



OPEN Systemic immune-inflammation index and uric acid mediate the association between obesity and hypertension in young and middleaged adults

Cheng Zuo¹, Zi-Duo Shen² & Yaojun Lu¹✉

Increasing evidence confirms that obesity, inflammation, and uric acid (UA) are important hypertension risk factors. However, the interplay among these factors in hypertension remains unclear. We explored this intricate relationship in young and middle-aged adults using data from the National Health and Nutrition Examination Survey (2011–2018). We analyzed the associations between obesity indicators, including weight-adjusted waist index (WWI), fat mass index (FMI), and visceral adiposity index (VAI) and hypertension, considering mediating roles of the systemic immune-inflammation index (SII) and UA. We included 5,166 participants aged 18–59 years, and 1,154 (22.34%) experienced hypertension. Patients with hypertension exhibited significantly elevated SII, UA, and obesity indicators than did those without hypertension ($p < 0.001$). Weighted logistic regression analysis revealed a positive correlation between WWI, FMI, VAI, and hypertension risk, with significant dose-response and nonlinear associations. SII and UA partially mediated the association between WWI and FMI with hypertension, with UA also mediating the VAI–hypertension link. Subgroup analyses indicated that the association between WWI, FMI, VAI, and hypertension was significant in most subgroups. Our findings highlight the strong association between obesity indicators and hypertension and underscore the importance of targeting inflammation and UA levels in managing hypertension risk among young and middle-aged adults.

Keywords Obesity, Hypertension, Systemic immune-inflammation index, Uric acid, Mediation analysis, NHANES

Hypertension (HT) is the leading cause of premature death from cardiovascular diseases, affecting over one billion people globally. Its prevalence continues to rise, posing a significant public health challenge. HT is also acknowledged as a key modifiable risk factor for both cardiovascular diseases and overall mortality^{1,2}. Previous research has identified obesity, dyslipidemia, physical inactivity, inflammation, and high uric acid (UA) levels as independent risk factors contributing to an elevated risk of HT^{3–7}. However, existing studies have primarily focused on the independent effects of each factor, while the potential mediating roles of inflammation and UA in the relationship between obesity and HT are less understood.

Obesity, a chronic metabolic condition, is closely linked to HT development. Various indicators are used to measure obesity, such as body mass index (BMI) for overall obesity and waist circumference (WC) for abdominal or central obesity⁸. Recently, the weight-adjusted waist index (WWI), fat mass index (FMI), and visceral adiposity index (VAI) have emerged as valuable measures of obesity, reflecting different aspects of this condition^{9,10}. Despite their increasing use, the impact of WWI, FMI, and VAI on HT in young and middle-aged adults has not yet been thoroughly investigated using data from the National Health and Nutrition Examination Survey (NHANES).

The systemic immune-inflammation index (SII) is a novel inflammation marker that combines neutrophil, lymphocyte, and platelet counts into a single index¹¹, offering insights into inflammation. The SII has gained attention for its predictive value in cardiovascular diseases, often outperforming traditional inflammation indicators in predicting cardiovascular events¹².

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Given the complex relationships among obesity, SII, UA, and HT, this study aimed to explore these associations in young and middle-aged adults using NHANES data. Specifically, we evaluated the associations between obesity indicators (WWI, FMI, and VAI) and HT and conducted mediation analyses to determine whether SII and UA mediate the relationship between these obesity indicators and HT.

Methods

Participants and study design

The NHANES is a thorough cross-sectional study organized by the National Center for Health Statistics. Launched in 1999, this biennial survey aims to evaluate the health and nutritional status of the U.S. population. It utilizes complex multistage probability sampling techniques to ensure a representative sample. All participants provided informed consent. More detailed information regarding the survey methodology can be found at <https://wwwn.cdc.gov/nchs/nhanes/Default.aspx>.

For this study, participants were drawn from the NHANES cycles conducted between 2011 and 2018. Initially, 39,156 individuals were considered; however, after excluding those under 18 or over 59 years of age, as well as individuals with missing data on HT status, SII, UA, WWI, FMI, and VAI, a total of 5,166 participants were ultimately included. A flowchart of the study population screening process is provided in Fig. 1.

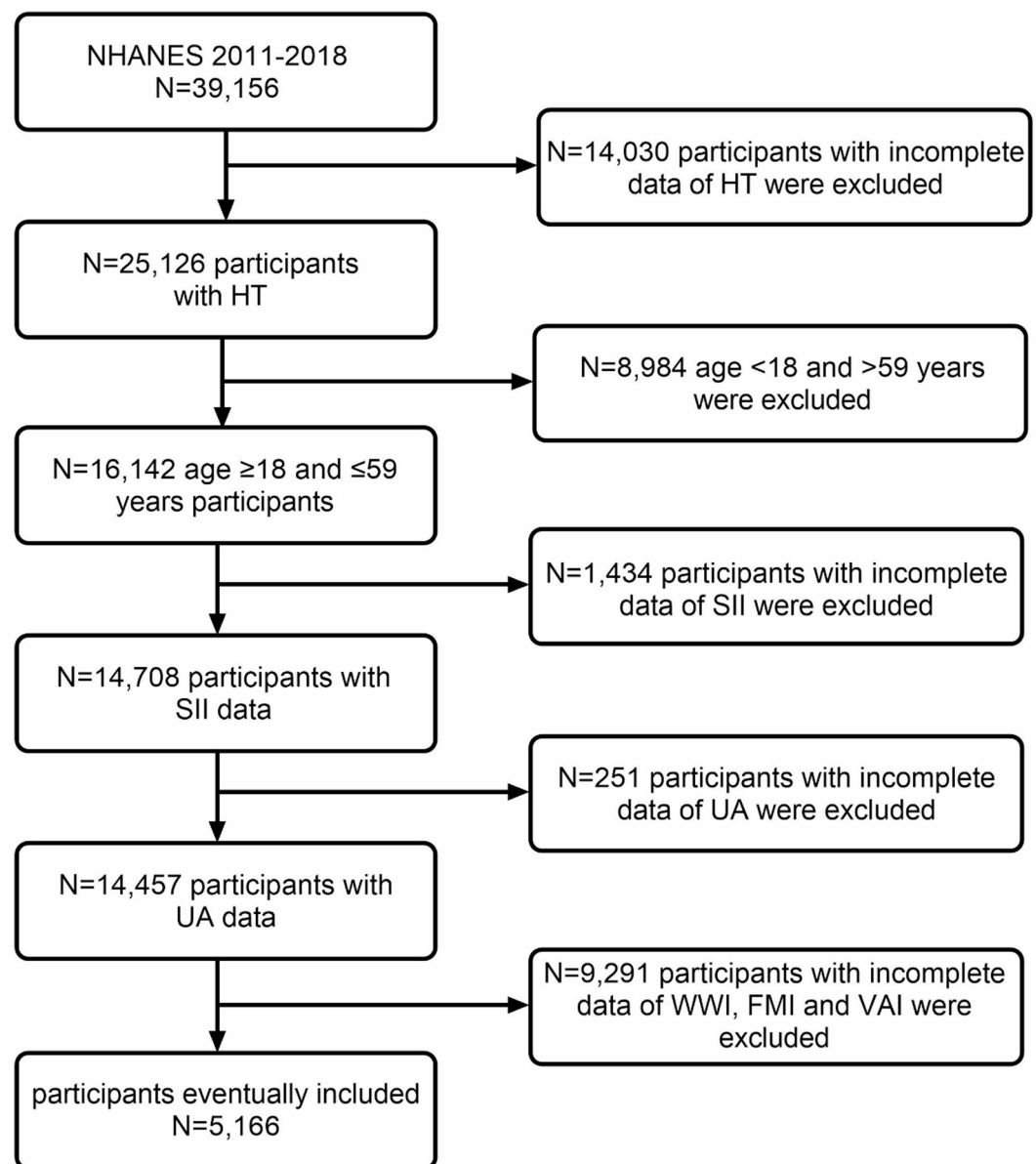


Fig. 1. Flowchart of the study design and participant inclusion. NHANES, National Health and Nutrition Examination Survey; HT, hypertension; SII, systemic immune-inflammation index; UA, uric acid; WWI, weight-adjusted waist index; FMI, fat mass index; VAI, visceral adiposity index.

Exposure variables

Licensed health technicians collected height, weight, and WC measurements at a mobile examination center (MEC) following standardized procedures. Participants were required to remove shoes and outer clothing to ensure accurate weight measurements. WC was assessed by placing a horizontal line at the narrowest point between the lowest rib and the iliac crest using a tape measure. Fat mass was evaluated through dual-energy X-ray absorptiometry, while the VAI was calculated based on BMI, WC, triglycerides (TG), and high-density lipoprotein cholesterol (HDL-C). In this study, WWI, FMI, and VAI were used as exposure variables and calculated as follows:

$$\begin{aligned} WWI &= \frac{WC}{\sqrt{\text{weight}}} \\ FMI &= \frac{\text{fat mass}}{\text{height}^2} \\ VAI \text{ (Male)} &= \frac{WC}{39.68 + 1.88 \times \text{BMI}} \times \frac{TG}{1.03} \times \frac{1.31}{HDL - C} \\ VAI \text{ (Female)} &= \frac{WC}{36.58 + 1.89 \times \text{BMI}} \times \frac{TG}{0.81} \times \frac{1.52}{HDL - C} \\ BMI &= \frac{\text{weight}}{\text{height}^2} \end{aligned}$$

In these formulas, WC was measured in cm, height in m, weight in kg, fat mass in kg, and TG and HDL-C levels in mmol/L.

Assessment of mediators

SII was calculated from complete blood count results, including platelet, neutrophil, and lymphocyte counts, using a Beckman Coulter HMX Hematology Analyzer at the MEC, and the results were documented as $\times 10^3$ cells/ μL . Detailed laboratory procedures for the complete blood count test can be found on the official NHANES website. The SII was calculated as:

$$SII = \frac{\text{platelet count} \times \text{neutrophil count}}{\text{lymphocyte count}}$$

Serum UA levels were measured as part of routine serum biochemical profiles from blood samples obtained at the MEC. UA concentrations were determined using the time-endpoint method, which monitors the change in absorbance of the colored product generated by the reaction of hydrogen peroxide, produced by the oxidation of UA, with 4-aminoantipyrine using 3,5-dichloro-2-hydroxybenzenesulfonate as a catalyst.

Outcome variable

The outcome variable in this study was HT, defined by meeting any one of the following criteria¹³: (1) a self-reported answer of “yes” to the questionnaire question “Ever told you had high blood pressure”; (2) confirmed use of oral antihypertensive medications, including calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, β -receptor antagonists, and diuretics; (3) a mean systolic blood pressure ≥ 140 mmHg or mean diastolic blood pressure ≥ 90 mmHg, based on three consecutive readings by trained and licensed personnel after participants had rested for five min. A fourth measurement was performed if any of the initial three readings were unsuccessful.

Study covariates

Covariates potentially influencing the association between obesity indicators (WWI, FMI, and VAI) and HT were selected based on clinical relevance and previous studies¹⁴. These covariates included age (years), sex (female, male), race and ethnicity (Mexican-American, other Hispanic, non-Hispanic white, non-Hispanic black, other race), education level (less than 11th grade, high school graduate, some college or above), marital status (living alone, married/living with a partner), annual household income ($< \$20,000$, $\geq \$20,000$), smoking behavior (never, former smoking, current smoking), drinking behavior, physical activity (inactive, moderate, vigorous, moderate and vigorous), diabetes, heart failure, coronary heart disease (CHD), angina pectoris (AP), myocardial infarction (MI), stroke, hepatopathy, kidney failure, and cancer.

Definitions for heart failure, CHD, AP, MI, stroke, hepatopathy, kidney failure, and cancer were based on self-reported questionnaire data. Diabetes was defined by meeting at least one of the following criteria¹⁵: glycosylated hemoglobin $\geq 6.5\%$, fasting blood glucose ≥ 7.0 mmol/L, self-reported physician diagnosis of diabetes, or self-reported use of insulin or hypoglycemic medications. Smoking behavior was described as having consumed at least 100 cigarettes during one's Lifetime. Drinking behavior was assessed through two 24-hour dietary recalls, with participants classified as drinkers if they reported alcohol consumption in at least one of the recalls. Detailed measurement procedures for these variables are available on the official NHANES website.

Statistical analysis

Considering the study design, which involved complex multistage probability sampling of the NHANES data, this study applied weighting to the data using the sample weight calculation method recommended by the NHANES

to enhance the reliability of the findings. The MissForest method based on random forests was performed to address missing values for potential confounders. Baseline data were examined for normal distribution, and due to the non-normal distribution of all continuous variables, they were reported as medians with interquartile ranges (IQRs). Categorical variables were expressed as frequencies (percentages). The Mann–Whitney U test was utilized for comparing continuous variables, whereas the chi-square test was applied to categorical variables.

Multivariate logistic regression analysis was conducted to investigate the association between obesity indicators (WWI, FMI, and VAI) and HT. To ensure robust conclusions, three regression models were developed to analyze potentially influential factors in different combinations. Additionally, trend analysis was performed after categorizing WWI, FMI, and VAI into quartiles, and restricted cubic spline (RCS) plots were generated to evaluate linear and nonlinear associations.

To further validate the reliability of findings from the regression models, subgroup analyses and interaction tests were conducted across age (18 to <40 years, 40 to <60 years), sex, race and ethnicity, education level, marital status, annual household income, diabetes, smoking behavior, and drinking behavior subgroups.

The study sought to explore both the direct effects of obesity indicators (WWI, FMI, and VAI) on HT and the indirect effects mediated by SII and UA. Correlations between SII and UA were assessed and mediation analyses conducted separately for SII and UA. Statistical significance was determined by a two-tailed *p*-value of <0.05.

Results

Characteristics of the study population

The baseline characteristics of the study population are summarized in Table 1. This study included 5,166 participants, with 1,154 (22.34%) that were diagnosed with HT. The median age of the participants was 39.00 years (IQR: 28.00–49.00), with a nearly equal distribution of men (2,582) and women (2,584). Compared to the non-HT group, the HT group displayed higher proportions of participants who were non-Hispanic blacks, married/living with a partner, individuals with annual household incomes <\$20,000, smoking behavior (former or current), and those with comorbid conditions such as diabetes, heart failure, CHD, AP, MI, stroke, hepatopathy, kidney failure, and cancer (*p*<0.05). Furthermore, the HT group possessed a significantly older median age and exhibited higher levels of neutrophil count, TG, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and obesity-related indices such as body weight, WWI, FMI, and VAI, compared to these factors in the non-HT group (*p*<0.05). Levels of UA and SII were also significantly elevated in the HT group (*p*<0.05).

Association between obesity indicators and HT

As presented in Table 2, weighted multivariate logistic regression analysis demonstrated a robust positive association between all three obesity indicators (WWI, FMI, and VAI) and the risk of HT. These associations remained statistically significant across all three models, even after adjusting for potential confounders such as demographics, socioeconomic factors, lifestyle behaviors, and comorbidities.

When analyzed as continuous variables, increases in WWI, FMI, and VAI were all associated with elevated odds of hypertension. Notably, WWI exhibited the strongest association, followed by FMI and VAI.

To further explore these associations, each obesity indicator was divided into quartiles. Participants in the highest quartile (Q4) of WWI exhibited almost a three-fold increased risk of HT compared to those in the lowest quartile, even after full adjustment. Similar patterns were observed for FMI and VAI, with progressively higher quartiles corresponding to significantly increased HT risk. These findings suggest a strong, graded association between excess adiposity (particularly central and visceral fat) and hypertension.

A significant dose-response association was observed for all models (*p* for trend <0.05). As presented in Fig. 2, the RCS plots further confirmed the nonlinear association between the obesity indicators (WWI, FMI, and VAI) and HT (*p*<0.05).

Correlation of SII and UA and their association with obesity indicators and HT

Pearson's product-moment correlation analysis confirmed no significant correlation between SII and UA (*r* = −0.013, *p* = 0.360). As presented in Supplementary Tables S1–S3, weighted linear regression analyses revealed significant correlations between all obesity indicators (WWI, FMI, and VAI) and SII (*p* for trend <0.05). Regarding UA, only FMI in Model 1 was not statistically significant (*p* for trend = 0.065), while the other models showed significant associations (*p* for trend <0.05).

As presented in Supplementary Tables S4 and S5, weighted logistic regression analyses indicated that participants with HT had significantly higher levels of SII and UA across all three models (*p* for overall <0.05).

The mediating role of SII and UA

The results of the mediation analysis, presented in Fig. 3, indicate that SII and UA partially mediated the association between WWI and FMI with HT. Specifically, SII mediated 4.42% (*p*<0.001) of the association for WWI and 3.70% (*p*<0.001) for FMI. UA mediated 14.90% (*p*<0.001) of the association for WWI and 10.11% (*p*<0.001) for FMI. Furthermore, UA mediated 33.05% (*p*<0.001) of the association between VAI and HT, whereas SII did not show a significant mediating effect in this context (*p* = 0.410).

Subgroup analysis of obesity indicators and HT

Supplementary Figures S1–S3 present the results of the subgroup analyses exploring the association between obesity indicators (WWI, FMI, and VAI) and HT, stratified by age, sex, race and ethnicity, education level, marital status, annual household income, diabetes, smoking behavior, and drinking behavior. The analysis revealed significant interactions between WWI and smoking behavior (*p* for interaction = 0.016), with the effects of WWI on HT varying by smoking behavior, although all effects remained significant. Interactions between

Characteristics	Overall	Non-hypertension	Hypertension	<i>p</i>
N, %	5166 (100)	4012 (77.66)	1154 (22.34)	
Age, years	39.00 [28.00, 49.00]	36.00 [26.00, 46.61]	48.00 [39.00, 55.00]	<0.001
Sex, n, %				0.052
Female	2584 (49.06)	2007 (49.94)	577 (45.99)	
Male	2582 (50.94)	2005 (50.06)	577 (54.01)	
Race and ethnicity, n, %				<0.001
Mexican-American	799 (10.77)	668 (11.78)	131 (7.25)	
Other Hispanic	558 (7.59)	439 (7.78)	119 (6.94)	
Non-Hispanic white	1810 (61.78)	1406 (61.30)	404 (63.46)	
Non-Hispanic black	1021 (10.33)	692 (9.18)	329 (14.36)	
Other race	978 (9.53)	807 (9.97)	171 (7.99)	
Education level, n, %				0.629
Less than 11th grade	1032 (14.73)	789 (14.56)	243 (15.30)	
High school graduate	1171 (22.53)	910 (22.25)	261 (23.49)	
Some college or above	2963 (62.75)	2313 (63.19)	650 (61.21)	
Marital status, n, %				<0.001
Living alone	2303 (40.20)	1847 (41.91)	456 (34.24)	
Married/Living with a partner	2863 (59.80)	2165 (58.09)	698 (65.76)	
Annual household income, n, %				0.020
<\$20,000	908 (12.73)	668 (12.15)	240 (14.77)	
≥\$20,000	4258 (87.27)	3344 (87.85)	914 (85.23)	
WWI	10.73 [10.21, 11.28]	10.63 [10.12, 11.17]	11.04 [10.62, 11.61]	<0.001
FMI	8.78 [6.60, 12.00]	8.39 [6.35, 11.44]	10.39 [7.71, 13.87]	<0.001
VAI	1.26 [0.76, 2.22]	1.19 [0.71, 2.08]	1.66 [0.99, 2.74]	<0.001
Height, m	1.69 [1.62, 1.76]	1.69 [1.62, 1.76]	1.70 [1.62, 1.77]	0.084
Weight, kg	79.10 [67.00, 93.30]	77.10 [65.00, 90.80]	87.70 [75.80, 101.70]	<0.001
Smoking behavior, n, %				<0.001
Never	3214 (59.18)	2617 (62.26)	597 (48.46)	
Former smoking	846 (19.37)	599 (18.15)	247 (23.60)	
Current smoking	1106 (21.45)	796 (19.59)	310 (27.94)	
Drinking behavior, n, %				0.390
NO	3696 (66.04)	2897 (66.48)	799 (64.50)	
YES	1470 (33.96)	1115 (33.52)	355 (35.50)	
Physical activity, n, %				0.426
Inactive	2806 (51.00)	2194 (51.86)	612 (48.04)	
Moderate	1125 (23.68)	869 (23.17)	256 (25.45)	
Vigorous	976 (20.58)	749 (20.25)	227 (21.74)	
Moderate and vigorous	259 (4.74)	200 (4.73)	59 (4.77)	
Diabetes, n, %				<0.001
NO	4590 (91.07)	3727 (94.61)	863 (78.73)	
YES	576 (8.93)	285 (5.39)	291 (21.27)	
Heart failure, n, %				<0.001
NO	5112 (99.07)	3996 (99.65)	1116 (97.03)	
YES	54 (0.93)	16 (0.35)	38 (2.97)	
CHD, n, %				0.001
NO	58714751.96 (99.02)	3997 (99.48)	1122 (97.44)	
YES	578853.56 (0.98)	15 (0.52)	32 (2.56)	
AP, n, %				<0.001
NO	5121 (99.13)	3999 (99.74)	1122 (96.98)	
YES	45 (0.87)	13 (0.26)	32 (3.02)	
MI, n, %				<0.001
NO	5101 (98.80)	3989 (99.43)	1112 (96.61)	
YES	65 (1.20)	23 (0.57)	42 (3.39)	
Stroke, n, %				<0.001
NO	5100 (98.94)	3987 (99.55)	1113 (96.84)	
YES	66 (1.06)	25 (0.45)	41 (3.16)	
Continued				

Characteristics	Overall	Non-hypertension	Hypertension	<i>p</i>
Hepatopathy, n, %				<0.001
NO	4994 (96.79)	3919 (97.75)	1075 (93.45)	
YES	172 (3.21)	93 (2.25)	79 (6.55)	
Kidney failure, n, %				0.001
NO	5064 (98.26)	3958 (98.68)	1106 (96.79)	
YES	102 (1.74)	54 (1.32)	48 (3.21)	
Cancer, n, %				<0.001
NO	4991 (95.62)	3911 (96.62)	1080 (92.16)	
YES	175 (4.38)	101 (3.38)	74 (7.84)	
Platelets, $\times 10^3$ cells/ μ L	231.00 [199.00, 270.00]	232.00 [200.00, 270.00]	228.00 [196.00, 270.00]	0.379
Neutrophils, $\times 10^3$ cells/ μ L	3.70 [2.90, 4.70]	3.60 [2.90, 4.60]	4.00 [3.10, 5.10]	<0.001
Lymphocytes, $\times 10^3$ cells/ μ L	2.00 [1.60, 2.40]	2.00 [1.60, 2.40]	2.00 [1.60, 2.40]	0.482
TG, mmol/L	1.05 [0.70, 1.58]	0.99 [0.67, 1.48]	1.24 [0.84, 1.95]	<0.001
TC, mmol/L	4.81 [4.19, 5.51]	4.76 [4.14, 5.46]	5.02 [4.40, 5.71]	<0.001
LDL-C, mmol/L	2.85 [2.30, 3.46]	2.82 [2.30, 3.44]	2.95 [2.43, 3.60]	0.001
HDL-C, mmol/L	1.32 [1.09, 1.60]	1.34 [1.11, 1.60]	1.24 [1.03, 1.53]	<0.001
UA, μ mol/L	309.30 [261.70, 368.80]	309.30 [255.80, 362.80]	339.00 [273.60, 392.60]	<0.001
SII	424.51 [310.64, 595.65]	418.64 [309.26, 576.53]	450.66 [315.00, 664.86]	0.013

Table 1. Baseline characteristics of the study population. WWI, weight-adjusted waist index; VAI, visceral adiposity index; FMI, fat mass index; CHD, coronary heart disease; AP, angina pectoris; MI, myocardial infarction; TG, triglycerides; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; UA, uric acid; SII, systemic immune-inflammation index.

diabetes and both FMI and VAI were also observed, with FMI showing a significant association with HT in both diabetic and non-diabetic patients ($p < 0.05$), while the VAI-HT association was significant only in non-diabetic patients ($p < 0.001$). There was also an interaction between FMI and smoking behavior (p for interaction = 0.001), but smoking behavior did not affect the significant correlation. Additionally, there was an interaction between VAI and sex (p for interaction = 0.026), but the VAI-HT association was significant for both sexes.

These findings indicate that the association between VAI and HT may be particularly relevant in non-diabetic individuals. Importantly, no significant interactions were observed for age, race and ethnicity, education level, marital status, annual household income, or drinking behavior, indicating that these factors do not substantially influence the relationship between obesity indicators and HT risk.

Discussion

In this study, we analyzed data from 5,166 participants across four cycles of NHANES (2011–2018), including 2,584 women and 2,582 men, where 1,154 (22.34%) participants were hypertensive. Our logistic regression analysis identified obesity indicators—WWI, FMI, and VAI—as independent risk factors for HT. Trend analysis revealed a significant dose-response association between these obesity indicators and HT, and RCS plots confirmed the presence of a nonlinear association. Mediation analyses further indicated that the SII and UA mediated some of the associations between obesity indicators and HT, except for the association between VAI and HT, where SII did not play a mediating role. Notably, our preliminary analysis confirmed no significant correlation between SII and UA. Subgroup analyses also highlighted that VAI was significantly associated with HT only in participants without diabetes, while other obesity indicators were consistently associated with HT across different subgroups.

Obesity is well recognized as a significant risk factor for various cardiovascular diseases, particularly HT, with approximately 70% of patients with HT being clinically comorbid with obesity¹⁶. While BMI is commonly used to assess overall obesity, it does not account for fat distribution, which is crucial since the biological impact of adipose tissue is location-dependent¹⁷. Visceral fat, for instance, has been shown to have more detrimental effects on metabolic processes than subcutaneous fat, even in individuals with a normal BMI¹⁸. In this context, our study is the first to establish the associations of WWI, FMI, and VAI with HT in a young-to-middle-aged population using NHANES data. Our findings revealed that these obesity indicators were significantly elevated in HT patients compared to levels in non-HT individuals and exhibited a significant nonlinear dose-response relationship with HT, independent of confounders. The mechanisms underlying the obesity-HT link are multifaceted, involving factors such as excessive activation of the sympathetic nervous system, overactivation of the renin-angiotensin-aldosterone system, insulin resistance, endothelial dysfunction, elevated leptin levels, and adiposopathy^{19,20}. These findings underscore the importance of using effective obesity indices to identify high-risk individuals for early intervention.

Before conducting mediation analysis, we examined the individual associations of SII and UA with HT. Both the SII and UA levels were found to be significantly associated with HT development. SII, a novel marker combining neutrophil, lymphocyte, and platelet counts, was introduced by Hu et al. in 2014 to assess systemic inflammation and immune responses¹¹. Previous studies have linked elevated SII levels with worse cardiovascular

	Model 1		Model 2		Model 3	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
WWI						
Continuous	2.14(1.92–2.40)	<0.001	1.90(1.67–2.16)	<0.001	1.73(1.51–1.98)	<0.001
Categories						
Q1(≤ 10.21)	ref		ref		Ref	
Q2(10.21–10.73)	2.37(1.62–3.49)	<0.001	1.84(1.23–2.74)	0.003	1.79(1.19–2.70)	0.006
Q3(10.73–11.28)	3.65(2.50–5.30)	<0.001	2.57(1.73–3.82)	<0.001	2.43(1.63–3.62)	<0.001
Q4(> 11.28)	5.24(3.69–7.43)	<0.001	3.51(2.43–5.06)	<0.001	2.93(1.99–4.31)	<0.001
P for trend	2.27(1.98–2.61)	<0.001	1.88(1.61–2.20)	<0.001	1.70(1.45–2.01)	<0.001
FMI						
Continuous	1.09(1.08–1.12)	<0.001	1.13(1.10–1.16)	<0.001	1.12(1.09–1.15)	<0.001
Categories						
Q1(≤ 6.60)	ref		ref		ref	
Q2(6.60–8.78)	1.67(1.21–2.29)	0.002	1.46(1.05–2.03)	0.024	1.55(1.11–2.17)	0.012
Q3(8.78–12.00)	2.30(1.67–3.16)	<0.001	2.29(1.63–3.22)	<0.001	2.32(1.64–3.27)	<0.001
Q4(> 12.00)	3.46(2.60–4.60)	<0.001	4.35(3.11–6.09)	<0.001	4.16(2.93–5.90)	<0.001
P for trend	1.13(1.10–1.16)	<0.001	1.17(1.13–1.20)	<0.001	1.15(1.12–1.20)	<0.001
VAI						
Continuous	1.14(1.09–1.20)	<0.001	1.12(1.07–1.17)	<0.001	1.08(1.03–1.13)	0.002
Categories						
Q1(≤ 0.76)	ref		ref		ref	
Q2(0.76–1.26)	1.67(1.25–2.23)	<0.001	1.53(1.14–2.06)	0.006	1.50(1.11–2.03)	0.011
Q3(1.26–2.22)	2.10(1.52–2.90)	<0.001	1.86(1.36–2.56)	<0.001	1.71(1.23–2.37)	0.002
Q4(> 2.22)	3.14(2.25–4.39)	<0.001	2.60(1.81–3.74)	<0.001	2.08(1.41–3.07)	<0.001
P for trend	1.44(1.31–1.59)	<0.001	1.36(1.21–1.52)	<0.001	1.24(1.11–1.40)	<0.001

Table 2. Association between the obesity indicator and risk of HT. Model 1: Univariate analysis. Model 2: Adjusted for age, sex, race and ethnicity, education level, marital status, and annual household income. Model 3: Adjusted for age, sex, race and ethnicity, education level, marital status, annual household income, smoking behavior, drinking behavior, physical activity, diabetes, heart failure, CHD, AP, MI, stroke, hepatopathy, kidney failure, and cancer. OR, odds ratio; CI, confidence interval; HT, hypertension; WWI, weight-adjusted waist index; FMI, fat mass index; VAI, visceral adiposity index; CHD, coronary heart disease; AP, angina pectoris; MI, myocardial infarction.

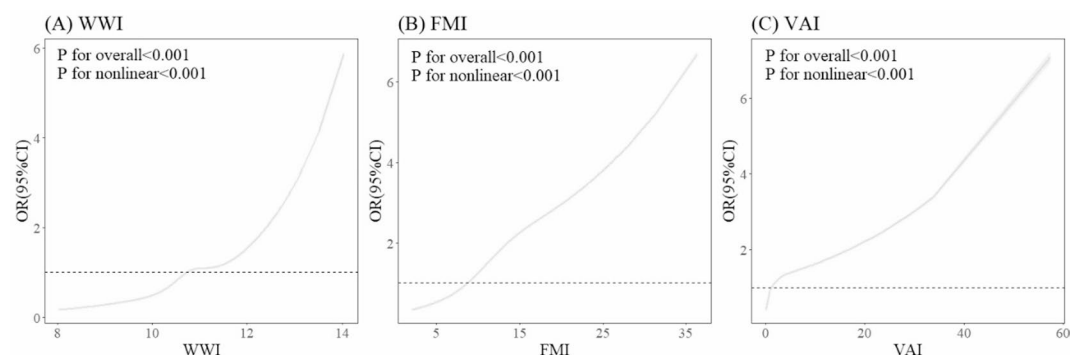


Fig. 2. The restricted cubic spline curve is used to model the relationship between obesity indicators and the risk of HT (A–C), adjusted for age, sex, race and ethnicity, education level, marital status, annual household income, smoking behavior, drinking behavior, physical activity, diabetes, heart failure, CHD, AP, MI, stroke, hepatopathy, kidney failure, and cancer. OR, odds ratio; CI, confidence interval; WWI, weight-adjusted waist index; FMI, fat mass index; VAI, visceral adiposity index; HT, hypertension; CHD, coronary heart disease; AP, angina pectoris; MI, myocardial infarction.

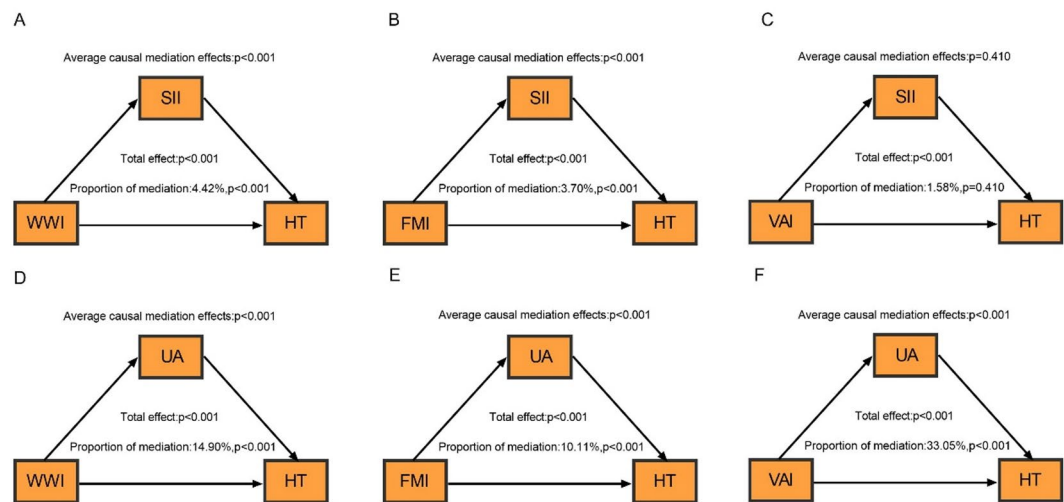


Fig. 3. Mediating effects of SII and UA on the association between obesity indicators and HT (A–F). In all mediation analyses, adjustments are made for the following covariates: age, sex, race and ethnicity, education level, marital status, annual household income, smoking behavior, drinking behavior, physical activity, diabetes, heart failure, CHD, AP, MI, stroke, hepatopathy, kidney failure, and cancer. HT, hypertension; SII, systemic immune-inflammation index; UA, uric acid; WWI, weight-adjusted waist index; FMI, fat mass index; VAI, visceral adiposity index; CHD, coronary heart disease; AP, angina pectoris; MI, myocardial infarction.

outcomes, including higher blood pressure and asymptomatic organ damage in patients with HT^{21,22}. Moreover, a study by Xu et al. further emphasized that compared to the neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and lymphocyte-to-monocyte ratio, SII may serve as a more effective systemic inflammation warning marker for hypertension²³. Furthermore, Shi et al. provided additional evidence supporting a nonlinear relationship between SII and hypertension. Their findings demonstrated that when SII was below the threshold of 501.2, it was not significantly associated with hypertension prevalence. However, among individuals with SII levels equal to or above 501.2, the prevalence of hypertension increased markedly with rising SII levels²⁴.

UA, recognized as a cardiovascular risk factor, has also been implicated in HT development²⁵. Research has consistently demonstrated that elevated UA levels remain an independent risk factor for HT, even after adjusting for confounders^{26,27}. For instance, Bombelli et al. reported that every 1 mg/dL increase in UA levels was associated with a 22% increase in the risk of cardiovascular death²⁸, and some studies indicate that lowering UA levels may help to reverse HT^{29,30}. Our findings are consistent with the existing literature regarding the roles of inflammation and UA in HT.

To further validate our findings, we performed subgroup analyses across various demographic and clinical characteristics, including age, sex, race and ethnicity, education level, marital status, annual household income, diabetes, smoking behavior, and drinking behavior. The results indicated that these factors did not significantly alter the associations between obesity indicators and HT, except for diabetes status. Specifically, while WWI and FMI were consistently associated with HT regardless of diabetes status, the association between VAI and HT was significant only in non-diabetic individuals. This may be due to the inherent metabolic abnormalities associated with diabetes, particularly dyslipidemia, that could influence VAI levels and their relationship with HT^{31,32}.

Our study focused on the mediating roles of SII and UA in the relationship between obesity indicators (WWI, FMI, and VAI) with HT. The mediation analyses confirmed that SII and UA mediated part of the association between WWI, FMI, and HT, with SII mediating 4.42% and 3.70%, and UA mediating 14.90% and 10.11%, respectively. For VAI, UA mediated 33.05% of its association with HT, while SII did not play a significant mediating role. These findings highlight the importance of systemic inflammation (as reflected by SII) and UA as potential biological pathways linking obesity, particularly central and visceral adiposity, to hypertension. The observed mediating effects suggest that these biomarkers may represent intermediate mechanisms through which excess adiposity contributes to elevated blood pressure. Notably, the greater mediating effect of UA, especially in the VAI–HT pathway, indicates a stronger role of metabolic dysfunction in the development of hypertension among individuals with visceral obesity, whereas the modest mediating role of SII underscores the contribution of chronic low-grade inflammation to obesity-related hypertension. From a clinical perspective, SII is a simple, cost-effective, and easily accessible index derived from routine complete blood counts, which makes it a practical tool for early identification of hypertensive risk, particularly in obese individuals. It may also serve as a valuable parameter for monitoring inflammatory status and assessing the potential benefit of interventions targeting systemic inflammation. Understanding these mediators not only provides mechanistic insight into the obesity–hypertension relationship but may also help inform more targeted prevention and treatment strategies that address both inflammation and metabolic abnormalities in at-risk populations.

This study had several strengths. First, we leveraged a large, nationally representative sample to explore the associations between multiple obesity indicators and HT. By using a combination of obesity indicators, we performed a comprehensive assessment of obesity from different perspectives. Second, we examined the

potential mediating roles of two uncorrelated markers, SII and UA, in the obesity-HT relationship. Finally, we adjusted for several key confounders and conducted subgroup analyses to ensure the reliability of our findings.

However, this study had some limitations. The cross-sectional design restricted our capacity to determine causality between obesity indicators and HT. Additionally, the findings are based on a U.S. adult population, which may not be fully generalizable to other populations. Finally, although we adjusted for several confounders, the potential for residual confounding cannot be completely ruled out.

In conclusion, our study highlights the complex interactions between obesity indicators (WWI, FMI, and VAI), SII, and UA in relation to HT. We found that elevated levels of these obesity indicators, as well as increased SII and UA levels, were significantly associated with a higher risk of HT. Notably, SII and UA partially mediated the relationship between WWI and FMI with HT, although SII did not mediate the association between VAI and HT. These findings suggest that strategies focused on weight loss, reducing inflammation, and lowering UA levels may be effective in preventing and managing HT, particularly in young and middle-aged populations.

Data availability

The datasets generated and analyzed during the current study are available in the NHANES repository, (<https://www.cdc.gov/nchs/nhanes/Default.aspx>).

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Author contributions

C.Z. and Y.L. conceived the study, C.Z. and Z.D.S compiled and analyzed the data, C.Z. drafted the manuscript, Z.D.S revised and edited the manuscript, and all authors reviewed and approved the final version of the manuscript.

Declarations

Competing interests

The authors declare no competing interests.

Additional information

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