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Association between the weight-adjusted-waist index and Familial hypercholesterolemia: a cross-sectional study

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Abstract

Objective The weight-adjusted-waist index (WWI) is a novel obesity measurement indicator, and this study aims to determine the relationship between WWI and Familial hypercholesterolemia (FH).

Methods Using data from the National Health and Nutrition Examination Survey (NHANES) from 2017 to March 2020, cross-sectional data from 3698 participants were analyzed. The study examined the correlation between WWI and FH using multivariate logistic regression and smooth curve fitting, and conducted subgroup analysis and interaction tests.

Results The study sample consisted of 3698 subjects for whom the overall probable prevalence of FH was 5.43% and increased with WWI tertile (quantile 1: 4.00%; quantile 2: 4.94%; quantile 3: 7.34%); individuals with the highest WWI tertile were significantly more likely to have FH than those with the lowest tertile (OR = 4.60,95% CI: 2.00-10.60). Subgroup analysis and interaction tests showed significant significance between WWI and personal history of early Atherosclerotic cardiovascular disease (ASCVD), family history of early ASCVD and probable prevalence of FH ($p < 0.05$).

Conclusion This study demonstrates a nonlinear positive correlation between WWI and FH. This may provide new ideas for the prevention and treatment of FH in the future.

Keywords Cross-sectional study, Weight-adjusted-waist index, Familial hypercholesterolaemia, Obesity, NHANES

Introduction

Familial hypercholesterolemia (FH) is a classic autosomal dominant hereditary disease, primarily caused by mutations in the low-density lipoprotein receptor (LDLR) gene, leading to disruptions in low-density lipoprotein metabolism within the body, resulting in abnormally high levels of low-density lipoprotein cholesterol (LDL-C) in the serum [1]. As FH patients are exposed to elevated serum LDL-C levels from birth, their risk of atherosclerotic cardiovascular disease (ASCVD) and mortality significantly increase [2]. Therefore, FH is one of the most severe of the lipid metabolism gene disorders. Research indicates that early screening and prompt initiation of drug therapy can effectively improve the survival rate of FH patients [3]. Despite FH receiving widespread attention from the international community, the diagnosis and treatment rates of FH still remain severely inadequate.

Obesity is the result of a multifactorial interaction in which genetic, metabolic, behavioural and environmental factors can contribute to the development of obesity [4].

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Over the past 30 years, obesity has emerged as a significant health issue. According to the World Health Organization (WHO), from 1990 to 2022, the global prevalence of obesity more than doubled, with approximately 16% of adults aged 18 and over worldwide classified as obese by 2022 [5]. Obesity is associated with numerous noncommunicable diseases, including cardiovascular diseases, diabetes, cancers, neurological disorders, chronic respiratory diseases, and digestive system disorders. Moreover, the increasing prevalence of obesity has serious economic implications. Without intervention, it is estimated that by 2030, the global cost of overweight and obesity will reach over 3 trillion dollars annually, surpassing 18 trillion dollars by 2060 [6].Therefore, an effective and precise assessment parameter for obesity is crucial for its effective monitoring. Currently, the adiposity indicators that are commonly used in clinical assessment of obesity have limitations. Body mass index (BMI) is a widely used tool for assessing and classifying obesity, however, it cannot distinguish between central and peripheral fat [7]. Waist circumference (WC) has been shown to have an independent association with increased cardiovascular risk, but its predictive ability of visceral adipose tissue at the individual level remains limited [8]. Waist-to-Hip Ratio (WHR) and Waist-to-Height Ratio (WHtR) can more accurately describe abdominal obesity, however, these indicators also have limitations in distinguishing between subcutaneous and visceral fat. The WWI proposed by Park [9] et al. is a new obesity index that may improve the accuracy of obesity classification and risk prediction, thus paving the way for more targeted treatment interventions and monitoring strategies.

The pathogenesis of FH is complex. Early studies have shown a certain correlation between LDL-C levels and the degree of obesity [10]. Simultaneously, a significant elevation of LDL-C levels in plasma is a hallmark of FH and a driving factor for the early onset of ASCVD. However, the relationship between WWI and the prevalence of FH has yet to be explored.

Therefore, this study aims to investigate the correlation between WWI and FH using data from the National Health and Nutrition Examination Survey (NHANES) from 2017 to March 2020 through multivariate logistic regression, smooth curve fitting and Subgroup analyses.

Methods

Survey description

All data in this study were collected by the National Center for Health Statistics of the Centers for Disease Control and Prevention in the NHANES during the period from 2017 to March 2020. This cross-sectional study employed a stratified, multistage probability cluster sampling method to ensure the inclusion of a representative sample of the non-institutionalized civilian population in the United States in our study [11]. The study protocol was approved by the Research Ethics Review Committee of the National Center for Health Statistics (NCHS). Written informed consent was obtained from all participants before their involvement.

Study population

Initially, a total of 15,560 participants was included in the study. However, individuals under 20 years old (N=6,328), those without available LDL-C data (N=5,330), and those without available WWI data (total N=204; waist circumference N=175; weight N=29) were excluded. Ultimately, our final pooled dataset analysis included 3,698 eligible adults.

WWI measurement and calculation

The WWI is a body measurement index based on WC and weight, used for assessing central obesity. In the NHANES study, trained health technicians accurately measured WC and weight. A higher value of WWI indicates a higher degree of central obesity [9]. In this analysis, we used WWI as the exposure variable. The WWI for each participant was calculated using a formula that involves dividing WC by the square root of weight, where WC is in centimeters and weight is in kilograms, and rounding the result to two decimal places.

$$WWI = \frac{WC}{\sqrt{Weight}}$$

Definition of FH

The Dutch Lipid Clinic Network (DLCN) criteria were used to define FH [12]. Diagnosis was based on LDL-C levels (where LDL-C levels≥325 counts as 8 points, 251≤LDL-C levels<325 counts as 5 points, 191≤LDL-C levels<251 counts as 3 points, 155≤LDL-C levels<191 counts as 1 point, LDL-C levels<155 counts as 0 points), additionally known gene defect counts as 8 points, personal history of early ASCVD counts as 2 points, personal history of early cerebrovascular or peripheral vascular disease counts as 1 point, first-degree relative's history of early ASCVD counts as 1 point, identification of tendon xanthomas during physical examination counts as 6 points, identification of lipid corneal arcus counts as 4 points. It is worth noting that lipid profiling measurements were performed only in participants who adhered to a fasting period of at least 8.5 h and no more than 24 h, ensuring the accuracy of these assessments. The study population was divided into probable FH (≥3 points) or unlikely FH (<3 points). Some DLCN criteria, such as genetic testing, family history of hypercholesterolemia, personal history of peripheral arterial

disease, and relevant physical examination findings, were not collected in NHANES and were not included in this analysis.

Covariates

Additionally, a series of covariates were considered in the analysis, including age, gender, race, smoking status, and alcohol consumption status. Anthropometric and laboratory covariates were also included, such as alkaline phosphatase (IU/L), blood urea nitrogen (mg/dL), gamma glutamyl transferase (IU/L), total cholesterol (mg/dL), triglycerides (mg/dL), high-density lipoprotein cholesterol (mg/dL), and low-density lipoprotein cholesterol (mg/dL). Hypertension was based on the following criteria: current prescription of antihypertensive medication, diagnosed hypertension, or recorded systolic blood pressure of 130 mmHg or higher, and diastolic blood pressure of 80 mmHg or higher [13]. hyperuricemia was defined based on serum uric acid levels, with a threshold of greater than 7 mg/dL for males and greater than 6 mg/dL for females [14]. Diabetes was defined as a self-reported diagnosis or fasting blood glucose of 126 mg/dL or higher [15]. All data related to these variables are publicly available on the website (https://www.cdc.gov/nchs/nhanes).

Statistical analysis

This study employed R software (version 4.2) and EmpowerStats (version 4.1) for statistical analysis. Based on the demographic characteristics of the participants, chi-square tests were used for categorical variables and independent samples t-tests for continuous variables. Multivariable logistic regression analysis was conducted to assess the correlation between WWI and FH. To explore the potential nonlinear relationship between WWI and FH, we utilized a weighted generalized additive model and smooth curve fitting. Mediation analysis was performed using parallel mediation models, with individual indicators as mediators, followed by stratified analysis and interaction testing to identify the association between WWI and FH in different population groups. Statistical significance was noted at two-sided $p<0.05$.

Results

Baseline characteristics

The analysis included a total of 3,698 participants with a mean age of 50.69±17.29 years. The gender distribution was relatively balanced, with males comprising 48.24% and females 51.76% of the sample. Participants were divided into three quartiles based on WWI values, namely 8.51–10.73 (quartile 1), 10.74–11.35 (quartile 2), and 11.35–14.14 (quartile 3). The study included 1,784 male participants and 1,914 female participants. The overall probable prevalence of FH was 5.43%, and it increased with higher WWI quartiles (quartile 1: 4.00%; quartile 2: 4.94%; quartile 3: 7.34%; $p<0.001$). Significant differences were observed between WWI and FH in terms of age, race, smoking status, alcohol consumption status, family history or personal history of early ASCVD, receiving lipid therapy (such as statins), hypertension, diabetes, hyperuricemia, alkaline phosphatase levels, blood urea nitrogen levels, gamma glutamyl transferase levels, total cholesterol levels, triglycerides levels, high-density lipoprotein cholesterol levels, and low-density lipoprotein cholesterol levels (all $p<0.05$). The results indicate that participants with higher WWI levels were more likely to be female, non-Hispanic white, and diagnosed with hypertension. Additionally, we observed that WWI levels increased with age, alkaline phosphatase levels, blood urea nitrogen levels, gamma glutamyl transferase levels, and triglyceride levels, while decreasing with increasing high-density lipoprotein cholesterol levels (Table 1).

Association between WWI and FH

(Table 2) shows the results of multivariate logistic regression analysis using three models. In the unadjusted [1.47 (1.19, 1.82) $p<0.001$], partially adjusted [1.41 (1.14, 1.74) $p=0.001$], and fully adjusted [2.38 (1.47, 3.84) $p<0.001$] models, there was a clear positive correlation between WWI and FH, and all three adjusted models were statistically significant. After full adjustment, for each unit increase in WWI levels, the FH incidence rate may increase by 138%. When WWI was converted into tertiles, compared to subjects in the lowest tertile, those in the highest WWI tertile had a 3.60-fold higher FH incident [4.60 (2.00, 10.60) $p<0.001$]. Furthermore, the results of the smooth curve fitting analysis confirmed a nonlinear positive correlation between WWI and FH (Figs. 1, 2).

Subgroup analyses

We conducted subgroup analyses and interaction tests on variable stratification, including gender, race, diabetes, hypertension, personal history of early ASCVD, family history of early ASCVD, and Receiving lipid therapy, to assess the correlation between WWI and FH and identified potential population differences (Fig. 3). Based on the results, we found that although other variables lacked interaction, there were significant statistical interactions between WWI and personal history of early ASCVD, family history of early ASCVD, and FH (all $p<0.05$). Furthermore, the positive correlation between WWI and FH was similar across different populations with different gender, race, diabetes, and hypertension statuses, which may be applicable to various populations.

Table 1 Baseline characteristics of participants by weight-adjusted-waist index tertiles

Characteristic	Weight-adjusted-waist index			*P*-value
	Tertile 1	Tertile 2	Tertile 3	
	(8.51–10.73)	(10.74–11.35)	(11.35–14.14)	
	N = 1224	*N* = 1235	*N* = 1239	
Age(years)	49.71 ± 17.77	49.95 ± 17.07	52.40 ± 16.91	< 0.001
Gender, n(%)				0.773
Male	582(47.55%)	595(48.18%)	607(48.99%)	
Female	642(52.45%)	640(51.82%)	632(51.01%)	
Race, n(%)				< 0.001
Mexican American	127(10.38%)	169(13.68%)	172(13.88%)	
Other Hispanic	114(9.31%)	137(11.09%)	124(10.01%)	
Non-Hispanic White	437(35.70%)	391(31.66%)	425(34.30%)	
Non-Hispanic Black	302(24.67%)	302(24.45%)	336(27.12%)	
Other Race	244(19.93%)	236(19.11%)	182(14.69%)	
Smoking behavior, n(%)				0.033
Yes	487(39.79%)	548(44.37%)	548(44.23%)	
No	737(60.21%)	687(55.63%)	691(55.77%)	
Drinking behavior, n(%)				< 0.001
Yes	203(16.58%)	172(13.93%)	118(9.52%)	
No	1021(83.42%)	1063(86.07%)	1121(90.48)	
Family history of early ASCVD, n(%)				< 0.001
Yes	112(9.15%)	166(13.44%)	197(15.90%)	
No	1112(90.85%)	1069(86.56%)	1042(84.10%)	
Personal history of early ASCVD, n(%)				< 0.001
Yes	54(4.41%)	42(3.40%)	59(4.76%)	
No	1170(95.59%)	1193(96.60%)	1180(95.24%)	
Receiving lipid therapy, n(%)				< 0.001
Yes	108(8.82%)	283(22.91%)	427(34.46%)	
No	1116(91.18%)	952(77.09%)	812(65.54%)	
Diabetes, n(%)				< 0.001
Yes	84(6.86%)	209(16.92%)	404(32.61%)	
No	1140(93.14%)	1026(83.08%)	835(67.39%)	
Hypertension, n(%)				< 0.001
Yes	258(21.08%)	481(38.95%)	679(54.80%)	
No	966(78.92%)	754(61.05%)	560(45.20%)	
Hyperuricemia, n(%)				< 0.001
Yes	113(9.23%)	187(15.14%)	229(18.48%)	
No	1111(90.77%)	1048(84.86%)	1010(81.52%)	
Alkaline phosphatase (IU/L)	69.79 ± 20.61	78.68 ± 26.16	85.78 ± 31.03	< 0.001
Blood urea nitrogen (mg/dL)	13.63 ± 4.39	14.54 ± 5.31	16.09 ± 7.43	< 0.001
Gamma glutamyl transferase (IU/L)	25.84 ± 35.14	34.11 ± 41.32	35.76 ± 78.19	< 0.001
Total cholesterol (mg/dL)	182.15 ± 38.28	186.67 ± 41.20	183.11 ± 42.53	0.015
Triglyceride (mg/dL)	85.19 ± 57.13	108.75 ± 63.02	120.67 ± 62.59	< 0.001
Low-density lipoprotein cholesterol(mg/dL)	107.25 ± 33.71	111.69 ± 36.01	107.48 ± 37.08	0.002
High-density lipoprotein cholesterol(mg/dL)	57.51 ± 16.65	52.90 ± 16.13	51.29 ± 14.30	< 0.001
Dutch Lipid Clinic Network score	0.37 ± 0.80	0.45 ± 0.88	0.56 ± 0.98	< 0.001
Familial hypercholesterolaemia, n(%)				< 0.001
probable	49(4.00%)	61(4.94%)	91(7.34%)	
improbable	1175(96.00%)	1174(95.06%)	1148(92.66%)	

Discussion

Our study aimed to investigate the correlation between WWI and FH among the US population. In this cross-sectional study involving 3698 adults, we found a nonlinear positive correlation between WWI and FH incidence rates, indicating that individuals with higher levels of WWI are more likely to have FH, and this relationship remained stable in fully adjusted models. In

Table 2 Association between weight-adjusted-waist index and familial hypercholesterolaemia

Exposure	OR(95% CI)		
	Model 1	**Model 2**	**Model 3**
Continuous WWI	1.47 (1.19, 1.82)	1.41 (1.14, 1.74)	2.38 (1.47, 3.84)
P-value	<0.001	0.001	< 0.001
WWI classifification			
Tertile 1(8.51–10.73)	Reference	Reference	Reference
Tertile 2(10.74–11.47)	1.25(0.85, 1.83)	1.26(0.85, 1.86)	2.74(1.21, 6.22)
P-value	< 0.001	0.243	0.016
Tertile 3(11.48–14.14)	1.90(1.19, 1.82)	1.78(1.24, 2.56)	4.60(2.00, 10.60)
P-value	< 0.001	0.001	< 0.001

Model 1: no covariates were adjusted. Model 2: age, gender, and race were adjusted. Model 3: age, gender, race, smoking behavior, drinking behavior, family history of early ASCVD, personal history of early ASCVD, diabetes, hypertension, hyperuricemia, receiving lipid therapy, alkaline phosphatase, blood urea nitrogen, gamma glutamyl transferase, total cholesterol, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol were adjusted

WWI, weight-adjusted-waist index

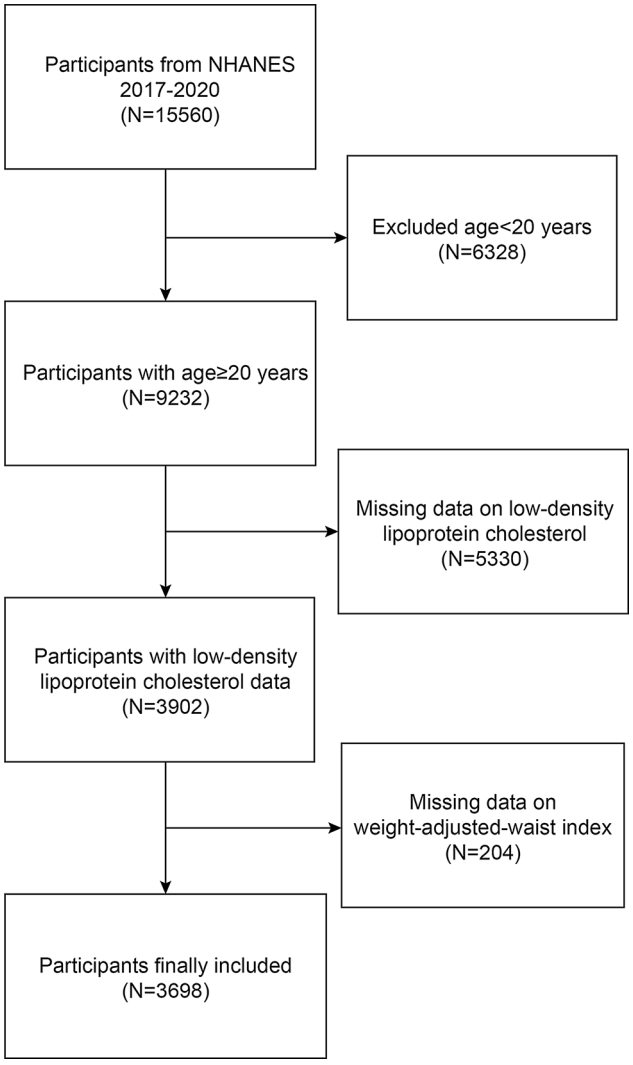

Fig. 1 Flow chart of participant selection. NHANES, National Health and Nutrition Examination Survey

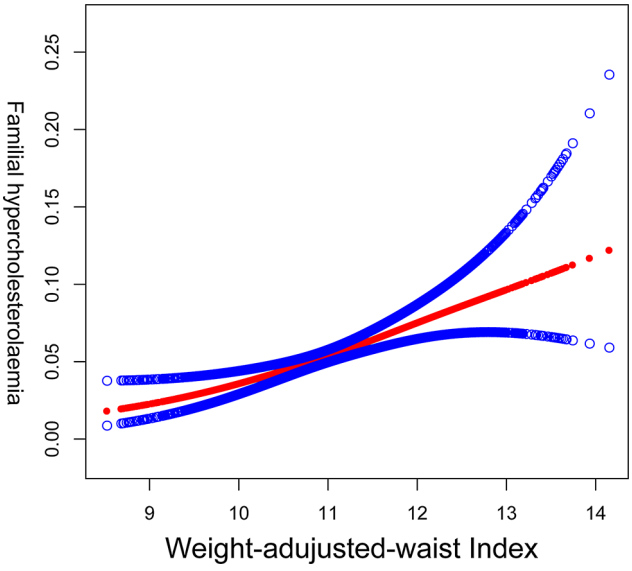

Fig. 2 The association between Weight-adjusted-waist index and Familial hypercholesterolemia. The solid red line represents the smooth curve fit between variables. Blue bands represent the 95$=% confidence interval from the fit

subgroup analyses and interaction tests, consistency in the relationship between WWI and FH was observed across gender, race, hypertension, and diabetes statuses. However, there was a significant association between WWI and FH among populations with a personal history of early ASCVD and a family history of early ASCVD.

BMI is associated with the prevalence of FH

Some studies indicate a certain correlation between BMI and FH incidence rates. A Greek study [16] on 1655 FH adults found that 68.4% of patients had BMI levels exceeding normal values, and the occurrence rate of ASCVD risk factors gradually increased with increasing BMI. Additionally, another study [17] on FH children showed that BMI was a promoting factor for changes

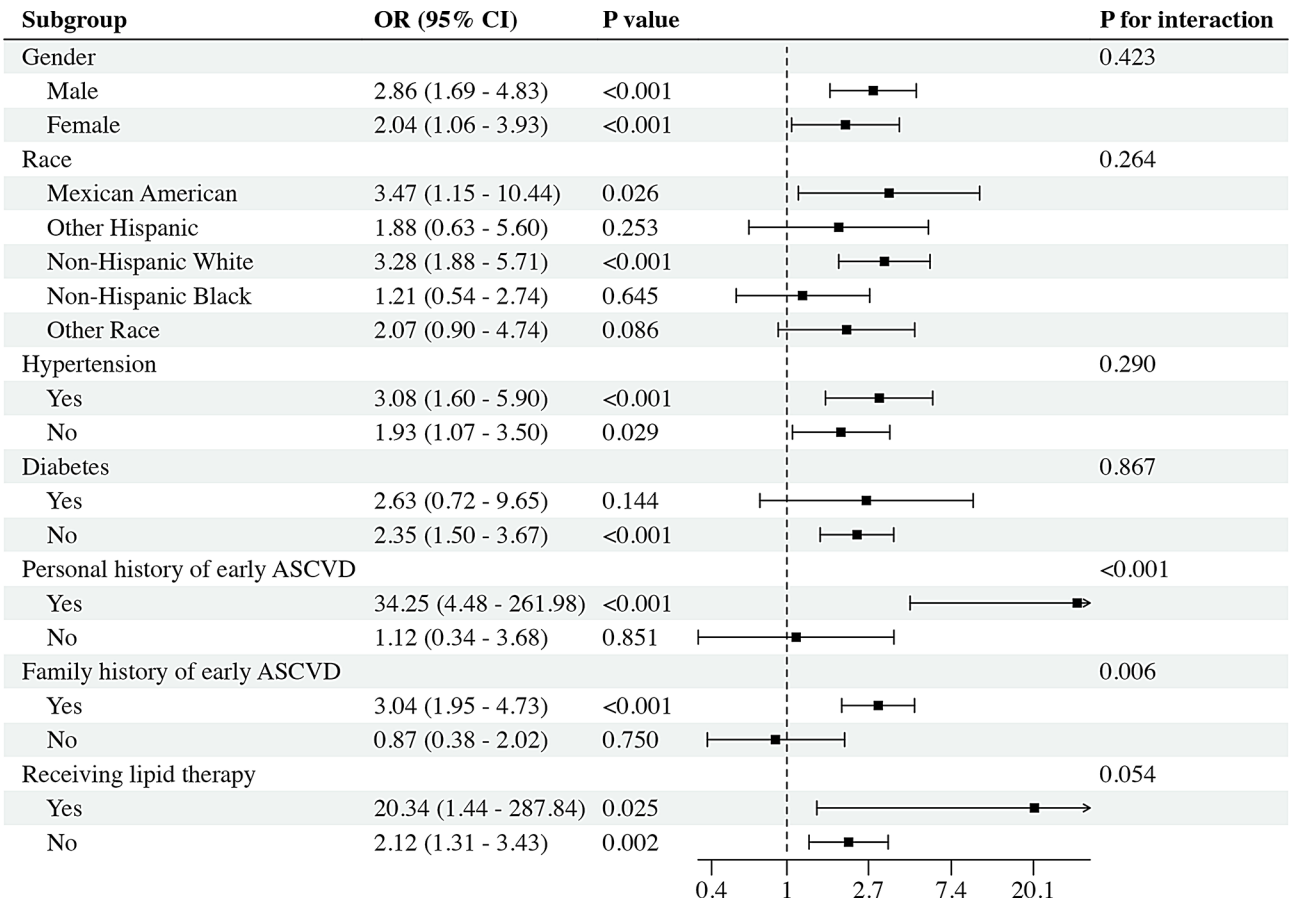

Fig. 3 Showcases the results of a subgroup analysis that focuses on the correlation between Weight-adjusted-waist index and the possible prevalence of Familial hypercholesterolemia

in lipid parameters in FH children, and a significant increase in LDL-C levels was a hallmark of FH.

WWI more accurately predicts FH than BMI

Although these pieces of evidence suggest an association between traditional obesity indicators and FH, the obesity paradox still exists [18]. The potential reasons for the debate may partly be attributed to the limitations of traditional indicators, which cannot differentiate between fat mass and muscle mass. WWI is a new obesity indicator that combines the benefits of WC while attenuating the association with BMI, accurately indicating central obesity and can be used to assess fat and muscle mass [9]. Therefore, WWI can serve as a more comprehensive and accurate obesity measurement method, which may more accurately demonstrate the correlation between obesity and FH. In recent studies [7], WWI has been found to be the strongest predictor of cardiovascular disease mortality, surpassing BMI and WC. This is similar to our research findings, where we also believe WWI may be an effective predictor of FH. Unlike BMI, which only focuses on weight and height relationships, WWI also considers waist circumference, aiding in capturing the risk of central obesity. With its simple calculation and powerful predictive ability for disease development, WWI holds great promise as a potential anthropometry measurement indicator.

Correlation between WWI and cardiovascular disease

To our knowledge, with previous research mainly focusing on the correlation between WWI and cardiovascular disease. Ding [19] et al. conducted a prospective study on 12,447 Chinese individuals and found a significant correlation between higher levels of WWI and increased risk of all-cause mortality and cardiovascular mortality. Zhang [20] et al. found that WWI may be an independent predictor of heart failure in a cross-sectional study of 25,509 individuals. Fang's research [21] showed a positive linear correlation between WWI and CVD, with greater significance in the under-50 age group. Previous domestic research has shown that 44.2% of FH patients suffer from cardiovascular disease, with early-onset ASCVD being one of the main clinical manifestations of FH, and male FH patients experiencing ASCVD before the age of 50, while female onset age is slightly later than males [22].

Correlation between WWI and FH

Similarly, our study is the first to investigate the correlation between WWI and probable prevalence of FH, found a nonlinear positive correlation between WWI and FH, consistent with the adverse consequences of WWI on cardiovascular health described in previous studies. This indicates that WWI may be an intervention indicator for reducing the risk of cardiovascular disease in the general adult population and a potentially effective factor screening for FH, emphasizing the importance of WWI in FH diagnosis and treatment.

Potential mechanisms between WWI and FH

Some potential mechanisms may explain the correlation between WWI and FH. FH is a genetically related hereditary disease, typically resulting from mutations or deletions in the LDLR gene, leading to defective synthesis, assembly, transport, and recycling of LDLR [23]. LDLR is a transmembrane glycoprotein widely distributed in various tissues of the body, with the highest expression in the liver, primarily involved in the metabolism of LDL [24]. The most common molecular alterations in the LDLR gene are small nucleotide variations present throughout the gene, mainly divided into spontaneous and induced mutations, with causes of induced mutations including radiation, chemicals, chronic inflammation, and oxidative stress. Firstly, the marker of abdominal obesity (WWI) has a greater impact on inflammatory markers than the marker of overall obesity (BMI) [25]. Caloric overload induces dysfunction of adipose tissue, promoting the production and release of various pro-inflammatory cytokines. The chronic inflammatory state resulting from the sustained presence of these cytokines may lead to many secondary consequences associated with increased risk of diseases, including an increased mutation rate in genes [26]. Secondly, central obesity can increase the oxidative stress response of individuals, and the adipose tissue will release more reactive oxygen species (ROS), an important deoxyribonucleic acid (DNA) damaging agent [27]. When ROS production exceeds the ability of cells to metabolize them, it leads to an excessive accumulation of ROS, which in turn disrupts cellular defenses, a process that regulates the genetic and epigenetic cascades of altered gene expression in humans [28]. In addition, while the oxidative stress response leads to DNA damage, DNA damage will induce the occurrence of inflammatory response, which then exacerbates the range of DNA damage, forming a vicious circle [29], and the oxidative stress and lipid peroxidation (LPO) accompanying infection and chronic inflammation may induce a variety of genetic diseases [30]. Finally, other coexisting disease states associated with obesity are also promoting factors for FH.

Superiority of the study

Compared with previous studies in this field, for example, studies in Europe [31], Japan [32], China [33] and other regions, there are some differences in the conclusions we may obtain. However, the strength of this study is that it was first collected using a stratified multistage probability sampling strategy based on NHANES data, thus improving the reliability and representability of our findings. Second, we used new data from 2017 to 2020, and the novelty of the data can be guaranteed. In addition, we used a new approach to obesity assessment that allowed us to make more accurate predictions of obesity-related risks. Finally, in our analysis method, we used a multivariate logistic regression model (logistic) adjusting for a range of relevant covariates to assess the impact of WWI on FH.

Limitations of the study

Nevertheless, this study has limitations, due to the relatively small number of FH patients, the results should be considered preliminary, and future research may benefit from increased sample sizes. Additionally, the study population primarily focused on adults, and whether similar conclusions can be drawn for adolescents remains uncertain. Despite adjusting our statistical models for most confounding factors, residual bias cannot be entirely ruled out. We acknowledge that our selection of patients did not involve explicit genetic diagnosis, potentially leading to the inclusion of individuals with other forms of hyperlipidemia, thus necessitating further investigation into genetically defined patients. Lastly, given the nature of the NHANES database, the scope of our study results fundamentally applies only to the U.S. population, and whether our conclusions are applicable to different ethnicities or countries outside the United States requires further exploration.

Conclusion

This study demonstrates a nonlinear positive correlation between WWI and the probable prevalence of FH. This may provide new insights for the diagnosis and treatment of FH in the future. However, our conclusions need to be confirmed by more high-quality prospective studies in the future.

Abbreviations

WWI	Weight-adjusted-waist circumference index
FH	Familial hypercholesterolemia
NHANES	National Health and Nutrition Examination Survey
ASCVD	Arteriosclerotic cardiovascular disease
LDLR	Low-density lipoprotein receptor
LDL-C	Low-density lipoprotein cholesterol
WHO	World Health Organization
BMI	Body mass index

WC	Waist circumference
WHR	Waist-to-Hip Ratio
WHtR	Waist-to-Height Ratio
NCHS	National Center for Health Statistics
DLCN	Dutch Lipid Clinic Network
ROS	Reactive oxygen species
DNA	Deoxyribonucleic acid

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Author contributions
XL, WZ, ZJ, and HZ designed the research. XL, WZ, ZJ, HZ, YW, FW, and SX collected, analyzed the data, and drafted the manuscript. XL, JQ, XR and MY revised the manuscript. XL and XR contributed equally to this work. All authors contributed to the article and approved the submitted version.

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Data availability
All data appearing in the article are available on the website (https://www.cdc.gov/nchs/nhanes).

Declarations

Ethics approval and consent to participate
The portions of this study involving human participants, human materials, or human data were conducted in accordance with the Declaration of Helsinki and were approved by the National Center for Health Statistics (NCHS) Ethics Review Board. The patients/participants provided their written informed consent to participate in this study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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