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Association of novel anthropometric indexes with metabolic syndrome and beyond, volume II

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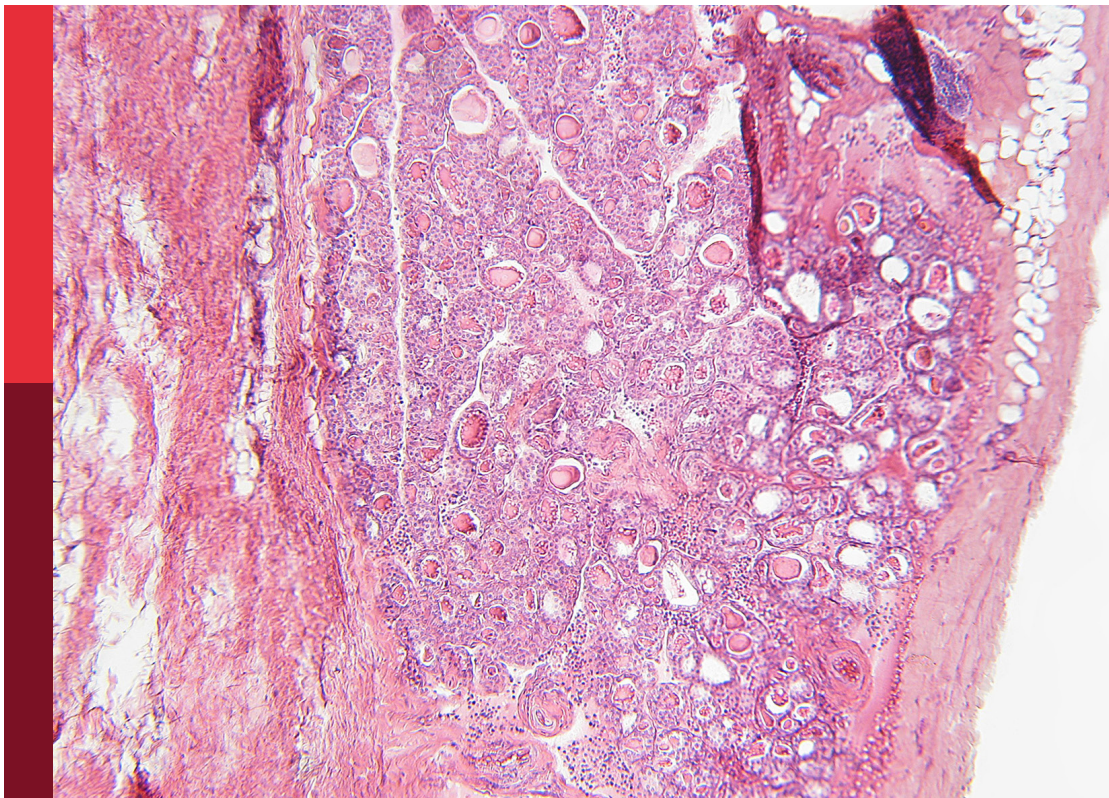

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Association of novel anthropometric indexes with metabolic syndrome and beyond, volume II

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Editorial: Association of novel anthropometric indexes with metabolic syndrome and beyond, volume II

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Editorial on the Research Topic
Association of novel anthropometric indexes with metabolic syndrome and beyond, volume II

Obesity has become a primary global health concern. One cannot deny the role of the increasing prevalence of obesity in the surging trend of cardiometabolic conditions such as type 2 diabetes (T2DM), hypertension (HTN), dyslipidemia, insulin resistance (IR), and many other conditions (1, 2). Hence due to the importance of the subject, we have tried to provide a more accurate definition for obesity to prevent, find and treat the affected cases more effectively. Body Mass Index (BMI), which is the weight/square of height, has been used to define obesity since the 70s; however, despite many benefits, it suffers from certain flaws, as it measures excess weight only rather than excess fat. Thus new anthropometric measures have recently emerged to define obesity whirls overcoming the known flaws of BMI (3, 4). In volume II of the Research Topic entitled "*Association of Novel Anthropometric Indexes with Metabolic Syndrome and Beyond*" similar to the previous volume, the links between these novel anthropometric indices, obesity, and cardiometabolic risk factors have been evaluated. Overall, most of the researches included in the current Research Topic were from China and the US. These studies assessed the role of new anthropometric measurements for early detection of obesity, metabolic syndrome (MetS), IR and their association with less studied comorbidities such as renal function.

Despite the virtues of the BMI measurement, it is incapable of distinguishing lean and fat body mass from one another; another critical flaw of BMI measurement is its various classifications based on age, ethnicity, and sex. An article by Al-Hazzaa et al. addressed this issue by comparing three BMI classifications on 2169 Saudi children. They reported the prevalence of overweight and obesity to be 31.1% based on the Saudi national growth references, 31.7% for the International Obesity Task Force, and 38.0% for the World Health

Organization. Regardless of the high prevalence of overweight and obesity in these children, the inconsistency of BMI measurements in estimating the prevalence of obesity based on various classifications is undeniable. Hence the use of novel anthropometric measurements to overcome these flaws is gaining more interest. In this regard, body composition parameters are shown to better reflect the association between obesity and metabolic disorders (5). In a study by Qi et al. on 12148 US adults, body composition, also known as adiposity, was assessed using dual-energy X-ray Absorptiometry (DXA). They found a positive association between the upper limb, torso, and whole-body fat mass percentage and odds of developing HTN, hypercholesterolemia, and T2DM. They also noted that increased adiposity was associated with higher risk of metabolic conditions in men than in women.

To define the association between obesity and vascular disorders such as ischemic stroke and atherosclerosis, the measurement of waist circumference (WC) is more recommended than BMI since it represents visceral fat accumulation (6); similarly, neck circumference (NC), despite being simple to measure, is significantly associated with adiposity. A study by Ren et al. on 431 stroke patients reported increased WC alongside with hypertriglyceridemia. Otherwise known as hypertriglyceridemia waist phenotype (HTWP), the condition was associated with higher odds of moderate to severe small artery occlusion strokes. Similarly, Fodra Fojas et al. used NC as a surrogate for body composition and assessed its association with dysglycemia, MetS, and non-alcoholic fatty liver disease (NAFLD) in an Emirati population. They found NC to be associated with dysglycemia, MetS, and NAFLD. Every one cm increase in NC was also shown to significantly increase the hazard of cardiovascular risk score by 15%. This highlights the importance of developing new measures with robust predictive properties. Taking these into account, Liu et al. in a study conducted on 721 overweight and obese Chinese participants developed new equations to estimate visceral obesity. The assessment of visceral obesity is of great importance since it is associated with genes linked with inflammation, oxidative stress, and cytokine dysregulation among others. They calculated the visceral fat area (VFA) to be equal to 3.7×age +2.4×WC+5.5×NC-443.6 in men and 2.8×age+1.7×WC+6.5×NC-367.3 in women with good predictive properties for visceral obesity.

Five studies from this topic focused on the laboratory indices and their associations with MetS. The use of laboratory indices can accompany anthropometric measurements for a better assessment, especially in those without visible adiposity. Both viral hepatitis and fatty liver disease can result in abnormal levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) (7). A study by Lin et al. on 2416 Taiwanese participants showed the ALT to AST ratio of higher than 1 to be a simple yet reliable index for MetS regardless of the presence of underlying viral hepatitis.

Due to the concordance of chronic inflammation and MetS, Wang et al. studied novel pro-inflammatory indices and their association with MetS in newly diagnosed T2DM patients. They assessed the ratio of monocyte (one of the key cells in the innate immune system) to high-density lipoprotein cholesterol (MHR) and monocyte to apolipoprotein A1 (MAR), and found them to be correlated with the metabolic risk factors such as triglycerides, high-density lipoprotein cholesterol (HDL-C), systolic and diastolic blood pressure, uric acid, IR, BMI, and WC. Moreover, MHR and MAR values above 3.57×10^8/mmol and 3.95×10^8/g, respectively, were shown to have a higher than 70% sensitivity and specificity in identifying MetS. A study by Duan et al. on 1452 Chinese participants assessed the predictive capacity of BMI, lipid accumulation product (LAP), body roundness index (BRI), Chinese visceral adiposity index (CVAI), body adiposity index (BAI), abdominal volume index (AVI), triglyceride glucose index (TYG), and visceral adiposity index (VAI). Interestingly, they found that the lipid-based set of LAP, TYG, CVAI and VAI had a higher predictive value than the anthropometry-based set of BMI, BRI, AVI and BAI, indicating their potential capacity as screening tools for MetS. Another laboratory index to predict MetS is hyperuricemia. While elevated serum levels of urate are associated with a broad spectrum of conditions, excess fat increases the production of hyperuricemia by affecting the liver. Thus, the assessment of hyperuricemia can illustrate a better view of the body's metabolic status as demonstrated by Wang et al. They showed that hyperuricemia is positively associated with increased TYG, TYG to HDL-C ratio, and IR. Another study by Zhao et al. on 14078 hypertensive patients also found a significant association between a novel anthropometric measure for obesity, called "weight-adjusted-waist index" (WWI), and hyperuricemia. This novel measure can distinguish between fat and muscle mass, reflecting central obesity. They found that every one-unit increase in the WWI increases the odds of developing hyperuricemia by 37% and 35% in men and women, respectively ((OR: 1.37; 95%CI: 1.25, 1.49) (OR: 1.35; 95%CI: 1.26, 1.45)). Thus, certain anthropometric measures and the laboratory indices together are believed to be intuited, whereas novel anthropometric measurements can illustrate some degree of the individual's metabolic status.

There is a notable association between obesity, especially central obesity, and chronic kidney dysfunction (8). In this regard, an article by Zhang et al. evaluated the association between "A body shape index" (ABSI), which is a marker of abdominal obesity and IR, and elevated "urinary albumin to creatinine ratio" (UACR) that is a marker of early kidney injury. This study, which consisted of 40726 adults with no primary kidney diseases, assessed the aforementioned ratio and its correlation with the adverse effects of visceral obesity on kidney function. Higher ABSI values are associated with UACR values higher than or equal to 30 mg/g. This finding is of particular importance since it indicates urinary workups can also be used for obesity risk assessment. It also highlighted the effects of obesity on renal function. Another study by Li et al. on 10858 US participants evaluated the association between body fat distribution and renal stones. This study used the Android to Gynoid ratio (A/G) obtained by DXA to represent visceral fat. They found that higher A/G ratio significantly increased the risk of renal stones among all US ethnic groups and sexes. Another study by Shen et al. studied this matter further by evaluating the association between the Metabolic Score for Insulin Resistance (METS-IR) and renal stones. In this study, conducted on 30612 adults, a significantly positive association was reported between METS-IR and renal stones. Wang et al. also found METS-IR to be associated with gallbladder stones, with every unit increase in METS-IR increasing the odds ratio of gallbladder stone by 3.3% (OR: 1.033, 95% CI (1.0258, 1.0403)).

Last but not least, the final article in this issue was a systematic review evaluating the association between the allostatic load (AL) mediators and MetS. The adaptive response mechanism to chronic stress with the aim of restoring the physiological stability is known as allostasis. This mechanism is mediated by the autonomic nervous system (ANS), the hypothalamic–pituitary–adrenal axis (HPA), the hypothalamic–pituitary–thyroid axis (HPT), somatotropic axes, the gonadal axis (HPG), the metabolic and immune system. AL index consists of various biomarkers that reflect the activity of the aforementioned axes. Two of the assessed biomarkers are dehydroepiandrosterone sulfate (DHEAS; a functional HPA axis antagonist) and cortisol. The systematic review concluded that MetS is associated with higher serum, salivary, hair, and urinary cortisol levels and lower levels of DHEAS.

To conclude, the articles included in this Research Topic points out the importance of new anthropometric measurements since obesity and MetS not only affect the cardiovascular system but also adversely affects the renal function and various functions involved in homeostasis. Proper anthropometric measurements can also give us a notion of the individual's current metabolic status and improve the risk assessment of various comorbidities. Laboratory workups alongside anthropometric measurements, therefore, can greatly help with the risk assessments.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Conflict of interest

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ORIGINAL RESEARCH
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A Reliable Estimate of Visceral Fat Area From Simple Anthropometric Measurements in Chinese Overweight and Obese Individuals

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Objective: Visceral obesity, reflected by the amount of visceral adipose tissue (VAT), is associated with multiple chronic diseases and metabolic disorders. The visceral fat area (VFA), measured by MRI, is the 'gold standard' for diagnosis of visceral obesity. In this study, a simple model to predict VFA was constructed to facilitate the identification and monitoring of patients who are at high risk of visceral obesity.

Methods: The 721 overweight and obese participants were divided into two groups according to sex, then randomly assigned to derivation and validation cohorts in a 1:2 ratio. Data from the derivation group were used to construct a multiple linear regression model; data from the validation group were used to verify the validity of the model.

Results: The following prediction equations, applicable to both sexes, were developed based on age, waist circumference (WC) and neck circumference (NC) that exhibited strong correlations with the VFA: VFA=3.7×age+2.4×WC+5.5×NC-443.6 (R^2 = 0.511, adjusted R^2 = 0.481, for men) and VFA=2.8×age+1.7×WC+6.5×NC-367.3 (R^2 = 0.442, adjusted R^2 = 0.433, for women). The data demonstrated good fit for both sexes. A comparison of the predicted and actual VFA in the verification group confirmed the accuracy of the equations: for men, R^2 = 0.489, adjusted R^2 = 0.484 and intra-class correlation coefficient (ICC) = 0.653 ($p < 0.001$) and for women: R^2 = 0.538, adjusted R^2= 0.536 and ICC = 0.672 ($p < 0.001$). The actual and predicted VFAs also showed good agreement in a Bland-Altman plot, indicating the significant correlations of both equations with the actual VFA.

Conclusions: Based on readily available anthropometric data, VFA prediction equations consisting of age, WC and NC were developed. The equations are robust, with good predictive power in both sexes; they provide ideal tools for the early detection of visceral obesity in Chinese overweight and obese individuals.

Keywords: visceral obesity, visceral fat area, visceral adipose tissue, prediction equation, waist circumference, neck circumference

INTRODUCTION

Obesity is a major public health disease globally, with a prevalence that is steadily increasing in both developed and developing countries. Obesity, especially visceral obesity, is associated with multiple chronic diseases, such as cardiovascular disease (CVD), insulin resistance, type 2 diabetes, and metabolic syndrome (MetS) (1–5). Compared with subcutaneous adipose tissue (SAT), visceral adipose tissue (VAT) expresses larger numbers of genes related to inflammation, oxidative stress, and cytokine production. Increased VAT accumulation is therefore associated with a more severe metabolic, dyslipidaemic, and atherogenic obesity phenotype (2, 3, 6). Accordingly, a fast and simple method for quantifying the regional distribution and content of abdominal fat, especially VAT, can aid in the diagnosis and treatment of obesity.

Numerous techniques for abdominal fat assessment are available for clinical use; these techniques include anthropometry, bioelectrical impedance analysis (BIA), and dual-energy X-ray absorptiometry (DXA) (3, 6). Modern imaging technologies allow accurate and efficient measurement of visceral obesity. Computed tomography (CT) and magnetic resonance imaging (MRI) are currently the 'gold standard' methods for direct quantification of the cross-sectional area (CSA) of abdominal fat (e.g., subcutaneous fat area [SFA] and visceral fat area [VFA]) used to classify the degree of abdominal obesity (2, 6, 7).

Because it does not involve ionising radiation, MRI has emerged as a powerful tool for repeatedly quantifying VFA in a non-invasive manner in population-wide studies (7). However, MRI measurements are time-consuming; moreover, imaging is expensive and may not be feasible for extremely obese patients because of scanner-specific weight and space restrictions. As an alternative to MRI, we constructed a simple model to derive predictive equations based on simple clinical variables; our model could be used as an auxiliary method of VFA measurement.

SUBJECTS AND METHODS

Subjects

Our study totally recruited 721 overweight and obese subjects based on body mass index (BMI) from April 2020 to February 2022 at Shanghai Jiao Tong University Affiliated Sixth People's Hospital, China. Overweight (BMI ≥24.0 to BMI <28.0 kg/m2) and obesity (BMI ≥28.0 kg/m2) were determined in accordance with the standard definitions proposed by the Working Group on Obesity in China. Included subjects were considered generally healthy, as there were no specific patient groups recruited. Pregnant women and those who have recently undergone abdominal surgery were excluded as these may affect the measurement of abdominal fat and/or the anthropometric assessments. All participants were assigned to two groups by gender, including 160 males and 561 females. The two groups were subdivided into derivation and validation cohorts randomly at a ratio of 1:2 for the construction and verification of the model. The study protocol was approved by the Ethics Committee of Shanghai Jiao Tong University and conformed to the Helsinki Declaration. All subjects provided informed consent and underwent abdominal MRI examination, anthropometric and laboratory measurements.

Anthropometric and Laboratory Assessments

The body weight and height of participants wearing light loose clothes were measured by a digital scale to subsequently calculate BMI = weight (kg)/height squared (m^2). Circumference measures were conducted by a trained examiner. The tape was placed horizontally and snug to the skin without compressing the soft tissue. Waist circumference (WC) was measured on the midline between the lowest rib margin and the iliac crest. Abdominal obesity was defined as a WC≥90.0 cm for men or a WC ≥85.0cm for women (8, 9). Hip circumference (HC) was measured at the point yielding the maximum circumference over the buttocks. Neck circumference (NC) was measured with head erect and eyes facing forward, horizontally at the upper margin of the laryngeal prominence.

All subjects had a low-fat diet one day before and venous blood samples were taken in the early morning after 8 hours fasting. Laboratory measurements included: alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyl transpeptidase (γ-GT), alkaline phosphatase (ALP), prealbumin (PAB), total bile acid (TBA), total bilirubin (TBiL), direct bilirubin (DBiL), blood urea nitrogen (BUN), serum creatinine (Scr), serum uric acid (SUA), retinol-binding protein (RBP), and cystatin C (Cys-C), total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), serum fasting blood glucose (FBG), hemoglobin A1c (HbA1c), insulin, C-peptide (CP). Hematological and common biochemical examinations were performed according to the manufacturer's protocol in the same lab using standard laboratory methods.

Measurement of Body Composition

Abdominal MRI examination was performed using a Philips Achieva 3.0-T magnetic resonance imaging system (Philips Medical Systems, Eindhoven, The Netherlands). Breath-hold fast imaging with a 40-ms repetition time, 2-ms echo time, 50-cm field of view, and 256 × 256 matrix was used to acquire the cross-sectional MR images. One 10-mm slice positioned at the L4 level with a clear outline was selected for analysis using SliceOmatic 5.0 software (TomoVision, Magog, Canada) by a medically trained technician. The psoas CSA, SFA, and VFA were measured using the following steps: regional threshold procedures were first applied using the "Region Growing" mode, after which manual delineation was used to draw borders among different tissues in the "edit mode" when necessary (10). The software calculated different colored areas and expressed the measurements in cm^2. VFA≥80cm^2 was defined as visceral obesity.

Statistical Analysis

All analyses were performed using SPSS version 26.0 (SPSS, Chicago, IL, USA), and a P-value < 0.05 (two-tailed tests) was considered statistically significant. All data were tested for

normality using the Kolmogorov–Smirnov test. Continuous variables with normal and non-normal distributions were respectively expressed as mean ± standard deviation (SD) and median (interquartile range, IQR), whereas categorical variables were expressed as percentages. Continuous variables were compared using the Student's t-test or the Mann-Whitney U-test and categorical variables were compared using the Chi-squared or Fisher's exact test. The Pearson or Spearman correlation was used to evaluate the relationship between different variables with VAT. Variables correlated with the VFA by correlation analysis were introduced into the stepwise multiple linear regression model within each sex. Thus, the independent predictors of VFA values were identified and screened out to develop the prediction equations. Further, the accuracy of the equations was verified on validation set by reliability analysis and Bland–Altman plot.

RESULTS

Baseline Characteristics

A total of 721 subjects meeting the inclusion criteria were recruited, ranging in age from 16 years to a maximum of 65 years. The average VFA value is higher in men than in women ($p<0.05$). 160 males and 561 females were respectively subdivided into derivation and verification cohorts randomly at a ratio of 1:2. For the male group, there were 53 subjects in the derivation cohort and 107 subjects in the validation cohort; for the female group, there were 187 subjects in the derivation cohort and 374 subjects in the validation cohort. **Table 1** lists the basic characteristics of each cohort. No statistically significant difference was observed between them ($p>0.05$).

Correlation Analysis

Bivariate correlation analysis was performed to identify the variables associated with the VFA values in both groups. The correlation coefficients of the potential predictor variables (used to develop the individual equations) with respect to the VFA are given in **Table 2**. In both sexes, age ($r = 0.41$; $P<0.01$ for men and $r = 0.28$; $P<0.01$ for women), BMI ($r = 0.46$; $P<0.01$ for men and $r = 0.53$; $P<0.01$ for women), WC measures ($r = 0.38$; $P<0.01$ for men and $r = 0.49$; $P<0.01$ for women), NC measures ($r = 0.47$; $P<0.01$ for men and $r = 0.51$; $P<0.01$ for women), FBG ($r = 0.53$; $P<0.01$ for men and $r = 0.44$; $P<0.01$ for women), HbA1c ($r = 0.44$; $P<0.01$ for men and $r = 0.47$; $P<0.01$ for women), and CP ($r = 0.30$; $P<0.05$ for men and $r = 0.39$; $P<0.01$ for women) showed significant associations with VFA. Then we plotted scatter plots for each of these seven variables and the dependent variable (VFA) separately and found a linear relationship between them. Both the independent and dependent variables were continuous variables. Thus, these seven variables that exhibited strong correlations with the VFA were further introduced into the stepwise multiple linear regression model.

TABLE 1 | Baseline Characteristics in the derivation and validation cohorts.

Characteristics	Male group (n = 160)			Female group (n = 561)		
	Derivation cohort (n = 53)	Validation cohort (n = 107)	P-value	Derivation cohort (n = 187)	Validation cohort (n = 374)	P-value
Age (years)	32.0 (27.0, 38.0)	32.0 (26.0, 38.0)	0.79	31.0 (27.0, 37.0)	31.0 (26.0, 35.3)	0.58
BMI (kg/m^2)	39.7 ± 6.0	40.0 ± 7.0	0.80	36.3 (32.8, 40.7)	36.1 (32.3, 41.1)	0.53
WC (cm)	121.0 (113.5, 134.2)	123.0 (113.0, 135.0)	0.96	110.0 (102.0, 122.0)	110.0 (100.0, 122.0)	0.67
HC (cm)	117.0 (110.0, 126.0)	118.0 (109.0, 127.0)	0.95	114.0 (106.0, 122.0)	113.0 (106.0, 123.0)	0.93
NC (cm)	45.6 ± 3.1	45.2 ± 4.0	0.43	38.5 (36.5, 41.0)	38.3 (36.5, 40.0)	0.34
SBP (mmHg)	141.2 ± 15.9	144.8 ± 17.4	0.20	129.0 (119.0, 143.0)	130.0 (119.8, 143.0)	0.52
DBP (mmHg)	89.3 ± 12.8	92.9 ± 12.1	0.08	84.5 (78.0, 92.0)	85.0 (79.0, 94.0)	0.64
ALT (U/L)	54.0 (38.0, 113.0)	67.0 (38.0, 100.8)	0.76	34.0 (24.0, 64.0)	36.0 (23.0, 62.0)	0.96
AST (U/L)	31.0 (21.5, 57.0)	34.0 (23.0, 51.0)	0.73	22.0 (18.0, 34.5)	24.0 (18.0, 36.3)	0.84
γ-GT (U/L)	51.0 (39.0, 79.5)	53.0 (37.0, 71.0)	0.52	30.0 (21.0, 52.5)	31.0 (21.0, 48.3)	0.79
ALP (U/L)	80.0 (62.5, 99.0)	77.0 (66.8, 91.8)	0.50	72.0 (62.0, 88.5)	73.0 (61.0, 87.0)	0.88
BUN (mmol/L)	4.9 (4.3, 5.8)	5.1 (4.4, 6.0)	0.75	4.6 (4.1, 5.4)	4.6 (3.9, 5.5)	0.27
Scr (mg/dL)	78.1 (68.1, 86.2)	76.0 (68.9, 84.9)	0.55	57.5 (52.0, 65.3)	58.2 (52.0, 64.9)	0.97
SUA (mg/dL)	489.0 (439.5, 547.0)	465.0 (393.0, 533.0)	0.15	392.0 (340.0, 445.0)	388.5 (331.8, 441.3)	0.62
TC (mmol/l)	5.2 ± 1.1	5.2 ± 0.8	0.98	5.2 (4.6, 5.8)	5.2 (4.5, 6.0)	0.65
TG (mmol/l)	2.4 (1.2, 3.2)	2.1 (1.4, 3.0)	0.32	1.5 (1.0, 2.0)	1.5 (1.1, 2.1)	0.24
HDL-c (mmol/l)	1.0 (0.9, 1.2)	1.1 (0.9, 1.3)	0.18	1.2 (1.0, 1.4)	1.2 (1.0, 1.4)	0.67
LDL-c (mmol/l)	3.1 ± 0.7	3.1 ± 0.6	0.58	3.2 ± 0.8	3.2 ± 0.8	0.79
FBG (mmol/l)	5.7 (4.8, 7.9)	5.9 (5.2, 7.2)	0.43	5.5 (5.0, 6.5)	5.4 (4.9, 6.4)	0.42
HbA1c (%)	6.1 (5.6, 7.7)	6.1 (5.6, 7.1)	0.87	5.6 (5.4, 6.2)	5.7 (5.4, 6.4)	0.42
CP (ng/ml)	4.5 (3.3, 5.7)	4.9 (4.0, 5.9)	0.24	3.9 (3.2, 5.1)	3.9 (3.1, 4.9)	0.57
VFA (cm^2)	221.2 (175.4, 271.3)	232.0 (187.8, 278.4)	0.44	155.3 (116.6, 203.2)	148.0 (115.0, 191.9)	0.35

Data are expressed as the mean ± SD or the median (IQR).

BMI, body mass index; WC, waist circumference; HC, hip circumference; NC, neck circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; ALT, alanine aminotransferase; AST, aspartate aminotransferase; γ-GT, γ-glutamyl transpeptidase; ALP, alkaline phosphatase; BUN, blood urea nitrogen; Scr, serum creatinine; SUA, serum uric acid; TC, total cholesterol; TG, triglyceride; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; FBG, fasting blood glucose; HbA1c, glycated hemoglobin; CP, C-peptide; VFA, visceral fat area.

TABLE 2 | The correlation coefficient of VFA with demographic and anthropometric variables in derivation cohort.

Variables	Male group (n = 53)	Female group (n = 187)
Age	0.41**	0.28**
BMI	0.36**	0.53**
WC	0.38**	0.49**
HC	/	0.36**
NC	0.45**	0.51**
SBP	/	0.41**
DBP	/	0.33**
ALT	/	0.27**
AST	/	0.26**
γ-GT	/	0.44**
Scr	/	-0.18*
SUA	/	0.21**
TC	/	0.21**
TG	/	0.32**
LDL-c	/	0.19**
FBG	0.53**	0.44**
HbA1c	0.44**	0.47**
CP	0.30*	0.39**

*Statistical significance *P<0.05; **P<0.01.*

BMI, body mass index; WC, waist circumference; HC, hip circumference; NC, neck circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; ALT, alanine aminotransferase; AST, aspartate aminotransferase; γ-GT, γ-glutamyl transpeptidase; Scr, serum creatinine; SUA, serum uric acid; TC, total cholesterol; TG, triglyceride; LDL-c, low-density lipoprotein cholesterol; FBG, fasting blood glucose; HbA1c, glycated hemoglobin; CP, C-peptide.

Equation Development

In the stepwise multiple linear regression model, the relatively optimal regression equations containing three anthropometric variables (age, WC and NC) for predicting the VFA were derived after multiple variables combination and modification by stepwise regression analysis. These three variables were present in both the male and female groups, but the specific equations were expressed differently. For men, VFA=3.7×Age+2.4×WC+5.5×NC-443.6. The model fitted well with an R^2 of 0.511 and an adjusted R^2 of 0.481. **Table 3** provides the regression coefficient and 95% confidence interval (CI) of each variable. The Durbin-Watson test of model residuals was 2.296, indicating that there was no significant correlation between the residuals. Based on the collinearity analysis, the tolerances were more than 0.5 and the variance inflation factor (VIF) values were less than 2, showing that there was no covariance among the independent variables. For women, VFA=2.8×Age+1.7×WC+6.5×NC-367.3 (R^2 = 0.442, adjusted R^2 = 0.433). As shown in **Table 3**, the model also demonstrated good fit in female group. In addition, **Figure 1** presents the residual scatter plots with the standardized predicted value on the X axis and the standardized residual on the Y-axis, to better appreciate the differences between values predicted and observed (i.e., the residuals) against the values predicted. The scatter points were randomly distributed and the slope was almost zero, which showed the variance homogeneity of the residuals. There was a linear trend in both sexes based on the scatter plots of the standardized predicted value and dependent VFA (**Figure 2**). We also observed that the residuals were approximately normally distributed through the histograms and normal P-P plots of the residuals. All the above results showed that the equations we established satisfied the assumptions of linear regression model and were statistically significant.

Verification of Equations

We further verified the accuracy of the equations in the validation cohorts respectively. A comparison of the predicted and actual VFA in the verification group confirmed the accuracy of the equations: for men, R^2 was 0.489 and the adjusted R^2 was 0.484; for women, R^2 was 0.538 and the adjusted R^2 was 0.536. On average, predicted and actual VFA values were 224 and 232 cm^2 in men and 159 and 148 cm^2 in women. The consistency of predicted and actual VFA on the same subject was evaluated using reliability analysis. In two-way random model and absolute agreement type, the values of intra-class correlation efficient (ICC) (single measures) were 0.653 for men and 0.672 for women (p<0.001). **Figure 3** is a Bland–Altman plot showing that in both sexes, the actual and predicted VFAs also showed good agreement; most of the differences were within the 95% limits of agreement. In addition, the mean value of the differences was close to zero. Therefore, it can be assumed that the predicted VFA showed a significant and high consistency with the actual VFA in both equations.

Previous researches have given different VFA prediction equations for two sexes as well: i) Bonora et al. : VFA=6.37×WC-453.7 (for men) and VFA=2.62×Age+4.04×WC-370.5 (for women) (11); ii) Brundavani et al. : VFA=1.09×weight+6.04×WC-2.29×BMI-382.9 (for men) and VFA=-0.86×weight+5.19×WC-278 (for women) (12); iii) Goel et al. : VFA=0.169×Age+5.7809 × BMI-4.4106×HC+4.342×WC+6.9548 (for men) and VFA=0.169×Age+

TABLE 3 | The establishment of new equations in male and female groups respectively.

Gender	Equation	R^2	Adjusted R^2	Durbin-Watson test	Variables	Coefficients	95%CI	P-value	Tolerance	VIF
Male	VFA=3.7×Age+2.4×WC+5.5×NC-443.6	0.511	0.481	2.296	Age	3.74	2.17, 5.30	0.000	0.907	1.103
					WC	2.39	1.15, 3.64	0.000	0.677	1.477
					NC	5.53	0.42, 10.64	0.035	0.735	1.361
					Constant	-443.59	-658.37, 228.81	0.000	/	/
Female	VFA=2.8×Age+1.7×WC+6.5×NC-367.3	0.442	0.433	2.176	Age	2.84	1.89, 3.78	0.000	0.982	1.019
					WC	1.69	1.07, 2.30	0.000	0.641	1.561
					NC	6.50	3.69, 9.32	0.000	0.650	1.538
					Constant	-367.28	-462.36, -272.20	0.000	/	/

WC, waist circumference; NC, neck circumference.

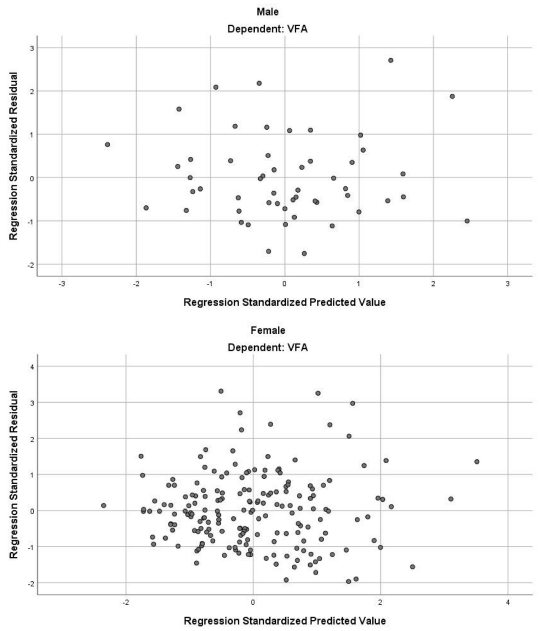

FIGURE 1 | The residual scatter plot of standardized predicted value and standardized residual.

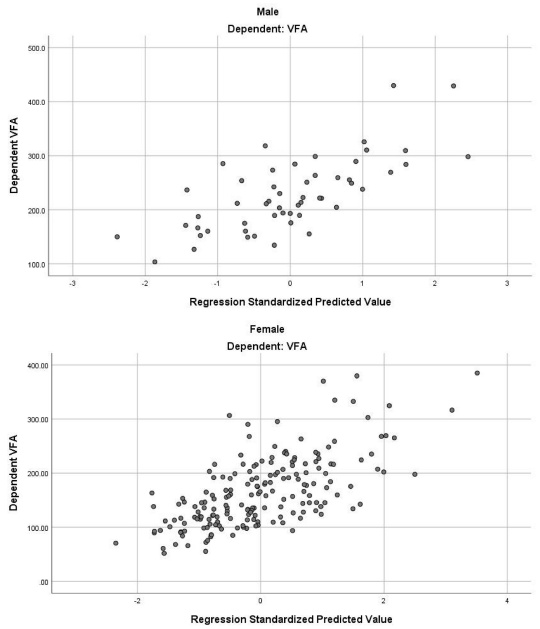

FIGURE 2 | The scatter plot of standardized predicted value and dependent VFA.

5.7809 × BMI-4.4106×HC+4.342×WC+16.2966 (for women) (13). We also validated these pre-existing equations separately in our validation cohorts, the corresponding R^2 and adjusted R^2 of them were all less than 0.45 (**Table 4**). The ICC values of their equations were less than ours likewise.

Therefore, the above results suggested that both sets of equations obtained by our stepwise regression analysis have excellent predictive performance and high application value in clinical promotion. For medical institutions where MRI examination of body composition is not available, clinicians can estimate VFA values more quickly and accurately by measuring waist and neck circumferences of each patient and substituting these simple anthropological indicators into the equations.

DISCUSSION

Visceral obesity, characterised by dysfunctional adipose tissue storage and ectopic triglyceride accumulation in several sites including the liver (4), increases the risks of metabolic disorders and CVD (2–4). Quantitative assessment of visceral obesity is

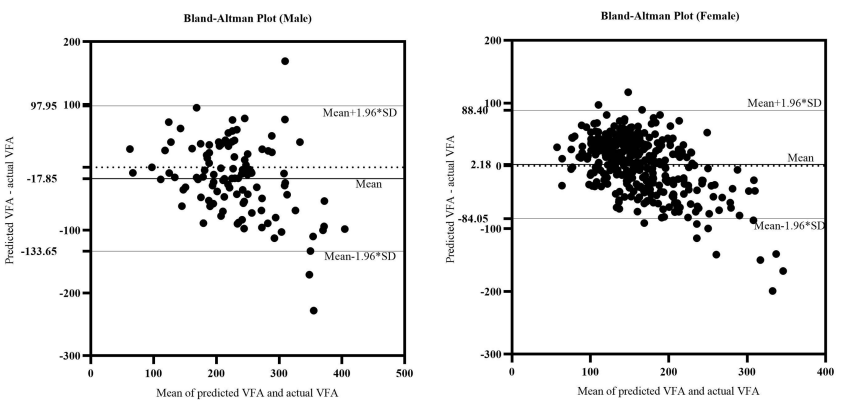

FIGURE 3 | The Bland-Altman plot of actual CAP and predicted CAP. The upper and lower horizontal solid lines in the picture represented the 95% limits of agreement. The middle horizontal solid line in the middle represented the average value of the difference. The horizontal dotted line indicated the position where the average value of the difference was zero.

TABLE 4 | The validation of the equations from our study and other studies.

	Equation	R^2	adjusted R^2	ICC
Our study				
male	VFA=3.7×Age+2.4×WC+5.5×NC-443.6	0.489	0.484	0.653
female	VFA=2.8×Age+1.7×WC+6.5×NC-367.3	0.538	0.536	0.672
Bonora et al. (11)				
male	VFA=6.37×WC-453.7	0.284	0.277	0.348
female	VFA=2.62×Age+4.04×WC-370.5	0.411	0.409	0.636
Brundavani et al. (12)				
male	VFA=1.09×Weight+6.04×WC-2.29×BMI-382.9	0.269	0.262	0.199
female	VFA=-0.86×Weight+5.19×WC-278	0.273	0.271	0.374
Goel et al. (13)				
male	VFA=0.169×Age+5.7809 × BMI-4.4106×HC+4.342×WC+6.9548	0.313	0.307	0.524
female	VFA=0.169×Age+5.7809 × BMI-4.4106×HC+4.342×WC+16.2966	0.318	0.316	0.403

WC, waist circumference; NC, neck circumference; BMI, body mass index.

therefore essential to determine the potential risks and establish an accurate prognosis. Because VAT is located in the abdominal cavity, under the surrounding abdominal and back muscles, it is difficult to measure. MRI has been used to quantitatively measure abdominal fat CSA and is considered the 'gold standard' method for assessment of VAT. However, while MRI is non-invasive, radiation-free, repeatable, and applicable to all age groups, its cost and time-consuming nature limit its wider adoption for large-scale screening or routine clinical practice. In light of these limitations, we developed a simple VFA prediction linear regression model to facilitate the early detection and quick assessment of visceral obesity.

The distributions and functions of adipose tissue vary between men and women because of differential sex hormone effects. On average, VAT mass is higher in men than in women, regardless of age (14). Estrogen promotes the accumulation of SAT in women and the deposition of visceral fat in men (15); in contrast, androgen excess is presumed to favour the expansion of VAT (16). Generally, men tend to accumulate more VAT, resulting in the classic 'apple' body shape that is also associated with an increased cardiometabolic risk. In contrast, premenopausal women typically accumulate more SAT on the hips, thighs, and buttocks; they are thus protected against the negative effects associated with obesity and MetS (15, 16). Considering these sexual differences, the derivation of corresponding VFA prediction equations required division of our study participants into two sex-based groups to allow the construction of separate prediction models. Through stepwise multiple linear regression analysis, the relatively optimal equations were then derived by determining three anthropometric variables: age, WC, and NC.

VAT deposition increased with age in both men and women. The increase was particularly large in postmenopausal women, in whom a decline in estrogen levels is associated with the accumulation of visceral fat (15). The hormonal changes are accompanied by an age-related shift in fat distribution (from subcutaneous to visceral) (17), which contributes to the age-related increase in VAT in both sexes (14). A stronger relationship between age and VAT before than after the age of 70 has been reported (18); a progressive increase in the mean VAT with age until approximately 65–70 years, followed by a gradual decrease thereafter (14), has also been reported. In a study population from the United Arab Emirates, Yoo et al. identified cut-off values of CT-measured VAT to predict MetS: 132.0 cm^2 in both sexes for individuals aged < 50 years, and 173 cm^2 in women and 124.3 cm^2 in men for individuals aged > 50 years (19). In the study by Brundavani, age did not contribute to the prediction of VAT, perhaps because the study population was between 40 and 80 years of age; the biological effects of peripheral fat mobilization on centralization and internalization had already occurred and age no longer had a significant effect (12).The predictive equations derived from our study clearly demonstrate that VAT increases with age. However, because our participants were not older than 65 years, an age cut-off for VAT decline could not be determined.

Waist circumference (WC) has been commonly used in the clinical setting as a rough estimate of visceral adiposity (2). Although WC cannot accurately distinguish between visceral and subcutaneous fat deposits (4, 20, 21), it remains an extremely simple and inexpensive method currently that correlates with visceral adiposity (2, 22). Jia et al. performed a receiver operating characteristic (ROC) curves analysis indicating that WC had the best accuracy in predicting visceral obesity in comparison with BMI and waist-to-hip ratio (WHR) (23). However, there is no consensus regarding the optimal anatomical site to measure WC. In several studies, the most practical measurement protocols for clinical use were (2, 20–22, 24): the superior border of the iliac crest, as described in the National Institutes of Health guidelines; below the lowest rib; the midpoint between these two sites, as recommended by the World Health Organization and International Diabetes Federation guidelines; minimal waist; and umbilicus. The higher mean WC value for men indicated a different pattern of body fat distribution than the pattern present in women. Previous studies reported absolute differences in WC measurements obtained at different sites, especially in women. For example, Bosy-Westphal et al. found that WC below the lowest rib was strongly associated with VAT and cardiometabolic risk factors in women (21). In the study by Pinho et al., minimal waist was significantly correlated with VAT (r = 0.70) and with a larger spectrum of cardiometabolic parameters among men (20). According to Seimon et al., WC measurements obtained at the midpoint between the lowest rib and iliac crest and at the minimal site were more closely correlated with MRI-measured VAT than were measurements at the umbilicus (r = 0.581, 0.563,

and 0.390, respectively; $p < 0.001$) (24). The authors thus recommended minimal waist measurement for effective estimation of VAT in postmenopausal obese women; notably, it does not require the palpation and the identification of two bony anatomical landmarks. Likewise, Johnson et al. proposed that WC measured at the narrowest site and at the midpoint between lowest rib and iliac crest were most strongly and consistently associated with the MetS and metabolic risk factors (25). A systematic review also indicated that WC measured at midline between the lowest rib and iliac crest was the most valid and reliable measure to assess visceral fat content and changes in visceral fat over time in both sexes (26). Therefore, the midpoint with a relatively high correlation with VAT was selected as the WC measurement site in our study. The different studies mentioned above suggested that valid comparisons among studies will require standardization of WC measurement protocols and the influence of SAT should also be considered when assessing WC measurements.

Neck circumference (NC) is a novel, easily accessible, and replicable anthropometric measurement that reflects ectopic fat distribution in the neck. A significant correlation between NC and VAT in both men and women has been reported in several studies (27–30). Li et al. found that neck fat area was positively associated with abdominal VAT in both sexes, which may explain the relationship between NC and VAT (28). Based on an analysis of ROC curves, Luo et al. determined that the areas under the curve for the ability of NC to determine visceral adiposity (VFA ≥ 80 cm^2) were 0.781 for men and 0.777 for women in China. The authors also obtained optimal cut-offs for identifying visceral obesity: ≥ 38.5 cm for men (sensitivity of 56.1% and specificity of 83.5%) and ≥ 34.5 cm for women (sensitivity of 58.1% and specificity of 82.5%) (29). Their findings indicated no differences in the sensitivity and specificity of NC vs. WC for the diagnosis of metabolic disorders. Nonetheless, as an emerging metric, NC has not yet been applied worldwide like WC. NC is a practical clinical predictor of VAT because it uses an explicit landmark, has low variability, and is minimally affected by breathing, diet, and position. Therefore, it could be promoted as a feasible measure of visceral obesity in parallel with WC in large-scale population studies and should be regularly used to monitor individuals with increased visceral adiposity.

We also validated several prediction equations obtained in previous studies and found that the validity of the equations established in our study was higher for a few reasons. First, our sample size was much larger, which improved the accuracy of our equations. Second, the participants in the previous studies came from Italy, Tirupati, and North India; the corresponding equations performed poorly in our Chinese study population. Third, our study specifically focused on overweight and obese individuals, whereas the other studies also included individuals of normal weight.

The key strengths of this study were its large sample size and the identification of NC as an important contributor to VFA. The limitations included the smaller proportion of men than women and the single-center design with only Asian participants. Therefore, the equations require further external validation in different ethnic groups and centers.

CONCLUSION

The equations developed in this study to predict VFA consist of simple anthropometric measures (age, WC and NC). Their demonstrated validity supports their use as surrogate tools to discern and monitor high-risk individuals with visceral obesity.

DATA AVAILABILITY STATEMENT

Due to the privacy of patients, the data related to patients cannot be available for public access but can be obtained from the corresponding author on reasonable request approved by the institutional review board of Shanghai Jiao Tong University Affiliated Sixth People's Hospital. Requests to access these datasets should be directed to yuhaoyong111@163.com.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Review Committee of Shanghai Jiao Tong University Affiliated Sixth People's Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

HL drafted the manuscript. DY and YT performed the statistical analysis. DY, DP and SL drafted the figure and legend. YX manipulated MRI. YB, JH, and HY designed the outline of the topic and helped on revising the manuscript. All authors contributed to the article and approved the submitted version.

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Monocyte to High-Density lipoprotein and Apolipoprotein A1 Ratios: Novel Indicators for Metabolic Syndrome in Chinese Newly Diagnosed Type 2 Diabetes

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Objective: Increasing evidence highlighted that chronic inflammation involved in the development of metabolic syndrome (MetS) and Type 2 diabetes mellitus (T2DM). This prospective study was aimed to assess the association between MetS and novel pro-inflammatory indicators like monocyte–to–high-density lipoprotein and monocyte–to–apolipoprotein A1 ratios (MHR and MAR) in Chinese newly diagnosed T2DM.

Method: A total of 605 Chinese newly diagnosed T2DM with complete and available data were enrolled in this study. Demographic and anthropometric information were collected. Laboratory assessments were determined by standard methods. MetS was based on the Chinese Diabetes Society definition. Multiple binomial logistic regression model was used to estimate the independent variables of MHR and MAR for MetS. Receiver operating characteristic (ROC) curve was conducted to assess the optimal cutoff value of MHR and MAR in identifying MetS.

Results: Overall, the prevalence of MetS was 60.2%. The correlation analysis showed that MHR and MAR were closely correlated with metabolic risk factors like body mass index, waist circumference, triglycerides, high-density lipoprotein cholesterol, systolic blood pressure, diastolic blood pressure, uric acid, and insulin resistance. MHR and MAR were also significantly associated with higher odds of MetS after adjustment for other confounders, the odds ratios (ORs) (95%CI) were 1.50 (1.14–1.97) and 2.26(1.79–2.87) respectively. Furthermore, MHR and MAR were also seemed to have higher area under the curve (AUC) for MetS than ApoA1 and monocyte alone from the ROC curve analysis ($P < 0.05$). The AUCs of MHR and MAR identifying MetS were 0.804 (95% CI: 0.768–0.839) and 0.840 (95% CI: 0.806–0.873) respectively ($P < 0.001$). The optimal cutoff

values of MHR and MAR were 3.57 × 10^8/mmol (sensitivity: 76.1%, specificity: 73.4%) and 3.95 × 10^8/g (sensitivity: 79.7%, specificity: 84.6%), respectively.

Conclusions: MHR and MAR were significantly associated with MetS. These two novel pro-inflammatory indicators may be useful markers for MetS in Chinese newly diagnosed T2DM.

Keywords: monocyte to high-density lipoprotein ratio, monocyte to apolipoprotein A1 ratio, metabolic syndrome, newly diagnosed type 2 diabetes, optimal cut-off value

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a kind of metabolic disease characterized by chronic hyperglycemia that often accompanied with other metabolic disorders like obesity, hypertension, and hyperlipidemia. Metabolic syndrome (MetS) has gradually become an increasing worldwide health problem that was associated with increased cardiovascular disease (CVD), stroke, and T2DM (1). MetS is closely correlated with T2DM, and epidemiological survey reported the prevalence of MetS was up to 68.1% in Chinese T2DM (2). Chronic low-concentration inflammation, cellular dysfunction, and oxidative stress participate in the occurrence and development of T2DM and MetS (3); the non-invasive detection index of "chronic low concentration inflammatory statues" can be an effective marker for in T2DM with MetS.

Circulating monocyte is a cluster of blood cell modulated by immune factors including tumor necrosis factors alpha (TNF-α) and Toll-like receptor (TLR) 2, TLR4, and TLR8 ligands that can interact with thrombocytes and endothelial cells, resulting in exaggerated inflammation and increased oxidative stress (4–6). These biological features provided a basis for monocyte involving in development of systematic inflammation disease like MetS, T2DM, and CVD (7). High-density lipoprotein (HDL-c) is considered as "good cholesterol" that can bind lipid molecules such as triglyceride (TG) and cholesterol and participate in the cholesterol clearance, resulting in decreased CVD risk (8). Monocyte–to–HDL-c ratio (MHR) was also recognized as indicators of oxidative stress and systemic inflammation, which has been identified as a predictive marker for some disease, such as CVD, polycystic ovarian syndrome (PCOS), and Parkinson's Disease (9–11). Besides fewer studies reported the predictive value of MHR for MetS in patients with PCOS (10, 12), there was no study that has focused on the potential ability of MHR for MetS in newly diagnosed T2DM. Apolipoprotein A1 (ApoA1) is a constituent of HDL-c produced by liver that participates in the process of peripheral cholesterol reverse transportation to the liver, which was also considered as protective proteins in CVD (13). Despite numerous studies have confirmed that the ratio of apolipoprotein B (ApoB) to ApoA1 is significantly correlated with MetS, no study has put insights to the association between monocyte to ApoA1 ratio (MAR) and MetS. Thereby, this prospective study was aimed to assess the association between MetS and novel pro-inflammatory indicators MHR and MAR in Chinese newly diagnosed T2DM, further evaluating the ability of MHR and MAR in identifying MetS.

STUDY DESIGN AND METHODS

Study Design and Participants

This cross-sectional study was consecutively conducted with newly diagnosed T2DM from the Department of Endocrinology at Longyan First Affiliated Hospital of Fujian Medical University who fulfilled the study criteria between January, 2021 and December, 2021. The T2DM was defined according to the World Health Organization (WHO) 2019 criteria: (1) fasting plasma glucose ≥126 mg/dl or 2-h postprandial ≥200 mg/dl during oral glucose tolerance test (OGTT) or HbA1C ≥6.5% or participants with classic symptoms of hyperglycemia or hyperglycemic crisis with random plasma glucose ≥200 mg/dl and (2) with negative diabetic autoimmune antibodies and excluded other specific types of diabetes. Previous unknown hyperglycemia status and c were considered as newly diagnosed T2DM. Participants were excluded if they met the following criteria: (1) presence of acute diseases that can interfere glucose metabolism; (2) presence of acute or chronic infection, obvious liver or renal dysfunction, anemia, hemolytic diseases, and bleeding that can interfere circulating monocyte count; (3) treatment with medications that can interfere circulating monocyte count; (4) currently receiving lipid-lowering therapies; (5) presence of secondary hypertension or a history of tumors; and (6) unwillingness to participate in this study. In this study, we estimated the sample size according to the requirement of multiple binomial logistic regression model; 12–14 variables may be put into the logistic regression model according to the principle of 5–10 events per variable, and the prevalence of MetS is about 50%–70% in newly diagnosed T2DM. Thus, we planned a sampling size of 500–600 participants (2). Overall, a total of 636 participants were screened. Among them, 605 participants meeting the inclusion and exclusion criteria were enrolled in this study. The flow diagram of excluded and included participant was presented in **Figure 1**. All procedures were conducted in accordance with the Declaration of Helsinki. This study was approved by the ethical committee of Longyan First Affiliated Hospital of Fujian Medical University (LY-2020-088). All participants enrolled in the study provided informed consent.

Anthropometric and Laboratory Assessments

Demographic information was collected by trained interviewers through a standard questionnaire and also obtained by a review of medical records and laboratory data, including gender, age,

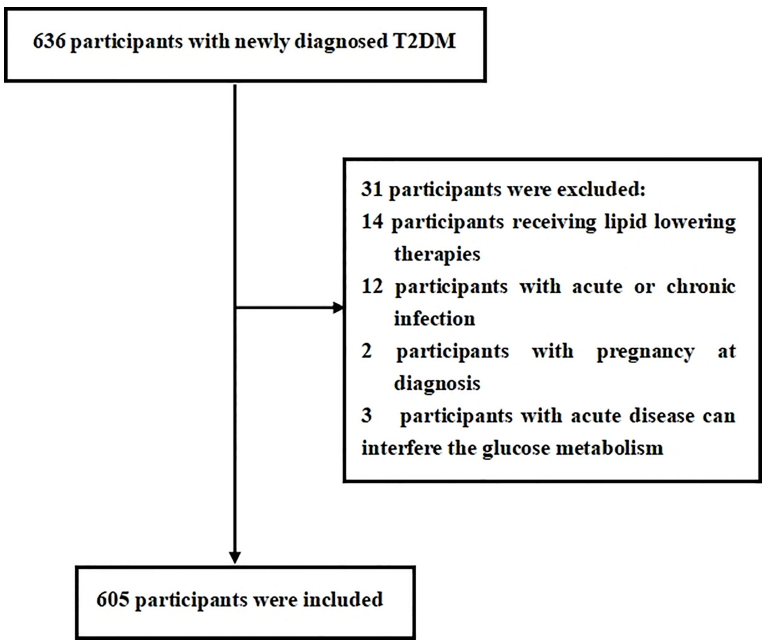

FIGURE 1 | Flow diagram of the participants excluded and included in this study.

and history of diseases that can interfere circulating monocyte, current or prior use of drugs, smoking, and drinking. Participants that smoke more than four cigarettes a week for at least 6 months continually or accumulative were considered as smoking according to standardized methodological recommendations of WHO for smoking surveys (14). Participants that drink more than once a year were considered as drinking according to global burden of disease study (15). Physical examination was conducted by the research nurses, including height, weight, waist circumference (WC), and blood pressure (BP). Participants wear hospital gowns and bare feet. Height and weight were measured to the nearest 0.1 cm and 0.1 kg, respectively. Weight was measured using the gauges real-time load cell, and height was measured using the gauges ultrasonic probe. Body mass index (BMI) was calculated as the weight divided by the square of height (kg/m^2). WC was measured at the natural depression between the iliac crest and 10th rib, which should be the narrowest part of the abdomen. Systolic and diastolic BP (SBP and DBP) were measured by an electronic sphygmomanometer with an appropriate cuff size after the participants take a rest for more than 5 min on at least three different occasions; the mean of three measurements was calculated as final BP.

Laboratory assessments were measured by standard methods using fasting venous blood samples that were taken between 8:00 a.m. and 9:00 a.m. after fasting overnight. Blood samples were taken into standardized tubes containing dipotassium ethylenedinitrilotetraacetic acid. Serum levels of the following variables were determined: creatinine, alanine aminotransferase (ALT), uric acid (UA), fasting blood glucose (FBG), serum insulin, HbA1c, diabetic autoimmune antibodies (GADA, IAA, and ICA), HDL-c, low-density lipoprotein (LDL-c), TGs, ApoA1, high-sensitivity C-reactive protein (hs-CRP), and complete blood count. Biochemical indexes were measured by an auto-biochemical analyzer (Roche Diagnostics Corporation). ApoA1 levels were measured by the polyethylene glycol–enhanced immunoturbidimetric assay (Maker, Chengdu, China). HbA1c was evaluated by high-performance liquid chromatography with a D10 set (Bio-Rad). Complete blood count was obtained using the Coulter LH 780 Analyzer (Beckman Coulter Ireland, Galway, Ireland). Homeostasis model assessment (HOMA-IR) was used to assess insulin sensitively. HOMA-IR was calculated with the following formula: fasting serum insulin (μU/ml) × fasting plasma glucose (mmol/l)/22.5 (16). MHR or MAR was calculated with the following formulas: the monocyte count divided by HDL-c or ApoA1 level.

Definition of Metabolic Syndrome

Participants were diagnosed with MetS according to Chinese diabetes guideline for MetS management (17). Participants that met three or more of the following criteria are considered to have MetS: (1) abdominal obesity: WC≥90 cm in men or ≥85 cm in women; (2) hyperglycemia: FBG ≥6.1 mmol/L or OGTT 2-h blood glucose≥7.8 mmol/L or previously diagnosed diabetes with treatment; (3) hypertension: BP ≥130/85 mmHg or currently under antihypertension therapy; (4) fasting TGs ≥1.70 mmol/L; and (5) fasting HDL-c <1.04 mmol/L. All participants in this study should fulfill the criteria for hyperglycemia and diagnosed as newly diagnosed T2DM.

Statistical Analysis

Data were analyzed by using the SPSS 23.0 software (SPSS Inc. IBM). Descriptive data are expressed as means ± standard deviation (SD). Discrete variables were summarized in frequency tables (N, %). Participants were divided into three groups based on tertiles of MHR and MAR. Statistical differences among groups were performed with one-way analysis of variance (ANOVA) followed by Tukey's test for multiple comparisons. Chi-squared ($\chi 2$) test or Fisher's exact test was used for comparison of categorical variables. Correlation between MHR, MAR, and metabolic parameters was evaluated by Pearson's or Spearman's correlation analysis. Multiple binomial logistic regression model was used to estimate the independent variables of MHR and MAR for MetS after adjusting for other covariates. The receiver operating characteristic (ROC) curves were used to assess the identifying value of MHR and MAR for MetS in newly diagnosed T2DM. Optimal cutoff value was based on the greatest value of the Youden's index. A two-tailed value of $P < 0.05$ was considered statistically significant.

RESULTS

Overall, a total of 605 newly diagnosed T2DM with complete and available data were included in the final analysis. Clinical and laboratory characteristics of participants were summarized in **Table 1**. Among them, 304 (50.2%) participants were men. The prevalence of MetS was 60.2% with a mean age of 53.4 ± 7.5 years. The MetS group was more likely to have hypertension as compared with the non-MetS group ($P < 0.05$). The BMI, WC, TG, SBP, DBP, UA, HOMA-IR, serum insulin, monocyte count, MAR, and MHR were significantly higher, whereas HDL-c and ApoA1 were significantly lower in the MetS group than the non-MetS group ($P < 0.05$). Moreover, the MHR and MAR were also calculated and divided into three tertiles. Clinical and laboratory characteristics of participants based on tertiles of MHR and MAR were summarized in **Tables 2**, **3**. Increasing trends were observed in BMI, WC, TG, SBP, DBP, UA, serum insulin, HOMA-IR, and monocyte count across the MHR and MAR tertiles ($P < 0.05$). In addition, decreasing trends were also observed in HDL-c and ApoA1 across the MHR and MAR tertiles ($P < 0.05$). Furthermore, participants in higher tertiles of MHR and MAR groups showed the higher prevalence of MetS and hypertension ($P < 0.05$).

The correlations between MHR, MAR, and metabolic parameters were presented in **Table 4**. The results showed that MHR and MAR were positively associated with BMI, WC, TG, SBP, DBP, UA, HOMA-IR, and monocyte count, whereas MHR and MAR were negatively associated with HDL-c and ApoA1 ($P < 0.05$). In addition, A positive correlation between MHR and MAR was also observed ($R = 0.762$, $P < 0.001$).

To determine independent variables of MHR and MAR for MetS, binomial logistic regression analysis was also performed (**Table 5**). The MHR and MAR were associated with MetS in an unadjusted model (model 0), and the odds ratios (ORs) (95%CI) were 2.50(2.12–2.98) and 3.17(2.57–3.91), respectively. The MHR and MAR were shown to be independently associated with MetS after adjustment for age and gender (model 1), and the ORs (95%CI) were 2.51 (2.11–2.98) and 3.18 (2.57–3.92), respectively. A significant association between MHR, MAR, and MetS was also found after further adjustment for HbA1c,

TABLE 1 | Clinical and laboratory characteristics of participants.

Variable	Total	Non-MetS (n = 241)	MetS (n = 364)	*P*
Age (year)	53.4 ± 7.5	52.8 ± 7.7	53.8 ± 7.5	0.103
Men, n (%)	304(50.2)	126(52.3)	178(48.9)	0.415
BMI (kg/m^2)	24.3 ± 3.1	23.1 ± 2.4	25.2 ± 3.0	< 0.001
HbA1c (%)	9.0 ± 1.1	9.0 ± 1.0	9.0 ± 1.2	0.521
WC (cm)	85.7 ± 6.9	82.6 ± 5.0	87.7 ± 7.2	< 0.001
TG (mmol/L)	2.14 ± 1.38	1.47 ± 0.88	2.59 ± 1.47	< 0.001
HDL-c (mmol/L)	1.10 ± 0.24	1.24 ± 0.20	1.01 ± 0.23	< 0.001
LDL-c (mmol/L)	3.48 ± 0.90	3.47 ± 0.88	3.49 ± 0.90	0.625
ApoA1 (g/L)	1.03 ± 0.21	1.14 ± 0.20	0.96 ± 0.19	< 0.001
Monocyte (10^9/L)	0.41 ± 0.10	0.37 ± 0.09	0.44 ± 0.10	< 0.001
UA (μmol/L)	352.1 ± 85.4	326.1 ± 72.7	370.4 ± 88.9	< 0.001
Creatinine (μmol/L)	70.5 ± 13.2	71.7 ± 13.5	69.7 ± 12.9	0.075
ALT (IU/L)	35.0 ± 9.0	34.9 ± 9.1	35.0 ± 9.0	0.874
SBP (mmHg)	132.0 ± 17.4	123.9 ± 13.4	139.1 ± 17.0	< 0.001
DBP(mmHg)	81.2 ± 9.8	76.8 ± 8.1	84.1 ± 9.8	< 0.001
Insulin (mU/ml)	27.6 ± 11.4	19.0 ± 7.7	33.9 ± 9.5	< 0.001
HOMA-IR	11.5 ± 6.2	8.7 ± 5.4	12.6 ± 6.0	< 0.001
hs-CRP (mg/L)	2.9 ± 0.9	2.9 ± 0.9	3.0 ± 1.0	0.788
Hypertension, n (%)	215(35.5)	37(15.4)	178(48.9)	< 0.001
Smoking, n (%)	218(36.0)	81(33.6)	137(37.6)	0.312
Drinking, n (%)	224(37.0)	79(32.8)	145(39.8)	0.079
MAR (10^8/g)	4.25 ± 1.69	3.34 ± 1.12	4.86 ± 1.73	< 0.001
MHR (10^8/mmol)	4.02 ± 1.58	3.09 ± 1.16	4.63 ± 1.53	< 0.001

TABLE 2 | Clinical and laboratory characteristics of participants based on tertiles of MHR (10^8/mmol).

Variable	T1 (<3.12)	T2 (3.12-4.57)	T3 (>4.57)	*P*
Age (year)	53.0 ± 7.5	53.2 ± 7.9	54.1± 7.3	0.33
Men, n (%)	100 (49.5)	102 (50.0)	102 (51.3)	0.937
BMI (kg/m^2)	22.3 ± 2.2^{ab}	24.4 ± 2.2^{ac}	26.3 ± 3.0^{bc}	< 0.001
HbA1c (%)	9.1 ± 1.2	8.9 ± 1.0	9.0 ± 1.1	0.314
WC (cm)	81.1 ± 4.3^{ab}	85.5 ± 5.1^{ac}	90.5 ± 7.4^{bc}	< 0.001
TG (mmol/L)	1.26 ± 0.89^{ab}	1.89 ± 0.71^{ac}	3.30 ± 1.51^{bc}	< 0.001
HDL-c (mmol/L)	1.30 ± 0.21^{ab}	1.06 ± 0.17^{ac}	0.93 ± 0.20^{bc}	< 0.001
LDL-c (mmol/L)	3.38 ± 0.88	3.55 ± 0.90	3.50 ± 0.93	0.156
ApoA1 (g/L)	1.09 ± 0.22^{ab}	1.04 ± 0.19^{ac}	0.96 ± 0.21^{bc}	< 0.001
Monocyte (10^9/L)	0.32 ± 0.06^{ab}	0.41 ± 0.05^{ac}	0.51 ± 0.08^{bc}	< 0.001
UA (umol/L)	298.8 ± 71.7^{ab}	357.2 ± 64.7^{ac}	402.8 ± 85.1^{bc}	< 0.001
Creatinine (umol/L)	71.6 ± 13.3	70.7 ± 13.9	69.2 ± 12.2	0.185
ALT (IU/L)	35.7 ± 9.9	34.0 ± 7.0	35.4 ± 9.9	0.108
SBP (mmHg)	119.3 ± 13.0^{ab}	131.6 ± 15.7^{ac}	146.5 ± 10.9^{bc}	< 0.001
DBP (mmHg)	77.0 ± 6.1^{ab}	79.7 ± 10.9^{ac}	87.9 ± 7.8^{bc}	< 0.001
Insulin (mU/ml)	16.9 ± 8.1^{ab}	26.4 ± 9.8^{ac}	34.5 ± 10.3^{bc}	< 0.001
HOMA-IR	7.2 ± 5.3^{ab}	11.1 ± 4.5^{ac}	14.1 ± 6.0^{bc}	< 0.001
hs-CRP (mg/L)	2.9 ± 0.9	3.0 ± 1.0	3.1 ± 0.9	0.373
Hypertension, n (%)	28 (13.9)^{ab}	56 (27.5)^{ac}	131 (65.8)^{bc}	< 0.001
Smoking,n (%)	66 (32.7)	75 (36.8)	77 (38.6)	0.439
Drinking,n (%)	72 (35.6)	74 (36.3)	78 (39.2)	0.735
MAR ($10^{8/}$g)	3.07 ± 0.86^{ab}	4.03 ± 0.77^{ac}	5.67 ± 1.97^{bc}	< 0.001
MetS, n (%)	60 (29.7)^{ab}	128 (62.7)^{ac}	176 (88.4)^{bc}	< 0.001

BMI, body mass index; UA, uric acid; TG, triglyceride; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; ApoA1, apolipoprotein A1; SBP, systolic blood pressure; DBP, diastolic blood pressure; HOMR-IR, homeostasis model assessment insulin resistance; hs-CRP, high-sensitivity C-reactive protein; MHR, monocyte–to–HDL-c ratio; MAR, monocyte-to-ApoA1 ratio. $^aP < 0.05$: T1 vs. T2. $^bP < 0.05$: T1 vs. T3. $^cP < 0.05$: T2 vs. T3.

BMI, LDL-c, ApoA1, monocyte, UA, and HOMA-IR (model 2), and the ORs (95%CI) were 2.24 (1.82–2.76) and 2.68 (2.14–3.35), respectively. After further additional adjustment for TG, WC, HDL-c, SBP, and DBP (model 3), the ORs remained significant, and the ORs (95%CI) were 1.50 (1.14–1.97) and 2.26(1.79–2.87), respectively. In addition, the ApoA1 and monocyte count were also associated with MetS in model 0, and the ORs (95%CI) were 0.76 (0.68–0.83) and 2.46 (1.99–3.03), respectively. A significant

TABLE 3 | Clinical and laboratory characteristics of participants based on tertiles of MAR (10^8/g).

Variable	T1 (<3.49)	T2 (3.12–4.56)	T3 (>4.56)	*P*
Age (year)	52.7 ± 7.3	54.1 ± 8.2	53.5 ± 7.1	0.199
Men, n (%)	101 (49.8)	95 (47.0)	108 (54.0)	0.371
BMI (kg/m^2)	23.0 ± 2.4^{ab}	24.4 ± 2.4^{ac}	25.7 ± 3.4^{bc}	< 0.001
HbA1c (%)	9.0 ± 1.1	8.9 ± 1.0	9.1 ± 1.1	0.247
WC (cm)	82.5 ± 5.1^{ab}	85.5 ± 5.8^{ac}	89.0 ± 7.9^{bc}	< 0.001
TG (mmol/L)	1.51 ± 0.87^{ab}	1.94 ± 1.02^{ac}	2.99 ± 1.67^{bc}	< 0.001
HDL-c (mmol/L)	1.25 ± 0.23^{ab}	1.10 ± 0.20^{ac}	0.96 ± 0.23^{bc}	< 0.001
LDL-c (mmol/L)	3.46 ± 0.91	3.48 ± 0.88	3.49 ± 0.93	0.965
ApoA1 (g/L)	1.19 ± 0.20^{ab}	1.04 ± 0.13^{ac}	0.86 ± 0.16^{bc}	< 0.001
Monocyte (10^9/L)	0.33 ± 0.06^{ab}	0.42 ± 0.06^{ac}	0.50 ± 0.10^{bc}	< 0.001
UA (μmol/L)	318.5 ± 70.3^{ab}	356.0 ± 74.1^{ac}	384.1 ± 96.9^{bc}	< 0.001
Creatinine (μmol/L)	71.8 ± 13.3	70.1 ± 13.1	69.6 ± 13.1	0.176
ALT (IU/L)	34.7 ± 8.8	35.6 ± 8.9	34.6 ± 9.4	0.520
SBP (mmHg)	123.5 ± 14.2^{ab}	132.7 ± 13.1^{ac}	143.2 ± 14.8^{bc}	< 0.001
DBP (mmHg)	76.0 ± 9.9^{ab}	81.0 ± 6.9^{ac}	86.6 ± 9.4^{bc}	< 0.001
Insulin (mU/ml)	19.8 ± 8.9^{ab}	26.1 ± 8.7^{ac}	33.8 ± 9.9^{bc}	< 0.001
HOMA-IR	8.2 ± 4.9^{ab}	10.9 ± 5.3^{ac}	14.0 ± 6.5^{bc}	< 0.001
hs-CRP (mg/L)	2.8 ± 0.9	3.0 ± 1.0	3.0 ± 0.9	0.255
Hypertension, n (%)	34 (16.7)^{ab}	67 (33.2)^{ac}	114 (57.0)^{bc}	< 0.001
Smoking, n (%)	72 (35.4)	71 (35.1)	75 (37.2)	0.777
Drinking, n (%)	77 (37.9)	72 (35.6)	75 (37.2)	0.880
MHR (10^8/mmol)	2.73 ± 0.82^{ab}	3.93 ± 0.93^{ac}	5.42 ± 1.53^{bc}	< 0.001
MetS, n (%)	53 (26.1)^{ab}	128 (63.4)^{ac}	183 (91.5)^{bc}	< 0.001

BMI, body mass index; UA, uric acid. TG, triglyceride. HDL-c, high-density lipoprotein cholesterol. LDL-c, low-density lipoprotein cholesterol. ApoA1, apolipoprotein A1.SBP, systolic blood pressure. DBP, diastolic blood pressure. HOMR-IR, homeostasis model assessment insulin resistance. hs-CRP, high-sensitivity C-reactive protein. MHR, monocyte–to–HDL-c ratio. MAR, monocyte-to-ApoA1 ratio. $^aP < 0.05$: T1 vs. T2. $^bP < 0.05$: T1 vs. T3. $^cP < 0.05$: T2 vs. T3.

TABLE 4 | Correlations between MHR, MAR and metabolic parameters.

Variable	MHR		MAR	
	R	*P*	R	*P*
Age (year)	0.045	0.27	0.035	0.384
HbA1c (%)	0.035	0.397	0.058	0.157
WC (cm)	0.502	< 0.001	0.355	< 0.001
BMI (kg/m^2)	0.51	< 0.001	0.334	< 0.001
TG (mmol/L)	0.44	< 0.001	0.418	< 0.001
LDL-c (mmol/L)	0.023	0.564	–0.018	0.651
HDL-c (mmol/L)	–0.751	< 0.001	–0.455	< 0.001
ApoA1 (g/L)	–0.281	< 0.001	–0.665	< 0.001
Monocyte (10^9/L)	0.885	< 0.001	0.749	< 0.001
MAR (10^8/g)	0.762	< 0.001	NS	NS
MHR (10^8/mmol)	NS	NS	0.762	< 0.001
UA (μmol/L)	0.505	< 0.001	0.342	< 0.001
Creatinine (μmol/L)	–0.075	0.066	–0.069	0.099
ALT (IU/L)	–0.012	0.764	–0.025	0.547
SBP (mmHg)	0.463	< 0.001	0.462	< 0.001
DBP (mmHg)	0.362	< 0.001	0.436	< 0.001
HOMA-IR	0.321	< 0.001	0.35	< 0.001
hs-CRP (mg/L)	0.016	0.678	0.019	0.713

BMI, body mass index; UA, uric acid; TG, triglyceride; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; ApoA1, apolipoprotein A1; SBP, systolic blood pressure; DBP, diastolic blood pressure; HOMR-IR, homeostasis model assessment insulin resistance; hs-CRP, high-sensitivity C-reactive protein; MHR, monocyte–to–HDL-c ratio; MAR, monocyte-to-ApoA1 ratio.

association between ApoA1, monocyte count, and MetS was also found in model 1, and the ORs (95%CI) were 0.77 (0.68–0.84) and 2.47 (1.98–3.03), respectively.

The ROC curve analysis was used to further evaluate the ability of MHR and MAR in identifying MetS. From the ROC curve analysis, the results showed a good identifying value of MHR and MAR for MetS. In addition, MHR and MAR showed higher area under the curve (AUC) in identifying MetS compared with ApoA1 and monocyte alone ($P < 0.05$). MAR also showed the highest AUC in identifying MetS. The AUC of MHR and MAR in identifying MetS was 0.804 (95% CI: 0.768–0.839, $P < 0.001$) and 0.840 (95% CI: 0.806–0.873, $P < 0.001$), respectively (**Figure 2**). The optimal cutoff values of MHR and MAR were 3.57×10^8/mmol (sensitivity: 76.1%, specificity: 73.4%) and 3.95×10^8/g (sensitivity: 79.7%, specificity: 84.6%), respectively (**Table 6**).

DISCUSSION

T2DM is a cluster of metabolic disease that often accompanied with MetS at the first diagnosis. Increasing evidence highlighted that inflammation involved in the development of MetS and T2DM. In this cross-sectional study, we mainly assessed the association between MetS and novel inflammatory indicators MHR and MAR in Chinese newly diagnosed T2DM. As expected, the results in the present study demonstrated that MHR and MAR were closely associated with metabolic risk factors. MHR and MAR were also significantly associated with higher odds of MetS after adjustment for other confounders. Furthermore, MHR and MAR were also seemed to have higher AUC value for MetS than ApoA1 and monocyte alone from the ROC curve analysis. These findings indicated that MHR and MAR can be novel markers for MetS in Chinese newly diagnosed T2DM.

TABLE 5 | Binomial Logistic Regression Analysis adjusted ORs (95% CIs) for the associations between MHR, MAR and the risk of MetS.

Models	MHR		MAR	
	OR (95%CI)	*P*	OR (95%CI)	*P*
Model 0	2.50 (2.12-2.98)	< 0.001	3.17 (2.57-3.91)	< 0.001
Model 1	2.51 (2.11–2.98)	< 0.001	3.18 (2.57–3.92)	< 0.001
Model 2	2.24 (1.82–2.76)	< 0.001	2.68 (2.14–3.35)	< 0.001
Model 3	1.50 (1.14–1.97)	0.004	2.26 (1.79–2.87)	< 0.001

Model 0 was an unadjusted model. Model 1 was adjusted for age and gender. Model 2 was additionally adjusted for HbA1c, BMI, LDL-c, ApoA1, monocyte, UA, and HOMA-IR based on model 1. Model 3 was additionally adjusted for TG, WC, HDL-c, SBP, and DBP based on model 2. BMI, body mass index; WC, waist circumference; HbA1c, glycated hemoglobin; UA, uric acid; TG, triglyceride; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; ApoA1, apolipoprotein A1; SBP, systolic blood pressure; DBP, diastolic blood pressure; HOMR-IR, homeostasis model assessment insulin resistance; hs-CRP, high-sensitivity C-reactive protein; MetS, metabolic syndrome; MHR, monocyte–to–HDL-c ratio; MAR, monocyte-to-ApoA1 ratio.

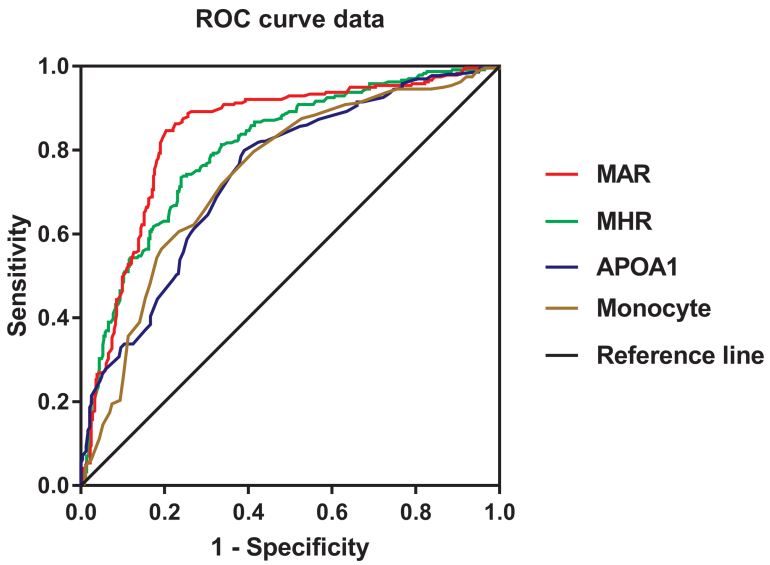

FIGURE 2 | Receiver operating characteristic curves for the cutoff value of MHR, MAR, monocyte, and ApoA1 to identify MetS.

In recent years, increasing evidence demonstrated that metabolic disorders can trigger inflammatory responses as a coping mechanism toward metabolic changes, leading to chronic inflammation occur. Thereby, chronic inflammation is widely considered as common denominator in many diseases such as obesity, MetS, T2DM, and CVD (7, 18, 19). The inflammatory process is continuous when chronic inflammation occurs, WBCs play an important role and involved in the process of inflammation that can secrete inflammatory cytokines, which can initiate and upregulate inflammatory responses. In the classification of WBCs, monocyte are produced from bone marrow and accumulated in circulatory system for a few days before migrating and differentiating into macrophages (20), which are known to stimulate the immune system and increase inflammation through releasing inflammatory cytokines like tumor necrosis TNF-α, interleukin-6, and monocyte chemoattractant protein 1 (4, 21). In addition, clinical studies also observed that peripheral total monocyte counts were increased parallel to the clustering of component of MetS in T2DM (22, 23). These biological features provided a basis for monocyte to may be a predictive marker for chronic inflammatory disease like MetS and T2DM. Despite the result in our study suggested that monocyte alone is capable of predicting MetS, the identifying value is not good enough with relatively lower AUC of 0.736. The ratio of monocyte to other anti-inflammatory factors may better reflect inflammatory state and has better identifying value for MetS in newly diagnosed T2DM.

HDL-c is capable of binding to lipid molecules that ensure that it has anti-inflammatory effects, which was also considered as an ideal marker of anti-inflammatory factors. More studies have put insights on the association between ratio of neutrophils, lymphocyte to HDL-c (NHR and LHR) or MHR and systematic inflammatory diseases. Chen et al. reported that NHR and LHR have strong predictive power for MetS in Chinese population (24). MHR was also considered as indicators of oxidative stress and systemic inflammatory disease. Several studies reported that MHR showed a powerful predictive value for chronic inflammatory disease like PCOS (10), peripheral artery disease (25), central retinal artery occlusion (26), Parkinson's Disease (11), nonalcoholic fatty liver disease (27), and ST-elevation myocardial infarction (28). Furthermore, Jiang et al. found that MHR was significantly related to all-cause and cardiovascular mortality in the general population independent of established risk factors (9). De Matteis et al. reported that MHR was independently correlated with vitamin D deficiency in healthy and metabolic women (29). All clinical findings indicated MHR can be a predictive marker for other kinds of chronic inflammatory disease like MetS. To our

TABLE 6 | ROC Curve Analysis of MHR and MAR in identifying MetS.

Variables	AUC(95% CI)	Cutoff value	Sensitivity (%)	Specificity (%)
MHR (10^8/mmol)	0.804 (0.768–0.839)	3.57	76.1	73.4
MAR (10^8/g)	0.840 (0.806–0.873)	3.95	79.7	84.6
Monocyte (10^9/L)	0.736 (0.692–0.770)	0.445	52.7	87.6
ApoA1 (g/L)	0.741 (0.701–0.781)	1.14	82.1	56

MetS, metabolic syndrome; ApoA1, apolipoprotein A1; MHR, monocyte–to–HDL-c ratio; MAR, monocyte-to-ApoA1 ratio.

expectation, the results in our study showed that MHR was significantly associated with higher odds of MetS and seemed to have a higher predictive value for MetS than monocyte alone, and more studies with enough follow-up should be conducted to further confirm these findings. ApoA1 is another kind of hypothetical markers for anti-inflammation produced by the liver and responsible for peripheral cholesterol transportation and redistribution, which was also well recognized as anti-inflammatory lipid proteins in CVD (13). Previous studies have focused on the association between APOB/ApoA1 and MetS. Several studies observed that APOB/ApoA1 was significantly associated with higher odds of MetS and insulin resistance in Chinese population and PCOS patients (30, 31). To further explore the potential effects of ApoA1 in predicting MetS, we analyzed the association between MAR and MetS. To our surprise, MAR was not only an independent risk factor of MetS but it also showed the highest AUC of 0.840 with 79.7% sensitivity and 84.6% specificity in identifying MetS. These findings indicated that MAR may be a more promising indicator of MetS for Chinese newly diagnosed T2DM, whereas more longitudinal studies compared with other inflammatory indicators are needed to further confirm these findings.

To our knowledge, this is the first study that confirmed the identifying value of MHR and MAR for MetS in Chinese newly diagnosed T2DM. The other strengths of this study adjusted several potential confounding variables in final analysis and included enough sample size that can represent the Chinese newly diagnosed T2DM population. Meanwhile, some limitations need to be mentioned. First, this study was designed as a cross-sectional study without follow-up, and it cannot directly reflect the associations MHR, MAR, and MetS. Second, the studied population is the Chinese newly diagnosed T2DM, and the optimal cutoff values of MHR and MAR may be not applicable to other races.

In conclusion, two novel indicators of MetS for Chinese newly diagnosed T2DM was found in this study. The results showed that MHR and MAR were significantly associated with MetS and seemed to have higher AUC value for MetS than ApoA1 and monocyte alone. All these findings indicated that MHR and MAR could be convenient and reliable predictors to screen for MetS in Chinese newly diagnosed T2DM, whereas more longitudinal studies are needed to further confirm these associations.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the ethical committee of Longyan First Affiliated Hospital of Fujian Medical University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

WW took charge of the software and contributed to writing—original draft. WW, ZC, XG, and MT conducted the investigation. MT contributed to data curation and writing-editing. All authors contributed to the article and approved the submitted version.

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Is the METS-IR Index a Potential New Biomarker for Kidney Stone Development?

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Objective: The purpose of this study was to examine whether the METS-IR index is associated with kidney stones in American adults.

Method: Participants from the National Health and Nutrition Examination Survey (NHANES) database from 2007-2018 were selected for logistic regression analysis, subgroup analyses, and the calculation of dose-response curves to assess the association between the METS-IR index and the incidence of kidney stones.

Result: This study enrolled 30,612 adults aged >20 years, 2901 of whom self-reported having had kidney stones in the past. And, after controlling for potential confounders, each unit increase in the METS-IR index was linked with a 1.23 percent rise in kidney stone incidence (OR= 1.0123, 95% CI: 1.0092 - 1.0155), with stratified analysis indicating that this was true in all subgroups. Between all groups, an elevated METS-IR index was related to kidney stone formation, and the dose-response curve revealed a positive non-linear connection between METS-IR index and kidney stone risk, with a threshold effect analysis revealing an inflection point value of 50.8314.

Conclusion: Higher METS-IR index is associated with the occurrence of kidney stones, and while no causative association can be shown, this is cause for concern.

Keywords: metabolic syndrome, kidney stones, METS-IR index, insulin resistance, NHENSE (National Health and Nutrition Examination Survey)

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INTRODUCTION

The kidney stone is a benign disease that affects the renal calyces, renal pelvis, and the junction of the renal pelvis and ureter and is one of the most common in urology (1). Current prevalence levels of kidney stones are high, and they have been increasing globally throughout the past few decades (2). According to the most recent survey study of the National Health and Nutrition Examination Survey (3), the prevalence of kidney stones is as high as 11% in the United States, 9% in Europe (1),

Abbreviations: MetS, Metabolic syndrome; IR, Insulin resistance; OR, Odds ratio; BMI, Body mass index; US, United States; PIR, Ratio of family income to poverty.

and 5.8% in China (4). Presently, minimally invasive endoscopic procedures such as percutaneous nephrolithotomy, flexible ureteroscopic lithotripsy and other endoscopic procedures are routinely used to treat kidney stones.A high recurrence risk exists even after completion of treatment (5). If not effectively treated, it may result in serious complications such as irreversible kidney damage and end-stage renal disease.It is becoming increasingly apparent that kidney stones are a significant public health concern, as well as a major economic burden for the healthcare system (6).

As a result of the high rates of recurrence and incidence of kidney stones, prevention should be considered a high priority.A multitude of systemic factors have been reported to be associated with an increased risk of kidney stones, suggesting that genetic, environmental, and nutritional influences may play an important role in stone development (7). It has become increasingly apparent that modifiable factors, including diet and lifestyle, can influence kidney stone development. Every time the conditions of living improve, the number of people suffering from metabolic syndrome increases due to high-fat and high-sugar diets. Metabolic syndrome (MetS) refers to a group of metabolic disorders, which include obesity (primarily abdominal obesity), fasting, postprandial hyperglycemia, hypertension, and dyslipidemia. It has been suggested that these conditions may be linked to a common mechanism: insulin resistance(IR) (8, 9). Increasingly, studies confirm an association between IR and major kidney stones. It is believed that IR increases the risk of urinary calcium stones by reducing the excretion of citrate in the urine (10). Metabolic syndrome components may contribute to the development of kidney stones through subclinical hyperinsulinemia and insulin resistance (11).

Hyperinsulinemic normoglycemic clamps (HECs) are currently the gold standard for assessing insulin sensitivity in peripheral tissues (12). Due to the complexity, time consuming nature, and resource consuming nature of this method, simpler metrics are often used to assess insulin resistance. The METS-IR index, a new metric for measuring insulin resistance (IR) as a simple, reliable, and reproducible predictive metric, has been proposed in 2018 (12, 13). Given the METS-IR index's role as a marker for IR, a possible correlation between the METS-IR index and renal calculi might be posited. Nevertheless, no previous study has investigated the relationship between the METS-IR index and kidney stones. Therefore, in the present study, we aimed to assess the value of the METS-IR index in the incidence of kidney stones in the United States (US) population.

MATERIALS AND METHODS

Study Population

Data for this study were obtained from the NHANES database based on big data mining methods and were conducted by the Centers for Disease Control and Prevention (CDC) (14, 15). NCHS's Institutional Review Board reviewed and approved the study protocol, as well as forms of consent signed by participants. Six consecutive two-year survey cycles, including the Kidney Stone Questionnaire, were used for the evaluation of our research. All participants were assessed with the KIQ026 survey (Do You Have Kidney Stones) and 59,842 completed the questionnaire. Exclusion criteria were as follows (**Figure 1**). Ultimately, 30612 cases were included in the study, including 2901 patients who self-reported renal calculi.

Data Collection and Definition

METS-IR index is intended to be used as an exposure variable. METS-IR= Ln((2 × fasting glucose) + fasting triglycerides) × body mass index)/[Ln(high-density lipoprotein cholesterol)]. An automated biochemical analyzer was used to

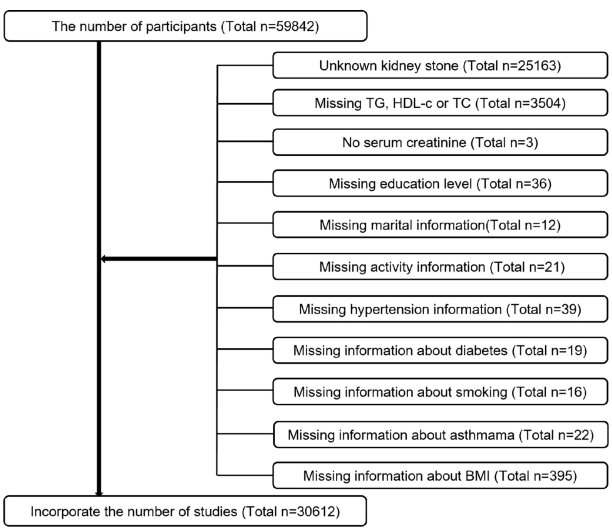

FIGURE 1 | Sample selection flowchart from NHANES 2007–2018.

determine fasting glucose and triglyceride concentrations. The serum triglyceride concentrations were measured using a Roche Modular P chemistry analyzer and a Roche Cobas 6000 chemistry analyzer. In addition, the questionnaire KIQ026 consists of a question to determine whether the respondent has ever experienced kidney stones. Studies have verified the validity of self-reported kidney stone status (3). A participant was deemed to have kidney stones if he answered "yes" to the question of whether he had ever experienced kidney stones. The outcome variable for this research was the occurrence of kidney stones.

An adjusted multivariate model was used to summarize potential confounders that might confound the association between METS-IR index and kidney stones. Covariates in our study included sex (male/female), age (years), race, education level, poverty to income ratio (PIR), marital status (married or living with partner/single), alcohol consumption (drinking or not), physical activity (vigorous/moderate/below moderate), cholesterol level (mg/dl), serum creatinine (mg/dl), blood calcium (mg/dl), albumin creatinine ratio (mg/g), body mass index (BMI), smoking status (smoking or not), hypertension, diabetes, asthma [a proven risk factor for stones (16)] and dietary intake factors including energy intake, fat intake, sugar intake and water intake, all participants were eligible for two 24-hour dietary recalls and our the average consumption of the two recalls will be used in our analysis. When missing values were less than 10% (17, 18), median values were directly used as a proxy. However, when missing values exceeded 10%, we converted these values into categorical variables and assessed them in tertiles, with the lowest tertile serving as a reference. On the CDC's website at www.cdc.gov/nchs/nhanes, you can find detailed information on all the measurement procedures used in the study.

Statistical Methods

A suitable NHANES sample weight was employed and the complicated multistage cluster survey design was accounted for in the analysis. Variables with continuous characteristics were expressed as means together with their standard deviations, and categorical characteristics were expressed as percentages. In order to determine the variability of clinical characteristics among groups, weighted Chi-square tests (categorical variables) and weighted variance analysis (continuous variables with a normally distributed distribution) or weighted Kruskal-Wallis`s H tests (continuous variables with a skewed distribution) were employed. Based on guidelines (19), multiple logistic regression models were used to examine the independent relationship between METS-IR index and different tertile groups of METS-IR index and kidney stones. In model 1, no adjustment for covariates was made. Model 2 was adjusted for sex, age, and race. Model 3 was adjusted for sex, age, race, education level, poverty-income ratio, marital status, alcohol intake, physical activity, cholesterol, serum creatinine, smoking status, hypertension, diabetes, asthma, energy intake, fat intake, sugar intake, and water intake. For further assessment of the relationship between METS-IR index and kidney stones, smooth curve fitting (penalized spline method) and generalized additive model (GAM) regression were conducted. Additionally, univariate linear regression models and two-piecewise linear regression models were constructed using the same covariates. To identify the best model, it was also necessary to conduct a logarithmic ratio test. The model was additionally used to determine whether a threshold exists. The inflection point connecting the segments based on the model had the highest likelihood, and was determined using a two-step recursive methodology. Moreover, an interaction term was added using a log-likelihood ratio test model in order to examine the heterogeneity of the association between subgroups. A statistically significant value was considered to be $p < 0.05$.Empower® software (www.empowerstats.com; X&Y Solutions, Inc., Boston, MA, USA) and R 3.4.3 (http://www.r-project.org, The R Foundation) were used to conduct all analyses.

RESULTS

An overview of the baseline demographic characteristics of the participants is provided in **Table 1**. There was a significant difference in the METS-IR index between the stone and non-stone groups, 47.291 ± 13.591vs 43.259 ± 12.936, p< 0.001.

Increased METS-IR Index Is Associated With a Higher Risk of Kidney Stones

The METS-IR index was positively related to the presence of kidney stones. In the fully adjusted model (model 3), the positive association remained stable (OR=1.0126, 95% CI: 1.0095 - 1.0158), indicating that a unit increase in METS-IR index was associated with a 1.26 percent increase in the risk of kidney stones. Additionally, we converted the METS-IR index from a continuous variable into a categorical variable (tertile) prior to performing a sensitivity analysis. In Tertile 2 and Tertile 3, the likelihood of kidney stones occurrence increased by 36.11% and 59.42%, respectively, compared with the lowest METS-IR index in the lowest tertile (Tertile 1), as illustrated in **Table 2**.

Metrics-IR's Dose Response and Threshold Effect on Kidney Stones

A generalized additive model and smoothed curve fitting have been used to analyze the relationship between METS-IR index and kidney stones. Results of our study demonstrated a nonlinear relationship between METS-IR index and kidney stones (**Figure 2** and **Table 3**). Based on a two-segment linear regression model, the METS-IR inflection point was calculated at 50.8314.As shown in **Table 3**, the OR on the left side of the inflection point was 1.0238 (95% CI: 1.0178-1.0299), whereas the OR on the right side of the inflection point was 1.0015 (log-likelihood ratio test, $p < 0.001$).

Subgroup Analysis

Subgroup analyses were performed in order to assess the robustness of the association between METS-IR index and

TABLE 1 | Baseline characteristics of participants,weighted.

Characteristic	Nonstone formers N=27711	Stone formers N=2901	P-value
Age (years)	46.812 ± 16.806	53.299 ± 15.576	<0.001
PIR	2.965 ± 1.600	2.982 ± 1.572	0.56
BMI (kg/m^2)	28.927 ± 6.829	30.623 ± 6.992	<0.001
Serum Cholesterol (mg/dl)	194.041 ± 41.436	192.268 ± 42.519	0.026
Serum Calcium (mg/dl)	9.392 ± 0.358	9.370 ± 0.379	0.016
Serum Creatinine (mg/dl)	0.875 ± 0.328	0.937 ± 0.570	<0.001
Urine Albumin Creatinine Ratio (mg/g)	31.026 ± 265.850	42.047 ± 267.225	<0.001
METS-IR Index	43.259 ± 12.936	47.291 ± 13.591	<0.001
Gender (%)			<0.001
Male	47.355	54.689	
Female	52.645	45.311	
Race (%)			<0.001
Mexican American	14.772	11.198	
White	65.680	76.974	
Black	11.301	5.717	
Other Race	8.247	6.112	
Education Level (%)			0.005
Less than high school	20.372	19.862	
High school	28.532	31.305	
More than high school	51.097	48.833	
Marital Status (%)			<0.001
Cohabitation	63.286	69.099	
Solitude	36.714	30.901	
Alcohol (%)			0.486
Yes	60.328	59.463	
No	18.519	19.386	
Unclear	21.152	21.151	
High Blood Pressure (%)			<0.001
Yes	30.098	46.704	
No	69.902	53.296	
Diabetes (%)			<0.001
Yes	8.752	17.998	
No	91.248	82.002	
Smoked			<0.001
Yes	43.575	49.511	
No	56.425	50.489	
Physical Activity (%)			<0.001
Never	26.738	31.021	
Moderate	31.829	31.227	
Vigorous	41.433	37.753	
Asthma (%)			<0.001
No	85.474	82.656	
Yes	14.526	17.344	
Total Kcal (%)			0.045
Tertile 1	24.748	24.100	
Tertile 2	28.386	30.899	
Tertile 3	30.846	30.930	
Unclear	16.020	14.071	
Total Sugar (%)			0.174
Tertile 1	23.723	24.460	
Tertile 2	24.612	23.062	
Tertile 3	24.438	25.611	
Unclear	27.226	26.867	
Total Water (%)			0.005
Tertile 1	23.778	22.598	
Tertile 2	28.903	30.070	
Tertile 3	31.299	33.261	
Unclear	16.020	14.071	
Total Fat (%)			0.005
Tertile 1	23.778	22.598	
Tertile 2	28.903	30.070	

(Continued)

TABLE 1 | Continued

Characteristic	Nonstone formers N=27711	Stone formers N=2901	P-value
Tertile 3	31.299	33.261	
Unclear	16.020	14.071	

Statistically significant: p<0.05; Mean+SD for continuous variables: P value was calculated by weighted linear regression model.
%for Categorical variables: P value was calculated by weighted chi-square test.
BMI, Body mass index (kg/m^2); PIR, Ratio of family income to poverty.

TABLE 2 | Analysis between METS-IR index with kidney stone formation.

Characteristic	Model 1 OR (95%CI)	Model 2 OR (95%CI)	Model 3 OR (95%CI)
METS-IR Index	1.0189 (1.0161, 1.0216)	1.0192 (1.0163, 1.0221)	1.0123 (1.0092, 1.0155)
Categories			
Tertile 1	1	1	1
Tertile 2	1.6182 (1.4602, 1.7933)	1.4631 (1.3175, 1.6249)	1.3611 (1.2239, 1.5137)
Tertile 3	2.0475 (1.8540, 2.2610)	1.9429 (1.7552, 2.1508)	1.5942 (1.4312, 1.7757)

Model 1 = no covariates were adjusted.
Model 2 = Model 1+ age,gender, race were adjusted.
Model 3 = Model 2+ gender, diabetes, blood pressure, education, marital status, serum calcium, PIR, asthma, total water, total kcal, total fat, total sugar, smoked, physical activity, alcohol use, serum creatinine, serum cholesterol, urine albumin creatinine ratio were adjusted.

kidney stones. All subgroup analyses indicated that an increased METS-IR index was positively associated with kidney stone occurrence (**Table 4**). We also tested for interactions between age, gender, hypertension, and diabetes mellitus.

DISCUSSION

Generally, kidney stones are a recurrent disease over the course of a lifetime. Recurrent stones are more likely to recur in the future and have a poorer prognosis (7).A low urine output, a high urinary calcium level, a high oxaluria level, and an abnormal urinary pH level can all contribute to stone formation (20).Due to the complex etiology of stones, large individual differences, regional differences, and high recurrence rates, a comprehensive study of risk factors for stones and the search for factors associated with stone recurrence are necessary to guide treatment and prevention.

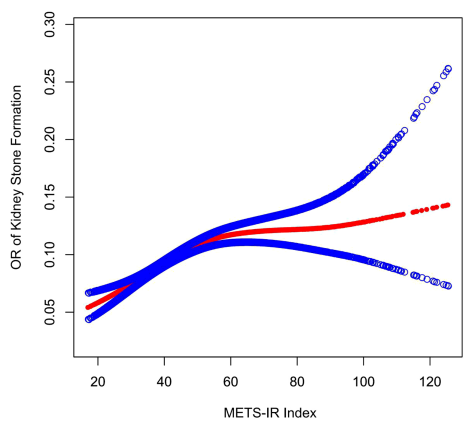

FIGURE 2 | Density dose–response relationship between METS-IR index with kidney stone formation. The area between two blue dotted lined is expressed as a 95% CI. Each point shows the magnitude of the METS-IR index and is connected to form a continuous line. Adjusted for all covariates except effect modifier.

As far as our knowledge is concerned, this is the first study to investigate the relationship between the METS-IR index and kidney stones and to demonstrate the predictive significance of METS-IR in the development of kidney stones. The results of this large cross-sectional study reveal that higher METS-IR scores are positively associated with an increased risk of kidney stone formation. Individuals in the highest tertile of METS-IR had a 0.59-fold greater risk of developing new kidney stones as compared to those in the lowest tertile. Moreover, this study not only evaluated the independent effects of METS-IR and the risk of kidney stone development, but also examined the dose–response relationship between the two factors and derived a threshold effect for METS-IR of 59.8314.In comparison to the left side of the inflection point, when METS-IR was at 59.8314, there was an increasing trend in kidney stone occurrence with increasing METS-IR (OR =1.0238, 95% CI: 1.0178-1.0299); however, when METS-IR was at 59.8314, the trend gradually plateaued compared to the right side of the inflection point (OR =1.0015, 95% CI. 0.9957-1.0073).The factors included in this study were stratified by sex, age, hypertension, and diabetes status, while the interaction test p-values were not statistically significant, indicating that this association was independent of age, hypertension, and diabetes, suggesting that it could be applied to all types of populations. Intriguingly, our results suggest that an elevated METS-IR index is associated with a greater risk of kidney stone formation among non-hypertensive and non-diabetic individuals than among hypertensive and diabetic individuals. First, the possibility exists that those

TABLE 3 | Two-piecewise linear regression and logarithmic likelihood ratio test explained the threshold effect analysis of METS-IR index on kidney stone.

METS-IR Index	ULR Test OR (95% CI)	PLR Test OR (95% CI)	LRT test P value
<50.8314umol/L	1.0121 (1.0089, 1.0152)	1.0238 (1.0178, 1.0299)	<0.0001
≥50.8314umol/L		1.0015 (0.9957, 1.0073)	

ULR, univariate linear regression; PLR, piecewise linear regression; LRT, logarithmic likelihood ratio test, statistically significant: p < 0.05.

TABLE 4 | Subgroup analysis between METS-IR index with kidney stone formation.

Characteristic	Model 1 OR (95%CI)	Model 2 OR (95%CI)	Model 3 OR (95%CI)	p for trend*	p for interaction*
Stratified by gender					0.4694
Male	1.0179 (1.0140, 1.0218)	1.0185 (1.0144, 1.0227)	1.0123 (1.0078, 1.0168)	<0.001	
Female	1.0191 (1.0152, 1.0230)	1.0201 (1.0161, 1.0241)	1.0117 (1.0072, 1.0161)	<0.001	
Stratified by age (years)					0.7463
20-39	1.0157 (1.0101, 1.0214)	1.0158 (1.0101, 1.0215)	1.0068 (1.0004, 1.0132)	0.025	
40-59	1.0202 (1.0156, 1.0248)	1.0207 (1.0160, 1.0254)	1.0128 (1.0076, 1.0180)	<0.001	
60-80	1.0195 (1.0148, 1.0243)	1.0187 (1.0138,	1.0117 (1.0064, 1.0171)	<0.001	
Stratified by hypertension					0.0651
NO	1.0189 (1.0149, 1.0230)	1.0193 (1.0150, 1.0236)	1.0152 (1.0107, 1.0197)	<0.001	
YES	1.0102 (1.0063, 1.0142)	1.0122 (1.0080, 1.0164)	1.0074 (1.0029, 1.0118)	0.001	
Stratified by diabetes					0.3559
NO	1.0163 (1.0130, 1.0195)	1.0172 (1.0138, 1.0207)	1.0134 (1.0098, 1.0170)	<0.001	
YES	1.0094 (1.0036, 1.0152)	1.0108 (1.0045, 1.0170) 0.000670	1.0075 (1.0011, 1.0140)	<0.001	

Model 1 = no covariates were adjusted.
Model 2 = Model 1+age,gender,race were adjusted.
Model 3 = adjusted for all covariates except effect modifier.
**Means only in model 3.*

with diabetes and hypertension may be more cognizant of healthy eating, after all, a high sugar diet is more likely to contribute to the development of metabolic syndrome (21, 22). In addition, Iran found that non -hypertensive people`s IR resistance will cause cardiovascular disease, and there is no such effect in people with hypertension (23). Another Japanese study found that the increase in IR levels in non -diabetic people will lead to increasing coronary heart disease and stroke probability (24). Hedblad et al. (25) reported that the HOMAIR distribution of non-diabetic individuals has the 75th percentage value (2.12 for men, 1.80 (for women). The risk of infarction is significantly higher than those without these HOMA-IR values.These results suggest that IR resistance is more likely to cause more severe consequences in non-diabetic and non-hypertensive populations. Although the research objects are different, this result also confirms to some extent that our results may be correct. Considering these findings, it is also suggested that the association between METS-IR index and kidney stones should be more closely monitored among healthy people.

The METS-IR index was first reported in 2018 and is considered to be an intuitive and reliable measure of inflammation that can be used in clinical decision making (12, 13). In a cohort study conducted in Korea, Kim et al. demonstrated that IR was associated with the development of kidney stones in Korean men (26). Another study from Japan also confirmed that metabolic syndrome can cause insulin resistance, which in turn increases the risk of kidney stones (11). There has been some research on the influence of IR on kidney stone formation as well. Insulin resistance has been shown to cause ammonia production to decline and sodium and bicarbonate reabsorption to increase, which results in a decrease in the pH of the urine (27). Likewise, insulin resistance may result in a reduction in renal ammonia production, which will lead to a reduction in ammonia buffering and further decrease urine pH (28). In urine with a pH below 5.5, less soluble uric acid is formed from urate, which can cause uric acid stones (29). Further, IR increases renal tubule citrate uptake and decreases urinary citrate levels (10), which is one of the primary causes of calcium stones. In light of the fact that METS-IR index and IR levels are positively correlated, it may be possible to explain why a higher METS -IR index is related to an increased risk of kidney stones.

Several advantages are associated with our study. The NHANES is a representative sample of the US population. It strictly adheres to a well-designed study protocol with high standards of quality assurance and quality control. Moreover, our results are robust when tested against a range of sensitivity analyses that confirm our primary analysis. Nonetheless, we recognize the limitations of our study. As a result of using the NHANES database, a cross-sectional study, we were not able to investigate a causal relationship between METS-IR and kidney stones. Additionally, the diagnosis of kidney stones was made on the basis of a questionnaire, which was unable to provide information on the size and type of kidney stones, and was susceptible to recall bias; and finally, detailed clinical variables, such as medication history and kidney stone type, were not included in the database and required further investigation. Upon confirmation of our findings, an RCT study in a multicenter environment will be conducted. In spite of these limitations, this study has the strength of suggesting a new index of kidney stone

incidence and demonstrating the relationship between METS-IR scores and kidney stones.

SUMMARY

According to the results of this cross-sectional analysis of a representative sample, a high METS-IR index is associated with an increase in the prevalence of kidney stones. Mets-IR shows promise as a new marker that can help guide prevention of kidney stones

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/supplementary material.

ETHICS STATEMENT

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

AUTHOR CONTRIBUTIONS

XS, YangC, YanC, HL, and GL performed the material preparation, collected the data, and analyzed the data. ZH wrote the original draft of the manuscript. All authors contributed to the study conception and design and commented on the previous versions of the manuscript, and read and approved the final manuscript.

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The association between a body shape index and elevated urinary albumin–creatinine ratio in Chinese community adults

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Background: Obesity, especially visceral obesity, seems to be one of the most decisive risk factors for chronic kidney disease. A Body Shape Index (ABSI) is an emerging body size measurement marker of visceral obesity. This study aimed to explore whether ABSI is associated with albuminuria in Chinese community adults.

Methods: This cross-sectional study enrolled 40,726 participants aged 40 or older from seven provinces across China through a cluster random sampling method. ABSI was calculated by body mass index, waist circumference, and height. Increased albuminuria was defined as urinary albumin–creatinine ratio (UACR) ≥ 30 mg/g, indicating kidney injury. For ABSI, we divided it by quartile cutoff points and tried to determine the association between ABSI levels and UACR by multiple regression analysis. DAG (Directed Acyclic Graph) was plotted using literature and expert consensus to identify potential confounding factors.

Results: The average age of subjects with elevated UACR was 61.43 ± 10.07, and 26% were men. The average age of subjects with normal UACR was 57.70 ± 9.02, and 30.5% were men. Multiple logistic regression analysis was conducted and demonstrated that the ABSI quartiles were related to elevated UACR positively (OR [95% CI] Q2 vs. Q1: 1.094 [1.004, 1.197]; OR [95% CI] Q3 vs. Q1: 1.126 [1.030, 1.231]; OR [95% CI] Q4 vs. Q1: 1.183 [1.080, 1.295], p for trend < 0.001) after adjustments for confounding factors. The stratified analysis further showed that with the mounting for ABSI levels, elevated UACR more easily occurred in the people characterized by the elderly, men, and hypertension.

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Conclusions: In Chinese community adults, people with higher ABSI levels can be deemed as high-risk individuals with UACR elevation, and it will be beneficial for them to lose weight and significantly reduce visceral fat.

KEYWORDS

a body shape index, albuminuria, visceral obesity, chronic kidney disease, body mass index

Introduction

Nowadays, chronic kidney disease (CKD) has been changed into a global public health threat. The estimated prevalence of CKD was 9.1% worldwide in 2017, ranking as the 12th leading cause of death (1). The onset of CKD is insidious, and it was easily advanced to end-stage renal disease (ESRD), which has a poor prognosis and high mortality, posing a heavy burden on public health and the economy (2). UACR, as a sensitive marker of early kidney injury, is currently used in clinical screening for CKD to identify high-risk populations (3).

There is a remarkable phenomenon that the prevalence of obesity in patients with CKD is high, mounting from 38.1% in 1999–2002 to 44.1% in 2011–2014 in the United States (4). A large population of European survey demonstrated that among the risk factors of new CKD, obesity is one of the strongest one (5). Body mass index (BMI), used for obesity measurement most commonly (6), remains limited by its inability to provide information on fat distribution and distinguish fat accumulation from muscle (7). Krakauer invented ABSI (8), which consists of waist circumference (WC), height, and BMI. High ABSI values correspond to high visceral fat, which not only predicts the risk of premature death independent of BMI, but also is a marker of abdominal obesity and insulin resistance in men (9).

pt?>A cohort study of 5,438 urban residents in Japan found that ABSI can predict subjects at risk of renal function decline more effectively than WC (10). A cross-sectional survey of 7,053 older people in South Korea showed that the ABSI had a better capacity to discriminate the CKD stage than BMI (11). However, to our knowledge, evidence of the relationship between ABSI and UACR in the large-sample population is lacking. Therefore, in this study, we collected data from 40,726 Chinese adults to explore the relationship between ABSI and albuminuria and identify high-risk individuals as early as possible to provide evidence for CKD prevention.

Methods

Participants and study design

Data from the cross-sectional study came from the REACTION (China's Risk Evaluation of cAncers in Chinese diabeTic Individuals, a lONgitudinal study), which recruited 47,808 individuals over the age of 40 from May to December 2011 in seven geographically diverse regional centers in China (Zhengzhou, Dalian, Luzhou, Shanghai, Wuhan, Guangzhou, and Lanzhou) (12). Participants with a diagnosis of primary kidney disease, a history of malignancy, prior use of antihypertensive medications (angiotensin-converting enzyme inhibitors or angiotensin receptor blockers), or lack of significant data were excluded. Finally, we enrolled 33,303 participants (Figure 1). The Clinical Research Ethics Committee approved this study of Ruijin Hospital, affiliated with Shanghai Jiao Tong University School of Medicine (2014-25). This study was performed according to the Declaration of Helsinki. All participants, before participation, provided informed consent.

Data collection

Trained investigators collected basic information about participants through standardized questionnaires, including age, gender, history of underlying diseases, medication history, lifestyle, smoking habits, and drinking habits. Anthropometric measurements include weight, height, WC, diastolic blood pressure (DBP), and systolic blood pressure (SBP). Participants removed their clothes and shoes before the measurement. Blood pressure was measured three times with a mercury sphygmomanometer and averaged. All subjects had to sit still for at least 5 min before the measurement. The definition of WC is the abdominal circumference connecting the lower margin of the thorax to the midpoint of the iliac crest, the hip circumference (HC) was defined as the length of the hip joint protrusion horizontally. Fasting blood samples and morning urine were collected after 10 h of fasting. Biochemical parameters included aspartate transferase (AST), alanine transferase (ALT), glutamyltransferase (GGT), fasting blood glucose (FBG), 2 h postprandial blood glucose (PBG), rapid insulin determination (0 min, 120 min), glycosylated hemoglobin A1c (HbA1c), triglyceride (TG), total cholesterol (TC), serum creatinine (Scr), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C).

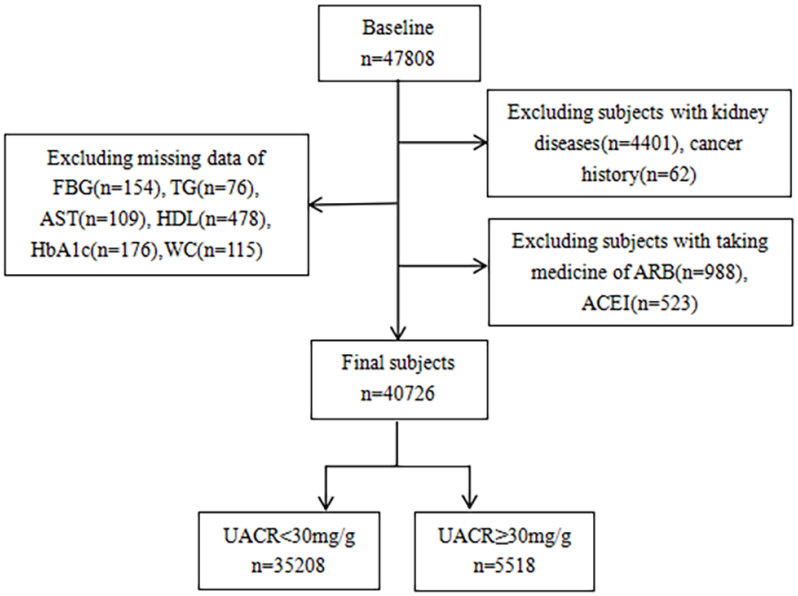

FIGURE 1
Flowchart of the study population.

Definition of variables

BMI is the weight (kg) divided by height squared (m^2). ABSI was calculated by WC (m)/[$BMI^{2/3}$ (kg/m^2) × $height^{1/2}$ (m)]. Waist-to-hip ratio (WHR) and waist-to-height ratio (WHtR) are WC divided by HC and WC divided by height, respectively. Smoking habits were defined as non-smoking, occasional smoking (less than one cigarette per day or less than seven cigarettes per week), and regular smoking (at least one cigarette per day). Normal blood pressure is defined as SBP of less than 120 and DBP of less than 80; hypertension was defined as SBP greater than 140 or DBP greater than 90; between the two categories is pre-hypertension. UACR was calculated as urinary albumin (mg)/urinary creatinine (g). According to the KDIGOCKD guidelines (13), UACR ≥ 30 mg/g was the definition of increased proteinuria, suggesting kidney damage. The UACR group was divided into two groups: normal proteinuria group: UACR < 30 mg/g and increased proteinuria: UACR ≥ 30 mg/g. For ABSI, we divide it by quartile cutoff points. eGFR was estimated from a simplified equation developed from data from the Modification of Diet in Renal Disease (MDRD) study as follows (14): eGFR (ml/min/1.73 m^2) = 186 × [SCr (mg/dl)/88.4]$^{-1.154}$ × $(age)^{-0.203}$ × (0.742 if women) × 1.233.

Statistical methods

We performed the Kolmogorov–Smirnov test to explore whether the continuous variables were normally distributed. Continuous variables were presented as mean ± SD or median (IQR) for skewed variables; the classification variables were represented by percentage (%). The Mann–Whitney *U* test was used to compare the difference between continuous variables, and the Chi-square test was used to compare the categorical variables. Logistic regression analysis was conducted to estimate odds ratios (ORs) and 95% confidence intervals (Cis) to determine the association between the ABSI quartile and increased proteinuria, with the lowest quartile as the reference group. We identify conf variables for the relationship between ABSI and albuminuria by reviewing the literature and drawing the DAG. After the univariate analysis between the confounders and UACR, the confounders with a *p*-value less than 0.2 were included in the final model, and the multiple logistic regression model of ABSI and all potential confounders was established, and the optimal model was fitted by stepwise backward regression method. To further investigate the association between ABSI quartile and increased risk of proteinuria, the relationship between gender, age (<60/≥60 years), and eGFR (<90/≥90 ml/min/1.73 m^2) was stratified. The software used for data analysis was SPSS Version 25.0 (IBM, Chicago, IL, USA). The results were considered statistically significant if the bilateral *p*-value < 0.05.

Results

Clinical characteristics of study participants

A total of 40,726 participants were recruited for the study; 29.9% were men, and 70.1% were women. The average age of

participants was 58.3 ± 9.26. Table 1 shows the clinical and biochemical demographics of the subjects, which are divided into two groups based on whether their UACR is elevated or not. Compared with the normal UACR group, the UACR ≥ 30 mg/g group was older, had higher rates of DM and CHD, and had higher LDL-C, WC, GGT, AST, BMI, HbA1c, FBG, PBG, SBP, DBP, and lower HDL-C, education level, and eGFR values (all $p< 0.001$)

Association of ABSI quartiles with increased UACR

By plotting DAG (Figure 2), we found that age, BMI, education level, smoking habits, sex, eGFR, blood pressure level, sedentary time, diabetes, LDL-C, physical activity, TG, FBG, diabetes, CHD, and smoking habits were confounders of the relationship between ABSI and albuminuria. Through single-factor analysis, statistically significant age, sex, smoking habits, CHD history, DM history, education status, blood pressure level, FBG, TG, LDL, and eGFR were selected as confounding factors for multivariate logistic regression analysis to investigate the relationship between ABSI quartiles and UACR elevation (Table 2). The correlation of model was significant (OR [95% CI] Q2 vs. Q1: 1.094 [1.001, 1.197]; OR [95% CI] Q3 vs. Q1: 1.126 [1.030, 1.231]; OR [95% CI] Q4 vs. Q1: 1.183 [1.080, 1.295], p trend < 0.001).

Association of ABSI quartiles with increased UACR in stratified analysis

Stratified analysis was adopted to further verify the stability of the correlation between ABSI and UACR in different populations after comprehensive adjustment of age, sex, smoking habits, CHD history, DM history, education status, blood pressure level, FBG, TG, LDL, and eGFR (Table 3). Stratified by sex (p-interaction = 0.026), ABSI in the fourth quartile was associated with increased UACR in women (OR [95% CI] Q4 vs. Q1: 1.144 [1.031, 1.268]); however, increased UACR has a significantly association with ABSI in the third and fourth quartile in men(OR [95% CI] Q3 vs. Q1: 1.245 [1.028, 1.507]; OR [95% CI] Q4 vs. Q1: 1.314 [1.080, 1.599]). When subjects have a normal blood pressure (SBP < 120 and DBP < 80) according to Stratification (p-interaction < 0.001), the probability of UACR increased gradually from the lowest quartile of ABSI to the highest quartile (OR [95% CI] Q2 vs. Q1: 1.228 [1.038, 1.452]; OR [95% CI] Q3 vs. Q1: 1.200 [1.008, 1.429]; OR [95% CI] Q4 vs. Q1: 1.235 [1.027, 1.485], p trend = 0.048). The same trend was observed at the pre-hypertension group (120 ≤ SBP < 140 and/or 80 ≤ DBP < 90) (OR [95% CI] Q3 vs. Q1: 1.229 [1.057, 1.428]; OR [95% CI] Q4 vs. Q1: 1.404 [1.225, 1.610], p trend < 0.001). However, the OR was highest in the hypertensive group (SBP ≥ 140 or DBP ≥ 90) (OR [95% CI] Q3 vs. Q1: 1.239 [1.075, 1.429]; OR [95% CI] Q4 vs. Q1: 1.449 [1.249, 1.682], p trend < 0.001). Stratified by age (p-interaction < 0.001), the elderly (age ≥ 60 years) in Q3 and Q4 were more likely to increase UACR (OR [95% CI] Q3 vs. Q1: 1.183 [1.025, 1.365]; OR [95% CI] Q4 vs. Q1: 1.372 [1.198, 1.572], p trend < 0.001). In the younger participants (age < 60 years), ABSI was also significantly associated with increased UACR (OR [95% CI] Q2 vs. Q1: 1.119 [1.001, 1.250]; OR [95% CI] Q3 vs. Q1: 1.142 [1.017, 1.283]; OR [95% CI] Q4 vs. Q1: 1.159 [1.113, 1.185], p trend = 0.027).

Discussion

In this study, we found that the ABSI levels are associated with increased UACR significantly, and correlation is abated after adjustment of smoking habits, FBG, diabetes history, LDL-C, and CHD history, indicating that history of smoking, blood glucose or lipid metabolic disorders, and history of CHD increase the risk of increased proteinuria in Chinese adults. Furthermore, stratified analysis showed that individuals with higher ABSI levels were more likely to have elevated UACR than those with lower ABSI levels, especially those in the elderly, men, and with hypertension. This study is the first multicenter, large-sample clinical to investigate the relationship between ABSI and UACR in Chinese adults. Early prevention and intervention of proteinuria are crucial; early detection and decreasing abnormal fat distribution may be helpful in preventing adverse outcomes such as CHD, obesity, and DM for patients.

With rapid economic development and lifestyle changes, the incidence of overweight and obesity has increased significantly worldwide. Given this growing trend, it is expected that as many as 57.8% of the population will be overweight or obese by 2030 (15). Obesity is divided into central obesity and peripheral obesity. An increase in visceral fat characterizes central obesity. Excess visceral fat can cause diabetes, hypertension, heart diseases, non-alcoholic fatty liver diseases, kidney disorders, cancer, and other health problems. Traditional anthropometric indicators include WC, BMI, WHtR, and WHR. BMI cannot distinguish fat accumulation from muscle, and WC cannot distinguish visceral fat from subcutaneous fat (16); magnetic resonance imaging (MRI) and computed tomography (CT) are considered to be the gold standard for the distribution of visceral obesity. However, they cannot be routinely used in epidemiological investigations due to the risk of radiation exposure, which is time-consuming and expensive. According to the study (17), ABSI is apparently associated with central obesity and has a better ability to predict type 2 diabetes mellitus (T2DM) than BMI. ABSI has been proved to be associated with all-cause mortality (8), metabolic syndrome (18), DM (19), and hypertension (20). Therefore, ABSI can better measure body size and is expected to become a new standard for health assessment.

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TABLE 1 Characteristics of the study population by UACR category.

Variables	UACR < 30 mg/g	UACR ≥ 30 mg/g	*p*-value
n	35,208	5,518	
Age, years	57.70 ± 9.02	61.43 ± 10.07	<0.001
Men, %	10,732 (30.5%)	1,436 (26%)	<0.001
BMI, kg/m^2	24.42 ± 3.70	24.94 ± 3.85	<0.001
WC, cm	85.00 (79.00,92.00)	87.00 (80.00,94.00)	<0.001
SBP, mmHg	127.67 (116.00,141.67)	137.33 (122.00,153.33)	<0.001
DBP, mmHg	76.00 (69.67-83.33)	78.33 (71.00,86.67)	<0.001
TC, mmol/L	5.03 (4.29,5.77)	4.93 (4.20,5.68)	<0.001
TG, mmol/L	1.32 (0.94,1.90)	1.54 (1.08,2.22)	<0.001
HDL, mmol/L	1.30 ± 0.34	1.26 ± 0.33	<0.001
LDL, mmol/L	2.81 (2.23,3.42)	2.92 (2.34,3.54)	<0.001
FBG, mmol/L	5.50 (5.10,6.09)	5.78 (5.20,6.90)	<0.001
PBG, mmol/L	7.30 (6.00,9.41)	8.47 (6.59,12.10)	<0.001
HbA1c, %	6.04 ± 0.93	6.52 ± 1.48	<0.001
AST, U/L	20.00 (17.00,24.00)	21.00 (17.00,26.00)	<0.001
GGT, U/L	20.00 (14.00,30.00)	21.00 (15.00,35.00)	<0.001
eGFR, ml/min	114.89 (102.73,128.79)	109.98 (96.76,125.11)	<0.001
Education level			
Less than high school, %	17,756 (50.8%)	3,173 (57.7%)	<0.001
High school, %	12,714 (36.3%)	1,706 (31.0%)	<0.001
College or more, %	4,512 (12.9%)	620 (11.3%)	<0.001
Smoking habits, %			
No	29,921 (85.0%)	4,804 (87.1%)	<0.001
Occasional	784 (2.2%)	103 (1.9%)	<0.001
Regular	4,185 (11.9%)	575 (10.4%)	<0.001
DM history, %			
Yes	3,229 (9.2%)	1,097 (19.9%)	<0.001
No	31,895 (90.6%)	4,412 (80.0%)	<0.001
CHD history, %			
Yes	1,189 (3.4%)	321 (5.8%)	<0.001
No	33,896 (96.3%)	5,172 (93.7%)	<0.001
ABSI quartiles			
Q1	9,023 (25.6%)	1,060 (19.2%)	<0.001
Q2	8,933 (25.4%)	1,308 (23.7%)	<0.001
Q3	8,877 (25.2%)	1,469 (26.6%)	<0.001
Q4	8,375 (23.8%)	1,681 (30.5%)	<0.001

Data expressed as mean ± SD for continuous variables or median (IQR) for skewed variables and percentage (%) for categorical variables.
BMI, body mass index; WC, waist circumstance; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglyceride; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; FBG, fasting blood glucose; PBG, 2-h post-load blood glucose; HbA1c, glycosylated hemoglobin; AST, aspartate transferase; GGT, gamma-glutamyl transferase; DM, diabetes mellitus; CHD, coronary heart disease; ABSI, A Body Shape Index; eGFR, estimated glomerular filtration rate.

The Dutch Prevention of Renal and Vascular End-Stage Disease (PREVEND) study, published in 2003, reported a prevalence of microalbuminuria of 21% or 13%, depending on central or peripheral obesity patterns (21). In a cross-sectional study of adults with T2DM, visceral obesity was significantly associated with UACR (22). Similarly, a follow-up study of 2,393 participants over 4 years observed that participants who had increased visceral fat mass had higher albuminuria (23). Notably, few studies have investigated the relationship between ABSI and proteinuria in individuals who are most likely to develop CKD and have underlying cardiovascular risk factors. Munkhaugen conducted a 20-year cohort study in Norway that assessed 75,000 volunteers and found a strong correlation between BMI and CKD risk, with obese people more likely to develop kidney disease (24). In another large population-based case–control study reported by Ejerblad, patients with a BMI of 25 kg/m^2 at age 20 had a threefold increased risk of new kidney disease, even after adjusting for hypertension and DM (25). In

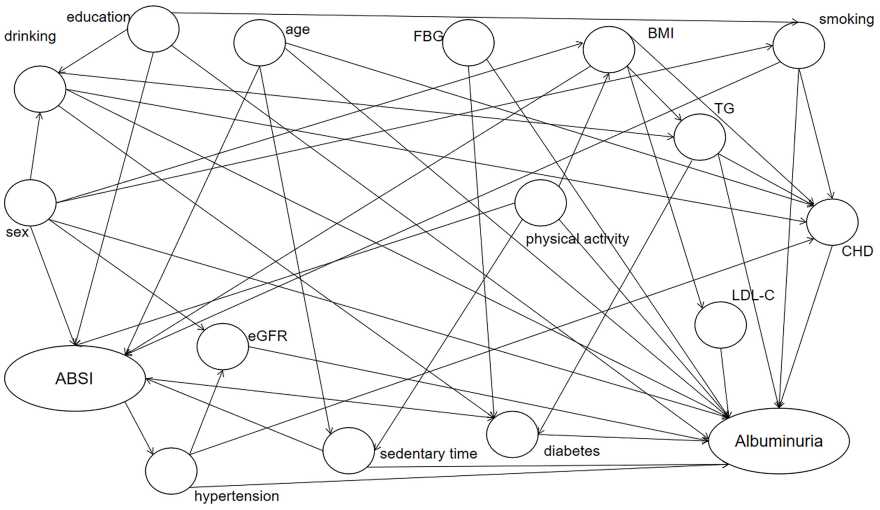

FIGURE 2
DAG diagram of the ABSI and albuminuria association study. Elliptic nodes represent independent variables ABSI and dependent variables albuminuria, circular nodes indicate possible confounders, and arrows indicate causality. ABSI, A Body Shape Index; BMI, body mass index; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol; CHD, coronary heart disease; eGFR, estimated glomerular filtration rate.

our study, which included 40,726 Chinese adults, we found that higher visceral obesity as assessed by ABSI was independently associated with an increased risk of proteinuria. These results are consistent with previous studies.

Multiple biological mechanisms may mediate the association between obesity and proteinuria. Recent studies have shown that adipose tissue can secrete adipose tissue-derived adipokines (26) and cytokines (27), such as leptin, which has local effects on mesangial cells, podocytes, and renal tubules, promoting glomerular hyperfiltration (28), which is an independent predictor of proteinuria (29). Participate in the pathogenesis of CKD. In addition, mechanisms such as insulin resistance (30), oxidative stress (31), systemic chronic low-level inflammation (32), and inappropriate activation of the renin–angiotensin–aldosterone system (33) are also involved in developing proteinuria. Prevention of REnal and Vascular ENd-stage Disease study data showed that men have a higher urinary albumin excretion, a known factor for progression of CKD, at any given age, plasma glucose, and BMI than women (34). Our data also showed a gender difference, and we speculated that this might be due to potential anti-fibrotic and anti-apoptotic effects of estrogen or deleterious pro-inflammatory effects of testosterone, as evidenced in animal studies (35). Moreover, age is a well-known independent risk factor for renal impairment, and albuminuria is more likely to occur in the elderly than in middle-aged adults (36). Chronic hypertension can lead to gradual thickening of the glomerular arteries, which can lead to atherosclerotic changes, decreased renal blood flow, decreased kidney function, and decreased filtration of the kidneys, thus leading to increased albuminuria.

Our study provides additional evidence to confirm the association between visceral fat and proteinuria as assessed by ABSI and demonstrates the value of ABSI as a simple, reliable, and effective screening tool for kidney disease risk. In clinical practice, improvements in the distribution and deposition of visceral fat, rather than just weight loss, should be proposed to

TABLE 2 Association between ABSI quartiles and UACR in the total population.

Variables	ABSI Quartiles				
	Q1	Q2	Q3	Q4	*p*-value for trend
Model					
OR (95% CI)	1	1.094 (1.001–1.197)	1.126 (1.030–1.231)	1.183 (1.080–1.295)	
p-value		<0.049*	<0.009*	<0.001***	<0.001

*p-value < 0.05; ***p-value < 0.001.
Model adjusted for age, sex, smoking habits, CHD history, DM history, education status, blood pressure level, FBG, TG, LDL, and eGFR.
OR, odds ratio; CI, confidential interval; ABSI, A Body Shape Index, CHD, coronary heart disease; DM, diabetes mellitus; FBG, fasting blood glucose; TG, triglycerides; LDL, low-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate.

TABLE 3 Association between ABSI quartiles and UACR in different participants.

Variable	ABSI Quartiles					
	Q1OR (95% CI), *p*-value	Q2OR (95% CI), *p*-value	Q3OR (95% CI), *p*-value	Q4OR (95% CI), *p*-value	*p*-value for trend	*p* for interaction
Gender						0.026
Women	1.0	1.095 (0.991–1.212)	1.121 (1.014–1.206)	1.144 (1.031–1.268)*	0.045	
Men	1.0	1.135 (0.929–1.387)	1.245 (1.028–1.507)*	1.314 (1.080–1.599)**	0.034	
Age, years						<0.001
<60	1.0	1.119 (1.001–1.250)*	1.142 (1.017–1.283)*	1.159 (1.113–1.185)*	0.027	
≥60	1.0	1.104 (0.949–1.285)	1.183 (1.025–1.365)*	1.372 (1.198–1.572)***	<0.001	
BP, mmHg						<0.001
SBP < 120 and DBP < 80	1.0	1.228 (1.038–1.452)*	1.200 (1.008–1.429)*	1.235 (1.027–1.485)*	0.048	
120 ≤ SBP < 140 and/or 80 ≤ DBP < 90	1.0	1.063 (0.912–1.240)	1.229 (1.057–1.428)*	1.404 (1.225–1.610)***	<0.001	
SBP ≥ 140 or DBP ≥ 90	1.0	1.147 (0.991–1.328)	1.239 (1.075–1.429)*	1.449 (1.249–1.682)***	<0.001	

*p-value < 0.05; **p-value < 0.01; ***p-value < 0.001.
Model adjusted for age, sex, smoking habits, CHD history, DM history, education status, blood pressure level, FBG, TG, LDL, and eGFR.
OR, odds ratio; CI, confidential interval; ABSI, A Body Shape Index, CHD, coronary heart disease; DM, diabetes mellitus; AST, aspartate transferase; FBG, fasting blood glucose; GGT, glutamyl transferase; TG, triglycerides; LDL, low-density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure.

reduce the associated risk of kidney disease and cardiovascular disease. We believe that ABSI should be used as part of a management strategy to reduce the risk of kidney disease in further clinical practice.

As we know, this study is the first cross-sectional study to explore the relationship between ABSI and elevated UACR with a large sample. However, some limitations need to be considered: First, it cannot clarify the causal relationship between ABSI and elevated UACR as it is a retrospective cross-sectional study, so further prospective studies are necessary. Secondly, the participants were all enrolled from China and were older than 40 years old, so our conclusions may not be applied to other regions and people. Finally, because the application of MRI or CT in such a large population is expensive and inconvenient, our study did not accurately assess visceral adipose tissue. However, previous studies have demonstrated the apparent association between ABSI and visceral adipose tissue, and we suggested that ABSI has the potential to be a reliable and simple tool in proteinuria screening for high-risk people.

Conclusion

This study demonstrated that increased ABSI levels positively correlated with elevated UACR among adults in the Chinese community. Albuminuria was increased in men, the elderly, and hypertension. Therefore, ABSI can be used as a clinical tool to identify the high-risk population of CKD in Chinese adults. Considering the significant association between visceral fat, proteinuria, and CKD, we should pay more attention to obese individuals and guide them to change their lifestyle and regular exercise, and weight loss is not the only significant benefit of reducing visceral fat deposition.

Data availability statement

All data used to support the conclusions of the study are not freely available in the view of the privacy principle of Chinese PLA General Hospital, and of protecting the privacy of participants.

Ethics statement

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

YZ analyzed the data and wrote the manuscript. WG, BL, and YL provided great help in the operation and application of SPSS. KC, AW, XT, LY, ZL, GQ, LC, QW, ZG, WW, and GN offered advice and assistance. YM contributed by revising the article. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

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Alanine aminotransferase to aspartate aminotransferase ratio and hepatitis B virus on metabolic syndrome: a community-based study

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Background: The serum aminotransferase elevation in metabolic syndrome (MetS) reflected hepatosteatosis, but there is a conflict with the coexistence of viral hepatitis, especially for the hepatitis B virus (HBV). Thus, this study aimed to investigate the relationship between the alanine aminotransferase (ALT)/aspartate aminotransferase (AST) ratio, MetS, and HBV infection in a rural Taiwanese population.

Methods: We conducted a cross-sectional analysis in southern Taiwan between March and December 2019. Multivariable logistic regression analyses adjusted for demographics, education, dietary behaviors, irregular exercise, substance use, and viral markers were performed to investigate the association between the ALT/AST ratio and MetS.

Results: Altogether, 2,416 participants (891 men and 1,525 women; mean age, 64.1 ± 14.9 years) were enrolled. Of the participants, 22.7% (n = 519) were seropositive for viral hepatitis. In the multivariable analysis, age [odds ratio (OR) 1.02, 95% CI 1.01–1.03, $p < 0.001$], ALT/AST ratio >1 (OR 2.63, 95% CI 2.15–3.21, $p < 0.001$), education (OR 0.96, 95% CI 0.94–0.98, $p < 0.001$), and HBV seropositivity (OR 0.70, 95% CI 0.52–0.95, $p = 0.021$) were associated with the risk of MetS. The area under the curve of the ALT/AST ratio was 0.62 (95% CI 0.60–0.64, $p < 0.001$), and the cutoff value was >0.852 for the Youden index.

Conclusion: An ALT/AST ratio >1 could be a simple index for MetS prediction during community checkups. In contrast to age and betel nut chewing, HBV

seropositivity and higher education might be inversely associated with MetS. Aggressive health promotion for MetS prevention has emerged as essential in participants without HBV and with lower education levels. Further large-scale, longitudinal studies are needed to unlink these correlations.

KEYWORDS

aminotransferase, community-based, education, metabolic syndrome, hepatitis B virus

Introduction

Metabolic syndrome (MetS) is hypervalent (13.6% to 30.1%) in southern Taiwan (1), which is also a viral hepatitis endemic area. Twelve percent to 15% of the adult population infected with hepatitis B virus (HBV) remains hepatitis B surface antigen (HBsAg)-positive (2), and the prevalence of hepatitis C virus (HCV) seropositivity is remarkably high (overall 2%–4% in Taiwan). Although HCV independently increases the MetS burden (1, 3), the association between HBV and MetS is diverse (4–7). Central obesity and fatty liver have emerged as significant components of MetS, while steatohepatitis increases the mortality risk in the population (8, 9). Both viral hepatitis and fatty liver could induce abnormal alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels (3, 7), the data of which can be obtained from community checkups. Moreover, the predictive effect of aminotransferases on MetS may be influenced by viral hepatitis and lifestyle factors, including diet, exercise, and personal habits.

Serum aminotransferases increase along with being overweight [body mass index (BMI) ≥ 25 kg/m^2] or obese (BMI ≥ 30 kg/m^2), although this is more prominent for ALT than for AST. After complete viral suppression in patients infected with HBV, ALT elevation indicated high BMI [adjusted odds ratio (OR) 1.78; 95% confidence interval (CI) 1.02–3.11] (10), and ALT levels were significantly higher in chronic HBV infection with MetS (7). In contrast to the De Ritis ratio (AST/ALT ratio > 2.0) for alcoholic hepatitis and >1.0 for cirrhosis/fibrosis (11), and ALT/AST ratio >1 could be independently associated with MetS (12, 13) and fatty liver disease (14, 15). The index might offer more predictive power when considering more confounders, including lifestyle variables and viral hepatitis.

Although aminotransferase can be easily checked during routine examinations, whether the ALT/AST ratio has a predictive impact on MetS in viral hepatitis endemic areas remains unknown. Thus, we aimed to investigate the relationship between the ALT/AST ratio, MetS, and HBV infection in a rural Taiwanese population.

Methods

Population and study design

This cross-sectional study included adult patients who participated in annual checkups from March to December 2019 in rural communities in southern Taiwan. We collected patient data on personal health habits, laboratory results, and viral markers of hepatitis. All participants signed an informed consent form and completed a questionnaire. After excluding those with incomplete data, 2,416 participants were enrolled in the final analysis (Figure 1). This study was approved by the Institutional Review Board and Ethics Committee of Chang Gung Memorial Hospital (IRB No. 201900222A3). According to a previous study reporting the correlation between the presence/absence of MetS and the ALT/AST ratio, the mean (standard deviation) ALT/AST ratio was 1.29 (0.42) and 1.09 (0.41) in men with and without MetS, respectively (16). The mean (standard deviation) ALT/AST ratio was 1.10 (0.35) and 0.87 (0.35) in women with and without MetS, respectively (16). Considering a type I error rate of 1% and power of 99%, a minimum sample size of 418 men and 226 women was required.

Questionnaire on lifestyle

The questionnaire on lifestyle and demographic characteristics, including sex, age, and educational level (number of years of education received), were included. Participants were asked the following questions regarding three substances and four healthy habits: "Do you smoke cigarettes, chew betel nuts, and regularly consume alcohol or alcohol-related beverages?" Participants were classified as "non-users" if they reported having never smoked, chewed, or drunk and "current/former users" if they reported being current users or previous users who had ceased chewing or smoking. Regarding diet, they were asked the following: "How often do you consume three portions of vegetables (1.5 bowls)? Two portions of fruit (one bowl)? Water intake of at least 1,500 ml per day?" and "How often do you have exercise, for at least >30 min, three times per week?" Responses were categorized as "never,"

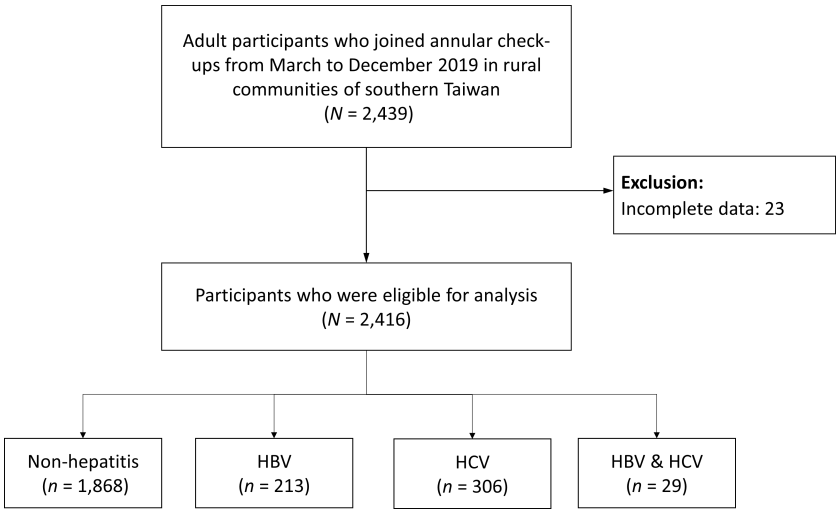

FIGURE 1
Enrollment of the study participants. HBV, hepatitis B virus; HCV, hepatitis C virus.

"seldom," "usually," or "always." For the evaluation, four responses were categorized into two-level frequencies: no—never/seldom and yes—usually/always.

Anthropometric measurements

Waist circumference was measured using a soft tap and defined at the umbilical level while standing without stress for a moment (17). For blood pressure measurements, all participants underwent two measurements *via* anthropometric equipment in the sitting position after 10 min of rest, and the mean arterial pressure (systolic and diastolic) was recorded (18).

Biochemistries and serological markers of hepatitis

Blood samples were obtained after fasting for 12 h and tested in the laboratory of the CGMH Hospital. Biochemical tests included serum AST, ALT, TG, LDL-C, HDL-C, TC (Roche Diagnostics, Cobas6000, C501, Germany), and HbA1c (Trinity Biotech, Premier, HB9210, USA). Hepatitis B surface antigen (HBsAg) was detected using routine standard ELISA (General Biological Corp., Hsinchu, Taiwan), and the anti-HCV antibody was evaluated using SP-NANBASE C-96 3.0 plate (General Biological Corp).

Definition of MetS

MetS was diagnosed based on the modified qualitative criteria of the International Diabetes Federation definition (19), requiring the presence of three or more of the following five criteria: 1) waist circumference >90 cm in men or >80 cm in women for Asians, 2) TG >150 mg/dl, 3) HDL-C <40 mg/dl in men or <50 mg/dl in women, 4) blood pressure >130/85 mmHg or current use of antihypertensive medications, and 5) glycohemoglobin (HbA1c) >5.7 or use of oral antidiabetic agents or insulin.

Statistical analysis

The demographic characteristics of the participants with different HBV and HCV statuses (none, HBV only, HCV only, and co-infection) were compared using the chi-square test for categorical variables and the independent sample *t*-test for continuous variables. Pairwise comparisons using the Bonferroni correction were performed when the overall test results were significant. We also compared the demographic characteristics between the MetS and non-MetS groups using the chi-square test for categorical variables and the independent sample *t*-test for continuous variables. Using the demographics/characteristics as explanatory variables, a series of univariate logistic regression analyses were performed to initially screen the potentially associated factors of MetS. The multivariable logistic regression model further included variables with significance levels <0.15 (20). Among the indicators of liver function (AST, ALT, and ALT/AST ratio > 1), ALT/AST ratio >1 was selected in the multivariable model to prevent multicollinearity. Finally, a receiver operating characteristic (ROC) curve analysis was conducted to evaluate the ability of the ALT/AST ratio to discriminate the presence of MetS. All tests were two-tailed,

and a p-value <0.05 was considered significant. Data analyses were performed using SPSS version 25 (IBM SPSS Inc., Chicago, IL, USA).

Results

Characteristics of participants

Table 1 presents the demographics and characteristics of the 2,416 participants who completed the health examination and the questionnaire. The mean age of the participants was 64.1 years [standard deviation (SD) 14.9 years], with 56.1% being >65 years. Women were predominant (63.1%). Nearly one-fourth of the participants (n = 548, 22.7%) were seropositive for viral hepatitis, of whom 213 (8.8%) had HBV, 306 (12.7%) had HCV, and 29 (1.2%) were co-infected with HBV and HCV. Approximately 70% of the participants did not exercise regularly, and the distribution difference among all subgroups was insignificant. Compared to HCV patients, those with HBV seropositivity were younger (61.1 ± 12.3 vs. 70.8 ± 10.0 years), had lower education levels (7.7 vs. 3.9 years), and had more alcoholic drinking but less betel nut chewing. Half of the participants (n = 1,262, 52.2%) had MetS. The HBV seropositive patients had fewer MetS components and a lower risk of MetS than HCV seropositive patients (41.8% vs. 58.8%). The participants with co-infection had higher ATL and AST levels than the other subgroups (p < 0.001), whereas the proportion of patients with an ALT/AST ratio >1 was slightly lower in the HCV subgroup.

TABLE 1 Demographics and characteristics of the study subjects according to the HBV and HCV status (N = 2,416).

Variable	Total	None	HBV only	HCV only	HBV and HCV	p-value
Number of subjects	2,416	1,868	213	306	29	
Female sex	1,525 (63.1)	1,160 (62.1)	138 (64.8)	210 (68.6)	17 (58.6)	0.149
Age, years	64.1 ± 14.9	63.3 ± 15.6	61.1 ± 12.3	70.8 ± 10.0[a,b]	67.9 ± 10.1	<0.001
Age groups						<0.001
<40 years	214 (8.9)	199 (10.7)	14 (6.6)	0 (0.0)[a,b]	1 (3.4)[c]	
40–64 years	846 (35.0)	653 (35.0)	104 (48.8)[a]	81 (26.5)[a,b]	8 (27.6)	
≥65 years	1,356 (56.1)	1,016 (54.4)	95 (44.6)[a]	225 (73.5)[a,b]	20 (69.0)	
Education level, years	6.5 ± 5.4	6.9 ± 5.5	7.7 ± 5.0	3.9 ± 4.2[a,b]	3.8 ± 4.4[a,b,c]	<0.001
Dietary behavior						
Vegetable intake ≥3 portions per day	1,608 (66.6)	1,279 (68.5)	140 (65.7)	173 (56.5)[a]	16 (55.2)	<0.001
Fruit intake ≥2 portions per day	1,351 (55.9)	1,079 (57.8)	118 (55.4)	140 (45.8)[a]	14 (48.3)	0.001
Water intake ≥1,500 cc per day	1,417 (58.7)	1,139 (61.0)	118 (55.4)	145 (47.4)[a]	15 (51.7)	<0.001
Irregular exercise	1,679 (69.5)	1,295 (69.3)	145 (68.1)	220 (71.9)	19 (65.5)	0.735
Substance use						
Smoking	433 (17.9)	332 (17.8)	37 (17.4)	58 (19.0)	6 (20.7)	0.931
Betel nut chewing	225 (9.3)	164 (8.8)	14 (6.6)	43 (14.1)[a,b]	4 (13.8)	0.010
Alcoholic drinking	243 (10.1)	183 (9.8)	29 (13.6)	29 (9.5)	2 (6.9)	0.314
Data of metabolic syndrome (MetS)						
Waist circumference (WC), cm	84.80 ± 10.8	84.76 ± 10.9	84.3 ± 10.7	85.2 ± 10.0	86.8 ± 10.8	0.564
Systolic blood pressure, mmHg	134.74 ± 20.3	134.66 ± 20.1	131.6 ± 21.0	137.0 ± 21.2[b]	139.3 ± 16.3	0.017
Diastolic blood pressure, mmHg	81.7 ± 12.3	81.8 ± 12.2	82.3 ± 13.1	80.4 ± 12.6	81.5 ± 11.9	0.270
High-density lipoprotein, mg/dl	51.0 ± 13.2	51.2 ± 13.0	52.9 ± 13.5	49.1 ± 13.9[b]	51.0 ± 15.4	0.011
Glycosylated hemoglobin, mg/dl	6.09 ± 1.07	6.08 ± 1.04	6.00 ± 1.03	6.26 ± 1.25[a,b]	6.10 ± 0.87	0.028
Triglyceride, mg/dl	137.6 ± 95.9	140.1 ± 98.7	117.8 ± 82.1[a]	137.4 ± 87.5	121.4 ± 73.1	0.011
Metabolic syndrome (MetS)	1,262 (52.2)	973 (52.1)	89 (41.8)[a]	180 (58.8)[b]	20 (69.0)[b]	<0.001
Liver and renal function						
AST, U/L	25.9 ± 13.8	24.8 ± 11.6	26.9 ± 11.2	29.8 ± 21.3[a]	46.1 ± 32.7[a,b,c]	<0.001
ALT, U/L	24.2 ± 19.1	23.4 ± 18.6	25.9 ± 17.7	26.1 ± 21.2	41.2 ± 29.7[a,b,c]	<0.001
ALT/AST ratio	0.90 ± 0.34	0.91 ± 0.34	0.94 ± 0.34	0.86 ± 0.29[a,b]	0.92 ± 0.26	0.036
ALT/AST >1	666 (27.6)	525 (28.1)	61 (28.6)	69 (22.5)	11 (37.9)	0.121

Data were presented as mean ± standard deviation or frequency and percentage. "a," "b," and "c" indicate significant differences versus the "None", "HBV only," and "HCV only" groups in the Bonferroni multiple comparison, respectively.
HBV, hepatitis B virus; HCV, hepatitis C virus; BMI, body mass index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; eGFR, estimated glomerular filtration rate.

Characteristics of MetS

Table 2 presents the demographics and characteristics of participants with and without MetS. Compared to the patients without MetS, those with MetS were older (67.0 ± 12.8 vs. 61.0 ± 16.4 years, $p < 0.001$), had lower education levels (5.5 ± 5.1 vs. 7.7 ± 5.6 years, $p < 0.001$), had less fruit intake at ≥2 portions per day (53.2% vs. 58.9%, $p = 0.004$), were more likely to do betel nut chewing (11.1% vs. 7.4%, $p = 0.002$), had significantly positive data of individual MetS components, and had higher AST (27.4 ± 15.8 vs. 24.2 ± 11.0, $p < 0.001$) and ALT levels (27.1 ± 21.0 vs. 21.0 ± 16.2 U/L, $p < 0.001$). The MetS group had a significantly higher ALT/AST ratio >1 (34.2% vs. 20.4%, $p < 0.001$) and higher proportion of HCV seropositivity (14.3% vs. 10.9%) than the non-MetS group. Meanwhile, the prevalence of HBV seropositivity was higher in the non-MetS group than in the MetS group (10.7% vs. 7.1%).

MetS-associated risk factors

The univariate logistic regression analyses revealed that the following covariates might be associated with MetS: age, education level, fruit intake, betel nut chewing, AST level, ALT level, ALT/AST ratio >1, and seropositivity to HBV and HCV (Table 3). After incorporating the variables whose significant

TABLE 2 Demographics and characteristics of the study subjects according to the status of MetS (*N* = 2,416).

Variable	MetS	Non-MetS	*p*
Number of subjects	1,262	1,154	
Female sex	803 (63.6)	722 (62.6)	0.588
Age, years	67.0 ± 12.8	61.0 ± 16.4	<0.001
Age groups			<0.001
<40 years	51 (4.0)	163 (14.1)	
40–64 years	408 (32.3)	438 (38.0)	
≥65 years	803 (63.6)	553 (47.9)	
Education level, years	5.5 ± 5.1	7.7 ± 5.6	<0.001
Dietary behavior			
Vegetable intake ≥3 portions per day	820 (65.0)	788 (68.3)	0.085
Fruit intake ≥2 portions per day	671 (53.2)	680 (58.9)	0.004
Water intake ≥1,500 cc per day	743 (58.9)	674 (58.4)	0.815
Irregular exercise	899 (71.2)	780 (67.6)	0.052
Substance use			
Smoking	236 (18.7)	197 (17.1)	0.297
Betel nut chewing	140 (11.1)	85 (7.4)	0.002
Alcoholic drinking	129 (10.2)	114 (9.9)	0.779
Data of metabolic syndrome (MetS)			
Waist circumference (WC), cm	89.9 ± 9.3	79.2 ± 9.4	<0.001
Systolic blood pressure, mmHg	141.5 ± 19.0	127.4 ± 19.1	<0.001
Diastolic blood pressure, mmHg	84.4 ± 12.4	78.6 ± 11.5	<0.001
High-density lipoprotein, mg/dl	45.5 ± 11.5	57.2 ± 12.2	<0.001
Glycosylated hemoglobin, mg/dl	6.4 ± 1.2	5.7 ± 0.78	<0.001
Triglyceride, mg/dl	175.0 ± 111.1	96.6 ± 50.4	<0.001
Liver and renal function			
AST, U/L	27.4 ± 15.8	24.2 ± 11.0	<0.001
ALT, U/L	27.1 ± 21.0	21.0 ± 16.2	<0.001
ALT/AST >1	431 (34.2)	235 (20.4)	<0.001
HBV and HCV status			<0.001
None	973 (77.1)	895 (77.6)	
HBV only	89 (7.1)	124 (10.7)	
HCV only	180 (14.3)	126 (10.9)	
HBV and HCV	20 (1.6)	9 (0.78)	

Data were presented as mean ± standard deviation or frequency and percentage.
MetS, metabolic syndrome; AST, aspartate aminotransferase; ALT, alanine aminotransferase; eGFR, estimated glomerular filtration rate; HBV, hepatitis B virus; HCV, hepatitis C virus.

TABLE 3 Association between demographics/characteristics and the risk of metabolic syndrome (*N* = 2,416).

Variable	Univariate analysis		Multivariable analysis[a]	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Female sex	1.05 (0.89–1.24)	0.588		
Age, years	1.028 (1.022–1.034)	<0.001	1.02 (1.01–1.03)	<0.001
Education level, years	0.93 (0.91–0.94)	<0.001	0.96 (0.94–0.98)	<0.001
Vegetable intake ≥3 portions per day	0.86 (0.73–1.02)	0.085	1.19 (0.92–1.55)	0.189
Fruit intake ≥2 portions per day	0.79 (0.67–0.93)	0.004	0.82 (0.63–1.05)	0.114
Water intake ≥1,500 cc per day	1.02 (0.87–1.20)	0.815		
Irregular exercise	1.187 (0.998–1.412)	0.052	1.12 (0.93–1.35)	0.227
Smoking	1.12 (0.91–1.38)	0.297		
Betel nut chewing	1.57 (1.18–2.08)	0.002	1.41 (1.05–1.90)	0.021
Alcoholic drinking	1.04 (0.80–1.35)	0.779		
AST, U/L	1.02 (1.01–1.03)	<0.001		
ALT, U/L	1.022 (1.016–1.028)	<0.001		
ALT/AST >1[b]	2.03 (1.69–2.44)	<0.001	2.63 (2.15–3.21)	<0.001
HBV and HCV status				
None	Reference		Reference	
HBV only	0.66 (0.50–0.88)	0.005	0.70 (0.52–0.95)	0.021
HCV only	1.314 (1.028–1.679)	0.029	1.03 (0.79–1.33)	0.836
HBV and HCV	2.04 (0.93–4.51)	0.077	1.52 (0.67–3.43)	0.312

OR, odds ratio; CI, confidence interval; BMI, body mass index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; eGFR, estimated glomerular filtration rate; HBV, hepatitis B virus; HCV, hepatitis C virus.
[a]Those variables whose significant levels were less than 0.15 were further included in the multivariable logistic regression model.
[b]Among the indicators of liver function (AST, ALT, ALT/AST ratio, and ALT/AST ratio >1), ALT/AST ratio >1 was chosen in the multivariable model to prevent the problem of multicollinearity.

levels were <0.15 in the univariate analyses, the multivariable model identified that older age (OR 1.02, 95% CI 1.01–1.03) and the presence of ALT/AST ratio >1 (OR 2.63, 95% CI 2.15–3.21) were significantly associated with a greater risk of MetS. By contrast, a high education level (OR 0.96, 95% CI 0.94–0.98) and HBV seropositivity (OR 0.70, 95% CI 0.52–0.95) were also significantly inversely related to the risk of MetS. Additionally, betel nut chewing was associated with a higher risk of MetS (OR 1.41, 95% CI 1.05–1.90).

Using the ALT/AST ratio to discriminate MetS

Due to the presence of an ALT/AST ratio >1 as an associated factor for MetS, we assessed its ability to discriminate the presence of MetS. The results revealed a modest discrimination performance with an area under the ROC curve of 61.8% (95% CI 59.5%–64.0%). The derived optimal cutoff determined by the Youden index was >0.852, with a sensitivity of 56.7% (95% CI 53.9%–59.4%) and a specificity of 62% (95% CI 59.1%–64.8%) (data not shown).

Discussion

This community-based participatory research investigates MetS-related factors, including diet, exercise, and education, and uses the ALT/AST ratio as a predictive index for MetS. Our findings suggest that an ALT/AST ratio >1 might increase the risk of MetS (OR 2.63), whereas high education and HBV seropositivity are inversely associated with MetS. The effects of the ALT/AST ratio and HBV seropositivity on MetS prediction differed. High ALT levels were significantly associated with MetS in women (21) and reflected central obesity with advanced steatohepatitis. In this study, an ALT/AST ratio >1 could be a simple index to predict MetS by considering all dietary content, healthy behaviors, and education, especially in viral hepatitis endemic areas. The diverse effects of the ALT/AST ratio and HBV seropositivity might exhibit unlinked pathophysiologies, such as hepatosteatosis or hepatic fibrosis in MetS.

Although serum viral load, AST, and ALT levels were independent predictors of histological grade (22), a single ALT or AST test could not offer a strong association between MetS and abnormal liver function, especially in patients with viral hepatitis. Chen et al. have also reported that men had a three times higher risk of MetS than women, who had fewer metabolic abnormalities and elevated ALT levels (12). The ALT/AST ratio is straightforward and feasible for use in community health examinations. The index can be presented as either hepatic fibrosis or steatosis in different studies (13–15). A previous study has reported that a higher ALT/AST ratio is associated with insulin resistance in metabolically unhealthy Korean

individuals (13). Moreover, ALT/AST ratio >1 was significantly associated with MetS in the Thai population (16); however, variables correlated with lifestyle and viral hepatitis were absent. Here, the ALT/AST ratio was independently associated with MetS. Zhao et al. have reported that the ALT/AST ratio could predict insulin resistance and MetS among the Chinese population (23), although this was not the case in our study, which had a high proportion of viral hepatitis. A high ALT/AST ratio is associated with fatty liver, a significant component of MetS, hypertriglyceridemia, and steatohepatitis.

Our findings further demonstrate that HBV infection is inversely associated with MetS, which is consistent with the findings of previous studies. Significant hepatic impairment in co-infection with HBV/HCV was observed, but patients with HBV had minor liver dysfunction, were younger, and had a higher education level (7.7 ± 5.0), healthy dietary behavior, and less betelnut chewing. Kuo et al. have reported that HBV infection was inversely associated with MetS only in lean patients (p = 0.002) but not in the general population (1). Joo et al. have reported that HBsAg seropositivity in Korean adults was associated with a lower risk of developing non-alcoholic fatty liver disease (NAFLD), indicating a possible effect of HBV infection on the pathogenesis of NAFLD in a cohort study (24). A body of evidence has also indicated that patients with chronic hepatitis B (CHB) have a lower incidence of NAFLD and steatohepatitis. A possible mechanism is that HBV viral activity might protect against hepatic steatosis and metabolic disturbances. The severity of steatosis was inversely associated with HBV viral load (25, 26). In an animal model, steatosis inhibited HBV replication by reducing HBV DNA and HBV-related antigens (27).

Nevertheless, patients with CHB with coexisting components of MetS are associated with more severe liver diseases. Li et al. have reported that fatty liver was significantly associated with higher HBsAg seroclearance in patients with CHB (28), while concurrent NAFLD might inhibit HBV replication and promote HBsAg seroclearance (29). However, the fatty liver also exacerbates liver fibrosis. Khalili et al. have reported that MetS was prevalent in this HBV group and independently associated with higher ALT levels (7). Moreover, Cai et al. have reported that HBV comorbidity with fibrosis increases the MetS component burden (30), and Yan et al. discovered that cirrhosis is prevalent in HBV with MetS (4.83% vs. 2.93%, compared with non-MetS; p = 0.002) (6). Additionally, Chan et al. revealed that overweight and concurrent fatty liver disease are associated with increased mortality risk and hepatocellular carcinoma in patients with CHB (31). Chien et al. have reported that patients who were unaware of their hepatitis B infection tended to have a higher risk of central obesity, hyperglycemia, insulin resistance, and MetS than those who were aware of their hepatitis B infection (OR 1.85, $p < 0.05$). In patients without MetS, HBV with MetS has a higher ALT level and ALT/AST ratio, suggesting a prominent hepatic inflammation and a predictor of steatohepatitis.

In addition to health promotion, regular physical exercise, cessation of alcohol or betelnut consumption, good dietary habits, aggressive follow-up, and early detection using the ALT/AST ratio may reduce MetS or steatohepatitis burden in chronic HBV infection/carriers.

Limitations

This study had several inherent limitations in its cross-sectional design. First, details of the hepatobiliary disease, fatty liver, antiviral therapeutic response, and viral load/activity were unavailable in the research. Nevertheless, the early implementation of HBV vaccination may influence personal lifestyles, behaviors, and insight for disease screening. Second, we lacked the sequential results of aminotransferase levels and detected all the factors influencing liver function. Although the ALT/AST ratio could not reflect an accurate level, the index is a different part of hepatic injury. Third, we could not obtain details of personal health conditions and medications associated with hepatic function. Finally, many non-invasive waist-to-height ratios or echography approaches could be used for predicting MetS (32, 33); however, interoperator variability and infeasible devices in community checkups limit their clinical application.

Conclusion

An ALT/AST ratio >1 is independently associated with MetS after adjusting for age, lifestyle, education level, and viral hepatitis seropositivity. Although HBV seropositivity and higher education are inversely associated with MetS, the ALT/AST ratio remains a reliable predictor of MetS and a simple index for community checkups. Nevertheless, the corresponding biological mechanisms of HBV in MetS remain to be elucidated, and future large-scale studies are needed to survey this association.

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

This study was reviewed and approved by The Institutional Review Board approved the study (IRB NO: 201900222A3). Written informed consent was obtained from individual or

guardian participants. The patients/participants provided their written informed consent to participate in this study.

Author contributions

All authors contributed to the statistical analysis and writing of the study. M-SL, H-SL, and M-YC participated in the study design, data acquisition, and critical review and wrote the manuscript. M-LC, M-HT, and Y-YH participated in the analysis and interpretation of data. Y-SL, M-ST, and C-LY collected the data and contributed to the study direction. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

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Prevalence of overweight and obesity among saudi children: A comparison of two widely used international standards and the national growth references

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Objective: To compare three body mass index (BMI) classifications that are used to assess the prevalence of overweight and obesity among Saudi children aged 6–13 years: the International Obesity Task Force (IOTF) age and gender cutoffs, the World Health Organization (WHO) growth references for school-aged children, and the Saudi (KSA) national growth references.

Methods: The sample comprised 2,169 children (52.5% girls) derived from two cross-sectional studies conducted in Riyadh and Jeddah during the 2017 and 2019 school years, respectively. Body weight and height were measured, and BMI was calculated.

Results: The proportions (%) of the participants who were classified as underweight, overweight, and obese varied according to the reference used: IOTF reference (13.8, 18.4, and 12.7), WHO reference (17.2, 19.1, and 18.9), and KSA reference (7.0, 22.4, and 9.3), respectively, indicating higher values for overweight and obesity prevalence when the WHO references were used. Kappa agreement measures between the three references were found to be high, with the coefficients ranging from 0.936 (between the IOTF and KSA references) to 0.849 (between the IOTF and WHO references). In all three classifications, girls exhibited lower overweight or obesity prevalence than

boys. Family income, but not paternal or maternal education, was significantly (p = 0.015) associated with overweight/obesity when using the IOTF standards. In addition, having a small family in the house was significantly (p < 0.05) associated with obesity, irrespective of the classification system.

Conclusion: Inconsistency was observed when estimating the prevalence of underweight, overweight, and obesity among Saudi children. However, when defining the overall prevalence of overweight plus obesity among Saudi children, the IOTF classification system performed in a similar way to the KSA references (31.1% versus 31.7%) compared to the WHO references (38.0%).

KEYWORDS

body mass index (BMI), children, International Obesity Task Force (IOTF), overweight, obesity, sociodemographic, underweight, World Health Organization (WHO)

Background

Childhood obesity is arguably the most serious recent public health challenge (1). Indeed, it is a worldwide public health concern with many major negative consequences (2, 3). Being overweight or obese in childhood and adolescence is associated with greater risk and earlier onset of chronic disorders, such as type 2 diabetes (2). Childhood and adolescent obesity have been shown to have adverse psychosocial consequences and lower educational attainment (3), and excess body weight in childhood and adolescence is more likely to lead to lifelong overweight and obesity (4, 5). Additionally, in a recent eight-country study, the economic impacts of obesity were found to be substantial in all eight countries, regardless of economic or geographical setting, ranging from 0.8% of gross domestic product (GDP) in India to 2.4% in Saudi Arabia (6).

The age-standardized prevalence of obesity increased globally from 0.7% (0.4–1.2%) in 1975 to 5.6% (4.8–6.5%) in 2016 in girls, and from 0.9% (0.5–1.3%) in 1975 to 7.8% (6.7–9.1%) in 2016 in boys (7). However, the prevalence of obesity was about 20% or more in several countries and regions, such as Polynesia and Micronesia, the Middle East and North Africa, the Caribbean, and the USA (7). In Saudi Arabia, the percentage of children classified as overweight or obese has significantly increased in the past two decades (8–11). A recent review of overweight and obesity among Saudi children found that the ranges of overweight and obesity were larger in boys (19.3–35.6%) than in girls (11.8–19.2%) (10).

The implementation of school-based BMI measurement has become popular as a potential approach to addressing overweight and obesity among youth (12). However, defining overweight and obesity in children and adolescents is not as straightforward as it is in adults. Usually, the International Obesity Task Force (IOTF) BMI cutoff values are used, which are set using data collected from six countries: Singapore, the Netherlands, Brazil, Hong Kong, the UK, and the USA (13). Another approach is to use the World Health Organization's (WHO) reference standards for children and adolescents aged 5–19 years, which are based on weight-for-height Z-scores (14). Both of these methods for defining overweight and obesity in children are generally valid; however, they often produce different results. Within the same population, the IOTF reference tends to yield the lowest values, and the WHO reference tends to yield the highest values (15–20). For instance, a study involving Saudi national data reported major differences between the use of Saudi growth charts of weight for age (21) and the WHO reference (14). The study concluded that the utilization of the WHO standards in Saudi Arabia, and possibly similar countries, increases the reported prevalence of undernutrition, stunting, and wasting, which potentially leads to unnecessary referrals, investigations, and parental concern (21).

Thus, it is challenging to determine the actual prevalence of underweight, overweight, and obesity among children and adolescents when such inconsistency exists among the most common international classification systems (13, 14). Therefore, the present study aimed to compare the three classifications that are used to assess overweight and obesity among Saudi children aged 6–13 years, namely the IOTF age and gender cutoff values (13), WHO growth references for school-aged children (14), and the Saudi (KSA) national growth references (22).

Methods

Population and sample

The population in this study consisted of healthy students of both sexes aged 6–13 years who attended public and private

primary schools in two major cities in Saudi Arabia. The sample was drawn from two cross-sectional studies conducted in Riyadh and Jeddah during the 2017 and 2019 school years, respectively (23, 24). Riyadh and Jeddah are the first- and second-most populated cities in Saudi Arabia, respectively. The two cities are also composed of a multiethnic population coming from all parts of the country. All healthy Saudi children enrolled in primary schools from grades 1–6 during the study periods were eligible for inclusion in the study. Detailed descriptions of the study design and sample selection were previously published (23, 24).

Briefly, the sample size was calculated assuming that the population proportion would yield the maximum possible sample size required (proportion = 0.50), with a 95% confidence level and a 4% margin of error. An additional 20% of participants were added to account for non-responders or missing data. A representative random sample was chosen from schools in each selected city using a multistage stratified cluster sampling technique. Stratification was based on sex (boys' and girls' schools are segregated in Saudi Arabia), major geographical location (east, west, north, and south), and type of school (public versus private). Participating children were selected from primary schools relative to the actual number of students in public and private schools in each city. Within each area, one private and two public schools were randomly selected. Then, classes were randomly selected from each of the six grades. All Saudi students in the designated classes were invited to participate in the study.

Anthropometric measurement and BMI classification

Measurements of body weight (to the nearest 100 g) and standing height (to the nearest 0.1 cm) were performed at the schools by trained researchers using calibrated portable scales (Seca 869, UK) and height measuring rods, respectively. Students wore minimal clothing and no shoes when the measurements were taken. Body mass index (BMI) was computed as the ratio of weight in kilograms divided by the squared height in meters.

The outcome measure in the present study was the classification of the BMI data into the categories of underweight, normal weight, overweight, and obesity. Two commonly used international reference standards (cutoff values) were used to classify the BMI data. The first was the extended IOTF age- and sex-specific BMI cutoff reference standards, which are based on data from children and adolescents in six countries: Brazil, Hong Kong, the Netherlands, Singapore, the UK, and the USA (13). The second was the WHO growth references for school-aged children and adolescents (5–19 years), published in 2007 and based on weight-for-height Z-scores (14). For comparison, we also included the KSA national growth references (from underweight to obesity), which were calculated from the z–scores of BMI for age for children and adolescents aged 5–18 years (22). The IOTF references provide percentile cut-offs corresponding to a BMI of 18.5, 25, and 30 kg/m2 at 18 years of age for underweight, over weight, and obesity, respectively (13). The prevalence of underweight, overweight, and obese are defined by the WHO (14) and the KSA (22) cut-off values as BMI-for-age less than 2 standard deviation (SD) scores below the mean, greater than 1 SD above the mean, and greater than 2 SDs above the mean, respectively. All three classification systems used are all based on the lambda (L), mu (M), and sigma (S) method (25, 26). The LMS parameters correspond to median BMI (M), coefficient of variation (S), and the power in the Box–Cox transformation (L), which transforms the data so that it closely resembles a normal distribution (25, 26).

Ethical approval

Ethical approval was obtained from the Institutional Review Board (IRB) at King Saud University, Riyadh (IRB Log Number: 17/0064/IRB) and Princess Nourah bint Abdulrahman University, Riyadh (IRB Log Number: 19-0014). The research procedures were conducted in accordance with the principles stated in the Declaration of Helsinki. Written informed consent was obtained from all parents/guardians of the participating children. In addition, approval for conducting this research in schools was attained from the Riyadh and Jeddah directorates of schools, the Ministry of Education, and the principals of the selected schools.

Statistical analysis

Data were entered into an SPSS data file, checked for accuracy, cleaned, and analyzed using the IBM-SPSS software, version 22 (Chicago, IL, USA). Descriptive statistics were obtained for the selected variables and reported as means and standard deviations or percentages for continuous or categorical variables, respectively. Differences between boys and girls in selected measurements were tested using the t-test for independent samples. Chi-square tests of proportions were used to test the differences in BMI classifications (prevalence rates) based on the IOTF, WHO, or KSA national growth references relative to selected sociodemographic factors. Kappa agreement measures for the whole sample were assessed between the three reference standards. Logistic regression analysis, adjusted for age, was used to test the associations of selected sociodemographic variables with overweight/obesity versus non-overweight/non-obesity among Saudi children. Furthermore, Spearman's rho correlation coefficients, while controlling for age, were calculated between obesity indices, based on the IOTF, WHO, and KSA reference standards, and selected variables. The

alpha level was set at 0.05, and a *p*-value less than the alpha level was considered significant.

Results

Table 1 presents the descriptive characteristics of the participants. The study included 2,169 participants (52.5% girls) who were between 6 and 13 years of age, and the mean age (SD) was 9.3 (1.7) years. There were significant differences in body weight (p = 0.001), BMI (p < 0.001), and maternal education (p = 0.005) relative to the sex of the participants. However, no significant differences were observed in age, height, paternal education, or family income relative to the sex of the participants.

The proportions (%) of the participants who were classified as underweight, normal weight, overweight, or obese using the IOTF, WHO, and KSA references relative to age are shown in Table 2. In general, it was found that the proportion of participants categorized as overweight or obese increased with age when all three classifications were used. Overall, the underweight and obesity prevalence rates were much lower when the KSA reference standards were used than when the other two references were used. Whereas the combined overweight and obesity prevalence was much higher when the WHO reference standards were used. This finding is depicted in Figure 1, which shows the prevalence of overweight or obesity by age groups for the three classifications. Also, Spearman's rho correlation coefficients, while controlling for age, between the three reference standards were fairly high (IOTF reference with WHO reference: r = 0.915, p < 0.001; IOTF reference with KSA reference: r = 0.914, p < 0.001; and WHO reference with KSA reference: r = 0.866, p < 0.001).

Figure 2 illustrates the prevalence of overweight or obesity based on the IOTF, WHO, or KSA references relative to sex. It is clear that, for either sex, the reported overweight or obesity prevalence was higher when the WHO reference standards were used compared to when the IOTF or KSA references were used. There were significant differences found between the boys' and girls' reference standards relative to sex (p values for the IOTF reference = 0.048, the WHO reference = 0.009, and the KSA reference = 0.005). In addition, Kappa agreement measures for the entire sample between the three reference standards were found to be fairly high; the coefficients were as follows: between the IOTF and KSA references = 0.936 (p < 0.001), between the WHO and KSA references = 0.862 (p < 0.001), and between the IOTF and WHO references = 0.849 (p < 0.001).

Table 3 displays the prevalence of underweight, normal weight, overweight, and obesity among the participating children when the IOTF, WHO, or KSA reference standards were used relative to selected variables. In each case, the prevalence rates of the BMI categories relative to sex, city,

TABLE 1 Descriptive characteristics of the participants relative to sex.

Variable	All	Boys	Girls	*p*-value *
	N = 2169	N = 1029	N = 1140	
Age	9.3 ± 1.7	9.3 ± 1.7	9.3 ± 1.7	0.824
Body weight (kg)	34.3 ± 15.4	35.5 ± 18.4	33.2 ± 12.2	0.001
Body height (cm)	133.3 ± 11.7	133.5 ± 11.1	133.1 ± 12.2	0.425
Body mass index (kg/m^2)	18.7 ± 5.9	19.3 ± 7.5	18.2 ± 4.1	< 0.001
Father's education (%)				0.403
Intermediate or less (¾ 9 years)	12.4	13.5	11.4	
High school	30.2	30.3	30.2	
University degree	46.5	45.0	47.8	
Post graduate degree	10.9	11.2	10.6	
Mother's education (%)				0.005
Intermediate or less (¾ 9 years)	14.3	16.8	12.0	
High school	30.6	29.0	32.1	
University degree	51.3	49.9	52.5	
Post graduate degree	3.8	4.3	3.4	
Family income (%) **				0.239
¾ 10,000 SR	30.1	28.7	31.3	
10,001-20,000 SR	44.9	46.6	43.3	
20,001-30,000 SR	18.6	18.9	18.3	
> 30,001 SR	6.4	5.8	7.1	

Data are means ± standard deviations or percentage.
*T-test for independent samples or Chi Squares tests for the proportion for the differences between boys and girls in continuous or categorical variables, respectively.
**US $ = 3.75 Saudi Riyal (SR).

TABLE 2 The prevalence of underweight, normal weight, overweight, and obesity among Saudi children using IOTF or WHO reference standards relative to age.

Age groups (years)	Reference standards *	Prevalence (%)			
		underweight	Normal weight	Overweight	Obesity
6	IOTF	26.7	53.5	5.8	14.0
	WHO	26.7	50.0	9.3	14.0
	KSA	5.8	69.8	12.8	11.6
7	IOTF	19.6	55.8	13.2	11.3
	WHO	21.9	47.2	15.8	15.1
	KSA	7.9	61.9	20.4	9.8
8	IOTF	18.8	58.2	12.2	10.8
	WHO	21.5	50.8	11.9	15.7
	KSA	6.6	68.0	18.2	7.2
9	IOTF	14.9	60.1	14.6	10.4
	WHO	19.1	51.2	15.1	14.6
	KSA	7.9	65.9	17.5	8.6
10	IOTF	10.2	48.8	26.5	14.5
	WHO	13.6	39.6	23.5	23.3
	KSA	7.2	50.8	30.3	11.5
11	IOTF	9.4	52.6	23.4	14.6
	WHO	13.0	37.8	27.3	21.9
	KSA	6.5	58.1	25.8	9.6
12	IOTF	7.5	56.1	23.5	12.9
	WHO	12.9	40.0	23.9	23.1
	KSA	5.9	62.4	24.3	7.5
13	IOTF	8.3	47.2	19.5	25.0
	WHO	8.3	47.2	13.9	30.6
	KSA	5.6	52.8	25.0	16.7
All	IOTF	13.8	55.1	18.4	12.7
	WHO	17.2	44.8	19.1	18.9
	KSA	7.0	61.3	22.4	9.3

P values of Chi Squares tests for the differences in prevalence categories across ages were < 0.001, < 0.001 and < 0.001 for IOTF, WHO and KSA, respectively.
*Overweight or obesity cut-offs are based on IOTF cut-off values (reference 13), WHO cut-off growth standards (reference 14), or Saudi (KSA) National growth references (reference 22).

family income, and number of family members living in the house were all significant (p-values ranged from < 0.001 to 0.034). However, there was no significant difference between the prevalence rates relative to school type, paternal, or maternal education when any reference standards were used.

Table 4 shows the logistic regression analysis results, adjusted for age, for selected sociodemographic variables relative to overweight/obesity versus non-overweight/non-obesity among the participants. There were significant associations ($p < 0.001$) between overweight/obesity and increasing age when all three classification standards were used. However, only when the WHO ($p = 0.043$) and KSA ($p = 0.036$) standards were used was there a significant association between overweight/obesity and sex (boys). In terms of geographic region, the incidence of overweight/obesity compared to the incidence of non-overweight/non-obesity was higher in children living in Riyadh than in children living in Jeddah when the references from the IOTF ($p = 0.031$) and KSA ($p = 0.005$) were used, but not when the WHO reference was used ($p = 0.122$). Furthermore, having a small family (2–5 members) in the house was associated with increased prevalence of overweight/obesity irrespective of the classification system (p values ranged from 0.017 to 0.025). Parental education levels did not show any significant association with overweight/obesity in all classification systems. Finally, a low to intermediate family income of (10,001–20,000 Saudi Riyals) was found to be significantly ($p = 0.015$) associated with overweight/obesity when using the IOTF standards.

Discussion

The present study aimed to compare the results of three different BMI classifications (the IOTF age and gender cutoffs, the WHO growth references for school-aged children, and the KSA national growth references) using data obtained from Saudi children aged 6–13 years. The findings showed that the proportions of the participants classified as overweight or

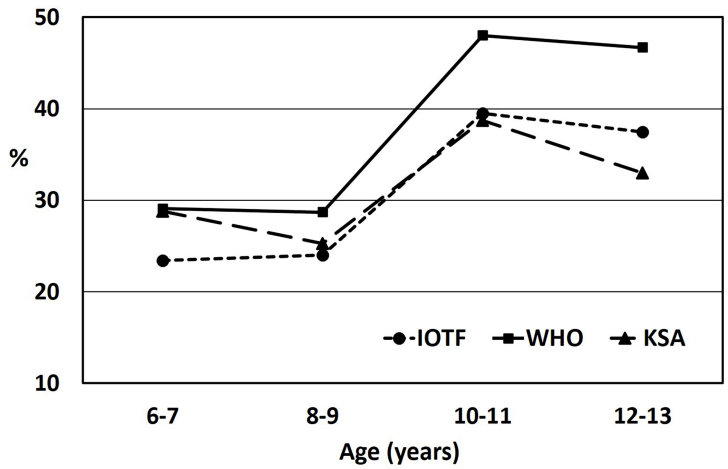

FIGURE 1
Overweight or obesity prevalence among Saudi children relative to age, based on International Obesity Task Force cut-off standards (IOTF), World Health Organization (WHO) reference standards, or Saudi (KSA) National growth references. Significant differences at $p < 0.001$ in all reference standards were found relative to age.

obese were fairly high, regardless of the classification system used. The IOTF cutoffs appear to be somewhat closer to the KSA growth references than to the WHO references. In all three classifications, girls exhibited lower overweight or obesity prevalence than boys. Family income, but not paternal or maternal education, was significantly associated with overweight/obesity when the IOTF standards were used. In addition, having a small family in the house was significantly associated with obesity, irrespective of the reference used. Hence, it seems that estimating the prevalence of underweight, overweight, and obesity among Saudi children yields inconsistent results when the IOTF, WHO, and KSA growth references are used.

Regardless of the BMI reference standards used, we observed a high prevalence of overweight and obesity among the participants, with somewhat variable levels of underweight status. It appears that the prevalence of overweight and obesity among Saudi children and adolescents has been rising over the

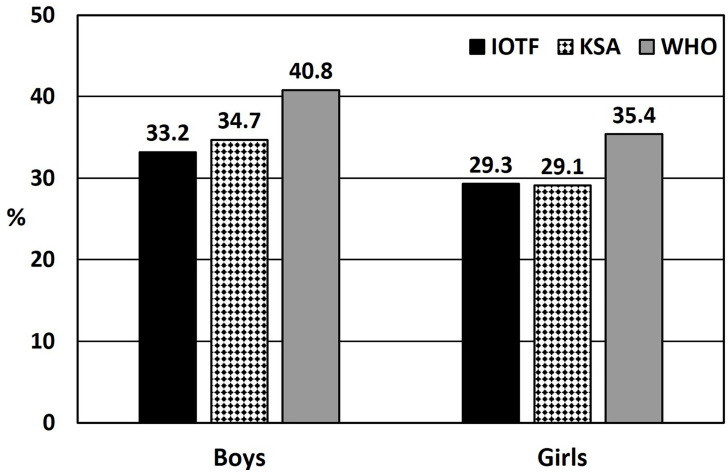

FIGURE 2
Overweight or obesity prevalence among Saudi children relative to sex, based on International Obesity Task Force cut-off standards (IOTF), World Health Organization (WHO) reference standards, or Saudi (KSA) National growth references. Significant differences between boys' and girls' reference standards (p values for IOTF = 0.048, WHO = 0.009, and KSA = 0.005).

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TABLE 3 The prevalence of underweight, normal weight, overweight, and obesity among Saudi children using IOTF or WHO reference standards relative to selected variables.

Variable	Reference standards *	Item	Prevalence (%)				*p*-value **
			underweight	Normal weight	Overweight	Obesity	
Sex	IOTF	Boys	14.8	52.0	18.0	15.2	0.002
		Girls	12.9	57.8	18.8	10.5	
	WHO	Boys	19.3	39.8	17.0	23.8	< 0.001
		Girls	15.3	49.3	20.9	14.4	
	KSA	Boys	6.8	58.5	22.4	12.3	< 0.001
		Girls	7.1	63.8	22.5	6.6	
City	IOTF	Riyadh	12.3	54.0	17.2	16.5	< 0.001
		Jeddah	15.2	56.0	19.5	9.3	
	WHO	Riyadh	15.5	44.8	16.8	22.9	< 0.001
		Jeddah	18.8	44.8	21.1	15.3	
	KSA	Riyadh	4.9	60.0	22.2	13.0	< 0.001
		Jeddah	8.9	62.5	22.7	6.0	
School type	IOTF	Public	14.4	55.4	18.2	12.0	0.293
		Private	12.3	54.2	19.1	14.4	
	WHO	Public	17.6	45.2	19.0	18.2	0.569
		Private	16.2	43.9	19.3	20.6	
	KSA	Public	7.1	62.3	21.3	9.3	0.234
		Private	6.6	58.7	25.3	9.4	
Father's education	IOTF	≤ Intermediate	14.9	50.9	18.2	16.0	0.355
		High school	15.4	57.1	16.6	10.9	
		University	13.0	55.1	19.2	12.8	
		Post graduate	11.6	54.7	20.3	13.4	
	WHO	≤ Intermediate	18.6	42.4	17.1	21.9	0.303
		High school	20.1	44.7	18.5	16.7	
		University	15.2	45.8	19.9	19.0	
		Post graduate	16.2	44.9	18.8	20.1	
	KSA	≤ Intermediate	7.4	57.6	21.6	13.4	0.248
		High school	8.0	63.7	20.2	8.1	
		University	6.6	60.9	23.4	9.1	
		Post graduate	5.6	61.5	24.4	8.5	
Mother's education	IOTF	≤ Intermediate	14.4	50.0	19.2	16.3	0.246
		High school	13.8	55.0	18.3	12.9	
		University	14.0	56.7	18.2	11.1	
		Post graduate	8.6	54.3	18.5	18.5	
	WHO	≤ Intermediate	19.9	39.9	15.4	24.8	0.063
		High school	16.8	45.4	19.7	18.2	
		University	17.2	46.1	19.5	17.3	
		Post graduate	11.1	44.4	21.0	23.5	
	KSA	≤ Intermediate	6.7	58.0	22.4	12.8	0.225
		High school	8.0	59.7	23.7	9.1	
		University	6.7	63.6	21.5	8.2	
		Post graduate	3.7	58.0	25.9	12.3	
Family income ***	IOTF	≤ 10,000 SR	15.6	55.2	17.2	12.0	0.032
		10,001-20,000	14.3	57.0	17.3	11.4	
		20,001-30,000	11.3	52.4	22.3	14.1	

(Continued)

TABLE 3 Continued

Variable	Reference standards *	Item	Prevalence (%)				*p*-value **
			underweight	Normal weight	Overweight	Obesity	
		> 30,001	11.0	47.1	24.3	17.6	
	WHO	≤ 10,000 SR	19.7	43.8	19.1	17.4	0.015
		10,001-20,000	17.8	47.0	18.6	16.6	
		20,001-30,000	14.0	42.3	20.7	23.0	
		> 30,001	13.2	41.9	17.6	27.2	
	KSA	≤ 10,000 SR	8.3	61.7	20.6	9.4	0.024
		10,001-20,000	7.5	63.3	21.0	8.3	
		20,001-30,000	4.6	58.2	27.8	9.4	
		> 30,001	5.8	54.7	25.5	13.9	
Family members living in the house	IOTF	< 5	15.1	53.3	19.9	11.7	0.022
		5-9	13.6	55.3	17.9	13.1	
		10 +	5.9	68.3	10.9	14.9	
	WHO	< 5	18.1	43.3	21.1	17.5	0.034
		5-9	17.3	45.1	17.9	19.7	
		10 +	9.9	58.4	13.9	17.8	
	KSA	< 5	7.3	60.9	23.8	8.1	0.077
		5-9	7.3	61.0	21.9	9.9	
		10 +	2.0	72.3	14.9	10.9	

*Overweight or obesity cut-offs are based on IOTF cut-off values (reference 13), WHO growth cut-off standards (reference 14), or Saudi growth references – KSA (reference 22).
**Differences in proportions between the selected variable items and prevalence rate.
**In Saudi Riyal (US $ = 3.75 Saudi Riyal).

last decades (9, 10). Recently, it was observed that the most important risk factors for obesity among Saudi children 5–9 years-of-age are parental characteristics, awareness of the degree of obesity burden, and lifestyle behaviors, such as frequent snacking, physical inactivity, and screen time (27). Also, among Saudi children and adolescents, obesity and other risk factors were found to have a significant impact on abnormal glucose metabolism (28). Therefore, efforts to prevent overweight and obesity in children must focus primarily on early identification, followed by appropriate reduction of common risk factors.

The present study found a higher prevalence of underweight, overweight, and obesity when the WHO reference standards were used compared to the IOTF cutoffs and the KSA national growth references. Currently, the use of age- and gender-specific BMI cutoffs is recommended to estimate overweight and obesity status among children and adolescents (13, 14, 29). However, it is somewhat challenging to estimate overweight and obesity prevalence when the most common international classification systems reveal different results (15–20, 30, 31). It appears that the discrepancies resulting from the use of the IOTF and WHO reference standards are due to differences in the cutoff values, the criteria used to select the sample, and the approaches used to define the cutoffs (32). An understanding of how the IOTF and WHO BMI standards for children and adolescents are constructed and their comparability may provide an explanation of their inherent limitations. In contrast to adult anthropometric cutoffs, which are based on mortality outcomes (33, 34), BMI cutoffs for children under the age of 18 years are statistically determined (13, 14). Indeed, it was reported that using the IOTF cutoffs and population-specific standards for childhood BMI failed to adequately predict cardiovascular disease risk factors in mid-adulthood from childhood BMI values (35). Accordingly, the choice of the reference standards used to express BMI data may influence the status of overweight and obesity among children from different populations. In addition, such differences in overweight and obesity, based on various cut-off references, may impact policy decision-making. In light of such limitations, many studies have argued that common references cannot be applied to children from different populations since they differ in their growth patterns (36–38). However, from the findings of the present study, it appears that the agreement between the IOTF and KSA references is much closer than that between the WHO and KSA references, when defining overweight plus obesity prevalence among Saudi children.

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TABLE 4 Results of logistic regression analysis, adjusted for age, of selected sociodemographic variables relative to overweight/obesity versus non-overweight/non-obesity among Saudi children.

Variable	Overweight/obesity versus non-overweight/non-obesity *						
	IOTF			WHO		KSA	
	aOR (95% CI)		*p-value*	aOR (95% CI)	*p-value*	aOR (95% CI)	*p-value*
Age	1.203 (1.138-1.272)	< 0.001	1.246 (1.181-1.315)	< 0.001	1.107 (1.048-1.169)	< 0.001	
Sex (girls = ref)	1.00		1.00		1.00		
Boys	1.136 (0.938-1.374)	0.191	1.207 (1.006-1.448)	0.043	1.223 (1.013-1.477)	0.036	
City (Jeddah = ref)	1.00		1.00		1.00		
Riyadh	1.258 (1.021-1.552)	0.031	1.171 (0.958-1.432)	0.122	1.344 (1.092-1.654)	0.005	
School type (private = ref)	1.00		1.00		1.00		
Public	0.900 (0.722-1.122)	0.349	0.902 (0.729-1.114)	0.338	0.871 (0.700-1.082)	0.212	
Members of Family in the house (≤ 10 = ref)	1.00		1.00		1.00		
6-9	1.537 (0.946-2.500)	0.083	1.468 (0.930-2.319)	0.099	1.556 (0.960-2.522)	0.072	
2-5	1.823 (1.105-3.007)	0.019	1.779 (1.111-2.849)	0.017	1.764 (1.073-2.899)	0.025	
Father education (postgraduate = ref)	1.00		1.00		1.00		
College degree	1.024 (0.740-1.417)	0.885	1.058 (0.774-1.447)	0.723	1.097 (0.794-1.515)	0.574	
High school	0.780 (0.544-1.118)	0.176	0.869 (0.616-1.227)	0.426	0.868 (0.607-1.241)	0.437	
< Intermediate	1.020 (0.656-1.585)	0.930	0.986 (0.644-1.510)	0.950	1.127 (0.728-1.744)	0.593	
Mother education postgraduate = ref)	1.00		1.00		1.00		
College degree	0.736 (0.450-1.204)	0.223	0.765 (0.473-1.238)	0.275	0.700 (0.431-1.138)	0.150	
High school	0.826 (0.494-1.381)	0.465	0.796 (0.481-1.316)	0.373	0.800 (0.482-1.329)	0.389	
< Intermediate	1.019 (0.582-1.785)	0.947	0.912 (0.528-1.577)	0.742	0.920 (0.529-1.599)	0.766	
Family income > 30,001 = ref)	1.00		1.00		1.00		
20,001-30,000	0.874 (0.560-1.283)	0.434	1.001 (0.664-1.508)	0.997	0.959 (0.634-1.451)	0.842	
10,001-20,000	0.614 (0.414-0.909)	0.015	0.724 (0.491-1.067)	0.103	0.696 (0.470-1.032)	0.071	
< 10,000	1.696 (0.455-1.065)	0.095	0.839 (0.553-1.273)	0.409	0.820 (0.536-1.253)	0.359	

*Non-overweight/non-obesity was used as a reference category. aOR, age adjusted odds ratio; CI, confidence interval; ref, reference category.
IOTF: International Obesity Task Force age- and sex-specific BMI cutoff reference standards. WHO: World Health Organization growth references for school-aged children and adolescents. KSA: Saudi National growth references calculated from the z–scores of BMI for age for children and adolescents from 5 to 18 years.

In terms of agreement measures, the Kappa agreement measures among the three reference standards were found to be fairly high, with the coefficients ranging from 0.936 between the IOTF and KSA references to 0.849 between the IOTF and WHO references. A lower Kappa coefficient (0.72) was reported between the IOTF and WHO references in a study with Brazilian children (39). Moreover, agreement between the IOTF and WHO references and French references ranged from moderate (Kappa = 0.43) to perfect (Kappa = 1.00) among French children (40). However, in a group of South American children, moderate agreements were observed between body fat estimated by dual-energy x-ray absorptiometry (DXA) and by the IOTF (Kappa = 0.61) and WHO (Kappa = 0.63) references, with the IOTF cutoffs showing the highest specificity (0.98 [0.94, 0.99]) (41). Data from a study conducted with Italian children and adolescents aged 5–17 years indicated that the WHO references had the highest sensitivity, while the IOTF classification had the highest specificity, in identifying obese subjects with clustered cardiometabolic risk factors (42).

Previous local, regional, and international studies have reported varying prevalence rates of overweight and obesity among children and adolescents when using the IOTF or WHO reference standards. Among Saudi adolescents from Riyadh, the IOTF reference reportedly produced more conservative (by 4–6%) estimates of overweight and obesity than the WHO reference standards (43). The average difference in overweight/obesity prevalence when using IOTF and WHO references in our study was 6.9%. In another study conducted on 6–16-year-old school children from Riyadh, the overall prevalence rates of overweight and obesity, as defined by the WHO 2007 growth standards, were reported to be 13.4% (14.2% for girls and 12% for boys) and 18.2% (18% for girls and 18.4% for boys), respectively (11). In comparison, in the present study with children aged 6–13 years, the overweight prevalence was higher (19.1%), but the obesity rate was similar (18.9%).

At the regional level, among a group of 10–14-year-old Kuwaiti adolescents, the prevalence of overweight and obesity calculated using Kuwaiti local reference data (36.7%) was significantly lower than that obtained using the IOTF (44.7%) or WHO (50.5%) reference standards (44). In another study, the prevalence of overweight and obesity among school children aged 10–13 years in Bahrain was calculated to be higher when the WHO reference was used compared to when the IOTF reference was used (17). Also, a school-based cross-sectional study conducted in eight Arab countries, including Saudi Arabia, involving adolescents aged 15–18 years showed that the use of the WHO standard resulted in a lower prevalence of overweight but a higher prevalence of obesity than the use of the IOTF reference standards (45).

Internationally, studies have shown varying degrees of consistency. Among 5–17-year-old Canadian children and adolescents, 16.4% of the participants were classified as overweight and 8.4% as obese when the IOTF reference was used, while 19.8% were classified as overweight and 11.7% as obese when the WHO standards were used (18). Moreover, the IOTF classification appears to be more specific when applied to identify overweight and obesity among indigenous Canadian school children aged 8–14 years than other systems, such as those of the Centers for Disease Control and Prevention (CDC) and the WHO (15). A recent study involving Cree youth revealed that participants classified as overweight by the IOTF classification system, but not by the WHO reference standards, displayed less severe clinical obesity (20). That is, false-positive subjects with obesity identified by WHO cutoffs were effectively classified as overweight by IOTF (20). Inconsistency was also apparent when the prevalence of underweight, overweight, and obesity among Malaysian children aged 6–14 years was estimated; use of the WHO reference resulted in a higher prevalence of overweight and obesity than the use of the IOTF reference (31). Thus, from previous studies' findings, it appears that the IOTF reference standards are more accurate than those of the WHO in identifying children and adolescents with obesity (15–20, 38).

Paternal or maternal education levels in the current study did not show any significant association with overweight/obesity in all classification systems. However, family income exhibited a significant association with overweight/obesity when the IOTF standards were used. However, when the WHO 2007 growth standards were used, overweight and obesity among school children from Riyadh aged 6–16 years appeared to significantly increase with higher socioeconomic status, including higher family income (11). In a study involving adolescents from eight Arab countries, including Saudi Arabia, major differences in obesity prevalence were found among the eight countries when both the IOTF and WHO reference standards were used, and the differences were attributed to a variety of factors, including socioeconomic status (45). Also, in a population-based cross-sectional study involving Pakistani children aged 5–12 years, a significant correlation was found between overweight and obesity status and high socioeconomic status, whereas body thinness was associated with low socioeconomic status and lower parental education (30). Interestingly, an analysis of data from a large number of children aged 6–9 years in 24 countries in the WHO European region showed that there was an inverse relationship between the prevalence of childhood overweight or obesity and parental education in high-income countries, and a positive correlation was observed in most of the middle-income countries (46).

Across all three classification systems used in this study, girls exhibited lower overweight or obesity incidence than boys. This finding aligns with results reported in some previous studies that used the IOTF or WHO cutoff references (10, 31, 47). However, others have reported mixed results (11, 15, 17, 20, 38). Finally, our findings revealed that having a small family in the house was significantly associated with increased prevalence of overweight/obesity irrespective of the reference used. This is an important finding of the present study. A recent study from the United States indicated that having more siblings is associated with lower BMI and decreased likelihood of obesity (48). It may be speculated that larger families may have a bigger reason to prepare and eat meals at home, which means better meal quality for children. Also, small families may be more inclined (and can afford) to eat outside home, which may include more fast foods. Another confounding factor for the relationship between obesity and family size may include family income, however, the correlation between family size and income was weak in the present study. It is possible that physical activity and dietary intake may influence body weight, but we did not assess these two factors in the present study.

The present study has some strengths and limitations. The strengths of this study include a relatively large sample size and

representative BMI data from children in two major Saudi cities. Also, measurements of weight and height were performed directly and did not rely on self-reporting. In addition, the sample was drawn from both public and private schools. The present study, however, has some limitations. First, the findings are limited to children aged 6–13 years and cannot be generalized to adolescents aged 14–17 years or preschoolers from 2-5 years. Second, the sample was drawn from urban areas and cannot be generalized to children residing in rural areas.

Conclusion

The proportions of the Saudi children who were classified as overweight or obese appeared to be fairly high, regardless of the classification system used. The IOTF cutoffs appear to be somewhat closer to the KSA growth references than to the WHO references. The Kappa agreement measures between the three references were found to be high, with the coefficients ranging from as high as 0.936 (between the IOTF and KSA references) to as low as 0.849 (between the IOTF and WHO references). In all three classifications, girls exhibited a lower incidence of overweight or obesity compared with boys. Family income, but not parental or maternal education, exhibited a significant positive association with obesity when using the IOTF standards. In addition, having a large family in the house was significantly associated with decreased obesity, irrespective of the IOTF or WHO references. It seems that using the IOTF, WHO, or KSA growth references to estimate the prevalence of underweight, overweight, and obesity among Saudi children leads to inconsistent results. However, the agreement between the IOTF and KSA references is much closer than that between the WHO and KSA references, which means that the IOTF classification system performed in a similar way to the KSA references (31.1% versus 31.7%) compared to the WHO references (38.0%) when assessing the overall prevalence of overweight plus obesity among Saudi children. Therefore, the choice of the currently available BMI classification systems has important implications for child health and the assessment of clinical obesity.

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

Ethical approval was obtained from the Institutional Review Board (IRB) at King Saud University, Riyadh (IRB Log Number: 17/0064/IRB) and Princess Nourah bint Abdulrahman University, Riyadh (IRB Log Number: 19-0014). Written informed consent to participate in this study was provided by the participants‘ legal guardian/next of kin.

Author contributions

Conceptualization: HA-H. Methodology: HA-H, AMA, MA, AAA, LJ, and RA. Investigation: HA-H, AMA, MA, AAA, LJ, RA, RB, and SA. Data collection and supervision: HA-H, AMA, MA, AAA, LJ, and RA. Statistical analysis: HA-H. Interpretation of the findings: HA-H, AMA, MA, AAA, LJ, RA, RB, and SA. Drafting the paper: HA-H. Reviewing and editing the draft: AMA, MA, AAA, LJ, RA, RB, and SA. All authors critically read, revised the draft for important intellectual content, approved the final version of the manuscript to be published, and agreed to be accountable for all aspects of the work.

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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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Body composition of the upper limb associated with hypertension, hypercholesterolemia, and diabetes

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The associations between segmental body composition and metabolic diseases remain equivocal. This study aimed to investigate this association using the example of U.S. adults. This cross-sectional study included 12,148 participants from the National Health and Nutrition Examination Survey (NHANES) (2011-2018). Multivariable logistic regression models were used to estimate associations between segmental body composition quartiles of hypertension, hypercholesterolemia, and diabetes. Among 12,148 participants, 3,569, 5,683, and 1,212 had hypertension, hypercholesterolemia, and diabetes, respectively. After adjusting for potential confounders, increased percent upper limb lean body mass was associated with a lower risk of hypertension (OR= 0.88, 95%CI: 0.84, 0.92, $P_{trend}<0.001$), hypercholesterolemia (OR= 0.93, 95%CI: 0.89, 0.96, $P_{trend}<0.001$), and diabetes (OR= 0.96, 95%CI: 0.95, 0.98, $P_{trend}<0.001$). Increased upper limb fat mass is associated with an increased risk of hypertension (OR= 1.11, 95%CI: 1.07, 1.15, $P_{trend}<0.001$), hypercholesterolemia (OR= 1.05, 95%CI: 1.01, 1.09, $P_{trend}=0.07$), and diabetes (OR= 1.03, 95%CI: 1.01, 1.05, $P_{trend}=0.014$). The same correlations were found in the torso and whole-body composition parameters. We observed that for women, lean body mass has a better protective effect on metabolic diseases [hypertension (OR= 0.88, 95%CI: 0.82, 0.93), hypercholesteremia (OR =0.86, 95%CI: 0.81, 0.92), diabetes (OR= 0.97, 95% CI: 0.85, 0.99)]; for men, increased body fat is associated with greater risk of metabolic disease[hypertension (OR= 1.24, 95%CI: 1.15, 1.33), hypercholesteremia (OR =1.09, 95%CI: 1.01, 1.18), diabetes (OR= 1.06, 95%CI: 1.01, 1.10)]. There were significant differences between different gender. These findings suggested that upper limb and torso adiposity should be considered when assessing chronic metabolic disease risk using body composition.

KEYWORDS

body composition, obesity, hypertension, hypercholesterolemia, diabetes

Introduction

Metabolic disease (MD) consists of various metabolic abnormalities, including hypertension, hyperlipidemia, and diabetes (1). According to data released by the National Health and Nutrition Examination Survey (NHANES), the incidence of metabolic syndrome is 24% and 22%, respectively, in men and women (2). So, MD is an emerging and severe public health concern worldwide (3). Hypertension and pre-hypertension are responsible for 8.5 million deaths from stroke, ischemic heart disease, other vascular diseases, and renal disease worldwide (4). Hypercholesterolemia is generally accepted as the second most crucial risk factor for developing cardiovascular disease after hypertension (5) and is a modifiable factor (6). Diabetes has become the ninth leading cause of death, and more than one million people die each year of diabetes (7). The global population with diabetes is projected to be 700 million by 2045 (8). Recently, various studies investigated risk factors of MD, but the current understanding remains incomplete.

However, identifying potentially modifiable risk factors is vital in preventing and managing MD (9), and obesity is one of the modifiable factors. Numerous studies linked obesity with a higher risk of hypertension, hypercholesterolemia, diabetes, and death (10, 11). Previous NHANES study has shown that dyslipidemia is the most common co-morbidity related to obesity, followed by hypertension and diabetes (12). It may be due to hormone changes, inflammation, oxidative stress, and insulin resistance levels (13–15). Usually, we use Body Mass Index (BMI) to reflect obesity, but BMI cannot accurately reflect body composition. Recent studies have proposed the "obesity paradox" (16, 17). Furthermore, the relationship between BMI and MD may vary by race (18–20) and gender (21, 22). so knowledge of body composition will help better understand the relationship between obesity and obesity-related metabolic risks (23, 24).

The body composition assessment is one of the cornerstones of studying human metabolism and physiology (25). Segmental body composition parameters may better reflect the effects of obesity (26, 27) and have received much attention in recent years. These parameters can be quickly assessed using dual-energy X-ray Absorptiometry (DXA). Calculating the masses of different components using two X-ray attenuators and measuring segmental body composition by subdividing the body using specific, well-defined cut lines (28). DXA is the preferred method for body composition (28) and has been widely used (29–31). Body fat indices measured by DXA may help further identify people at risk for hypertension even when they have normal BMI (32).

The relationship between body composition and MD has been studied (33). However, few studies have been conducted on segmental body composition parameters and MD. The connections between segmental obesity and MD remain equivocal. For example, studies have found no strong evidence that body composition is a significant determinant of hypertension and diabetes (34, 35). In contrast, a study from the UK showed that hypertension was directly related to a fat mass percentage (FM%) and inversely associated with lean mass percentage (LM%) (36). Diabetes is associated with reduced LM %, but the relationship between FM% and diabetes is unclear (37). Besides, few studies on the relationship between hypercholesterolemia and body composition. Notably, total FM% or LM% may not reflect specific segmental obesity status. Therefore, we evaluated FM% and LM% of each body segment to clarify the relationship between segmental obesity and MD.

This study aimed to investigate the associations of segmental body composition with hypertension, hypercholesterolemia, and diabetes.

Materials and methods

Study population

NHANES is a multistage, nationally representative study designed to assess health and nutrition measurements (38). NHANES collected person-level demographic, health, and nutrition information from personal interviews and a standardized physical examination in a mobile examination center (MEC) (39). The survey examines a nationally representative sample of approximately 5,000 people every year. NHANES was performed by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention (CDC) and was approved by the institutional review board of the National Center for Health Statistics. All participants signed a written informed consent form.

DXA is usually only performed in people aged 8-59. We restricted the analysis for this study to people aged 20 to 59 who were eligible for DXA examinations between 2011 and 2018. Pregnant women and people who weighed more than 450 pounds or were taller than 6'5" were already prohibited from DXA. Due to body components outside the scan region, alignment issues, overlapping arms or legs, excessive X-ray noise brought on by morbid obesity, and other factors that prevented the body area from being adequately evaluated, DXA results were considered invalid. Finally, 12148 participants were enrolled in the study.

DXA measurements

DXA scan was performed using Hologic Discovery model A densitometers (Hologic, Inc., Bedford, Massachusetts), using software version Apex 3.2. Original scan results were analyzed

with Hologic APEX version 4.0 software with NHANES BCA option to derive fat and lean mass. Trained and certified radiology technologists administered the DXA examinations. The University of California, San Francisco (UCSF) reviewed and analyzed each participant and phantom scan using standard radiologic techniques and NHANES-specific protocols. To ensure the accuracy and consistency of the results, the UCSF conducted expert reviews on all of the analyzed participant scans (40–43).

The torso region was defined as the area from the inferior edge of the chin as the upper borders to the oblique lines that cross the femoral necks and converge below the pubic symphysis as the lower perimeter, with vertical boundaries lateral to the ribs. The area below the lower borders of the torso was defined as the leg region (44, 45). Fat mass/lean mass was divided by segment weight to determine the segmental FM% and LM%. The left arm LM%, for instance, is calculated by dividing the left arm lean mass by the entire mass of the left arm.

Main outcome

Hypertension was defined as systolic blood pressure (SBP) ≥ 140 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg, or a positive answer to "The doctor said you have high blood pressure." Systolic and diastolic blood pressure values were assessed three to four times with a mercury sphygmomanometer using a conventional protocol. Three measurements were averaged to determine the SBP and DBP. Hypercholesterolemia is defined using total serum cholesterol: serum total cholesterol ≥ 200 mg/dL or "your doctor has said you have elevated cholesterol levels" or both. Diabetes was defined as the participant's self-reported diagnosis or glycated hemoglobin (HbA1c) ≥ 6.5% or both. A further detailed description of examination protocol, quality control, and safety procedures is available on the NHANES website.

Covariates

Baseline information on demographics and lifestyles was gathered utilizing a standardized questionnaire. Age was the age at the time screening was performed. The race was classified as non-Hispanic white and other racial groups (non-Hispanic black, non-Hispanic Asian, Mexican-American, other Hispanic groups, and other races). Marital status was divided into married and other (widowed, divorced, separated, never married, living with a partner). The ratio of family income to poverty means the ratio of family income to poverty guidelines. Smokers were defined as participants who had smoked at least 100 cigarettes during their lifetime. Drinking is defined as no drinking and more than one drink per drink. The Physical Activity Questionnaire's activity type and intensity determine activity-specific MET values (46–49). Participants were divided into low and high physical activity categories before analysis (low physical activity was defined as 500 MET/week or less; high physical activity was defined as 500 MET/week or more) (50). Qualified researchers take anthropometric measurements like height, weight, arm circumference, and waist circumference and are taken by standard protocols. BMI was calculated as weight (kg) divided by standing height squared (m^2). Serum samples were processed, stored under appropriate refrigeration (2-8°C), and shipped to the University of Minnesota Advanced Research Diagnostic Laboratory (ARDL) for analysis. Detailed specimen collection and processing instructions are discussed in the NHANES Laboratory Procedures Manual (LPM).

Statistical analysis

NHANES has a complex, multistage, probability cluster design. We processed the data according to the tutorials provided by NHANES; this included weighting according to sample weights and multi-period combined weights and the underestimation of variance due to this design scheme adjustments. Multiple imputations were used to impute variables with missing values. Characteristics of the case and control groups were compared in each of the three outcomes, $\chi 2$ tests were used to compare categorical variables, and T-student tests to compare continuous variables.

According to preliminary analysis, fat and lean body mass on the left and right are closely related (Figure 1), so LM% and FM% are represented by the average. The study expressed arm, leg, torso, and total LM and FM percent as quartiles and examined them as rank variables since body composition measures were not distributed normally. The first quartile was considered as a reference to explain any connections between body composition and MD, as reported by other studies on the NHANES population.

The correlations between segmental body composition quartiles for hypertension, hypercholesterolemia, and diabetes were estimated using binary logistic regression models. Odds ratios (OR) and 95% confidence intervals (95% CI) are provided. The model included body composition parameters separately to avoid over-tuning due to high correlations. The model was first adjusted for age and gender to form Model 1; on this basis, multi-factor adjustments were made to further adjust for the race, marital status, family income, smoking, drinking, physical activity, HbA1c, high-density lipoprotein-cholesterol (HDL-C), triglycerides, total cholesterol, SBP, DBP.

Further analyses were stratified by age and sex. The age subgroup analysis was divided into a middle-aged group (age >40) and a youth group (age ≤40) because the participants' ages ranged from 20 to 59. Data were analyzed using R 4.1.0; all tests were two-sided, and $P<0.05$ was considered statistically significant.

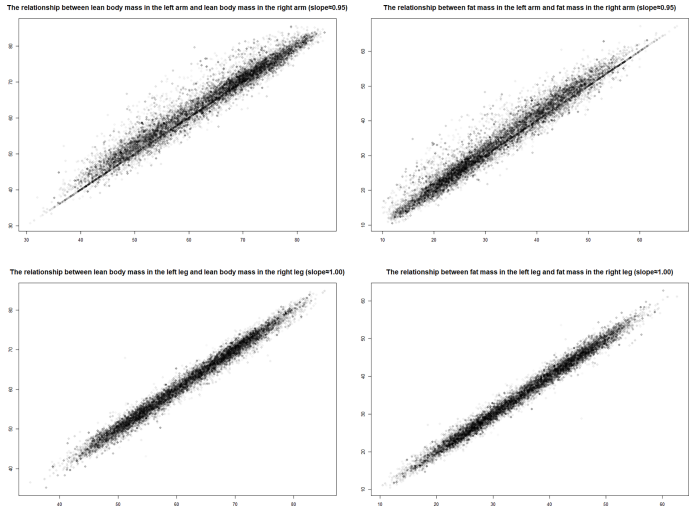

FIGURE 1
Lean mass and body fat percentage in left and right.

Results

Participant characteristics

The characteristics of the participants are shown in Table 1. The case group had a higher BMI, larger arm and waist circumferences, and was more likely to be older, married, smokers, and less physically active. Compared to the non-hypercholesterolemia group, the hypercholesterolemia group had a higher percentage of men, non-Hispanic whites, and higher incomes. The diabetic group had fewer non-Hispanic people, fewer drinkers, and lower incomes than the non-diabetic group.

Association of body composition parameters with metabolic disease

Table 2 illustrates the relationship between body composition characteristics and MD. After adjustment of age and gender, participants in the highest quartile of the arm LM% [hypertension (OR=0.83, 95%CI: 0.79, 0.87), hypercholesteremia (OR=0.86, 95%CI: 0.82, 0.91), diabetes (OR=0.89, 95%CI: 0.87, 0.91)], torso LM% [hypertension (OR=0.80, 95%CI: 0.77, 0.83), hypercholesteremia (OR=0.84, 95%CI: 0.80, 0.88), diabetes (OR=0.88, 95%CI: 0.86, 0.89)], and total LM%[hypertension (OR=0.86, 95%CI: 0.82, 0.89), hypercholesteremia (OR=0.89, 95%CI: 0.85, 0.93), diabetes (OR=0.93, 95%CI: 0.91, 0.95)] had a lower risk of metabolic disease.

An opponent association was found for the arm FM% [hypertension (OR=1.19, 95%CI: 1.15, 1.23), hypercholesteremia (OR=1.17, 95%CI: 1.11, 1.23), diabetes (OR=1.10, 95%CI: 1.08, 1.13)], torso FM%[hypertension (OR=1.26, 95%CI: 1.22, 1.31), hypercholesteremia (OR=1.20, 95%CI: 1.15, 1.26), diabetes (OR=1.14, 95%CI: 1.12, 1.16)], and total FM% [hypertension (OR=1.19, 95%CI: 1.15, 1.24), hypercholesteremia (OR=1.14, 95%CI: 1.09, 1.19), diabetes (OR=1.08, 95%CI: 1.06, 1.10)].

Except for the total LM% and total FM% in hypercholesteremia and diabetes, this association is constant even after accounting for several factors. A similar relationship was not generally found in leg body composition, only in the relationship between leg fat mass percentage and hypertension.

The relationship of segmental body composition on metabolic disease across age and gender

Based on Model 2, a subgroup analysis was conducted, and the three outcomes yielded various findings. We discovered no discernible interaction between age and body composition characteristics for determining the risk of hypertension (Figure 2). The protective effect of lean body mass is observed to be larger in middle-aged individuals than in young adults in the subgroup analysis of hypercholesterolemia, particularly in arm LM% [age>40 (OR=0.92, 95%CI: 0.86, 0.97) vs. age ≤ 40 (OR=0.94, 95%CI: 0.90, 0.98)] and torso LM%[age>40 (OR=0.91, 95%CI: 0.85, 0.97) vs. age ≤ 40 (OR=0.97, 95%CI: 0.93, 1.02)] (Figure 2). In the subgroup analysis of diabetes, we can be found same relationship in the arm LM% [age>40 (OR=0.93, 95%CI: 0.90, 0.96) vs. age ≤ 40 (OR=0.99, 95%CI: 0.97, 1.00)] and torso LM% [age>40 (OR=0.93, 95%CI: 0.90, 0.96) vs. age ≤ 40 (OR=0.99, 95%CI: 0.98, 1.00)] (Figure 2).

TABLE 1 Baseline characteristics in case and control groups: NHANES 2011-2018.

Characteristics	Hypertension (N=3569)	Non-Hypertension (N=8579)	P_{value}	Hypercholesterolemia (N=5683)	Non-Hypercholesterolemia (N=6465)	P_{value}	Diabetes (N=1212)	Non-Diabetes (N=10936)	P_{value}
Age, y	45.91(0.21)	37.33(0.25)	<0.001	44.36(0.23)	35.42(0.24)	<0.001	48.02(0.31)	39.02(0.23)	<0.001
Female, %	46.82	50.94	<0.001	47.18	51.97	0.01	49.67	49.73	0.46
Non-Hispanic White, %	33.73	35.30	0.94	36.39	33.47	<0.001	24.50	35.98	<0.001
Married, %	50.35	47.59	<0.001	55.36	42.29	<0.001	56.52	47.50	<0.001
Smoker, %	47.46	36.52	<0.001	43.57	36.37	<0.001	43.81	39.28	<0.001
Drinker, %	68.93	71.31	0.099	70.33	70.86	0.735	61.39	71.63	<0.001
High physical activity, %	63.43	71.26	<0.001	65.69	71.83	<0.001	56.93	70.29	<0.001
Income	2.92(0.06)	2.94(0.05)	0.77	3.14(0.05)	2.74(0.05)	<0.001	2.72(0.08)	2.95(0.05)	<0.001
Arm circumference, cm	35.54(0.14)	32.92(0.10)	<0.001	34.18(0.12)	33.16(0.11)	<0.001	36.81(0.21)	33.38(0.09)	<0.001
Waist circumference, cm	106.78(0.47)	95.52(0.34)	<0.001	101.71(0.44)	95.83(0.40)	<0.001	113.32(0.75)	97.40(0.33)	<0.001
BMI, kg/m^2	32.00(0.19)	28.05(0.14)	<0.001	29.98(0.19)	28.39(0.16)	0.05	34.42(0.33)	28.70(0.14)	<0.001
SBP, mmHg	128.55(0.65)	112.18(0.43)	<0.001	119.44(0.48)	114.27(0.52)	<0.001	122.74(1.42)	116.25(0.36)	<0.001
DBP, mmHg	77.03(0.52)	68.25(0.27)	<0.001	72.95(0.31)	68.61(0.34)	<0.001	72.67(0.90)	70.54(0.27)	<0.001
HDL-C, mmol/l	1.29(0.01)	1.37(0.01)	<0.001	1.36(0.01)	1.34(0.01)	<0.001	1.16(0.01)	1.36(0.01)	0.02
Triglyceride, mmol/l	2.01(0.04)	1.56(0.03)	<0.001	2.13(0.03)	1.27(0.02)	<0.001	2.51(0.10)	1.61(0.02)	0.35
Total cholesterol, mmol/l	5.08(0.03)	4.83(0.02)	<0.001	5.62(0.03)	4.24(0.01)	<0.001	4.95(0.05)	4.90(0.02)	<0.001
HbA1c, %	5.84(0.02)	5.41(0.01)	<0.001	5.71(0.02)	5.37(0.01)	<0.001	7.70(0.06)	5.35(0.01)	<0.001
Arm lean mass, %	61.39(0.20)	58.80(0.35)	<0.001	61.69(0.22)	59.56(0.25)	<0.001	61.07(0.18)	56.04(0.52)	<0.001
Arm fat mass, %	32.45(0.18)	34.01(0.23)	<0.001	32.21(0.20)	33.61(0.22)	<0.001	32.61(0.15)	36.07(0.38)	<0.001
Leg lean mass, %	61.45(0.17)	61.20(0.21)	0.36	61.49(0.17)	61.27(0.20)	0.24	61.39(0.15)	61.29(0.34)	0.44
Leg fat mass, %	35.21(0.18)	35.63(0.22)	0.15	35.18(0.18)	35.49(0.21)	0.37	35.31(0.15)	35.62(0.36)	0.81
Torso lean mass, %	67.21(0.18)	63.76(0.21)	<0.001	67.58(0.21)	64.81(0.19)	<0.001	66.65(0.16)	61.49(0.29)	<0.001
Torso fat mass, %	31.17(0.19)	34.80(0.22)	<0.001	30.75(0.22)	33.71(0.20)	<0.001	31.76(0.17)	37.10(0.29)	<0.001
Total lean mass, %	64.53(0.15)	63.10(0.18)	<0.001	64.73(0.16)	63.48(0.16)	<0.001	64.30(0.13)	62.19(0.28)	<0.001
Total fat mass, %	32.46(0.16)	34.22(0.19)	<0.001	32.23(0.17)	33.72(0.17)	<0.001	32.75(0.14)	35.32(0.28)	<0.001

Data are mean (SE) or percentage. P value was estimated using χ^2 for proportions, T test for means. NHANES, National Health and Nutrition Examination Survey; Income: A ratio of family income to poverty guidelines; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); HDL-C, high density lipoprotein -Cholesterol; HbA1c, glycated hemoglobin A1c. All estimates accounted for complex survey designs, and all percentages were weighted.

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When assessing the risk of diabetes, the risk effect of segmental FM% gain is considerably bigger in middle-aged individuals than in young adults [arm body fat (OR=1.04, 95%CI: 1.01, 1.08), torso body fat (OR=1.07, 95%CI: 1.04, 1.10), total body fat (OR=1.04, 95%CI: 1.01, 1.07)] (Figure 2).

Meanwhile, gender differences exist in the impact of segmental body composition on metabolic disease (Figure 3). Increased LM% had a stronger protective effect on metabolic disease in women, particularly in the arm [hypertension (OR=0.88, 95%CI: 0.82, 0.93), hypercholesteremia (OR=0.86, 95%CI: 0.81, 0.92), diabetes (OR=0.97, 95%CI: 0.85, 0.99)] (Figure 3). Conversely, increased FM% was associated with a higher risk of metabolic disease in men, particularly in torso FM % [hypertension (OR=1.24, 95%CI: 1.15, 1.33), hypercholesteremia (OR=1.09, 95%CI: 1.01, 1.18), diabetes (OR=1.06, 95%CI: 1.01, 1.10)] (Figure 3).

Discussion

According to our study's findings on segmental body composition, the percentage of lean body mass and body fat in the arm and torso were strongly associated with metabolic disease. The association persisted, and the trend remained statistically significant after potential confounders were considered. On this basis, we also found that when assessing metabolic disease risk, body fat has a more substantial effect in men and lean body mass has a more significant impact in women. For middle-aged adults (age > 40 years), upper limb lean body mass and torso body fat had more significant effects on hypercholesterolemia and diabetes than young adults (age ≤ 40 years). Because of this, our findings imply that segmental body composition characteristics are essential to include when evaluating metabolic risk.

To our knowledge, this is the first study to examine the relationship between segmental body composition and metabolic disease. According to a survey conducted on black Africans, body composition is not the leading cause of high blood pressure (35). Another study conducted among South Asians found no strong evidence that body composition could explain type 2 diabetes risk differences (34). Contrary to our findings, which may be caused by different methods of assessing body composition and different ethnic groups in the study population. In a study from the Korea National Health and Nutrition Examination Survey (51), it was discovered that among non-obese and obese individuals in the lowest tertile of the leg fat ratio to total fat, there was a decreased prevalence of hypertension, diabetes, and metabolic syndrome. This differs from our findings because the participants in our study had a higher BMI and were from different ethnicities. Furthermore, cohort studies (52) have shown that body fat distribution in women has shifted from the lower to the upper body in recent years, which may also be responsible for the disparity. According to a study from a Chinese population, the total skeletal muscle index and body fat % were substantially linked to high OR in pre-hypertension and hypertension, and arm lean body mass was more closely correlated with systolic and diastolic blood pressure than leg lean body mass (53). In a Korean study, men's torso fat mass percentage was strongly correlated

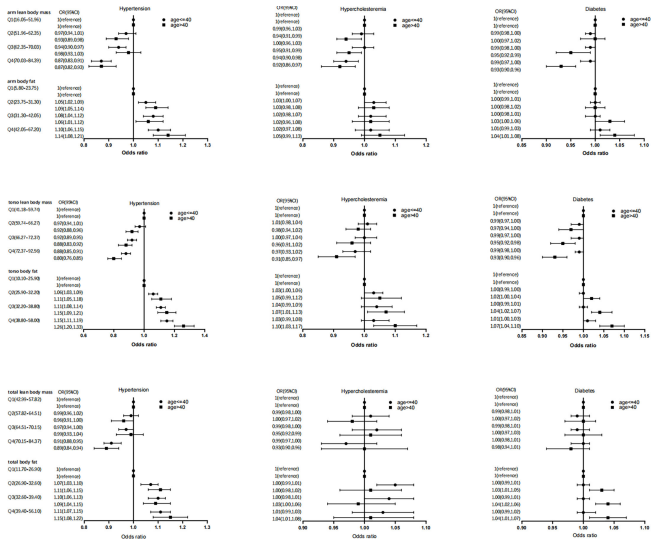

FIGURE 2
Association of segmental body composition with metabolic disease, at different ages.

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TABLE 2 Associations of body composition parameters with Hypertension, Hypercholesteremia, Diabetes in NHANES 2011-2018.

Body composition parameters	N	Hypertension				Hypercholesteremia				Diabetes			
		model 1	P trend	model 2	P trend	model 1	P trend	model 2	P trend	model 1	P trend	model 2	P trend
Arm LM%													
Q1(16.05-51.96)	3065	reference	<0.001	reference	<0.001	reference	<0.001	reference	<0.001	reference	<0.001	reference	<0.001
Q2(51.96-62.35)	3065	0.93 (0.91,0.96)		0.96 (0.93,0.98)		0.96 (0.93,0.99)		0.97 (0.95,1.00)		0.97 (0.95,0.98)		1.00 (0.98,1.01)	
Q3(62.35-70.03)	2890	0.92 (0.89,0.95)		0.96 (0.93,0.99)		0.95 (0.91,0.99)		0.97 (0.95,1.00)		0.93 (0.91,0.95)		0.98 (0.96,0.99)	
Q4(70.03-84.39)	3128	0.83 (0.79,0.87)		0.88 (0.84,0.92)		0.86 (0.82,0.91)		0.93 (0.89,0.96)		0.89 (0.87,0.91)		0.96 (0.95,0.98)	
Arm FM%													
Q1(5.80-23.75)	3108	reference	<0.001	reference	<0.001	reference	<0.001	reference	0.07	reference	<0.001	reference	0.014
Q2(23.75-31.30)	2894	1.09 (1.05,1.12)		1.07 (1.04,1.09)		1.10 (1.07,1.14)		1.03 (1.00,1.06)		1.03 (1.01,1.04)		1.00 (0.99,1.02)	
Q3(31.30-42.05)	2970	1.09 (1.06,1.13)		1.06 (1.03,1.09)		1.10 (1.06,1.15)		1.03 (1.00,1.06)		1.05 (1.03,1.08)		1.02 (1.00,1.03)	
Q4(42.05-67.20)	3176	1.19 (1.15,1.23)		1.11 (1.07,1.15)		1.17 (1.11,1.23)		1.05 (1.01,1.09)		1.10 (1.08,1.13)		1.03 (1.01,1.05)	
Leg LM%													
Q1(36.44-53.56)	2996	reference	<0.001	reference	<0.001	reference	0.01	reference	0.36	reference	0.84	reference	0.42
Q2(53.56-61.52)	3066	0.99 (0.96,1.02)		1.00 (0.97,1.03)		0.99 (0.96,1.03)		1.00 (0.97,1.03)		1.02 (1.00,1.04)		1.02 (1.00,1.03)	
Q3(61.52-69.18)	2964	0.97 (0.94,1.01)		0.99 (0.95,1.02)		1.01 (0.97,1.05)		1.01 (0.98,1.05)		1.01 (0.99,1.04)		1.01 (0.99,1.03)	
Q4(69.18-85.04)	3122	0.90 (0.86,0.94)		0.93 (0.89,0.97)		0.97 (0.92,1.02)		0.99 (0.95,1.04)		1.00 (0.97,1.02)		1.01 (0.99,1.03)	
Leg FM%													
Q1(10.70-27.20)	3121	reference	<0.001	reference	<0.001	reference	0.004	reference	0.27	reference	0.37	reference	0.54
Q2(27.20-35.15)	2959	1.08 (1.04,1.12)		1.06 (1.03,1.09)		1.04 (1.01,1.08)		1.02 (0.99,1.05)		1.02 (1.00,1.03)		1.00 (0.99,1.02)	
Q3(35.15-43.50)	3070	1.10 (1.06,1.15)		1.08 (1.04,1.12)		1.04 (1.00,1.08)		1.01 (0.97,1.05)		1.02 (1.00,1.04)		1.00 (0.99,1.02)	
Q4(43.50-61.85)	2998	1.12 (1.07,1.17)		1.08 (1.03,1.13)		1.05 (1.00,1.10)		1.01 (0.97,1.06)		1.01 (0.99,1.04)		0.99 (0.97,1.01)	
Torso LM%													
Q1(41.18-59.74)	3183	reference	<0.001	reference	<0.001	reference	<0.001	reference	<0.001	reference	<0.001	reference	<0.001
Q2(59.74-66.27)	3070	0.91 (0.88,0.94)		0.95 (0.92,0.97)		0.98 (0.95,1.01)		0.99 (0.97,1.02)		0.93 (0.91,0.95)		0.98 (0.96,1.00)	
Q3(66.27-72.37)	2933	0.84 (0.82,0.87)		0.90 (0.87,0.93)		0.94 (0.91,0.98)		0.98 (0.95,1.01)		0.90 (0.88,0.91)		0.97 (0.95,0.99)	
Q4(72.37-92.56)	2962	0.80 (0.77,0.83)		0.86 (0.83,0.89)		0.84 (0.80,0.88)		0.94 (0.91,0.98)		0.88 (0.86,0.89)		0.96 (0.95,0.98)	
Torso FM%													
Q1(10.10-25.90)	2978	reference	<0.001	reference	<0.001	reference	<0.001	reference	<0.001	reference	<0.001	reference	<0.001
Q2(25.90-32.20)	2933	1.07 (1.04,1.10)		1.06 (1.03,1.09)		1.13 (1.09,1.17)		1.04 (1.01,1.07)		1.02 (1.01,1.03)		1.00 (0.99,1.01)	
Q3(32.20-38.80)	3062	1.14 (1.11,1.17)		1.10 (1.08,1.13)		1.17 (1.12,1.21)		1.05 (1.02,1.09)		1.06 (1.04,1.07)		1.02 (1.01,1.03)	
Q4(38.80-58.00)	3175	1.26 (1.22,1.31)		1.18 (1.14,1.22)		1.20 (1.15,1.26)		1.06 (1.03,1.10)		1.14 (1.12,1.16)		1.03 (1.02,1.05)	
Total LM%													
Q1(42.99-57.82)	3149	reference	<0.001	reference	<0.001	reference	<0.001	reference	0.17	reference	<0.001	reference	0.1

(Continued)

TABLE 2 Continued

Body composition parameters	N	Hypertension				Hypercholesteremia				Diabetes			
		model 1	P trend	model 2	P trend	model 1	P trend	model 2	P trend	model 1	P trend	model 2	P trend
Q2(57.82-64.51)	3049	0.94 (0.91,0.97)		0.97 (0.95,1.00)		0.96 (0.93,1.00)		1.00 (0.97,1.03)		0.97 (0.96,0.99)		1.00 (0.98,1.01)	
Q3(64.51-70.15)	2920	0.94 (0.91,0.97)		0.98 (0.95,1.01)		0.97 (0.93,1.01)		1.01 (0.98,1.04)		0.97 (0.95,0.99)		1.00 (0.99,1.02)	
Q4(70.15-84.37)	3030	0.86 (0.82,0.89)		0.91 (0.88,0.94)		0.89 (0.85,0.93)		0.98 (0.94,1.02)		0.93 (0.91,0.95)		0.99 (0.97,1.01)	
Total FM%													
Q1(11.70-26.90)	3090	reference	<0.001	reference	<0.001	reference	<0.001	reference	0.08	reference	<0.001	reference	0.04
Q2(26.90-32.60)	2889	1.10 (1.07,1.13)		1.08 (1.05,1.11)		1.10 (1.06,1.14)		1.03 (1.00,1.07)		1.04 (1.02,1.06)		1.02 (1.00,1.03)	
Q3(32.60-39.40)	3040	1.12 (1.09,1.16)		1.09 (1.06,1.12)		1.10 (1.05,1.14)		1.03 (0.99,1.06)		1.05 (1.03,1.07)		1.02 (1.01,1.03)	
Q4(39.40-56.10)	3129	1.19 (1.15,1.24)		1.12 (1.08,1.16)		1.14 (1.09,1.19)		1.03 (0.99,1.07)		1.08 (1.06,1.10)		1.01 (1.00,1.03)	

LM%, lean mass percentage; FM%; fat mass percentage.
Model 1: Adjusted for age and gender.
Model 2: Adjusted for age, gender, race, marital status, the ratio of family income to poverty, smoking, alcohol consumption, physical activity, HbA1c, HDL-C, triglycerides, SBP, DBP, total cholesterol.

with hypercholesterolemia and was closely associated with hypertension (54). Similar to our findings, we analyzed multiple outcomes and segmental body compositions simultaneously.

The mid-upper arm circumference (MUAC) is regarded as a straightforward and reliable criterion for assessing obesity (55) and screening fat distribution (56) previously. However, these studies were conducted on children. Recent research has shown that MUAC can be used to detect central obesity and insulin resistance (57) and diagnose sarcopenia (58). Shi et al. (59) showed that MUAC was significantly associated with metabolic syndrome in middle-aged and older people. According to research, upper arm obesity may be a sign of central obesity, systemic obesity, or sarcopenia (60). Most of these studies were conducted in Asia, and we do not know if these conclusions hold in Americans. Although it makes sense to use MUAC to evaluate metabolic disease risk, additional research is required to

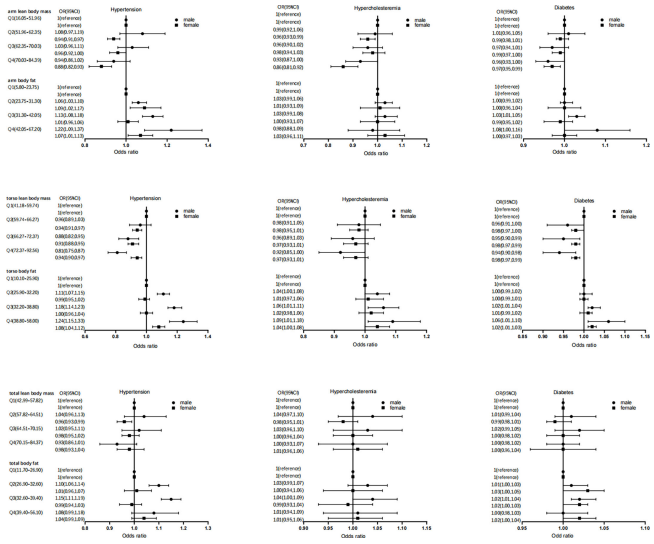

FIGURE 3
Association of segmental body composition with metabolic disease, at different gender.

comprehend this phenomenon fully. Based on MUAC, our study further proved the relationship between upper arm body composition and metabolic disease.

This study reveals that biologically based hypertension, hypercholesterolemia, and diabetes are related to the body composition of the upper arm and torso. In addition to reducing strength, muscle loss may also disrupt normal metabolism. First, the Skeletal muscle is the leading site of glucose utilization. A decrease in muscle mass is associated with a lower basal metabolic rate. It exacerbates insulin resistance (61), an established risk factor for hypertension (62), and affects the development of diabetes. Loss of muscle mass may enhance inflammation and oxidative pathways (62), associated with metabolic disease risk (63, 64). The second, loss of muscle mass, is associated with increased arterial stiffness (65), which may mediate hypercholesterolemia and hypertension (62, 66). In recent years, studies have shown that skeletal muscle functions as an endocrine organ that can produce and secrete hundreds of muscle factors associated with adverse clinical outcomes in patients with cardiovascular disease (67). Conversely, abdominal obesity might induce sarcopenia *via* the activation of proinflammatory cytokines, such as interleukin-6 and tumor necrosis factor-a. Narasimhulu et al. reported that increased hyperglycaemia and inflammation are associated with cellular pyroptosis, leading to significant loss of muscle cells and adverse remodelling (68).

This study has important clinical implications. We noted that the arm and torso body composition were strongly associated with metabolic disease. This finding provided indirect evidence that arm and torso body composition may better reflect whether there is a metabolic disorder than other segmental body composition parameters. Increasing muscle mass, particularly in the muscles of the upper limbs, had a more significant protective impact against metabolic diseases in women. For men, maintaining body fat in the low range is more conducive to reducing the risk of metabolic diseases. In the clinical analysis of body composition, more attention should be paid to the distribution of fat and lean body mass in the arm and torso. Targeting this link between segmental body composition and metabolic disease can be countered by protein supplementation (69) and increased resistance exercise (70). Sex hormones are known to affect muscle mass (71, 72). In earlier animal studies, male rats were also more susceptible to the harmful effects of diabetes on body composition than female rats (73). Estrogen is an antioxidant and sarcolemmal stabilizer that appears crucial for muscle protein turnover, benefits skeletal muscle contractile abilities, and guards against muscle deterioration (74). Testosterone is involved in energy balance, glucose metabolism, insulin sensitivity, and lipid metabolism. Low testosterone levels are associated with increased fat mass (especially central obesity) and decreased lean mass in men (75). Reduced sex hormone secretion with age (76) may also explain the effect of body composition on the onset of metabolic diseases in middle-aged people.

The advantage of this study is that the sample size is large. We strictly follow the variance estimation and weighted processing scheme provided by NHANES, and we use the latest DXA data and be sure to be contemporaneous. However, we also acknowledge that there are some limitations to the study. First, the type of study is cross-sectional, which is bound to limit the determination of causality. Because of this, there may be a potential reverse causality, in which chronic metabolic abnormalities lead to segmental muscle loss and fat accumulation. Prospective cohort studies are needed in future studies to assess the order of these associations. Second, after menopause, estrogen levels decrease muscle mass decreases, and fat mass increases (77). However, in this study, the age was limited to 59 years old, so the number of postmenopausal women was negligible. Third, participants with invalid DXA data were excluded, partly because of excess body weight, although this part of the data was not significant. Finally, despite the exclusion of minors, the participants were relatively young, depending on the conventional demographic age structure. It may have prevented our results from generalized to other groups, such as the elderly (age>60).

Conclusions

In conclusion, we report the association between segmental body composition and metabolic disease. In the upper limbs and torso, increased lean body mass is a protective factor for metabolic disease, and a higher fat percentage is a risk factor for metabolic disease. This relationship varies by sex and age. Our results imply that, in addition to overall body fat and lean mass percentage, we should consider body composition in upper limbs and torso segments when assessing metabolic disease risk. However, additional cohort studies are required to confirm these findings.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by NCHS Research Ethics Review Board (ERB) Approval. The patients/participants provided their written informed consent to participate in this study.

Author contributions

LF was responsible for funding acquisition. QQ and KS contributed to study design. YR, ZL, LF, YW, DZ, SS and HW carried out the clinical assessments. QQ and KS were responsible for data curation. QQ and KS analyzed the data. QQ wrote the manuscript, which was critically reviewed by all other authors. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

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Associations between neck circumference and markers of dysglycemia, non-alcoholic fatty liver disease, and dysmetabolism independent of Body Mass Index in an Emirati population

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Aim: Neck circumference (NC) is quick and easy to measure and may be a useful surrogate marker for body composition. We investigated NC as a potential marker of dysglycemia, MetS, and NAFLD.

Methods: 674 individuals were recruited at the Imperial College London Diabetes Centre in a study of sleep apnea prevalence. Of these, 547 (Age 46 ± 11.4 years, Body Mass Index (BMI) 31 ± 6 kg/m^2, 279 (51%) female, 113 normal glucose tolerance (NGT), 108 Prediabetes, 326 Type 2 diabetes (T2DM)) met all inclusion criteria for analysis. NC was measured at the thyroid cartilage, and collar size was recorded. Analysis was performed using univariate and multivariate linear regression.

Results: Adjusted for BMI, sex, and age, NC was 0.65 ± 0.3 cm greater in prediabetes (p = 0.0331), and 1.07 ± 0.28 cm greater in T2DM, compared with NGT (p = 0.0002). Adjusting for BMI, sex, and glycemic status, 1-cm increase in NC was associated with a 1.04 ± 1.01 U/L (p <0.0001) increase in ALT and, additionally, correcting for statin use, a 0.03 ± 0.01 mmol/L reduction in HDL (p <0.0001) and a 0.1 ± 0.02 increase in TC : HDL. A 1 cm increase in NC was associated with a 1.15 ± 1.02% (p <0.0001) increase in 10-year AHA cardiovascular risk in individuals over 40 years old and a 0.16 ± 0.02 (p <0.0001) increase in NAFLD fibrosis score. The neck circumference was associated with the hazard of new onset of deranged ALT adjusted for age, sex, glycemic status, and BMI (hazard ratio 1.076 (95% CI 1.015–1.14, p = 0.0131) and with the incidence of Fatty Liver Index associated with high probability of NAFLD (hazard ratio 1.153 (95% CI 1.019–1.304), p = 0.0239).

Conclusion: NC is associated with dysglycemia, components of the MetS, and factors predictive of NAFLD, but does not appear to independently predict

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subsequent progression to high risk of liver fibrosis in this predominantly diabetic population.

KEYWORDS

neck circumference, obesity, dysglycemia, NAFLD, MetS

Introduction

The prevalence of obesity is increasing worldwide, as are comorbidities including Type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD). The body mass index (BMI) criterion is endorsed by both the National Institutes of Health and the World Health Organization for defining and classifying obesity (1). However, the use of BMI as an index of adiposity has been debated, primarily because it does not reflect body fat distribution (2–4). Evidence from observational studies suggests that body fat distribution more accurately predicts cardiovascular outcomes in obese individuals (5).

Alternatives to BMI used to assess body composition include skinfold thickness, waist circumference (WC), hip circumference (HC), body adiposity index (BAI), and waist to hip ratio (WHR) (6, 7). WHR has been shown to be more strongly associated with CVD events and T2DM mortality compared with WC and BMI (8). Among the Emiratis, WHR has been reported to be a better predictor of T2DM than BMI (9). WHR measurement can be time-consuming and more prone to errors, however. Relevant anatomical landmarks can also be obscured in obese individuals.

The neck circumference (NC) has also been proposed as a measure of body composition (10, 11). NC is recognized as a risk factor for obstructive sleep apnea, which is itself associated with CVD, cardiac arrhythmias, and heart failure. NC can be measured without requiring the patient to undress, and NC landmarks may be better preserved compared with those used to measure WC in the context of obesity. NC does not vary with food intake and has been associated with central adiposity (12).

It has been suggested that NC acts as a marker of risk for the metabolic syndrome (MetS) as well as its individual features in both adult and pediatric populations (13–16), although a direct association of MetS diagnosis with NC was not demonstrated in a recent meta-analysis (17). The components and features of MetS, including dysglycemia and non-alcoholic fatty liver disease (NAFLD), have also been directly linked with NC (18–20), although population-specific cut-off points on stratified categories, such as sex and age, may be needed for reliable association of NC with MetS (21–23).

NC therefore shows some promise in assessing metabolic risk and screening for conditions associated with diabetes and obesity. Here we investigated NC as a potential marker of MetS, dysglycemia, and NAFLD in an Emirati outpatient cohort of people with normoglycemia, prediabetes, or T2DM.

Methods

Participant recruitment and disposition

Patients were recruited in the Abu Dhabi Sleep Apnea (ADSA) research project (N = 674), a study of sleep apnea prevalence at Imperial College London Diabetes Centre (ICLDC), an outpatient diabetes and endocrinology institute in Abu Dhabi, United Arab Emirates (UAE). Written informed consent for the involvement in the sleep apnea study was obtained from all research participants, and another for the use of anonymized medical data for research purposes were derived from all patients at the time of the first visit to the center. The ADSA study was approved by the ICLDC Research Ethics Committee and followed the Declaration of Helsinki, 1996. NC was measured at the level of the thyroid cartilage, and collar size was recorded; participants completed a questionnaire including the STOP-BANG (Snoring, Tiredness, Observed apnea, blood Pressure, BMI, Age, NC, and Gender) criteria for sleep apnea. Participant information, including BMI, blood pressure, diabetes status, smoking status, medications, and contemporaneous HbA1c, full blood count, lipid profile, and liver function tests, was retrieved from the electronic medical records. Diabetes and smoking status were derived from the individual patient records. No participant reported alcohol use. Medication compliance was assessed based on the prescriptions of physicians and/or clinic notes. HbA1c was measured using the VARIANT II system (Bio-Rad). Biochemical parameters were assessed using the Cobas platform (Roche).

For the purposes of statistical analysis, individuals with secondary diabetes, type 1 diabetes, or MODY were excluded (n = 22). Individuals diagnosed with impaired glucose tolerance, impaired fasting glucose, or previous gestational diabetes were considered to have prediabetes. Individuals without a record of parameters for the calculation of cardiovascular risk and NAFLD fibrosis score were excluded from further analysis (n = 105). Four individuals had serological evidence of active viral hepatitis

infection and were therefore excluded from the analysis. In total, 547 individuals were included in the statistical analysis. Baseline characteristics of the included participants are presented in Table 1.

Statistical analysis

Data are presented as mean ± standard deviation. Statistical analysis was performed using the R language for Statistical Computing version 4.1.3 with the *survival* and *icenReg* packages. NAFLD Fibrosis Score was calculated as (−1.675 + 0.037 ∗ Age (years) + 0.094 ∗ BMI + 1.13 ∗ (presence of prediabetes or diabetes) + 0.99 ∗ (AST/ALT) − 0.013 ∗ Platelets (10^9/L) − 0.66 ∗ Albumin (g/dl)). The Fatty Liver Index (FLI) was calculated as (FLI coefficient/(1 + FLI coefficient) ∗ 100) where the FLI coefficient is exp(0.953 ∗ ln(Triglycerides) + 0.139 ∗ BMI + 0.718 ∗ ln(GGT (IU/L)) + 0.053 ∗ Waist circumference − 15.745), with an FLI score of ≥60 indicating a high risk of fatty liver disease. The Hepatic Steatosis Index (HSI) was calculated as (8 ∗ ALT/AST) ∗ BMI + 2 ∗ (if female) + 2 ∗ (if Type 2 Diabetes), with an HSI score of ≥36 indicating high risk for fatty liver disease. The FIB4 score was calculated as (Age (years) ∗ AST (IU/L))/(Platelets (10^9/L) ∗ sqrt(ALT (IU/L))). Ten-year cardiovascular risk was calculated using the Pooled Cohort Equations for White individuals (24). Linear regression models were used for adjustment for covariates in the analysis of the association between neck circumference and study outcome measures; logistic regression models were used to adjust for covariates in comparisons between glycemic status groups. Cox proportional hazards models were used for prospective analysis of progression to type 2 diabetes in individuals with prediabetes or diabetes at enrolment, while Cox regression with adjustment for left censoring according to the methods of Wei Pan (1999) using the specific implementation by Anderson-Bergman (2020) was used to investigate the longitudinal relationship between neck circumference and ALT. Derangement of ALT was defined as ≥33 IU/L in males and ≥25 IU/L in females according to ACG criteria (25) while interval to progression to type 2 diabetes was defined as the time in years between enrolment and first recorded HbA1c ≥6.5%, clinical diagnosis of type 2 diabetes, or prescription of hypoglycemic medication for type 2 diabetes. Significance was assessed at the level of $p < 0.05$; no correction was made for multiple comparisons.

Results

Relationships between NC and glycemic status

The mean neck circumference at enrollment was 35.1 ± 3.1 cm in individuals with normal glucose tolerance, 37.4 ± 3.2 cm in individuals with prediabetes, and 38.9 ± 3.3 cm in

TABLE 1 Baseline characteristics of participants included in statistical analysis. Values are presented as mean ± standard deviation.

Grouping	NGT	Pre	T2DM
Number	113	108	326
Female (%)	74.3%	51.9%	42.6%
Age	35.4 ± 10.3	44.5 ± 10.6	50.3 ± 9.2
BMI	28.5 ± 6.1	30.3 ± 5.4	32.1 ± 5.9
NC	35.1 ± 3.1	37.4 ± 3.2	38.9 ± 3.3
sBP (mmHg)	116.9 ± 13.6	123.6 ± 15.8	128.3 ± 17.7
dBP (mmHg)	68.7 ± 9.8	73.9 ± 11.9	75.5 ± 10.3
HbA1c (%)	5.1 ± 0.4	5.6 ± 0.8	7 ± 1.5
ALT (IU/ml)	19.8 ± 12.9	25.9 ± 13.9	27.2 ± 15.5
AST (IU/ml)	18.4 ± 6.4	20.4 ± 8.5	20.1 ± 9.5
HDL (mmol/L)	1.5 ± 0.4	1.4 ± 0.4	1.2 ± 0.3
LDL (mmol/L)	3 ± 0.8	3 ± 0.9	2.6 ± 0.9
TG (mmol/L)	1.1 ± 0.6	1.3 ± 0.8	1.7 ± 1
FLI ≥60	14 (35.9%)	37 (48.1%)	221 (70.2%)
HSI ≥36	67 (59.3%)	87 (80.6%)	305 (93.6%)
STOP BANG Score	1.8 ± 1.5	2.9 ± 1.8	3.6 ± 1.8

NGT, normal glucose tolerance; Pre, prediabetes; T2DM, type 2 diabetes mellitus; BMI, body mass index; NC, neck circumference; sBP, systolic blood pressure; dBP, diastolic blood pressure; HbA1c, glycated hemoglobin; ALT, alanine transaminase; AST, aspartate aminotransferase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglycerides.

people with type 2 diabetes. In each of these groups, NC was significantly greater in men than in women (38.3 ± 2.8 cf 34 ± 2.3, p <0.0001; 39.5 ± 2.4 cf 35.5 ± 2.6, p <0.0001; 40.2 ± 2.8 cf 37.1 ± 3, p <0.0001, respectively). After adjusting for age, sex, and BMI in logistic regression, neck circumference was significantly increased in people with prediabetes compared with those with normal glucose tolerance (difference 0.65 ± 0.3 cm, p = p = 0.0331). In the same analysis, type 2 diabetes was significantly associated with increased neck circumference compared with the normal glucose tolerance group (difference 1.07 ± 0.28 cm, p = 0.0002). The relationships between NC and sex-stratified glycemic status are presented in Figure 1.

Among 171 individuals with normal glucose tolerance or prediabetes at enrollment and subsequent HbA1c measurement (median follow-up 4.6 (2.3–6.5) years), four with NGT and 26 with prediabetes at enrollment progressed to type 2 diabetes. The neck circumference was significantly and independently associated with an increased hazard of subsequent progression to type 2 diabetes, adjusted for BMI (neck circumference: hazard ratio 1.141, 95% CI 1.004–1.296, p = 0.043, BMI: hazard ratio 1.043, 95% CI 0.977–1.114, p = 0.207). NC was not a significant predictor when further adjusted for age, sex, or prediabetes, although this analysis was limited by the small number of available endpoints for each covariate. NC did not significantly predict incident retinal or renal microvascular complications either in univariate analysis or when adjusted for age, sex, HbA1c, blood pressure, smoking status, and BMI over a median follow-up period of 4.8 (IQR 2.3–6.1) years.

Relationships between NC and hazard of liver disease

The relationship between neck circumference and log-transformed serum ALT was approximately linear (r = 0.407, p <0.0001, Pearson), as illustrated in Figure 2A. Adjusting for body mass index, sex, and glycemic status, a 1-cm increase in NC was significantly and independently associated with a 1.04 ± 1.01 U/L (p <0.0001) increase in ALT and a 1.05 ± 1.01 U/L (p <0.0001) increase in gamma-GT (GGT), illustrated in Figure 2B. Male sex and type 2 diabetes diagnosis were significantly and positively associated with ALT, while male sex, prediabetes, and type 2 diabetes were significantly and positively associated with GGT, consistent with previous reports (25, 26).

In univariate linear regression, a 1-cm increase in NC was significantly associated with a 0.16 ± 0.02 increase in NAFLD fibrosis score (p <0.0001, see also Figure 2F); this analysis was not adjusted for age or diabetes status since these are components of the risk score, but did remain significant when adjusted for sex. The univariate association between NAFLD fibrosis score and neck circumference remained significant in 272 individuals with an FLI score of ≥60, suggestive of NAFLD,

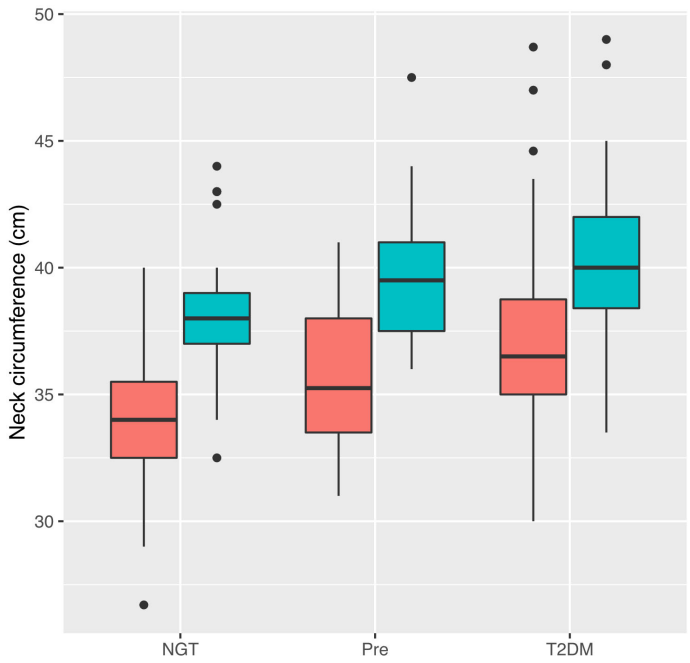

FIGURE 1
Relationship between neck circumference and glycemic status stratified by sex. Tukey plot represents median, interquartile range (IQR) and IQR ± 1.5 * IQR. Male participants are represented by blue and female participants by red. NGT, normal glucose tolerance; Pre, prediabetes; T2DM, Type 2 diabetes mellitus.

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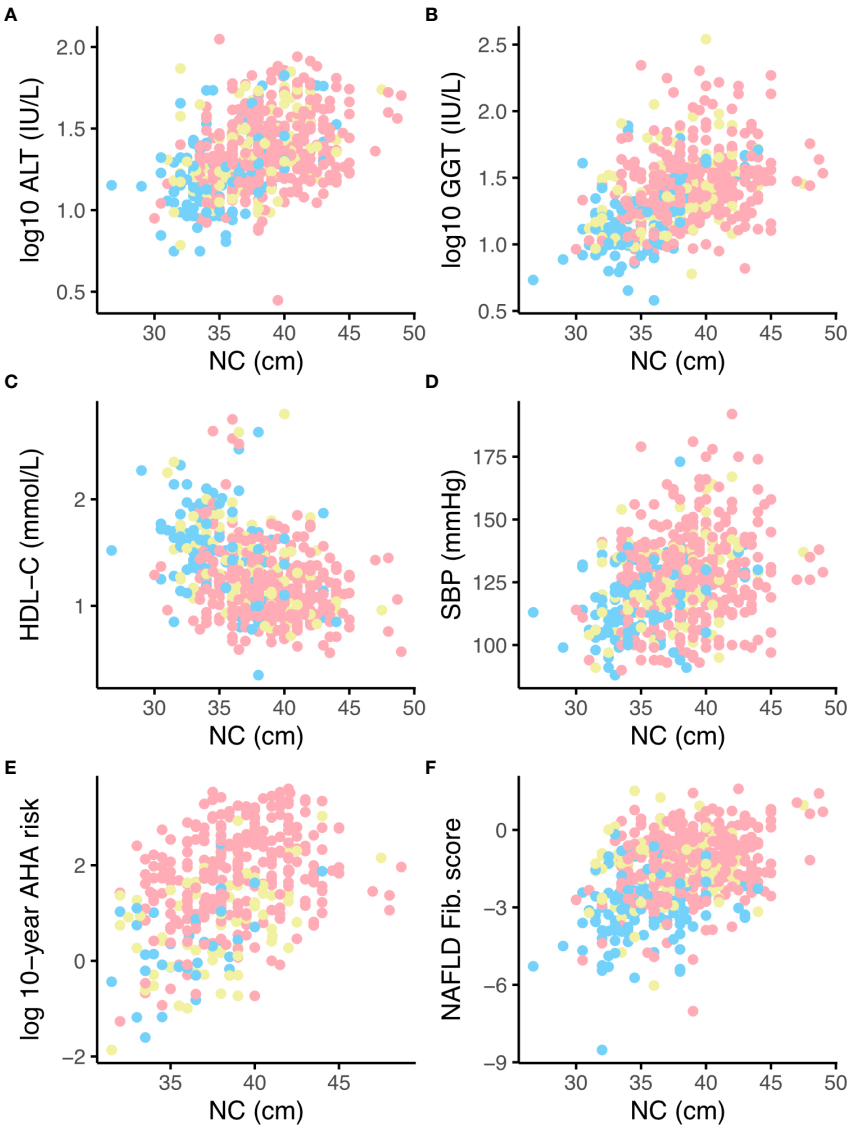

FIGURE 2
Relationships between neck circumference (NC) and liver function tests, lipid profile, blood pressure, AHA 10-year cardiovascular risk and NAFLD Fibrosis score, stratified by glycaemic status. NGT = blue, Prediabetes = yellow, Type 2 diabetes = pink. Panels **(A)** log-transformed ALT, **(B)** log-transformed GGT, **(C)** HDL-cholesterol (HDL-C), **(D)** systolic blood pressure **(E)** log-transformed 10-year cardiovascular risk assessed by AHA pooled-cohort equations, **(F)** NAFLD fibrosis score. ALT, alanine transaminase; GGT, gamma-glutamyl transferase; SBP, systolic blood pressure; AHA, American Heart Association; NAFLD, non-alcoholic fatty liver disease.

at recruitment (0.08 ± 0.02 increase in NAFLD fibrosis score per 1-cm increase in NC, p = 0.0004). A 1-cm increase in NC was also significantly associated with a 2.72% increase in FIB4 score (p <0.0001) in the group as a whole and a 2.11% increase in FIB4 score in individuals with an FLI suggestive of NAFLD at enrollment (p = 0.0287). These analyses are limited by missing data for waist circumference, and therefore the HSI NAFLD risk score was also calculated. In 459 individuals with an HSI score ≥36, suggestive of the presence of NAFLD, a 1% increase in NC was associated with a 0.12 ± 0.02 increase in NAFLD fibrosis score (p <0.0001) and a 2.55% increase in FIB4 score (p = 0.0002).

NC was positively and independently associated with incident elevation of ALT in Cox proportional hazards regression adjusted for age, sex, BMI, and glycemic status (hazard ratio 1.076 (95% CI 1.015–1.14, p = 0.0131) per 1-cm increase in NC); both prediabetes and type 2 diabetes were also significant predictors (hazard ratios 2.044 (95% CI 1.377–3.034), 2.148 (95% CI 1.419–3.25), respectively, see also Figure 3). In a subset of 395 participants with sufficient data, NC remained significantly associated with new

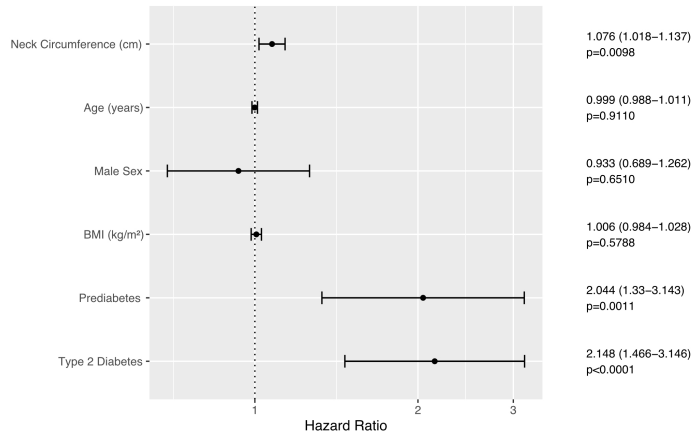

FIGURE 3
Forest plot illustrating Cox Proportional Hazards model of onset of elevation of ALT (≥33 in males, ≥25 in females). Error bars represent the 95% confidence interval of the hazard ratio.

derangement of ALT when adjusted for waist-hip ratio instead of BMI. Stratifying for sex and adjusting for age, BMI, and glycemic status, NC was also significantly and independently associated with progression to FLI ≥60 in individuals with low FLI-assessed risk of NAFLD at enrollment (hazard ratio 1.153 (95% CI 1.019–1.304), p = 0.0239, see also Figure 4). During the follow-up period, 53 participants (47 with HSI ≥36 at enrollment) progressed to a NAFLD Fibrosis Score of ≥0.676, while 12 participants (11 with HSI ≥36 at enrollment) progressed to a FIB-4 score of ≥2.67, both cut-offs for high risk of advanced fibrosis. NC predicted progression to the high NAFLD Fibrosis Score cut-off of ≥0.676 during the follow-up period in univariate and analysis and when adjusted for sex (hazard ratio 1.076, p <0.01. However, NC did not significantly predict progression to NAFLD Fibrosis Score ≥0.676 when adjusted for BMI or diabetes status, or in univariate analysis when limited to patients with an HSI ≥36. In univariate or multivariate analysis, NC did not predict progression to the FIB-4 cut-off of ≥2.67, either in the entire study population or in individuals with HSI ≥36, although this analysis was limited by the small number of endpoints.

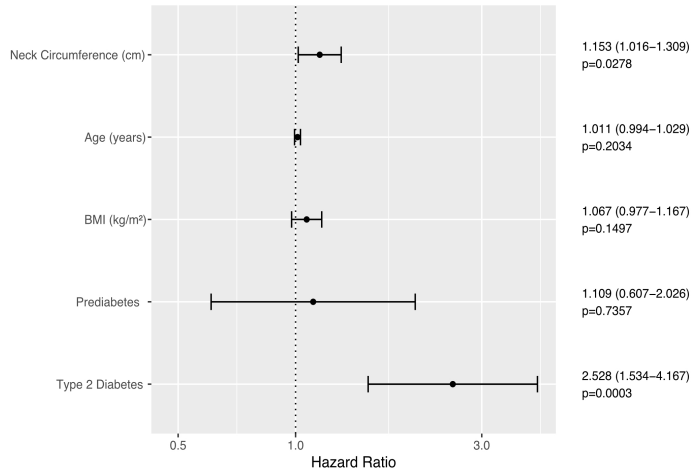

FIGURE 4
Forest plot illustrating Cox Proportional Hazards model of time to first FLI ≥60 in individuals with FLI <60 at enrolment. Error bars represent the 95% confidence interval of the hazard ratio.

Relationship between NC and cardiovascular risk factors

A 1-cm increase in NC was significantly associated with an increase in systolic blood pressure blood pressure of 0.65 ± 0.24 mmHg (p = 0.0066), adjusted for age, sex, glycemic status, and antihypertensive use (see also Figure 2D), and a reduction in HDL-C of 0.03 ± 0.01 mmol/L (p <0.0001) adjusted for age, sex, glycemic status, and BMI. In 384 participants aged ≥40 years, NC was associated with an increase in the 10-year AHA cardiovascular risk score of 1.15 ± 1.02% (p <0.0001) per 1-cm increase (Figure 2E). NC was negatively associated with HDL (Figure 2C) and positively associated with a 0.1 ± 0.02 increase in TC : HDL (p <0.0001) adjusted for age, sex, glycemic status, and statin use, and hence, along with systolic blood pressure, two of the modifiable risk factors included in the Qrisk lifetime cardiovascular risk equation. Although NC was not significantly associated with incident macrovascular disease (new records of ICD-10 codes I20, I21, I24, I25, I63, I70, and I73) in a longitudinal Cox proportional hazards analysis adjusted for age, sex, glycemic status, blood pressure, LDL-C, and smoking status, although since ICLDC is not primarily a cardiology center and these diagnostic codes were therefore based on patient recall, this analysis may have been limited by under-reporting of events.

Discussion

Metabolic anomalies arising from obesity have been attributed to visceral or upper body subcutaneous fat deposits, predominantly elevated levels of free fatty acids (FFA) mediated by insulin resistance (27–29), The increase in FFA concentrations is positively associated with interrelated MetS components—abdominal obesity, hypertension, dysglycemia, and hyperlipidemia, which share underlying pathways including inflammation, the final common pathway (29–32). MetS is the clustering of these components, and its global prevalence has been reported to be 20%–25% in adults and up to 19% in children with type 1 diabetes (33). The Metabolic Syndrome, dysglycemia, and NAFLD are all highly prevalent among Emirati nationals in the UAE, at 33.6%, 40.0%, and 34.7%, respectively (34–36). Assessments of prevalence are, however, limited by the lack of a unified MetS definition since multiple criteria from the World Health Organization (WHO), National Cholesterol Education Program (NCEP), International Diabetes Federation (IDF), American Association of Clinical Endocrinologists (AACE), and European Group of Insulin Resistance (EGIR) are all used in clinical research (37).

The association of neck adiposity with MetS has been recognized since the early 1950s (38). Ben-Noun et al. reported positive correlations between NC, CVD risk factors, and blood pressure, as well as corresponding changes in both (39–41). NC among participants in the Framingham Heart Study was associated with CVD risk factors after adjusting for BMI and VAT (28). In keeping with these previous findings, we found positive associations between NC and sBP, 10-year cardiovascular risk, and modifiable lifetime cardiovascular risk factors. Compartmentalization of neck fat accumulation in a study by Torriani et al. found that neck adipose tissue (NAT), most notably posterior cervical NAT (NATpost) and subcutaneous NAT (NATsc), was associated with CVD risk factors and MetS, and more prominently among women (32). The higher association in women compared to men was similarly observed in other studies (28) and was partly ascribed to higher upper body FFA in women (42). These findings and the results of this study, particularly the positive, significant, association of male sex and T2DM with ALT and GGT, require further research.

A systematic review and meta-analysis performed in 2017 (43) found that NC is an accurate tool for assessing overweight and obesity in both males and females and across different age groups, although cut-off points for different populations were suggested. This was also the recommendation of a systematic review of the association between NC with cardiometabolic risk in adolescents (23), which found the relatedness of NC with BMI, WC, and MetS. In contrast, a similar systematic review and meta-analysis in an adult population did not find an association of NC with MetS but only with BMI, WC, hypertension, fasting blood sugar (FBS), total cholesterol (TC), LDL-C, sBP, diastolic blood pressure (DBP), and low HDL-C concentrations. However, heterogeneity between studies was high, therefore findings were advised to be taken with caution (17). In this study, although NC was positively associated with several MetS risk factors, it was not found to be so with new retinopathy, maculopathy, or microalbuminuria. A recent study by Sobhani et al. found that BMI was a consistent predictor of triglycerides and increased hepatic enzymes, although the relevance of NC was not indicated (44). Other recent studies have reported that obesity is involved with microvascular disease progression, including retinopathy in T2D (45, 46). These reports may again underscore the need for additional studies and population-specific NC cut-offs for appropriate correlations with obesity, MetS, and other related conditions such as dysglycemia and fatty liver.

A more recent systematic review, authored by a group from the UAE, reported a weak association between NC and BMI (47). In another study in 2021 with Emirati adults as participants, results similarly showed a poor correlation between NC and BMI, WC, and WHR (48). However, a study on adult females in the UAE in 2015 reported a significant positive relationship between NC and obesity (49). Although this may be related to having female participants as previously discussed, conflicting results, including several outcomes of the current study again, signify the need for further investigation of NC along with other obesity anthropometric measures in this population and region.

NC is correlated with ultrasound-assessed liver fat content in adult non-obese (50–53) and pediatric and adolescent obese (54) populations. NC was positively associated with intensity of histologically assessed liver steatohepatitis but not with the presence of steatosis or presence of fibrosis in a study of 119 predominantly female, non-diabetic obese patients undergoing bariatric surgery (55). NC was not significantly associated with the intensity of steatohepatitis in multivariate regression with BMI and WC, although each measure was equally weakly associated (R = 0.2 for all) in univariate analysis and the number of endpoints analyzed was relatively small given the expected collinearity between these variables (55). Despite a large proportion of our patients with an HSI suggestive of hepatic steatosis at enrollment, a surprisingly small number of individuals went on to be predicted to be at high risk of fibrosis according to the FIB-4 score during follow-up. The FIB-4 score has been observed to have an unexpectedly high false-negative rate in patients with type 2 diabetes, particularly at the intermediate-risk cut-off of 1.3 (56, 57). The FIB-4 score is also reported to have a high false negative rate in individuals under the age of 35 years and an increased false positive rate in individuals over 65, partially attributed to the inclusion of age in the FIB-4 calculation (57).

Study strengths and limitations

The study strengths include the number of individuals in whom NC was measured and the consistent quality of data for follow-up. The NC measurements were taken as part of a research protocol and in a single centre, increasing the reliability of the source data. Our dataset allowed us to explore associations of NC with subsequent incidence of adverse metabolic characteristics, where much of the existing literature examines correlational relationships with prevalent disease. Additionally, this is a population-specific investigation of NC as a potential assessment tool for obesity and related disorders. Study limitations include the retrospective nature of a part of the study, which relied on the retrieval of electronic medical records. This study is also based on clinical data and may therefore be subject to reporting bias for clinical endpoints. The measurement of WC and HC, although performed by trained clinical staff, may have been inaccurate because of challenges in locating anatomical landmarks. A prospective study with the inclusion of comprehensive, well-defined parameters would be valuable.

Conclusions

In an Emirati cohort, NC was associated with dysglycemia and markers of MetS. Our data suggest that NC could play a role in identifying people with prediabetes or diabetes who are at increased risk of NAFLD but do not support an association between NC and incident liver fibrosis.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by the Research Ethics Committee, Imperial College London Diabetes Centre. The patients/participants provided their written informed consent to participate in this study.

Author contributions

EF: study design, data acquisition, and manuscript writing. AB: study design, statistical analyses, and manuscript writing. NL: data interpretation and manuscript editing. All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Conflict of interest

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

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Association of METS-IR index with prevalence of gallbladder stones and the age at the first gallbladder stone surgery in US adults: A cross-sectional study

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Objective: The purpose of this study was to assess the correlation between the metabolic score for insulin resistance (METS-IR) index and gallbladder stoneprevalence in US adults, as well as the age at first gallbladder stone surgery.

Methods: A logistic regression analysis, subgroup analysis, and dose-response curve were computed for participants in the 2017-2018 National Health and Nutrition Examination Survey (NHANES) to assess the relationship between the METS-IR index and gallbladder stone prevalence and age at first surgery for gallbladder stones.

Results: This study ultimately included 9452 participants aged >20 years, of whom 534 self-reported a history of gallbladder stones, and after adjusting for all confounders, each unit increase in METS-IR index was associated with a 3.3% increase in gallbladder stone prevalence (OR= 1.033, 95% CI: 1.0258, 1.0403) along with an earlier age at first gallbladder stone surgery 0.26 years (β= -0.26, 95% CI: -0.35, -0.17), stratified analysis showed that increased METS-IR index was associated with increased prevalence of gallbladder stones in all subgroups, and the dose-response curve showed a positive linear correlation between METS-IR index and prevalence of gallbladder stones, while a negative linear correlation was observed between increased METS-IR index and age at first gallbladder stone There was a negative linear correlation between age at surgery.

Conclusion: The METS-IR index has been positively associated with gallbladder stone prevalence, thereby contributing to age at first surgery for gallbladder stones. However, the causal relationship between the METS-IR and gallbladder stones cannot be concluded.

KEYWORDS

gallbladder stones, age at first gallbladder stone surgery, METS-IR index, insulin resistance, metabolic syndrome, prevalence

1 Introduction

A gallstone is a benign biliary disorder with symptoms such as abdominal discomfort, epigastric pain, nausea, vomiting, and loss of appetite (1). The presence of this condition increases the risk of cholecystitis, pancreatitis, biliary obstruction, and gallbladder cancer (2). Globally, there are ethnic and racial differences when it comes to the prevalence of gallstone disease and gallstone formation. It is estimated that approximately 10% of white adults in Western countries have gallbladder stones(GSD), while the prevalence among African Americans and East Asians is lower than others (1), and the prevalence increases with age, eventually reaching 30% in older populations, regardless of gender, in their 70s (3). Health care costs associated with gallbladder stones are approximately $6 billion per year (4). Over 20 million people suffer from gallbladder stones. Moreover, complications can have serious consequences, increasing health care costs and in some cases even posing an immediate danger to the patient. Therefore, identifying gallbladder stones' risk factors is especially critical for preventing their development.

Living conditions are improving, but the prevalence of metabolic syndrome remains high. A metabolic syndrome is characterized by an array of metabolic disorders, including obesity (especially abdominal obesity), postprandial hyperglycemia, hypertension, and dyslipidemia. It is widely recognized that an increase in obesity is associated with higher morbidity and mortality from several of the most prevalent diseases in the Western world, including gallstones (5, 6). Metabolic syndrome and gallbladder stones share common risk factors, the most relevant being abdominal obesity and insulin resistance, both of which are associated with increased cholesterol synthesis, excessive biliary cholesterol secretion, and elevated biliary lithogenicity in the body (7). Insulin resistance, one of the central mechanisms of the metabolic syndrome, has been reported to be associated with the development of gallbladder stones (8). In peripheral tissues, insulin sensitivity is currently assessed by the high insulin normoglycemic clamp (HEC) (9). Due to its complexity, time, and resource consumption, insulin resistance is often assessed using simpler metrics. A novel insulin resistance (IR) metric was developed in 2018 as a simple, reliable, and reproducible predictor of IR (6). It can be hypothesized that the METS-IR index relates to gallbladder stones, since it has been proposed as a marker of IR. It has not been previously evaluated whether METS-IR index is associated with gallbladder stones. As such, in this study we examined the METS-IR index's role in gallbladder stone development in the adult United States population.

Abbreviations: NHANES, National Health and Nutrition Examination Survey; BMI, body mass index; PIR, ratio of family income to poverty; NCHS, National Center for Health Statistics; CI, confidence interval; OR, odds ratio; MetS, metabolic syndrome; IR, insulin resistance; TG, Triglyceride; TC, Cholesterol; FPG, fasting plasma glucose.

2 Materials and methods

2.1 Study population

This study used clinical data from the NHANES from 2017-2018 to determine baseline clinical variables. Our data included information on participants who explicitly answered whether they had gallbladder stones and their age when they had their first gallbladder stone surgery. A total of 9254 people participated in the survey. Exclusion criteria were as follows (Figure 1). Finally a total of 4793 cases were included in this study, including 534 self-reported gallbladder stone history.

2.2 Data collection and definition

METS-IR index was designed as an exposure variable. METS-IR= Ln[(2 × fasting glucose) + fasting triglycerides) × body mass index]/[Ln(high-density lipoprotein cholesterol)]. An automated biochemical analyzer was used to determine triglyceride and fasting blood glucose levels enzymatically. With the Roche Cobas 6000 chemistry analyzer and the Roche Modular P, serum triglyceride concentrations were determined. Gallbladder stones and age at the time of first gallbladder stone surgery were assessed *via* questionnaires, including "Ever been told you have gallbladder stones?" and "Age when first had gallbladder surgery?.". The results obtained by intersecting the participants who answered the age of the first gallbladder surgery with those who answered that they had gallbladder stones were considered to be the participants who had the first surgery for gallbladder stones. The occurrence of gallbladder stones and age at first gallbladder stone surgery were designed as outcome variables.

Multivariable adjusted models have been constructed to assess whether potential confounding factors may be involved in the association between METS-IR index and gallbladder stones. Covariates in our study included sex (male/female), age (years), race, education level, poverty to income ratio (PIR), marital status (married or living with partner/single), alcohol consumption (drinking or not), physical activity (vigorous/moderate/below moderate), cholesterol level (mg/dl), smoking status (smoking or not), hypertension, diabetes mellitus, and dietary intake factors, including energy intake, fat intake, sugar intake, and water intake, all participants underwent two 24-hour dietary recalls in years 2017-2018, and the average consumption of the two recalls will be used in our analyses. The details of the measurement procedures for the study variables can be found at http://www.cdc.gov/nchs/nhanes/. All NHANES protocols were implemented in accordance with the U.S. Department of Health

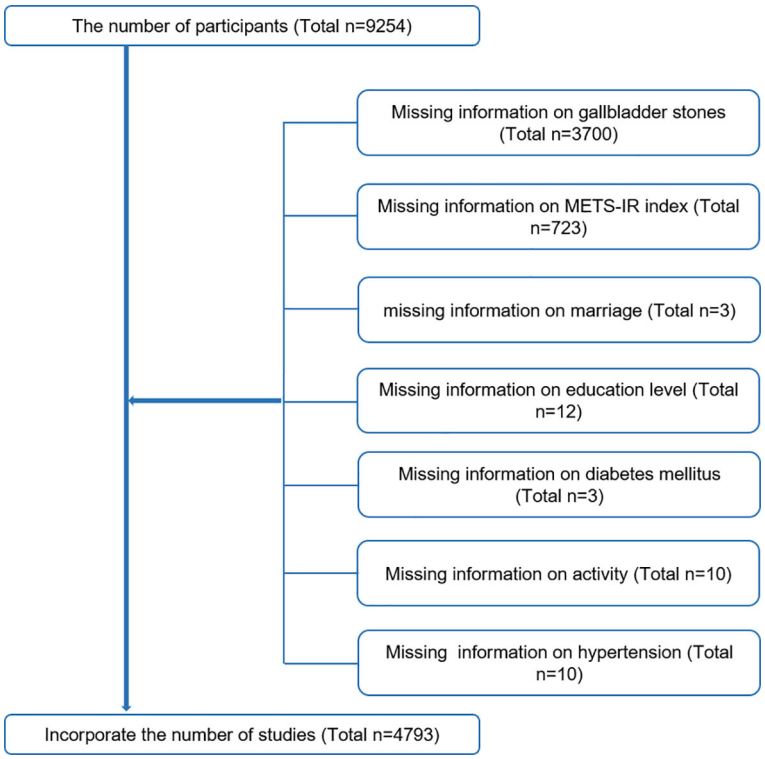

FIGURE 1
Sample selection flowchart from NHANES 2017–2018.

and Human Services (HHS) Human Research Subject Protection Policy and were reviewed and standardized annually by the NCHS Research Ethics Review Committee. All subjects who participated in the survey signed informed consent forms. All data in this study were released free of charge by NHANES without additional authorization or ethical review.

2.3 Statistical methods

To illustrate the complex, multistage sampling design used in selecting a representative noninstitutionalized U.S. population, the sampling weights, stratification, and clustering provided in the NHANES study were applied to all statistical analyses. To exclude the problem of cointegration, we used the cointegration test, when VIF greater than 5 was considered to have cointegration problem. Continuous variables were represented with weighted survey means and 95% confidence intervals, and categorical variables were represented with weighted survey means and 95% confidence intervals. The presence of gallbladder stones and the time to first gallbladder stone surgery were investigated in three different models using multiple logistic regression analyses based on the guidelines (10). In model 1, no adjustment for covariates was made. Model 2 was adjusted for sex, age and race, marital status, and education level. Model 3 was adjusted for all variables. An analysis of the relationship between METS-IR index and gallbladder stone prevalence and age at first surgery was carried out using smoothed curve fitting (penalized spline method) and generalized additive model (GAM) regression. In cases where a nonlinear relationship is present, an inflection point value is derived by a likelihood ratio test. Next, multiple regression analyses were conducted stratified by sex, age, race, hypertension, and diabetes. $P < 0.05$ was considered statistically significant. All analyses were performed using Empower software www.empowerstats.com; X&Y Solutions, Inc., Boston, MA, USA) and R version 4.0.2 (http://www.R-project.org, The R Foundation).

3 Results

Listed below are the basic demographic characteristics of the participants (Table 1). METS-IR index was 50.10 (48.08,52.12) in the gallbladder stone group, which was higher than 43.81 (42.89,44.74) in the normal group, $p < 0.0001$. Compared to the normal group, the age at the time of the disease, the proportion of women, hypertension, and diabetes were significantly higher in the gallbladder stone population than in the normal group ($P < 0.05$).

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TABLE 1 Baseline characteristics of participants, weighted.

Characteristic	Nonstone formers (n = 4259)	Stone formers (n = 534)	P-value
Age (years)	47.25 (46.05,48.46)	56.47 (55.38,57.55)	<0.0001
Serum Cholesterol (mg/dl)	189.88 (186.41,193.36)	187.70 (182.31,193.10)	0.3459
METS-IR Index	43.81 (42.89,44.74)	50.10 (48.08,52.12)	<0.0001
Gender			<0.0001
Male	50.95 (48.81,53.08)	26.02 (21.40,31.25)	
Female	49.05 (46.92,51.19)	73.98 (68.75,78.60)	
Race			0.0526
Mexican American	16.13 (12.16,21.07)	13.11 (9.56,17.71)	
White	62.23 (56.41,67.71)	70.05 (61.46,77.43)	
Black	11.20 (8.01,15.44)	7.04 (4.98,9.87)	
Other Race	10.45 (7.98,13.57)	9.80 (5.74,16.23)	
Education Level			0.8148
Less than high school	11.28 (9.60,13.21)	10.13 (7.32,13.84)	
High school	27.03 (23.55,30.81)	28.36 (22.25,35.38)	
More than high school	61.69 (57.06,66.12)	61.51 (55.77,66.95)	
Marital Status			0.3617
Cohabitation	63.31 (60.52,66.02)	60.75 (54.14,66.98)	
Solitude	36.69 (33.98,39.48)	39.25 (33.02,45.86)	
Alcohol			0.014
Yes	6.94 (5.38,8.91)	3.97 (1.93,7.97)	
No	8.08 (7.18,9.08)	3.76 (1.84,7.52)	
Unclear	84.98 (83.09,86.69)	92.27 (86.73,95.62)	
High Blood Pressure			<0.0001
Yes	30.29 (27.63,33.08)	49.67 (43.52,55.82)	
No	69.71 (66.92,72.37)	50.33 (44.18,56.48)	
Diabetes			<0.0001
Yes	10.07 (8.92,11.34)	22.81 (18.16,28.25)	
No	89.93 (88.66,91.08)	77.19 (71.75,81.84)	
Smoked			0.0603
Yes	41.75 (38.99,44.56)	48.22 (39.75,56.80)	
No	58.25 (55.44,61.01)	51.78 (43.20,60.25)	
Physical Activity			0.0002
Never	23.54 (21.46,25.75)	29.00 (23.78,34.85)	
Moderate	28.39 (25.38,31.61)	35.61 (28.51,43.40)	
Vigorous	48.07 (45.99,50.17)	35.39 (29.54,41.71)	
PIR			0.0166
<1.3	17.78 (16.24,19.43)	16.80 (12.43,22.32)	
≥1.3,<3.5	30.97 (27.28,34.92)	40.13 (32.33,48.45)	
≥3.5	40.97 (36.62,45.47)	32.07 (27.01,37.60)	
Unclear	10.28 (8.37,12.56)	11.00 (8.14,14.69)	
Total Kcal			0.0091
Lower	37.71 (35.66,39.80)	47.10 (40.42,53.89)	
Higher	45.08 (42.80,47.38)	39.92 (33.35,46.88)	
Unclear	17.21 (14.86,19.85)	12.98 (9.89,16.84)	
Total Sugar			0.8265
Lower	34.10 (31.72,36.56)	35.98 (30.18,42.22)	
Higher	35.00 (32.21,37.89)	34.23 (27.46,41.70)	
Unclear	30.91 (27.73,34.28)	29.80 (24.89,35.22)	

(Continued)

TABLE 1 Continued

Characteristic	Nonstone formers (n = 4259)	Stone formers (n = 534)	P-value
Total Water			0.012
Lower	37.13 (35.24,39.05)	45.64 (39.02,52.42)	
Higher	45.66 (43.32,48.02)	41.38 (35.12,47.94)	
Unclear	17.21 (14.86,19.85)	12.98 (9.89,16.84)	
Total Fat			0.012
Lower	37.13 (35.24,39.05)	45.64 (39.02,52.42)	
Higher	45.66 (43.32,48.02)	41.38 (35.12,47.94)	
Unclear	17.21 (14.86,19.85)	12.98 (9.89,16.84)	

For continuous variables: survey-weighted mean (95% CI), P-value was by survey-weighted linear regression.
For categorical variables: survey-weighted percentage (95% CI), P-value was by survey-weighted Chi-square test.

3.1 A higher METS-IR index is associated with a higher prevalence of gallbladder stones

According to the results of collinearity test, the VIF values of all covariates are less than 5, there is no collinearity problem, and all of them are included in the regression model. There was a positive correlation between METS-IR index and gallbladder stones (Table 2). According to the fully adjusted model (model 3) (OR=1.033, 95% CI: 1.0258, 1.0403), there was a 3.3% increase in gallbladder stoneprevalence for every unit increase in METS-IR index. For sensitivity analysis, we converted the METS-IR index into a categorical variable (tertile). The odds ratio for gallbladder stoneprevalence was greater by 1.9859 in Tertile 3 (OR=2.9859, 2.2853, 3.9014) than in Tertile 1, the lowest METS-IR index tertile.

3.2 Analysis of the dose-response and threshold effects of METS-IR on the prevalence of gallbladder stones

An additive generalized model and smoothed curve fitting were used to investigate the relationship between METS-IR index and gallbladder stoneprevalence. In Figure 2, we found a linear correlation between the METS-IR index and gallbladder stonesprevalence.

3.3 Subgroup analysis

In order to assess the robustness of the association between METS-IR index and gallbladder stoneprevalence, subgroup analyses were conducted. In the whole subgroup analysis, although the METS-IR index showed a positive increase with increasing prevalence of gallbladder stones in all subgroups, it still had different risk effects in different subgroups (Table 3). In the gender subgroup, elevated METS-IR was associated with a higher prevalence of gallbladder stones in female(OR=1.0382,95%CI:1.0294, 1.0470) patients compared to males(OR=1.0206,95%CI:1.0064, 1.0350). In the age subgroup, elevated METS-IR was found to be associated with a higher prevalence of gallbladder stones in the younger age subgroup. In the hypertensive and diabetic subgroups, elevated METS-IR was associated with a higher prevalence of gallbladder stones than in the non-hypertensive and non-diabetic groups. Finally, in the racial stratification, we found that elevated METS-IR was associated with a higher prevalence of gallbladder stones in white and other populations.

TABLE 2 Analysis between METS-IR index with gallbladder stone prevalence.

Characteristic	Model 1 OR (95%CI)	Model 2 OR (95%CI)	Model 3 OR (95%CI)
METS-IR Index	1.0315 (1.0253, 1.0377)	1.0379 (1.0311, 1.0447)	1.0330 (1.0258, 1.0403)
Categories			
Tertile 1	1	1	1
Tertile 2	1.8199 (1.4079, 2.3525)	1.9242 (1.4748, 2.5104)	1.8026 (1.3766, 2.3604)
Tertile 3	2.9243 (2.2957, 3.7250)	3.5126 (2.7205, 4.5354)	2.9859 (2.2853, 3.9014)

Model 1=no covariates were adjusted.
Model 2=Model 1+age, gender, race education, marital status were adjusted.
Model3=Model 2+, diabetes, blood pressure, PIR, total water, total kcal, total sugar, smoked, physical activity, alcohol use, serum cholesterol were adjusted.

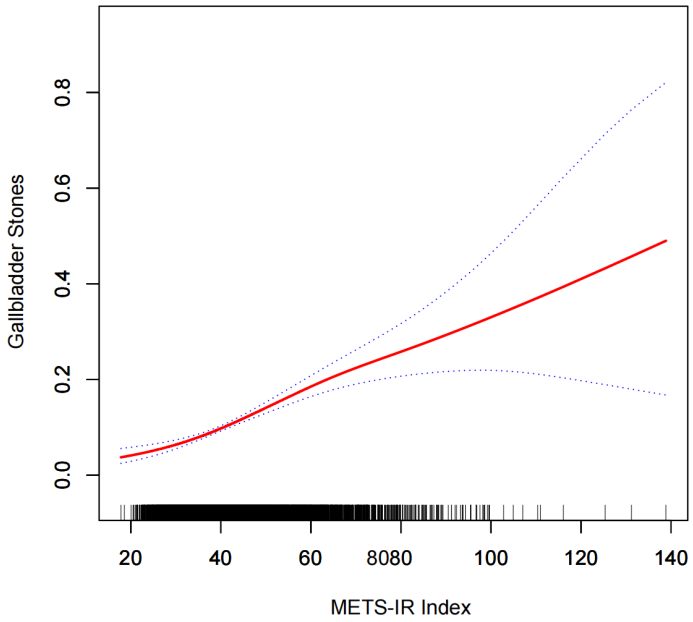

FIGURE 2
Densitometric dose-response relationship between METS-IR index and gallbladder stone prevalence. The area between the upper and lower dashed lines is indicated as the 95% CI. the red line is connected by the magnitude of the METS-IR index into a continuous line. Adjustments were made for all covariates except for effect modifiers.

TABLE 3 Subgroup analysis between METS-IR index with gallbladder stone prevalence.

Characteristic	Model 1 OR (95%CI)	Model 2 OR (95%CI)	Model 3 OR (95%CI)
Subgroup analysis stratified by gender			
Male	1.0226 (1.0110, 1.0344)	1.0283 (1.0154, 1.0414)	1.0206 (1.0064, 1.0350)
Female	1.0378 (1.0302, 1.0455)	1.0418 (1.0336, 1.0501)	1.0382 (1.0294, 1.0470)
Subgroup analysis stratified by age (years)			
20-39	1.0458 (1.0328, 1.0590)	1.0523 (1.0384, 1.0664)	1.0499 (1.0344, 1.0655)
40-59	1.0368 (1.0257, 1.0480)	1.0386 (1.0270, 1.0503)	1.0313 (1.0190, 1.0438)
60-80	1.0231 (1.0131, 1.0332)	1.0238 (1.0134, 1.0343)	1.0164 (1.0052, 1.0278)
Subgroup analysis stratified by hypertension			
YES	1.0262 (1.0174, 1.0352)	1.0341 (1.0243, 1.0441)	1.0265 (1.0161, 1.0370)
NO	1.0305 (1.0214, 1.0396)	1.0381 (1.0282, 1.0481)	1.0365 (1.0261, 1.0469)
Subgroup analysis stratified by diabetes			
YES	1.0227 (1.0112, 1.0344)	1.0320 (1.0182, 1.0459)	1.0299 (1.0155, 1.0444)
NO	1.0292 (1.0216, 1.0369)	1.0359 (1.0277, 1.0442)	1.0346 (1.0261, 1.0432)
Subgroup analysis stratified by race			
Mexican American	1.0238 (1.0091, 1.0386)	1.0341 (1.0176, 1.0509)	1.0273 (1.0100, 1.0450)
White	1.0322 (1.0230, 1.0416)	1.0399 (1.0298, 1.0500)	1.0351 (1.0241, 1.0463)
Black	1.0331 (1.0200, 1.0463)	1.0302 (1.0164, 1.0441)	1.0289 (1.0142, 1.0438)
Other Race	1.0329 (1.0157, 1.0504)	1.0449 (1.0261, 1.0641)	1.0361 (1.0153, 1.0572)

Model 1=no covariates were adjusted.
Model 2=Model 1+age, gender, race education, marital status were adjusted.
Model3=Model 2+, diabetes, blood pressure, PIR, total water, total kcal, total sugar, smoked, physical activity, alcohol use, serum cholesterol were adjusted.
The subgroup analysis was stratified by sex, race, age, diabetes and hypertension, not adjusted for the stratification variable itself.

3.4 METS-IR may be associated with earlier age at first gallbladder stone surgery

As a result of fully adjusted model 3, we found that each 1-unit increase in METS-IR index elevation was associated with 0.26 years earlier age at first gallbladder stone surgery (β= -0.26, 95% CI: -0.35, -0.17) (Table 4).

3.5 Analysis of the dose response and threshold effect of METS-IR on age at first gallbladder stone surgery

Using a generalized additive model and smoothed curve fitting, we examined the relationship between METS-IR index and the age at first gallbladder stone surgery. Figure 3 shows that METS-IR index and age at first gallbladder stone surgery are linearly correlated (negative).

4 Discussion

In a representative sample of US adults, this study demonstrated that METS-IR index increases were associated with an increase in gallbladder stoneprevalence of 3.3% for each unit increase in METS-IR index. Additionally, we found that elevated METS-IR was associated with an earlier age at first gallbladder stone surgery, a study that has never been published before. As a chronic disease causing morbidity, quality of life, and medical costs, gallbladder stones are especially important to prevent. These pressures continue to increase worldwide. Preventing gallbladder stones can be improved by finding populations that are adaptable to the METS-IR index.

TABLE 4 Analysis between METS-IR index with age at the first gallbladder stone operation.

Characteristic	Model 1 β (95%CI)	Model 2 β (95%CI)	Model 3 β (95%CI)
METS-IR Index	-0.24 (-0.33, -0.15)	-0.25 (-0.34, -0.17)	-0.26 (-0.35, -0.17)

Model 1=no covariates were adjusted.
Model 2=Model 1+age, gender, race education, marital status were adjusted.
Model3=Model 2+, diabetes, blood pressure, PIR, total water, total kcal, total sugar, smoked, physical activity, alcohol use, serum cholesterol were adjusted.

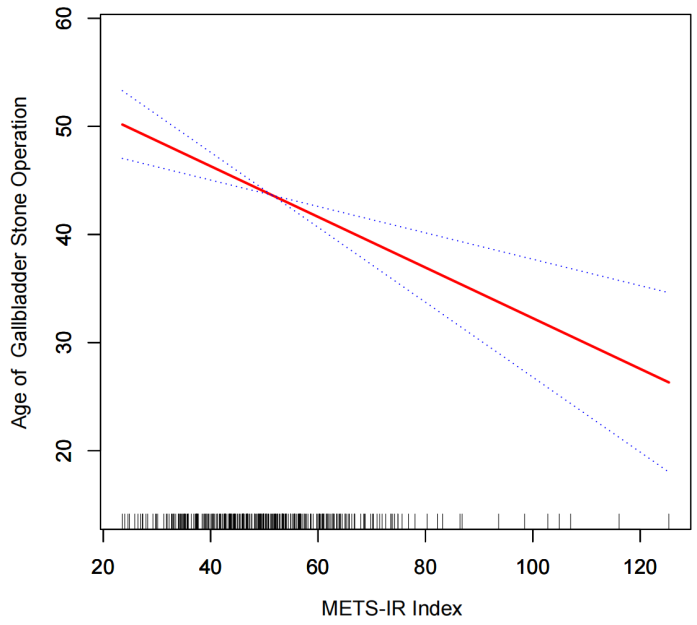

FIGURE 3
Dense dose-response relationship between METS-IR index and age at the time of first gallbladder stone surgery. The area between the upper and lower dashed lines is indicated as the 95% CI. the red line is connected by the magnitude of the METS-IR index into a continuous line. Adjustments were made for all covariates except for effect modifiers.

Consequently, we performed a sensitivity subgroup analysis and found that the METS-IR index is positively correlated with the prevalence of gallbladder stones in almost every population. However, when we performed a sensitivity subgroup analysis, we found that the METS-IR index was positively associated with the prevalence of gallbladder stones in almost all populations, but there were still subtle differences in the different subgroups. In fact, age as a risk factor for cholelithiasis remains controversial. Many studies have reported that age is the main risk factor for gallstones (11, 12), but some studies have found that the effects of metabolic syndrome and obesity on gallstones are stronger in younger participants (13). Therefore, further studies on the effect of age on gallbladder stones are still needed. As for the effect of gender on gallbladder stones, our results are consistent with previous studies reporting that in female patients (1, 14), more severe insulin resistance or metabolic syndrome is associated with a higher incidence of gallbladder stones. According to a Korean study (15), insulin resistance is associated with gallstones in non-hypertensive and non-diabetic individuals. Chen et al. (16) found that elevated METS-IR index was associated with increased asthma prevalence in non-hypertensive and non-diabetic populations, while Shen et al. (6) had similar findings in their study of METS-IR index and kidney stone prevalence. Although the above two studies were conducted on different subjects, they also reflect that our findings may be correct. There was a significant correlation between METS-IR index usage and age, sex, race, hypertension, and diabetes subgroups, indicating a high prevalence of METS-IR index use among gallbladder stone sufferers.

There are millions of people in developed countries suffering from gallstone disease. About 10-15% of the population is thought to be affected by the disease. It can occur at any age and in any gender, but women and people over 50 years of age tend to be more affected (17, 18). Gallbladder stones are most commonly treated with cholecystectomy, but about one-third of the population has surgical complications that persist for a long time and adversely affect their health (19, 20), such as dyspepsia and postoperative pain. When primary prevention strategies are identified to prevent gallbladder stones from forming, clinical outcomes may be significantly improved in patients with gallbladder stones. In this study, METS-IR was also found to be an important factor to consider when determining whether a gallbladder stone has to be surgically removed. According to our results, for every 1 unit increase in METS-IR index, the age at first gallbladder stone surgery will be advanced by 0.26 years. Smoothing curve fitting even showed a linear negative correlation of METS-IR for age at first gallbladder stone surgery. This finding is promising and has not yet been reported. We hypothesize that treatment and management of IR at a younger age may be beneficial in improving or reducing gallbladder stone occurrence. The veracity of this result may be limited by the sample size and needs to be further confirmed by a multicenter large sample prospective study.

The METS-IR index was first reported in 2018 as a practical and intuitive predictor of IR for clinical decision-making (6, 16). It has now been shown that IR can cause gallbladder stones to develop or become exacerbated in many studies, and visceral obesity and hepatic insulin resistance may be central to promoting cholesterol bile supersaturation and gallstone formation (21). Studies show that insulin resistance causes cholesterol supersaturated bile to be produced in high-risk Hispanic populations, resulting in altered gallbladder function leading to gallbladder stones (8). Gallbladder stone formation may also be related to insulin resistance in postmenopausal Korean women with abdominal obesity (22). The formation of cholesterol gallstones was significantly predisposed to mice with isolated hepatic insulin resistance (LIRKO mice), which are deficient in insulin receptors in the liver (23). Another *in vivo* experiment showed that mice with high protein and high quality diets developed sludge and gallstones more quickly (7). According to one study, pioglitazone is an antidiabetic that prevents gallstone formation, liver damage, and gallbladder damage, and guinea pigs treated with pioglitazone showed beneficial changes in the biliary cholesterol and bile acids, blood glucose, insulin, and lipid distribution (24). All of the above reports suggest that IR plays a key role in the development of gallbladder stones, and the fact that METS-IR index is positively correlated with IR levels could explain the association of higher METS-IR indexes with increased prevalence of gallbladder stones.

It has several advantages, including the fact that NHANES represents the U.S. population and follows a rigorous study protocol with extensive quality assurance and quality control. Furthermore, our results were adjusted for confounding covariates to ensure that they would be reliable and applicable to a wider variety of individuals. It is important to note, however, that our study is not without limitations. Since our study was based on the NHANES database, which is a cross-sectional study, we were unable to establish a causal link between the METS-IR index and gallbladder stones. As a second limitation, gallbladder stones were diagnosed based on a questionnaire, which is prone to recall bias. Finally, the database did not provide detailed clinical variables, such as medication history and specific stone composition. While the present study has some limitations, it was able to demonstrate a correlation between METS-IR index and the prevalence of gallbladder stones and the age at which gallbladder stones were first discovered.

5 Summary

A higher METS-IR index is associated with an earlier prevalence of gallbladder stones and an earlier age of first gallbladder stone surgery. Although a causal relation between the relationship is not established, treating and giving IR at a

young age may improve or minimize the occurrence of gallbladder stones and postpone the age of first gallbladder stone operation.

Data availability statement

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

Ethics statement

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

Author contributions

Data analysis and manuscript writing: JW, MC. Study design and statistical advice: JW, JY, YC. Manuscript editing: JY, YC, JR, MX. Validation and review: YC, JR, MX. Quality control: MC. All authors agreed on the journal to which the article was to be submitted and agreed to take responsibility for all aspects of the work.

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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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Positive association between weight-adjusted-waist index and hyperuricemia in patients with hypertension: The China H-type hypertension registry study

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Background and aims: The relationship between the new obesity index weight-adjusted-waist index (WWI) and hyperuricemia is unclear. We aimed to explore the association of the WWI and hyperuricemia among the hypertensive population.

Methods: A total of 14,078 hypertension participants with complete data were included in our study. WWI was calculated by waist circumference divided by the square root of weight. Specifically, men with 420 μmol/L and women with 360 μmol/L were considered to have hyperuricemia.

Results: The prevalence of hyperuricemia was 61.1% in men and 51.4% in women. On the whole, multivariate logistic regression analyses found that there was a linear positive correlation of WWI with hyperuricemia in both men (OR: 1.37; 95%CI: 1.25, 1.49) and women (OR: 1.35; 95%CI: 1.26, 1.45). Subgroup analysis found that the relationship between WWI and hyperuricemia was stable in stratified subgroups (all *P*-interactions >.05).

Conclusion: WWI showed a positive association with hyperuricemia among hypertension patients.

KEYWORDS

weight-adjusted-waist index, hyperuricemia, hypertension, obesity, Chinese population

Introduction

The incidence rate and prevalence of hyperuricemia are on the rise worldwide. Based on the results of two nationally representative cross-sectional surveys conducted in China, the prevalence of hyperuricemia among Chinese adults has risen from 11.1% in 2015–2016 to 14.0% in 2018–2019 (1). Survey data in America indicates that hyperuricemia affected about 43.3 million people and was prevalent in 21.4% of the population (2). In Japan, approximately 25.8% suffered from hyperuricemia (3). Hyperuricemia can cause kidney stones and gout (4). In addition, high serum uric acid (SUA) is also closely related to hypertension (5), cardiovascular disease (6), chronic kidney disease (7), diabetes (8), and obesity (9). The long-term prevention and treatment of hyperuricemia causes a heavy burden on economic development and people's lives and health worldwide. Therefore, we urgently need to find a changeable and measurable index to reduce the occurrence of hyperuricemia risk events.

Uric acid is the final metabolite of human purine compounds and is mainly excreted by the kidney. Hyperuricemia results from the body producing too much uric acid or excreting it insufficiently (10). Relevant studies show that excessive fat deposition in obese patients acts on the liver and adds to the production of uric acid (11). In addition, obesity can also cause insulin resistance, raise the risk of kidney damage, and impair uric acid elimination from the kidney (12, 13). It is worth noting that a variety of cytokines secreted by adipocytes also promote the production of uric acid through the regulation of the human metabolism (14). Many epidemiological studies have found that body mass index (BMI), which is the commonly used obesity index, has been related to SUA and hyperuricemia for a long time (15–17). Recently, obesity based on BMI has been questioned. BMI cannot distinguish between fat and muscle mass, so its association with hyperuricemia is not stable. A cross-sectional study conducted by Huang et al. in 1284 members of the Chinese general population found that there was no significant relationship between BMI and hyperuricemia (18). Accordingly, increasing studies have explored the connection between new obesity indicators, SUA, and hyperuricemia. The weight-adjusted-waist index (WWI) is a new obesity anthropometric index proposed in 2018 (19). Compared with BMI, WWI can better distinguish fat and muscle mass components, and it mainly reflects the problem of central obesity and is not affected by weight (20).

As we all know, obesity is a risk element for hypertension (21). Previous epidemiological studies also show that hyperuricemia is an independent risk factor for hypertension (22). Relevant studies confirm, that WWI can predict the occurrence of hypertension and is better than BMI (23). However, there is no study to explore the effect of WWI on SUA level and hyperuricemia in hypertensive patients. Considering the higher risk of adverse events in this high-risk group, it is essential to make clear the exact association between WWI, SUA level, and hyperuricemia in patients with hypertension. Therefore, this study aims to assess the association between WWI, SUA level, and hyperuricemia risk in the Chinese H-type hypertension population and clarify the dose-response relationship between them to provide the basis for early identification of patients with hyperuricemia.

Methods

Participants

The data analyzed in this study was derived from the China Hypertension Registry Study (Registration number: ChiCTR1800017274). The research design and methods have been published in previous articles (24). Briefly, the study was conducted in Wuyuan County in Jiangxi Province of China. Patients with hypertension and aged ≥18 years were eligible participants. Any one of sitting systolic blood pressure (SBP) ≥140 mmHg, diastolic blood pressure (DBP) ≥90 mmHg, or taking antihypertensive agents was regarded as hypertension. The exclusion criteria of this study included (1) inability to prove informed consent due to psychological or nervous system injury, (2) not able to follow up according to the protocol or due to a planned relocation, and (3) study physicians deem patient not suitable for inclusion or unable to complete follow-up. The ethics committee of the Institute of Biomedical Research of Anhui Medical University approved the protocol. All participants signed informed consent.

A total of 14,268 participants completed the survey. We excluded participants who were nonhypertensive (n = 34) and had data missing (n = 156). Finally, 14,078 participants were enrolled in our analysis (Figure S1).

Data collection

Demographic information, including sex, age, lifestyle data (smoking and drinking), medication information, and medical history, was gathered by questionnaire used by the research staff. After having a rest for 10 minutes, an electronic sphygmomanometer (Omron; Dalian, China) was used to acquire the participants' information on blood pressure; the measurement was repeated three times with an interval of 1 minute. The mean value of three independent measurements for SBP and DBP were taken for analysis. Blood samples were obtained by venipuncture at baseline and processed and analyzed at Biaojia Biotechnology, sited in Shenzhen in Guangdong Province, China, for homocysteine, serum total cholesterol, triglyceride, uric acid, high density lipoprotein, low density lipoprotein, and eGFR.

Anthropometric measurements

Anthropometric indices, such as height, weight, and waist circumference (WC), were also collected. The height was obtained by using a fixed vertical ruler and standard right angle device on participants without shoes. Weight was also gained without shoes. WC was measured when standing with a tape measure at the end of expiration. BMI was calculated by dividing body weight (kg) by the square of height (m). WWI was calculated as WC (cm) divided by the square root of weight (kg) (19).

Based on previous studies on obesity and hyperuricemia, we divided WWI into four groups according to its quartile. WWI quartiles in males were defined as follows: <10.4 cm/√kg (Q 1), ≥10.4 and <10.8cm/√kg (Q 2), ≥10.8 and <11.2 cm/√kg (Q 3), and ≥11.2 cm/√kg (Q 4). WWI quartiles in females were <10.8 cm/√kg (Q 1), ≥10.8 and <11.3cm/√kg (Q 2), ≥11.3 and <11.8 cm/√kg (Q 3), and ≥11.8 cm/√kg (Q 4).

Definition of hyperuricemia

The level of SUA in the present study was measured by automated clinical analyzers (Beckman Coulter). Specifically, men with 420 μmol/L and women with 360 μmol/L were considered to have hyperuricemia (25, 26).

Statistical analysis

Baseline characteristics described continuous variables with mean ± SD and categorical variables with percentage (%). The Chi-square (x2) tests or ANOVA were used to evaluate the differences among the groups by WWI quartiles. Multivariate logistic regression was used to evaluate the OR and 95% CI of the correlation between WWI and hyperuricemia. The fitted smoothing curve and generalized additive model were also used to examine the dose-response correlation of WWI with SUA and the risk of hyperuricemia. At the same time, we converted WWI into classification variables and calculated the *P* trend value. We constructed three models to evaluate the independent correlation between WWI with SUA and hyperuricemia. Model 1 was a crude model, unadjusted. Model 2 was adjusted for age, current smoking, and current drinking. Model 3 was adjusted for age, current smoking, current drinking, heart rate, stroke, Diabetes mellitus, coronary heart disease, antihypertensive drugs, lipid-lowering drugs, glucose-lowering drugs, homocysteine, serum total cholesterol, triglyceride, high density lipoprotein, low density lipoprotein, and eGFR. All the covariates were selected on the basis of their clinical importance, statistical significance in the univariable analyses, and the estimated variables change of at least 10% of potential confounding effects (27). Moreover, we also performed subgroup analyses to test the robustness of the results in different subgroups.

The statistical package R (R Foundation for statistical Computing) and Empower (R) (www.empowerstats.com) were used to perform all analyses. A two-tailed *P* <.05 was deemed statistically significant.

Results

Baseline characteristics of study participants

The quartiles of the WWI show participants' baseline characteristics in Table 1: 6695 men and 7383 women with hypertension with complete data were brought into the final analysis. The mean age of men was 63.8 ± 9.8 years and that of women was 63.9 ± 8.9 years. The mean WWI of men was 10.8 ± 0.7 cm/√kg and that of women was 11.4 ± 0.8 cm/√kg. The BMI, WC, coronary heart disease, glucose-lowering drugs, and uric acid were significantly higher in the higher WWI group in both men and women. In men, higher WWI levels were correlated with higher levels of antihypertensive drugs, triglycerides, low density lipoprotein, and lower levels of current drinkers and current smokers. In women, stroke and homocysteine were significantly higher and eGFR levels were lower in the group with higher WWI.

Association between WWI and hyperuricemia

Table 2 describes the results of multivariate regression for correlation analyses of WWI with hyperuricemia. Generally, there were significant positive associations of WWI and hyperuricemia in both men and women. After fully adjusting for confounding factors, per one unit increase in WWI, the risk of hyperuricemia was raised by 37% (OR: 1.37; 95% CI: 1.25, 1.49) among men and by 35% (OR: 1.35; 95% CI: 1.26, 1.45) among women. Then, we grouped WWI as the categorical variable for further analysis. Among men, in model 3, compared with Q1, the risk of hyperuricemia was found raised in Q2 (OR: 1.25; 95% CI: 1.07, 1.45), Q3 (OR: 1.52; 95% CI: 1.30, 1.77), and Q4 (OR: 1.77; 95% CI: 1.50, 2.08), respectively (*P* for trend <.001). Among women, also taking the lowest quartile (Q1) as the reference group, the incidence of hyperuricemia raised with the increase of WWI, Q2 (OR: 1.20; 95% CI: 1.03, 1.39), Q3 (OR: 1.51; 95%CI: 1.30, 1.75), and Q4 (OR: 1.98; 95% CI 1.69, 2.31) respectively (*P* for trend <.001). The positive correlation between WWI with SUA both in men and women are shown in Table S1.

We also used the fitted smoothing curve and generalized additive model to confirm the linearly positive association between WWI with SUA and hyperuricemia for men and women (Figure 1, Figure S2).

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TABLE 1 Baseline characteristics of participants stratified by quartiles of weight-adjusted-waist index (WWI).

Variables	Total	WWI (cm/√kg)				P value
		Q1 (<10.4)	Q2 (≥10.4, <10.8)	Q3 (≥10.8, <11.2)	Q4 (≥11.2)	
Men						
n	6695	1674	1673	1674	1674	
Age, y	63.8 ± 9.8	63.5 ± 9.4	62.7 ± 9.8	63.3 ± 10.0	65.7 ± 9.7	<0.001
BMI, kg/m2	23.4 ± 3.9	21.4 ± 4.7	23.2 ± 3.2	24.1 ± 3.0	24.9 ± 3.5	<0.001
WC, cm	84.3 ± 9.9	75.0 ± 7.4	82.9 ± 7.4	87.1 ± 7.1	92.3 ± 8.5	<0.001
Heart rate, bpm	74.6 ± 13.9	73.0 ± 13.7	73.7 ± 13.5	74.8 ± 13.2	76.9 ± 14.9	<0.001
Stroke, n (%)	566 (8.5)	136 (8.1)	133 (7.9)	146 (8.7)	151 (9.0)	0.652
Diabetes mellitus, n (%)	1068 (16.0)	183 (10.9)	226 (13.5)	314 (18.8)	345 (20.6)	<0.001
Coronary heart disease, n (%)	368 (5.5)	74 (4.4)	78 (4.7)	93 (5.6)	123 (7.3)	<0.001
Current smoking, n (%)	3236 (48.3)	878 (52.5)	788 (47.1)	787 (47.0)	783 (46.8)	0.002
Current drinking, n (%)	2668 (39.9)	693 (41.4)	682 (40.8)	666 (39.8)	627 (37.5)	0.096
Medication use, n (%)						
Antihypertensive drugs	4324 (64.6)	1055 (63.1)	1068 (63.8)	1081 (64.6)	1120 (66.9)	0.109
Lipid-lowering drugs	235 (3.5)	50 (3.0)	53 (3.2)	73 (4.4)	59 (3.5)	0.138
Glucose-lowering drugs	287 (4.3)	47 (2.8)	58 (3.5)	83 (5.0)	99 (5.9)	<0.001
Laboratory results, mean						
Homocysteine, μmol/L	20.6 ± 13.8	20.5 ± 13.3	20.2 ± 13.3	20.6 ± 14.7	20.9 ± 13.9	0.573
Serum total cholesterol, mmol/L	4.9 ± 1.1	4.9 ± 1.0	4.9 ± 1.0	5.0 ± 1.1	5.0 ± 1.1	0.006
Triglyceride, mmol/L	1.7 ± 1.3	1.3 ± 1.1	1.7 ± 1.2	1.8 ± 1.4	1.9 ± 1.2	<0.001
Uric acid, mmol/L	465.6 ± 118.7	443.3 ± 113.2	459.5 ± 114.0	474.0 ± 119.7	485.7 ± 123.5	<0.001
High density lipoprotein, mmol/L	1.5 ± 0.4	1.7 ± 0.5	1.5 ± 0.4	1.5 ± 0.4	1.4 ± 0.4	<0.001
Low density lipoprotein, mmol/L	2.8 ± 0.8	2.7 ± 0.7	2.8 ± 0.8	2.9 ± 0.8	3.0 ± 0.8	<0.001
eGFR, mL/min/1.73 m^2	85.7 ± 20.4	86.6 ± 20.7	86.8 ± 19.9	86.1 ± 20.6	83.3 ± 20.2	<0.001
		Q1 (<10.8)	Q2 (≥10.8, <11.3)	Q3 (≥11.3, <11.8)	Q4 (≥11.8)	*P value*
Women,						
n	7383	1846	1845	1846	1846	
Age, y	63.9 ± 8.9	61.0 ± 9.3	62.9 ± 8.4	64.3 ± 8.3	67.3 ± 8.5	<0.001
BMI, kg/m2	23.8 ± 3.6	22.1 ± 3.5	23.5 ± 3.2	24.5 ± 3.4	25.1 ± 3.5	<0.001
WC, cm	83.4 ± 9.8	74.3 ± 7.4	81.7 ± 6.8	86.1 ± 7.3	91.4 ± 8.5	<0.001
Heart rate, bpm	78.6 ± 14.2	78.1 ± 15.3	78.1 ± 13.5	78.3 ± 13.9	79.9 ± 13.8	<0.001
Stroke, n (%)	409 (5.5)	93 (5.0)	97 (5.3)	107 (5.8)	112 (6.1)	0.497
Diabetes mellitus, n (%)	1520 (20.6)	262 (14.2)	373 (20.2)	417 (22.6)	468 (25.4)	<0.001
Coronary heart disease, n (%)	360 (4.9)	82 (4.4)	83 (4.5)	84 (4.6)	111 (6.0)	0.076
Current smoking, n (%)	406 (5.5)	88 (4.8)	95 (5.2)	87 (4.7)	136 (7.4)	<0.001
Current drinking, n (%)	380 (5.1)	93 (5.0)	95 (5.2)	104 (5.6)	88 (4.8)	0.687
Medication use, n (%)						
Antihypertensive drugs	4797 (65.0)	1121 (60.7)	1220 (66.2)	1218 (66.0)	1238 (67.1)	<0.001
Lipid-lowering drugs	266 (3.6)	55 (3.0)	77 (4.2)	67 (3.6)	67 (3.6)	0.284
Glucose-lowering drugs	456 (6.2)	68 (3.7)	108 (5.9)	132 (7.2)	148 (8.0)	<0.001
Laboratory results, mean						
Homocysteine, μmol/L	15.8 ± 7.3	15.5 ± 7.9	15.6 ± 6.9	15.7 ± 7.0	16.4 ± 7.4	<0.001
Serum total cholesterol, mmol/L	5.4 ± 1.1	5.3 ± 1.1	5.4 ± 1.2	5.4 ± 1.1	5.3 ± 1.2	<0.001
Triglyceride, mmol/L	1.9 ± 1.3	1.6 ± 1.1	2.0 ± 1.3	2.0 ± 1.3	2.1 ± 1.3	<0.001
Uric acid, mmol/L	379.0 ± 106.0	355.3 ± 99.7	372.7 ± 103.9	383.6 ± 104.3	404.3 ± 110.1	<0.001
High density lipoprotein, mmol/L	1.6 ± 0.4	1.7 ± 0.4	1.6 ± 0.4	1.6 ± 0.4	1.5 ± 0.4	<0.001
Low density lipoprotein, mmol/L	3.1 ± 0.8	3.0 ± 0.8	3.2 ± 0.8	3.2 ± 0.8	3.2 ± 0.8	<0.001
eGFR, mL/min/1.73 m^2	89.8 ± 19.6	92.6 ± 19.1	91.1 ± 19.1	90.1 ± 18.8	85.5 ± 20.5	<0.001

BMI, Body mass index; WC, waist circumference; eGFR, estimated glomerular filtration rate.

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TABLE 2 Association between the weight-adjusted-waist index and hyperuricemia in different models.

WWI (cm/√kg)	N	Events, n (%)	Model 1		Model 2		Model 3	
			OR	95% CI	OR	95% CI	OR	95% CI
Men								
Per 1unit increment	6695	4090 (61.1)	1.42	1.32, 1.54	1.43	1.33, 1.55	1.37	1.25, 1.49
Q1 (<10.4)	1674	880 (52.6)	1		1		1	
Q2 (≥10.3, <10.8)	1673	1002 (59.9)	1.35	1.17, 1.55	1.33	1.16, 1.53	1.25	1.07, 1.45
Q3 (≥10.8, <11.2)	1674	1072 (64.0)	1.61	1.40, 1.85	1.60	1.39, 1.84	1.52	1.30, 1.77
Q4 (≥11.2)	1674	1136 (67.9)	1.91	1.66, 2.19	1.93	1.68, 2.23	1.77	1.50, 2.08
P for trend				<0.001		<0.001		<0.001
Women								
Per 1unit increment	7383	3797 (51.4)	1.45	1.37, 1.55	1.41	1.32, 1.50	1.35	1.26, 1.45
Q1 (<10.8)	1846	762 (41.3)	1		1		1	
Q2 (≥10.8, <11.3)	1845	895 (48.5)	1.34	1.18, 1.53	1.31	1.15, 1.49	1.20	1.03, 1.39
Q3 (≥11.3, <11.8)	1846	994 (53.8)	1.66	1.46, 1.89	1.60	1.40, 1.82	1.51	1.30, 1.75
Q4 (≥11.8)	1846	1146 (62.1)	2.33	2.04, 2.66	2.18	1.90, 2.50	1.98	1.69, 2.31
P for trend				<0.001		<0.001		<0.001

Model 1 was adjusted for none.
Model 2 was adjusted for Age, Current smoking, Current drinking.
Model 3 was adjusted for Age, Current smoking, Current drinking, Heart rate, Stroke, Diabetes mellitus, Coronary heart disease, Antihypertensive drugs, Lipid-lowering drugs, Glucose-lowering drugs, Homocysteine, Serum total cholesterol, Triglyceride, High density lipoprotein, Low density lipoprotein, eGFR.

Sensitivity analyses

We also conducted a sensitivity analysis to assess whether BMI has a confounding effect on the association of WWI and the risk of hyperuricemia. As shown in Table S2, the correlation of WWI (continuous and categorical variables) with hyperuricemia was not changed by adjusting BMI. Even when BMI was well-controlled (normal BMI: ≥18.5, <24 Kg/m2), the correlation of WWI and hyperuricemia remain significant (Table S3).

Subgroup analyses

To confirm whether the correlation of WWI with hyperuricemia is stable in different subgroups, subgroup analyses were performed (Figures 2, 3). The results show that no significant differences were found in the subgroups of age, BMI, current smoking, current drinking, antihypertensive agents, and eGFR among both men and women (all *P* for interaction >.05).

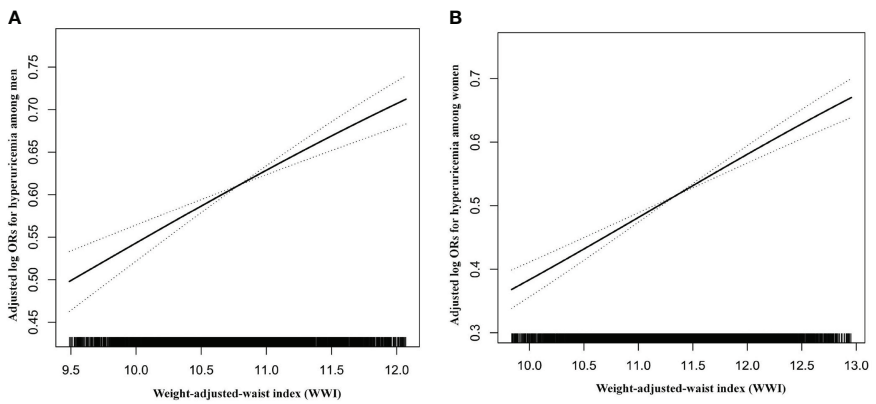

FIGURE 1
Dose–response relationship between WWI and hyperuricemia. **(A)** Men; **(B)** Women. All adjusted for age, heart rate, stroke, diabetes mellitus, coronary heart disease, current smoking, current drinking, antihypertensive drugs, lipid-lowering drugs, glucose-lowering drugs, homocysteine, serum total cholesterol, triglyceride, high density lipoprotein, low density lipoprotein, and eGFR.

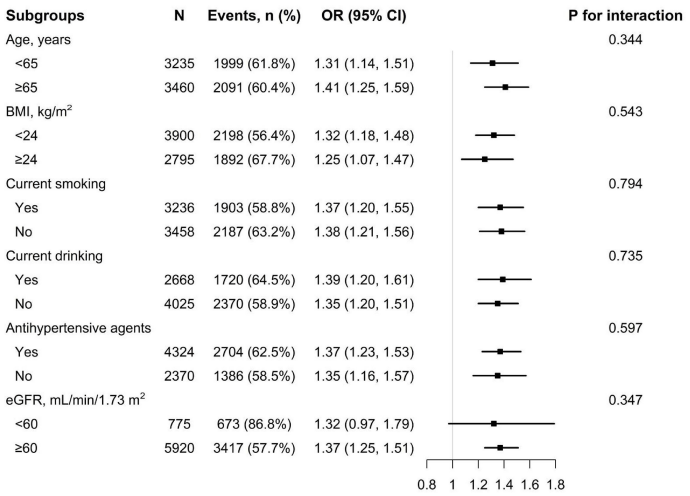

FIGURE 2
Subgroup analysis of the association between WWI and hyperuricemia among men. Each subgroup analysis is adjusted if not stratified for age, heart rate, stroke, diabetes mellitus, coronary heart disease, current smoking, current drinking, antihypertensive drugs, lipid-lowering drugs, glucose-lowering drugs, homocysteine, serum total cholesterol, triglyceride, high density lipoprotein, low density lipoprotein, and eGFR.

Discussion

In this cross-sectional study based on a large sample size, we examined the correlation of WWI, a new obesity index, with hyperuricemia in people with hypertension for the first time. In the fully adjusted model, we found a positive correlation of WWI with SUA level and the risk of hyperuricemia in both men and women, and these results were stable in subgroup analyses. Even after adjusting for BMI and when BMI was well-controlled (normal BMI: ≥18.5, <24 Kg/m2), the results remain significant.

Previous studies report that the traditional obesity index, BMI, is related to SUA and hyperuricemia changes. A large cross-sectional study included 90,047 Japanese and 14,734 American participants, and the results showed that higher BMI was an independent risk element for hyperuricemia in both Japanese and American populations (15). Previously,

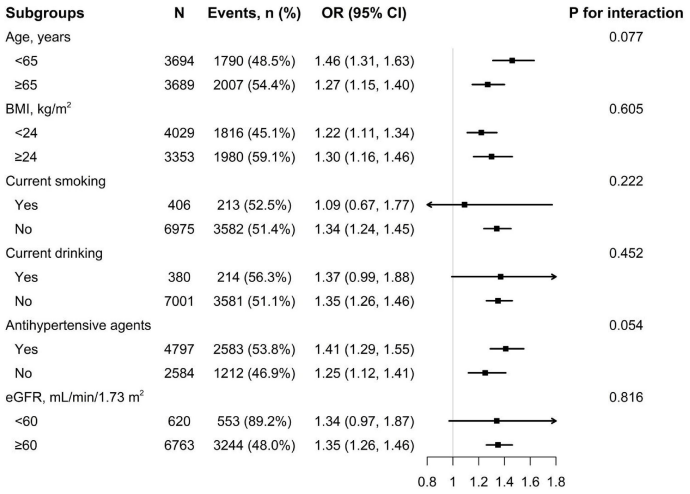

FIGURE 3
Subgroup analysis of the association between WWI and hyperuricemia among women. Each subgroup analysis is adjusted if not stratified for age, heart rate, stroke, diabetes mellitus, coronary heart disease, current smoking, current drinking, antihypertensive drugs, lipid-lowering drugs, glucose-lowering drugs, homocysteine, serum total cholesterol, triglyceride, high density lipoprotein, low density lipoprotein, and eGFR.

Ishizaka et al. conducted a 2-year routine health screening for 3153 participants and analyzed their data, demonstrating that there was a positive correlation of BMI with SUA concentration (16). Similarly, through the retrospective analysis of 39,736 healthy subjects, Wang et al. reported that BMI was positively correlated with SUA (17). Compared with those who were underweight (BMI < 18.5kg/m^2), the prevalence of hyperuricemia in overweight people (BMI: 23–27.5kg/m^2) was about 2.98 times more and that in obese people (BMI ≥ 27.5kg/m^2) was 5.96 times more. However, another study, also aimed at the Chinese population, indicated that there was a short-of-significant correlation of BMI with hyperuricemia (18). This phenomenon may be due to the limitation of BMI (28) and the existence of the obesity paradox (16, 29).

In order to better explore the correlation between obesity and hyperuricemia, some recent studies tend to use nontraditional obesity indicators as a measure of obesity to examine the exact relationship between them. A cross-sectional study of 174,698 Chinese adults by Liu et al. aimed to explore the correlation between new obesity indicators and hyperuricemia. The results show that, after adjusting for confounding factors, the cardiometabolic index (CMI) and lipid accumulation product (LAP) index highest quartile groups' OR were 2.049 (95%CI: 1.824, 2.302; p <.001) and 4.332 (95%CI:3.938, 4.765; p <.001), respectively (30). Another cross-sectional study of 1284 ordinary people by Huang et al. showed that, after dividing the fatty liver index (FLI) and visceral adiposity index (VAI) into three groups, the risk of hyperuricemia in the highest third was 3.58 and 3.11 times that in the lowest third (18). Previously, a cross-sectional study of 11,345 participants found that both the body roundness index (BRI) and body shape index (ABSI) were significantly associated with hyperuricemia (31). However, most of these nontraditional obesity indicators are complex to calculate and have poor operability in practical application, and they were discussed in the general population.

WWI is a new obesity anthropometric index (19) proposed by Park et al. in 2018. It is calculated as WC (cm) divided by the square root of weight (kg), and under this background, WWI may weaken the correlation with BMI so as to mainly reflect the true central obesity independent of body weight. In a cross-sectional study of 602 65-year-old participants in the Anshan geriatric study, Kim et al, found that WWI can better distinguish fat and muscle mass components compared with BMI (20). Similarly, the prospective cohort study conducted by Ding et al. in 12,447 hypertensive participants also confirmed that WWI can better identify obesity than BMI to a certain extent (32). It is well-known that hypertension is a high-risk element for hyperuricemia (33). Li et al. conducted a cohort study containing 10,338 nonhypertensive participants and found that, compared with the lowest group of the four WWI groups, the risk ratio of hypertensive events in the highest group was 1.50 (95% CI: 1.24, 1.82; P <.001); that is, WWI was significantly correlated with the risk of hypertension (23). However, data on the impact of WWI on the high-risk population with high SUA hypertension is still lacking. In our study, we first report a positive correlation between WWI and hyperuricemia in patients with hypertension, and this relationship was stable even after adjusting for BMI and when BMI was well-controlled (normal BMI: ≥18.5, <24 Kg/m^2).

The potential mechanism of the positive correlation between WWI and hyperuricemia can be explained by the role of abdominal fat as a marker of ectopic fat excess. The increase of WWI may reflect the dysfunction of adipose tissue, thereby causing an increase in uric acid secretion and inhibiting uric acid excretion. First, excessive fat deposition in obese patients will act on the liver, affect the metabolism of purine (34), and raise the production of uric acid (11). Second, obesity can cause insulin resistance, raise the risk of renal damage, and then damage the renal treatment of uric acid (12, 13). It is worth noting that a variety of cytokines secreted by adipocytes (such as adipokines and leptin) also promote the production of uric acid through the regulation of human metabolism (14, 35, 36).

The main advantages of our study were the large population-based sample size, including a large number of patients with hypertension, and subgroup analysis to test the robustness of the results. However, this study also has some limitations that need attention. First, this study was a cross-sectional design, so we were unable to determine the causal relationship correlation of WWI with hyperuricemia. Second, although we adjusted for possible covariates, the potential residual confounding factors may still exist. Third, recent epidemiological studies show that dietary factors are also a cause of hyperuricemia (37); however, our study did not collect the dietary status of uric acid metabolism, such as seafood and animal offal. Fourth, information on the use of drugs to reduce uric acid was not collected and may affect the diagnosis of hyperuricemia. However, considering that other studies did not include this factor, we believe that our results are still reliable. Fifth, the participants in this study are mainly concentrated in southern China. Therefore, whether these conclusions can be extrapolated to other nationalities remains to be further studied.

Conclusion

In the hypertensive population, we found an independent positive relationship of WWI and the occurrence of hyperuricemia risk events. The results suggest that the WWI index can be used as a simple and effective intervention indicator and may have preventive value for the hyperuricemia population in southern China.

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

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The protocol was approved by the ethics committee of the Institute of biomedical research of Anhui Medical University. All participants provided written informed consent before entering the study.

Author contributions

PZ wrote the manuscript. PZ, YX, and YS participated in the literature search, data analysis, and data interpretation. WS extracted and collected data. XS, GQ, CD, JL, WZ, CY, TW, and LZ conceived of the study and participated in its design and coordination. XC and HB participated in the study design and provided critical revision. All authors read and approved the final manuscript.

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Conflict of interest

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

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2022.1007557/full#supplementary-material

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Association between body fat distribution and kidney stones: Evidence from a US population

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Objectives: We aimed to evaluate the relationship between the proportion of Android to Gynoid ratio and the incidence of kidney stones among US adults.

Methods: Participants aged 20-59 years from the 2011-2018 National Health and Nutrition Examination Survey (NHANES) database were selected to assess the association between Android to Gynoid ratio and kidney stone prevalence using logistic regression analysis, subgroup analysis and calculation of dose-response curves.

Results: This study ultimately included 10858 participants, of whom 859 self-reported a history of kidney stones. And after adjusting for all confounders, an increased Android to Gynoid ratio was associated with an increased prevalence of kidney stones (OR=2.75, 95% CI:1.62-4.88). And subgroup analysis showed an increased prevalence of kidney stones in women (OR=3.55, 95% CI: 1.54-8.22), non-diabetic (OR=2.59, 95% CI: 1.45-4.60), 60 > age ≥ 40 years (OR=3.51, 95% CI: 1.83-6.71), Mexican-American (OR=4.35, 95% CI: 1.40- 13.53) and white (OR=3.86, 95% CI: 1.82-8.18) groups, there was a significant positive association between A/G ratio and kidney stones. In contrast, in the hypertensive subgroup, the A/G ratio was associated with kidney stones in all groups.

Conclusions: Higher Android to Gynoid ratio is associated with a high prevalence of kidney stone disease.

KEYWORDS

kidney stones, Android to Gynoid ratio, obesity, fat distribution, DXA

Abbreviations: NHANES, National Health and Nutrition Examination Survey; OR, Odds ratio; CI, Confidence interval; A/G ratios, Android to Gynoid ratio; DXA, Dual-energy X-ray absorptiometry; US, United States; PIR, Ratio of family income to poverty; KSD, Kidney stones disease; BMI, Body mass index.

Introduction

Kidney stones disease (KSD) are among the most common and common diseases in urology and are caused by the abnormal accumulation of certain crystalline substances (such as calcium oxalate, calcium phosphate, uric acid, and drugs) in the kidney and are characterized by high prevalence and easy recurrence (1–3). A study based on data from the National Health and Nutrition Examination Survey (NHANES) reported that the prevalence of self-reported kidney stones in the United States was 11%, and the prevalence was 2% (4), which is an approximately 2.5-fold increase from the national prevalence (3.2%) in 1980 (5). Despite the fact that there are many treatment options for kidney stones, including extracorporeal shock wave lithotripsy (ESWL), rigid or flexible ureteroscopic stone extraction (URS/RIRS), and percutaneous nephrolithotripsy (PCNL), there is no single therapy that can cure them completely. The recurrence rate of kidney stones is 11% at two years, about 20% at five years, and up to 60% at five years in patients with recurrent attacks (6, 7). Without timely and effective treatment, kidney stones may cause extremely serious consequences such as permanent kidney damage and end-stage renal disease (8, 9). Furthermore, the costs associated with stone disease have risen significantly, with one study showing that kidney stone costs increased from approximately $2 billion in 2000 to over $3.79 billion in 2007 (10). Kidney stones have now become a very serious public health problem. Therefore it is of critical importance to investigate the risk factors for kidney stones and to take appropriate measures to prevent their occurrence.

Obesity has now become one of the serious health problems affecting the health of the global population (11, 12). Obesity can increase the risk of KSD (13, 14). Nevertheless, previous studies have primarily used body mass index (BMI) to assess obesity. Although BMI data are readily available and easy to calculate, they do not distinguish between adipose tissue, muscle tissue, and the distribution of adipose tissue throughout the body and are subject to inter- and intra-examiner variations. Sometimes even contradictory results are obtained (15). The reason may be that adults with similar BMIs have different fat distributions (16), and different fat distributions may have different health implications (17). For example, a lower risk of cardiometabolic dysfunction was observed in patients with gynoid fat distributions (characterized by preferential fat deposition in the buttocks and thighs, also referred to as pear patterns) compared to people with Android patterns (characterized by increased fat deposited in the trunk region, also referred to as apple patterns) (18).

For measuring body fat content and distribution, computed tomography (CT) and magnetic resonance imaging (MRI) are often considered the gold standard. However, the high radiation produced by CT, the lengthy acquisition and analysis times associated with MRI, and the higher costs of both techniques have limited their use in clinical and research settings. Dual-energy X-ray absorptiometry (DXA), on the other hand, is also sufficiently accurate and involves less radiation exposure, a shorter scan time, and a lower cost (19–21). Furthermore, DXA is well correlated with CT/MRI for measuring fat mass (FM) (19). Therefore, DXA measurements are increasingly being used in studies to assess the connection between obesity and a range of diseases (20, 22, 23).

An Android to Gynoid ratio (A/G ratio) is a DXA-based fat distribution index. Numerous studies have shown that the A/G ratio is strongly associated with insulin resistance and cardiovascular disease (24, 25), both of which are risk factors for KSD (26–28). Nevertheless, it remains unclear whether this potentially different fat distribution affects the prevalence of KSD. Therefore, in the present study, we aimed to assess the relationship between the A/G ratio and the prevalence of KSD in the United States (US) population.

Materials and methods

Study population

Data for the evaluation of this study were obtained from NHANES from 2011 to 2018. This is a survey conducted by the Centers for Disease Control and Prevention (CDC) every two years for public health surveillance in the U.S. The NHANES study protocol was reviewed and approved by the Institutional Review Board of the National Center for Health Statistics (NCHS), and all participants provided written informed consent. All methods were conducted in accordance with relevant guidelines and regulations. Our study examined data from four consecutive two-year survey cycles. All participants were evaluated with the KIQ026 survey (Do you have kidney stones) and a total of 39,156 people participated in the questionnaire. The exclusion criteria are shown in the figure (Figure 1). In total, 10858 cases were included in this study, of which 859 had a self-reported history of kidney stones.

Data collection and definition

A/G ratios (Variable Name: DXXAGRAT) were designed as exposure variables. Relevant data were obtained by performing DXA measurements on subjects. DXA examinations were obtained by trained and certified radiologic technologists using a Hologic Discovery Model A densitometer (Hologic, Inc., Bedford, Massachusetts). The examination excluded subjects who were pregnant (urine pregnancy test and/or self-reported positive at the time of the DXA examination), self-reported a history of X-ray contrast (barium) use within the past seven days, or measured more than 450 pounds or more than 6'5" (DXA table limit). Whole-body scans were obtained on a

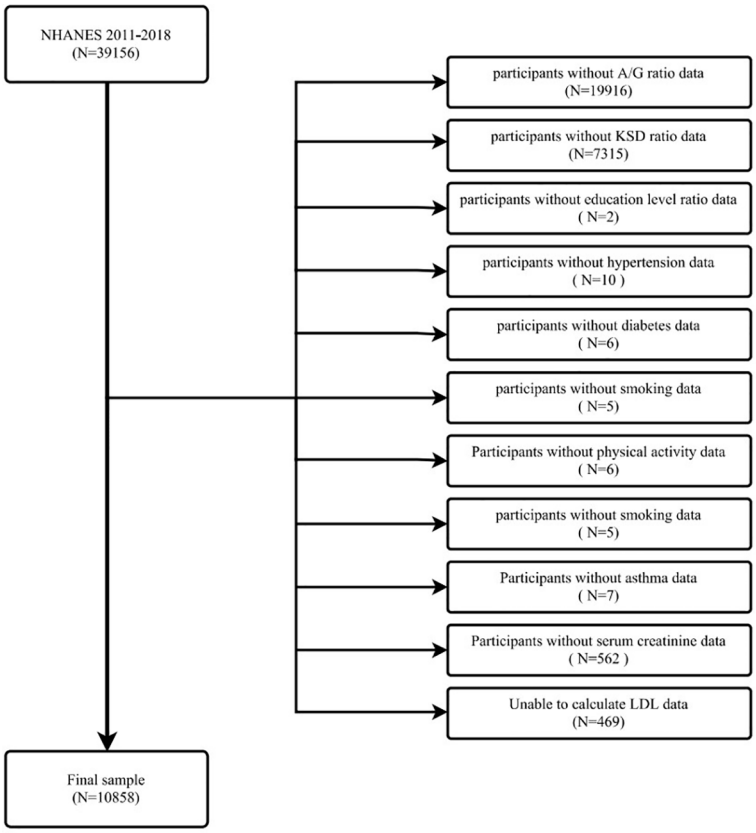

FIGURE 1
The participants selecting flow chart.

Hologic Discovery A densitometer (Hologic, Inc., Bedford, MA) using software version Apex 3.2. The Android and Gynoid regions were determined by the HOGIC APEX software used in the scan analysis for automatic delineation (29). Finally, the Android/Gynoid ratio was calculated based on the measured Android (Variable Name: DXXANFM) and Gynoid (Variable Name: DXXGYFM) data. For more information, please refer to: https://wwwn.cdc.gov/Nchs/Nhanes/2017-2018/DXXAG_J.htm. The occurrence of kidney stones (Variable Name: KIQ026) was designed as an outcome variable. The questionnaire KIQ026 (ever had kidney stones)? was used to assess kidney stones; if the participant answered "yes," he was considered to have kidney stones.

In order to summarize potential confounders that could confound the relationship between A/G ratio and KSD, adjusted multivariate models were used. The following covariates were selected: age, gender, race, education level, poverty to income ratio (PIR), marital status, alcohol consumption, smoking status, physical activity, METS-IR, BMI, diabetes, hypertension, asthma, laboratory tests (cholesterol level, serum creatinine, blood calcium, blood phosphorus, blood uric acid, cholesterol, triglyceride, HDL, LDL, glycosylated hemoglobin) and some dietary intake factors (total energy intake, total fat intake, total sugar intake and total water intake). A 24-hour dietary recall was completed by all participants, and the average intake of the two recalls will be used in the analysis. The dietary intake factors had a high number of missing values, which we converted to categorical variables. We assessed these variables in tertile, with the lowest tertile serving as the reference group and missing values set as dummy variables. These covariates were determined using self-report questionnaires, interviews, physical examinations, and laboratory measurements. Information on age, gender, race/ethnicity, PIR, smoking, alcohol consumption, history of hypertension, and history of diabetes were determined by questionnaire. Information on the dietary intake of the participants was obtained through interviews. Participants' BMI and waist circumference were obtained by physical examination, and laboratory measurements were used for the remaining covariates. Cholesterol, triglyceride, and uric acid concentrations in serum or plasma were measured using the timed-endpoint method. The timed rate biuret method was used to measure phosphorus in blood, and the indirect (or diluted) I.S.E. (ion selective electrode) method was used to measure calcium concentrations in serum, plasma, or urine (uses indirect (or

diluted) I.S.E. (ion selective electrode) methodology to measure calcium concentration, the modular chemistry side uses the Jaffe rate method (kinetic alkaline picrate) to determine serum, plasma, or urine Creatinine concentrations in creatinine, Tosoh Automated Glycohemoglobin Analyzer HLC-723G8 was used to measure glycosylated hemoglobin in patients, HDL data were obtained using Roche/Hitachi Cobas 6000 Analyzer, patients with excess LDL deficiency, we used Friedewald formula to recalculate the patient's LDL. Details of the study variables used are all publicly available at www.cdc.gov/nchs/nhanes/.

Statistical methods

To illustrate the complex, multi-stage sampling design used to select a representative non-institutionalized U.S. population, the sampling weights, strata, and subgroups provided in the NHANES study were applied to all statistical analyses. Continuous variables are expressed as weighted means and 95% CIs, and categorical variables are expressed as weighted proportions and 95% CI. We first did a VIF covariate screening of all covariates and removed the covariate if the VIF value was greater than five, considered to have sharedness. Based on the guidelines (30), three different logistic regression models were used to examine the relationship between the A/G ratio and KSD. In model 1, no covariates were adjusted. Model 2 was adjusted for age, gender and race, marital status, and education level, while Model 3 was adjusted for age, gender and race, marital status, education level, alcohol consumption, smoking status, physical activity, METS-IR, diabetes, hypertension, asthma, cholesterol level, serum creatinine, blood calcium, blood phosphorus, blood uric acid, cholesterol, triglyceride, HDL, LDL, glycosylated hemoglobin, total energy intake, total fat intake, total sugar intake and total water intake. A smoothed curve fit (penalized spline method) and generalized additive model (GAM) regression were then performed to further assess the relationship between A/G ratio and KSD. Multiple regression analysis was then conducted stratified by age, gender, race, diabetes, and hypertension mellitus. Moreover, interaction terms were added using a log-likelihood ratio test to test for heterogeneity in the association between subgroups. $P < 0.05$ was considered statistically significant. All analyses were performed using Empower software (www.empowerstats.com; X&Y Solutions, Inc., Boston, MA, USA) and R version 3.4.3 (http://www.R-project.org, The R Foundation).

Results

Characteristics of the study population

The analysis involved 11327 participants, including 895 patients with kidney stones (Table 1). In the stone group, A/G ratio was significantly higher than in the non-stone group ($1.05 > 0.99$, $p<0.0001$).

Elevated A/G ratio was associated with increased prevalence of kidney stones

VIF values for all covariates for covariate screening were less than 5, so all covariates were included in the final model. A multifactorial logistic regression analysis was performed showing a 1.75-fold increase in the prevalence of kidney stones for each unit increase in the A/G ratio (OR=2.75, 95% CI:1.62-4.88) (Table 2). We then converted the A/G ratio from a continuous variable to a categorical variable (triplet). The results showed a 41% higher likelihood of kidney stones in the highest tertile (tertile 3) compared to the lowest A/G ratio in the lowest tertile (tertile 1), as shown in Table 2.

Subgroup analysis

To assess the robustness of the association between the A/G ratio and the prevalence of kidney stones, a subgroup analysis was performed (Table 3). The results showed that in the hypertensive subgroup, all increases in the A/G ratio were positively associated with the prevalence of kidney stones. In contrast, in the diabetic subgroup, only the non-diabetic group had a significant positive association of A/G ratio with kidney stones (OR=2.59, 95% CI: 1.45-4.60). In the age subgroup, a significant positive association between A/G ratio and kidney stones was found only in the group of $40 \leq age < 60$ (OR=3.51, 95% CI: 1.83-6.71). Among the ethnic subgroups, a significant positive association between A/G ratio and kidney stones was found in Mexican Americans (OR=4.35, 95% CI: 1.40-13.53) and Whites (OR=3.86, 95% CI: 1.82-8.18). In the gender subgroup, a significant positive association between A/G ratio and kidney stones was found only in the female group (OR=3.55, 95% CI: 1.54-8.22). In addition, we tested for interactions with age, sex, race, hypertension, and diabetes mellitus. However, no correlations were detected with interactions meeting statistical significance ($p > 0.05$ for all interactions)

Analysis of dose-response and threshold effects of A/G ratio on the prevalence of KSD

Using a generalized additive model and smoothed curve fitting, a relationship between A/G ratio and kidney stones was further investigated. Our results show that the A/G ratio is linearly and positively correlated with the KSD (Figure 2).

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TABLE 1 The characteristics of the participants selected.

Characteristic	Nonstone formers N=9999	Stone formers N=859	P-value
Age	39.23 (38.74,39.72)	43.51 (42.47,44.56)	<0.0001
Serum Calcium (MG/DL)	9.37 (9.36,9.38)	9.34 (9.30,9.39)	0.2245
Serum Creatinine (MG/DL)	0.86 (0.85,0.86)	0.87 (0.84,0.90)	0.3303
Cholesterol (MG/DL)	190.63 (189.25,192.00)	194.20 (190.48,197.92)	0.0536
Serum phosphorus (MG/DL)	3.72 (3.70,3.74)	3.65 (3.59,3.71)	0.0228
Uric acid (MG/DL)	5.32 (5.28,5.36)	5.38 (5.27,5.50)	0.2692
HDL(MG/DL)	53.79 (53.21,54.38)	50.34 (48.90,51.78)	<0.0001
HBA1C(MG/DL)	5.49 (5.46,5.51)	5.71 (5.61,5.81)	0.0001
LDL(MG/DL)	110.32 (109.22,111.42)	113.97 (110.76,117.17)	0.0318
Triglyceride (MG/DL)	132.59 (129.90,135.27)	149.45 (142.59,156.32)	<0.0001
METS-IR	42.43 (41.94,42.92)	46.93 (45.67,48.19)	<0.0001
BMI	28.72 (28.46,28.98)	30.81 (30.15,31.48)	<0.0001
Waistline	97.39 (96.77,98.02)	103.31 (101.92,104.70)	<0.0001
Android to Gynoid ratio	0.99 (0.99,1.00)	1.05 (1.03,1.07)	<0.0001
Android fat mass	2425.66 (2375.35,2475.97)	2943.12 (2817.65,3068.58)	<0.0001
Gynoid fat mass	4711.65 (4648.13,4775.16)	5067.54 (4883.02,5252.07)	0.0003
Visceral adipose tissue volume	526.75 (515.08,538.42)	699.65 (668.59,730.71)	<0.0001
Total fat	27187.60 (26815.40,27559.80)	29957.26 (29056.16,30858.35)	<0.0001
Gender			0.4968
Male	50.57 (49.35,51.78)	48.75 (43.76,53.77)	
Female	49.43 (48.22,50.65)	51.25 (46.23,56.24)	
Race			<0.0001
Mexican American	17.01 (14.44,19.92)	14.30 (11.02,18.35)	
White	61.25 (57.42,64.94)	72.05 (66.55,76.96)	
Black	12.14 (10.16,14.45)	6.71 (5.16,8.69)	
Other Race	9.61 (8.50,10.84)	6.94 (5.14,9.30)	
Education Level (%)			0.7453
Less than high school	18.63 (16.56,20.90)	17.78 (14.97,20.98)	
High school	30.43 (28.40,32.55)	32.22 (27.05,37.86)	
More than high school	50.93 (47.97,53.89)	50.01 (44.70,55.31)	
Marital Status (%)			0.0015
Cohabitation	61.84 (59.90,63.74)	67.75 (63.66,71.59)	
Solitude	38.16 (36.26,40.10)	32.25 (28.41,36.34)	
PIR			0.4507
<1.39	21.57 (19.61,23.68)	20.71 (18.06,23.64)	
1.39-3.49	31.76 (29.81,33.78)	35.24 (30.59,40.20)	
≥3.49	39.84 (36.94,42.81)	38.34 (33.36,43.58)	
Unclear	6.83 (5.91,7.87)	5.70 (3.85,8.35)	
Alcohol (%)			0.6265
Yes	60.94 (58.62,63.20)	61.01 (56.01,65.79)	
No	15.95 (14.40,17.64)	17.37 (13.71,21.76)	
Unclear	23.11 (21.34,24.99)	21.62 (17.47,26.43)	
Smoked			0.015
Yes	40.65 (38.89,42.43)	46.57 (41.80,51.39)	
No	59.35 (57.57,61.11)	53.43 (48.61,58.20)	
Hypertension (%)			<0.0001
Yes	21.22 (19.99,22.51)	36.89 (32.56,41.45)	
No	78.78 (77.49,80.01)	63.11 (58.55,67.44)	

(Continued)

TABLE 1 Continued

Characteristic	Nonstone formers N=9999	Stone formers N=859	P-value
Diabetes (%)			<0.0001
Yes	5.00 (4.48,5.57)	11.92 (9.31,15.14)	
No	95.00 (94.43,95.52)	88.08 (84.86,90.69)	
Physical Activity (%)			0.0795
Never	20.87 (19.78,22.02)	25.06 (21.37,29.16)	
Moderate	28.37 (27.03,29.74)	26.97 (23.42,30.84)	
Vigorous	50.76 (49.27,52.25)	47.97 (43.44,52.53)	
Asthma			0.1986
No	84.39 (83.25,85.47)	82.62 (79.81,85.11)	
Yes	15.61 (14.53,16.75)	17.38 (14.89,20.19)	
Total Kcal (%)			0.2265
Tertile 1	26.56 (25.19,27.98)	30.26 (26.08,34.81)	
Tertile 2	28.77 (27.48,30.10)	29.06 (24.77,33.76)	
Tertile 3	29.40 (28.14,30.70)	25.50 (21.65,29.79)	
Unclear	15.26 (14.20,16.39)	15.17 (12.34,18.52)	
Total Sugars (%)			0.6518
Tertile 1	24.26 (23.08,25.49)	26.51 (22.58,30.85)	
Tertile 2	24.34 (23.15,25.56)	22.65 (19.51,26.13)	
Tertile 3	23.91 (22.62,25.26)	23.46 (20.20,27.06)	
Unclear	27.49 (26.19,28.82)	27.38 (23.66,31.44)	
Total Water (%)			0.6317
Tertile 1	25.94 (24.68,27.24)	26.71 (22.92,30.88)	
Tertile 2	28.99 (27.80,30.21)	30.75 (27.04,34.73)	
Tertile 3	29.81 (28.49,31.17)	27.36 (23.38,31.74)	
Unclear	15.26 (14.20,16.39)	15.17 (12.34,18.52)	
Total Fat (%)			0.6317
Tertile 1	25.94 (24.68,27.24)	26.71 (22.92,30.88)	
Tertile 2	28.99 (27.80,30.21)	30.75 (27.04,34.73)	
Tertile 3	29.81 (28.49,31.17)	27.36 (23.38,31.74)	
Unclear	15.26 (14.20,16.39)	15.17 (12.34,18.52)	

Discussion

KSD has a complex etiology, a high recurrence rate, and a wide range of individual variations. Therefore, examining KSD's risk factors is essential for both prevention and treatment. According to our knowledge, this is the first study to investigate the association between A/G ratios and the prevalence of nephrolithiasis. According to our analysis of four consecutive NHANES two-year cycles (2011–2018) of a nationally representative population, the A/G ratio is predictive of kidney stone occurrence, and the higher the A/G ratio, the higher the risk.

This correlation may be due to a number of reasons. First, an increase in the A/G ratio generally represents an abnormal increase in fat content in the Android region. Android region contains the liver, pancreas, and kidneys. There have been numerous studies demonstrating that fat accumulation in these structures can have harmful effects both directly and indirectly on the body (31–33). An accumulation of fat in the liver and pancreas is associated with multiple indicators of inflammation (34), and inflammation has been strongly linked to kidney stone formation (35). The accumulation of fat in and around the kidneys may have a significant impact on kidney function and blood pressure (36). A study in obese animals found that increased renal sinus fat may increase blood pressure and kidney interstitial pressure by compressing the blood vessels that leave the kidney (37). Local ischemia may also result from this phenomenon, which can result in renal tubular injury (38). Lipid accumulation within the kidney parenchyma, in turn, can result in lipotoxicity, inflammation, oxidative stress, and kidney fibrosis (39, 40). These factors have been shown to be risk factors for KSD in numerous studies (35, 41, 42). In addition, the gynoid

TABLE 2 Analysis between A/G ratio with kidney stone formation.

Characteristic	Model 1 OR (95%CI)	Model 2 OR (95%CI)	Model 3 OR (95%CI)
A/G ratio	4.17 (2.89, 6.02)	5.04 (3.25, 7.82)	2.75 (1.62, 4.68)
Categories			
Tertile 1	1	1	1
Tertile 2	1.17 (0.95, 1.45)	1.22 (0.98, 1.52)	0.99 (0.78, 1.26)
Tertile 3	1.85 (1.51, 2.28)	2.01 (1.59, 2.52)	1.41 (1.07, 1.85)
P for trend	<0.001	<0.001	0.002

Model 1 = no covariates were adjusted.
Model 2 = Model 1+age, gender, race, education, marital status were adjusted.
Model 3 = Model 2+age, gender and race, marital status, education level, alcohol consumption, smoking status, physical activity, METS-IR, diabetes, hypertension, asthma, cholesterol level, serum creatinine, blood calcium, blood phosphorus, blood uric acid, cholesterol, triglyceride, HDL, LDL, glycosylated hemoglobin, total energy intake, total fat intake, total sugar intake and total water intake were adjusted.

region contains the buttocks and part of the thighs. Adipose tissue in this region is generally considered to have a health-promoting effect (43), and an increase in the ratio may indicate that the damaging factors begin to outweigh the protective factors, leading to the development of KSD. Second, both KSD and A/G ratio are closely related to intestinal flora. Studies have shown that increased abundance of Faecalibacterium prausnitzii in the intestine of obese adolescents who underwent fecal transplantation was associated with a lower A/G ratio (44), whereas calcium oxalate stones were negatively associated with the abundance of Faecalibacterium spp (45). Therefore, the correlation between high A/G ratio and increased prevalence of KSD may also be mediated by changes in the abundance or species of intestinal flora. This requires further study. Third. Studies have shown that the lower the serum carotenoid content, the higher the A/G ratio in Chinese (46). In addition, the higher prevalence of kidney stones is also positively correlated with low serum carotenoid content (47). Finally, it has been shown that higher Android/Gynoid ratios are associated with steady-state model assessment of insulin resistance (HOMA-IR) values, metabolic syndrome (METS), nonalcoholic fatty liver disease (NAFLD), and triglyceride glycemic index levels (22, 48, 49),

TABLE 3 Subgroup analysis between A/G ratio with kidney stone formation.

Characteristic	Model 1	Model 2	Model 3	P for trend*	P for Interaction*
Gender					0.4189
Male	7.38 (4.22, 12.91)	3.77 (2.07, 6.85)	1.97 (0.98, 3.99)	0.192	
Female	6.66 (3.45, 12.88)	6.36 (3.27, 12.37)	3.55 (1.54, 8.22)	0.006	
Race					0.1285
Mexican American	3.33 (1.54, 7.21)	3.72 (1.42, 9.76)	4.35 (1.40, 13.53)	0.0126	
White	5.07 (3.05, 8.42)	7.66 (4.18, 14.02)	3.86 (1.82, 8.18)	0.001	
Black	2.40 (0.86, 6.69)	1.73 (0.54, 5.60)	1.32 (0.29, 5.92)	0.753	
Others	6.15 (2.16, 17.50)	5.31 (1.43, 19.77)	1.40 (0.30, 6.60)	0.697	
Diabetes					0.4508
Yes	2.85 (0.93, 8.68)	4.58 (1.19, 17.62)	4.30 (0.95, 19.37)	0.181	
No	3.64 (2.45, 5.41)	4.41 (2.75, 7.07)	2.59 (1.45, 4.60)	0.008	
Hypertension					0.8256
Yes	2.53 (1.34, 4.78)	3.97 (1.85, 8.51)	3.59 (1.49, 8.64)	0.073	
No	3.56 (2.23, 5.68)	4.06 (2.34, 7.07)	2.28 (1.15, 4.51)	0.029	
Age					0.0881
<40	1.97 (1.03, 3.77)	3.52 (1.70, 7.30)	1.72 (0.64, 4.63)	0.382	
40-59	4.09 (2.60, 6.45)	6.24 (3.58, 10.88)	3.51 (1.83, 6.71)	<0.001	

Model 1 = no covariates were adjusted.
Model 2 = Model 1+age, gender, race, education, marital status were adjusted.
Model 3 = Model 2+age, gender and race, marital status, education level, alcohol consumption, smoking status, physical activity, METS-IR, diabetes, hypertension, asthma, cholesterol level, serum creatinine, blood calcium, blood phosphorus, blood uric acid, cholesterol, triglyceride, HDL, LDL, glycosylated hemoglobin, total energy intake, total fat intake, total sugar intake and total water intake were adjusted.
*Means only in model 3.

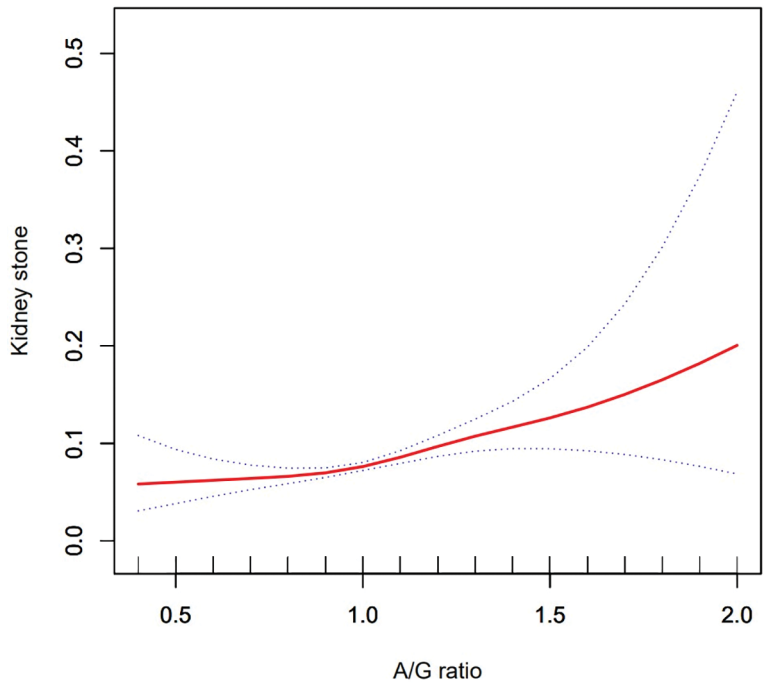

FIGURE 2
Density dose–response relationship between Android to Gynoid ratio with kidney stone formation. The area between two dotted lined is expressed as a 95% CI.

which are also risk factors for KSD (26, 50–52), were also positively correlated, which may account for the association of KSD with the A/G ratio.

We also stratified the variables by age, sex, race, hypertension, and diabetes status in this study. There was a positive correlation between the prevalence of the A/G ratio and the KSD in all subgroups when unadjusted. After adjusting for all variables, this correlation was statistically significant in all groups only if they were grouped according to hypertension. However, the correlation between A/G ratio and KSD was more significant in the hypertensive group. This may be because hypertension itself is a risk factor for KSD (53), so it enhances this correlation. Interestingly, diabetes itself is also a risk factor for KSD. However, in the diabetes subgroup, the correlation between A/G ratio and KSD was lost in the diabetic group. This may be because several glucose-lowering drugs can prevent kidney stone formation. For example, metformin prevents kidney stone formation by attenuating oxalic acid-induced lipid peroxidation products-induced tubular damage and by inhibiting the expression of osteopontin (OPN) and monocyte chemoattractant protein 1 (MCP-1) (54, 55). Rosiglitazone may also inhibit renal crystal deposition by ameliorating tubular damage due to oxidative stress and inflammatory responses through multiple pathways (56, 57). Another possible explanation is that a high-sugar, high-fat diet is more likely to lead to metabolic syndrome (58), whereas diabetic patients are generally more conscious of dietary management and are relatively more protective, which may be more beneficial in preventing KSD formation. Furthermore, when stratified by gender, the relationship between A/G ratio and KSD was statistically significant only in the female population. This is similar to previous studies on A/G ratios. This may be due to the fact that the fat distribution in the female group is dominated by Gynoid pattern fat distributions. Thus, the female group may accumulate relatively more fat in the Android region before showing an increase in the A/G ratio (59), this may have a greater impact on the body. Sex hormones may also play an important role, with sex hormones shifting to androgen production as Android body fat increases (60).

However, after adjusting for all confounding variables. This correlation was only significant among Caucasians and Mexican-Americans in stratification by race. It may be due to the fact that black groups appear to be less affected by obesity than other races (61). Further, in stratification by age, a significant positive association was found between the A/G ratio and the prevalence of KSD only in groups older than 40 years of age. This is probably because aging adipose tissue promotes insulin resistance and lipid penetration (62, 63). In addition, aging reduces the ability of adipose tissue to store free fatty acids, causing a lipotoxic environment and systemic

lipotoxicity (64). This, in turn, leads to kidney damage, which in turn contributes to kidney stone formation (35, 42).

The study has several advantages. First of all, this is the first comprehensive analysis of the correlation between the A/G ratio and KSD. Second, NHANES follows a well-designed study protocol with extensive quality assurance and quality control. In addition, the large representative sample size makes our results more reliable and generalizable to the entire US multi-ethnic adult population. Furthermore, the wide range of covariates used for adjustment enhances the accuracy of statistical inferences.

Of course, our study has some limitations. First, our study was based on the NHANES database, which is a cross-sectional study, and we were unable to obtain a causal relationship between the A/G ratio and kidney stones. Second, out of the DXA test results, many of our data were based on self-reporting, which may have some recall and reporting bias, such that a small number of asymptomatic urinary stones may be excluded. Third, the database did not provide more detailed information, such as medication history and stone composition. It is therefore necessary to conduct further research in order to confirm our results and explore in more detail the correlation between the A/G ratio and KSD.

Conclusion

Based on a cross-sectional study of a US population, we found that a high A/G ratio was associated with an increased prevalence of kidney stones. This may have significant implications for the prevention and treatment of kidney stones. Therefore, this needs to be validated by further studies and the potential mechanisms explored.

Data availability statement

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

Author contributions

GL, HL, and YH: Conceptualization, Methodology, Software. QH, XS, and YC: Visuali-zation, Investigation. MC, JX, and ZH: Writing - review & editing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

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Predictive ability of obesity- and lipid-related indicators for metabolic syndrome in relatively healthy Chinese adults

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Background and objective: Metabolic syndrome (MetS) is an important risk factor for cardiovascular complications and kidney damage. Obesity- and lipid-related indices are closely related to MetS, and different indices have different predictive abilities for MetS. This study aimed to evaluate the predictive value of eight obesity- and lipid-related indicators, namely, body mass index (BMI), lipid accumulation product (LAP), body roundness index (BRI), Chinese visceral adiposity index (CVAI), body adiposity index (BAI), abdominal volume index (AVI), triglyceride glucose index (TYG), and visceral adiposity index (VAI), for MetS.

Methods: A total of 1,452 relatively healthy people in Beijing were enrolled in 2016, and the correlation between the eight indicators and MetS was analyzed by multivariate logistic regression. The receiver operating characteristic (ROC) curve and the area under the curve (AUC) were used to analyze the predictive ability of the eight indicators for MetS. The Delong test was used to compare the AUC values of the eight indicators. MetS was defined according to the Chinese Guidelines for the Prevention and Treatment of Type 2 Diabetes (2020 edition), the revised National Cholesterol Education Program Adult Treatment Group (NCEP-ATPIII), and the International Diabetes Federation (IDF).

Results: Using these three sets of criteria, LAP, TYG, CVAI, and VAI, which are based on blood lipids, had higher AUC values for MetS prediction than BMI, BRI, AVI, and BAI, which are based on anthropometry. LAP had the highest AUC

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values of 0.893 (0.874–0.912), 0.886 (0.869–0.903), and 0.882 (0.864–0.899), separately, based on the three sets of criteria.

Conclusion: The eight obesity- and lipid-related indicators had screening value for MetS in relatively healthy people, and of the eight indicators, LAP performed the best.

KEYWORDS

metabolic syndrome, lipid accumulation product, obesity, lipid, adults, healthy

Introduction

Metabolic syndrome (MetS) is a group of conditions characterized by cardiometabolic risk, including obesity (especially central obesity), elevated blood pressure, elevated blood glucose, elevated triglyceride (TG), and decreased high-density lipoprotein cholesterol (HDL-c) levels (1). These are important risk factors for atherosclerotic cardiovascular disease (CVD) and type 2 diabetes (T2DM), which can lead to severe complications, such as arteriosclerosis, decreased renal function, myocardial infarction, and cerebral infarction (2–4). Therefore, screening for MetS in relatively healthy people is of great significance in understanding their disease status or predisease status in advance, preventing related diseases caused by MetS in advance, and reducing the waste of public health resources and the medical burden.

Visceral fat accumulation is an important feature of MetS. However, the gold standards for assessing visceral fat, such as magnetic resonance imaging (MRI) and computed tomography (CT), involve exposure to radiation or are expensive and time-consuming. People are starting to use simple measures to assess visceral fat. Body mass index (BMI) is the most common anthropometric index used in epidemiological and clinical studies to classify overweight and obesity but is affected by differences in age, sex, and race and does not distinguish between fat and muscle mass (5, 6). Therefore, a variety of obesity- and lipid-related indicators have gradually been developed to assess visceral fat and predict MetS.

The body roundness index (BRI), body adiposity index (BAI), and abdominal volume index (AVI) are all new anthropometric indicators that can be used to effectively evaluate visceral obesity and make up for the deficiencies of BMI (7–9). The BRI has shown a superior ability to predict atherosclerosis in overweight/obese people (10), and it also does well in predicting MetS (11). The BAI has been shown to predict hypertensive events and screen for coronary heart disease risk (12, 13). The AVI reflects visceral fat content by assessing total abdominal volume, which is associated with impaired glucose tolerance (IGT) and diabetes mellitus (DM) (9, 14) and has strong predictive power for MetS in adolescents (15). The lipid accumulation product (LAP), visceral adiposity index (VAI), Chinese visceral adiposity index (CVAI), and triglyceride glucose index (TYG) are recently developed indices for estimating visceral fat based on a combination of abdominal obesity index [waist circumference (WC), BMI], blood glucose, and circulating lipids (HDL-C, TG) (6, 16–18). The LAP and TYG play an important role in identifying DM and prediabetes mellitus (19) and have a good ability to predict MetS (20–22). Both the VAI and CVAI can be used as markers of cardiometabolic risk (16, 23). All of these indicators show certain predictive power for MetS, but the best indicator to evaluate MetS is still controversial. The purpose of our study was to evaluate the performance of eight obesity- and lipid-related indicators (BMI, LAP, BRI, CVAI, BAI, AVI, TYG, and VAI) in predicting MetS in a relatively healthy population in China under three sets of criteria. Meanwhile, we were in search of the best sole indicator among the eight indicators to predict MetS.

Abbreviations: LAP, lipid accumulation product; BRI, body roundness index; CVAI: Chinese visceral adiposity index; AVI, abdominal volume index; BAI, body adiposity index; TYG, triglyceride glucose; VAI, visceral adiposity index.

Materials and methods

Study design and participants

The study was conducted at the Chinese PLA General Hospital in 2016 and recruited volunteers from Beijing, China. In this study, 2,217 volunteers aged ≥18 years were initially recruited. A total of 765 subjects were excluded according to the following exclusion criteria (Supplementary Figure 1): a) those with respiratory diseases, such as chronic obstructive pulmonary disease, asthma, bronchiectasis, etc.; b) those with musculoskeletal disease or rheumatologic disease, such as sarcopenia, fracture, rheumatoid arthritis, etc.; c) those with one of the following diseases in the previous 6-month period: liver cirrhosis, stroke, myocardial

infarction, and malignant tumor; d) those unable to cooperate with the tests and sample collection; and e) those lacking the required data. Ultimately, 1,452 people were included in the study. This study was performed in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Chinese People's Liberation Army General Hospital. All the participants provided signed informed consent and agreed to participate in this survey.

The information collected in this study included sociodemographic characteristics, medical history, family history, laboratory tests, etc. Anthropometric data, including weight, height, WC, hip circumference, and blood pressure, were measured by professional researchers according to standard protocols. The participants wore light clothing and were barefoot when their weight and height were measured. WC was measured using a flexible plastic tape measure at the navel level after the patient exhaled, and hip circumference was measured at the widest part of the hip. Blood pressure was measured in the participant's non-dominant arm using automated electronic equipment; after a 5-min rest, blood pressure was measured in a 1-min interval thrice. The mean systolic and diastolic blood pressures of the three readings were recorded using a questionnaire.

Biochemical measurements

Participants fasted for at least 8 h for the collection of venous blood to measure fasting blood glucose (FBG), creatinine (Cr), total cholesterol (TC), TG, HDL-C, low-density lipoprotein cholesterol (LDL-C), and other biochemical indicators. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. The formulas for calculating BMI, LAP (24), BRI (7), CVAI (17), BAI (8), AVI (9), TYG (18), and VAI (16) are shown in Supplementary Table 1.

Definition of MetS

MetS was defined according to the Chinese Guidelines for the Prevention and Treatment of Type 2 Diabetes (2020 edition) (25), the revised National Cholesterol Education Program Adult Treatment Group (NCEP-ATPIII) (26), and the International Diabetes Federation (IDF) (27) (Supplementary Table 2).

Statistical analysis

The normal distribution of variables was assessed by the Kolmogorov–Smirnov test. The homogeneity of variance was assessed by the Levene test or one-way ANOVA. Categorical variables are presented as percentages, and continuous variables are described as the mean ± standard deviation (SD) for normally distributed data or the median (interquartile range) for skewed data. Comparisons between groups were performed using the Student's *t*-test, the chi-square test, or the Mann-Whitney *U* test. Binary logistic regression analysis was used to assess the relationship between obesity- and lipid-related indices and the incidence of MetS. Data were summarized as odds ratios (ORs) and regression coefficients [95% confidence intervals (CIs)]. The ORs indicated the change in the odds per unit increase in the anthropometric measures. When performing binary logistic regression, adjustments were made for the participants' age, systolic blood pressure, diastolic blood pressure, TC, and eGFR. Adjusted variables were diagnosed by collinearity according to the following criteria: variance inflation factor (VIF) >10 or tolerance of approximately 0.1, condition index >30, and variance ratio >50%. Selected variables were not collinear. Receiver operating characteristic (ROC) analysis was used to compare the diagnostic performance of logistic models. Internal ten-fold cross-validation and penalty regression for validation. The tuning of the hyperparameters lambda and alpha was done through grid search, and the best models were reported in different groups with the highest mean validation AUC. The source codes were posted on github (https://github.com/yotasama/cv.elasticnet.r).

The ROC of the sole index analysis was used to compare the diagnostic performance of obesity- and lipid-related indices for MetS. Youden's index (sensitivity + specificity − 1) was used to determine the optimal cutoff point of each indicator. All statistical analyses were performed using R.4.2.0 with package glmnet v4.1-4 and IBM SPSS statistical software, version 25 (IBM Corporation, Armonk, New York, NY, USA). The AUC values of all indicators were compared using the DeLong test and calculated using MedCalc Version 19.0 software (Ostend, Belgium). Differences were considered statistically significant at *P*-values of <0.05.

Results

General characteristics of the participants

The demographic characteristics, anthropometric measurements, and obesity- and lipid-related indices are presented in Table 1. **A** total of 1,425 subjects were enrolled, consisting of 615 men with an average age of 58.07 ± 13.57 years and 837 women with an average age of 58.26 ± 13.25 years.

Different characteristics of people with or without MetS

Participants were divided into groups based on sex and whether they had MetS according to the Chinese criteria (2020) (Table 2). In men with MetS, the values of the eight obesity- and

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TABLE 1 Basic characteristics of the participants.

Variable	Male	Female	Total
N	615	837	1,452
Age (years)	58.07 ± 13.57	58.26 ± 13.25	58.18 ± 13.38
Height (cm)	171.26 ± 5.61	159.48 ± 5.50	164.47 ± 8.04
Weight (kg)	73 ± 12.04	61.65 ± 9.85	66.46 ± 12.20
WC (cm)	91.3 ± 9.11	83.39 ± 9.35	86.74 ± 10.04
HC (cm)	100.0 ± 5.85	97.99 ± 6.79	98.83 ± 6.48
BMI (kg/m^2)	24.84 ± 3.6	24.26 ± 3.91	24.50 ± 3.79
TG (mmol/L)	1.38 (0.93, 1.97)	1.23 (0.93, 1.72)	1.29 (0.93, 1.83)
TC (mmol/L)	4.63 ± 0.93	4.84 ± 0.94	4.75 ± 0.94
HDL-C (mmol/L)	1.31 ± 0.34	1.53 ± 0.38	1.44 ± 0.38
FPG	5.57 ± 1.70	5.43 ± 1.39	5.49 ± 1.53
SBP (mmHg)	126.6 ± 14.7	124.16 ± 17.32	125.17 ± 16.30
DBP (mmHg)	75.44 ± 9.63	70.91 ± 10.06	72.83 ± 10.13
eGFR (ml/min/1.73 m^2)	91.61 ± 19.0	89.13 ± 17.19	90.18 ± 18.00
LAP	35.4 (20.79, 58.95)	32.67 (18.94, 48.32)	34.05 (19.75, 52.78)
BRI	4.63 ± 1.04	3.88 ± 1.24	3.96 ± 1.16
CVAI	120.16 (93.19, 146.66)	101 (70.69, 124.72)	110.26 (78.93, 133.95)
AVI	16.91 ± 3.27	14.26 ± 3.07	15.38 ± 3.42
BAI	26.66 ± 2.80	30.74 ± 3.98	29.01 ± 4.07
TYG	8.73 ± 0.64	8.59 ± 0.57	8.65 ± 0.60
VAI	1.45 (0.88, 2.49)	1.55 (1, 2.51)	1.51 (0.95, 2.51)

WC, waist circumference; HC, hip circumference; BMI, body mass index; TG, triglycerides; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; LAP, lipid accumulation product; BRI, body roundness index; CVAI, Chinese visceral adiposity index; AVI, abdominal volume index; BAI, body adiposity index; TYG, triglyceride glucose; VAI, visceral adiposity index.

lipid-related indicators and clinical indicators (SBP, DBP, TG, HDL-C) were significantly increased compared with those of men without MetS ($P < 0.001$). No significant differences in age, height, TC, or eGFR ($P > 0.05$) were noted. In women with MetS, the values of the eight obesity- and lipid-related indicators and clinical indicators (SBP, DBP, TG, HDL-C) were significantly increased compared with those of women without MetS ($P < 0.001$); however, height and TC were not statistically significant ($P > 0.05$). Overall, the values of the eight obesity- and lipid-related indicators and clinical indicators (SBP, DBP, TG, and HDL-C) were significantly increased in participants with MetS compared with those without MetS ($P < 0.001$). TC and eGFR were not significantly different ($P > 0.05$).

MetS prevalence and its association with obesity and lipid index

We compared the diagnostic efficacy of MetS with different diagnostic criteria in this population. Under the different criteria, the prevalence of MetS ranged from 21% [China (2020 edition) criteria] to 31.3% (NCEP-ATPIII criteria). We found statistically significant differences in the prevalence of MetS between the China (2020 edition) criteria and the NCEP-ATPIII and IDF criteria, whereas no statistically significant differences were noted between the NCEP-ATPIII and IDF criteria (Table 3). Using the China (2020 edition) criteria, the prevalence of MetS among men was significantly greater than that among women ($\chi^2 = 29.725$, $P < 0.001$), but there was no significant difference in the prevalence of MetS among men and women using the NCEP-ATPIII and IDF standards ($P > 0.05$). In addition, according to multivariate logistic regression analysis, BMI, LAP, BRI, CVAI, AVI, BAI, TYG, and VAI were significantly associated with MetS among all three criteria ($P < 0.001$). After adjusting for age, systolic blood pressure, diastolic blood pressure, TC, and eGFR, the OR value of TYG was 35.069 (22.057–55.757, $P < 0.001$) based on the China (2020 edition) criteria. Using the NCEP-ATPIII criteria, the OR value of TYG was 53.435 (33.535–85.145, $P < 0.001$), and using the IDF criteria, the OR value of TYG was 21.464 (14.726–31.286, $P < 0.001$). Among the three criteria, the LAP group model had the best overall AUC values: China (2020 edition) AUC = 0.925, NCEP-ATPIII criteria AUC = 0.909, and IDF criteria AUC = 0.903 (Table 4). The multivariate logistic regression analysis results for the NCEP-ATPIII and IDF standards are shown in Supplementary Tables 3, 4. The internal 10-fold cross-validation and penalty regression for validation are shown in Supplementary Tables 5–13.

TABLE 2 Characteristics of participants with or without MetS (China 2020).

Variable	Male			Female			Total		
	MetS−	MetS+	*P*-value	MetS−	MetS+	*P*-value	MetS−	MetS+	*P*-value
N	444	171		703	134		1,147	305	
Age (years)	58.56 ± 14.00	56.82 ± 12.35	0.133	57.03 ± 13.47	64.67 ± 9.79	<0.001	57.62 ± 13.691	60.27 ± 11.93	0.001
Height (cm)	171.03 ± 5.77	171.87 ± 5.13	0.078	159.47 ± 5.53	159.54 ± 5.31	0.889	163.94 ± 7.96	166.45 ± 8.04	<0.001
Weight (kg)	70.73 ± 12.26	78.87 ± 9.51	<0.001	60.56 ± 9.74	67.38 ± 8.36	<0.001	64.50 ± 11.87	73.83 ± 10.49	<0.001
WC (cm)	88.89 ± 8.75	97.56 ± 6.77	<0.001	81.63 ± 8.71	92.61 ± 6.85	<0.001	84.23 ± 9.44	94.57 ± 7.49	<0.001
HC (cm)	98.83 ± 5.75	102.96 ± 5.00	<0.001	97.15 ± 6.47	102.41 ± 6.73	<0.001	97.80 ± 6.25	102.72 ± 5.82	<0.001
BMI (kg/m^2)	24.13 ± 3.63	26.69 ± 2.79	<0.001	23.84 ± 3.93	26.46 ± 2.92	<0.001	23.95 ± 3.82	26.59 ± 2.85	<0.001
TG (mmol/L)	1.15 (0.85, 1.51)	2.16 (1.81, 2.95)	<0.001	1.15 (0.88, 1.52)	1.9 (1.51, 2.42)	<0.001	1.15 (0.87, 1.52)	2.02 (1.72, 2.8)	<0.001
TC (mmol/L)	4.59 ± 0.95	4.73 ± 0.86	0.066	4.81 ± 0.93	4.98 ± 0.98	0.066	4.72 ± 0.94	4.84 ± 0.92	0.058
HDL-C (mmol/L)	1.41 ± 0.32	1.05 ± 0.23	<0.001	1.58 ± 0.38	1.30 ± 0.31	<0.001	1.51 ± 0.36	1.16 ± 0.29	<0.001
FPG (mmol/L)	5.31 ± 1.23	6.27 ± 2.41	<0.001	5.17 ± 0.98	6.79 ± 2.23	<0.001	5.23 ± 1.08	6.50 ± 2.34	<0.001
SBP (mmHg)	124.43 ± 14.39	132.11 ± 14.10	<0.001	120.69 ± 15.41	142.33 ± 15.35	<0.001	122.14 ± 15.13	136.6 ± 15.49	<0.001
DBP (mmHg)	73.86 ± 9.23	79.56 ± 9.45	<0.001	69.28 ± 9.38	79.49 ± 9.18	<0.001	71.05 ± 9.58	79.52 ± 9.32	<0.001
eGFR (ml/min/1.73 m^2)	91.78 ± 19.32	91.15 ± 18.16	0.705	89.91 ± 17.52	85.02 ± 14.72	0.003	90.63 ± 18.25	88.46 ± 16.99	0.061
LAP	28.71 (17.18, 40.53)	69.12 (53.36, 109.12)	<0.001	28.75 (17.29, 41.28)	64.94 (49.14, 87.83)	<0.001	28.75 (17.19, 41.04)	67.08 (52.52, 96.51)	<0.001
BRI	3.79 ± 0.98	4.75 ± 0.87	<0.001	3.66 ± 1.15	5.05 ± 1.00	<0.001	3.71 ± 1.09	4.88 ± 0.94	<0.001
CVAI	110.35 (84.13, 133.54)	152.16 (132.38, 170.49)	<0.001	92.27 (64.82, 115.80)	136.13 (122.1, 153.78)	<0.001	98.59 (70.66, 121.51)	142.82 (126.79, 165.71)	<0.001
AVI	16.05 ± 3.07	19.16 ± 2.65	<0.001	13.67 ± 2.81	17.34 ± 2.53	<0.001	14.59 ± 3.13	18.36 ± 2.75	<0.001
BAI	26.24 ± 2.76	27.74 ± 2.59	<0.001	30.33 ± 3.87	32.90 ± 3.88	<0.001	28.74 ± 4.01	30.01 ± 4.11	<0.001
TYG	8.50 ± 0.47	9.35 ± 0.59	<0.001	8.47 ± 0.49	9.22 ± 0.52	<0.001	8.48 ± 0.48	9.29 ± 0.57	<0.001
VAI	1.11 (0.75, 1.61)	2.97 (2.23, 4.49)	<0.001	1.39 (0.93, 2.13)	3.01 (2.13, 4.55)	<0.001	1.29 (0.86, 1.93)	2.99 (2.19, 4.5)	<0.001

WC, waist circumference; HC, hip circumference; BMI, body mass index; TG, triglycerides; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; LAP, lipid accumulation product; BRI, body roundness index; CVAI, Chinese visceral adiposity index; AVI, abdominal volume index; BAI, body adiposity index; TYG, triglyceride glucose; VAI, visceral adiposity index.

Receiver operating characteristic analysis

The abilities of BMI, LAP, BRI, CVAI, AVI, BAI, VAI, and TYG to predict MetS were analyzed by ROC curves based on the different criteria (Table 5). We found that LAP had the highest AUC values of 0.893 (0.874–0.912), 0.886 (0.869–0.903), and 0.882 (0.864–0.899) for the three diagnostic criteria. Second, the AUC values of CVAI, TYG, and VAI were all greater than 0.8. The subgroup analysis based on sex found that LAP had the highest AUC value for all three diagnostic criteria followed by CVAI, TYG, and VAI (Figure 1). Using the Guidelines for the Prevention and Treatment of Type 2 Diabetes in China (2020 edition) as the diagnostic criteria for MetS, in men, the AUC of LAP was the greatest at 0.90 (0.874–0.926) followed by VAI (AUC = 0.896). In women, LAP exhibited the greatest AUC of 0.882 (0.853–0.911) followed by CVAI (AUC = 0.870). Using NCEP-ATPIII as the diagnostic criteria, LAP exhibited the greatest AUC of 0.889 (0.863–0.915) followed by VAI (AUC = 0.875) in men. In women, LAP exhibited the greatest AUC of 0.885 (0.862 to 0.908) followed by TYG (AUC = 0.883). Using IDF as the diagnostic criteria, in men, LAP exhibited the greatest AUC of 0.884 (0.857 to 0.911) followed by CVAI (AUC = 0.868).

TABLE 3 Prevalence of MetS by different criteria.

Criterion	Male (*n* = 615)			Female (*n* = 837)			Total (*n* = 1,452)		
	MetS−	MetS+	%	MetS−	MetS+	%	MetS−	MetS+	%
China (2020)	444	171	27.8	703	134	16.0*	1,147	305	21.0
NCEP-ATPIII	418	197	32.0	579	258	30.8	997	455	31.3$^{\&}$
IDF	433	182	29.6	589	248	29.6	1,022	430	29.6$^{\&}$

*P < 0.05 compared with male patients; $^{\&}$P < 0.05 compared with China (2020).

TABLE 4 Predictive value of the eight obesity- and lipid-related indices in the China (2020) criteria and multivariate logistic regression analysis.

	Male			Female			All		
	OR	*P*	AUC	OR	*P*	AUC	OR	*P*	AUC
Index	1.251 (1.171–1.337)	<0.001	0.781	1.152 (1.085–1.223)	<0.001	0.874	1.209 (1.157–1.263)	<0.001	0.822
LAP	1.063 (1.050–1.075)	<0.001	0.915	1.060 (1.048–1.073)	<0.001	0.939	1.062 (1.054–1.071)	<0.001	0.925
BRI	2.748 (2.181–3.462)	<0.001	0.809	2.378 (1.914–2.955)	<0.001	0.901	2.57 (2.206–2.993)	<0.001	0.853
CVAI	1.041 (1.033–1.050)	<0.001	0.869	1.051 (1.039–1.063)	<0.001	0.924	1.044 (1.038–1.05)	<0.001	0.902
AVI	1.407 (1.305–1.518)	<0.001	0.820	1.485 (1.359–1.624)	<0.001	0.908	1.451 (1.374–1.532)	<0.001	0.871
BAI	1.196 (1.114–1.284)	<0.001	0.732	1.119 (1.061–1.180)	<0.001	0.862	1.065 (1.03–1.101)	<0.001	0.775
TYG	45.563 (22.641–91.690)	<0.001	0.911	26.128 (13.651–50.012)	<0.001	0.935	35.069(22.057–55.757)	<0.001	0.919
VAI	4.025 (3.104–5.218)	<0.001	0.916	2.044 (1.732–2.411)	<0.001	0.916	2.445 (2.145–2.788)	<0.001	0.895

Adjusted factors: systolic blood pressure, diastolic blood pressure, total cholesterol, and eGFR.
BMI, body mass index; LAP, lipid accumulation product; BRI, body roundness index; CVAI, Chinese visceral adiposity index; AVI, abdominal volume index; BAI, body adiposity index; TYG, triglyceride glucose; VAI, visceral adiposity index.

In women, LAP exhibited the greatest AUC of 0.883 (0.860–0.906) followed by TYG (AUC = 0.866). A pairwise comparison of the AUC values for predicting MetS using the eight indicators based on the three criteria found that the AUC values for LAP were higher than those of the other seven indices, and the difference was statistically significant ($P < 0.05$). However, no statistically significant differences were noted between LAP and TYG using the NCEP-ATPIII criteria. Moreover, we found that BRI had the best forecasting ability for MetS among the four anthropometric indicators (BMI, BRI, AVI, and BAI), and the

TABLE 5 Area under the curve of seven obesity- and lipid-related indices with the different metabolic syndrome criteria.

Group	Variable	MetS-China (2020) criterion		MetS-NCEP-ATPIII criterion		MetS-IDF criterion	
		AUC (95% CI)	*P*-value	AUC (95% CI)	*P*-value	AUC (95% CI)	*P*-value
All	BMI	0.75 (0.722–0.779)	<0.001	0.722 (0.695–0.749)	<0.001	0.745 (0.719–0.771)	<0.001
	LAP	0.893 (0.874–0.912)	<0.001	0.886 (0.869–0.903)	<0.001	0.882 (0.864–0.899)	<0.001
	BRI	0.804 (0.779–0.829)	<0.001	0.775 (0.751–0.799)	<0.001	0.805 (0.783–0.828)	<0.001
	CVAI	0.86 (0.84–0.88)	<0.001	0.832 (0.811–0.853)	<0.001	0.845 (0.825–0.865)	<0.001
	AVI	0.823 (0.80–0.847)	<0.001	0.756 (0.731–0.782)	<0.001	0.781 (0.757–0.805)	<0.001
	BAI	0.587 (0.55–0.623)	<0.001	0.641 (0.611–0.671)	<0.001	0.665 (0.635–0.695)	<0.001
	TYG	0.874 (0.853–0.895)	<0.001	0.877 (0.858–0.895)	<0.001	0.854 (0.833–0.874)	<0.001
	VAI	0.849 (0.825–0.872)	<0.001	0.864 (0.844–0.885)	<0.001	0.845 (0.823–0.867)	<0.001
Male	BMI	0.742 (0.701–0.783)	<0.001	0.739 (0.699–0.779)	<0.001	0.781 (0.744–0.818)	<0.001
	LAP	0.90 (0.874–0.926)	<0.001	0.889 (0.863–0.915)	<0.001	0.884 (0.857–0.911)	<0.001
	BRI	0.777 (0.740–0.815)	<0.001	0.782 (0.746–0.819)	<0.001	0.827 (0.795–0.859)	<0.001
	CVAI	0.835 (0.803–0.866)	<0.001	0.836 (0.805–0.867)	<0.001	0.868 (0.841–0.895)	<0.001
	AVI	0.788 (0.751–0.825)	<0.001	0.793 (0.757–0.829)	<0.001	0.838 (0.808–0.868)	<0.001
	BAI	0.659 (0.613–0.706)	<0.001	0.665 (0.620–0.709)	<0.001	0.699 (0.655–0.742)	<0.001
	TYG	0.886 (0.859–0.913)	<0.001	0.872 (0.843–0.90)	<0.001	0.841 (0.809–0.873)	<0.001
	VAI	0.896 (0.870–0.923)	<0.001	0.875 (0.846–0.904)	<0.001	0.850 (0.819–0.882)	<0.001
Female	BMI	0.749 (0.707–0.792)	<0.001	0.711 (0.675–0.747)	<0.001	0.722 (0.687–0.758)	<0.001
	LAP	0.882 (0.853–0.911)	<0.001	0.885 (0.862–0.908)	<0.001	0.883 (0.860–0.906)	<0.001
	BRI	0.830 (0.796–0.864)	<0.001	0.775 (0.743–0.806)	<0.001	0.797 (0.767–0.827)	<0.001
	CVAI	0.870 (0.842–0.898)	<0.001	0.849 (0.824–0.875)	<0.001	0.854 (0.828–0.88)	<0.001
	AVI	0.842 (0.810–0.873)	<0.001	0.771 (0.739–0.802)	<0.001	0.794 (0.764–0.823)	<0.001
	BAI	0.710 (0.661–0.758)	<0.001	0.689 (0.651–0.727)	<0.001	0.705 (0.668–0.742)	<0.001
	TYG	0.858 (0.825–0.891)	<0.001	0.883 (0.859–0.907)	<0.001	0.866 (0.840–0.892)	<0.001
	VAI	0.815 (0.776–0.854)	<0.001	0.859 (0.831–0.887)	<0.001	0.843 (0.814–0.873)	<0.001

BMI, body mass index; LAP, lipid accumulation product; BRI, body roundness index; CVAI, Chinese visceral adiposity index; AVI, abdominal volume index; BAI, body adiposity index; TYG, triglyceride glucose; VAI, visceral adiposity index.

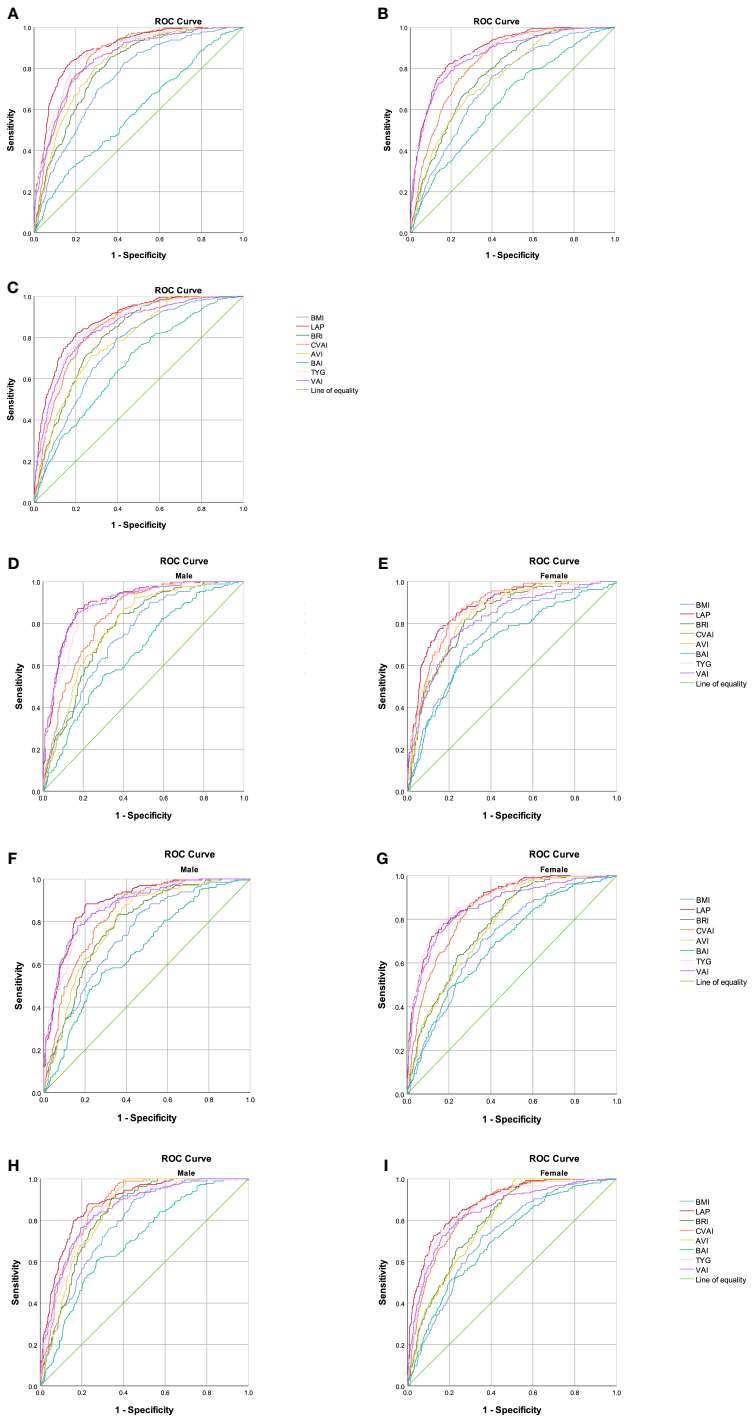

FIGURE 1
Comparison of the diagnostic values of BMI, LAP, BRI, CVAI, BAI, AVI, TYG, and VAI in predicting metabolic syndrome using three criteria in a relatively healthy Chinese population. **(A)** Chinese (2020 edition) criteria; **(B)** NCEP-ATPIII criteria; **(C)** IDF criteria. Chinese (2020) criteria: **(D)** obesity- and lipid-related indices for a relatively healthy Chinese population, men; **(E)** obesity- and lipid-related indices for a relatively healthy Chinese population, women. NCEP-ATPIII criteria: **(F)** obesity- and lipid-related indices for a relatively healthy Chinese population, men; **(G)** obesity- and lipid-related indices for a relatively healthy Chinese population, women. IDF criteria: **(H)** obesity- and lipid-related indices for a relatively healthy Chinese population, men; **(I)** obesity- and lipid-related indices for a relatively healthy Chinese population, women.

difference was statistically significant ($P < 0.05$) (Supplementary Tables 16–18). The optimal cutoff values of the eight obesity- and lipid-related indicators for predicting MetS in the three sets of criteria are displayed in Table 6 and Supplementary Tables 14, 15.

Discussion

Given the economic development and lifestyle changes, the prevalence of MetS is increasing worldwide and has become an important public health issue (28). In developed countries, such as the United States, the prevalence rate of MetS is 34.7% according to the National Health and Nutrition Examination Survey (2011–2016) (29). In China, the largest developing country, the prevalence of MetS has shown an increasing tendency. Analysis of China Nutrition and Health Surveillance data (2015–2017) found that the prevalence of metabolic syndrome among residents aged 20 years and older was 31.1% (30). The MetS diagnostic criteria are also being modified and improved, and the IDF and NECP-ATPIII criteria are the most widely used worldwide. Due to differences among ethnic groups, China has developed criteria for the diagnosis of MetS. In the MetS diagnostic criteria of the Chinese Guidelines for the Prevention and Treatment of Type 2 Diabetes (2020 edition), the cutoff points of WC, HDL-C, and FPG are different from those of the IDF and NECP-ATPIII criteria. This difference may explain why the prevalence of MetS found in this study with the China (2020 edition) criteria is lower than that with the NCEP-ATPIII and IDF criteria.

In this study, we investigated the ability of the eight obesity- and lipid-related indicators, namely, BMI, LAP, BRI, CVAI, BAI, AVI, TYG, and VAI, to predict MetS in relatively healthy people under different diagnostic criteria. We found that these eight obesity- and lipid-related indicators had reliable predictive value for MetS. Furthermore, LAP outperformed the other seven parameters in predicting MetS. Following the model design, it was discovered that the best logistic models were those using LAP, age, SBP, DBP, TC, and eGFR, which is consistent with our practice of utilizing a sole indicator to forecast MetS. Therefore, we conclude that LAP is superior for predicting MetS in relatively healthy Chinese adults. These results demonstrate that LAP is a simple and powerful tool for clinical use. This is the first study to assess the ability of these eight obesity- and

TABLE 6 The cutoff, sensitivities, specificities, and Youden's index of each variable for the screening of metabolic syndrome in the China (2020) criteria.

Group	Variable	Optimal cutoff values	Youden's index	Sensitivity (%)	Specificity (%)
All	BMI	24.10	0.396	82.6	57.0
	LAP	46.3	0.656	83.6	82.0
	BRI	3.99	0.489	84.9	64.0
	CVAI	119.06	0.595	86.9	72.6
	AVI	16.02	0.522	81.3	70.9
	BAI	31.91	0.137	31.1	82.6
	TYG	8.83	0.629	84.3	78.6
	VAI	2.23	0.569	74.8	82.1
Male	BMI	24.01	0.374	85.4	52.0
	LAP	46.28	0.698	87.1	82.7
	BRI	3.99	0.464	83.6	62.8
	CVAI	119.06	0.540	91.2	62.8
	AVI	16.23	0.469	92.4	54.5
	BAI	27.30	0.25	55.6	69.4
	TYG	8.85	0.645	85.4	79.1
	VAI	1.77	0.681	85.4	82.7
Female	BMI	25.35	0.417	68.7	73.0
	LAP	47.02	0.62	79.1	82.9
	BRI	4.21	0.544	82.1	72.3
	CVAI	114.39	0.614	87.3	74.1
	AVI	15.14	0.561	82.1	74
	BAI	32.02	0.356	61.2	74.4
	TYG	8.81	0.608	82.8	78.0
	VAI	2.24	0.518	73.1	78.7

BMI, body mass index; LAP, lipid accumulation product; BRI, body roundness index; CVAI, Chinese visceral adiposity index; AVI, abdominal volume index; BAI, body adiposity index; TYG, triglyceride glucose; VAI, visceral adiposity index.

lipid-related indicators to predict MetS in a relatively healthy population under different diagnostic criteria.

BMI, BRI, AVI, and BAI are all calculated based on anthropometric measurements, and our results show that these indicators are closely related to MetS. BMI has been shown to be a risk factor for various cardiovascular and metabolic diseases and mortality (31), but it cannot distinguish between subcutaneous and visceral fat (6, 32). BRI is a novel obesity-related index that uses WC and height to estimate body fat and visceral adipose tissue (7). Rico-Martin et al. (11) found that BRI was a better predictor of MetS among different ethnic and racial groups than BMI. This finding is consistent with our study, where we found that BRI has better predictive power for MetS than the other three anthropometric constructs (BMI, AVI, BAI). The AUC of BRI for women with MetS can be as high as 0.83 using the China (2020 edition) standards. In addition, AVI is calculated using the total abdominal volume assessment from the symphysis pubis to the xiphoid process to reflect visceral fat content. Perona et al. (15) found that WC and AVI had a strong ability to predict MetS in adolescents when using the IDF criteria. Wu et al. (33) found that AVI had good performance in identifying MetS in non-overweight/obese Chinese adults (men, 0.743; women, 0.819), which is similar to our results with the Chinese (2020 edition) criteria (men, 0.775; women, 0.831). The BAI also showed some predictive ability for MetS in a Colombian population and among Chinese postmenopausal women (34, 35). In our study, BAI was relatively weak in predicting MetS with an AUC less than 0.8, which may be due to different ethnic groups and population characteristics. Although BMI, BRI, AVI, and BAI can all predict MetS, the combination of anthropometric values and lipid-related indicators exhibited a better ability to predict MetS in our study.

LAP, CVAI, VAI, and TYG are new proxies for central obesity and lipid accumulation and can be used to assess visceral fat distribution and reflect visceral fat dysfunction by combining anthropometric markers with lipid or glucose markers. In this study, we found that the AUC values of LAP, CVAI, VAI, and TYG for the three sets of criteria were all greater than 0.8, showing good predictive performance. Since Kahn (24) proposed the LAP, several studies have found that LAP has a good ability to predict MetS (36–38), and it is calculated based on sex to better reflect the relationships between fat accumulation and lipid toxicity and cardiac metabolic disease (39). Guo et al. (40) compared the ability of LAP, VAI, BAI, and WHtR to predict MetS in low-income rural adults in Xinjiang, China, and found that LAP was a better indicator to predict MetS than the other three factors. In a Brazilian population free of cardiovascular disease and type 2 diabetes, LAP had a reliable diagnostic value for MetS compared with classic anthropometric measures (BMI, WC, waist-to-height ratio, waist-to-hip ratio) when using the American Heart Association (AHA)/National Heart, Lung and Blood Institute (NHLBI), IDF, and harmonized AHA/NHLBI and IDF standards (41). In a cross-sectional study of 552 healthy Argentine men, the AUC for LAP in predicting MetS was 0.91 (42). Our study also showed that LAP had the strongest predictive ability for MetS with a maximum AUC of 0.90. These results underscore the importance of LAP in predicting MetS in clinical practice. Xia et al. (17) believe that CVAI is a reliable and applicable indicator for evaluating visceral fat dysfunction in Chinese people and even for evaluating the metabolic health status of Asian people. Our study shows that CVAI also has a good ability to predict MetS with AUC values greater than 0.8 for all three criteria. In addition, VAI reflects abdominal fat distribution and dyslipidemia and is associated with insulin resistance (IR), abnormal glucose balance, and an increased risk of cardiovascular disease in adults (43, 44). Our previous study in patients with chronic kidney disease found that VAI had a good ability to predict MetS (45), which is consistent with the findings of this study. TYG, a product of TG and FPG, is a new visceral fat assessment tool that is associated with IR (46, 47). A Chinese study also confirmed the ability of the TYG index to identify metabolically unhealthy Chinese adults and those at high risk of cardiovascular and metabolic diseases (48). Lee et al. (49) found that TYG was a good predictor of MetS in metabolically obese but normal-weight individuals in Korea with an AUC between 0.855 and 0.868. In our study, TYG also had excellent predictive ability with an AUC between 0.841 and 0.886. The occurrence of MetS in central obesity may be closely related to the increase in visceral adipose tissue, the decrease in subcutaneous tissue expansion, and the metabolic changes in triglycerides stored in different organs, which may explain the better predictive ability of the four indicators for MetS (50).

The study had several limitations. First, this study was a cross-sectional study with a limited sample size, and we could not determine the causal relationships. Second, the survey included only individuals belonging to the relatively healthy population in China, so caution should be taken when generalizing the results to other races and groups. Third, the study did not document details about long-term medication use, education, or health status, which may have influenced the results. Finally, this is a cross-sectional study of the relatively healthy population in a community with an imbalanced proportion of controls and patients.

Conclusion

Our study shows that using different criteria, LAP, TYG, CVAI, and VAI have significant predictive efficacy for MetS in a relatively healthy population in China. LAP exhibits the best predictive efficacy, regardless of sex.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of the Chinese People's Liberation Army General Hospital. The patients/participants provided their written informed consent to participate in this study.

Author contributions

HJ and XmC, conceptualization. YD and WZ, visualization. YC, XL, ZD and YZ, funding acquisition. YD and WZ, formal analysis. ZF, YW, DZ, XS, XzC, and GC, resources. YD and WZ, writing—original draft preparation. ZL, YN and YZ, writing–review and editing. QL, HP and HL, 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.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2022.1016581/full#supplementary-material

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Association of primary allostatic load mediators and metabolic syndrome (MetS): A systematic review

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Allostatic load (AL) exposure may cause detrimental effects on the neuroendocrine system, leading to metabolic syndrome (MetS). The primary mediators of AL involve serum dehydroepiandrosterone sulfate (DHEAS; a functional HPA axis antagonist); further, cortisol, urinary norepinephrine (NE), and epinephrine (EPI) excretion levels (assessed within 12-h urine as a golden standard for the evaluation of the HPA axis activity and sympathetic nervous system activity). However, the evidence of an association between the primary mediators of AL and MetS is limited. This systematic review aimed to critically examine the association between the primary mediators of AL and MetS. PubMed and Web of Science were searched for articles from January 2010 to December 2021, published in English. The search strategy focused on cross-sectional and case–control studies comprising adult participants with MetS, obesity, overweight, and without chronic diseases. The STROBE checklist was used to assess study quality control. Of 770 studies, twenty-one studies with a total sample size (n = 10,666) met the eligibility criteria. Eighteen studies were cross-sectional, and three were case–control studies. The included studies had a completeness of reporting score of COR % = 87.0 $\pm$ 6.4%. It is to be noted, that cortisol as a primary mediator of AL showed an association with MetS in 50% (urinary cortisol), 40% (serum cortisol), 60% (salivary cortisol), and 100% (hair cortisol) of the studies. For DHEAS, it is to conclude that 60% of the studies showed an association with MetS. In contrast, urinary EPI and urinary NE had 100% no association with MetS. In summary, there is a tendency for the association between higher serum cortisol, salivary cortisol, urinary cortisol, hair cortisol, and lower levels of DHEAS with MetS. Future studies focusing on longitudinal data are warranted for clarification and understanding of the association between the primary mediators of AL and MetS.

KEYWORDS

allostatic load, cortisol, dehydroepiandrosterone sulfate, epinephrine, norepinephrine, metabolic syndrome, primary marker

1 Introduction

Metabolic syndrome (MetS) is defined as the cluster of co-existence of high blood pressure, abdominal obesity, low high-density lipoprotein (HDL) cholesterol, elevated triglycerides, and hyperglycemia (1, 2). These metabolic abnormalities have been linked to the development of type 2 diabetes (T2DM) and cardiovascular diseases (CVDs) (3). Globally, the prevalence of MetS is estimated to affect over 20% of the adult population in the USA (4), China (5), Europe (6), as well as developing countries (7, 8). The potential causal and influencing factors of MetS may be genetic, environmental (e.g., socioeconomic status, urbanicity), psychosocial (e.g., perceived stress, depression), behavioral (e.g., physical activity), and biographical (e.g., education, childhood adversity) factors that are often conditioned by sex and age (9, 10). A current meta-analysis study that involved total patients (n = 162,450) reported that MetS increased adverse cardiovascular events and mortality rates (11). Similarly, a previous systematic review reported that cumulative stress termed "allostatic load (AL)" is associated with CVDs, diabetes, and MetS (12). A very well-evaluated index for the assessment of chronic stress is the AL index, which reflects the impact of chronic stress on different allosteric systems and pathways (13, 14). Allostasis is an adaptive response mechanism to chronic stress to restore physiological stability through the autonomic nervous system (ANS), the hypothalamic–pituitary–adrenal axis (HPA), the hypothalamic–pituitary–thyroid axis (HPT), somatotropic axes (i.e., growth hormones [GH], insulin-like growth factors [IGF-I and III] and their associated carrier proteins and receptors), gonadal axis (HPG), and the metabolic and immune system (15–18). Moreover, AL is the strain on the body resulting from repeated up and downregulation of physiologic stress response, as well as by the elevated activity of physiologic systems under chronic challenge, the changes in metabolism, and the impact of wear and tear on several organs and tissues that predispose the organism to disease (19, 20).

The concept of the measurement of allostasis and AL is integrated with the AL index, which was first discussed by Seeman et al. (21). Seeman et al. (21) assessed AL using 10 biomarkers. The gold standard for the evaluation of AL is the measurement of 24 biomarkers, which are summarized into an index (22) and theoretically differentiated into primary and secondary mediators of the AL index (23, 24). The primary mediators of AL consist of four biomarkers involving serum dehydroepiandrosterone sulfate (DHEAS; a functional HPA axis antagonist); 12-h urinary cortisol excretion (an integrated measure of 12-h HPA axis activity); and 12-h epinephrine (EPI) and norepinephrine (NE) excretion levels (integrated indices of 12-h sympathetic nervous system activity) (25). The remaining six biomarkers, which are considered secondary mediators of AL, overlap with the biomarkers used in the diagnosis of MetS (14). It has been shown that there is a co-activation of the HPA axis and sympathetic adrenal medullary system (SAM) under stress (26). While the HPA axis secretes glucocorticoids (e.g., cortisol), the SAM secretes catecholamines (e.g., EPI and NE). Stress can alter glucocorticoid function to enhance gluconeogenesis and free fatty acids (FFA) by differentiation of pre-adipocytes leading to central fat accumulation and MetS development (27). On the one hand, cortisol helps to regulate SAM to create optimum homeostasis when an individual encounters acute stress. On the other hand, chronic stress leads to prolonged activation of SAM and alterations in HPA axis function in the cardiovascular, metabolic, immunologic, and central nervous systems (28). Higher cortisol levels lead to obesity and MetS (29, 30). Additionally, both dehydroepiandrosterone (DHEA) and its sulfate ester DHEAS are steroid hormones connected to stress (31). Physiologically, both DHEA and DHEAS exert anti-glucocorticoid activity (32, 33), and catecholamine synthesis and secretion (34). Low DHEAS levels and an age-related decline in DHEAS may cause higher circulating cortisol in peripheral target tissues, contributing to insulin resistance, obesity, and MetS (35, 36).

Furthermore, catecholamines such as EPI and NE modulate corticotrophin-releasing hormone (CRH) and adrenocorticotropic hormone (ACTH) during both acute and chronic stress challenges (37, 38). Ebert et al. (39) revealed that psychological stress mediated the development of MetS through the release of EPI and NE. Increasing doses of catecholamines show greater lipolytic effects on visceral fats *via* the β_1- and β_2-adrenoceptors (40). Furthermore, Ziegler et al. (41) reported that β-adrenergic blocking drugs may lead to impaired metabolism, hyperglycemia, and insulin resistance due to the inhibition of EPI stimulation. There is an emerging interest in understanding how the biomarkers of AL and MetS are connected and influence each other. Current systematic reviews have concentrated on AL and health (42), health risk behaviors and AL (12), basal cortisol levels, and MetS (43). Also, chronic stress effects on glucocorticoids and catecholamines have been reported to be an influencing factor for MetS and CVDs (44). Thus, understanding the linkage between AL and MetS is of clinical relevance. Yet, the evidence for the association between the primary mediators of AL and MetS is limited. Thus, the main aim of the current systematic review is to critically examine the associations of the primary mediators of AL and MetS in the literature. In addition, the study aims to analyze these associations in a wide range of populations.

2 Methods

2.1 Study protocol

The current systematic review was conducted and reported based on the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) (45). The completed PRISMA statement checklist is provided as a supplementary material (Supplementary Tables 1, 2).

2.2 Data source and search strategy

Two electronic databases, PubMed and Web of Science, were searched for articles published from January 2010 to December 2021 in English. The search strategy was based on the medical subject heading (MeSH) and non-MeSH search terms of keywords and the Boolean operators AND/OR ([Allostatic load; Allostatic overload; AL; Metabolic syndrome; MetS; Cortisol; Epinephrine; Norepinephrine; Dehydroepiandrosterone sulfate and DHEAS]). For additional information, the Cochrane library and the reference lists of systematic reviews found from the search were screened for related articles.

2.3 Eligibility criteria for study selection

The studies included in this systematic review met the following eligibility criteria: (I) observational studies (i.e., cross-sectional or case–control study) with an adult population (i.e., 18 years and above) that involved (II) study populations affected by MetS, obesity or overweight and control group; (III) studies examining the association between primary AL mediators: cortisol; epinephrine; norepinephrine; dehydroepiandrosterone sulfate and MetS, and (IV) original full-text studies in English. Exclusion criteria used in this systematic review were: (I) reviews, meta-analyses, case reports, expert opinions, trials, studies using animals or children, conference proceedings, and editorials, (II) duplication of the same data and population; and (III) studies using populations with other comorbidities except for individuals with MetS, overweight, or obesity. The Authors (FO and AB) established the search criteria for the study. The searches using the criteria established above for the selection of full-text articles were performed by one author (FO). Disagreements were resolved by a discussion with the second author (AB).

2.4 Data extraction

The titles and abstracts of articles identified *via* the search were screened for relevance and cross-checked for eligibility. Full-text reports of relevant articles were also screened for their eligibility. Information on the search results is provided in Figure 1. Information from the included studies was extracted (see Table 1 for more details). Data extraction was performed by one author (FO).

2.5 Assessment of study methodological quality

The Joanna Briggs Institute (JBI) critical appraisal tool was used to assess the methodological quality of the included studies (67). The questions in the JBI included: (a) a clear description of study objectives; (b) clear description of inclusion and exclusion criteria for study participants; (c) a clear description of the population; (d) clearly describing the method of measurement of exposure; (e) characteristics of the mediator/moderator and outcome variables reported; (f) identifying and measuring potential confounders; (g) control of confounders; and (h) appropriate statistics used in answering study objectives. The JBI score assigns a maximum of 8 points (for cross-sectional studies) and 10 points (for case–control studies), indicating the highest study quality. For this systematic review, overall points of ≥5 for all cross-sectional and overall points of ≥6 for case–control studies were considered sufficient for inclusion. The studies were independently reviewed by one author (FO). This JBI tool has been used in other studies, making it a relevant tool to be used in this systematic review (68, 69).

2.6 Assessment of study quality control

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Checklist was used for study quality control assessment (70). The checklist contains a total of 22 items, which evaluated the reporting of each study's title, abstract, introduction, methodology, results, and discussion. One author (FO) evaluated the studies for each item on the STROBE checklist as "yes," "no," or "not applicable" and calculated the number and percentage (%) of the included studies matching each item on the STROBE checklist. The completeness of reporting (COR) was calculated from the formula: COR (%) = (yes ÷ (yes + no) × 100) for each included study. A COR score of (if 0%–49% of items were met) was considered low, (if 50%–74% of items were met) was considered "moderate," and (if ≥75% of items were met) was considered "high." A similar protocol has been used in a study published elsewhere (12).

2.7 Statistical methods

All studies derived from the two databases that provided data on primary mediators of AL and MetS were considered eligible for analysis using Microsoft Excel version 16.63.1 (Microsoft Corporation, Redmond-Washington, USA). The included studies reported the associations between primary mediators of AL and MetS, usually using descriptive statistics (i.e., means and standard deviations) and inferential statistical models. Descriptive statistics, mainly frequency distributions, were used to report all the pooled measurements of the primary mediators of AL (i.e., salivary cortisol, serum cortisol, urinary cortisol (UFC), hair cortisol concentration (HCC), DHEAS, urinary EPI, and urinary NE) and their association with MetS.

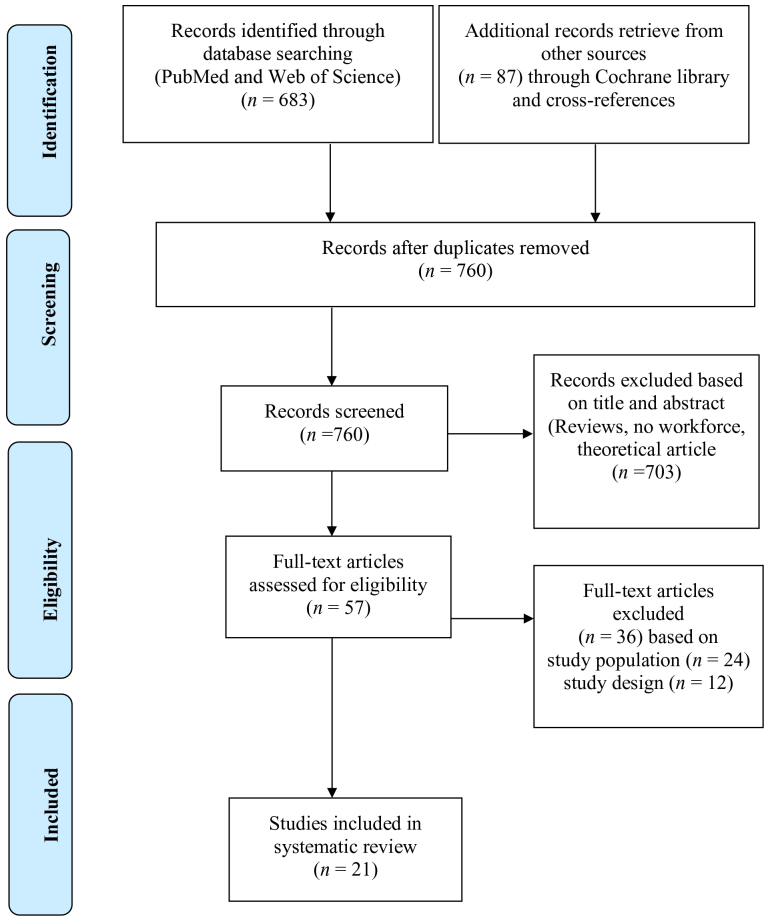

FIGURE 1
PRISMA flow diagram of search results.

3 Results

3.1 Main characteristics of studies included

The search of the databases (PubMed, *n* = 173 and Web of Science, *n* = 510) yielded 683 studies. Additional records retrieved from other sources through the Cochrane library and cross-references yielded 87 studies, resulting in an overall 770 studies. Out of these studies, 57 studies were assessed for eligibility after excluding 703 studies. Only 21 studies were considered for this systematic review after excluding 24 studies based on the study population and 21 studies based on study design. The included studies had a total number of participants (*n* = 10,666) with ages between 18 and 75 years. The sample size ranged from 37 to 4,225 participants within different populations (i.e., MetS, without MetS, workers, veterans, overweight, and obese). The included studies were published on different continents, consisting of: Europe (*n* = 8), Asia (*n* = 5), North America (*n* = 3), South America (*n* = 3), Africa (*n* = 1), and Australia (*n* = 1). Eighteen studies were cross-sectional, and three were case–control studies. Studies that reported cortisol as the primary mediator of AL were grouped into long-term cortisol measures (i.e., urinary cortisol [UFC] and hair cortisol concentration [HCC]) and short-term cortisol measures (i.e., salivary and serum cortisol). From the included studies, four studies measured UFC, two studies measured HCC, nine studies measured salivary cortisol, and nine studies measured serum cortisol. DHEAS was measured in six studies as a primary mediator of AL. Urinary EPI and urinary NE were measured in one study as primary mediators of AL (see Table 1 for details).

TABLE 1 Study characteristics of the association between the primary mediators of AL and MetS (n = 21).

Author/Date (Country)	MetS diagnosis	Sample		Primary AL mediators	Measurement techniques of primary AL mediators	Association between primary mediators of AL and MetS (Adjustment)	JBI Score
		N (sex %)	MetS (%)				
1. Cross-sectional studies							
Mazgelytė et al. (46) (Lithuania)	IDF	163 adults Men = 100%	MetS = 23.3 without MetS = 76.7	HCC	High-performance liquid chromatography	Significant association (p <0.005) was observed for higher HCC between participants with MetS (85.73 [150.88] ng/g) in comparison without MetS (36.50 [98.26] ng/g). (Non-adjusted).	8
				Serum cortisol	Enzyme-linked immunoassay	No significant association (p = 0.168) was observed for serum cortisol concentration between participants with MetS (221.78 [94.29] ng/ml) and participants without MetS (200.62 [128.15] ng/ml). (Non-adjusted).	
				Salivary cortisol	Enzyme-linked immunoassay	No significant association (p = 0.193) observed for salivary cortisol concentration between participants with MetS (9.16 [6.78] ng/ml) and participants without MetS (11.09 [9.85] ng/ml). (Non-adjusted).	
Lehrer et al. (47) (USA)	NCEP-ATP III (2004)	228 adults Men = 32% Women = 68%	Not applicable	HCC	Enzyme-linked immunoassay	Higher HCC was positively associated with MetS severity (b = 0.344, SE = 0.126, *95% CI* [0.106, 0.605]).(Adjusted for age, sex, race/ethnicity, income, medication use, physical activity, nervous and calm personality, hair washing, and bleach use).	7
Martins et al. (48) (Brazil)	NCEP-ATP III (2001)	80 adults Men = 43.7% Women = 56.3%	MetS = 50.0 without MetS = 50.0	Salivary cortisol	Radioimmunoassay	No significant association (p = 0.47) was observed for basal salivary cortisol between participants with MetS (44.4 ± 3.1 nmol/L) and participants without MetS (46.5 ± 2.9 nmol/L). (Non-adjusted).	5
Udenze et al. (49) (Nigeria)	NCEP-ATP III (2001)	100 adults Women = 100%	MetS = 50.0 without MetS = 50.0	Serum cortisol	Enzyme-linked immunoassay	No significant association (p = 0.437) was observed for serum cortisol between participants with MetS (12.80 ± 4.79 µg/dl) and participants without MetS (10.83 ± 6.59 µg/dl). (Non-adjusted).	5
Damgaard–Olesen et al. (50) (Denmark)	IDF	303 adults Men = 100%	Mets = 29.7 without MetS = 70.3	DHEAS	TurboFlow-Liquid Chromatography-Mass Spectrometry LC-MS/MS	No significant association (p = 0.23) was observed for DHEAS between participants with MetS (*Geometric Mean* = 4,527 nmol/L) and participants without MetS (*Geometric Mean* = 4,185 nmol/L). (Non-adjusted).	8
Constantinopoulos et al. (51) (Greece)	IDF	37 adults. Men = 47% Women = 53%	MetS = 51.4 without MetS = 48.6	UFC	Chemiluminescence immunoassay	Significant association (p >0.01) was observed for higher 24-h UFC for participants with MetS (116.8 ± 106.6 µg/24-h) in comparison to participants without MetS (71.3 ± 62.7 µg/24-h). (Non-adjusted).	6
				Serum cortisol	Chemiluminescence immunoassay	Significant association (p >0.01) for higher serum cortisol was observed between participants with MetS (16.6 ± 7.2 µg/ml) in comparison to participants without MetS (10.7 ± 4.1 µg/ml). (Non-adjusted).	
				Salivary cortisol	Chemiluminescence immunoassay	Significant association (p >0.01) was observed for higher salivary cortisol between participants with MetS (0.87 ± 0.4 µg/ml) in comparison with participants without MetS (0.46 ± 0.21 µg/ml). (Non-adjusted).	
Corbalán-Tutau et al. (52) (Spain)	IDF	70 adults Women = 100%	MetS = 57.0 without MetS = 43.0	Salivary Cortisol	Radioimmunoassay	Significant associations (p <0.05), in daily circadian markers for lower salivary cortisol levels (nmol/l) in participants with MetS in comparison participants without MetS. 8 am: MetS (17.1 ± 1.0 nmol/l) vs without MetS (25.3 ± 1.6 nmol/l). 14 pm: MetS (10.6 ± 0.3 nmol/l) vs without MetS (11.9 ± 0.4 nmol/l).	8

(Continued)

TABLE 1 Continued

Author/Date (Country)	MetS diagnosis	Sample		Primary AL mediators	Measurement techniques of primary AL mediators	Association between primary mediators of AL and MetS (Adjustment)	JBI Score
		N (sex %)	MetS (%)				
						23 pm: MetS (5.0 ± 0.2 nmol/l) vs without MetS (6.3 ± 0.3 nmol/l) (Non-adjusted).	
Almadi et al. (53) (Australia)	IDF	204 adults Men = 100%	MetS = 31.9 without MetS = 68.1	Salivary Cortisol	Electrochemiluminescence	Significant association (p <0.05) was observed for higher salivary cortisol between stress group with MetS (326.9 ± 153.3 nmol/L) in comparison with non-stress group without MetS (267.3 ± 99.2 nmol/L). (Adjusted for age, type of work, physical activity, awakening time, and work overcommitment).	8
Fabre et al. (54) (Belgium)	IDF & NCEP-ATP III (2001)	149 adults Men = 100%	MetS = 44.3 without MetS = 55.7	Serum Cortisol	Chemiluminescence immunoassay	No significant association (p >0.05) was observed for serum cortisol between participants with MetS (13.7 [5.7–23.6] µg/dl) and participants without MetS (13.3 [5.9–29.4] µg/dl). (Adjusted for age and BMI).	8
**Mattei et al. (55) (USA)	AHA/ NHLBI	1318 adults Men = 27.8% Women = 72.2%	MetS = 67.6 without MetS = 32.4	UFC	Direct immunoenzymatic colorimetric method	No significant association (p >0.05) between UFC (mg/g creatinine) (OR = 1, 95% CI [0.995,1.004]) and participants with MetS. (Adjusted for age and sex).	8
				DHEAS	Electrochemiluminescence	No significant association (p >0.05) was observed for DHEAS (OR = 1, 95% CI [1,1] ng/ml) and MetS. (Adjusted for age and sex).	
				Urinary EPI	Direct immunoenzymatic colorimetric method.	No significant association (p >0.05) was observed between 12-h urinary EPI (µg/g creatinine) (OR = 0.97, 95% CI [0.938, 1.00]) and MetS. (Adjusted for age and sex).	
				Urinary NE	Direct immunoenzymatic colorimetric method.	No significant association (p >0.05) was observed between 12-h urinary NE (µg/g creatinine) (OR = 1, 95% CI [0.998, 1]) and MetS. (Adjusted for age and sex).	
Jang et al. (56) (Korea)	IDF	46 adults Men = 59% Women = 41%	MetS = 26.0 without MetS = 74.0	Salivary Cortisol	Competitive enzyme immunoassay	Significant association (p = 0.0001) was observed for higher midnight salivary cortisol levels between participants with MetS (70 ± 42.4 ng/dl) in comparison with participants without MetS (48.1 ± 36.8 ng/dl). (Non-adjusted).	8
Baudrand et al. (57) (Chile)	NCEP-ATP III (2004)	221 adults Men = 26.2% Women =73.8%	MetS = 58.8 without MetS = 41.2	UFC	High-performance liquid Chromatography (HPLC)	No significant association (p = 0.196) was observed for UFC between participants with MetS (21.13 [11.3–28.1 µg/24 h]) and participants without MetS (24.81 [13.8–31.2 µg/ 24 h]). (Non-adjusted).	8
Esteghamati et al. (58) (Iran)	NCEP-ATP III (2001)	285 adults Men = 43.5% Women = 56.5%	MetS = 42.1 without MetS = 57.9	Serum cortisol	Radioimmunoassay	No significance association (p >0.05) was observed for serum cortisol between males and females with MetS (15.16 ± 5.04 µg/dl) and with males and females without MetS (14.56 ± 4.66 µg/dl). (Non-adjusted). Significant association (p <0.05) for higher serum cortisol in males with MetS (17.74 ± 5.1 µg/dl). (Adjusted for age, WC, and BMI).	6
Park et al. (59) (Korea)	NCEP-ATP III (2004)	1881 adults Men = 43.9% Women = 56.1%	Mets = 27.3 without MetS = 72.7	Serum Cortisol	Radioimmunoassay	Significant association was observed for both males (b = 1.084, SE = 0.021, p = 0.000) and females (b = 1.031, SE = 0.015, p = 0.040) with higher serum cortisol (µg/dl) and MetS. (Adjusted for age and BMI).	6
Austin-Ketch et al. (60) (USA)	NCEP-ATP III (2001)	102 adults Men =	MetS = 17.7 without	Salivary Cortisol	Chemiluminescence immunoassay	No significant association (p = 0.930) was observed for salivary cortisol and the presence of MetS (F [2, 63] = 0.072; partial η (= 0.002). (Non-adjusted)	8

(Continued)

TABLE 1 Continued

Author/Date (Country)	MetS diagnosis	Sample		Primary AL mediators	Measurement techniques of primary AL mediators	Association between primary mediators of AL and MetS (Adjustment)	JBI Score
		N (sex %)	MetS (%)				
		59.8% Women = 40.2%	MetS = 82.3			Significance difference (p = 0.05) was observed in mean diurnal AUC values between males with MetS and males without MetS. (Non-adjusted).	
Bengtsson et al. (61) (Sweden)	NCEP-ATP III (2001)	175 adults Men = 48% Women = 52%	MetS = 16.6 without MetS = 83.4	Salivary Cortisol	Radioimmunoassay	Significant association (p = 0.02) was observed for higher salivary cortisol awakening response percentage (CAR%) for women with MetS (CAR% = 91.4 [17.0 nmol/L] in comparison to men without MetS (CAR% = 38.5[13.1nmol/L]. (Non-adjusted).	8
62 (Taiwan)	AHA/ NHLBI	585 adults Men = 100%	MetS = 33.3 without MetS = 66.7	DHEAS	Electrochemiluminescence	Significant (p >0.001) association was observed for higher DHEAS between participants with MetS (3.1 ± 2.0 µmol/L) in comparison with participants without MetS (2.4 ± 1.6 µmol/L). (Non-adjusted).	8
Phillips et al. (63) (United Kingdom)	IDF	4255 adults Men = 100%	MetS = 13.7 without MetS = 86.3	Serum cortisol	Radioimmunoassay	No significant association between serum cortisol and MetS was observed (OR = 1.31; 95%CI: 0.98, 1.76; p = 0.07). (Adjusted for age, place of service, ethnicity, marital status, alcohol consumption, smoking, household income and education grade).	8
				DHEAS	Radioimmunoassay	Higher DHEAS concentrations significantly reduced MetS (OR = 0.56, 95% CI 0.46–0.69, p <0.001). (Adjusted for age, place of service, ethnicity, marital status, alcohol consumption, smoking, household income and education grade).	
2. Case–control studies							
Garcez et al. (64) (Brazil)	JIS	250 adults Women = 100%	MetS = 20.0 Controls = 80.0	Salivary Cortisol	Chemiluminescence immunoassay	No significant associations were observed for daily circadian cortisol changes between participants with MetS and participants without MetS. awakening cortisol levels: MetS (5.37 ± 4.10 nmol/l) vs without MetS (6.03 ± 5.39 nmol/l, p = 0.57), salivary cortisol levels after work: MetS (2.78 ± 2.87 nmol/l) vs without MetS (2.78 ± 2.85 nmol/l, p = 0.93). (Adjusted for age).	9
Kazakou et al. (65) (Greece)	AHA/ NHLBI	I59 adults Men = 42.1% Women = 57.9%	MetS = 54.1 Controls = 45.9	Serum cortisol	Chemiluminescence immunoassay	No significant association (p >0.05) was observed for serum cortisol between participants with MetS (466.27 ± 146.23 nmol/L) and participants without MetS (455.24 ± 168.30 nmol/L). (Non-adjusted).	9
Özçelik et al. (66) (Turkey)	NCEP-ATP III (2001)	55 adults. Women = 100%	MetS = 63.6 Controls = 36.4	UFC	Immunoenzymatic colorimetric method	Significant association (p <0.05) was observed for lower serum DHEAS between participants with MetS (116 [68.00–152.00] µg/dl) in comparison without MetS (166.50[138.00–213.75 µg/dl]). (Non-adjusted).	7
				Serum cortisol	Immunoenzymatic colorimetric method	Significant association (p <0.001) was observed for higher serum cortisol between participants with MetS (18.77 [9.60–25.41] µg/dl) in comparison with participants without MetS (12.71 [11.29–15.70] µg/dl). (Non-adjusted).	
				DHEAS	Electrochemiluminescence	Significant association (p <0.05) was observed for lower DHEAS between participants with MetS (116 [68.00–152.00] µg/dl) in comparison without MetS (166.50 [138.00–213.75] µg/dl). (Non-adjusted).	

*Key: IDF, International Diabetes Federation; AHA/NHLBI, American Heart Association/National Heart, Lung, and Blood Institute; MetS, Metabolic syndrome; DHEAS, Dehydroepiandrosterone sulfate; NCEP-ATP III, National Cholesterol Education Program's Adult Treatment Panel III; UFC, Urinary free cortisol; CAR%, cortisol awakening response percentage; JIS, Joint Interim Statement; HCC, hair cortisol concentrations; SC, Serum cortisol; BMI, Body mass index; WC, Waist circumference; JBI, The Joanna Briggs checklist for analytical cross-section studies and case–control studies.
**Additional data was obtained from the Authors.

3.2 Main results

The results are reported based on the different primary mediators of AL and its association with MetS. Afterwards, the results are summarized with the findings. Two studies (55, 57) found no significant associations, whereas two studies (51, 66) found significant associations between UFC and MetS. Two studies (46, 47) found significant associations between HCC and MetS. Four studies (46, 48, 60, 64) found no significant association, whilst six studies (51–53, 56, 60, 61) found significant associations between salivary cortisol and MetS. Six studies (46, 49, 54, 58, 63, 65) found no significant associations, but four studies (51, 58, 59, 66) found significant associations between serum cortisol and MetS. Two studies (50, 55) found no significant associations, while three studies (62, 63, 66) found significant associations between DHEAS and MetS. One study (55) found no significant associations between urinary EPI, urinary NE, and MetS.

3.3 Summary of results

Regarding cortisol, it can be summarized that UFC (12-h or 24-h) showed a significant association with MetS in 50% of the studies, and HCC showed a significant association with MetS in 100% of the studies. Short-term measures including serum cortisol showed a significant association with MetS in 40% of the studies, and salivary cortisol showed a significant association with MetS in 60% of the studies, respectively. In 60% of the studies, DHEAS showed a significant association with MetS. Both urinary EPI and NE (12-h) showed no significant association with MetS in 100% of the studies.

4 Assessment heterogeneity

4.1 Metabolic syndrome diagnoses criteria

There were variations in the diagnosis of MetS in the included studies. Six studies used the "Third National Cholesterol Education Program and Adult Treatment Panel" (NCEP-ATP III) 2001 criteria, and three studies used the 2004 criteria. Seven studies used the "International Diabetes Federation" (IDF) criteria. Three studies used the 2005 criteria of the "American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI). One study used the "Joint Interim Statement" (JIS) criteria. One study used both IDF and NCEP-ATP III (2001) criteria. The different institutional criteria used in the diagnosis of MetS are explained in detail in a study by Alberti et al. (2).

4.2 Assessment criteria for primary allostatic load markers: Measurement of cortisol

UFC (12-h or 24-h) was measured in four studies with chemiluminescence immunoassay (51), direct immunoenzymatic colorimetric method (55), high-performance chromatography (57), and electrochemiluminescence immunoassay (66). HCC was measured in two studies using enzyme-linked immunoassay (47) and high-performance chromatography (46). Salivary cortisol was measured in nine studies with enzyme-linked immunoassay (46), chemiluminescence immunoassay (51, 60, 64), radioimmunoassay (RIA) (48, 52, 61), electrochemiluminescence immunoassay (53), and competitive enzyme immunoassay (56). Serum cortisol was measured in eight studies with enzyme-linked immunoassay (46, 49, 51, 54, 65), RIA (58, 59), and electrochemiluminescent immunoassay (66).

4.3 Assessment criteria for primary allostatic load markers: Measurement of DHEAS

DHEAS was measured in five studies with the turboFlow-LC-MS/MS method (50), chemiluminescent immunoassay (55, 66), electrochemiluminescent immunoassay (62), and RIA (63).

4.4 Assessment criteria for primary allostatic load markers: Measurement of epinephrine and norepinephrine

In one study, urinary EPI and urinary NE (12-h) were measured using a 2-CAT enzyme immunoassay read on a Dynex MRX 96-well plate reader (55).

4.5 Study methodological quality

Applying the JBI tool, twenty studies representing 95.2% were judged very well to excellent (≥6 to ≥10) while one study representing 4.8% was judged fairly good (≥5). The summary of scores of the included studies is presented in Tables 2, 3.

4.6 Study quality control

The STROBE Checklist for study quality control assessment was performed on the 21 included studies. From the included studies, one study had moderate score (COR = 50%–74%), and twenty studies had high score (COR = ≥75%). The mean COR

score for the included studies was 87.0 ± 6.4% suggesting a higher study quality control (see Table 4).

5 Discussion

This systematic review examines the association between primary mediators of AL and the presence of MetS. The systematic review further highlights psychosocial, environmental, anthropometric, and socio-demographic factors influencing the association between the primary mediators of AL and MetS. Regarding the primary AL mediator cortisol, it is to be noted that MetS is associated with higher HCC and in some studies further with UFC, serum cortisol and salivary cortisol. In addition, the other HPA axis-related marker, DHEAS, showed a significant association with MetS. On the other hand, regarding primary mediators of the autonomic nervous system, there is no significant association between urinary EPI, urinary NE, and MetS. The findings of the current systematic review demonstrate that chronic stress leading to higher cortisol levels and low DHEAS levels may be associated with a hyperresponsive HPA axis. In the pathogenesis of MetS, this occurs.

Also, the two studies (51, 66) that reported an association between UFC and MetS involved participants with a body mass index (BMI = 39.3–52.4 kg/m^2). In contrast, the other two studies (55, 57) that reported no association between UFC and MetS had participants with a BMI of 29.2–32.9 kg/m^2. The results indicate that adults with higher BMI or obesity are most likely to have MetS and a hyperresponsive HPA axis due to increased cortisol levels. The results confirm a previous systematic review that reported that obesity appears to be related to a hyperresponsive HPA axis (72). An increase in body weight may lead to chronic low-grade inflammation, which may provoke an increased production of pro-inflammatory cytokines. The increased production of pro-inflammatory cytokines may cause chronic HPA axis activation, leading to visceral obesity and MetS (73). The discrepancies in the findings on the association between UFC and MetS in this systematic review may be attributed to the ethnicity variation in the diagnosis of MetS. This may be due to the varying measurement techniques employed in the various studies. Alberti et al. (2) reported different ethnicity variations in the diagnosis of MetS. Also, none of the included studies used the gold standard in measuring UFC, i.e., 24-h UFC measured by liquid chromatography with tandem mass spectrometry (LC-MS/MS) (74). Hence, longitudinal research focusing on the gold standard for measuring UFC and its association with MetS across different ethnicities is vital for understanding chronic stress's effects on metabolic abnormalities.

The literature review showed inconsistent findings based on sex for the association between salivary cortisol and serum cortisol with MetS. Similar findings based on cortisol and sex have been reported in another systematic review (72). Significant associations between higher serum cortisol (59) and higher cortisol awakening response (CAR) (61) were found for both men and women with MetS. Bengtsson et al. (61) further reported an association between CAR and depressive symptoms in women. CAR is the measure of the dynamics of the HPA axis response upon awakening (75). A dampened CAR shows impaired HPA axis reactivity and has been suggested to be associated with metabolic abnormalities (75, 76). On the contrary, Esteghmati et al. (58) found only an association between serum cortisol and MetS in men.This shows that cortisol is a key marker in the stress response in both men and women. This calls for future research to study stress effects on HPA axis dysregulation and metabolic abnormalities in both sexes. Additionally, the literature review found mixed findings for the association between salivary and serum cortisol and MetS in workers. The studies in poultry workers (64) and police officers (60) found no association between salivary cortisol and MetS. In contrast, Almadi et al. (53) found associations between salivary cortisol and MetS in different workers (i.e., veterinary, agricultural, textile, and poultry industries). Also, the only study (63) that measured serum cortisol in veterans of the Vietnam-era USA army found no association with MetS. Notably, a previous systematic review reported that the effects of job strain and MetS appear to be significant (77). This shows that different job strain may affect the neuroendocrine systems differently in the pathogenesis of MetS. Hence, workplace health promotion programs geared toward stress management are needed to prevent the adverse effects of job strain on the neuroendocrine system of workers (78).

In this systematic review, some studies (50, 55) reported no associations between DHEAS and MetS, while others did (62, 63, 66). Furthermore, Chen et al. (62) found that participants with MetS had a higher DHEAS (3.1 ± 2.0 μmol/L) as compared to participants without MetS (2.4 ± 1.6 μmol/L). This could be due to steroid biosynthetic defects of the adrenal glands or functional adrenal hyperplasia, and age-related changes in the adrenal secretory pattern of the participants (Age = 67.8 ± 8.4) employed in their study (79). DHEAS declines with age and may lead to age-specific diseases such as obesity and MetS (44). This age-related decline in DHEAS is attributed to a mechanism termed "adrenopause" (80). There are limited studies investigating the association between DHEAS and MetS. Hence, the interplay between DHEAS and MetS warrants further study.

The only study (55) that reported on urinary NE and urinary EPI found no significant association with MetS. Foremost, Zouhal et al. (40) demonstrated that increased levels of catecholamines lead to lipolytic effects on visceral fats by β_1- and β_2-adrenoceptors. Conversely, β-adrenergic blocking drugs inhibit EPI stimulation, leading to impaired glucose metabolism, hyperglycemia, and insulin resistance (41). While most of the NE is secreted by the sympathetic nerve endings, the adrenal glands secrete EPI (81). Thus, these catecholamines, which play

TABLE 2 Joanna Briggs Institute (JBI) scores for cross-sectional studies.

Study	Participants and setting described in detail,including similarity of controls	Criteria for inclusion clearly defined and exposures similarly measured	Exposure measured invalid and reliable way	Objective, standard criteria used for measurement of condition	Confounding factors identified	Strategies to deal with confounding factors stated	Outcomes measured invalid and reliable way	Appropriate statistical analysis used?
Mazgelytė et al. (46) (Lithuania)	+	+	+	+	+	+	+	+
Lehrer et al. (47) (USA)	+	+	+	–	+	+	+	+
Martins et al. (48) (Brazil)	+	–	+	+	–	–	+	+
Udenze et al. (49) (Nigeria)	+	+	+	+	–	–	+	+
Damgaard-Olesen et al. (50) (Denmark)	+	+	+	+	+	+	+	+
Constantinopoulos et al. (51) (Greece)	+	+	+	+	–	–	+	+
Corbalán-Tutau et al. (52) (Spain)	+	+	+	+	+	+	+	+
Almadi et al. (53) (Australia)	+	+	+	+	+	+	+	+
Fabre et al. (54) (Argentina)	+	+	+	+	+	+	+	+
Mattei et al. (55) (USA)	+	+	+	+	+	+	+	+
Jang et al. (56) (Korea)	+	+	+	+	+	+	+	+
Baudrand et al. (57) (Chile)	+	+	+	+	+	+	+	+
Esteghamati et al. (58) (Iran)	+	+	+	+	–	–	+	+
Park etal. (59) (Korea)	+	+	+	+	–	–	+	+
Austin-Ketch et al. (60) (USA)	+	+	+	+	+	+	+	+
Bengtsson et al. (61) (Sweden)	+	+	+	+	+	+	+	+
Chen et al. (62) (Taiwan)	+	+	+	+	+	+	+	+
Phillips et al. (63) (United Kingdom)	+	+	+	+	+	+	+	+

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TABLE 3 Joanna Briggs Institute (JBI) scores for Case–control studies.

Study	Group comparable in the presence of disease in cases and absence of diseases in controls	Cases and controls matched appropriately	Same criteria used for identifying cases and controls	Exposure measured invalid and reliable way	Exposure measured in same way as cases and controls	Confounding factors identified	Strategies to deal with confounding factors stated	Outcomes measured in standard, valid and reliable way for cases and controls	Exposure period of interest long enough to be meaningful	Appropriate statistical analysis used?
Garcez etal. (64) (Brazil)	+	+	+	+	+	+	+	+	-	+
Kazakou etal. (65) (Greece)	+	+	+	+	+	+	+	+	-	+
Özçelik etal. (66) (Turkey)	+	+	+	+	+	-	-	+	-	+

roles under stress conditions to foster thermogenesis and secretion of insulin, may operate in a divergent fashion in the pathogeneses of MetS (41). From a research perspective, measuring 12-h urine collections for EPI and NE may be labor-intensive and impractical due to poor adherence (14). These findings should be interpreted with caution due to insufficient data.

Most studies used immunoassays for the measurement of cortisol. It should be noted that urine contains conjugated cortisol and other metabolites (82). Assessing UFC and salivary cortisol may lead to cross-reactivity of the antibodies in the immunoassays with other metabolites in urine and steroids in saliva (82, 83). Serum cortisol may not reflect the unbound (free) cortisol levels due to changes in albumin or cortisol binding globulin levels (74). Hence, using the LC-MS/MS to measure 24-h urinary cortisol is the gold standard (74). Mass spectrometry provides reliable cortisol measurement outcomes and prevents cross-reactivity of metabolites (74, 82, 84). Although Alberti et al. (2) released the joint interim statement concerning the diagnosis of MetS, only one study (64) used the joint interim statement criteria for the diagnosis of MetS in the included studies. Thus, caution should be taken when interpreting these results.

5.1 Strengths and limitations

This is the first systematic review to be conducted on the association between primary mediators of AL and MetS using cross-sectional and case–control studies. The large sample size and different populations in the included studies broaden the perspective on how the primary mediators of AL are associated with MetS. Despite these strengths, there are limitations to be reported. The cross-sectional data may prevent the cause–effect relationship between the primary mediators of AL and MetS at the time of measurement due to modifications of these mediators in the long term. The included studies had a wide difference in their methodologies. Most studies used different measurement techniques in measuring the primary mediators of AL, especially cortisol. This makes it difficult to make vivid comparisons and generalizations. Also, the included studies employed different institutional criteria for the diagnosis of MetS. This creates heterogeneity in the diagnosis of MetS. These factors could not be controlled in this systematic review. Additionally, only studies in English were included, which could have omitted potential studies published in other languages for inclusion.

6 Conclusion

The present systematic review revealed that there is a tendency for an association between higher UFC, HCC, serum cortisol, salivary cortisol, and lower DHEAS with MetS. There is

TABLE 4 STROBE Statement—A checklist of items and the completeness of reporting score (COR %) for the included studies (n = 21).

	Item No.	Recommendation	Criteria Met (N, %) Yes	No	N/A
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	21 (100)	0 (0)	0 (0)
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	21 (100)	0 (0)	0 (0)
Introduction					
Background/ rationale	2	Explain the scientific background and rationale for the investigation being reported	21 (100)	0 (0)	0 (0)
Objectives	3	State-specific objectives, including any prespecified hypotheses	21 (100)	0 (0)	0 (0)
Methods					
Study design	4	Present key elements of study design early in the paper	21 (100)	0 (0)	0 (0)
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	21 (100)	0 (0)	0 (0)
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case–control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	N/A 3 (100) 16 (76.1)	N/A 0 (0) 2 (9.6)	N/A 0 (0) 3 (14.3)
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case–control study*—For matched studies, give matching criteria and the number of controls per case	3 (100)	0 (0)	0 (0)
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	19 (90.4)	2 (9.6)	0(0)
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	21 (100)	0 (0)	0 (0)
Bias	9	Describe any efforts to address potential sources of bias	19 (90.4)	2 (9.6)	0 (0)
Study size	10	Explain how the study size was arrived at	20 (95.2)	1 (4.8)	0 (0)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	21 (100)	0 (0)	0 (0)
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	20 (95.2)	1 (4.8)	0 (0)
		(*b*) Describe any methods used to examine subgroups and interactions	21 (100)	0 (0)	0 (0)
		(*c*) Explain how missing data were addressed	3 (14.3)	2 (9.6)	16 (76.1)
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case–control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	20 (95.2)	1 (4.8)	0 (0)
		(*e*) Describe any sensitivity analyses	20 (95.2)	0 (0)	1 (4.8)
Results					
Participants	13*	(a) Report numbers of individuals at each stage of study—e.g., numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed	21 (100)	0 (0)	0 (0)
		(b) Give reasons for non-participation at each stage	5 (23.8)	3 (14.3)	13 (61.9)
		(c) Consider use of a flow diagram	0 (0)	21 (100)	0 (0)
Descriptive data	14*	(a) Give characteristics of study participants (e.g., demographic, clinical, social) and information on exposures and potential confounders	19 (90.4)	1 (4.8)	1 (4.8)

(Continued)

TABLE 4 Continued

	Item No.	Recommendation	Criteria Met (*N*, %) Yes	No	N/A
		(b) Indicate number of participants with missing data for each variable of interest	2 (9.6)	1 (4.8)	18 (85.6)
		(c) *Cohort study*—Summarize follow-up time (e.g., average and total amount)	N/A	N/A	N/A
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	N/A	N/A	N/A
		Case–control study—Report numbers in each exposure category, or summary measures of exposure	3 (100)	0 (0)	18 (0)
		Cross-sectional study—Report numbers of outcome events or summary measures	19 (90.4)	2 (9.6)	0 (0)
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included	19 (90.4)	2 (9.6)	0 (0)
		(*b*) Report category boundaries when continuous variables were categorized	13 (61.9)	1 (4.8)	7 (33.3)
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	13 (61.9)	5 (23.8)	3 (14.3)
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	21 (100)	0 (0)	0 (0)
Discussion					
Key results	18	Summarize key results with reference to study objectives	21 (100)	0 (0)	0 (0)
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11 (52.4)	10 (47.6)	0 (0)
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15 (71.4)	6 (28.6)	0 (0)
Generalisability	21	Discuss the generalizability (external validity) of the study results	9 (42.9)	12 (57.1)	0 (0)
Other information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13 (61.9)	7 (33.3)	1 (4.8)
Completeness of Reporting mean of the 21 studies (%)			**87.0 ± 6.4%**		

"*" refer to Vandenbroucke et al., (71).

no association between urinary NE and urinary EPI with MetS. Different assays for measuring the primary mediators of AL and the association of MetS may yield different outcomes. Research focusing on the standardization of measurement protocols for the primary mediators of AL would be vital for uniformity, comparability, and generalization. It is helpful to identify a cluster of biomarkers from the MetS diagnosis that best reflects the primary mediators of AL in order to foster preventive measures for individuals with altered levels of primary mediators. Future studies focusing on longitudinal data are warranted for clarification and understanding of the association between the primary mediators of AL and MetS.

Data availability statement

The datasets generated for this study are available upon reasonable request to the corresponding author.

Author contributions

FO and AB conceived the research question. FO wrote the first draft of the manuscript with the support of AB. FO, AB and P-MW discussed the results. All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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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/fendo.2022.946740/full#supplementary-material

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Hypertriglyceridemic waist phenotype: Association with initial neurological severity and etiologic subtypes in patients with acute ischemic stroke

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Objective: To explore the relationship of hypertriglyceridemic waist phenotype (HTWP) with initial neurological severity and etiologic subtypes in patients with acute ischemic stroke.

Methods: The data for this study were collected from hospitalized patients within 72 h of acute ischemic stroke onset at the Department of Neurology of the Affiliated Hospital of Beihua University from 1 July 2020 to 30 June 2022. The initial neurological severity was assessed by the National Institute of Health Stroke Scale (NIHSS) on the day of admission: NIHSS <6 was defined as mild stroke, and NIHSS ≥6 as moderate to severe stroke. HTWP was defined by fasting serum triglycerides ≥1.7 mmol/L and waist circumference ≥90 cm in men and ≥80 cm in women. Differentiation of etiologic subtypes was based on the method reported in the Trial of Org 10 172 in Acute Stroke Treatment. Multivariate logistic regression analysis was used to analyze the association of HTWP with initial neurological severity and etiologic subtypes.

Results: The study included 431 patients. Compared with the normal waist–normal blood triglyceride group, patients with HTWP had reduced risks of moderate to severe stroke [odds ratio (OR): 0.384, 95% confidence interval (CI): 0.170–0.869; P = 0.022]. In addition, the risk of small-artery occlusion stroke was 2.318 times higher in the HTWP group than in the normal triglyceride–normal waist (NWNT) group (OR: 2.318, 95% CI: 1.244–4.319; P = 0.008).

Conclusion: Initial neurological severity was less severe in patients with HTWP, and HTWP was associated with an increased risk of small-artery occlusion stroke.

KEYWORDS

waist circumference, ischemic stroke, hypertriglyceridemia, severity, etiology

Introduction

Stroke is a disease with high morbidity and mortality worldwide and is a major contributor to disability (1). With the rapid development of China's economy and the improvement in people's living standards, exposures to some cerebrovascular risk factors like smoking, overweight or obesity, hypertension, and diabetes mellitus are on the rise; the incidence of stroke has continued to increase over the past 30 years, and China faces the highest burden of stroke in the world (2, 3). Ischemic stroke is the most common type of cerebrovascular disease, constituting 69.6% and 77.8% of stroke incidence and prevalence, respectively, in China (3). Although revolutionary progress has been made by intravenous thrombolysis and intravascular therapy in hyperacute cerebral infarction in recent years (4, 5), substantial challenges remain to enhance the curative effect of traditional medicine therapy when patients miss the thrombolytic time window, especially those patients with disorders of motor function and activities of day-to-day living, which carry enormous consequences for societies and economies (6). Thus, controlling risk factors, early diagnosis, accurate assessment of initial neurological severity, and appropriate treatment are of great significance for the prognosis of ischemic stroke.

Though obesity is an independent risk factor for ischemic stroke, numerous studies have shown an inverse association between obesity and clinical prognosis in patients with ischemic stroke, and this phenomenon is known as the obesity paradox (7–11). However, obesity does not fully account for the influence of body fat distribution, and further studies found that waist circumference (WC) could more accurately reflect the accumulation of visceral fat and the degree of atherosclerosis; thus, it was more strongly related to ischemic stroke than body mass index (BMI) (12, 13). The Northern Manhattan Stroke Study indicated that abdominal obesity is an independent, potent risk factor for ischemic stroke (12), but higher WC has been linked to milder baseline stroke severity and better functional outcomes among patients with acute ischemic stroke (14, 15). Apart from obesity, a prospective cohort study showed that triglycerides (TGs) are positively associated with ischemic stroke (16). In contrast, clinical data from retrospective observational studies suggest that patients with higher TG also manifest milder neurological severity and better early outcomes (17, 18). Based on the above research findings, it seemed that an obesity paradox existed in ischemic stroke despite different obesity measures. However, recent studies found that the obesity paradox does not apply to all individuals, and whether it exists is affected by numerous factors such as sex, uric acid, and insulin sensitivity (19–21). Importantly, a large sample size retrospective study found that obesity was not associated with the risk of death in the first month after stroke, and patients with higher BMI had a stroke at a younger age, suggesting that the obesity paradox in stroke is not real and may be caused by selection bias (22).

Currently, only computed tomography (CT) and magnetic resonance imaging (MRI) can accurately measure the content of visceral fat (23–25), but these imaging techniques are not suitable for health screening in large populations because of the high cost and radiation exposure. Since the measurement of WC alone is ineffective in distinguishing between subcutaneous and visceral adipose tissues (26), the concept of hypertriglyceridemic waist phenotype (HTWP) (defined as coexisting hypertriglyceridemia and an elevated WC) was put forward by Lemieux et al. (27) to solve the abovementioned problem, which was used as a simple marker to identify individuals with metabolic abnormalities and increased visceral fat (28–30). To date, two prospective studies have shown that HTWP is associated with an increased risk of ischemic stroke (31, 32). Nevertheless, there is no research on the association between HTWP and the clinical manifestation of acute ischemic stroke. Hence, this retrospective cohort study aimed to evaluate the effects of the HTWP on initial neurological severity and etiologic subtypes in patients with acute ischemic stroke.

Materials and methods

Inclusion and exclusion criteria

The data for this study were collected from consecutive hospitalized patients at the Department of Neurology of the Affiliated Hospital of Beihua University from 1 July 2020 to 30 June 2022. The research proposal was approved by the Medical Ethics Committee of the Affiliated Hospital of Beihua University (2021-R-17). The inclusion criteria included the following: 1) in line with the Chinese 2018 guidelines for the early management of patients with acute ischemic stroke (33), all patients were diagnosed by brain CT and MRI examinations; 2) the study sample consists of consecutive first-ever acute ischemic stroke patients with an onset ≤72 h; 3) the patients and their families were aware of the study and signed a consent form; and 4) complete and detailed clinical data sets were available. The exclusion criteria were as follows: 1) CT or MRI examination of the brain indicating cerebral hemorrhage or non-acute vascular brain lesions, 2) previous history of stroke with neurological impairment, 3) a history of taking lipid-lowering drugs 1 month before the investigation, and 4) transient ischemic attacks without ischemic lesions visible on MRI performed within 24 h of stroke onset.

Data collection

According to the World Health Organization standardized protocols, trained professionals completed physical examinations (e.g., resting blood pressure, WC) on admission. Blood pressure was measured by an electronic sphygmomanometer (OMRON HEM-

7211), and each patient was measured two consecutive times at an interval of 2 min while resting for at least 15 min before, and the average was taken as the final result. WC was measured with a tapeline to the nearest 0.1 cm at the midpoint between the lower margin costal arch and anterior superior iliac spine at the end of expiration (34). For partially paralyzed and bedridden patients with acute ischemic stroke, their WC was measured at the level of the umbilicus using a measuring tape (14). All patients underwent diagnostic tests, including routine and biochemical blood tests, brain CT and MRI scans, and cerebrovascular, cervical vascular, and cardiac ultrasound.

Definitions of the HTWP and other phenotypes

According to the criteria for metabolic syndrome in the Chinese population established by the International Diabetes Federation, hypertriglyceridemia was defined as TG ≥1.7 mmol/L and abdominal obesity as WC ≥90 cm for men and ≥80 cm for women (34). Patients were divided into three groups: 1) normal waist–normal blood TG (NWNT): TG <1.7 mmol/L and WC <90 cm (men) or <80 cm (women); 2) elevated waist–normal blood TG (EWNT)/normal waist–elevated blood TG (NWET): TG <1.7 mmol/L and WC ≥90 cm (men) or ≥80 cm (women)/TG <1.7 mmol/L and WC ≥90 cm (men) or ≥80 cm (women); and 3) HTWP: TG ≥1.7 mmol/L and WC ≥90 cm (men) or ≥80 cm (women).

Diagnostic criteria for initial neurological severity and etiologic subtypes

The National Institute of Health Stroke Scale (NIHSS) was independently assessed by two neurologists on the day of admission, and the consistency test was conducted to assess the results. NIHSS on admission was used as the main indicator to evaluate the initial neurological severity of an acute ischemic stroke, categorized as mild (0–5), moderate (6–13), or severe (≥14) (35). According to clinical manifestations, imaging, and laboratory examinations, the patients were divided into four etiologic subtypes based on the method reported in the Trial of Org 10 172 in Acute Stroke Treatment (36, 37): 1) large-artery atherosclerosis (LAA), 2) small-artery occlusion (SAO), 3) cardioembolism (CE), and 4) stroke of other determined etiology and undetermined etiology (SOE and SUE).

Diagnostic criteria of risk factors for stroke

Smokers indicated continuous or accumulative smoking for 6 months or more (38). Alcohol drinkers reported taking more than 14 standard drinks per week for men and seven standard drinks per week for women, following the National Institute on Alcohol Abuse and Alcoholism guidelines (39). Hypertension was designated as systolic blood pressure (SBP) ≥140 mmHg, diastolic blood pressure (DBP) ≥90 mmHg, or taking antihypertensive therapy (40). Diabetes was considered fasting blood glucose at least at the level of 7.0 mmol/L or taking hypoglycemic therapy (41). Atrial fibrillation and coronary heart disease (CHD) were based on a self-reported history and the results of an electrocardiogram at admission. Anemia was defined as hemoglobin <130 g/L in men and <120 g/L in women or those taking anti-anemia therapy (42). Physical activity was defined as the performance of heavy physical labor or regular physical exercise for more than 1 year, more than three times per week, and for at least 30 min per session.

Statistical method

SPSS 19.0 statistical software (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis. The Shapiro–Wilk normality test was performed based on the data obtained. Non-normal distribution data were expressed as median and quartile range. Differences between continuous variables were compared using the Mann–Whitney test (two groups) or the Kruskal–Wallis test (multiple groups). Enumeration data were expressed as frequency and percentage, and comparisons between groups were performed using the χ^2 test. Because atrial fibrillation occurs only in CE and SUE, atrial fibrillation was not included in the stroke subtype model. Multivariate logistic regression analysis was used to identify independent risk factors, and the odds ratio (OR) and 95% confidence interval (CI) were calculated. P <0.05 was considered statistically significant.

Results

From 1 July 2020 to 30 June 2022, 549 hospitalized patients within 72 h of stroke onset were included in this study; after screening, 431 of them met the inclusion criteria, as shown in the flowchart (Figure 1). The patients' demographic and clinical characteristics are shown in Table 1. The median patient age was 64 (interquartile range: 58–72) years, and 67.05% were men. Among the 431 patients included, 346 (80.28%) had mild stroke, and 85 (19.72%) had moderate or severe stroke on admission. Compared with patients with mild stroke, patients with moderate to severe stroke at admission had higher rates of atrial fibrillation (P < 0.001). In contrast, patients with moderate to severe stroke at admission had less physical activity (P = 0.003).

As shown in Table 2, patients were assigned to three groups according to their WC and TG data. There were 108, 163, and 103 patients in the NWNT, EWNT/NWET, and HTWP groups, respectively. Age, the proportion of hypertension, diabetes,

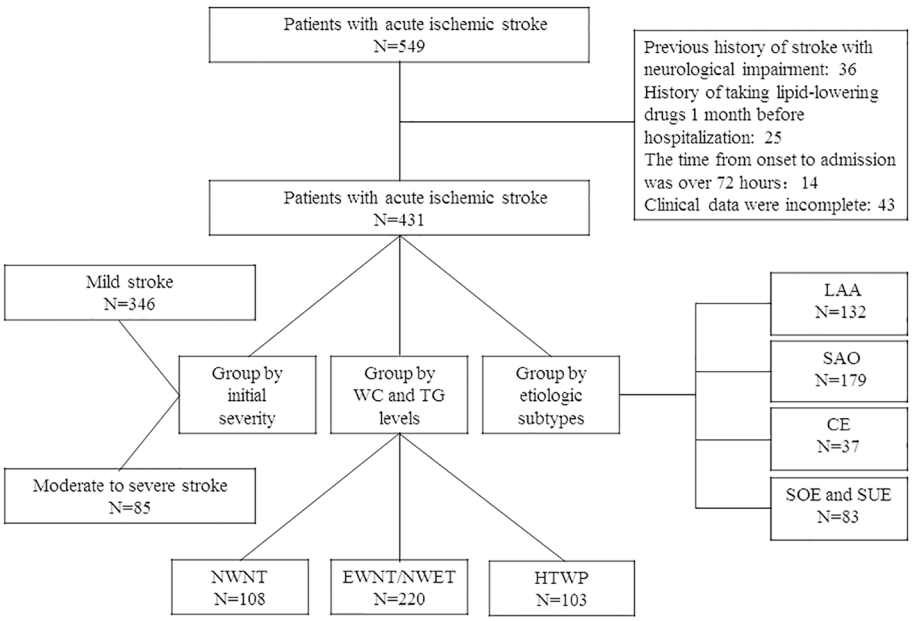

FIGURE 1
Flowchart of the research object selection.

TABLE 1 Characteristics of the patients stratified by initial neurological severity.

Variables	Total $N = 431$	Mild stroke $N = 346$	Moderate to severe stroke $N = 85$	*P*-value
Age (years)	64.0 (58.0–72.0)	64.5 (57.0–71.0)	64.0 (58.0–75.5)	0.337
Gender (male)	289 (67.05)	234 (67.63)	55 (64.71)	0.607
Residence (rural)	131 (30.39)	105 (30.35)	26 (30.59)	0.965
Educational level (≥ high school)	131 (30.39)	109 (31.50)	22 (25.88)	0.313
Hypertension	331 (76.80)	263 (76.01)	68 (80.00)	0.435
Diabetes	151 (35.03)	118 (34.10)	33 (38.82)	0.414
Atrial fibrillation	30(6.96)	16 (4.62)	14 (16.47)	<0.001
Coronary heart disease	100 (23.20)	79 (22.83)	21 (24.71)	0.714
Anemia	39 (9.05)	31 (8.96)	8 (9.41)	0.896
Smoker	212 (49.19)	167 (48.27)	45 (52.94)	0.44
Alcohol drinker	141 (32.71)	117 (33.82)	24 (28.24)	0.326
Physical activity	250 (58.00)	230 (66.47)	42 (49.41)	0.003
Etiologic subtypes				<0.001
LAA	132 (30.63)	101 (29.19)	31 (36.47)	
SAO	179 (41.53)	167 (48.27)	12 (14.12)	
CE	37 (8.58)	24 (6.94)	13 (15.29)	
SOE and SUE	83 (19.26)	54 (15.61)	29 (34.12)	
WC and TG data				0.030
NWNT	108 (25.06)	78 (22.54)	30 (27.78)	
EWNT/NWET	220 (51.04)	179 (51.73)	41 (18.64)	
HTWP	103 (23.90)	89 (25.72)	14 (16.47)	

Values are expressed as median (Q1–Q3) or n (%).
LAA, large-artery atherosclerosis; SAO, small-artery occlusion; CE, cardioembolism; SOE and SUE, stroke of other determined etiology and undetermined etiology; NWNT, normal waist–normal blood triglycerides; EWNT, elevated waist–normal blood triglycerides; NWET, normal waist–elevated blood triglycerides; HTWP, hypertriglyceridemic waist phenotype.

CHD, initial neurological severity, and etiology types showed statistically significant differences among the three groups ($P < 0.05$). Compared with the NWNT group, the proportion of hypertension, diabetes, and CHD in the HTWP group was higher ($P < 0.05$), while age was lower ($P < 0.05$).

As shown in Table 3, compared with patients with NWNT, single-factor logistic regression analysis showed that patients with HTWP had reduced risks of moderate to severe stroke (OR: 0.409, 95% CI: 0.202–0.826; $P = 0.013$, Table 3). Furthermore, the association of WC and TG data with initial neurological severity was assessed by three different multivariate logistic regression analysis models. After adjusting for various potential confounding factors, including age, sex, residence and education levels, hypertension, diabetes, atrial fibrillation, CHD, anemia, smoking, alcohol consumption, physical activity, and stroke etiologic subtypes, this pattern of significant association remained (OR: 0.384, 95% CI: 0.170–0.869; P = 0.022, Table 3).

As shown in Table 4, all patients were divided into four groups according to stroke etiologic subtypes, including 132, 179, 37, and 83 patients in the LAA, SAO, CE, and SOE and SUE groups, respectively. The stroke etiologic subtypes differed by age, the proportion of CHD and anemia, initial neurological severity, and WC and TG data. Compared with patients with NWNT, multivariate logistic regression analysis showed that patients with HTWP had increased risks of SAO (OR: 2.318, 95% CI: 1.244–4.319; $P = 0.008$, Table 5) and reduced risks of CE (OR: 0.131, 95% CI: 0.033–0.528; $P = 0.004$, Table 5) after adjusting for various potential confounding factors such as age, sex, residence and education levels, hypertension, diabetes, CHD, anemia, smoking, alcohol drinking, and physical activity.

Discussion

To our best knowledge, this is the first study to evaluate the association of HTWP with the clinical manifestation of acute ischemic stroke. In this study, we found that patients with HTWP had a reduced risk of moderate-to-severe stroke at admission. We also found that the etiological subtype of stroke in patients with HTWP was more likely to be SAO.

In recent years, epidemiologic studies have shown that HTWP is an independent risk factor for ischemic stroke and could be used as a simple tool to screen individuals with a high risk for ischemic stroke (31, 32). Data from a large prospective cohort study of 95,015 participants in the Kailuan community in Tangshan, China, indicated that HTWP had an unadjusted hazard ratio (HR) of 1.75 (95% CI: 1.48–2.06) for future ischemic stroke, and the HR remained significant (HR: 1.23, 95% CI: 1.01–1.49) after adjustment for confounders (31). In

TABLE 2 Characteristics of the patients stratified by WC and TG data.

Variables	NWNT N = 108	EWNT/NWET N = 220	HTWP N = 103	*P*-value
Age (years)	66.0 (59.3–74.0)	65.0 (57.0–71.8)	63.0 (56.0–68.0)*	0.007
Gender (male)	80 (74.07)	147 (66.82)	62 (60.19)	0.100
Residence (rural)	36 (33.33)	65 (29.55)	30 (29.13)	0.743
Educational level (≥ high school)	43 (39.81)	68 (30.91)	30 (29.13)	0.183
Hypertension	81 (75.00)	159 (72.27)	91 (88.35)*	0.005
Diabetes	18 (16.67)	78 (35.45)*	55 (53.40)*	<0.001
Atrial fibrillation	10 (9.26)	18 (8.18)	2 (1.94)	0.067
Coronary heart disease	25 (23.15)	42 (19.09)	33 (32.04)*	0.037
Anemia	14 (12.96)	20 (9.09)	5 (4.85)	0.184
Smoker	58 (53.70)	106 (48.18)	48 (46.60)	0.536
Alcohol drinker	35 (32.41)	75 (34.09)	31 (30.10)	0.773
Physical activity	71 (65.74)	140 (63.64)	61 (59.22)	0.602
Initial neurological severity				0.030
Mild stroke	78 (22.54)	179 (51.34)	89 (25.72)	
Moderate to severe stroke	30 (27.78)	41 (18.64)	14 (16.47)	
Etiologic subtypes				0.009
LAA	40 (37.04)	62 (28.18)	30 (29.13)	
SAO	31 (28.70)	97 (44.09)	51 (49.51)	
CE	16 (14.81)	18 (8.18)	3 (2.91)	
SOE and SUE	21 (19.44)	43 (19.55)	19 (18.45)	

Values are expressed as median (Q1–Q3) or n (%).
LAA, large-artery atherosclerosis; SAO, small-artery occlusion; CE, cardioembolism; SOE and SUE, stroke of other determined etiology and undetermined etiology; NWNT, normal waist–normal blood triglycerides; EWNT, elevated waist–normal blood triglycerides; NWET, normal waist–elevated blood triglycerides; HTWP, hypertriglyceridemic waist phenotype.
*P < 0.05 compared with NWNT.

TABLE 3 Odds ratio (95% confidence interval) for moderate to severe stroke according to WC and TG data.

	NWNT	NWET/EWNT	HTWP
Unadjusted	1.000 (Ref)	0.596 (0.347–1.023)	0.409 (0.202–0.826)
P-value		0.060	0.013
Model 1	1.000 (Ref)	0.591 (0.341–1.024)	0.401 (0.195–0.826)
P-value		0.061	0.013
Model 2	1.000 (Ref)	0.540 (0.301–0.969)	0.358 (0.162–0.789)
P-value		0.039	0.011
Model 3	1.000 (Ref)	0.555 (0.300–1.028)	0.384 (0.170–0.869)
P-value		0.061	0.022

Model 1: adjusted for age, gender, residence, and education level; model 2: adjusted for model 1, hypertension, diabetes, atrial fibrillation, coronary heart disease, anemia, smoker, alcohol drinker, and physical activity; model 3: adjusted for model 2 and stroke etiologic subtypes.

addition, a prospective cohort study that surveyed 4,081 participants over 35 years of age without a stroke history showed that HTWP was significantly associated with an increased risk of ischemic stroke before and after adjustment for confounding factors; the HR and 95% CI were 1.94 (1.27–2.96) and 1.71 (1.05–2.78), respectively (32).

Although no studies have evaluated the impact of HTWP on initial neurological severity, a series of studies have shown that lower TG levels and smaller WC are associated with more severe stroke (14, 15, 43, 44). Weir et al. found that lower TG levels were associated with more severe initial neurological impairment and higher mortality following acute stroke (43). Similarly, Tziomalos et al. reported that lower TG levels are associated with more severe stroke and appear to predict in-hospital mortality in patients with acute ischemic stroke (44). Moreover, Kang et al. found that higher WC at admission was associated with milder baseline stroke severity and better functional outcomes following acute ischemic stroke (14, 15). In line with the above research findings, our data showed that patients with HTWP were more likely to have a mild stroke. In our view, part of the reason for the above results might be linked to the difference in patients' socioeconomic status. In China, individuals with higher family incomes tend to be overweight or slightly obese and are more likely to receive better treatment and secondary prevention after an ischemic stroke (45). Another important reason might be that individuals with HTWP are

TABLE 4 Characteristics of the patients stratified by stroke etiologic subtypes.

Variables	LAA *N* = 132	SAO *N* = 179	CE *N* = 37	SOE and SUE *N* = 83	*P*-value
Age (years)	65.5 (59.0–74.5)	63.0 (56.5–69.0)	68.0 (60.0–77.0)	63.0 (57.0–71.0)	0.008
Gender (male)	93 (70.45)	119 (66.48)	23 (62.16)	54 (65.06)	0.737
Residence (rural)	38 (28.79)	53 (29.61)	11 (29.73)	29 (34.94)	0.794
Educational level (≥ high school)	36 (27.27)	56 (31.28)	11 (29.73)	28 (33.73)	0.772
Hypertension	108 (81.82)	135 (75.42)	30 (81.08)	58 (69.88)	0.198
Diabetes	48 (36.36)	65 (36.31)	11 (29.73)	27 (32.53)	0.821
Coronary heart disease	30 (22.73)	29 (16.20)	24 (64.86)	17 (20.48)	<0.001
Anemia	16 (12.12)	5 (2.79)	8 (21.62)	10 (12.05)	<0.001
Smoker	66 (50.00)	88 (49.16)	17 (45.95)	41 (49.40)	0.979
Alcohol drinker	45 (34.09)	64 (35.75)	9 (24.32)	23 (27.71)	0.393
Physical activity	81 (61.36)	122 (68.16)	23 (62.16)	46 (55.42)	0.235
Initial neurological severity					<0.001
Mild stroke	101 (76.52)	167 (93.30)	24 (64.86)	54 (65.06)	
Moderate to severe stroke	31 (23.48)	12 (6.70)	13 (35.14)	29 (34.94)	
WC and TG data					0.009
NWNT	40 (30.30)	31 (17.32)	16 (43.24)	21 (25.30)	
EWNT/NWET	62 (46.97)	97 (54.19)	18 (48.65)	43 (51.81)	
HTWP	30 (22.73)	51 (28.49)	3 (8.11)	19 (22.89)	

Values are expressed as median (Q1–Q3) or n (%). LAA, large-artery atherosclerosis; SAO, small-artery occlusion; CE, cardioembolism; SOE and SUE, stroke of other determined etiology and undetermined etiology; NWNT, normal waist–normal blood triglycerides; EWNT, elevated waist–normal blood triglycerides; NWET, normal waist–elevated blood triglycerides; HTWP, hypertriglyceridemic waist phenotype.

TABLE 5 Odds ratio (95% confidence interval) for stroke etiologic subtypes according to WC and TG data.

	NWNT	NWET/EWNT	HTWP
LAA			
Unadjusted	1.000 (Ref)	0.667 (0.409–1.087)	0.699 (0.392–1.244)
P-value		0.104	0.223
Model 1	1.000 (Ref)	0.715 (0.435–1.175)	0.792 (0.437–1.436)
P-value		0.186	0.443
Model 2	1.000 (Ref)	0.696 (0.417–1.162)	0.719 (0.384–1.346)
P-value		0.166	0.302
SAO			
Unadjusted	1.000 (Ref)	1.959 (1.195–3.212)	2.436 (1.380–4.301)
P-value		0.008	0.002
Model 1	1.000 (Ref)	1.186 (1.119–3.046)	2.200 (1.231–3.933)
P-value		0.016	0.008
Model 2	1.000 (Ref)	1.779 (1.057–2.994)	2.318 (1.244–4.319)
P-value		0.030	0.008
CE			
Unadjusted	1.000 (Ref)	0.512 (0.250–1.050)	0.173 (0.049–0.611)
P-value		0.068	0.006
Model 1	1.000 (Ref)	0.525 (0.253–1.088)	0.181 (0.050–0.655)
P-value		0.083	0.009
Model 2	1.000 (Ref)	0.622 (0.273–1.415)	0.131 (0.033–0.528)
P-value		0.257	0.004

Model 1: adjusted for age, gender, residence, and education level; model 2: adjusted for model 1, hypertension, diabetes, coronary heart disease, anemia, smoker, alcohol drinker, and physical activity.

more likely to have hypertension, diabetes, and ischemic heart disease (46, 47), and they will often use prophylactic drugs to effectively control these stroke risk factors and reduce the probability of experiencing moderate to severe ischemic stroke.

Notably, studies have shown that visceral fat accumulation is associated with an increased risk of small vascular disease and lacunar infarction (48, 49). In addition, Pinto et al. found that patients with CE and SUE had greater initial neurological severity on admission and the worst prognosis either in terms of disability or mortality, while those with SAO had the least initial neurological severity at admission and the best prognosis (50). Our results suggest that HTWP was associated with SAO; therefore, we speculate that the reason why patients with HTWP were more prone to mild stroke might be related to lacunar infarction. Lemieux et al. revealed that individuals with HTWP exhibited the atherogenic metabolic triad (hyperinsulinemia, elevated apo B, and small-dense low-density lipoprotein), further leading to the development of early atherosclerosis and an increased risk of CHD (27). Furthermore, Chen et al. also found that individuals with HTWP presented higher serum uric acid levels, suggesting that hyperuricemia could be a pathophysiologic link between HTWP and atherothrombosis (51). It is worth noting that some studies have shown that insulin resistance and hyperuricemia are independent risk factors for lacunar infarction (52, 53). Thus, we speculate that patients with HTWP have insulin resistance and hyperuricemia and are more prone to lacunar stroke, but the specific mechanism needs to be further studied.

It is difficult to measure the weight of patients with acute ischemic stroke because many hemiplegic or unconscious patients cannot stand on the scale without assistance. By measuring WC and serum fasting TG, we can easily and quickly assess the patients' visceral fat status. Therefore, HTWP can be a simple measure of visceral fat in patients with acute ischemic stroke. There are a few limitations to this study. Firstly, due to the retrospective design of this study, a causal association between HTWP and initial neurological severity in patients with acute ischemic stroke cannot be inferred. Moreover, we did not follow up on stroke patients over a long period, and the relationship between HTWP and long-term outcomes in patients with acute ischemic stroke is unclear. Additionally, our study group included only Chinese patients, and our findings may not apply to other ethnic groups.

Data availability statement

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

Ethics statement

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

Author contributions

All the authors participated sufficiently in the work and approved the final version of the article. YR, F-LK and F-EL designed the study. YR and F-LZ developed the methodology. YR, Z-HQ, W-HW, X-GD and SH collected the data. YR performed the analysis and wrote the article.

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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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Comparison of different insulin resistance surrogates to predict hyperuricemia among U.S. non-diabetic adults

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Purpose: Although it has been well-acknowledged that insulin resistance (IR) plays a critical role in the development of hyperuricemia (HU), specific relationship between IR and HU in non-diabetic patients remains rarely studied, and there is still no large-scale research regarding this issue. This study aims to explore the association between triglyceride glucose (TyG), TyG with body mass index (TyG-BMI), the ratio of triglycerides divided by high-density lipoprotein cholesterol (TG/HDL-C), metabolic score for insulin resistance (METS-IR), and the risk of HU in non-diabetic patients in The United States of America.

Patients and methods: Data from the National Health and Nutrition Examination Survey (NHANES) enrolling a representative population aged ≥18-year-old were included to calculate these four indexes. Logistic regression analysis was applied to describe their associations and calculate odds ratios (OR) while the Receiver Operating Characteristic curve was utilized to assess the prediction ability of these four indexes.

Results: A total of 7,743 people (3,806 males and 3,937 females, mean age: 45.17 ± 17.10 years old) were included in this study, among whom 32.18% suffered from HU. After adjustment for sex, age, ethnicity, education background, smoking status, drinking status, systolic blood pressure (SBP), diastolic blood pressure (DBP), metabolic equivalent values (METs), total cholesterol, low-density lipoprotein cholesterol, and estimated glomerular filtration rate, it showed that all four indexes were closely related to HU. Compared with the lowest quartile, OR of the highest quartile of these four indicators for HU were as following respectively: TyG: 5.61 (95% CI: 4.29–7.32); TyG-BMI: 7.15 (95% CI: 5.56–9.20); TG/HDL-C: 4.42 (95% CI: 3.49–5.60); METS-IR: 7.84 (95% CI: 6.07–10.13). TyG, TyG-BMI, TG/HDL-C and METS-IR had moderate discrimination ability for HU, with an AUC value of 0.66 (95% CI: 0.65–0.68), 0.67 (95% CI: 0.65-0.68), 0.68 (95% CI: 0.67-0.69) and 0.68 (95% CI: 0.66–0.69) respectively. Each index showed better prediction ability for HU risk in females than in males.

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Conclusion: It was found that the risk of HU was positively associated with the elevation of TyG, TyG-BMI, TG/HDL-C and METS-IR in a large-scale population of U.S., and TyG-BMI and METS-IR have a better ability to identify HU in both genders.

KEYWORDS

hyperuricemia, insulin resistance surrogates, diabetes, National Health and Nutrition Examination Survey, American

1 Introduction

Elevated serum urate (SU) level, known as hyperuricemia (HU), has emerged as a major global public health issue that associated with gout and a wide spectrum of diseases. HU is caused by increased production of uric acid in and/or decreased excretion of uric acid from the body. Epidemiological studies have shown that HU is an independent risk factor for cardiovascular diseases. It is estimated that a quarter of all deaths in developed countries are related to cardiovascular diseases (CVD) (1). In addition, the mortality rate of CVD ranks top among all lethal factors internationally. According to the Global Burden of Diseases report published by the World Health Organization, 17,858,000 people died from cardiovascular diseases (CVD) in 2016, accounting for 31.4% of all deaths (2).

Insulin resistance (IR) refers to a reduced biological effectiveness of insulin on effector organs (3). High glucose levels, as a result of IR, can contribute to obesity, metabolic syndrome, cardiovascular diseases, and other chronic diseases (4). In order to evaluate IR severity, a homeostatic IR assessment model and a quantitative insulin sensitivity index are used, which require insulin measurement or invasive testing, making it not suitable for large-scale epidemiological studies. In this study, as in previous epidemiological studies, non-insulin-based fasting IR indicators, known as surrogates, were used to identify IR levels, including the triglyceride glucose (TyG), TyG with body mass index (TyG-BMI), the ratio of triglycerides divided by high-density lipoprotein cholesterol (TG/HDL-C) and metabolic score for insulin resistance (METS-IR) (5–8).

Although some studies have explored the correlation between IR and HU, studies comparing the prediction ability of different IR indicators in patients with HU remain rare (9, 10). In addition, previous studies mainly focus on the general population including diabetics, ignoring the potential risk of IR in non-diabetic populations with HU (11, 12). The association among TyG, TyG-BMI, TG/HDL-C, METS-IR and HU in non-diabetic patients is still unclear. Therefore, this study will explore the predictive value of TyG, TyG-BMI, TG/HDL-C and METS-IR in non-diabetic patients with HU, identifying an optimal predictor of HU.

2 Material and methods

2.1 Study population

NHANES is a cross-sectional survey designed to assess the health and nutritional status of, non-institutionalized population in the United States. The survey adopted a complex, stratified, multistage, and probability-cluster sampling design pattern. All of the datasets were downloaded and analyzed directly (http://www.cdc.gov/nchs/nhanes/htm). Data of NHANES 2011–2018 cycle was selected. All 9,940 individuals were above 18 years old (18-80 years old), and had integrate data sets of uric acid (UA), fasting glucose (FPG), total cholesterol (TC), body mass index (BMI), high-density lipoprotein cholesterol (HDL-C) and total triglyceride (TG). Among them, 2,197 participants were excluded for information lack of "hypoglycemic medication" and "diabetes diagnosis", thus 7,743 patients were enrolled into the final analysis. Figure 1 is a flowchart of participant enrollment.

2.2 Definitions of TyG, TyG-BMI, TG/HDL-C and METS-IR score

The non-insulin-based IR indices of TyG, TG/HDL-C and METS-IR were calculated by the following equations: $TyG = \ln[(TG\ (mg/dL) \times FPG\ (mg/dL)/2]$; $TyG\text{-}BMI = TyG \times BMI$; $TG/HDL\text{-}C = TG\ (mg/dL)/HDL\text{-}C\ (mg/dL)$; $METS\text{-}IR = \ln[(2 * FPG\ (mg/dL)) + TG\ (mg/dL)] * BMI/\ln(HDL\text{-}C\ (mg/dL))$ (5–8).

2.3 Serum uric acid measurement

The main indicator of this study was HU. Use Beckman UniCel® DxC800 Synchron or Beckman Synchron LX20 (Beckman Coulter, Inc., Brea, CA, USA) to detect serum uric

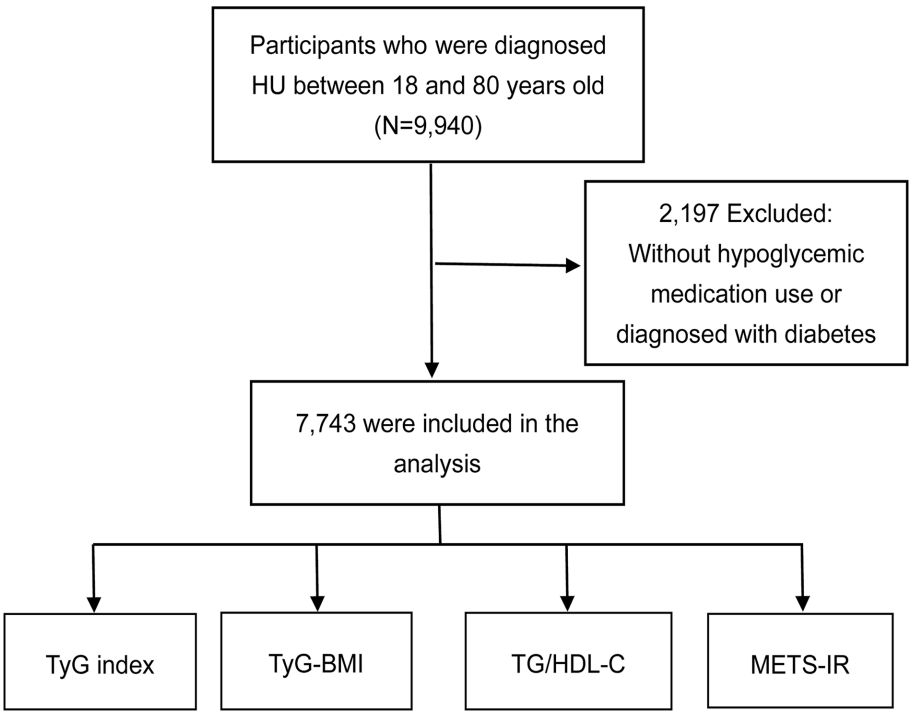

FIGURE 1
Flowchart of the study. HU, hyperuricemia; TyG, triglyceride glucose; TyG-BMI, triglyceride glucose with body mass index; TG/HDL-C, the ratio of triglycerides divided by high-density lipoprotein cholesterol; METS-IR, metabolic score for insulin resistance.

acid levels through oxidizing uric acid to form allantoin and H_2O_2. HU was defined as those with a UA level ≥6.0 mg/dL (13).

2.4 The diagnosis of diabetes

Diabetes was diagnosed when patients met one or more following criteria: (1) patients reporting a diagnosis of diabetes by their doctors ("doctor told you have diabetes"); (2) glycohemoglobin (HbA1c)>6.5%; (3) fasting blood glucose≥7.0mmol/l; (4) random blood glucose≥11.1mmol/l; (5) oral glucose tolerance test (OGTT) two-hour blood glucose≥11.1 mmol/L.

2.5 Covariates

Covariates were chosen based on the literature and conceptual significance (9, 11, 12). Covariates included gender, age, ethnicity, education level, smoking, drinking, systolic blood pressure (SBP), diastolic blood pressure (DBP), metabolic equivalent value (MET), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and estimated glomerular filtration rate (eGFR). Among them, gender, age and ethnicity were derived from NHANES interviews. Educational level was divided into three categories: less than high school, high school, and more than high school. Smoking status was categorized into three types: never (no more than 100 cigarettes in lifetime), former (more than 100 cigarettes in lifetime and had quit smoking up to the survey), and current (more than 100 cigarettes in lifetime and is still smoking every several days at least). Drinking status was defined based on self-reports to the question: "In the past 12 months, on those days that you drank alcoholic beverages, on the average, how many drinks did you have?" Blood pressure (systolic and diastolic) were measured in the mobile examination centers using standardized techniques. The Global Physical Activity Questionnaire was used in NHANES to measure physical activity. Participants reported how many days per week and minutes per day they engaged in moderate-intensity physical activity. We calculated total MET-minutes by multiplying the total number of minutes spent doing various activities per week by the metabolic equivalents estimated from the Compendium of Physical Activities. Hyperlipidemia was defined as TG≥150 mg/dl, hypercholesterolemia or lipid-lowering medication. Individuals who met at least one of the following criteria were defined as the hypercholesterolemia: (1) TC ≥200mg/dL; (2) LDL-C ≥130mg/dL; (3) HDL-C <40mg/dL for males; <50mg/dL for females. Hypertension was defined as blood pressure ≥140/90mmHg, a record of a diagnosis of hypertension, or prescription of

antihypertensive drugs in the health questionnaires. NHANES datasets also provided laboratory results of TC, LDL-C and serum creatinine. eGFR was estimated by CKD-EPI creatinine equation (14).

2.6 Statistical analysis

According to NHANES analytic guidelines, sample weights were incorporated into all analyses for the complexity of survey design (15). The sampling weight was calculated by following formula: fasting sub-sample 10-year mobile examination center (MEC) weight = fasting sub-sample 2-year MEC weight/4. Continuous data are reported as mean ± standard error if normally distributed and as median and interquartile range (IQR) for non-normally distributed data. Categorical variables are presented as numbers in percentage. The Student's t-test (normal continuous data) or Kruskal Wallis test (non-normal continuous data) were used for comparisons between HU group and non-HU group. Differences in categorical variables were analyzed *via* the chi-square test. Pooled odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to assess the association between four IR surrogates and HU. Area under Receiver Operating Characteristic curve (ROC) was adopted to measure the discrimination ability of different IR surrogates for HU. The cut-off value for the indices was determined by the highest Youden index in the ROC curves. In addition, in the analysis of AUC, we also performed Bootstrap resampling (times = 500) as a sensitivity analysis to verify the stability of the results, and the programming language of construction was shown in Supplementary material - Methods. In this study, the R packages "doBy", "stringr" and "CBCgrps" were used for descriptive statistics; "survival" was used for logistic regression and ORs calculation; "plotrix" and "pROC" were used for plotting (16–21). All statistical analyses were carried out with the statistical software R (http://www.R-project.org, The R Foundation) and EmpowerStats software (http://www.empowerstats.com, X&Y Solutions, Inc., Boston, MA). P-value<0.05 (two-sided) was considered as statistically significant.

3 Results

3.1 Baseline characteristics

Baseline characteristics are shown in Table 1. A total of 7743 people (3806 males and 3937 females, mean age: 45.17 ± 17.10 years old) were included in the study, among whom the prevalence of HU was 32.18%. Participants with HU tended to be older (mean age: 45.81 ± 17.27 years old) than those without HU (mean age: 44.86 ± 17.01 years old), and HU was more common in males (76.61%) than in females (23.39%). Besides, most of HU patients were non-Hispanic White individuals (67.90%). The HU group had lower values of HDL-C and eGFR, and higher values of BMI, TC, TG, LDL-C, FPG, UA, SBP and DBP than non-HU group. TyG, TyG-BMI, TG/HDL-C and METS-IR of the HU group were higher than non-HU one, and the difference was statistically significant (P<0.05).

3.2 Association between four IR surrogates and HU risk

Table 2 displays the effect sizes of the association between the four IR surrogates quartiles and HU. In the unadjusted model, we observed a positive correlation between four IR surrogates and HU. After adjustment for gender, age, ethnicity, education background, smoking, drinking, SBP, DBP and MET, results showed that the 4th quartile of TyG, TyG-BMI, TG/HDL-C and METS-IR had 4.87-, 6.99-, 4.58- and 6.70-fold HU risk than those in the 1st quartile (Model 2). Similarly, in fully adjusted models, four IR surrogates all had significant ORs for the presence of HU (p<0.05) (Model 3).

3.3 AUCs and cut-off values of four IR surrogates for HU prediction

The AUC values of TyG, TyG-BMI, TG/HDL-C and METS-IR to discriminate HU are shown in Table 3, Figures 2, 3. TG/HDL-C and METS-IR had higher AUC of 0.68, followed by TyG-BMI (AUC=0.67), TyG (AUC=0.66). The optimal cut-off value of TG/HDL-C and METS-IR based on the specificity and sensitivity was 1.77 and 39.52. Both TyG-BMI and METS-IR showed higher accuracy (AUC=0.68) than TyG and TG/HDL-C (AUC=0.64) in HU prediction of males (Figure 3A). The optimal cut-off value of TyG-BMI and METS-IR were 231.26 and 39.52, respectively. Similarly, the AUC value of TyG-BMI and METS-IR are the highest in females (Figure 3B). In combination, four IR surrogates had similar prediction ability of HU in both genders.

Then, we compared the prevalence of HU with escalating four IR surrogates. We found that the prevalence of HU tended to increase with the increase in the four IR surrogates (Table S1–S3). The cut-off value we obtained is a rather important turning point, above which the prevalence of HU almost doubles, both in the male and female population.

Similarly, the above results were validated for stability in the Bootstrap resampling (times = 500) analysis (Figures S1–S3).

4 Discussion

In this large-scale study that contains prospective and nationally-respresentative samples aged 18-80 years old of U.S. (N=7,743), it was found that the prevalence of HU was 32.18%

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TABLE 1 Baseline characteristics of subjects.

Variables	Total n=7743	Without HU n=5251	With HU n=2492	P-value
Age (years)	45.17 ± 17.10	44.86 ± 17.01	45.81 ± 17.27	0.02
Gender (n, %)				<0.01
Male	3806 (49.15%)	1890 (35.99%)	1909 (76.61%)	
Female	3937 (50.85%)	3361 (64.01%)	583 (23.39%)	
Ethnicity (n, %)				0.39
Non-Hispanic White	5156 (66.59%)	3463 (65.95%)	1692 (67.90%)	
Non-Hispanic Black	762 (9.84%)	524 (9.98%)	238 (9.55%)	
Mexican American	662 (8.55%)	457 (8.70%)	205 (8.23%)	
Others	1163 (15.02%)	807 (15.37%)	357 (14.33%)	
Education (n, %)				0.01
Less than high school	336 (4.34%)	239 (4.55%)	97 (3.89%)	
High school	2543 (32.84%)	1669 (31.78%)	873 (35.03%)	
More than high school	4864 (62.82%)	3343 (63.66%)	1522 (61.08%)	
BMI (kg/m^2)	28.43 ± 6.71	27.30 ± 6.14	30.79 ± 7.21	<0.01
Smoking (n, %)				<0.01
Never	4448 (57.45%)	3142 (59.84%)	1306 (52.42%)	
Former	1805 (23.31%)	1085 (20.67%)	719 (28.85%)	
Now	1490 (19.24%)	1024 (19.50%)	467 (18.74%)	
Drinking	2.68 ± 2.37	2.47 ± 2.14	3.09 ± 2.74	<0.01
MET (ml/kg/min)	2400.00 (880.00-6200.00)	2340.00 (840.00-5760.00)	2640.00 (960.00-7200.00)	<0.01
TC (mg/dl)	190.84 ± 39.58	189.27 ± 39.50	194.13 ± 39.54	<0.01
TG (mg/dl)	89.00 (61.00-130.00)	80.00 (57.00-115.00)	108.00 (77.00-162.00)	<0.01
LDL-C (mg/dl)	113.49 ± 34.15	111.62 ± 34.06	117.46 ± 34.00	<0.01
HDL-C (mg/dl)	55.43 ± 16.36	58.34 ± 16.38	49.36 ± 14.54	<0.01
FPG (mg/dl)	99.00 ± 9.72	97.83 ± 9.31	101.43 ± 10.09	<0.01
eGFR (ml/min/1.73 m^2)	97.21 ± 21.08	99.60 ± 20.06	92.23 ± 22.26	<0.01
UA (mg/dl)	5.30 (4.40-6.30)	4.70 (4.10-5.30)	6.80 (6.30-7.40)	<0.01
SBP (mmHg)	120.21 ± 16.29	118.56 ± 15.75	123.67 ± 16.85	<0.01
DBP (mmHg)	70.16 ± 11.17	69.29 ± 10.73	71.97 ± 11.85	<0.01
TyG	8.42 ± 0.60	8.31 ± 0.56	8.67 ± 0.60	<0.01
TyG-BMI	240.65 ± 63.66	227.61 ± 56.91	267.88 ± 68.25	<0.01
TG/HDL-C	2.39 ± 2.70	1.95 ± 1.98	3.31 ± 3.62	<0.01
METS-IR	41.39 ± 11.88	38.79 ± 10.40	46.82 ± 12.91	<0.01
Hyperlipidemia (n, %)	5052 (65.25%)	3210 (61.13%)	1840 (73.84%)	<0.01
Hypertension (n, %)	2521 (32.56%)	1463 (27.86%)	1056 (42.38%)	<0.01
Lipid lowering medications (n, %)	1093 (14.12%)	679(12.93%)	413 (16.57%)	<0.01
Antihypertensive medications (n, %)	289 (3.73%)	156 (2.97%)	132 (5.30%)	<0.01

HU, hyperuricemia; BMI, body mass index body mass index; MET, metabolic equivalent value; TC, total cholesterol; TG, total triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; FPG, fasting glucose; eGFR, estimated glomerular filtration rate; UA, uric acid; SBP, systolic blood pressure; DBP, diastolic blood pressure; TyG, triglyceride glucose; TyG-BMI, triglyceride glucose with body mass index; TG/HDL-C, the ratio of triglycerides divided by high-density lipoprotein cholesterol; METS-IR, metabolic score for insulin resistance.

for all (50.16% in males and 14.80% in females). There was an increased incidence of HU due to lifestyle and dietary changes, as well as aging (22). Therefore, early identification and control of IR in patients with HU before clinical symptoms may assist the management of HU and the prevention of its IR-driven comorbidities.

As an indirect method, measurement of IR surrogates was simple, economical, and convenient. Four surrogates, based on biochemical indexes of human body, were selected for IR, including TyG, TyG-BMI, TG/HDL-C and METS-IR. IR was closely related to glycolipid metabolism while previous researches have pointed out the significant association between these four surrogate indexes and the presence of IR (6, 12, 23–25). Our present study considered non-diabetic individuals in general population and expanded the sample size based on previous studies (7,743 *vs* 1,067) (26). This study not only

TABLE 2 ORs and 95% CIs for highest versus the lowest quartiles in logistic regressions predicting presence of HU.

Variables	Model 1	Model 2	Model 3
TyG			
Q2	2.02 (1.75, 2.32)	1.93 (1.56, 2.38)	1.88 (1.51, 2.33)
Q3	2.87 (2.49, 3.30)	3.04 (2.45, 3.78)	3.02 (2.41, 3.79)
Q4	5.63 (4.84, 6.56)	4.87 (3.84, 6.17)	5.61 (4.29, 7.32)
TyG-BMI			
Q2	2.16 (1.87, 2.49	2.07 (1.67, 2.56)	1.99 (1.60, 2.48)
Q3	3.18 (2.76, 3.67)	3.15 (2.53, 3.94)	2.96 (2.35, 3.73)
Q4	4.93 (4.25, 5.72)	6.99 (5.49, 8.89)	7.15 (5.56, 9.20)
TG/HDL-C			
Q2	1.74 (1.50, 2.02)	1.62 (1.30, 2.01)	1.56 (1.24, 1.95)
Q3	2.88 (2.49, 3.33)	2.59 (2.09, 3.22)	2.52 (2.01, 3.17)
Q4	5.76 (4.97, 6.67)	4.58 (3.66, 5.73)	4.42 (3.49, 5.60)
METS-IR			
Q2	2.21 (1.91, 2.55)	1.99 (1.61, 2.47)	2.06 (1.65, 2.58)
Q3	3.31 (2.86, 3.83)	2.90 (2.33, 3.61)	3.07 (2.44, 3.88)
Q4	5.65 (4.86, 6.56)	6.70 (5.29, 8.47)	7.84 (6.07, 10.13)

Notes: Values are odds ratio (95%CI) derived from multivariable logistic regression models.
Model 1: unadjusted.
Model 2: adjusted for gender, age, ethnicity, education, smoking, drinking, SBP, DBP and MET.
Model 3: adjusted for all variables in model 2 and TC, LDL-C and eGFR.
TyG, triglyceride glucose; TyG-BMI, triglyceride glucose with body mass index; TG/HDL-C, the ratio of triglycerides divided by high-density lipoprotein cholesterol; METS-IR, metabolic score for insulin resistance; MET, metabolic equivalent value; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate.

further confirmed, in line with other existing studies, that IR surrogates were independently and positively correlated with the presence of HU, but also provided a simpler and more economical choice to distinguish IR status in non-diabetic patients with HU in clinic (12, 27).

Further ROC analysis proved that compared with TyG and TG/HDL-C, TyG-BMI and METS-IR excelled in IR discrimination in both gender groups. Given that obesity plays a vital role in the pathophysiology of IR (28, 29), combing obesity indicator with TyG should have better results

TABLE 3 AUC and cut-off values of four IR surrogates for prediction of HU.

Variables	AUC (95% CI)	Cut-off	Specificity	Sensitivity
Total				
TyG	0.66 (0.65-0.68)	8.44	0.62	0.62
TyG-BMI	0.67 (0.65-0.68)	224.16	0.54	0.70
TG/HDL-C	0.68 (0.67-0.69)	1.77	0.63	0.65
METS-IR	0.68 (0.66-0.69)	39.52	0.59	0.67
Males				
TyG	0.64 (0.62-0.66)	8.48	0.61	0.60
TyG-BMI	0.68 (0.67-0.70)	231.26	0.65	0.62
TG/HDL-C	0.64 (0.63-0.66)	1.78	0.55	0.67
METS-IR	0.68 (0.66-0.70)	39.52	0.61	0.66
Females				
TyG	0.66 (0.64-0.69)	8.44	0.64	0.61
TyG-BMI	0.71 (0.69-0.73)	241.00	0.62	0.70
TG/HDL-C	0.66 (0.63-0.68)	1.77	0.66	0.58
METS-IR	0.71 (0.68-0.73)	42.50	0.68	0.63

TyG, triglyceride glucose; TyG-BMI, triglyceride glucose with body mass index; TG/HDL-C, the ratio of triglycerides divided by high-density lipoprotein cholesterol; METS-IR, metabolic score for insulin resistance.

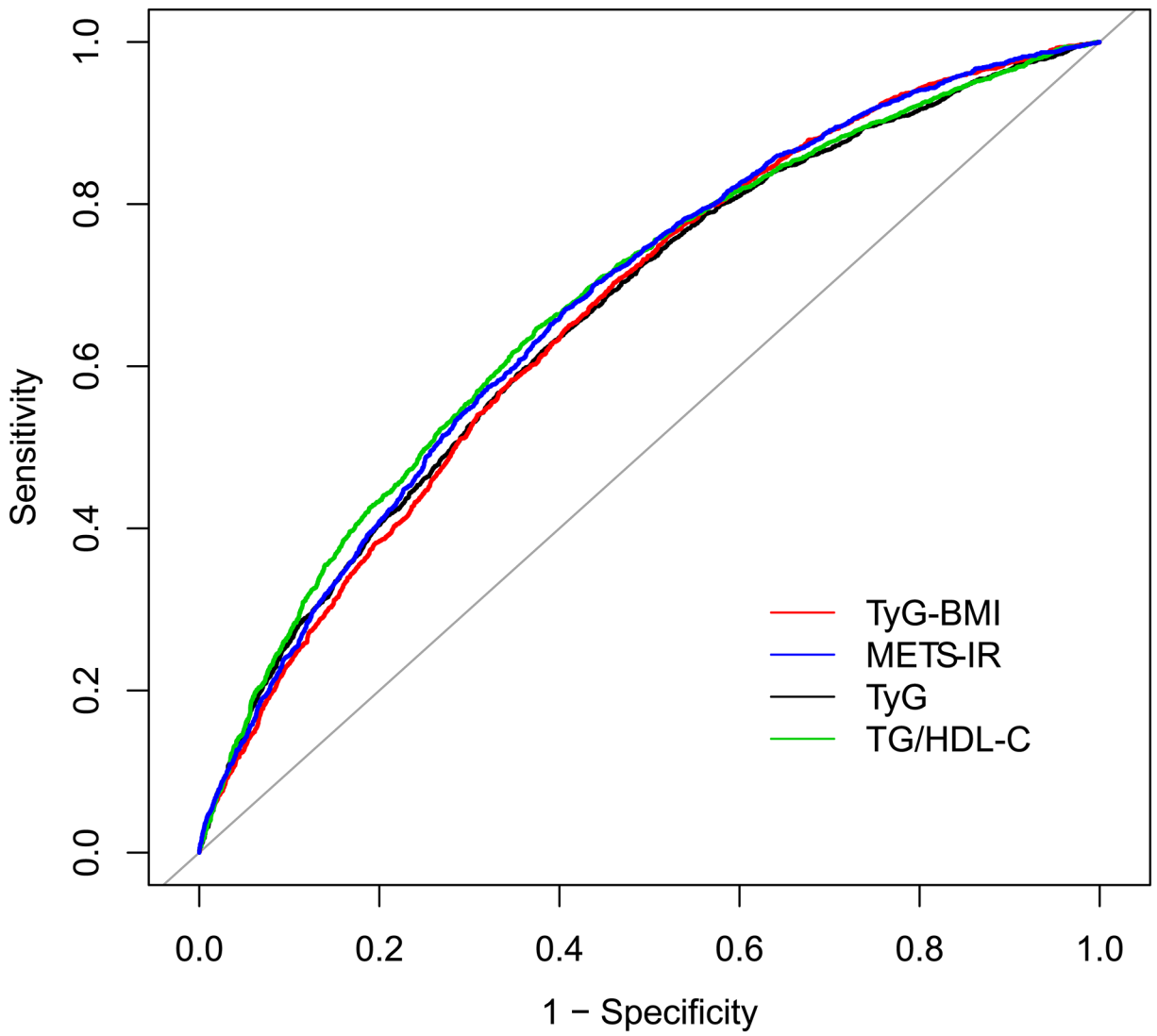

FIGURE 2
ROC for different IR surrogates to predict HU. HU, hyperuricemia; TyG, triglyceride glucose; TyG-BMI, triglyceride glucose with body mass index; TG/HDL-C, the ratio of triglycerides divided by high-density lipoprotein cholesterol; METS-IR, metabolic score for insulin resistance.

theoretically. Our results are consistent with a previous research originated from NHANES, which indicated TyG-BMI had a significant and positive correlation with HU. METS-IR is a novel index that combines non-insulin fasting laboratory values and anthropometric measurements, both of which can be easily obtained in primary care evaluation, to assess insulin sensitivity and detect IR cases (8, 30). However, studies of Liu et al. had different results, suggesting that TG/HDL-C was most strongly associated with HU (11). Such a discrepancy may be attributed to: firstly, the level of insulin secretion and sensitivity greatly differs by ethnicity (31); secondly, obesity, which plays an important role in IR; thirdly, difference in sample size. All in all, ethnic-based, larger-scale studies are needed to elucidate this disparity.

In addition, we also found gender differences in these four indicators of IR and HU: they showed better predictive effect in females than males. Similar findings were reported by a study conducted in 2020 which revealed that elevated UA was

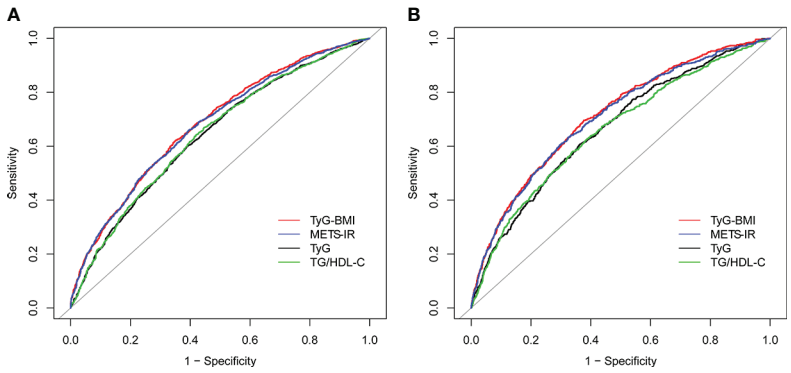

FIGURE 3
ROC for different IR surrogates to predict HU in **(A)** males; and **(B)** females. HU, hyperuricemia; TyG, triglyceride glucose; TyG-BMI, triglyceride glucose with body mass index; TG/HDL-C, the ratio of triglycerides divided by high-density lipoprotein cholesterol; METS-IR, metabolic score for insulin resistance.

associated with a higher risk of IR and such an association was more pronounced in female patients. This difference may be attributable to different sex hormones and adipokines, which cause more insulin-sensitive characteristics of females (32). Considering previous research results, it is agreed that more attention should be paid to the application of IR substitutes as predictors of HU in females.

This study has both advantages and limitations. Present study is the first large-scale research with nationally-representative samples to examine the association between these four non-insulin-based indicators of IR and HU, which increased the statistical strength and confirmed the reliability of reported results. However, several limitations should also be noted. First of all, the causal relationship between these IR indicators and HU cannot be well explained by this study. Secondly, retrospective data in our study may have recall bias. Thirdly, the study population was solely from the United States, for which conclusions may not be generalizable.

5 Conclusion

In this study, it was found that the risk of HU was positively associated with the elevation of TyG, TyG-BMI, TG/HDL-C and METS-IR in a large-scale population of U.S. Among the four IR surrogates, TyG-BMI and METS-IR had pronounced discrimination ability to HU. Moreover, all four IR surrogates had better prediction ability for HU in females. To sum up, four IR surrogates are recommended as complementary markers for the assessment of HU risk both in clinic and in future epidemiological studies in non-diabetic populations. Yet more researches are in need to provide reference for different gender groups.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by National Centre for Health Statistics Institutional Ethics Review Board. The patients/participants provided their written informed consent to participate in this study.

Author contributions

HW: writing-most of manuscript, data curation and processing. JZ: writing-part of the manuscript, data curation. YP: writing-part of the manuscript, data processing. SQ, HL and YT: software, writing—review and editing, and supervision. ZT: methodology, writing—review and editing, and supervision. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2022.1028167/full#supplementary-material

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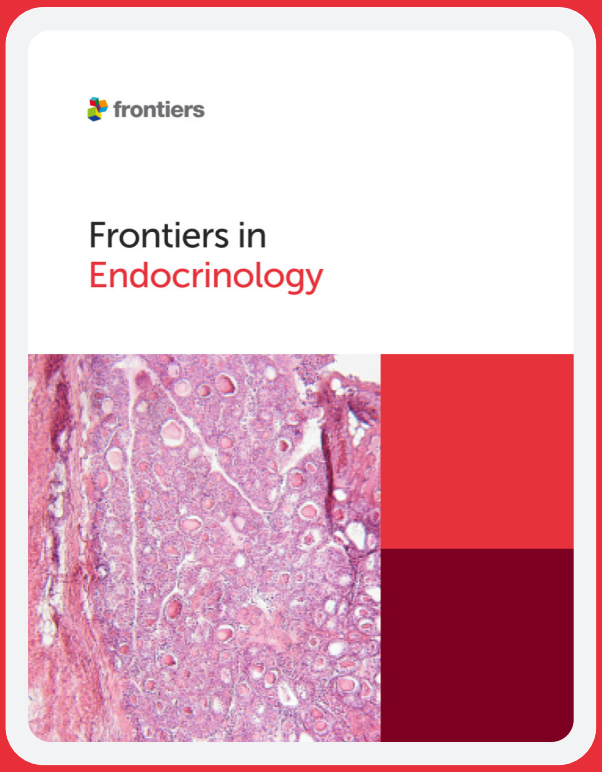

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