess the degree of adherence to a healthy diet and physical activity of menopausal women in Jordan and determine the most influential factors. Healthy diet and exercise can play a vital role in the health of women during menopause. Adherence to a healthy diet and exercise can minimize the risk of chronic diseases and comorbidities and play a crucial role in managing lifestyle-related diseases (27).

In this study, the women's degree of adherence to a healthy diet and exercise was moderate, this could be related to that most of study participants were married and housewife's, which means they spend most of their time doing housework and taking care of family. In addition, this may be related to their different health status, ages, education levels and levels of awareness of the benefits and advantages of a healthy diet and exercise. Physical activity was influenced by the women's age, place of residence, education level, occupation, marital status, body mass index (BMI), parity and socioeconomic status (4, 28). This result is consistent with that of previous studies that observed moderate physical activity among the participants (6, 9, 29). By contrast, other studies observed sedentary physical activity and poor diet among their study participants (30–33).

A healthy diet consists of food with fiber, water, vitamins, minerals, proteins, carbohydrates, and fats (29). A healthy diet can reduce the risk of diseases and enhance quality of life (34). Moreover, adequate nutritional fulfillment can considerably reduce the negative consequences of menopause (29). The results of the present study revealed that more than half of the participants ate refined food items once a month or less, dined out less than once a month, ate three meals a day and ate ghee, butter, cream, and mayonnaise once a month or less. This result was satisfactory, because insulin resistance is likely to develop in individuals who consume large amounts of refined carbohydrates (14). Consumption of refined grains, foods high in saturated fats, desserts, and beverages sweetened with sugar can result in severe menopausal symptoms (35). Thus, a possible explanation for the result is that most of the participants were housewives and highly educated. This result is consistent with that of a previous study that found that most of the participants did not skip meals and followed a meal pattern (33, 36). Furthermore, a previous study determined that the intake of mayonnaise and liquid oils of the participants was high (37). By contrast, another study observed that high-calorie foods such as fats, bread, cereals, sweets, meat and oil were consumed in excess amounts by the participants (9), and Tasleem et al. (38) reported that the most consumed food group in their study was dairy.

Meanwhile, few participants reported eating salty snacks 3–6 times a week, eating saturated fats 2–3 times a month, eating sprouted pulses and green vegetables in every meal as their main diet, consuming sugar in their coffee and tea 3–6 times a week, eating fruits and a salad less than once a week, drinking sweetened beverages 3–6 times a week and eating fried food at least once a day. This result

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TABLE 3 Adherence to diet and exercise in different items.

Item	*F (%)*
1. How often do you eat meals in a day (including tea, coffee, fruits, salads, snacks)?	
A. >6 times	14 (4)
B. 6 times	12 (4.7)
C. 5 times	41 (13.7)
D. 4 times	65 (21.7)
E. 3 times	167 (55.9)
2. How often do you drink sweetened beverages like soft drinks, juices, etc.?	
A. At least once daily	80 (26.8)
B. 3–6 times a week	17 (5.7)
C. 1–2 times a week	70 (23.4)
D. 2–3 times a month	44 (14.7)
E. Once a month or less	88 (29.4)
3. How often do you eat sweets such as Laddu, Barfi, Jalebi, Kulfi, Chocolate, Halwa, Rice pudding, etc.?	
A. At least once daily	113 (37.8)
B. 3–6 times a week	41 (13.7)
C. 1–2 times a week	69 (23.1)
D. 2–3 times a month	34 (11.4)
E. Once a month or less	42 (14)
4. How often do you eat fried foods such as Puri, Parathas, Kachori, Tikki, Bhature, Pakoras, Samosas etc.?	
A. At least once daily	16 (5.4)
B. 3–6 times a week	36 (13)
C. 1–2 times a week	99 (33.1)
D. 2–3 times a month	58 (19.4)
E. Once a month or less	87 (29.1)
5. How often do you eat high salty snacks such as Namkeen, Bhujia, Pickles, Chutney, Papad etc.?	
A. At least once daily	26 (8.7)
B. 3–6 times a week	30 (10)
C. 1–2 times a week	84 (28.1)
D. 2–3 times a month	62 (20.7)
E. Once a month or less.	97 (32.4)
6. How often do you consume sugar and honey in tea, coffee, curd, lassi, etc.?	
A. At least once daily	96 (32.1)
B. 3–6 times a week	28 (9.4)
C. 1–2 times a week	42 (14)
D. 2–3 times a month	29 (9.7)
E. Once a month or less.	104 (34.8)
7. How often do you eat fruit and salad?	
A. Every time in the main diet	42 (14)
B. At least once a day	118 (39.5)
C. 3–4 times a week	85 (28.4)
D. 1 time a week	36 (12)
E. Less than once a week	18 (6)
8. How often do you eat sprouted pulses and green vegetables?	
A. Every time in the main diet	29 (9.7)
B. At least once a day	43 (14.4)
C. 3–4 times a week	93 (31.1)
D. 1 time a week	94 (31.4)
E. Less than once a week	40 (13.4)
9. How often do you eat saturated fat like mutton fat, egg yolks, etc.?	
A. At least once daily	57 (19.1)
B. 3–6 times a week	72 (24.1)
C. 1–2 times a week	101 (33.8)
D. 2–3 times a month	30 (10)
E. Once a month or less	39 (13)
10. How often do you eat refined food items like burgers, pizza, etc.?	
A. At least once daily	5 (1.7)
B. 3–6 times a week	7 (2.3)
C. 1–2 times a week	33 (11)
D. 2–3 times a month	66 (22.1)
E. Once a month or less	188 (62.9)
11. How often do you eat ghee, butter, cream, mayonnaise, etc.?	
A. At least once daily	11 (3.7)
B. 3–6 times a week	11 (3.7)
C. 1–2 times a week	49 (16.4)
D. 2–3 times a month	68 (22.7)
E. Once a month or less	160 (53.5)
12. How often do you eat out of the house (such as wedding, party, family function etc.)?	
A. More than 3 times a week	8 (2.7)
B. More than once a week	20 (6.7)
C. 2 times in a month	46 (15.4)
D. 1 time in a month	51 (17.1)
E. Less than 1 time in a month	174 (58.2)
13. How many days do you exercise in a week?	
A. Daily	23 (7.7)
B. 5–6 times a week	15 (5)
C. 3–4 times a week	38 (12.7)
D. 1–2 times a week	104 (34.8)
E. Never	119 (39.8)
14. How much time do you exercise for each session?	
A. >40 min	20 (6.7)
B. 30–40 min	39 (13)
C. 20–30 min	31 (10.4)
D. 20–10 min	63 (21.1)
E. <10 min	146 (48.8)

N = 299.

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TABLE 4 Predictors of adherence to diet and physical activity using simple linear regression.

		For predictor				For model			
	Predictors	Coefficients Beta	*t*	*p*	*F*	*p*	*R*	R^2	Adjusted R^2
	Age	0.206	3.68	**0.000****	13.56	0.000	0.206	0.042	0.039
	Educational level								
	- Illiterate vs. primary or secondary	0.146	2.58	**0.010****	6.68	0.010	0.146	0.021	0.018
	- Illiterate vs. diploma	0.019	0.329	0.742	0.108	0.742	0.019	0.000	−0.003
	- Illiterate vs. BSC and postgraduate	−0.148	−2.635	**0.009****	6.943	0.009	0.148	0.022	0.019
Model 1	Employment status								
	- Employee vs. housewife	0.065	1.148	0.252	1.317	0.252	0.065	0.004	0.001
	- Employee vs. other	0.028	0.498	0.619	0.248	0.619	0.028	0.001	−0.002
	Place of residence								
	- Village = 0	0.080	1.405	0.161	1.973	0.161	0.080	0.006	0.003
	- Town = 1								
	Governorate								
	- Irbid vs. Ajlun	−0.036	−0.623	0.530	0.395	0.036	0.001	−0.002	−0.530
	- Irbid vs. Jerash	0.022	0.381	0.703	0.145	0.703	0.022	0.000	−0.003
	- Irbid vs. Al-Mafraq	−0.032	−0.556	0.578	0.310	0.578	0.032	0.001	−0.002
	Marital status								
	- Married vs. single	0.013	0.224	0.823	0.050	0.823	0.013	0.000	−0.003
	- Married vs. widow	0.092	1.615	0.107	2.609	0.107	0.092	0.008	0.005
	- Married vs. divorced	−0.044	−0.776	0.438	0.602	0.438	0.044	0.002	−0.001
	Number of births								
	- Nulliparous vs. one	0.031	0.546	0.585	0.298	0.585	0.031	0.001	−0.002
	- Nulliparous vs. two	−0.167	−2.976	**0.003****	8.855	0.003	0.167	0.028	0.025
	- Nulliparous vs. three or more	0.088	1.556	0.121	2.421	0.121	0.088	0.008	0.005
Model 1	Economic status								
	- Less than 400 vs. between 400–800	−0.070	−1.227	0.221	1.506	0.221	0.070	0.005	0.002
	- Less than 400 vs. more than 800	0.023	0.407	0.684	0.166	0.684	0.023	0.001	−0.003
	Chronic disease								
	- Yes = 0	−0.071	−1.241	0.216	1.539	0.216	0.071	0.005	0.002
	- No = 1								
	Smoking								
	- Yes = 0	0.036	0.641	0.522	0.411	0.522	0.036	0.001	−0.002
	- No = 1								
	Smoking type								
	- Cigarette vs. bubbly	−0.055	−0.959	0.338	0.920	0.338	0.055	0.003	0.000
	- Cigarette vs. electronic cigarette	−0.119	−2.103	**0.036****	4.424	0.036	0.119	0.014	0.011
	Hormonal therapy								
	- Yes, now vs. yes previously	−0.002	−0.031	0.975	0.001	0.975	0.002	0.000	−0.003
	- Yes, now vs. no	−0.069	−1.220	0.223	1.488	0.223	0.069	0.005	0.002
	Body mass index (BMI)	0.136	2.364	**0.019****	5.589	0.019	0.136	0.018	0.015

$p < 0.05$ (two-tailed). Significant value of less than 0.05.

indicated that the participants had poor dietary habits. Low fruit and vegetables intake can affect bone density and thus increase the risk of osteoporosis. Fruits and vegetables include antioxidants that can mitigate the negative effects of reactive oxygen species on the quantity and quality of ovarian follicles; thus, they can lengthen the reproductive lifespan (32). In addition, low-intensity menopausal symptoms are associated with high consumption of healthy grains and vegetables (34). To avoid heart and metabolic problems, the

TABLE 5 Predictors of adherence to diet and physical activity using stepwise linear regression.

	Predictors	Coefficients Beta	(95%CI)	*t*	*p*	*F*	*p*	*R*	R^2	Adjusted R^2
	Age	0.145	(0.025, 216)	2.749	**0.014****					
Model 2	Number of births									
	- Nulliparous vs. two	0.123	(−5.709, −0.218)	−2.124	**0.034****	7.123	0.000	0.260	0.068	0.058
	Educational level									
	- Illiterate vs. primary or secondary	0.120	(0.115, 3.850)	2.089	**0.038****					

Model 2: F (343.54) = 7.123; df = (3); R^2 = 0.068; Adjusted R^2 = 0.058, p = 0.000 (two-tailed). Significant value of less than 0.05.

appropriate consumption of calcium and foods containing calcium, such as dairy products, fruits, and vegetables, should be emphasized (39). Thus, early nutritional instruction is required, because a woman's bad eating habits may continue into the menopausal stage (34).

This result is consistent with that of a previous study that found that the intake of fruits and vegetables was low among the participants (9, 32, 34, 36, 38, 40). Conversely, another study reported the lowest intake for proteins, carbohydrates, fats, calcium, magnesium, phosphorus and iron among its participants (33).

High and low levels of physical activity can impact estrogen production. Therefore, women should be encouraged to consider their degree of physical activity (29). The results of the present study revealed that most of the participants did not exercise weekly, and each exercise session lasted less than 10 min. Meanwhile, few participants reported exercising 5–6 times a week, with each exercise session lasting more than 40 min. This result may be explained by the overweight state and age of the participants. The skeletal muscle fatty acid intake system and β oxidation pathways are activated during exercise, which can help enhance energy expenditure and reduce body fat (17). The absorption and use of glucose by skeletal muscles can be boosted by exercise (17). Thus, exercise is important for weight loss and can minimize the risk of comorbidities. This result is consistent with that of a previous study that showed that the majority of the female participants did not engage in physical activity (14, 32). By contrast, Lewandowska et al. (19) reported that the majority of the participants in their study had an adequate level of exercise, that is, more than 600 metabolic equivalents min/week.

According to the study results, a relationship existed between age, completing primary or secondary education, having BSC and postgraduate degrees, having two children, smoking electronic cigarettes, the body mass index (BMI), and adherence to a healthy diet and physical activity during menopause.

In this study, a positive relationship was observed between age and adherence to a healthy diet and physical activity, which may be related to the women's understanding of the importance of adherence owing to their wisdom and life experiences, which may increase their awareness of the benefits of long-term adherence. In addition, having a healthy lifestyle and well-being are prioritized with age. The mean age of the study participants was 44.90 years, which is consistent with that in a previous study in Jordan that recorded the mean age at 48.5 ± 5.0 years (8). Al-Smadi (6) reported that women between the ages of 45 and 50 years accounted for the highest proportion of the total population of menopausal women in Jordan. This result is similar to that of Ranasinghe et al. (32), who recorded the mean age as 49.9 ± 3.9 years, and that of Tiwari et al. (33), who recorded the mean age as 48.58 ± 3.38 years. However, in the study of Assaf et al. (1), the mean age of the Jordanian female participants was 50.5 ± 4.8 years. Meanwhile, Chen et al. (41), Dunneram et al. (14), Moradi et al. (42), Nournezhad et al. (9), and Ozcan (25) found that the mean age of the participants in their study was above 50 years. Conversely, other studies reported a mean age of less than 45 years (43).

Women with a high education level may be highly knowledgeable about health-related topics and healthy lifestyles (25). Thus, women's health promotion and preventative behaviors were found to be positively affected by their education level (44). In addition, highly educated women may be conscious of menopausal symptoms and the psychological and physical changes that occur during menopause (45). In the present study, most of the participants had BSC and postgraduate degrees, but a negative relationship was observed between having BSC and postgraduate degrees and adherence to a healthy diet and physical activity, and a positive relationship was observed between completing primary or secondary education and adherence to a healthy diet and physical activity. This result contradicts the belief that a woman with a high education level will demonstrate high adherence, which may be related to the different sample sizes between the two categories. Moreover, a high percentage of the study participants were employees, had three or more births and had low or middle-level income. Such factors may limit the women's time and money for adherence to a healthy diet and physical activity. This result is similar to that of a previous study in Jordan that reported that most of the female participants had a BSC degree (1, 8). Previous studies also found that most of the female participants completed primary education or had an education level that was below high school (9, 19, 25, 32, 33, 41, 43).

In this study, most of the participants were married, were housewives and had more than three children, which may explain their lack of physical activity and exercise. In addition, a positive relationship was observed between having two children and adherence to a healthy diet and physical activity. This result contradicts previous findings that revealed that having children may prevent women from exercising regularly and having a healthy lifestyle (41). Jordanian women are responsible for various aspects of their family life, including caring for their grandchildren and their aging parents and in-laws (1). The result of the present study is consistent with that of a previous study that found that most of the menopausal participants were married (1, 8, 32, 33, 41, 43). Another study in Jordan observed that most of the menopausal participants were housewives and had children (8). More et al. (36), Nournezhad et al. (9), Ozcan (25), Ranasinghe et al. (32), and Tasleem et al. (38) also found that most of the menopausal women in their study were housewives. However, Assaf et al. (1) reported that most women in Jordan were employed and had five or more children. Other studies reported that most menopausal women were retired and had two children (19).

Employment can increase a woman's total family income and empowerment (1). Women's satisfaction with their income is reflected in their use of health services and compliance with preventive health measures (46). In the present study, most of the participants had a monthly income of less than JOD 800. However, Bustami et al. (8) found that most menopausal women in Jordan had a monthly income of less than JOD 500. Ranasinghe et al. (32) reported that most of their study participants were from the upper and upper-middle class. However, Assaf et al. (1) found that perceived family income in Jordan was unsatisfactory, and Tiwari et al. (33) observed that the economic status of their research participants was low.

In the present study, most of the participants were nonsmokers and had never undergone hormonal therapy, which are in line with the results of a previous study in Jordan that reported that most of the female participants were nonsmokers and had never undergone hormonal therapy (8). Galfo et al. (43), Lewandowska et al. (19), Nournezhad et al. (9), Ozcan (25), and Ponichter et al. (34) also found that most women are nonsmokers. However, in the present study, a significant negative relationship was observed between electronic cigarette smoking and adherence to a healthy diet and physical activity. This finding may be related to the fact that electronic cigarettes contain nicotine, which is an addictive substance that may affect the brain chemistry and distract women from maintaining their healthy lifestyle habits. Another factor that may cause women to ignore the importance of adherence to a healthy diet and physical activity may be the false claims made by electronic cigarettes, such as optimism, relaxation and stress relief.

The mean body mass index (BMI) of the study participants was 28.96, which meant that they were overweight. This finding could be related to the participants' lack of regular physical activity, as most reported that they never exercised, and those who exercised reported participating in an exercise session that lasted less than 10 min. However, physical activity can reduce the risk of obesity (41). Thus, interventions to improve physical activity should be suggested to address the increasing prevalence of obesity (32). This result is similar to that of Bustami et al. (8), who found that the majority of Jordanian menopausal women is overweight. Previous studies also reported the overweight state of their female participants (15, 19, 25, 34). Another study reported that 93% of its female participants had a higher-than-normal body mass index (BMI) (9), but other studies reported standard and normal BMIs among their participants (14, 32, 38, 41, 43).

Strength and limitations

The present study is the first to assess the degree of adherence to a healthy diet and physical activity of menopausal women in Jordan and determine the most influential factors.

The sample size, response rate of the study was sufficient, sampling recruitment was from northern region. Adherence to healthy lifestyle are an effective strategy to delay and prevent the development and progression of menopausal symptoms in Jordan. This study identifies the most confounding factors that might impact the development of healthy intervention program.

Nevertheless, this study has limitations that should be considered when interpreting the findings. Firstly, the adopted cross-sectional quantitative design may not be sufficient to identify all the potential factors that may influence adherence to a healthy diet and physical activity among the menopausal women. Secondly, this study provides a limited representation of the female population of Jordan, focusing on specific regional attributes. Consequently, this could restrict the generalizability of the study's findings. Thirdly, the use of an online questionnaire may limit the generalizability of the results. In addition, the self-reported weight and height may be underestimated or overestimated. Lastly, other activities that occurred concurrently with the survey may affect the results, and "history" may have influenced how the women responded to the survey questions (47).

Conclusion

This study increases our understanding about the level of adherence to diet and physical activity among the menopausal women. Also, fills knowledge gap in the literature, and enhance our awareness of the requirements to improve adherence to diet and physical activity. In addition, it sheds light in the factors affecting adherence to diet and physical activities. This study demonstrated a moderate degree of adherence to a healthy diet and physical activity among menopausal women.

Age, having two children and completing primary or secondary education were statistically significant and the strongest predictors of adherence to a healthy diet and physical activity among the menopausal women. Future research should validate the results of this study and investigate other factors that may affect adherence to a healthy diet and physical activity among menopausal women. Also, conducting a future interventional studies to provide menopausal women with information and education related to physical activity and a healthy diet, and increase their awareness regarding the importance of healthy diet and physical activity. Furthermore, Suggestions can be offered to healthcare professionals for developing personalized strategies for lifestyle adjustment, as well as comprehensive interventions that encompass dietary regulation and physical activity for menopausal women. Moreover, mixed-methods and qualitative studies should be conducted to improve understanding of the factors that may predict adherence to a healthy diet and physical activity.

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 Institution Review Board of the Al-Balqa Applied University which assigned the approval number 5/6/23. 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

RA: Conceptualization, Formal analysis, Visualization, Writing – original draft. EM: Investigation, Methodology, Project administration, Writing – review & editing. ME: Conceptualization, Data curation, Validation, Writing – original draft. FH: Conceptualization, Data curation, Supervision, Validation, Writing – review & editing.

SA: Data curation, Formal analysis, Methodology, Writing – review & editing, 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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EDITED BY
Zhendong Liu,
Shandong First Medical University, China

REVIEWED BY
Luana Lara Rocha,
Federal University of Minas Gerais, Brazil
Shelly R. McFarlane,
University of the West Indies, Jamaica
Fadwa Hammouh,
American University of Madaba, Jordan

*CORRESPONDENCE
Wilter C. Morales-García
✉ wiltermorales@upeu.edu.pe

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Association between cardiovascular risk and maternal perception of BMI in Peruvian schoolchildren

Margoth Ccari Mamani[1], Jhosset Flores Martínez[1], Raquel Chilón Llico[1], Liset Z. Sairitupa-Sanchez[2], Sandra B. Morales-García[3], Oriana Rivera-Lozada[4] and Wilter C. Morales-García[5,6,7,8]*

[1]Escuela Profesional de Nutrición Humana, Facultad de Ciencias de la Salud, Universidad Peruana Unión, Lima, Perú, [2]Escuela Profesional de Psicología, Facultad de Ciencias de la Salud, Universidad Peruana Unión, Lima, Perú, [3]Departamento Académico de Enfermería, Obstetricia y Farmacia, Facultad de Farmacia y Bioquímica, Universidad Científica del Sur, Lima, Perú, [4]Facultad de Educación, Universidad Nacional Mayor de San Marcos, Lima, Perú, [5]Escuela de Medicina Humana, Facultad de Ciencias de la Salud, Universidad Peruana Unión, Lima, Perú, [6]Escuela de Posgrado, Universidad Peruana Unión, Lima, Perú, [7]Facultad de Teología, Universidad Peruana Unión, Lima, Perú, [8]Sociedad Científica de Investigados Adventistas, SOCIA, Universidad Peruana Unión, Lima, Perú

Introduction: In the modern era, the maternal perception of children's nutritional status has emerged as a critical area of study, given its potential influence on nutritional interventions and long-term child health. The relationship between this perception and children's Body Mass Index (BMI) by age is particularly intriguing, as it may reveal discrepancies between perception and reality.

Objective: The aim of this study was to evaluate Peruvian mothers' perception of their children's Body Mass Index (BMI) in relation to age and to determine how this perception associates with the children's cardiovascular risk. The study also analyzed sociodemographic factors that might influence this perception.

Methods: The study included 130 mothers of schoolchildren aged 5 to 11 from a school in Lima. Mothers' perceptions of their children's weight were assessed using pictograms, and sociodemographic characteristics were collected through a questionnaire. Weight and height measurements were taken to calculate BMI, and waist circumference was measured to classify cardiovascular risk.

Results: A total of 57.4% of the schoolchildren presented with excess malnutrition, and 51.5% of the mothers incorrectly classified the actual BMI/Age of their children (kappa 0.11; $p \leq 0.05$). Additionally, it was found that the schoolchild's age is associated with the mother's failure to accurately perceive her child's weight (OR 1.59). Lastly, there was a significant association between maternal perception and cardiovascular risk ($p \leq 0.05$).

Conclusion: There is a significant discrepancy between maternal perception and the actual nutritional status of children, which can increase cardiovascular risk. It is necessary to implement intervention and education strategies targeted at parents to enhance the recognition and management of childhood overweight and obesity.

KEYWORDS

maternal perception, overweight and obesity, schoolchildren, cardiovascular risk, Peruvian

1 Introduction

Childhood obesity has emerged as a significant public health challenge in the 21st century (1). According to the World Health Organization (WHO), this phenomenon has seen alarming growth, having tripled from 1975 to 2016, leading to approximately 2.8 million annual deaths (2). Lobstein et al. (3) underscores this concern, noting that globally 13% of children are overweight and 11% suffer from obesity (4).

In Latin America and the Caribbean, the situation is equally alarming. It is estimated that overweight affects 30.6% of the population, including 3.9 million preschoolers and 75 million school-aged children (5–7). In Peru, specifically, the National Center for Food and Nutrition (CENAN) reported that during 2017–2018, four out of ten children aged 5 to 9 were overweight, a rate that has doubled in the last decade. Metropolitan Lima, the capital district, showed a concerning 49.3% prevalence in this age group (8).

Childhood obesity is a concern in its own right and is also a predictor of adult obesity, thereby increasing the risk of non-communicable diseases and early adult mortality (9, 10). Factors such as poor dietary habits and sedentary behaviors, largely influenced by the environment and parental habits, contribute to this epidemic (11).

In this context, parental perception, especially that of mothers, regarding their children's weight plays a critical role. Mothers, traditionally the primary caregivers, significantly influence their children's dietary habits (12, 13). However, studies have shown that many mothers with overweight or obese children tend to underestimate their weight, thus reducing the likelihood of taking preventive actions and engaging in weight-loss interventions for their children (14–18). This misperception was highlighted by Trejo et al. (19), who found that most Peruvian parents with overweight or obese children did not accurately perceive their children's weight (19).

To better understand the determinants of this perception, factors associated with inaccurate perception of children's weight have been studied. Sociodemographic characteristics like the educational level of mothers, ethnic background, and knowledge about healthy eating have been identified as factors linked to misperceptions of children's weight (19–27). These characteristics, in connection with perceptions of children's body image, may be crucial in identifying risk groups and developing preventive strategies against childhood overweight and obesity. Hence, this study aims to assess Peruvian mothers' perception of the Body Mass Index (BMI) in relation to their children's age and to determine its association with the children's cardiovascular risk, while also examining the sociodemographic factors that might influence this perception.

1.1 Hypothesis

The perception of Peruvian mothers about the Body Mass Index (BMI) of their children in relation to their age is significantly associated with the cardiovascular risk of these children. It is expected that sociodemographic factors influence the accuracy of this maternal perception, thereby contributing to cardiovascular risk in the Peruvian pediatric population.

2 Materials and methods

2.1 Design and participants

A descriptive, analytical, and cross-sectional study was designed. The sample size was calculated using the G* Power 3.1.9.7 program for an *a priori* analysis. To determine the required sample size for our study, an *a priori* calculation was performed using the G*Power software version 3.1.9.2. A medium effect size (0.3), an alpha significance level of 0.05, and a statistical power of 80% (1-β = 0.80) were established. The necessary sample size calculated was 108 mother–child dyads. Dyads of mothers and children aged 5 to 11 years were included, involving biological mothers and their children who are stable residents in the area. Mothers with chronic illnesses or training in nutrition or health were excluded, as were children with pathologies that prevent anthropometric evaluation. The study ensured diversity in education, nutritional knowledge, and socioeconomic status. Informed consent and availability for follow-up were also required.

2.2 Ethical procedures

Initially, the Ethics Committee of a Peruvian university (2212-2022/UPEU-FCS-*CF*) thoroughly reviewed and approved our research protocol. Before the commencement of data collection, an informational session was held with the participating mothers. During this session, the purpose and objectives of the research were thoroughly explained. The importance of their participation was emphasized, and they were assured that their involvement would be entirely voluntary. Once the mothers had a clear understanding of the study, they were presented with an informed consent document. This document outlined the study's procedures, participants' rights, and guarantees of confidentiality. Mothers who chose to participate in the study signed this document, thus confirming their understanding and voluntary consent. The mothers were assured that all information collected during the study would be treated confidentially and that both their identities and those of their children would remain anonymous. Strict protocols were established to ensure that data was stored and managed securely and responsibly. This study adhered to the guidelines and principles set forth in the Helsinki Declaration, a set of ethical recommendations and principles for conducting research involving human beings (28).

2.3 Variables

2.3.1 Mother's perception of BMI

The Collins scale ("Collins BMI Measurement Test") was utilized to assess mothers' perception of their children's BMI. Validated in the study "Body Figure Perceptions and Preferences Among Preadolescent Children," this scale achieved a test–retest reliability level of 0.91 (29). This instrument has been employed in Latin American child populations aged 6 to 10, sharing characteristics similar to our study population (14). The scale categorizes BMI/Age using seven anatomical silhouettes for both males and females, depicting the child's physical appearance. These silhouettes progress in robustness, aligning with WHO classification parameters. Each silhouette is associated with a BMI value, ranging from 12.1 kg/m^2 to 35.5 kg/m^2:

silhouettes 1–2 signify underweight; 3–5, normal weight; 6, overweight; and 7, obesity. These figures did not exhibit the specified BMI values when presented. Mothers were asked to select the silhouette that, in their perception, resembled their child's body image, using the question, "Which image identifies your child?" The perceived BMI values were then compared with the actual BMI derived from weight and height measurements. This comparison facilitated an analysis of whether there is an accurate or inaccurate perception of the child's actual weight.

2.3.2 Mother's sociodemographic characteristics questionnaire

Data was collected regarding the mother's age, her child's age, educational level (classified as: "no studies," "primary," "secondary," and "higher education"), and birth region (classified as: "coast," "mountains," and "jungle").

2.3.3 Mother's knowledge of healthy eating

The questionnaire "Knowledge about healthy food among Peruvian public university students" was used to determine mothers' knowledge of healthy eating. Based on a literature review of nutrition and the WHO's nutritional pyramid, the questionnaire includes 16 questions on healthy eating knowledge, each correct answer scoring 2 points. Maternal knowledge was categorized into three levels: <17 points indicating low knowledge; 17 to 25 points as medium knowledge; and > 25 points as high knowledge. It has a Kuder Richardson reliability coefficient of 80.7%, validating its application (30).

2.3.4 Anthropometric measurements

Two professional nutritionists conducted anthropometric measurements. Weight was measured using a SECA 750 floor mechanical scale, calibrated to zero and with a capacity of 150 kg. Measurements were taken with the child in light clothing and barefoot. Height was measured using a CENAN-standardized wooden stadiometer, capable of measuring up to 199 cm. The child was positioned with their head according to the Frankfurt plane, heels together at the lower end, and feet angled between 45 to 60 degrees.

2.3.5 Body mass index

The BMI/Age diagnosis followed the World Health Organization's criteria for children aged 5 to 19 years (31). Underweight is defined as a value less than or equal to −2 SD (Standard Deviations), normal weight as greater than -2SD and less than or equal to +1SD, overweight as greater than +1SD and less than or equal to +2SD, and obesity as greater than +2SD and less than or equal to +3SD.

2.3.6 Abdominal circumference

A self-retracting LUFKIN steel tape measure, with a range up to 200 cm and a resolution of 1 mm, was used to determine abdominal circumference. The abdominal circumference was categorized by sex and age (AC/A) into low cardiovascular risk (< p75), high cardiovascular risk (≥ p75 and < p90), and very high cardiovascular risk (≥ p90) (32).

2.4 Statistical analysis

A correlation was established between maternal perception of their children's BMI/Age and associated sociodemographic factors. Additionally, the association between maternal perception and cardiovascular risk was identified. The collected data were analyzed using SPSS version 26.0, with a focus on the study's objectives. Quantitative variables were described using measures of central tendency and dispersion, and qualitative variables were presented with absolute frequency and percentage. The concordance between maternal perception and their children's BMI/Age was determined using the Kappa coefficient ($p \leq 0.05$). Bivariate logistic regression analysis was employed to evaluate sociodemographic factors associated with maternal perception. The relationship between maternal perception and cardiovascular risk, diagnosed by abdominal circumference, was examined using the non-parametric Pearson chi-square test ($p \leq 0.05$), and both variables were also correlated using Cramer's V coefficient.

3 Results

3.1 Participant characteristics

Table 1 details the characteristics of schoolchildren ($n = 130$) and their mothers ($n = 130$) in Lima, Peru, in 2023. The children were aged between 5 to 11 years ($M = 8$, SD = 1.8), with a majority being female (51.5%). The average Body Mass Index (BMI) was 19.4 kg/m^2 ± 3.7, with 43.1% classified as normal weight, 30.8% overweight, and 26.2% obese. The average abdominal circumference was 67.4 cm ±9.7. In terms of cardiovascular risk based on abdominal circumference, 46% were at low risk, 23% at high risk, and 31% at very high risk. Regarding the mothers, their age range was between 20 to 60 years ($M = 29.5$, SD = 7.4). The majority of the mothers were between 25 to 60 years old (78%), came from the coastal region (60%), had a higher education level (85%), and possessed a medium level of knowledge about healthy eating (71%).

3.2 Preliminary analysis

When associating maternal perception with the actual BMI/Age diagnosis of their children (Table 2), it was observed that 48.5% of mothers accurately perceived their children's weight status with a kappa coefficient of 0.119 (minimal agreement) ($p = <0.05$). Of these, those with normal weight were correctly classified in 43.1% ($n = 56$) of cases, and those with overweight in 5.4% ($n = 7$) of cases. Of the group of mothers (51.6%) who had an inaccurate perception, 25.4% ($n = 33$) underestimated their overweight children as normal weight; while mothers with obese children underestimated them as "normal weight" in 18.5% ($n = 24$) and "overweight" in 7.7% ($n = 10$) of cases.

3.3 Sociodemographic factors and maternal perception of child weight

Table 3 displays the sociodemographic characteristics of the 130 surveyed mothers. Of these, 84.6% had higher education and the remaining 15.4% secondary education. Regarding birth region, 60% of mothers were from the coast, 37% from the mountains, and 3% from the jungle. In terms of maternal knowledge about healthy eating, 72% demonstrated medium knowledge, while 14% were classified with high knowledge. Regression analysis between variables indicated that education level, birth region, and knowledge about healthy eating

TABLE 1 Descriptive characteristics of schoolchildren and mothers ($n = 130$), Lima – Peru, 2023.

Schoolchildren characteristics	*M* (SD)/*n* (%)
Age	8 ± (1.8)
Child's BMI	19.4 ± (3.7)
Abdominal circumference	67.47 ± (9.7)
Gender	
Male	63 (48.5%)
Female	67 (51.5%)
Children's nutritional status (BMI)	
Normal	56 (43.1%)
Overweight	40 (30.8%)
Obesity	34 (26.2%)
Cardiovascular risk diagnosis (AC)	
Low risk	60 (46%)
High risk	30 (23%)
Very high risk	40 (31%)

Mothers' characteristics	*M* (SD)/*n* (%)
Age	29.5 ± (7.4)
Age range	
20 to 25 years	27 (21%)
25 to 60 years	101 (78%)
Over 60 years	2 (1%)
Region of birth	
Coast	78 (60%)
Highlands	48 (37%)
Jungle	4 (3%)
Mother's education	
Secondary school	20 (15%)
Higher education	110 (85%)
Knowledge level about healthy eating	
Low knowledge	20 (15%)
Medium knowledge	92 (71%)
High knowledge	18 (14%)

BMI, Body Mass Index; AC, Abdominal Circumference; M, Mean; SD, Standard Deviation; n: Participants; %: Proportion.

did not significantly correlate with maternal perception ($p > 0.05$). However, it was found that the child's age from 5 to 11 years (OR 1.59) significantly affected the mother's inaccurate perception of her child's weight ($p < 0.05$).

3.4 Maternal perception of BMI and its association with cardiovascular risk in children

Table 4 shows a significant association between maternal perception of their children's Body Mass Index (BMI) and the classification of cardiovascular risk based on abdominal circumference. Adequate maternal perception predominantly correlated with low risk (36.2%), while inadequate perception was notably linked with very high cardiovascular risk (27.7%). Additionally, 15.4% of inadequate perceptions were associated with high risk. The statistical significance of the association ($p < 0.05$) and a Cramer's V coefficient of 0.607 indicate a strong correlation between mothers' perception of their children's weight and the actual classification of cardiovascular risk.

4 Discussion

The epidemic of childhood obesity, with its association with non-communicable diseases and increased mortality, is particularly concerning in Peru. Over the last decade, the rates of overweight children have doubled, especially in Metropolitan Lima (33, 34). Maternal perception of their children's weight is critical, as mothers play a key role in shaping family eating habits. Studies indicate that many mothers underestimate the weight of their overweight or obese children (19). Additionally, sociodemographic factors, such as the mother's educational level and knowledge about healthy eating, have been linked to inaccurate perceptions of child weight (21, 24). This study assesses Peruvian mothers' perception of their children's BMI and its relation to cardiovascular risk, hypothesizing that this perception significantly associates with cardiovascular risk in children and is influenced by sociodemographic factors, underscoring the importance of addressing this perception for effective preventive strategies.

The current study addressed maternal perception of their children's BMI/Age compared to the actual BMI/Age, revealing a significant discrepancy between the two. No association was found between the mother's sociodemographic factors (such as education, birth region, and knowledge about healthy eating) and perception of their children's BMI. However, a significant relationship was identified when considering the child's age. Additionally, a strong correlation was established between maternal perception and the children's cardiovascular risk, assessed through abdominal circumference. These findings underscore the complexity of parental perception regarding their children's nutritional status. The discrepancies observed between different studies can be attributed to varied methodologies used to assess parental perception, whether verbal or visual (18, 22, 35). However, it's crucial to consider ongoing cultural and social changes. In contemporary society, significant epidemiological and dietary transitions are occurring. In this context, what was previously classified as overweight in children may now be perceived as "normal weight" by family and society. The rising prevalence of childhood obesity has desensitized society to excess weight, normalizing this condition to some extent. Furthermore, a lack of awareness may lead parents to base their perceptions on visual comparisons with other children, who may also be overweight (36). Parental perception is complex, influenced by various factors including the relationship between the observer and the observed, the individual characteristics of both, and the observer's prior beliefs and experiences (37).

Maternal perception of their children's nutritional status, especially concerning BMI/Age, is an increasingly relevant topic in nutritional research. The present study identified a significant association between the child's age and the mother's inaccurate

perception of BMI/Age. Specifically, within the 5 to 11 year age range, there is a tendency for mothers to misperceive their children's actual BMI/Age. Although no direct comparisons with children outside this age range were made, these findings align with existing literature suggesting that age influences parental perception of nutritional status. Research by Ramirez et al. (16) and Zhang et al. (38) reported challenges in maternal perception mainly in ages between 4 and 9 years. Conversely, studies like that of AlHasan et al. (20) suggest that identifying overweight and obesity is more challenging in younger children, aged 2 to 4 years. Cultural beliefs associating early weight gain with health and well-being, and expectations of outgrowing overweight with growth and increased physical activity, may contribute to these perception differences, as discussed by Alshahrani et al. (37) and Esteban-Vasallo et al. (39).

The study revealed a concerning discrepancy between maternal perception of their children's nutritional status and the actual cardiovascular risk they face. Notably, 43.1% of overweight or obese children, not correctly identified by their mothers, exhibited a high and very high risk of developing cardiovascular diseases based on abdominal circumference. Conversely, only 10.8% of children whose nutritional status was accurately perceived by their mothers presented a high or very high cardiovascular risk. These findings emphasize the importance of parental perception in identifying and managing cardiovascular risk in children. Although most studies on maternal

TABLE 2 Maternal perception of BMI of their children (Ages = 5–11 years, $n = 130$), Lima – Peru, 2023.

Maternal perception	Child's BMI								*p*-value Kappa
	Normal		Overweight		Obesity		Total		
	n	%	*n*	%	*n*	%	n	%	
Normal	56	43.10%	33	25.40%	24	18.50%	113	86.90%	$p < 0.05$
Overweight	0	0%	7	5.40%	10	7.70%	17	13.10%	$K = 0.119$
Obesity	0	0%	0	0%	0	0%	0	0%	
Total	56	43.10%	40	30.80%	34	26.20%	130	100%	

$p < 0.05$, K, Kappa value.

TABLE 3 Bivariate analysis of sociodemographic factors and maternal perception of child's weight ($n = 130$), Lima – Peru, 2023.

Variables	Descriptive analysis		Bivariate analysis		
	Maternal perception		Odds ratio	IC 95%	*p*-value
Child's age	5 years – 11 years ($M = 8$. SD = 1.8)		1.59	0.086–0.358	0.004
Education level	Adequate	Inadequate			
Secondary	5.40%	9.20%	0.49	0.166–1.468	0.575
Higher	41.50%	43.10%	–	–	
Birth region					
Coast	28.50%	31.50%	1.07	0.139–8.285	
Highlands	16.90%	20.00%	0.87	0.106–7.155	0.991
Jungle	1.50%	1.50%	–	–	
Knowledge level about healthy eating					
Low knowledge	6.90%	7.70%	1.39	0.346–5.611	
Medium knowledge	33.10%	38.50%	1.68	0.531–5.334	0.667
High Knowledge	6.90%	6.90%	–	–	

95% CI: 95% confidence interval.

TABLE 4 Association between inadequate maternal perception of child's BMI and cardiovascular risk ($n = 130$), Lima – Peru, 2023.

Maternal perception	Cardiovascular risk classification (abdominal circumference)								*p*-value
	Low risk		High risk		Very high risk		Total		
	n	%	*n*	%	*n*	%	*n*	%	
Adequate	47	36.2%	10	7.7%	4	3.1%	61	46.9%	
Inadequate	13	10.0%	20	15.4%	36	27.7%	69	53.1%	<0.05
Total	60	46.2%	30	23.1%	40	30.8%	130	100%	

V Cramer = 0.607.

perception have focused on BMI/Age as the primary indicator, other markers are crucial. A recent study supports this, noting that parental underestimation of children's weight status directly correlates with a higher risk of cardiovascular disease (40). Abdominal circumference emerges as a critical anthropometric indicator. Unlike BMI/Age, which measures excess weight relative to height, abdominal circumference directly measures central adiposity, a factor closely associated with increased cardiovascular disease risk. BMI/Age has limited sensitivity in detecting excess adiposity, possibly leading to underestimations of the actual risk (41). The implications of these findings are significant, considering the progression of cardiovascular diseases. As noted by Santos et al. (42), cardiovascular risk can begin in early childhood and persist asymptomatically until adulthood.

4.1 Implications

The discrepancy between maternal perception and the actual nutritional status of children underscores the importance of integrating nutritional education into Peru's academic curriculum. This integration serves as a strategy to enhance knowledge about healthy habits. Health professionals need to be cognizant of this perceptual gap and should focus on improving communication and education directed toward parents and caregivers. These stakeholders require effective resources to recognize and manage childhood overweight and obesity. The development of public policies is crucial to strengthen nutritional education and raise awareness about childhood obesity. This includes campaigns that address misconceptions and foster a clear understanding of associated risks. Additionally, the inclusion of anthropometric measures such as abdominal circumference in routine health check-ups for children is worth considering. From a theoretical perspective, it is essential to investigate how cultural beliefs and social norms influence parental perception. Understanding these influences is key to identifying barriers and facilitators in combating childhood obesity.

4.2 Limitations

This study contributes to a limited body of research on maternal perception related to BMI/Age and abdominal circumference in Peruvian schoolchildren. However, several significant limitations should be noted: Firstly, the study was conducted among schoolchildren and their mothers residing in an urban area, which may explain the sample's homogeneity, characterized by generally high maternal education and moderate maternal knowledge about healthy eating. Secondly, the sample was collected from an urban school in Lima through convenience sampling, and therefore might not be representative, limiting the generalizability of the current findings. It's essential to recognize that our study has limitations that could impact the interpretation of our findings. The cross-sectional nature of our study precludes the establishment of causal relationships between maternal perception and the actual nutritional status of children. Although significant associations were identified, we cannot conclusively assert that inaccurate maternal perception directly leads to higher cardiovascular risk in children. Longitudinal studies are recommended for more precise insights. Additionally, our study focused mainly on maternal perception, neglecting the perspectives of other caregivers, such as fathers, grandparents, or guardians. Each caregiver, with their unique cultural and experiential background, could offer a distinct viewpoint on the child's nutritional status. Excluding these caregivers may have led to overlooking important aspects of parental perception. Lastly, while we considered some sociodemographic variables, there are other factors that might influence maternal perception, including cultural beliefs, media exposure, and mothers' personal experiences with weight and nutrition.

4.3 Conclusion

In conclusion, this study reveals a discrepancy between mothers' perceptions and the actual nutritional status of their children, indicating a tendency to underestimate weight in cases of overweight or obesity, which may contribute to increased cardiovascular risk. These findings highlight the necessity of directing nutritional interventions toward parents of school-aged children, especially at critical ages where maternal perception is likely to be less accurate. For public health, this study recommends implementing educational programs that enhance parents' ability to recognize and address overweight and obesity, as well as advocating for policies that promote greater awareness and prevention of cardiovascular risk from childhood. It is vital for intervention strategies to assess the impact of maternal perceptions and their influence on family health behaviors.

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 research involving humans was approved by the Ethics Committee of the Peruvian Union University (2212-2022/UPEU-FCS-CF). The studies were conducted in accordance with local legislation and institutional requirements. The legal guardians or closest relatives of the participants provided written informed consent for participation in this study.

Author contributions

MM: Conceptualization, Data curation, Formal analysis, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. JM: Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. RL: Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. LS-S: Conceptualization, Data curation, Formal analysis, Funding acquisition, Software, Supervision, Writing

– original draft, Writing – review & editing. SBM-G: Methodology, Validation, Visualization, Software, Writing – review & editing. OR-L: Conceptualization, Data curation, Formal analysis, Funding acquisition, Resources, Software, Supervision, Visualization, Writing – original draft, Writing – review & editing. WM-G: Conceptualization, Data curation, Methodology, Project administration, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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Conflict of interest

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

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EDITED BY
Zhendong Liu,
Shandong First Medical University, China

REVIEWED BY
Xianfeng Wu,
Shanghai Jiao Tong University, China
Pengcheng Liu,
China Pharmaceutical University, China

*CORRESPONDENCE
Yanmei Lou
✉ hitila@sina.com
Changyi Wang
✉ wangchangyi2002@163.com

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Association between serum albumin concentration change trajectory and risk of hypertension: a cohort study in China

Yinxing Liu[1,2,3], Shan Xu[1], Hongen Chen[1], Shuhong Dai[1], Jiejing Hao[1], Xi Chen[4], Ji Zhang[1,2], Siguo Li[5], Jun Liu[2], Fulan Hu[4], Yanmei Lou[6]* and Changyi Wang[1,2]*

[1]Department of Non-Communicable Disease Prevention and Control, Shenzhen Nanshan Center for Chronic Disease, Shenzhen, Guangdong, China, [2]Department of Epidemiology and Health Statistics, School of Public Health, Zunyi Medical University, Zunyi, Guizhou, China, [3]Department of Tuberculosis Prevention and Control, Zunyi Center for Disease Control and Prevention, Zunyi, Guizhou, China, [4]Department of Biostatistics and Epidemiology, School of Public Health, Shenzhen University Health Science Center, Shenzhen, Guangdong, China, [5]Shenzhen Key Laboratory of Molecular Epidemiology, Shenzhen Center for Disease Control and Prevention, Shenzhen, China, [6]Department of Health Management, Beijing Xiaotangshan Hospital, Beijing, China

Background: We sought to assess the risk of hypertension based on the trajectory of changes in serum albumin concentrations.
Methods: A total of 11,946 nonhypertension adults aged 30–60 years who underwent at least 3 medical examinations between 2009 and 2016 were included in this study. Group-based trajectory models were obtained for 4 category groups, and logistic regression models were used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for each category group of serum albumin concentration and the risk of hypertension.
Results: During a mean follow-up period of 4.30 years, 1,537 hypertension events occurred in 11,946 subjects without hypertension. A high stable trajectory of serum albumin concentrations (OR, 0.70, 95% CI, 0.51–0.96) was associated with a significantly lower risk of developing hypertension. The results of the sensitivity analysis of the high stable trajectory (OR, 0.64, 95% CI, 0.43–0.96) remained statistically significant. Subjects with normal weight and those ≥45 years of age had a significantly lower risk of hypertension at moderate increase ($P = 0.053$ or 0.026) and high stable trajectories ($P = 0.011$ or 0.016). In males and overweight subjects, the risk of hypertension was significantly lower in the high stable trajectory ($P = 0.038$ or 0.044).
Conclusion: In this study, we found that moderate increase in serum albumin concentrations and a high stable trajectory were significantly associated with a reduced risk of hypertension in subjects aged ≥45 years and those with normal weight and that high stable serum albumin concentrations were significantly associated with a reduced risk of hypertension in males and overweight subjects.

KEYWORDS

serum albumin, trajectory of change, hypertension, cohort study, risk

1 Introduction

Hypertension is an independent risk factor for cardiovascular disease; it can lead to a variety of diseases, including stroke, coronary artery disease, aortic aneurysm, renal failure, heart failure, and death. A large screening study based on 17 million adults in China found the prevalence of hypertension to be 37.2% (1). Therefore, it is particularly important to

identify predictors of hypertension and to develop policies to prevent the development of cardiovascular disease.

Serum albumin is a unique multifunctional protein that is synthesized by liver parenchymal cells. As the most abundant protein in plasma, serum albumin accounts for approximately 50% of total plasma protein (2). Serum albumin maintains normal permeability of the microvascular wall, reduces blood viscosity, and inhibits platelet aggregation (3, 4). A longitudinal study by Schalk showed that older adults with decreased serum albumin concentrations, even within the normal range, may be at increased risk for cardiovascular disease (5). In addition, a study of 354 patients with essential hypertension showed an inverse correlation between worsening circadian blood pressure and the serum albumin concentration (6). A 4-year longitudinal study in Japan found that a reduced serum albumin concentration was an important predictor of hypertension (7). A cross-sectional study conducted in Norway reported that serum albumin concentrations were positively associated with systolic and diastolic blood pressure in healthy subjects (8). Based on the above findings, it is reasonable to assume that long-term changes in serum albumin concentrations have a differential effect on the development of hypertension. In this study, adults aged 30–60 years who underwent physical examinations at Xiaotangshan Hospital in Beijing from 2009 to 2016 were enrolled to investigate the correlation between trajectories of changes in serum albumin concentrations and hypertension.

2 Methods

2.1 Study population

This cohort included adults aged 30–60 years who underwent a comprehensive health examination at Beijing Xiaotangshan Hospital between 2009 and 2016 based on ≥3 health examinations and excluded participants with hypertension, cancer, stroke, coronary artery disease, myocardial infarction, renal disease, and liver disease at baseline, with the final 11,946 participants (6,644 males and 5,302 females) constituting the longitudinal cohort of this study.

The study was approved by the Ethics Committee of Beijing Xiaotangshan Hospital (No. 202006), and the study procedures were conducted in accordance with the 1964 Declaration of Helsinki. The requirement for informed consent was waived because only routine health screening data were used for the analysis.

2.2 Data collection

Data on the subjects' demographic characteristics (age, sex), medical history and medications were collected by standardized face-to-face questionnaires, while anthropometric, clinical and biochemical parameters were collected by trained physicians and nurses.

Smoking status (current and/or at least 100 cigarettes in lifetime) and alcohol consumption (Drinking alcohol 12 or more times at different times last year, ≥25 g/day for men and ≥15 g/day for women) were recorded. Trained physicians and nurses measured participants' height, weight, resting heart rate, systolic blood pressure and diastolic blood pressure. The subjects' height and weight were measured while they were dressed casually and without shoes. Body mass index was calculated by dividing body weight (kg) by height squared (m^2). After at least 5 min of rest, the systolic and diastolic blood pressures of the participants' arms were measured three times with an electronic sphygmomanometer (HEM-770AFuzzy, Omron, Japan) in a seated position, with a 2-min interval between each blood pressure measurement.

Venous blood samples were collected after an overnight fast of at least 8 h. Serum albumin was measured using the bromophenol green contrast method (9). Serum uric acid, white blood cell count creatinine (WBC), total cholesterol, triglyceride, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) concentrations were measured using an automated biochemistry analyzer (Model 7600; Hitachi, Tokyo, Japan). Fasting plasma glucose was measured by the glucose dehydrogenase method (Merck, Darmstadt, Germany). Alanine aminotransferase (ALT), aspartate aminotransferase (AST) and blood urea nitrogen concentrations were measured with an automated analyzer.

2.3 Definitions

Hypertension was defined by any of the following criteria: (1) self-reported physician diagnosis of hypertension, (2) the use of antihypertension medication within the past 2 weeks, or (3) systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure <90 mm Hg (10).

Prehypertension was defined as subjects with systolic blood pressure ≥120 mmHg and <139 mmHg and/or diastolic blood pressure ≥80 mmHg and <89 mmHg (11).

2.4 Statistical analysis

Data management and analysis were performed using StataS/E version 15 (StataCorp, TX) R software version 4.0.5 (www.r-project.org). A *P*-value of 0.05 was considered statistically significant.

We used group-based trajectory modeling (GBTM) with age as the time scale to explore joint longitudinal changes in serum albumin. The trajectories of study subjects were modeled and grouped using Stata's Proc Traj program (12), a semiparametric mixture model that allows for joint modeling of trajectories for multiple outcomes, which assumes that each participant belongs to only one group and that each group has a different trajectory. Various GBTM models were run before selecting the best model regarding the number of groups and trajectory shapes (constant, linear, quadratic, cubic). First, to determine the optimal number of different groups to describe the heterogeneity in the longitudinal development of serum albumin, various models using 1–7 different groups were fitted, and the model with the least Bayesian information criterion (BIC) (13), mean posterior probability not less than 0.7 and sufficient sample size in each multitrajectory group (>5% of the samples) was selected as the

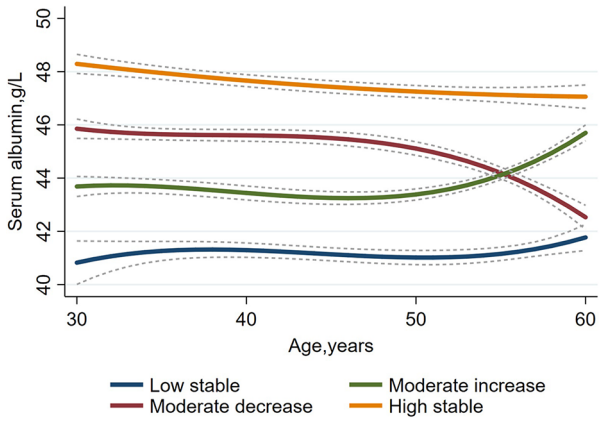

FIGURE 1
A group-based trajectory model to investigate serum albumin trajectories in a Chinese population aged 30–60 years (n = 11,946).

best model, resulting in 4 groups of serum albumin trajectories. Figure 1 shows the four different trajectories of the serum albumin concentration.

Subsequent data analysis was performed using R software, and continuous variables that did not follow a normal distribution were described by the median [interquartile range (IQR)] and analyzed using the Mann–Whitney U-test. Categorical variables were expressed as counts (%) and analyzed using the χ^2 test or Fisher's exact test. Student's t-test was used to compare continuous variables across trajectories, and the Kruskal–Wallis test or χ^2 test was used to compare the incidence of hypertension across trajectory groups. The time to follow-up was defined as the date from first entry into the cohort to confirmation of follow-up or hypertension diagnosis. Odds ratios (ORs) and 95% confidence intervals (CIs) for hypertension were estimated using multivariate logistic regression models with low stability as the reference group to determine differences in the risk of hypertension across trajectory groups.

The covariates included all baseline variables, and three logistic regression models were fitted: Model 1 (unadjusted), Model 2 (adjusted for age, sex, and follow-up time), and Model 3 (further adjusted for smoking, alcohol consumption, diabetes, obesity, body mass index, resting heart rate, systolic and diastolic blood pressure, fasting plasma glucose, triglycerides, total cholesterol, uric acid, blood urea nitrogen, creatinine, LDL-C, HDL-C, WBC, ALT, and AST). In addition, we performed sensitivity analyses excluding subjects who were prehypertension at baseline and excluding subjects diagnosed with hypertension two years before follow-up to assess the robustness of the logistic regression results. We also performed stratified analyses by age, sex, and weight status (normal vs. overweight).

Cumulative average, standard deviation, baseline and end-stage serum albumin concentrations during 2009–2016 were ranked from smallest to largest and divided into five equal quintiles (Q1–Q5). Baseline-stage serum albumin: <42.00, 42.00 to <44.00, 44.00 to <45.10, 45.10 to <47.00, and ≥47.00. Standard deviation serum albumin: <1.516, 1.516 to <2.050, 2.050 to <2.417, 2.417 to <3.000, and ≥3.000. Cumulative average serum albumin: <42.737, 42.737 to <44.033, 44.033 to <44.975, 44.975 to <46.267, and ≥46.267. End-stage serum albumin: <43.00, 43.00 to <45.00, 45.00 to <46.00, 46.00 to <47.00, and ≥47.00. We added details to the study by examining serum albumin concentrations at baseline, cumulative average serum albumin concentrations (cumulative serum albumin concentration from baseline to the last year of follow-up divided by the number of years of follow-up), end-stage serum albumin concentrations in the last year of follow-up, and standard deviations (all available serum albumin concentrations from 2009 to 2016).

3 Results

3.1 Baseline characteristics of the trajectory groups

The study cohort included 11,946 subjects without hypertension at baseline, aged 42 years (IQR, 36.00–48.00 years), 55.62% of whom were male. A total of 1,537 (12.87%) hypertension events occurred during a mean follow-up period of 4.30 years. Table 1 summarizes the baseline characteristics of subjects in the 4 serum albumin change trajectory groups, including sex, age, smoking, alcohol consumption, obesity rate, body mass index, resting heart rate, systolic blood pressure, fasting plasma glucose, triglycerides, uric acid, blood urea nitrogen, creatinine, LDL-C, HDL-C, WBC, ALT, and AST (ptrend <0.05). Diastolic blood pressure, total cholesterol, and prevalence of diabetes did not differ between the 4 trajectory groups. Supplementary Table S1 demonstrates the baseline characteristics grouped by the occurrence of hypertension events. Age, male proportion, smoking, alcohol consumption, prevalence of diabetes, obesity rate, body mass index, resting heart rate, systolic and diastolic blood pressure, fasting plasma glucose, triglycerides, total cholesterol, uric acid, blood urea nitrogen, creatinine, LDL-C, WBC, ALT, and AST were higher in hypertension patients than in nonhypertension patients (ptrend <0.01), whereas HDL-C concentrations in hypertension patients were significantly lower than those in nonhypertension patients (ptrend <0.001).

3.2 Association between the trajectory of change in serum albumin concentrations and the risk of hypertension

Logistic regression models were used to estimate the association between the 4 serum albumin trajectory groups and the risk of hypertension (Models 1–3; Table 2). In the crude model, the risk of hypertension decreased with a high baseline. High serum albumin levels reduced the risk of hypertension with a low stable trajectory as a control, moderate decrease trajectory (OR, 1.01, 95% CI, 0.83–1.24), moderate increase trajectory (OR, 0.93, 95% CI, 0.76–1.14), and high stable trajectory (OR, 0.84, 95% CI, 0.65–1.09) (P = 0.058) (Table 2). After adjusting the model for age and sex (Model 2), the serum albumin high stable trajectory was significantly associated with a reduction in the

TABLE 1 Baseline characteristics of study variables by different trajectories of serum albumin.

Variables	All participants (n = 11,946)	Low stable (n = 986, 8.25%)	Moderate decrease (n = 5,162, 43.21%)	Moderate increase (n = 4,665, 39.05%)	High stable (n = 1,133, 9.49%)	P
Age, years	42 (36–48)	46 (40–52)	41 (35–47)	43 (38–49)	39 (34–46)	<0.001
Male, n (%)	6,644 (55.62)	316 (32.05)	3,281 (63.56)	2,197 (47.10)	850 (74.96)	<0.001
Body mass index, kg/m^2	24.53 (22.39–26.66)	24.00 (22.12–26.39)	24.63 (22.52–26.73)	24.45 (22.30–26.62)	24.71 (22.58–26.84)	<0.001
Resting heart rate, beats/min	73 (70–81)	72 (70–80)	74 (70–81)	72 (70–80)	76 (71–84)	<0.001
Systolic blood pressure, mmHg	111 (105–120)	110 (100–118)	113 (107–120)	110 (102–120)	117 (110–123)	<0.001
Diastolic blood pressure, mmHg	71 (68–78)	70 (67–78)	72 (68–78)	70 (68–78)	72 (68–79)	0.056
Fasting plasma glucose, mmol/L	5.19 (4.90–5.55)	5.11 (4.84–5.46)	5.21 (4.92–5.56)	5.18 (4.89–5.54)	5.24 (4.94–5.58)	<0.001
Triglycerides, mmol/L	1.21 (0.84–1.81)	1.05 (0.76–1.56)	1.27 (0.87–1.90)	1.15 (0.81–1.69)	1.41 (0.96–2.10)	<0.001
Total cholesterol, mmol/L	4.83 (4.25–5.45)	4.84 (4.26–5.55)	4.83 (4.25–5.44)	4.83 (4.26–5.43)	4.81 (4.28–5.47)	0.822
HDL-C, mmol/L	1.34 (1.14–1.57)	1.42 (1.20–1.66)	1.31 (1.12–1.53)	1.36 (1.16–1.60)	1.26 (1.08–1.51)	<0.001
LDL-C, mmol/L	2.94 (2.46–3.43)	2.85 (2.36–3.40)	2.98 (2.49–3.45)	2.90 (2.43–3.40)	3.00 (2.54–3.54)	<0.001
Uric acid, μmoI/L	314.30 (256.40–377.00)	284.00 (236.80–341.50)	325.80 (265.00–386.40)	301.00 (248.80–363.40)	338.10 (279.00–402.60)	<0.001
Blood urea nitrogen, mmol/L	4.7 (3.95–5.59)	4.56 (3.85–5.44)	4.80 (4.00–5.63)	4.64 (3.87–5.50)	4.84 (4.10–5.70)	<0.001
Creatinine, μmol/L	79.3 (68.7–90.10)	75.30 (68.34–86.05)	81.3 (68.80–91.50)	78.10 (68.88–89.00)	80.00 (68.20–89.72)	<0.001
WBC, 10^9/L	5.77 (4.89–6.80)	5.60 (4.79–6.59)	5.80 (4.90–6.84)	5.70 (4.83–6.75)	5.90 (5.09–6.90)	<0.001
ALT, U/L	19.00 (14.00–27.60)	16.40 (12.85–22.00)	20.00 (14.00–28.90)	18.00 (13.40–26.00)	22.00 (15.00–32.00)	<0.001
AST, U/L	19.00 (16.30–23.00)	18.40 (16.00–21.57)	19.30 (16.60–23.10)	18.90 (16.10–22.60)	20.00 (17.00–24.00)	<0.001
Current smoker, n (%)	2,033 (17.02)	110 (11.16)	993 (19.24)	695 (14.90)	235 (20.74)	<0.001
Alcohol consumption, n (%)	3,728 (31.21)	212 (21.50)	1,818 (35.22)	1,248 (26.75)	450 (39.72)	<0.001
Diabete, n (%)	617 (5.16)	47 (4.77)	258 (5.00)	252 (5.40)	60 (5.30)	0.756
Obesity, n (%)	1,672 (14.00)	119 (12.07)	729 (14.12)	637 (13.65)	187 (16.50)	0.020

Median (interquartile range) unless indicated.
HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; WBC, white blood cell count; ALT, alanine transaminase; AST, aspartate aminotransferase.

incidence of hypertension (OR, 0.67, 95% CI, 0.52–0.90). Further adjustment for smoking, alcohol consumption, diabetes, obesity, body mass index, resting heart rate, systolic and diastolic blood pressure, fasting plasma glucose, triglycerides, total cholesterol, uric acid, blood urea nitrogen, creatinine, LDL-C, HDL-C, WBC, ALT, and AST (Model 3) only slightly weakened the association but did not affect the significant association between the serum albumin high stable trajectory and the incidence of hypertension (OR, 0.70, 95% CI, 0.51–0.96) ($P < 0.001$). In the sensitivity analysis, after excluding subjects with prehypertension at baseline, the association between a high stable trajectory of serum albumin concentrations and the risk of hypertension remained statistically significant in the fully adjusted model (OR, 0.66, 95% CI, 0.44–0.98) but was not significant in the moderate decrease and moderate increase trajectories. Figure 2 depicts the person-year incidence of hypertension before and after the sensitivity analysis was performed.

3.3 Association between the cumulative average serum albumin during 2009–2016 and the risk of hypertension

In the crude model, the risk of hypertension decreased with an increase in cumulative mean serum albumin. High serum albumin levels reduced the risk of hypertension, using Q3 as a control, Q1 (OR, 1.30, 95% CI, 1.10–1.54), Q2 (OR, 1.08, 95% CI, 0.91–1.28), Q4 (OR, 1.03, 95% CI, 0.87–1.23) and Q5 (OR, 1.02, 95% CI, 0.86–1.21) (ptrend = 0.278) (Table 3). After adjusting the model for age and sex (Model 2), high cumulative mean serum albumin levels remained significantly associated with a reduction in the incidence of hypertension. Further adjustment for smoking, alcohol consumption, diabetes, obesity, body mass index, resting heart rate, systolic and diastolic blood pressure, fasting plasma glucose, triglycerides, total cholesterol, uric acid, blood urea nitrogen, creatinine, LDL-C, HDL-C, WBC, ALT, and AST (Model 3) only slightly weakened the association but did not affect the significant association between cumulative mean serum albumin. Significant associations between cumulative mean serum albumin and the occurrence of hypertension were Q1 (OR, 1.07, 95% CI, 0.87–1.31), Q2 (OR, 0.96, 95% CI, 0.78–1.17), Q4 (OR, 0.86, 95% CI, 0.71–1.06) and Q5 (OR, 0.74, 95% CI, 0.60–0.92) (ptrend = 0.001). With each 1-SD increase in cumulative mean serum albumin, the risk of hypertension decreased by 8% (OR, 0.92, 95% CI, 0.88–0.96). In the sensitivity analysis, after excluding subjects with prehypertension at baseline, the association between the cumulative mean serum albumin concentration and the risk of hypertension remained significant in the fully adjusted Model Q5 (OR, 0.58, 95% CI, 0.42–0.81) (ptrend = 0.008), with each 1-SD increase in cumulative mean serum albumin associated with a 15% reduction in the risk of hypertension (OR, 0.85, 95% CI, 0.77–0.90).

3.4 Stratified analysis

Stratified analyses were performed by sex, age, and whether or not subjects were overweight. After full adjustment of the model, subjects with normal weight and those ≥45 years of age had a significantly lower risk of hypertension at moderate increase ($P = 0.053$ or 0.026)

TABLE 2 Association between serum albumin change trajectory and risk of hypertension.

	Low stable	Moderate decrease	Moderate increase	High stable	*P**
n (cases)	986 (131)	5,162 (694)	4,665 (582)	1,133 (130)	
Person-years	4,251	21,720	20,693	4,666	
Incidence (per 1,000 person-years)	3.08	3.20	2.81	2.79	
Model 1[a]	1.00 (ref)	1.01 (0.83–1.24)	0.93 (0.76–1.14)	0.84 (0.65–1.09)	0.058
Model 2[b]	1.00 (ref)	0.85 (0.69–1.06)	0.90 (0.73–1.12)	**0.67 (0.52–0.90)**	0.061
Model 3[c]	1.00 (ref)	0.93 (0.74–1.19)	0.96 (0.76–1.22)	**0.70 (0.51–0.96)**	0.091
Sensitivity analysis ($n = 10,092$)[d]					
n (cases)	832 (75)	4,346 (414)	3,978 (366)	936 (73)	
Person-years	3,691	18,406	17,916	3,841	
Incidence (per 1,000 person-years)	2.03	2.25	2.04	1.90	
Model 1[a]	1.00 (ref)	0.98 (0.81–1.20)	0.97 (0.77–1.22)	0.72 (0.53–1.01)	0.355
Model 2[b]	1.00 (ref)	0.81 (0.63–1.03)	0.91 (0.76–1.24)	**0.59 (0.35–0.89)**	0.312
Model 3[c]	1.00 (ref)	0.91 (0.68–1.24)	1.05 (0.79–1.42)	**0.64 (0.43–0.96)**	0.428

Data are odds ratios (ORs) and 95% confidence intervals (CIs).
[a]Crude model.
[b]Adjusted for age, sex, and follow-up time.
[c]Adjusted for covariates in Model 2 as well as smoking, alcohol consumption, diabete, obesity, body mass index, resting heart rate, systolic and diastolic blood pressure, fasting plasma glucose, triglycerides, total cholesterol, uric acid, blood urea nitrogen, creatinine, LDL-C, HDL-C, WBC, ALT, and AST.
[d]Excluding participants with pre-hypertension at baseline.
*$P < 0.05$ indicates a statistically significant difference in the association between different serum albumin trajectories and risk of hypertension, and $P \geq 0.05$ indicates no statistically significant difference.
Bolded text in this table indicates that the data are statistically significant.

and high stable trajectories ($P = 0.011$ or 0.016). In males and overweight subjects, the risk of hypertension was significantly lower in the high stable trajectory group ($P = 0.038$ or 0.044), using a low stable trajectory as a reference. Females and age <45 years did not significantly reduce the occurrence of hypertension in any of the trajectory groups (Table 4). The incidence of hypertension was significantly higher in males, subjects aged ≥45 years, and overweight subjects than in females, subjects aged <45 years, and normal weight subjects (Supplementary Table S2).

Cumulative average, standard deviation, baseline and end-stage serum albumin concentrations during 2009–2016 were ranked from smallest to largest and divided into five equal quintiles (Q1-Q5), with Q3 as the control. After full adjustment using the model, cumulative average serum albumin values were associated with increased hypertension prevalence during 2009–2016 for Q5 (OR, 0.74, 95% CI, 0.60–0.92). With serum albumin standard deviation Q5 (OR, 1.26, 95% CI, 1.04–1.54) ($P < 0.001$). Q1 of serum albumin at baseline was associated with an decreased incidence of hypertension (OR, 0.76, 95% CI, 0.61–0.95) ($P < 0.001$). There was no significant relationship between the end-stage serum albumin concentration and the prevalence of hypertension (Figure 3). Cumulative average, standard deviations, baseline-stage and end-stage serum albumin concentrations were then stratified by sex, age and body mass index (Supplementary Table S3).

The maximum, minimum, baseline-stage, end-stage, cumulative average and standard deviations of serum albumin concentrations from 2009 to 2016 were described as the median (IQR) according to the different trajectory groups. As shown in Supplementary Table S4, there were statistically significant differences ($P < 0.001$) in the maximum, minimum, baseline-stage, end-stage, cumulative average and standard deviations of serum albumin levels in the different trajectory groups.

4 Discussion

To our knowledge, this is the first study to examine the trajectories of serum albumin concentrations and the risk of hypertension in China. In this study, we identified different trajectories of serum albumin concentrations in adults by a group-based trajectory modeling approach. The traditional study approach of dividing participants into subgroups based on various characteristics, while usually ignoring population heterogeneity, may lead to inability to accurately identify internal relationships. There may be unusually large individual differences in serum albumin concentration levels and dynamics over time, and therefore dynamic trajectories of serum albumin concentrations may more accurately predict the risk of hypertension.

Overall, in this retrospective cohort study from 2009 to 2016 at Beijing Xiaotangshan Hospital, four different trajectories of serum albumin concentrations were observed in normal adults. Notably, the risk of developing hypertension was significantly lower in the high stable trajectory groups compared to the low stable group. This association was independent of sex, age, and whether overweight, and remained significant in male, age ≥45 years, normal weight, and overweight subjects. Sensitivity analyses revealed an association between high stable trajectory and prehypertension after full adjustment for covariates, with increases in the standard deviation of serum albumin concentrations and baseline serum albumin concentrations significantly associated with an increased probability of developing hypertension and increases in the cumulative mean of serum albumin concentrations significantly associated with a decreased probability of developing hypertension.

The cumulative incidence of hypertension in the study subjects was 12.87%, similar to the 9.77% observed in Liaoning, China, over a period of 4–6 years (14). The results of this study suggest that the incidence of hypertension is lower when serum albumin is in the high stability group. Previous cross-sectional studies have described the association between serum albumin and the risk of hypertension, and it has been suggested that serum albumin concentrations have been identified as protective factors against cardiovascular disease and are involved in several biologically active processes, such as maintenance of blood colloid permeation, transport and binding of various metabolites *in vivo*, and extracellular oxidative defense (2, 15). It has been suggested that serum albumin may influence blood pressure through a

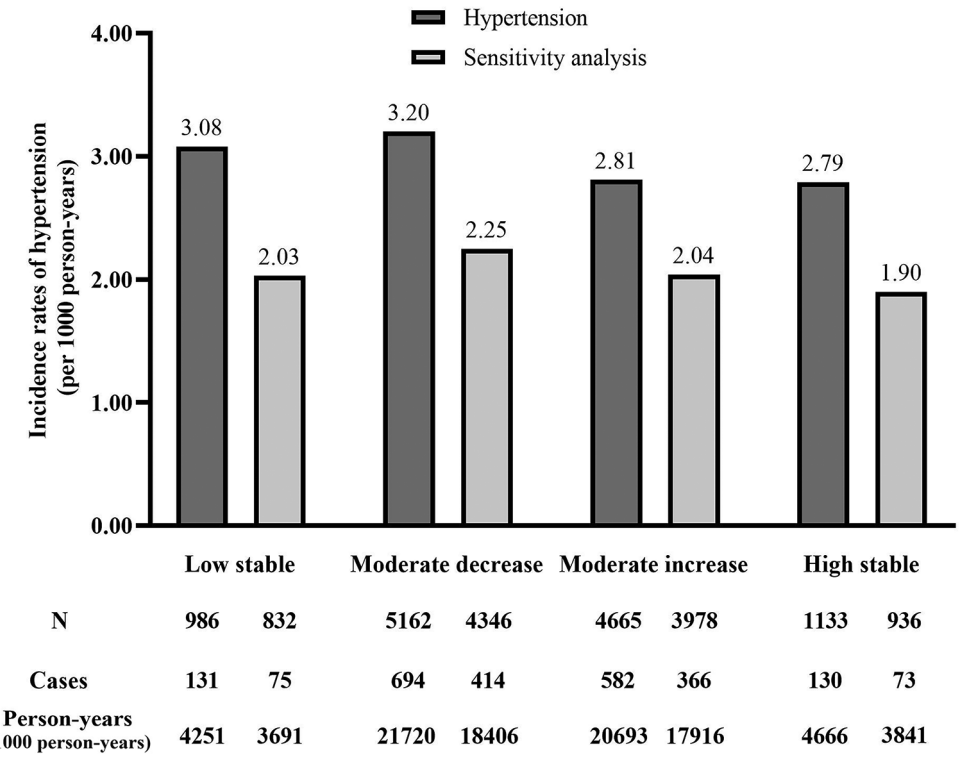

FIGURE 2
Incidence rates of hypertension in different serum albumin category groups (per 1,000 person-years). Hypertension indicates the annual incidence of hypertension in person-years. Sensitivity analysis indicates the annual incidence of hypertension in person-years after performing sensitivity analysis.

positive correlation mechanism with potassium concentration, which leads to a negative correlation between serum albumin and aldosterone (16). A positive relationship between albumin and potassium may inhibit the renin–angiotensin–aldosterone system, thus preventing hypertension development (17). There are also studies suggesting that the association between serum albumin and blood pressure may be linked to the binding of serum albumin to tryptophan, which has been shown to lower blood pressure (18–22), but tryptophan has not been shown to have a significant effect on blood pressure in other studies (23). It has also been suggested that serum albumin concentrations may affect intravascular osmotic pressure, which in turn affects blood pressure (24). At the same time, previous longitudinal studies have described an association between serum albumin trajectories and risk of hypertension. A five-year retrospective follow-up study in Japan found a positive association between serum albumin and serum potassium and a negative association with the development of hypertension (16). In a longitudinal cohort study in Korea, hypoalbuminemia was an important predictor of early hypertension progression (25).

TABLE 3 Association between cumulative average serum albumin during 2009–2016 and risk of hypertension.

	Cumulative average serum albumin during 2009–2016					*P*	Per 1-SD increase
	Q1	Q2	Q3	Q4	Q5		
n (cases)	2,389 (286)	2,389 (360)	2,389 (306)	2,398 (295)	2,381 (290)		11,946 (1,537)
Person-years	11,804	9,670	10,562	10,257	9,042		51,335
Incidence (per 1,000 person-years)	2.42	3.72	2.90	2.88	3.21		3.03
Model 1[a]	**1.30 (1.10–1.54)**	1.08 (0.91–1.28)	1.00 (ref)	1.03 (0.87–1.23)	1.02 (0.86–1.21)	0.278	0.98 (0.94–1.02)
Model 2[b]	1.05 (0.88–1.25)	0.91 (0.76–1.09)	1.00 (ref)	**0.81 (0.68–0.98)**	**0.69 (0.57–0.83)**	**<0.001**	**0.90 (0.87–0.94)**
Model 3[c]	1.07 (0.87–1.31)	0.96 (0.78–1.17)	1.00 (ref)	0.86 (0.71–1.06)	**0.74 (0.60–0.92)**	**0.001**	**0.92 (0.88–0.96)**
Sensitivity analysis ($n = 10,092$)[d]	1.17 (0.85–1.60)	1.04 (0.77–1.42)	1.00 (ref)	0.82 (0.61–1.13)	**0.58 (0.42–0.81)**	**0.008**	**0.85 (0.77–0.90)**

Data are odds ratios (ORs) and 95% confidence intervals (CIs).
[a]Crude model.
[b]Adjusted for age, sex, and follow-up time.
[c]Adjusted for covariates in Model 2 as well as smoking, alcohol consumption, diabete, obesity, body mass index, resting heart rate, systolic and diastolic blood pressure, fasting plasma glucose, triglycerides, total cholesterol, uric acid, blood urea nitrogen, creatinine, LDL-C, HDL-C, WBC, ALT, and AST.
[d]Adjusted for covariates in Model 3 and further excluding participants with pre-hypertension at baseline.
Bolded text in this table indicates that the data are statistically significant.

TABLE 4 Association between serum albumin change trajectory and risk of hypertensive stratified by sex, age and BMI.

	N (cases)	Low stable	Moderate decrease	Moderate increase	High stable	*P*
Male	6,644 (1,126)	1.00 (ref)	0.87 (0.63–1.22)	0.89 (0.63–1.25)	**0.68 (0.46–0.98)**	0.114
Female	5,302 (411)	1.00 (ref)	0.93 (0.64–1.34)	1.05 (0.75–1.49)	0.58 (0.27–1.08)	0.728
Age <45 years	7,196 (757)	1.00 (ref)	1.10 (0.70–1.80)	1.24 (0.79–2.02)	0.86 (0.50–1.48)	0.636
Age ≥45 years	4,750 (780)	1.00 (ref)	0.85 (0.64–1.14)	**0.76 (0.58–1.00)**	**0.57 (0.37–0.87)**	**0.008**
Normal	5,157 (352)	1.00 (ref)	0.71 (0.47–1.05)	**0.64 (0.43–0.95)**	**0.51 (0.29–0.88)**	**0.014**
Overweight	6,789 (1,185)	1.00 (ref)	0.96 (0.72–1.30)	1.02 (0.77–1.37)	**0.68 (0.47–0.99)**	0.170

All analyses were adjusted age, sex, smoking, alcohol consumption, diabete, obesity, body mass index, resting heart rate, systolic and diastolic blood pressure, fasting plasma glucose, triglycerides, total cholesterol, uric acid, blood urea nitrogen, creatinine, LDL-C, HDL-C, WBC, ALT, AST, and follow-up time.
Data are odds ratios (ORs) and 95% confidence intervals (CIs).
Bolded text in this table indicates that the data are statistically significant.

In this study, our analysis of sex differences showed that the relationship between the four serum albumin concentration trajectories and hypertension varies by sex. Specifically, male subjects were significantly more likely to have hypertension than female subjects, and the incidence of hypertension was significantly lower in the high stable trajectory group, using the low stable trajectory as a reference group. Although hypertension occurs in both males and females, it tends to be significantly higher in males than in females in the same age group (26, 27). A longitudinal study of 3,872 participants in Japan found that for every standard deviation increase in the serum albumin concentration, the risk of hypertension decreased in both males and females (7). Our study showed that the trajectory of serum albumin concentrations was only associated with the incidence of hypertension in males. We found a higher prevalence of hypertension in subjects ≥45 years of age and a stronger association between moderate increase and high stable trajectories and hypertension risk in subjects ≥45 years of age, indicating a significant decrease in hypertension prevalence. In humans, serum albumin levels in both males and females peak at age 20 and begin to decline with age, according to a cross-sectional study in the UK (28), the difference between males and females may be hormonal. The results of this study showed that in normal weight subjects, there was a difference between moderate increase and high stable serum albumin level trajectories and a low incidence of hypertension, while among overweight subjects, there was a difference between a high stable trajectory and a low incidence of hypertension. People who are

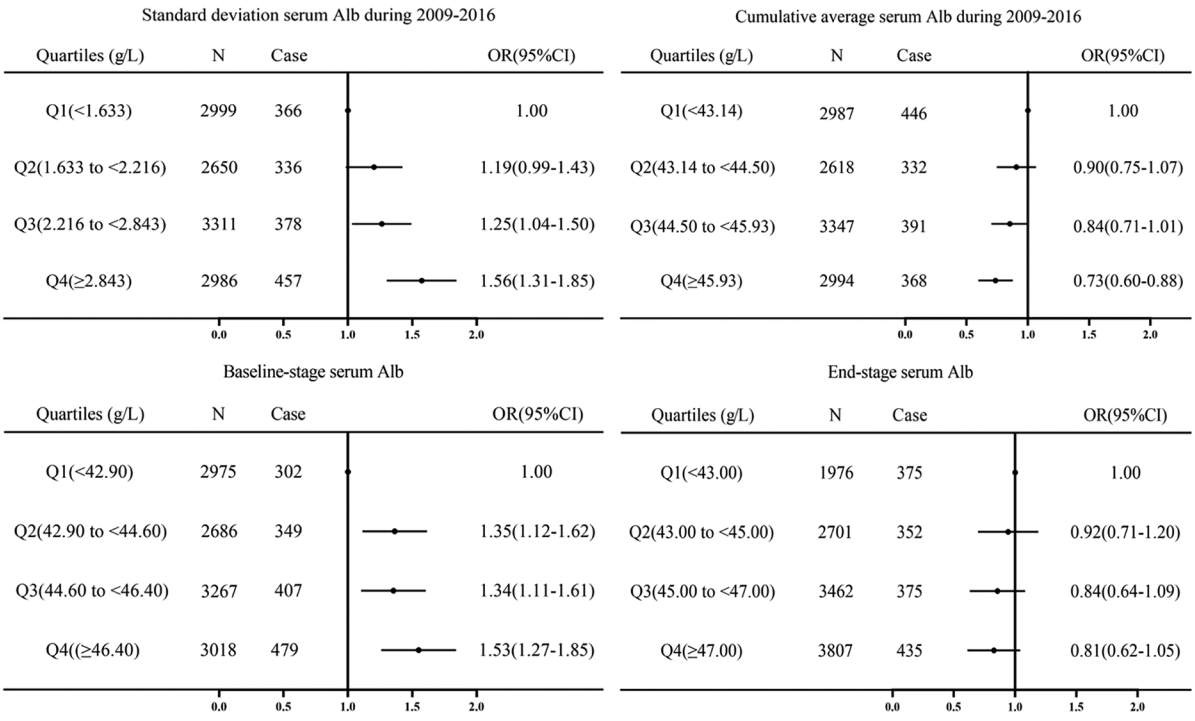

FIGURE 3
Cumulative average, standard deviation, baseline-stage and end-stage of serum albumin from 2009 to 2016 were divided into quintiles, with Q3 as the control group, and logistic regression adjusted for sex, age, smoking, alcohol consumption, diabete, obesity, body mass index, resting heart rate, systolic and diastolic blood pressure, fasting plasma glucose, triglycerides, total cholesterol, uric acid, blood urea nitrogen, creatinine, LDL-C, HDL-C, WBC, ALT, AST, and follow-up time after posterior odds ratios (ORs) and 95% CIs.

classified as overweight are more likely to have high blood pressure than those who are not. From 2009 to 2016, the cumulative mean and annual increases in serum albumin concentrations increased, and these increases were associated with the incidence of hypertension. A trend study conducted in Japan between 1980 and 2010 showed a 1.5-fold increase in the effect of being overweight on high blood pressure compared to normal weight people (29). In a study of 131,395 Asian adults, overweight was associated with high blood pressure in all age groups (30), which is consistent with the results of the current study. Overweight and obesity have been linked to several diseases, including chronic inflammation (31). In addition, inflammation may be a major cause of the decrease in serum albumin concentrations (32). Since inflammation is one of the known pathophysiological mechanisms of hypertension, one theory is that low serum albumin is associated with hypertension.

Although the underlying mechanisms linking serum albumin trajectories to the development of hypertension have not been fully elucidated, this finding provides some evidence that the optimal state of serum albumin may be a pattern of high stability within the normal range. Hypertension, as the most important risk factor for cardiovascular disease, causes great physical discomfort to patients and imposes a huge economic burden on patients and their families. Therefore, it is extremely important to propose early interventions for preventive measures against risk factors.

The most important advantage of our study is the large sample size and longitudinal retrospective cohort study design. There are limitations to the study that should be noted. First, the number of patients with hypertension was relatively small during the study period (7 years). Further studies are needed to investigate changes in serum albumin concentrations over time. Second, because the data came from highly educated employees and the proportion of males was high, the study was generally not representative. Therefore, more research is needed in the future to validate our findings.

5 Conclusion

In summary, our population-based trajectory modeling approach identified four different trajectories of serum albumin concentrations in Chinese adults. We found that a moderate increase in serum albumin concentrations and a high stable trajectory were significantly associated with a reduced hypertension risk in subjects ≥45 years of age and of normal weight. A high stable trajectory of serum albumin concentrations was significantly associated with a reduced risk of hypertension in both males and overweight subjects.

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 Department of Health Management, Beijing Xiaotangshan Hospital, Beijing, China. 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

YL: Conceptualization, Software, Writing – original draft, Writing – review & editing. SX: Methodology, Project administration, Writing – review & editing. HC: Writing – review & editing. SD: Writing – review & editing. JH: Writing – review & editing. XC: Writing – review & editing. JZ: Writing – review & editing. SL: Writing – review & editing. JL: Writing – review & editing. FH: Writing – review & editing. YL: Writing – review & editing. CW: Writing – review & editing.

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Conflict of interest

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

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2024.1325899/full#supplementary-material

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EDITED BY
Zhendong Liu,
Shandong First Medical University, China

REVIEWED BY
Emmanuel Andrès,
Hôpitaux Universitaires de Strasbourg, France
Gustavo Duarte,
New Zealand Blood Service, New Zealand

*CORRESPONDENCE
Yunbo Zhang
✉ zhangyunbo1982@126.com

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Hospitalization of patients with nutritional anemia in the United States in 2020

Jie Tian, YangYang Fan, Xin Wei, Jiangli Li, ZeLong Yang, Xiaolin Na and Yunbo Zhang*

Department of Environmental Hygiene, Public Health College, Harbin Medical University, Harbin, Heilongjiang, China

Background: Nutritional anemia is highly prevalent and has triggered a globally recognized public health concern worldwide.

Objective: To better understand the prevalence of anemia and the state of nutritional health in developed countries to inform global nutritional health and better manage the disease.

Method: We employed the Healthcare Cost and Utilization Project (HCUP)-2020 National Inpatient Health Care Data (NIS), administered by The Agency for Healthcare Research and Quality. Nutritional anemia was diagnosed according to the International Classification of Diseases, 10th Revision (ICD-10). Matching analysis and multivariate regression were used to adjust for patient and hospital characteristics. Controls were obtained by stratifying and matching for age and sex.

Results: The 2020 HCUP-NIS database encompassed a survey over 6.4 million hospitalized patients, among which 1,745,350 patients diagnosed with anemia, representing approximately 26.97% of the hospitalized population, over 310,000 were diagnosed with nutritional anemia, and 13,150 patients were hospitalized for nutritional anemia as primary diagnosis. Hospitalization rate for nutritional anemia exhibited an increased age-dependent increase nationwide, especially among females, who displayed 1.87 times higher than males. Notably, in comparison to the control group, individuals of the Black race exhibit a higher prevalence of nutritional anemia (case group: 21.7%, control group: 13.0%, $p < 0.001$). In addition, hospitalization rates were higher among low-income populations, with lower rates of private insurance (case group: 18.7%, control group: 23.5%, $p < 0.001$) and higher rates of Medicaid insurance (case group: 15.4%, control group: 13.9%, $p < 0.001$). In areas characterized by larger urban centers and advanced economic conditions within the urban–rural distribution, there was an observed increase in the frequency of patient hospitalizations. Iron deficiency anemia emerged as the predominant subtype of nutritional anemia, accounting for 12,214 (92.88%). Secondary diagnosis among patients hospitalized for nutritional anemia revealed that a significant number faced concurrent major conditions like hypertension and renal failure.

Conclusion: In economically prosperous areas, greater attention should be given to the health of low-income individuals and the older adult. Our findings hold valuable insights for shaping targeted public health policies to effectively address the prevalence and consequences of nutritional anemia based on a overall population health.

KEYWORDS

HCUP NIS, nutritional anemia, hospitalization, public health, iron deficiency anemia

1 Introduction

Nutritional anemia is a disease characterized by inadequate formation of hemoglobin or the production of red blood cells is insufficient due to the relative or absolute reduction in essential nutrients required for blood production within the body, such as iron, folic acid, and vitamin D, resulting in low hematopoietic function (1). This condition is most prevalent among infants and young children aged 6 months to 2 years (2), pregnant or lactating women, and individuals with impaired nutrients absorption due to gastrointestinal disorders (3–5). Nutritional anemia can lead to a lack of oxygen in the body, causing the patient to feel tired, weak, and experience symptoms such as dizziness, panic, and shortness of breath. Severe anemia may affect the functioning of the heart, lungs, and other organs, leading to serious problems such as palpitations, angina, and difficulty breathing (6, 7). Nutritional anemia during childhood may lead to poor concentration, reduced learning ability, and delayed mental development (8). Nutritional anemia in pregnant women increases the risk of preterm birth, low birth weight and fetal growth retardation and affects the normal functioning of the immune system, reducing the body's resistance to disease and increasing the risk of infection (9, 10).

The World Health Organization estimates that approximately a quarter of the global population is suffering from anemia (11). Nutritional anemia tends to be underestimated due to absence of immediate life-threatening consequences, leading to reduced attention from both the individuals and the general public. In 2021, anemia affected approximately 24.3% of the global population across all age groups with totaling 1.92 billion cases, contrasting with rates of 28.2% and 1.50 billion cases recorded in 1990 (12). Although the United States has a lower incidence of anemia compared to the global average, a previous research based on the National Health and Nutrition Examination Survey (NHANES) database indicated an almost doubling of cases, rising from 4.03% in 1999 to 6.49% in 2020 (13). Other studies (14, 15) have also shown that the prevalence of anemia in the U.S. has been increasing every year for the last 20 years, which serves as a warning highlighting the need to pay greater attention to anemia. However, its sample size was relatively small, and it lacked detailed information including subtypes of anemia, the causes of anemia as well as the hospitalization and care of patients. In order to better understand the epidemiological characteristics of nutritional anemia as well as medical treatment in the United States, we performed a comprehensive analysis of nutritional anemia based on the Healthcare Cost and Utilization Project (HCUP)-2020 National Inpatient Medical Data (NIS), which is managed by the Agency for Healthcare Research and Quality (AHRQ). The aim of present study is to offer valuable recommendations to governments and the general public, contributing to the enhancement of human health.

2 Methods

2.1 Data source

For research purposes, we analyzed the 2020 HCUP-NIS database. The HCUP is a database series developed under the auspices of the Agency for Healthcare Research and Quality (AHRQ) that contains all patient encounter, clinical, and nonclinical information since 1988. It is the largest publicly available database of inpatient care information available in the United States. The HCUP-NIS contains discharge data from more than 1,000 hospitals and represents a stratified sample of 20% of community hospitals, which enable research on a wide range of health policy issues, including cost and quality of health services, medical practice patterns, access to health care programs, treatment outcomes at the national, state, and local levels.

2.2 Study design and sample

This study conducted a descriptive analysis of all patients hospitalized for nutritional anemia in the 2020 HCUP-NIS dataset. The dataset contained a total of 6,471,165 hospitalized patients, in which nutritional anemia was diagnosed according to the International Classification of Diseases, Tenth Revision (diagnostic codes: ICD-10/D50~D53, See Supplementary materials for details), and a total of 13,150 patients with the first diagnosis (hospitalized for nutritional anemia) were included. Since age and gender are extremely important influences on nutritional anemia, adjustments were made to mitigate their effects on other variables. Due to the absence of gender information for one case in 13,150 patients, we could only match 13,149 patients in a ratio of 1:5 stratified by age and sex (16), resulting in a total of 65,745 controls (individuals not suffering from nutritional anemia) being included in present study. All patient data have been de-identified.

2.3 Element descriptions

We did a systematic analysis of variables such as age, gender, race, income, insurance class, patient care, and location of the patient for control and case groups included in the analysis. Age is classified according to the age segment of the HCUP database itself: < 1 year, 1–17 years, 18–44 years, 45–64 years and ≥ 65 years. Gender was classified into male and female. Racial classification included White, Black, Hispanic, Asian/Pacific Islander, Native American, and Other. Median household income national quartile annual variance for patient was classified as First quartile (1–49,999), Second quartile (50000–64,999), Third quartile (65000–85,999), and Fourth quartile (>86,000). Type of insurance was classified as Medicare, Medicaid, Private insurance, Self-pay, No charge, and Other. Location of patient was classified as Large Central Metro (≥ 1 million population), Large Fringe Metro (≥ 1 million population), Medium Metro (250000–999,999 population), Small Metro (50000–249,999 population), Micropolitan, and Noncore. Patient care status was classified as Discharged to home or self care, Transfer: short-term hospital, Transfer: other type of facility, Home health care, against medical advice, Died in hospital, Discharged alive, and destination unknown. Location of Hospital was classified as New England, Middle Atlantic, East North Central, West North Central, South Atlantic, East South Central, West South Central, Mountain, and Pacific.

2.4 Statistical analysis

The data were processed using the official website SAS software code after obtaining the official license from HCUP. All data were

statistically analyzed by SPSS version 26. Means (M) and standard deviations (SD) were calculated and T-tests were used for continuous variables, and frequencies and percentages were presented for categorical variables. Differences between the control and case groups were assessed by chi-square test (p *value* < 0.05 as statistically significant). Regression analysis was used to adjust for each hospital variable. Tool GraphPad Prism 8 for graphic design.

3 Results

3.1 Nutritional anemia prevalence trends 2016–2020

In 2020, there were a total of 6,471,165 hospitalizations in the United States HCUP database. About 1,745,350 patients diagnosed with anemia, representing approximately 26.97% of the hospitalized population. Among them, a total of 315,004 were diagnosed with nutritional anemia (N for All-Listed). The prevalence was 4.87%, implying that 4–5 out of every 100 hospitalizations were for nutritional anemia. In addition, 13,150 were hospitalized for nutritional anemia as the first diagnosis (N for DX1).

Since 2016, the number of hospitalizations for patients with nutritional anemia has slightly trended downward, from 15,278 in 2016 to 13,150 in 2020, a decrease of about 13.93% (Figure 1). Among all the types of nutritional anemia, iron deficiency anemia was the main type of anemia accounting for 92.88%, while other types nutritional anemia such as folic acid, Vitamin B12, and other nutrient deficiencies resulting in anemia accounted for only 7.12% in 2020.

3.2 Demographic and statistical characteristics

The average age of patients hospitalized with nutritional anemia as the first diagnosis was 63.34 years (95% confidence interval: 62.99–63.66), and the mean length of hospitalization was 3.29 days (95% CI: 3.23–3.34), average cost per hospitalized patient was $39,147.07. Both the number of hospitalized patients and the length of hospitalization increased with advancing age. Among all the patients with nutritional anemia, the number of female patients was 1.88 times higher than male patients, and over half of the hospitalized patients were older adult, with 56.5% being older than 65 years (Table 1). There were relatively more Black and Hispanic individuals in the case group compared to controls, with the primary contrast observed between Black and White individuals (White: 60.4% vs. 71.1%; Black: 21.7% vs. 13.0%, $p < 0.001$). Income and nutritional anemia prevalence were negatively correlated, with higher prevalence in the low-income group. In addition, among payment types, the case group had a relatively high proportion of Medicare and Medicaid coverage and a relatively low proportion of private coverage (18.7% vs. 23.5%, $p < 0.001$). Compared to the control group, patients with nutritional anemia showed a higher inclination towards opting self-care at home after discharge from the hospital (70.1% vs. 60.1, $p < 0.001$) rather than continuing treatment in other health care units or choosing home care health care. The data showed that larger cities tended to have a higher incidence of nutritional anemia, with large central cities accounting for 31.2% of the cases, compared to only 6.7% in non-core cities.

3.3 Distribution of patients by region

As shown in Figure 2, a notable concentration of nutritional anemia patients were located in the eastern region (>20%), especially with the highest distribution in the Atlantic region, followed by the northeastern region, and the lowest prevalence in the Mountain region as well as the northwestern region (Detailed values are given in Table 1).

3.4 Results of regression analysis of variables

The regression analysis outcomes were presented in Table 2, revealing a notable association ($p < 0.001$) between nutritional

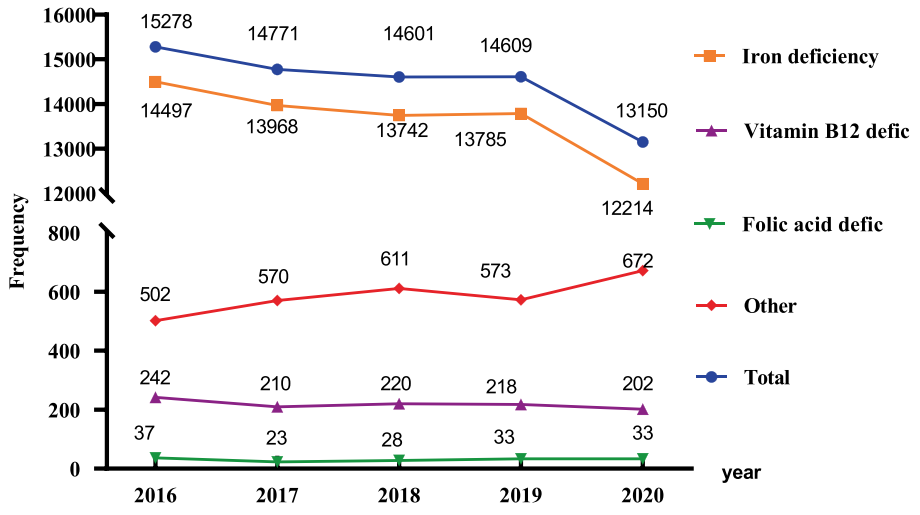

FIGURE 1
Nutritional anemia trend graph from 2016 to 2020.

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TABLE 1 Study sample characteristics of nutritional anemia (case group vs. matched group).

Characteristic	Individuals with a diagnosis of nutritional anemia	Effective percentage	Individuals without a diagnosis of nutritional anemia	Effective percentage	*p*
Age in years, *n* (%)					1.00
<1	18	0.2	90	0.2	
1–17	474	3.6	2,370	3.6	
18–44	1884	14.3	9,420	14.3	
45–64	3,345	25.4	16,725	25.4	
≥65	7,429	56.5	37,140	56.5	
Gender, *n* (%)					1.00
Female	8,581	65.3	42,905	65.3	
Race, *n* (%)					<0.001
White	7,766	60.4	45,547	71.1	
Black	2,787	21.7	8,303	13.0	
Hispanic	1,508	11.7	6,425	10.0	
Asian/Pacific Islander	303	2.4	1,588	2.5	
Native American	82	0.6	370	0.6	
Other	403	3.1	1860	2.9	
Annual median household income national quartile, *n* (%)					<0.001
1–49,999	4,419	34.1	19,087	29.5	
50,000–64,999	3,419	26.4	17,618	27.2	
65,000–85,999	2,822	21.8	14,994	23.2	
>86,000	2,283	17.6	12,988	20.1	
PAY, *n* (%)					<0.001
Medicare	7,585	57.7	36,948	56.3	
Medicaid	2022	15.4	9,136	13.9	
Private insurance	2,451	18.7	15,460	23.5	
Self-pay	728	5.5	2070	3.2	
No charge	66	0.5	165	0.3	
Other	288	2.2	1883	2.9	
Disposition of patient (uniform), *n* (%)					<0.001
Discharged to home or self care	9,209	70.1	39,497	60.1	
Transfer:short-term hospital	146	1.1	1,325	2.0	
Transfer: other type of facility	1,581	12.0	10,429	15.9	
Home health care	1804	13.7	11,460	17.4	
Against medical advice	340	2.6	954	1.5	
Died in hospital	66	0.5	2028	3.1	
Discharged alive, Destination unknown	–*	-	22	0.0	
Patient location, *n* (%)					<0.001
Large Central Metro	4,080	31.2	17,977	27.5	
Large Fringe Metro	3,272	25.0	15,913	24.3	
Medium Metro	2,727	20.9	13,920	21.3	
Small Metro	1,089	8.3	6,327	9.7	
Micropolitan	1,037	7.9	6,350	9.7	
Noncore	871	6.7	4,927	7.5	

(Continued)

TABLE 1 (Continued)

Characteristic	Individuals with a diagnosis of nutritional anemia	Effective percentage	Individuals without a diagnosis of nutritional anemia	Effective percentage	*p*
Census division of hospital, *n* (%)					<0.001
New England	676	5.1	3,378	5.1	
Middle Atlantic	2038	15.5	9,075	13.8	
East North Central	1868	14.2	9,617	14.6	
West North Central	770	5.9	4,749	7.2	
South Atlantic	3,113	23.7	13,947	21.2	
East South Central	948	7.2	4,081	7.1	
West South Central	1,683	12.8	7,944	12.1	
Mountain	525	4.0	4,266	6.5	
Pacific	1,529	11.6	8,088	12.3	
Hospitalizations, *n* (%)					
Total	13,150	100	65,745	100	

*indicates a value less than 10.

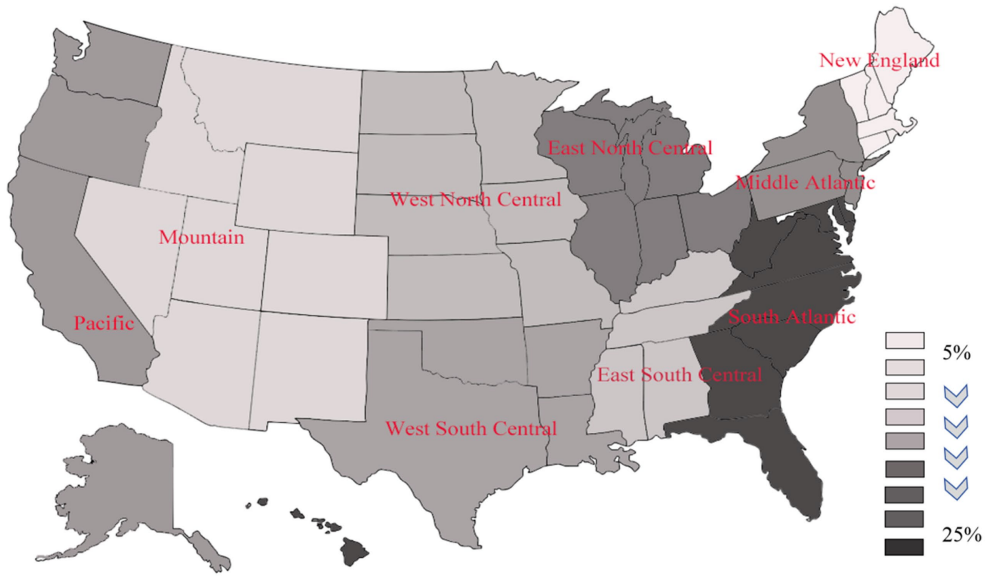


FIGURE 2
Regional distribution of nutritional anemia in the United States in 2020.

anemia and age, race, whether admission was chosen, location of the hospital, the presence of multiple injuries, length of hospitalization, mode of payment, income, and the transfer of the patient into and out of the hospital. While gender and month of admission yielded statistically insignificant findings. Regarding age and race, advanced age emerged as a risk factor, indicating that older individuals are more likely to develop nutritional anemia. Additionally, there is a higher prevalence of nutritional anemia among racial groups other than white race. Furthermore, a negative correlation was observed between factors such as economic income, length of hospitalization, and the prevalence of the disease.

3.5 Statistics on other secondary diagnoses of patients with nutritional anemia

Statistical findings of secondary diagnoses of 13,150 patients hospitalized with nutritional anemia revealed a substantial occurrence of underlying conditions, including hypertension, hyperlipidemia, and renal failure. The top 12 diseases in secondary diagnoses are presented in Figure 3, with specific details shown in Table 3. Notably, among top related 12 diseases, 26.9% of patients with nutritional anemia suffered from hypertension, 21.1% suffered from hyperlipidemia diseases, and 15.3% suffered from diseases such as infectious diseases.

3.6 Statistical results of secondary diagnoses of patients who died during hospitalization

Among the 66 deaths from nutritional anemia (Figure 4), it was shown by their second diagnosis that 23 cases (34.85%) suffered from acute respiratory failure with hypoxia, 7 cases (10.61%) suffered from heart failure, and 5 cases (7.58%) suffered from sepsis (Figure 4).

TABLE 2 Association of adverse hospital outcomes in nutritional anemia.

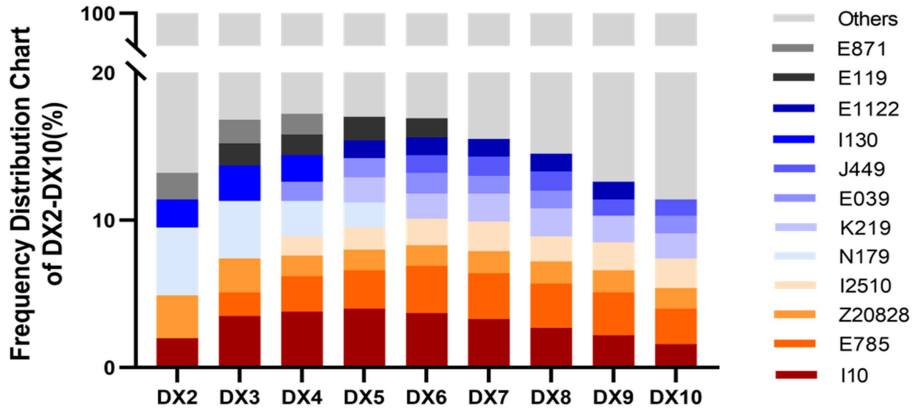
Variables	Odds ratio	95% Confidence interval		*p*
		Lower	Upper	
AGE	1.002	1.001	1.003	<0.001
FEMALE	1.004	0.963	1.047	0.85
RACE	1.078	1.060	1.097	<0.001
AMONTH	1.004	0.998	1.009	0.19
ELECTIVE	0.189	0.171	0.210	<0.001
HOSP_DIVISION	0.975	0.967	0.984	<0.001
MULTINJURY	0.267	0.224	0.319	<0.001
LOS	0.939	0.932	0.947	<0.001
PAY	0.970	0.951	0.990	0.003
PL_NCHS	0.944	0.930	0.957	<0.001
TRAN_IN	0.902	0.858	0.947	<0.001
TRAN_OUT	0.880	0.852	0.908	<0.001
ZIPINC_QRTL	0.901	0.884	0.918	<0.001

HOSP_DIVISION, Location of the hospital; MULTINJURY, Multiple damage; LOS, Length of hospitalization; PAY, Payment Methods; PL_NCHS, Urban–rural divide; TRAN_IN, Transferred to hospital; TRAN_OUT, Transferred to other health units.

4 Discussion

This article provides a comprehensive description of the inpatient burden among individuals with nutritional anemia based on cross-sectional analysis of a nationally representative hospitalization database. Our analysis of patient and hospital observations revealed that over one-fourth of hospitalized patients suffer from anemia, and nearly 5% of them have nutritional anemia. Specifically, more than 90% of patients hospitalized with nutritional anemia exhibited the iron-deficiency anemia subtype, with primarily affecting individuals over 65 years old. Hospitalizations were more frequent in females and in economically developed regions, particularly among low-income populations. Secondary diagnoses indicated a significant presence of cardiovascular and renal conditions, with acute respiratory and heart failures associated with fatal cases. Our findings warrant significant attention. We have identified that the prevalence of anemia among hospitalized patients remains unacceptably high. This calls for serious consideration within the healthcare sector. It is imperative to implement measures for the prevention and management of this issue. Additionally, gaining insights into the regional variations in anemia prevalence can facilitate more effective resource allocation and inform the development of healthcare policies.

Compared with previous studies (13, 15, 17), our research contributed significant insights into hospitalizations related to nutritional anemia. We conducted basic analyses to delve into the disease's etiology and explored the impact of factors like age, gender, race, and economic conditions. The results showed that the number of nutritional anemia patients demonstrated a positive correlation with age, partially explaining the increase in hospitalizations and extended lengths of stay among older individuals. Additionally, age-related declines in bodily functions and immunity, along with reduced mobility, may account for the



I10: Idiopathic hypertension E785:Unspecified hyperlipidemia
Z20828:Contact and exposure to other infectious diseases
I2510 Atherosclerotic heart disease N179 Acute renal failure NOS
K219Gastro-esophageal reflux disease without esophagitis
E039 Unspecified hypothyroidism J449 Unspecified chronic obstructive pulmonary disease
I130Acute pericarditis E11 Non-insulin-dependent diabetes mellitus
E871 Low osmolality and hyponatremia

FIGURE 3
Distribution of the top 12 diseases.

TABLE 3 Frequency statistics of the top 12 diseases.

Disease code	ICD-10-CM Diagnosis:Other diagnoses 2 to 10										
	DX2	DX3	DX4	DX5	DX6	DX7	DX8	DX9	DX10	Totals	Valid percent
I10	258	459	506	523	493	440	354	291	208	3,532	26.9
E785	204	311	341	415	411	394	385	316	–*	2,777	21.1
Z20828	381	308	189	179	182	193	194	194	188	2008	15.3
I2510	267	237	266	249	250	202	166	225	–	1862	14.2
N179	605	508	318	224	–	–	–	–	–	1,655	12.6
K219	217	221	228	254	241	–	–	–	–	1,161	8.8
E039	185	152	177	172	158	153	–	–	–	997	7.6
J449	170	171	151	151	158	–	–	–	–	801	6.1
I130	312	234	248	–	–	–	–	–	–	794	6.0
E1122	157	153	157	160	163	–	–	–	–	790	6.0
E119	189	204	171	194	–	–	–	–	–	758	5.8
E871	207	180	239	–	–	–	–	–	–	626	4.8

–* denote no value; DXn, Other diagnostics; I10, Idiopathic hypertension; E785, Unspecified hyperlipidemia; Z20828, Contact and exposure to other infectious diseases; I2510, Atherosclerotic heart disease; N179, Acute renal failure NOS; K219, Gastro-esophageal reflux disease without esophagitis; E039, Unspecified hypothyroidism; J449, Unspecified chronic obstructive pulmonary disease; I130, Acute pericarditis; E1122, Non-insulin-dependent diabetes mellitus; E871, Low osmolality and hyponatremia.

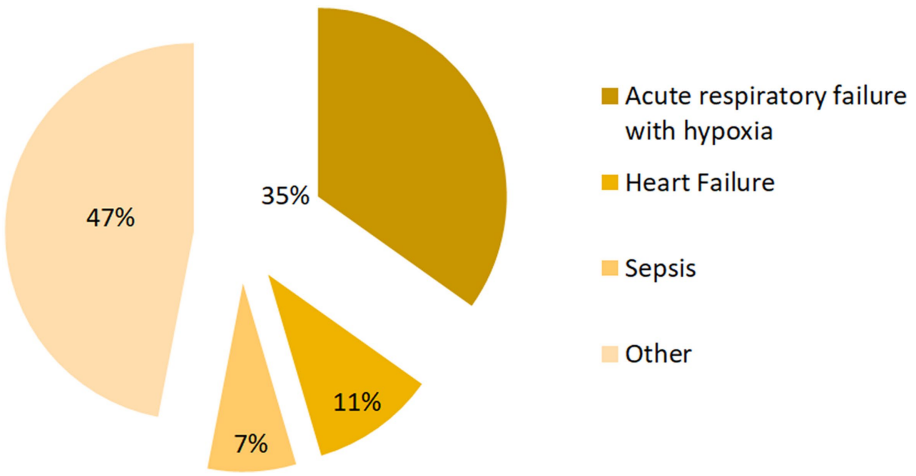


FIGURE 4
Secondary diagnosis in cases of death during hospitalization with nutritional anemia.

higher hospitalization rates among the older adult compared to young adults (18–20). Furthermore, the higher number of female patients can be attributed to physiological factors like menstrual loss and abnormal uterine bleeding (21, 22).

Economic conditions play a significant role in influencing nutritional anemia, where lower income is associated with higher prevalence. A notable difference in the prevalence of first quartile income was observed compared to the control group, consistent with existing literature (23, 24). This phenomenon could potentially be attributed to the limited access to healthy food in areas where economically disadvantaged and vulnerable populations reside (25, 26). In addition, the disparity in payment methods was evident through a lower prevalence of private insurance and a higher rate of Medicaid insurance compared to the control group, showcasing the potential impact of economic conditions on payment methods. This underscores the substantial influence of income on hospital admissions for nutritional anemia (27). Urbanization has been linked to an increase in anemia-related hospitalizations, with a notable concentration of nutritional anemia cases in the eastern and northwestern regions of the country. The urban low-income population constitutes the main population of hospitalization, which might be connected to life and work pressure, patients' awareness of medical care, and the potential for reduced food expenditures due to financial stress among low-income urban individuals, ultimately leading to nutritional deficiencies. Moreover, certain remote and economically disadvantaged regions may see limited access to medical care due to financial constraints. This is all worth

exploring in depth in future studies. Besides, hospitalizations for nutritional anemia in the United States are a gradual decline from 2016 to 2020, which is slightly different from the previous studies (13, 17). This decline could be attributed to the implementation of health policies and healthcare reforms in the previous years, alongside ongoing advancements in medical care and improving economic conditions. The main type of nutritional anemia is iron-deficiency anemia, which accounts for 92.88% of the prevalence. Addressing this, increasing the consumption of iron-rich foods or iron supplements stands out as a viable approach to mitigate anemia (28, 29).

In this study, we also found that nutritional anemia often coexisted with many other diseases, such as idiopathic hypertension, unspecified hyperlipidemia, infectious diseases, etc. Therefore, it is suggested individuals with nutritional anemia should pay close attention to monitoring the occurrence of these diseases. In addition, the second diagnosis of 66 deaths were 23 cases (34.85%) with acute respiratory failure with hypoxia and 7 cases (10.61%) with heart failure, which were the main comorbidities this may be associated with nutritional anemia (22, 30–34). Early detection of the causes of nutritional anemia and correction of malnutrition, nutritional supplementation and a balanced diet are key to preventing adverse outcomes. Many experts have indicated that investment in education can reduce the risk of anemia later in life, so raising awareness of nutritional health for all is a viable recommendation for reducing anemia (35–37). Currently, Nutritional counselling during antenatal care (38, 39), provision of micronutrients, management of family planning (40), dissemination of nutritional information and rational distribution of medical care for management of underlying chronic diseases are all feasible ways to reduce the prevalence of anemia (41).

Several limitations of this study should be acknowledged. Firstly, the focus of the article is limited to nutritional anemia, while other causes of anemia are not described. Secondly, the accuracy of the diagnostic results could not be independently verified. Thirdly, the presence of duplicate inpatients was not ascertainable, raising uncertainty regarding the exclusion of duplicated cases. Lastly, the severity of nutritional anemia in hospitalized patients were not available, which may result in overlooking the influence of severity when investigating the relationships between anemia and other variables.

5 Conclusion

In this study, we performed a descriptive analysis of nutritional anemia using the HCUP-NIS database. The findings revealed a notably high prevalence of anemia and nutritional anemia among hospitalized patients in the United States. Vulnerable groups, including older individuals and those with lower income levels, appeared to be at heightened risk for nutritional anemia. Furthermore, nutritional anemia frequently co-occured with various comorbidities such as hypertension, hyperlipidemia, etc. Hence, there is a pressing need to bolster public health management initiatives and enact relevant measures aimed at improving the overall health status of the population.

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. The HCUP-NIS database is available for public access. (https://www.hcup-us.ahrq.gov/).

Author contributions

JT: Formal analysis, Writing – original draft, Data curation. YF: Writing – original draft, Validation. XW: Investigation, Writing – original draft. JL: Conceptualization, Writing – original draft, Investigation. ZY: Data curation, Writing – original draft. XN: Supervision, Writing – review & editing. YZ: Funding acquisition, Project administration, 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/fpubh.2024.1333069/full#supplementary-material

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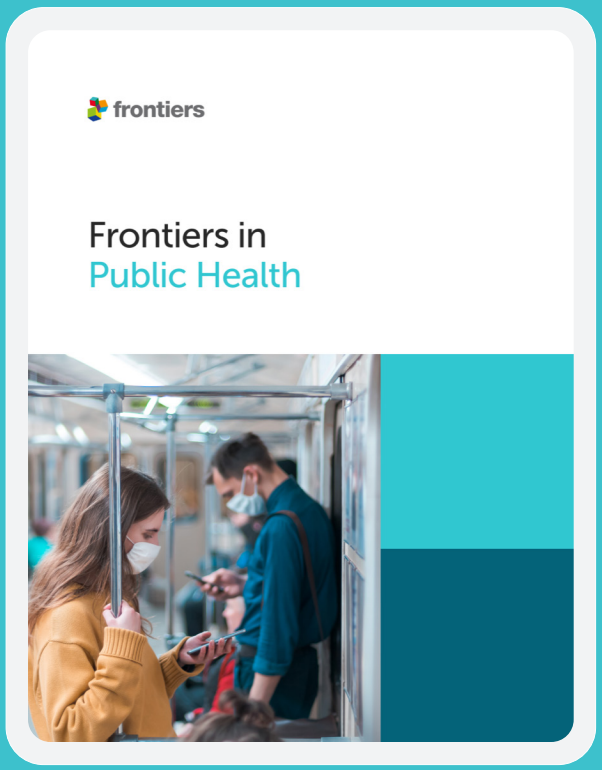

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