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ORIGINAL RESEARCH

J-Shaped Relationship Between Weight-Adjusted-Waist Index and Cardiovascular Disease Risk in Hypertensive Patients with Obstructive Sleep Apnea: A Cohort Study

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Background: A newly introduced obesity-related index, the weight-adjusted-waist index (WWI), emerges as a promising predictor of cardiovascular disease (CVD). Given the known synergistic effects of hypertension and obstructive sleep apnea (OSA) on cardiovascular risk, we aimed to explore the relationship between the WWI and CVD risk specifically within this high-risk cohort.

Methods: A total of 2265 participants with hypertension and OSA were included in the study. Multivariate Cox regression analysis was used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for CVD events. The restricted cubic spline (RCS) was used to further evaluate the nonlinear dose-response relationship.

Results: During a median follow-up period of 6.8 years, 324 participants experienced a CVD event. Multivariate Cox regression analysis revealed that compared to the reference group, the HRs for the second, third, and fourth groups were 1.12 (95% CI, 0.79–1.59), 1.35 (95% CI, 0.96–1.89), and 1.58 (95% CI, 1.13–2.22), respectively. Moreover, RCS analysis illustrated a clear J-shaped relationship between the WWI and CVD risk, particularly notable when WWI exceeded 11.5 cm/$\sqrt{\text{kg}}$, signifying a significant increase in CVD risk.

Conclusion: There was a J-shaped relationship between WWI and CVD in hypertensive patients with OSA, especially when the WWI was greater than 11.5 cm/$\sqrt{\text{kg}}$, the risk of CVD was significantly increased.

Keywords: hypertensive, obstructive sleep apnea, weight-adjusted-waist index, cardiovascular disease, visceral obesity

Introduction

Cardiovascular diseases (CVDs), which mainly include coronary heart disease (CHD), stroke, and other diseases, are among the leading causes of death and serious complications worldwide.[1,2] The incidence of CVD is expected to continue rising globally due to aging populations and unhealthy lifestyles, posing a significant health concern.[3,4] Hypertension, one of the most prevalent disorders, has been identified as a primary contributor to CVD.[5] Recent studies have increasingly shown that hypertensive patients with obstructive sleep apnea (OSA) face an elevated risk of exacerbating cardiovascular complications.[6–8]

Obesity, a health problem characterized by excessive accumulation of fat due to prolonged energy intake surpassing expenditure, has been shown in previous studies to notably elevate the risk of CVD.[9–11] However, most prior assessments

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of obesity have relied on body mass index (BMI), which fails to distinguish between fat and muscle mass.[12,13] Notably, research has indicated that among various forms of obesity, visceral obesity—marked by fat accumulation around abdominal organs—particularly correlates with CVD.[14,15] Recent investigations suggest that analyzing body composition and fat distribution enhances the accurate evaluation of adverse metabolic traits and offers better predictive value for overall health status.[16,17] Weight-adjusted-waist index (WWI), a novel measure of central obesity, has emerged as a valuable tool, calculated as waist circumference (WC) divided by weight squared.[18] WWI integrates WC with body weight, preserving WC-related indicators' advantages while mitigating the correlation between WC and BMI.[19] Studies have established significant links between elevated WWI and various diseases, including hypertension, urinary albumin, arterial stiffness, osteoporosis, and heart failure.[20–24] Furthermore, previous research indicates that WWI outperforms BMI, WC, and Waist-to-Hip Ratio (WHtR) as a predictor of CVD mortality.[25,26]

Recent studies have independently linked increased WWI levels to a higher risk of cardiovascular mortality. However, the specific connection between WWI and the occurrence of new cases of CVD in hypertensive patients with OSA remains unclear. Consequently, this study sought to examine the link between WWI levels and the risk of CVD among hypertensive patients with OSA. Studying the relationship between WWI and cardiovascular disease is critical to developing improved prevention strategies aimed at delaying cardiovascular events in this population.

Materials and Methods

2.1. Study PopulationSpecific information on UROSAH research has been published in several places and will not be described here.[6,27–29] Between 2011 and 2013, we collected 3605 hypertensive patients with suspected OSA. During the subsequent follow-up period, 276 participants lost follow-up. A total of 2585 participants were diagnosed with OSA. In addition, we excluded participants who had a history of CVD or lacked WWI data at baseline. Thus, the final sample available for analysis consisted of 2265 participants (Figure S1).

This study adheres to the Declaration of Helsinki and received approval from the Ethics Committee of the People's Hospital of Xinjiang Uygur Autonomous Region (No. 2019030662). Informed consent was obtained from all participants, who also signed informed consent forms.

Data Collection and Definitions

WVarious basic information and laboratory data of participants were collected through electronic medical records. Detailed measurements of the corresponding indicators, specific definitions of lifestyle and diseases can be found in the Supplementary Material. $\mathrm{BMI} = \mathrm{weight\ (kg)/height\ (m^2)}$, $\mathrm{WHtR} = \mathrm{WC/height}$, $\mathrm{WWI\ (cm/\sqrt{kg})} = \mathrm{WC/\sqrt{weight}}$.

Blood samples for all biochemical indices were required to be collected in the morning after at least 8 hours of fasting and obtained by an automated biochemical analyzer (Hitachi 7600–020/ISE; Hitachi, Tokyo, Japan). The estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI formula.[30,31]

Sleep Study

Participants in the study were tested with a polysomnography (PSG) at night in a sleep laboratory. They are scored by the appropriate experts. The details of sleep testing and scoring are described in the Supplementary Materials. We used the apnea hypopnea Index (AHI) to assess OSA severity, classifying OSA severity as mild (AHI $\geq$ 5 but $<$ 15), moderate (AHI $\geq$ 15 but $<$ 30), and severe (AHI $\geq$ 30).

Outcomes

In this study, our primary focus was on the initial occurrence of CVD events, which included both CHD and stroke. CHD events were specifically identified as fatal or non-fatal myocardial infarction, unstable angina, and coronary artery revascularization procedures, whereas stroke encompassed both ischemic and hemorrhagic types. For those seeking an in-depth definition of CVD events, the Supplementary Materials offer comprehensive details. Data collection was extensive, utilizing hospital records, outpatient examinations, and telephone interviews to gather follow-up information. Notably, an independent, blinded clinical events committee rigorously adjudicated all clinical endpoints. Participants'

follow-up person-years were calculated as the time from the first examination until the first cardiovascular event, death, or the date of the last follow-up, whichever came first.

Statistical Analysis

According to WWI, all participants were equally divided into four groups. To assess the incidence rate of CVD, we employed the Kaplan-Meier method. Collinearity was tested using the variance inflation factor, as detailed in Table S1, while the Schoenfeld residuals method, shown in Figure S2, was used to test the proportional hazards assumption. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated through Cox regression analysis. The dose-response relationship between WWI and CVD was further analyzed by the restricted cubic splines (RCS). The receiver operating curve (ROC) was used to compare the predictive value of WWI and BMI. Finally, subgroup analysis and extensive sensitivity analysis further demonstrated the stability of the results. Detailed descriptions of the statistical methods used can be found in the Supplementary Material. All statistical analyses were performed using R software (version 4.1.1), with a two-sided significance level set at 0.05.

Results

Baseline Characteristics

The study included 2265 participants, categorized by WWI quartiles as shown in the Table 1. Those in the higher WWI quartile were younger, more prone to current smoking and drinking, and presented with higher BMI, WC, diastolic blood pressure (DBP), estimated glomerular filtration rate (eGFR), triglycerides (TG), fasting plasma glucose (FPG), and AHI. In contrast, their levels of high-density lipoprotein (HDL) cholesterol were lower. Additionally, they exhibited a higher incidence of diabetes, a greater tendency to take statins and aspirin, and were more frequently

Table 1 Baseline Characteristics

Variables	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P-value
N	566	566	565	568	
Male, n (%)	346 (61.13%)	422 (74.56%)	407 (72.04%)	383 (67.43%)	<0.001
Age, y	52.27 (11.42)	50.63 (10.05)	48.21 (10.28)	47.36 (10.60)	<0.001
Drinking status, n (%)					<0.001
Never	376 (66.43%)	314 (55.48%)	330 (58.41%)	345 (60.74%)	
Past	37 (6.54%)	37 (6.54%)	38 (6.73%)	53 (9.33%)	
Current	153 (27.03%)	215 (37.99%)	197 (34.87%)	170 (29.93%)	
Smoking status, n (%)					0.019
Never	352 (62.19%)	301 (53.18%)	305 (53.98%)	345 (60.74%)	
Past	52 (9.19%)	68 (12.01%)	61 (10.80%)	52 (9.15%)	
Current	162 (28.62%)	197 (34.81%)	199 (35.22%)	171 (30.11%)	
Diabetes, n (%)	78 (13.78%)	85 (15.02%)	123 (21.77%)	128 (22.54%)	<0.001
BMI, kg/m^2	24.01 (1.49)	26.93 (0.61)	29.27 (0.73)	33.41 (2.85)	<0.001
WC, cm	91.36 (7.47)	97.62 (5.43)	102.91 (6.55)	111.72 (8.73)	<0.001
SBP, mmHg	139.20 (18.20)	139.57 (20.36)	139.13 (18.80)	141.67 (21.26)	0.098
DBP, mmHg	89.80 (13.12)	92.06 (14.76)	91.91 (13.90)	93.06 (14.18)	0.001
eGFR, mL/min/1.73 m^2	98.68 (19.40)	94.26 (17.87)	94.78 (20.19)	109.75 (18.31)	<0.001
TC, mmol/L	4.61 (1.37)	4.58 (1.09)	4.50 (1.16)	4.58 (1.18)	0.440
TG, mmol/L	1.89 (1.46)	2.36 (1.98)	2.29 (1.53)	2.14 (1.69)	<0.001
HDL-C, mmol/L	1.21 (0.34)	1.11 (0.26)	1.05 (0.26)	1.05 (0.28)	<0.001
LDL-C, mmol/L	2.66 (0.83)	2.63 (0.81)	2.59 (0.77)	2.68 (0.79)	0.258
FPG, mmol/L	5.06 (1.25)	5.26 (1.42)	5.34 (1.44)	5.51 (1.73)	<0.001
AHI, events/h	18.96 (14.44)	23.89 (17.41)	26.23 (19.76)	30.72 (23.50)	<0.001

(*Continued*)

Table 1 (Continued).

Variables	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P-value
Medications, n (%)					
Statins	153 (27.03%)	188 (33.22%)	206 (36.46%)	220 (28.82%)	<0.001
Aspirins	146 (25.80%)	179 (31.63%)	219 (38.76%)	238 (41.90%)	<0.001
ACEIs/ARBs	250 (44.17%)	243 (42.93%)	281 (49.73%)	270 (47.54%)	0.085
β-blockers	96 (16.96%)	109 (19.26%)	111 (19.65%)	117 (20.60%)	0.454
CCBs	333 (58.83%)	333 (58.83%)	358 (63.36%)	338 (59.51%)	0.341
Diuretics	49 (8.66%)	47 (8.30%)	58 (10.27%)	64 (11.27%)	0.287
OSA therapy, n (%)					<0.001
Untreated	544 (96.11%)	532 (93.99%)	511 (90.44%)	508 (89.44%)	
Regular oral appliance treatment	9 (1.59%)	15 (2.65%)	24 (4.25%)	31 (5.46%)	
Regular CPAP treatment	13 (2.30%)	19 (3.36%)	30 (5.31%)	29 (5.11%)	

Notes: Data are expressed as mean (standard deviation), or n (%).
Abbreviations: BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein; LDL-C, low-density lipoprotein; FPG, fasting plasma glucose; AHI, apnea-hypopnea index; ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; CCBs, calcium channel blockers; OSA, obstructive sleep apnea; CPAP, continuous positive airway pressure.

treated for OSA. Apart from these, no other statistically significant differences were found between the four groups for the other indicators.

Association Between WWI and CVD Risk

During a median follow-up period of 6.8 years, 324 individuals (14.30%) developed CVD, with 201 cases of CHD and the remainder experiencing stroke. The Kaplan-Meier analysis revealed that participants in the highest WWI quartile had a significantly increased cumulative incidence of CVD compared to those in the lowest WWI quartile (Figure 1). Table 2 shows the relationship between WWI and CVD and its subtypes. WWI is significantly and positively associated with the risk of CVD (per SD increase; HR, 1.22; 95% CI: 1.12–1.34), CHD (per SD increase; HR, 1.20; 95% CI: 1.07–1.34), and stroke (per SD increase; HR, 1.26; 95% CI: 1.09–1.46). Additionally, in multivariable models, the HR for CVD in the second quartile (Q2) was 1.78 (95% CI, 1.31–2.43), in the third quartile (Q3) was 1.70 (95% CI, 1.15–2.53), and in the fourth quartile (Q4) was 1.91 (95% CI, 1.16–3.14), compared to the first quartile (Q1). Furthermore, Outcomes for CVD, CHD, and stroke remained robustly significant in the fully adjusted model.

The RCS analysis revealed a significant J-shaped correlation between WWI and CVD risks. Initially, the risk of CVD, including CHD and stroke, decreased as WWI increased. However, once the WWI exceeded 11.5 cm/$\sqrt{\text{kg}}$, these risks began to escalate significantly (Figure 2). Moreover, in the threshold analysis, for every 1 cm/$\sqrt{\text{kg}}$ increase in WWI, participants with WWI less than 11.5 cm/$\sqrt{\text{kg}}$ had a 33% reduction in the incidence of CVD (HR, 0.67; 95% CI, 0.57–0.79), WWI 11.5 cm/$\sqrt{\text{kg}}$ or above had a 94% increased incidence of CVD in participants (HR, 1.94; 95% CI, 1.70–2.22) (Table 3).

Comparative Analysis of Three Obesity Indicators

We utilized ROC analysis assess the predictive value of WWI, BMI and WC for CVD risk (Figure S3). The area under the curve (AUC) for CVD indicated that WWI had a significantly larger AUC (AUC=0.622) compared to BMI and WC (Figure S3A and Table S2). This trend was consistent when examining the AUC values for CHD and stroke as well (Figures S3B, S3C and Table S2). These findings bolster the argument that WWI proves to be a more precise predictor of CVD risk in individuals with hypertension and OSA compared to conventional obesity.

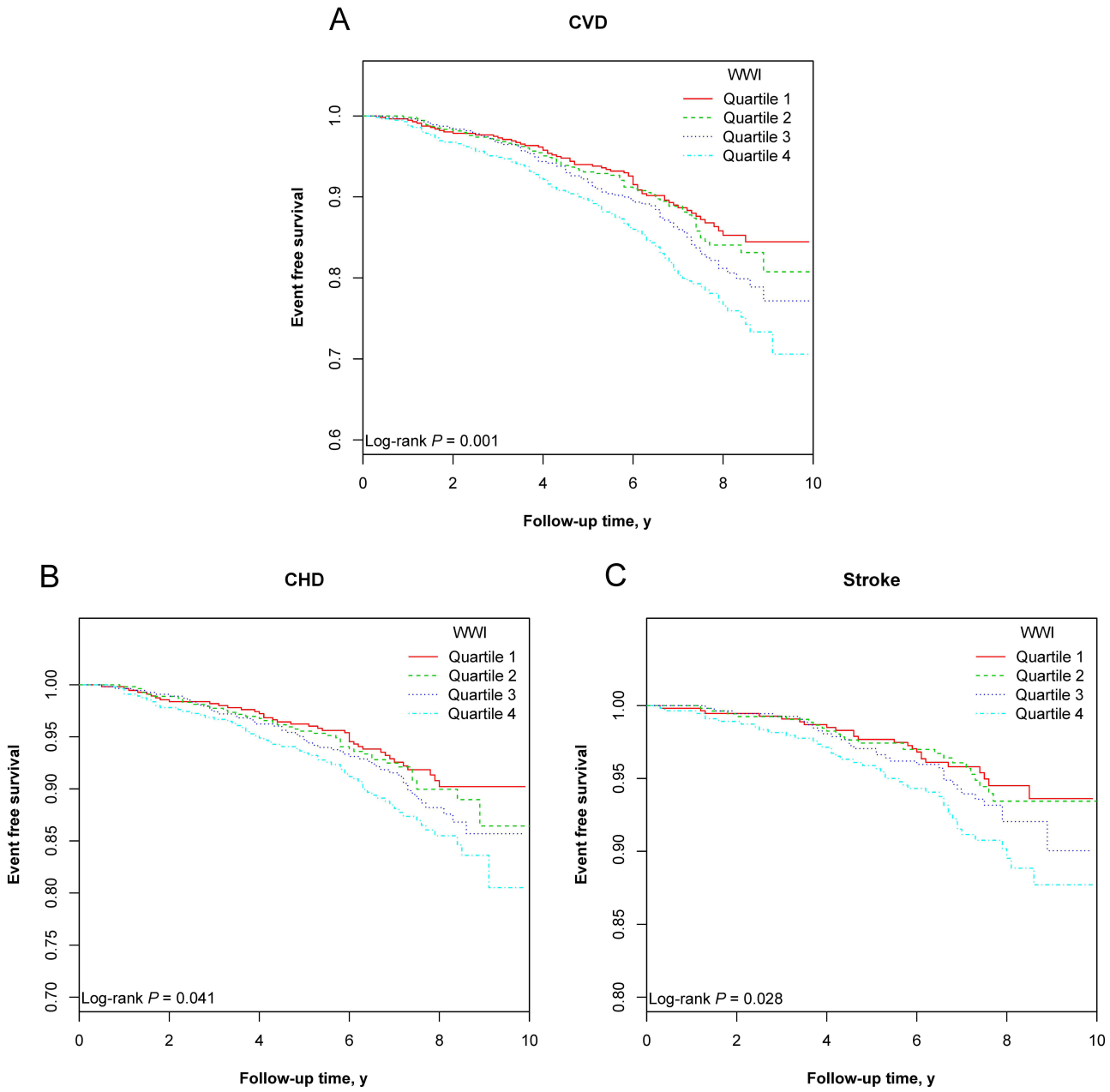

Figure 1 Cumulative incidence curves stratified by WWI quartiles. (**A**) CVD. (**B**) CHD. (**C**) Stroke.

Subgroup and Sensitivity Analysis

In subgroup analyses, where we stratified the data according to various factors, we found that overall outcomes for CVD and CHD, as well as stroke, remained consistent across these subgroups (Figure 3). Importantly, we did not observe an interaction between WWI and these stratification factors, further supporting the stability of our findings. To ensure the robustness of our Results, we conducted extensive sensitivity analyses, excluding newly diagnosed patients who were followed for less than 2 years, the results were consistent (Table S3). Additionally, when we utilized competing risk models, we obtained similar results, as indicated in Table S4. To enhance the reliability of our findings, we also excluded patients who had received treatment for OSA. Remarkably, even after this exclusion, our results remained consistent and reliable (Table S5). Furthermore, our assessment of the E-values indicated that the impact of unmeasured confounders on our results was minimal, reinforcing the overall reliability of our findings (Table S6).

Table 2 Association of WWI with Incident CVD Events

Exposure	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)	Model 4 HR (95% CI)	Model 5 HR (95% CI)
CVD					
Continuous					
WWI, per 1 cm/√kg increase	1.25 (1.16, 1.36)	1.28 (1.18, 1.39)	1.26 (1.16, 1.37)	1.22 (1.12, 1.34)	1.22 (1.12, 1.34)
WWI quartiles					
Quartile 1	Reference	Reference	Reference	Reference	Reference
Quartile 2	1.11 (0.79, 1.56)	1.11 (0.79, 1.57)	1.12 (0.80, 1.58)	1.14 (0.81, 1.62)	1.12 (0.79, 1.59)
Quartile 3	1.34 (0.97, 1.85)	1.39 (1.00, 1.93)	1.37 (0.98, 1.90)	1.35 (0.96, 1.89)	1.35 (0.96, 1.89)
Quartile 4	1.78 (1.31, 2.43)	1.88 (1.37, 2.56)	1.81 (1.32, 2.48)	1.60 (1.15, 2.24)	1.58 (1.13, 2.22)
P for trend	<0.001	<0.001	<0.001	0.004	0.004
CHD					
Continuous					
WWI, per 1 cm/√kg increase	1.23 (1.11, 1.36)	1.25 (1.13, 1.39)	1.23 (1.11, 1.37)	1.20 (1.07, 1.34)	1.20 (1.07, 1.34)
WWI quartiles					
Quartile 1	Reference	Reference	Reference	Reference	Reference
Quartile 2	1.15 (0.75, 1.76)	1.16 (0.75, 1.78)	1.17 (0.76, 1.80)	1.19 (0.77, 1.84)	1.15 (0.74, 1.78)
Quartile 3	1.34 (0.89, 2.02)	1.40 (0.93, 2.12)	1.36 (0.90, 2.07)	1.34 (0.87, 2.05)	1.35 (0.88, 2.07)
Quartile 4	1.70 (1.15, 2.53)	1.81 (1.22, 2.70)	1.74 (1.16, 2.60)	1.57 (1.02, 2.41)	1.54 (1.00, 2.36)
P for trend	0.005	0.002	0.005	0.034	0.038
Stroke					
Continuous					
WWI, per 1 cm/√kg increase	1.30 (1.14, 1.49)	1.32 (1.16, 1.51)	1.31 (1.15, 1.50)	1.26 (1.09, 1.46)	1.26 (1.09, 1.46)
WWI quartiles					
Quartile 1	Reference	Reference	Reference	Reference	Reference
Quartile 2	1.04 (0.59, 1.84)	1.04 (0.59, 1.84)	1.04 (0.59, 1.84)	1.07 (0.60, 1.90)	1.06 (0.60, 1.89)
Quartile 3	1.34 (0.79, 2.28)	1.37 (0.81, 2.34)	1.37 (0.80, 2.35)	1.36 (0.79, 2.36)	1.36 (0.78, 2.36)
Quartile 4	1.91 (1.16, 3.14)	1.98 (1.19, 3.27)	1.92 (1.15, 3.19)	1.66 (0.97, 2.85)	1.66 (0.96, 2.85)
P for trend	0.005	0.004	0.006	0.043	0.044

Notes: Model 1: not adjusted (univariate). Model 2: adjusted for age and sex. Model 3: Model 2 plus adjustment for smoking status, drinking status, SBP, DBP, and diabetes. Model 4: Model 3 plus adjustment for eGFR, TC, TG, HDL-C, LDL-C, FPG, and AHI. Model 5: Model 4 plus adjustment for use of antidiabetic drugs, aspirins, statins, OSA therapy, and antihypertensive drugs.
Abbreviations: CVD, Cardiovascular disease; CHD, Coronary heart disease; SD, standard deviation; HR, hazards ratio; CI, confidence interval.

Discussion

In our study, we present a new obesity index, the WWI, specifically developed to assess the risk of CVD and its subtypes in patients with hypertension and OSA. We discovered a J-shaped correlation between WWI and CVD risk, with an inflection point at 11.5 cm/$\sqrt{\text{kg}}$, where the risk significantly increases with higher WWI values. Notably, similar trends were observed for the CVD subtypes CHD and stroke. This emphasizes the critical role of managing visceral obesity, as indicated by WWI, in reducing the risk of CVD in hypertensive patients with OSA. However, we wish to clarify that our conclusions do not propose WWI as the sole parameter for making treatment decisions. Instead, we posit that WWI, with its demonstrated correlation to CVD risk, should be considered an integral part of a multifactorial risk assessment. It is our belief that the incorporation of WWI into existing risk prediction models can enhance their predictive accuracy by providing additional insight into the role of central obesity.

Given the increasing prevalence of obesity and obesity-related diseases in modern society, assessing obesity effectively in clinical practice is crucial. This assessment is particularly important for identifying hypertensive patients with OSA who are at risk for CVD. While there are numerous indicators for evaluating obesity, BMI stands out as the most widely utilized anthropometric measure due to its straightforward calculation method. However, BMI is not without its limitations. Research indicates that Asians tend to have a higher percentage of body fat and more visceral adipose tissue compared to other racial or ethnic groups at the same BMI levels.[32–34] Furthermore, BMI's ability to differentiate between fat mass and lean body mass is limited, which compromises its effectiveness in accurately assessing obesity.[35,36]

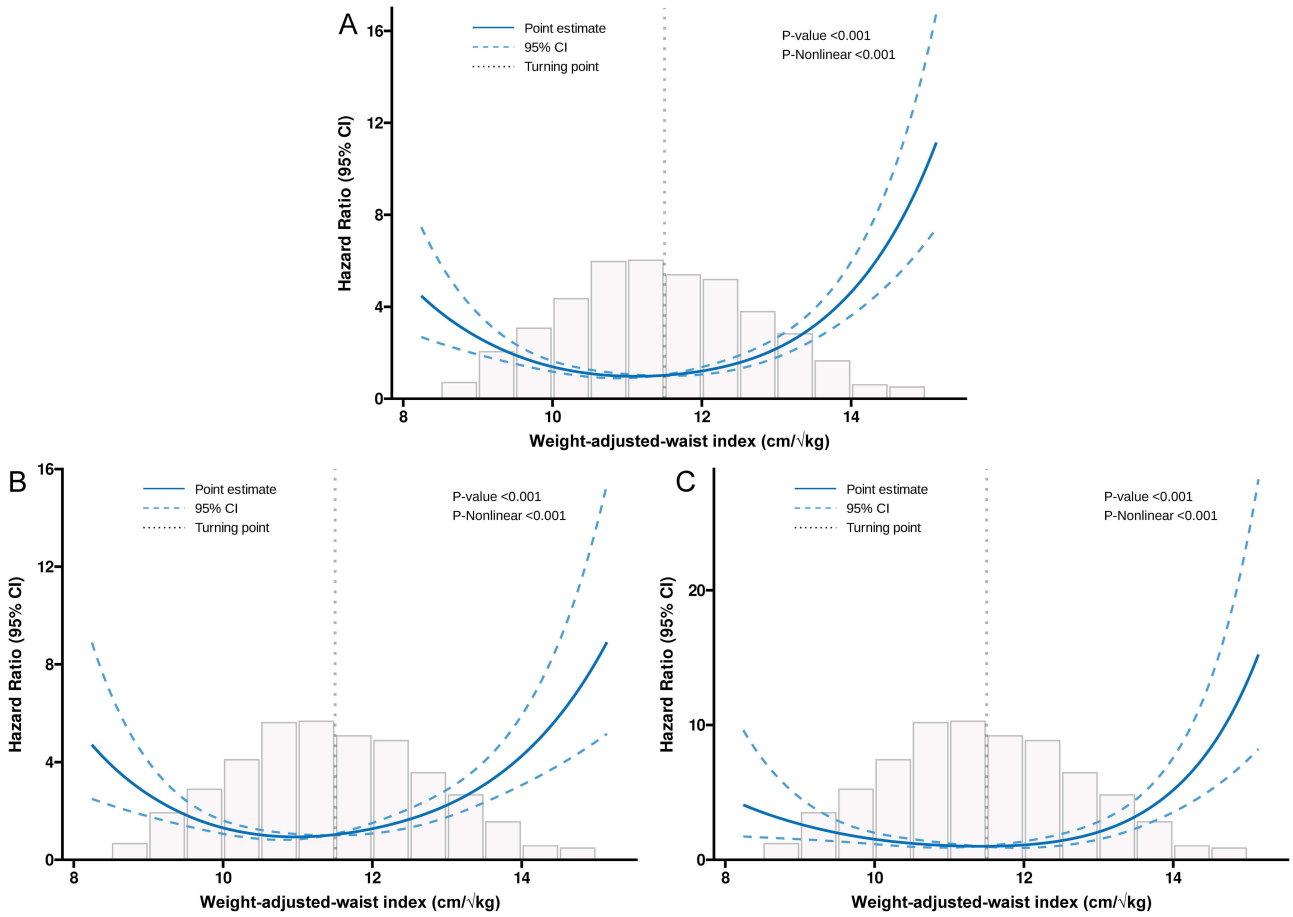

Figure 2 Dose-response associations of WWI with incident study outcomes. (**A**) CVD. (**B**) CHD. (**C**) Stroke.

WC is proposed as an alternative measure, particularly effective for detecting central obesity. It is considered a better indicator of metabolic obesity due to its strong association with visceral fat.[37–39] Nevertheless, WC's disregard for height can lead to inaccuracies in estimating abdominal obesity across different statures, highlighting its limitations.[40,41] Furthermore, evidence suggests a negative association between WC and CVD mortality, questioning its reliability.[18] WHtR is another metric used to overcome some limitations of BMI and WC, offering a better indication of obesity and CVD risk.[41] However, WHtR is not without its flaws, being influenced by age and other factors, and showing limited effectiveness in overweight and obese youth.[42,43]

In light of these limitations, we introduce the WWI, a novel metric combining WC with body weight. The WWI aims to retain the benefits of WC measurements while reducing their correlation with BMI. This index provides a more

Table 3 Threshold Effect Analysis of the Association of WWI with Incident CVD Events

Outcomes	CVD HR (95% CI) P-value	CHD HR (95% CI) P-value	Stroke HR (95% CI) P-value
Inflection point	11.5	11.5	11.5
WWI (< 11.5)	0.67 (0.57, 0.79) <0.001	0.68 (0.56, 0.84) <0.001	0.65 (0.50, 0.84) 0.001
WWI (≥ 11.5)	1.94 (1.70, 2.22) <0.001	1.88 (1.58, 2.23) <0.001	2.06 (1.66, 2.55) <0.001
P for log-likelihood ratio test	<0.001	<0.001	<0.001

Notes: Adjusted for age, sex, smoking status, drinking status, SBP, DBP, diabetes, eGFR, TC, TG, HDL-C, LDL-C, FPG, AHI, use of antidiabetic drugs, aspirins, statins, OSA therapy, and antihypertensive drugs.

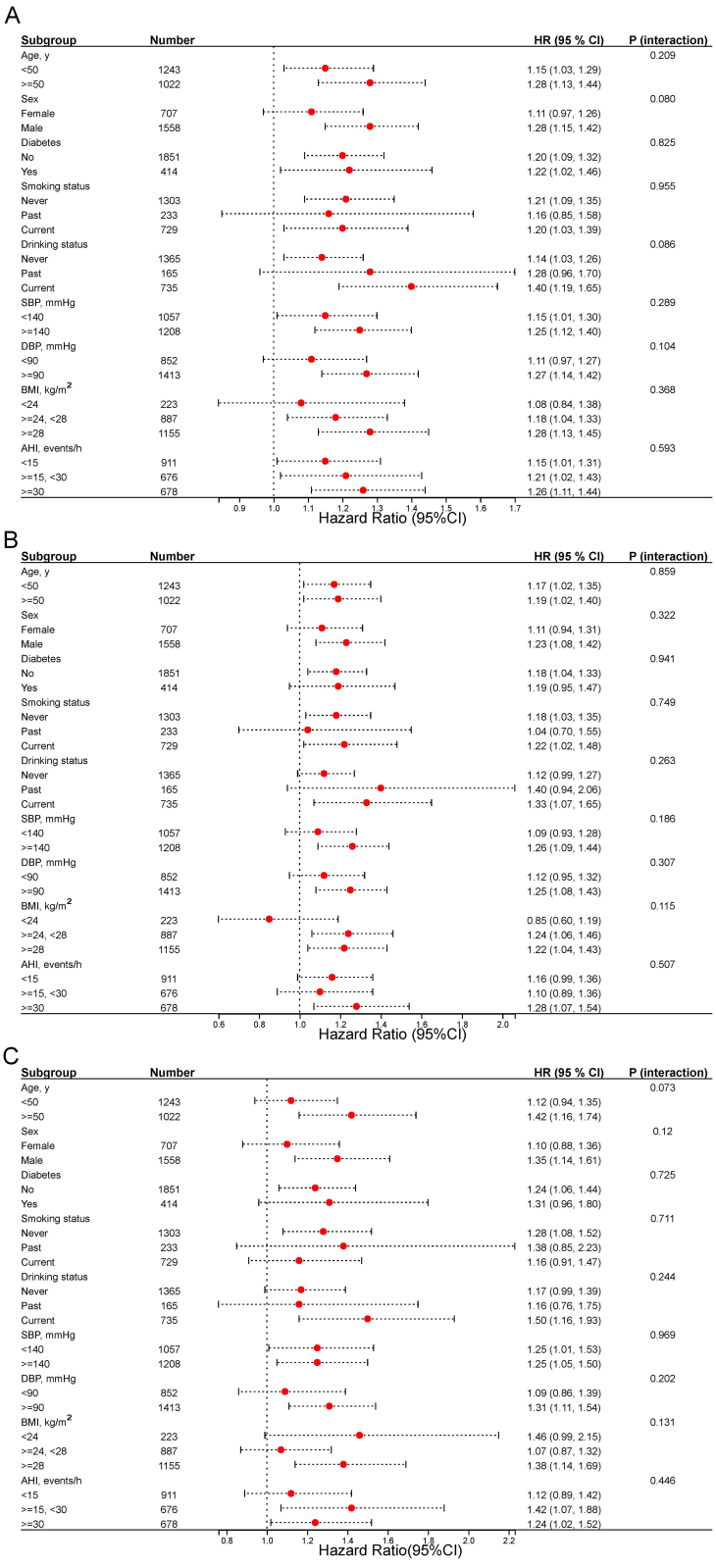

Figure 3 Association between WWI (per SD increment) and study outcomes in various subgroups. (**A**) CVD. (**B**) CHD. (**C**) Stroke.

accurate representation of visceral obesity and has been validated by studies as a superior predictor of obesity-related disease morbidity and mortality.[18,19,25]

Our study is basically consistent with previous studies, indicating a significant positive correlation between central visceral obesity, as measured by the WWI, and CVD along with its subtypes.[18,19,22,25] Specifically, a national cohort study in South Korea demonstrated that WWI is a superior predictor of CVD mortality compared to BMI, WC, and WHtR, highlighting its predictive power.[18] Furthermore, WWI is strongly associated with arterial stiffness, a known risk factor for CVD. Research involving hypertensive patients has shown a positive correlation between WWI and brachial-ankle pulse wave velocity across different BMI categories. This suggests that WWI could be a valuable factor in managing arterial stiffness, alongside blood pressure control, to mitigate the risk of future CVD events.[22] Additionally, WWI's reliability extends to predicting stroke subtypes of CVD, where a significant relationship between higher WWI levels and increased stroke incidence was observed.[19] The unique focus of our study was on evaluating the impact of the WWI on CVD risk in patients with hypertension and OSA. We discovered a J-shaped correlation between WWI and CVD risk. This underscores the importance of addressing central visceral obesity, as indicated by WWI, to mitigate the risk of future cardiovascular events in this demographic.

Several mechanisms potentially explain the link between the WWI and CVD. Initially, an elevated WWI may indicate adipose tissue dysfunction, leading to an increased production of pro-inflammatory cytokines.[44] These cytokines play a crucial role in the formation, progression, erosion, and rupture of atherosclerotic plaques, subsequently triggering cardiovascular events.[45,46] Moreover, central obesity is known to enhance oxidative stress, which significantly contributes to atherosclerosis development.[47,48] This is exacerbated by the fact that adipose tissue in obese individuals releases an abundance of reactive oxygen species (ROS).[49] The overproduction of ROS diminishes the availability of nitric oxide (NO), a critical molecule for vascular health. When superoxide reacts with NO, it forms harmful hydrogen peroxide, resulting in endothelial dysfunction and further vascular damage.[50] Additionally, obesity often coexists with other conditions such as impaired glucose tolerance, hypertriglyceridemia, and hypertension, each of which independently elevates the risk of CVD.[51]

This study pioneers the investigation of the relationship between the WWI and CVD, along with its subtypes, in patients with hypertension and OSA. We identified a significant J-shaped relationship between WWI and CVD risks, which remained consistent even after conducting multiple sensitivity analyses and adjusting for a wide range of variables. While our findings are compelling, several limitations should be noted. One such limitation is the potential underrepresentation of non-obese individuals with OSA in our study population. The unique characteristics of OSA in non-obese patients, which may differ from those typically associated with obesity, require further exploration. The mechanisms and management of OSA in non-obese populations are not well understood and merit additional research. Given this limitation, we recommend that future research should focus on the distinct characteristics and needs of non-obese individuals with OSA. Further investigation is needed to explore the mechanisms underlying OSA in this population and to develop tailored management strategies. Understanding these nuances is crucial for the development of personalized treatment plans and for optimizing health outcomes in non-obese individuals with OSA. Additionally, we relied on baseline WWI measurements, which may not account for long-term changes. Thirdly, due to the observational nature of this study, we cannot definitively establish causality. Fourthly, despite comprehensive adjustments, the potential for unmeasured confounding factors exists. However, the strength of the evidence, as indicated by E-values, suggests a low probability that these findings could be invalidated. Finally, it is important to acknowledge that there may be some heterogeneity among different populations. Since our study population consisted exclusively of Chinese individuals, caution should be exercised when generalizing these results to other populations. Therefore, we are eager to see the inclusion of a wider range of populations and more comprehensive information in future studies to strengthen and validate these findings.

Conclusion

Our study reveals a J-shaped correlation between the WWI and the risk of CVD in hypertensive patients with OSA. We identified an inflection point at 11.5 $m/\sqrt{kg}$, beyond which the risk significantly increases. This suggests that monitoring WWI could be crucial for interventions designed to lower CVD risk. Nonetheless, it is essential to consider the potential

heterogeneity across populations and the interactions between factors and WWI. Therefore, conducting additional longitudinal studies is crucial to fully understand and clarify the causal relationships.

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Disclosure

The authors report no conflicts of interest in this work.

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