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Original Article

Association of Waist Circumference with All-cause and Cardiovascular Mortality in Diabetes from the National Health and Nutrition Examination Survey 2003–2018

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Abstract

Background and objectives: Waist circumference (WC) is closely associated with metabolic diseases, including diabetes mellitus (DM), metabolic syndrome, and mortality. However, the correlation between WC and mortality varies across populations and has rarely been examined specifically in patients with DM. In this study, we explored the relationships between WC and both all-cause and cardiovascular mortality among individuals with DM.

Methods: Participants from the National Health and Nutrition Examination Survey 2003–2018 included 3,151 women and 3,473 men with DM who had baseline WC measurements. Survival data were collected from enrollment until December 31, 2019. Cox proportional hazard models were adjusted for demographic features and other confounders. Restricted cubic spline curves and threshold effect analyses were performed separately for men and women. Sensitivity analyses were conducted to minimize reverse causality.

Results: Among 6,624 participants with DM, 621 women and 871 men died during median follow-ups of 6.8 and 6.3 years, respectively. WC demonstrated a U-shaped association with all-cause and cardiovascular mortality in women, and a J-shaped trend in men. The optimal WC thresholds for minimizing mortality risk were 107.0 cm for women and 89.0 cm for men. For women, adjusted hazard ratios for all-cause mortality were 0.97 (95% confidence interval (CI): 0.96–0.98, $P < 0.001$) for WC below 107.0 cm and 1.04 (95% CI: 1.02–1.05, $P < 0.001$) for WC above 107.0 cm. In men, the corresponding ratios were 0.94 (95% CI: 0.90–0.97, $P < 0.001$) for WC below 89.0 cm and 1.03 (95% CI: 1.02–1.05, $P < 0.001$) for WC above 89.0 cm.

Conclusions: WC showed a U-shaped association with all-cause and cardiovascular mortality in women and a J-shaped association in men among U.S. adults with DM from the National Health and Nutrition Examination Survey. Further research is needed to explore the underlying mechanisms rather than promoting preconceived notions about an optimal WC.

Keywords: Waist circumference; Obesity; All-cause; Cardiovascular; Mortality; Diabetes; Nonlinear; National Health and Nutrition Examination Survey.

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Introduction

Over the past three decades, the global incidence of diabetes mellitus (DM) has significantly increased, adversely affecting morbidity, mortality, and healthcare costs.[1,2] Obesity, a known risk factor for type 2 DM and associated with higher mortality in the general population, presents a complex relationship when using body mass index (BMI) as an indicator.[3] In diabetic patients, some studies indicate a positive correlation between BMI and mortality,[4,5] while others report an inverse or U-shaped relationship.[6–9] Furthermore, the "obesity paradox" suggests that overweight or obese DM pa-

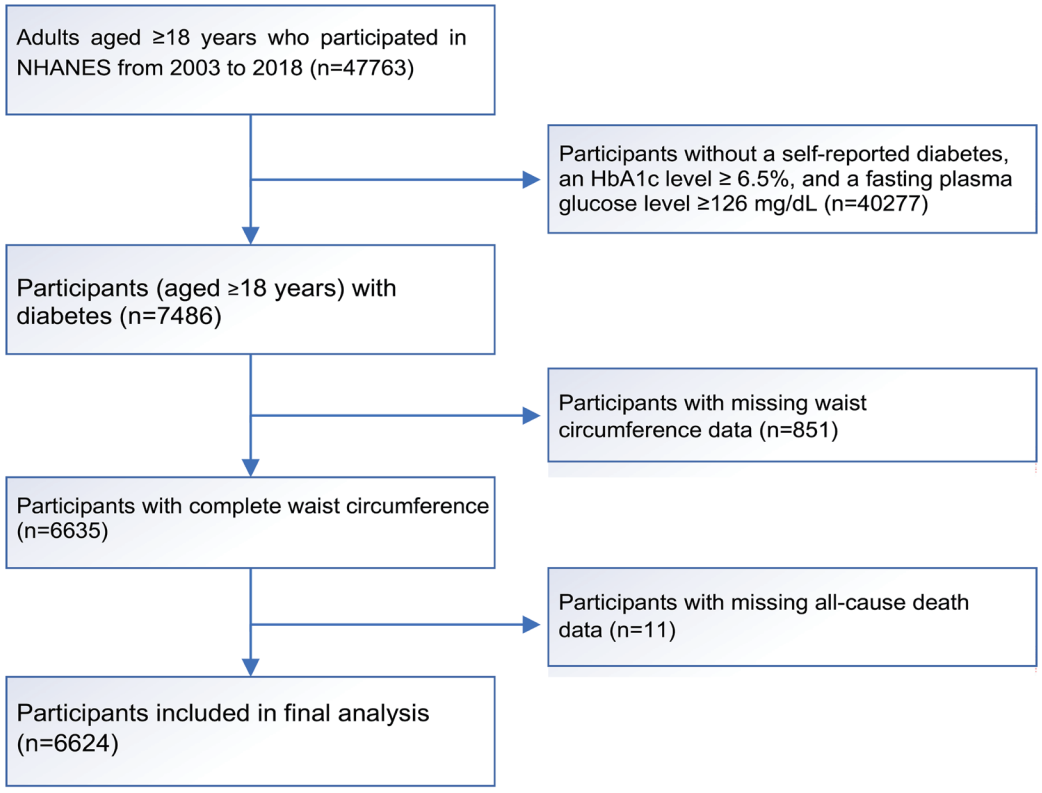

Fig. 1. Flowchart of the study population. HbA1c, glycated hemoglobin; NHANES, National Health and Nutrition Examination Survey.

tients may have lower mortality than their leaner counterparts.[10–12]

Alternative metrics, such as waist circumference (WC), have been studied less frequently than BMI, warranting further investigation into their impact on mortality in DM patients.[13] Compared to BMI, WC is often considered a more reliable indicator of type 2 DM incidence or prevalence.[14,15] Similar to BMI, research on the relationship between WC and all-cause mortality has yielded inconsistent results, with some studies showing positive associations,[16,17] others negative,[18,19] and some showing no association at all.[20] The UK Biobank study revealed a U-shaped relationship between WC and mortality risk in the general population.[13] Consequently, the association between WC and mortality risk remains controversial across different populations, with limited research specifically examining this relationship in patients with DM.

Therefore, we aimed to explore the association between WC and both all-cause and cardiovascular disease (CVD) mortality risk, stratified by sex, among U.S. individuals with DM, utilizing data from the National Health and Nutrition Examination Survey (NHANES) 2003–2018. Additionally, we sought to determine sex-specific WC thresholds associated with the lowest mortality risk in this population.

Materials and methods

Subjects and design

The NHANES was established to assess the health and nutritional status of U.S. citizens on a national level. To ensure the broad generalizability of findings to the U.S. population, a multistage, complex probability sampling strategy was utilized.[21] The NHANES study adheres to the principles of the Helsinki Declaration (as revised in 2013). The National Center for Health Statistics Ethics Review Board approved the study (approval IDs available at https://www.cdc.gov/nchs/nhanes/irba98.htm) and authorized public use of NHANES data. All participants provided written informed consent. Adults with DM (age ≥ 18) from the NHANES 2003–2018 were included in this study. DM was defined as glycated hemoglobin (HbA1c) ≥6.5%, fasting plasma glucose ≥126 mg/dL, or self-reported diagnosis. Individuals lacking all-cause mortality data (n = 11) or WC measurements (n = 851) were excluded. The final analysis included 6,624 eligible subjects with DM (Fig. 1).

Exposure and outcome variables

The primary exposure variable was WC (cm), measured alongside height and weight using standard methods outlined by the U.S. Centers for Disease Control and Prevention (CDC) (http://cdc.gov/nchs/nhanes). Outcome variables included all-cause and CVD mortality, primarily ascertained by cross-referencing NHANES data with the National Death Index. A linked mortality file with cause-specific death information was available from baseline through December 31, 2019. Participants without death record match during follow-up were assumed to be alive. CVD mortality was determined using ICD-10 classification codes (I00-I09, I11, I13, I20-I51, and I60-I69).

Covariates

Based on previous research, covariates were selected to account for risk indicators of all-cause mortality and potential confounders. The fully adjusted models included age (years), education

(<high school, high school equivalent, or >high school), BMI (kg/m^2), ethnicity (non-Hispanic White, non-Hispanic Black, Mexican American, other Hispanic, or other Race), mean systolic (SBP) and diastolic (DBP) blood pressure (mmHg), poverty-to-income ratio, physical activity (sedentary, low, moderate, or high), smoking status, drinking (yes/no), DM duration (years), DM family history (yes/no), and comorbidities (hypertension, cancer, coronary atherosclerotic heart disease [CAD], stroke, heart failure (HF), and dyslipidemia) (yes/no), HbA1c (%), serum low-density lipoprotein cholesterol (LDL-c, mg/dL), high-density lipoprotein cholesterol (HDL-c, mg/dL), and estimated glomerular filtration rate (eGFR, mL/m/1.73m^2). Alcohol consumption was defined as drinking (≥12 drinks/year) or no drinking based on self-reported data. Comorbidity information was collected by trained interviewers based on the question: "{Have you/Has SP} ever been told by a doctor or other health professional that {you/s/he} had {comorbidity name}?". The collected data were reviewed for completeness and consistency.[22] Laboratory measurements were performed using the Roche Cobas 6000 (c501 module) analyzer for standard biochemical indices.[22]

Statistical analysis

We adhered to CDC's statistical analysis recommendations (https://wwwn.cdc.gov/nchs/nhanes/tutorials/default.aspx). Baseline characteristics are presented as frequencies (%) for categorical variables and as means ± standard deviations or medians (interquartile ranges) for continuous variables. Differences in means, medians, or percentages between sexes were evaluated using one-way Analysis of Variance (ANOVA), Kruskal-Wallis, or chi-squared tests. Cox proportional hazard regression was employed to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for all-cause and CVD mortality associated with continuous or categorical WC levels. Three Cox regression models were constructed sequentially: Crude model without adjustments, Model 1 adjusted for education, ethnicity, drinking, smoking, poverty-to-income ratio, physical activity, age, CAD, and DM family history, and Model 2 adjusted for covariates in Model 1 plus HF, hypertension, dyslipidemia, cancer, stroke, DM duration, SBP, DBP, HDL-c, LDL-c, glycohemoglobin, eGFR, and BMI. Covariates were included as potential confounders in the final models if they changed the estimates of WC level on all-cause mortality by more than 10%. To assess the potential nonlinear association between continuous WC and mortality, we used restricted cubic splines to determine whether the independent variable should be divided into intervals. Segmented regression was applied to fit each interval, and log-likelihood ratio tests were conducted to compare a linear model with a segmented regression model, deriving a *P*-value for the nonlinearity of the smooth curve fitting. The threshold level of WC was determined at the inflection point with the highest model probability.[13]

Multiple imputation via chained equations was used to address missing data, generating five imputed datasets within the R multiple imputation framework.[23] Sensitivity analyses were conducted to assess the robustness of key outcomes across subgroups defined by age (≥60 and <60 years), smoking status (current, former, and never), BMI (obesity [≥30 kg/m^2], overweight [25 to <30 kg/m^2] and normal [18.5 to <25 kg/m^2]), previous CVD or malignancy (yes/no), and eGFR (<60 and ≥60 mL/m/1.73m^2). Additionally, a complete case analysis was performed to evaluate if missing data biased the results. Subjects with less than one year of follow-up were also excluded to reduce potential reverse causality bias.

All analyses were performed using R 3.3.2 (http://www.R-project.org, The R Foundation) and the EmpowerStats program. Statistical significance was established using a two-sided test with a $P < 0.05$.

Results

Baseline features of included individuals with DM by sex

The cohort of 6,624 patients with DM had a mean age of 60.8 ± 13.7 years, with females comprising 47.6% of the population. During a median follow-up of 6.8 years for men and 6.3 years for women, 621 women and 871 men died. Table 1 presents baseline sociodemographic and clinical characteristics by sex. Women had significantly higher mean values for SBP, BMI, total cholesterol, HDL-c, LDL-c, eGFR, and a greater proportion of individuals with a low education level, family history of DM, a sedentary lifestyle, cancer, hypertension, and dyslipidemia (all $P < 0.05$). In contrast, women had significantly lower values for age, WC, DBP, poverty-to-income ratio, serum glucose level, as well as lower proportions of Non-Hispanic White subjects, drinkers, current smokers, and individuals with CAD or HF (all $P < 0.05$). No significant differences were identified between sexes in HbA1c, triglycerides, diabetes duration, or stroke prevalence (all $P > 0.05$).

Relationships of the baseline WC with all-cause and CVD deaths

As shown in Table 2, baseline WC (as a continuous variable) was negatively and significantly correlated with total mortality in women in both the crude model (HR = 0.99, 95% CI: 0.98–0.99, $P < 0.001$) and Model 1 (HR = 0.99, 95% CI: 0.99–1.00, $P = 0.015$). However, this relationship was not significant in Model 2 (HR = 1.01, 95% CI: 1.00–1.02, $P = 0.168$). For men, continuous WC was significantly and positively associated with all-cause mortality in Model 2 (HR = 1.03, 95% CI: 1.02–1.04, $P < 0.001$). When subjects were stratified into WC tertiles, no clear linear correlation with all-cause mortality was observed in the adjusted models. Additionally, neither categorical nor continuous WC was significantly correlated with CVD mortality in Model 2 for either sex (all $P > 0.05$). These findings suggest a possible nonlinear association between WC and death from all causes and CVD.

Two-piecewise linear regression analysis with restricted cubic splines

Interestingly, adjusted smoothed plots exhibited a U-shaped relationship for women and a J-shaped association for men between WC and the risks of all-cause and CVD mortality (Fig. 2). Using a two-piecewise regression approach, WC was negatively correlated with all-cause mortality below 107.0 cm for women and 89.0 cm for men after adjusting for confounders (Table 3). Specifically, each 1 cm increase in WC reduced the risk of all-cause death by 3% in women (HR = 0.97, 95% CI: 0.96–0.98, $P < 0.001$) and by 6% in men (HR = 0.94, 95% CI: 0.90–0.97, $P = 0.001$) in Model 2. The risk of all-cause mortality reached its lowest at these threshold values (107.0 cm for women and 89.0 cm for men). Conversely, WC above these thresholds was positively associated with all-cause mortality, with each 1 cm increase raising the risk by 4% in women (HR = 1.04, 95% CI: 1.02–1.05, $P < 0.001$) and by 3% in men (HR = 1.03, 95% CI: 1.02–1.05, $P < 0.001$) in Model 2.

Similarly, below these thresholds, CVD mortality risk significantly decreased with increasing WC only among men (HR = 0.91, 95% CI: 0.86–0.97, $P = 0.005$), but not among women (HR = 0.98, 95% CI: 0.96–1.00, $P = 0.089$) in Model 2. Above the thresholds, CVD

Table 1. Baseline characteristics of 6,624 diabetic participants in the NHANES 2003–2018

Variables	Total	Women	Men	*P*-value
N	6,624	3,151	3,473	
Age, years	60.8 ± 13.7	60.4 ± 13.8	61.1± 13.6	0.043
Race/ethnicity, n (%)				<0.001
Non-Hispanic White	2,312 (34.9)	1,001 (31.8)	1,311 (37.7)	
Non-Hispanic Black	1,717 (25.9)	869 (27.6)	848 (24.4)	
Mexican American	1,268 (19.1)	626 (19.9)	642 (18.5)	
Other Hispanic	653 (9.9)	346 (11.0)	307 (8.8)	
Other Race	674 (10.2)	309 (9.8)	365 (10.5)	
Education, n (%)				<0.001
<high school	2,322 (35.1)	1,157 (36.7)	1,165 (33.5)	
High school	1,542 (23.3)	724 (23.0)	912 (26.3)	
>high school	2,760 (41.7)	756 (24.0)	1,406 (40.5)	
Smoking, n (%)				<0.001
Never	2,826 (42.7)	1,671 (53.0)	1,155 (33.3)	
Former	1,636 (24.7)	724 (23.0)	912 (26.3)	
Current	2,162 (32.6)	756 (24.0)	1,406 (40.5)	
Drinking, n (%)	3,937 (59.4)	1,397 (44.3)	2,540 (73.1)	<0.001
Physical activity, n (%)				<0.001
Sedentary	2,297 (34.7)	1,237 (39.3)	1,060 (30.5)	
Low	1,805 (27.2)	846 (26.8)	959 (27.6)	
Moderate	2,303 (34.8)	1,006 (31.9)	1,297 (37.3)	
High	219 (3.3)	62 (2.0)	157 (4.5)	
Poverty to income ratio	1.9 (1.0–3.4)	1.7 (0.9–3.0)	2.1 (1.1–3.8)	<0.001
Diabetes family history, n (%)	4,317 (65.2)	2,121 (67.3)	2,196 (63.2)	<0.001
Diabetes duration, years	9.0 (3.0–16.8)	9.0 (3.2–17.0)	9.0 (3.0–16.5)	0.268
Comorbidities, n (%)				
CAD	679 (10.3)	219 (7.0)	460 (13.2)	<0.001
Heart failure	601 (9.1)	257 (8.2)	344 (9.9)	0.013
Stroke	557 (8.4)	270 (8.6)	287 (8.3)	0.655
Hypertension	4,308 (65.0)	2,137 (67.8)	2,171 (62.5)	<0.001
Dyslipidemia	3,781 (57.1)	1,828 (58.0)	1,953 (56.2)	0.004
Cancer	914 (13.8)	435 (13.8)	479 (13.8)	0.013
Physical examination				
BMI, kg/m^2	32.2 ± 7.2	33.3 ± 7.8	31.1 ± 6.5	<0.001
waist circumference, cm	108.9 ± 16.0	108.0 ± 15.9	109.8 ± 16.0	<0.001
Mean SBP, mm Hg	131.9 ± 19.8	132.9 ± 20.6	130.9 ± 19.0	0.001
Mean DBP, mm Hg	68.8 ± 13.8	67.6 ± 13.7	69.9 ± 13.8	<0.001
Laboratory data				
Serum glucose, mg/dL	157.8 ± 62.5	155.9 ± 62.8	159.5 ± 62.1	0.018
Glycohemoglobin, %	7.4 ± 2.3	7.4 ± 2.8	7.4 ± 1.8	0.941
Total cholesterol, mg/dL	188.3 ± 49.4	195.6 ± 49.0	181.9 ± 48.9	<0.001
HDL-c, mg/dL	48.2 ± 14.3	51.9 ± 14.7	44.9 ± 13.1	<0.001
LDL-c, mg/dL	107.7 ± 42.7	109.2 ± 42.5	106.2 ± 42.9	0.005
Triglycerides, mg/dL	146.0 (83.0–253.0)	149.0 (85.9–254.4)	142.1 (81.0–250.2)	0.052
eGFR, mL/m/1.73m^2	84.8 ± 24.1	85.6 ± 25.1	84.1 ± 23.2	0.015
Death, n (%)	1,492 (22.5)	621 (19.7)	871 (25.1)	<0.001

Note: Mean ± standard deviations or median (interquartile) for continuous variables, and Number (%) for categorical variables. BMI, body mass index; CAD, coronary atherosclerotic heart disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; NHANES, National Health and Nutrition Examination Survey; SBP, systolic blood pressure.

Table 2. Associations of waist circumference (WC) with all-cause or CVD mortality among diabetic participants in the NHANES 2003–2018

	Crude model		Model 1		Model 2	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
All-cause mortality						
Women						
WC (continuous)	0.99 (0.98, 0.99)	<0.001	0.99 (0.99, 1.00)	0.015	1.01 (1.00, 1.02)	0.168
WC Tertile						
T1	Reference		Reference		Reference	
T2	0.69 (0.57, 0.83)	<0.001	0.67 (0.55, 0.81)	<0.001	0.79 (0.63, 0.98)	0.036
T3	0.63 (0.52, 0.77)	<0.001	0.78 (0.63, 0.96)	0.018	1.12 (0.81, 1.57)	0.488
Men						
WC (continuous)	1.00 (1.00, 1.01)	0.339	1.00 (1.00, 1.01)	0.653	1.03 (1.02, 1.04)	<0.001
WC Tertile						
T1	Reference		Reference		Reference	
T2	1.06 (0.90, 1.26)	0.458	0.87 (0.73, 1.03)	0.106	1.04 (0.86, 1.27)	0.675
T3	1.13 (0.96, 1.33)	0.142	1.03 (0.87, 1.23)	0.705	1.49 (1.11, 2.01)	0.008
CVD mortality						
Women						
WC (continuous)	0.99 (0.98, 1.00)	0.005	0.99 (0.98, 1.00)	0.139	1.00 (0.98, 1.02)	0.951
WC Tertile						
T1	Reference		Reference		Reference	
T2	0.65 (0.47, 0.89)	0.008	0.64 (0.46, 0.88)	0.007	0.71 (0.48, 1.03)	0.074
T3	0.64 (0.46, 0.88)	0.006	0.82 (0.58, 1.16)	0.263	1.08 (0.62, 1.88)	0.777
Men						
WC (continuous)	1.00 (0.99, 1.01)	0.546	1.00 (0.99, 1.00)	0.304	1.01 (0.99, 1.04)	0.244
WC Tertile						
T1	Reference		Reference		Reference	
T2	1.12 (0.85, 1.48)	0.421	0.93 (0.70, 1.24)	0.614	1.12 (0.80, 1.58)	0.511
T3	0.96 (0.72, 1.28)	0.780	0.87 (0.64, 1.18)	0.377	1.23 (0.73, 2.08)	0.445

Model 1: adjusted for age, ethnicity, education, smoking, drinking, physical activity, poverty-to-income ratio, diabetes family history, and CAD. Model 2: adjusted for Model 1 plus hypertension, dyslipidemia, heart failure, stroke, cancer, diabetes course, SBP, DBP, LDL-c, HDL-c, glycohemoglobin, eGFR, and BMI. BMI, body mass index; CAD, coronary atherosclerotic heart disease; CI, confidence interval; CVD, cardiovascular disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL-c, high-density lipoprotein cholesterol; HR, hazard ratio; LDL-c, low-density lipoprotein cholesterol; NHANES, National Health and Nutrition Examination Survey; SBP, systolic blood pressure; T1 to T3, Tertile 1 to 3.

mortality risk exhibited marginally significant increases with rising WC in both women (HR = 1.03, 95% CI: 1.00–1.06, $P = 0.049$) and men (HR = 1.02, 95% CI: 1.00–1.04, $P = 0.071$) (Table 3).

Sensitivity analyses

After stratifying by age, smoking status, BMI group, previous CVD or cancer, and eGFR, baseline WC presented a U-shaped trend for all-cause mortality in almost all subgroups of women, except for the "non-elderly" and "Normal BMI" groups. Similarly, U-shaped curves between WC and CVD mortality were also observed in most female subgroups (Fig. 3). For men, baseline WC revealed a J-shaped association with all-cause or CVD mortality in most subgroups, except for the "non-elderly" and BMI subgroups (Fig. 4). Excluding subjects with missing covariate values (Fig. 5) or less than one year of follow-up (Fig. 6) did not substantially alter the main results.

Discussion

We found a nonlinear association between baseline WC and mortality in the NHANES dataset of U.S. diabetic adults. Even after adjusting for confounders, the relationship was U-shaped in women, with the lowest risk in the central obesity range (WC = 107.0 cm), and J-shaped in men, with the minimum risk in the normal WC range (WC = 89.0 cm). Given the differing WC ranges for men and women, we assessed them separately in this study. Initially, as shown in Table 2, the linear regression model did not reveal a significant association between WC and mortality, mir-

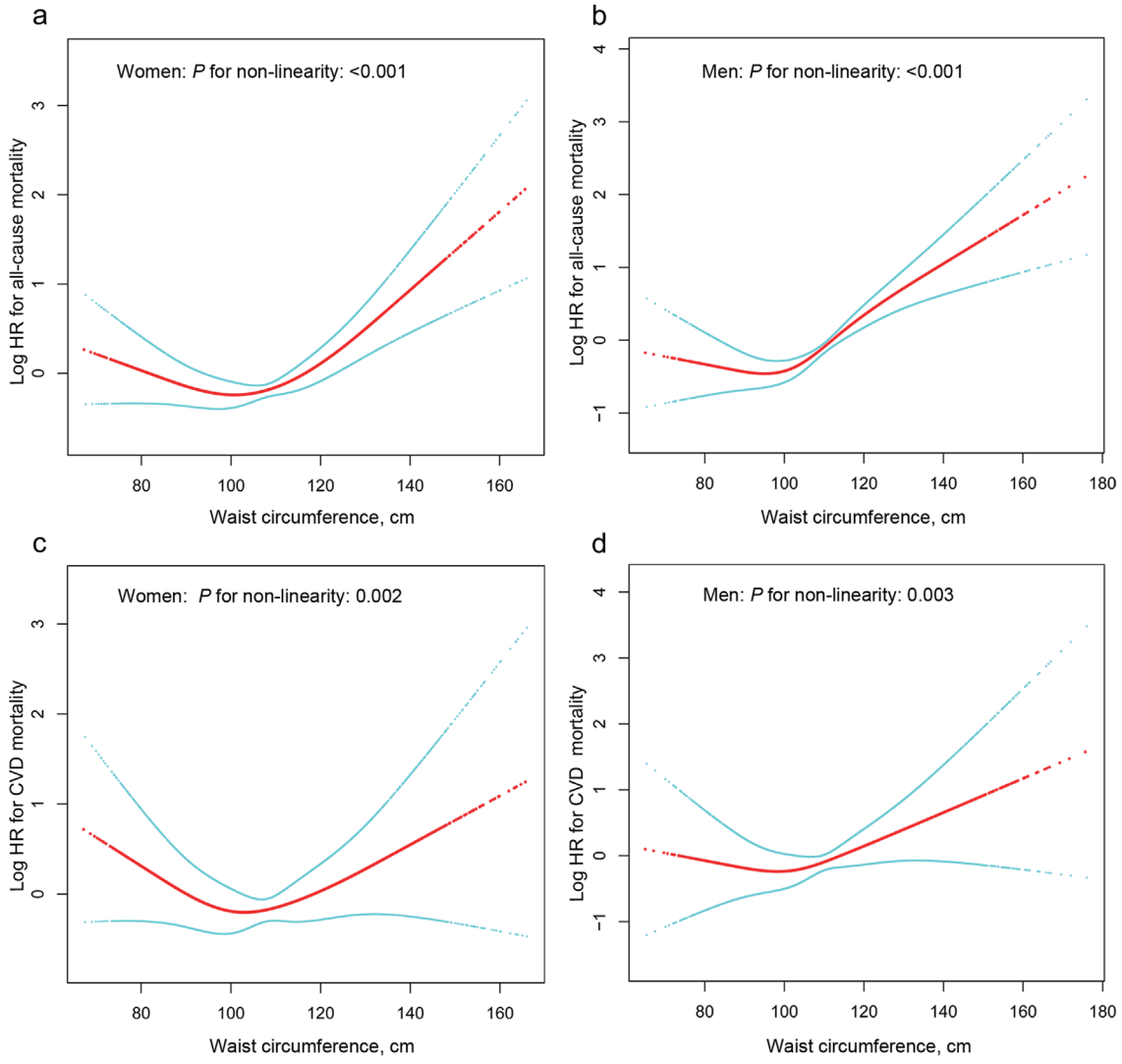

Fig. 2. Nonlinear associations of waist circumference with all-cause and CVD mortality: women (a, c) and men (b, d). The solid red line represents the smooth curve fit between WC and mortality. The blue curves are the 95% CIs of the fit. CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; WC, waist circumference.

roring previous findings from the NHANES general population.[20] We observed a marked increase in all-cause and CVD mortality risk with elevated baseline WC beyond specific threshold values, aligning with results from prior studies involving non-diabetic subjects.[16,17,22,24,25] In a sample of diabetic patients, WC has been positively associated with all-cause mortality.[5] This association was also observed in the Action to Control Cardiovascular Risk in Diabetes Trial.[26] However, the Fremantle Diabetes Study found no such link between WC and mortality for either sex.[27] Additionally, while a U-shaped pattern between all-cause mortality and WC was detected among type 2 diabetic subjects from the UK Biobank population, WC's impact on mortality diminished beyond certain turning points.[13] The discrepancies in these findings may be attributed to variations in sample size, ethnicity, health status, baseline WC levels, and diabetes duration. In general, the right half of the U- or J-shaped curve might be explained by the effects of visceral adipose tissue.[17] WC exhibits a stronger correlation with visceral fat than BMI.[22] Visceral adipose tissue modulates adipocyte biology by increasing the expression of pro-inflammatory adipokines and decreasing that of anti-inflammatory adipocytokines.[28] Consequently, this leads to an atherogenic, diabetogenic, and inflammatory milieu, ultimately promoting metabolic dysregulation and cardiovascular damage.[29]

In the present study, intriguingly, lower WC (<thresholds) levels significantly altered the positive association between WC and mortality risk. Specifically, for individuals with WC below the established thresholds, the risk of all-cause death decreased by 3% in women and 6% in men with each 1 cm increase in WC, even after adjusting for potential confounders in Model 2. This finding is partially consistent with the previous research by Cho *et al*.,[19] which demonstrated a decreased mortality risk with increasing WC below 85 cm in men and 80 cm in women among a South Korean health check-up population. Furthermore, other studies have also reported a significantly negative correlation between all-cause mortality and WC.[18,30–33] However, this inverse relationship was primarily observed in older or ill individuals, not all of whom

Table 3. Threshold effect analysis of WC on all-cause and CVD mortality among 6,624 NHANES 2003–2018 participants with diabetes

	Crude Model		Model 1		Model 2	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
All-cause mortality						
Women						
WC < 107.0 cm	0.98 (0.97, 0.99)	<0.001	0.99 (0.97, 1.00)	0.119	0.97 (0.96, 0.98)	<0.001
WC > 107.0 cm	1.00 (0.99, 1.01)	0.633	1.02 (1.01, 1.03)	0.003	1.04 (1.02, 1.05)	<0.001
P for log likelihood ration test	0.017		<0.001		<0.001	
Men						
WC < 89.0 cm	1.00 (0.96, 1.04)	0.946	0.91 (0.87, 0.94)	<0.001	0.94 (0.90, 0.97)	0.001
WC > 89.0 cm	1.00 (1.00, 1.01)	0.344	1.01 (1.00, 1.01)	0.051	1.03 (1.02, 1.05)	<0.001
P for log likelihood ration test	0.866		<0.001		<0.001	
CVD mortality						
Women						
WC < 107.0 cm	0.98 (0.96, 0.99)	0.010	0.97 (0.95, 0.99)	0.001	0.98 (0.96, 1.00)	0.089
WC > 107.0 cm	1.00 (0.98, 1.01)	0.633	1.02 (1.00, 1.03)	0.083	1.03 (1.00, 1.06)	0.049
P for log likelihood ration test	0.217		0.003		0.002	
Men						
WC < 89.0 cm	0.98 (0.92, 1.04)	0.550	0.89 (0.84, 0.94)	<0.001	0.91 (0.86, 0.97)	0.005
WC > 89.0 cm	1.00 (0.99, 1.01)	0.737	1.00 (0.99, 1.01)	0.865	1.02 (1.00, 1.04)	0.071
P for log likelihood ration test	0.605		0.002		0.003	

Model 1: adjusted for age, ethnicity, education, smoking, drinking, physical activity, poverty-to-income ratio, diabetes family history, and CAD. Model 2: adjusted for Model 1 plus hypertension, dyslipidemia, heart failure, stroke, cancer, diabetes course, SBP, DBP, LDL-c, HDL-c, glycohemoglobin, eGFR, and BMI. BMI, body mass index; CAD, coronary atherosclerotic heart disease; CI, confidence interval; CVD, cardiovascular disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL-c, high-density lipoprotein cholesterol; HR, hazard ratio; LDL-c, low-density lipoprotein cholesterol; NHANES, National Health and Nutrition Examination Survey; SBP, systolic blood pressure; T1 to T3, Tertile 1 to 3, WC, waist circumference.

had DM.[18,30–33] In the general population, U- or J-shaped associations between WC and mortality can also be detected.[22,34] In the UK Biobank Type 2 DM subgroup, a U-shaped trend between WC and all-cause mortality was observed, similar to our findings. However, the two-piecewise linear regression was not conducted in their study, making it unclear if a significantly negative relationship existed between WC and mortality before the turning points.[13] The Fremantle Diabetes Study also did not report such a negative relationship in either sex, possibly due to the relatively small sample size.[27] This study is the first to report a significantly negative association between WC and total or CVD mortality risk among DM patients before the thresholds. Notably, optimal WC cutoff points showed substantial gender disparities, with females exhibiting the lowest mortality risk at 107 cm WC, significantly higher than the central obesity definition of 88 cm. This suggests that the WC-related "obesity paradox" is particularly pronounced among female DM patients, consistent with a recent Chinese study.[35] However, the mechanisms behind these gender differences remain unclear and may involve metabolic responses to weight cycling and sex hormones.[36]

In observational epidemiological research, this inverse relationship known as the "obesity paradox" was initially hypothesized due to the unexpected finding that overweight or obese individuals could have a longer life expectancy than those with normal weight.[13] This phenomenon has been frequently reported in previous investigations using BMI as an obesity measure.[10–12] Among patients with DM, a meta-analysis including 414,587 subjects also showed a remarkable inverse relationship of all-cause mortality with BMI (<31kg/m^2 for men and <28kg/m^2 for women, respectively).[9] However, the WC-related "obesity paradox" is rarely reported in DM patients.[10,27] Previous studies have explored possible reasons for the negative relationships between BMI or WC and mortality, including survival or selection bias, malnutrition-inflammation complex syndrome, and toxic material storage.[18,30–32,37] These explanations are also applicable to the present study, as DM is a chronic wasting disease.[18] Selection bias, which suggests that a lower WC may indicate the presence of severe diseases in individuals with DM, leading to death, was considered the primary issue in the inverse association.[37] To minimize selection bias, we conducted subgroup analyses and observed that the negative relationship between WC and mortality tended to vanish among patients without prior CVD or cancer in both sexes. Another possible explanation for the inverse association is survival bias, as subjects in the lowest WC tertile were older than those in the higher tertiles, particularly among women (data not shown). The negative relationships also tended to disappear in younger subgroups, suggesting that the left half of the U- or J-shaped curve might be an artifact of anthropometric measures rather than an actual biological advantage of excess fat storage.[22] WC alone is insufficient, as it does not account for the effect of height, which is

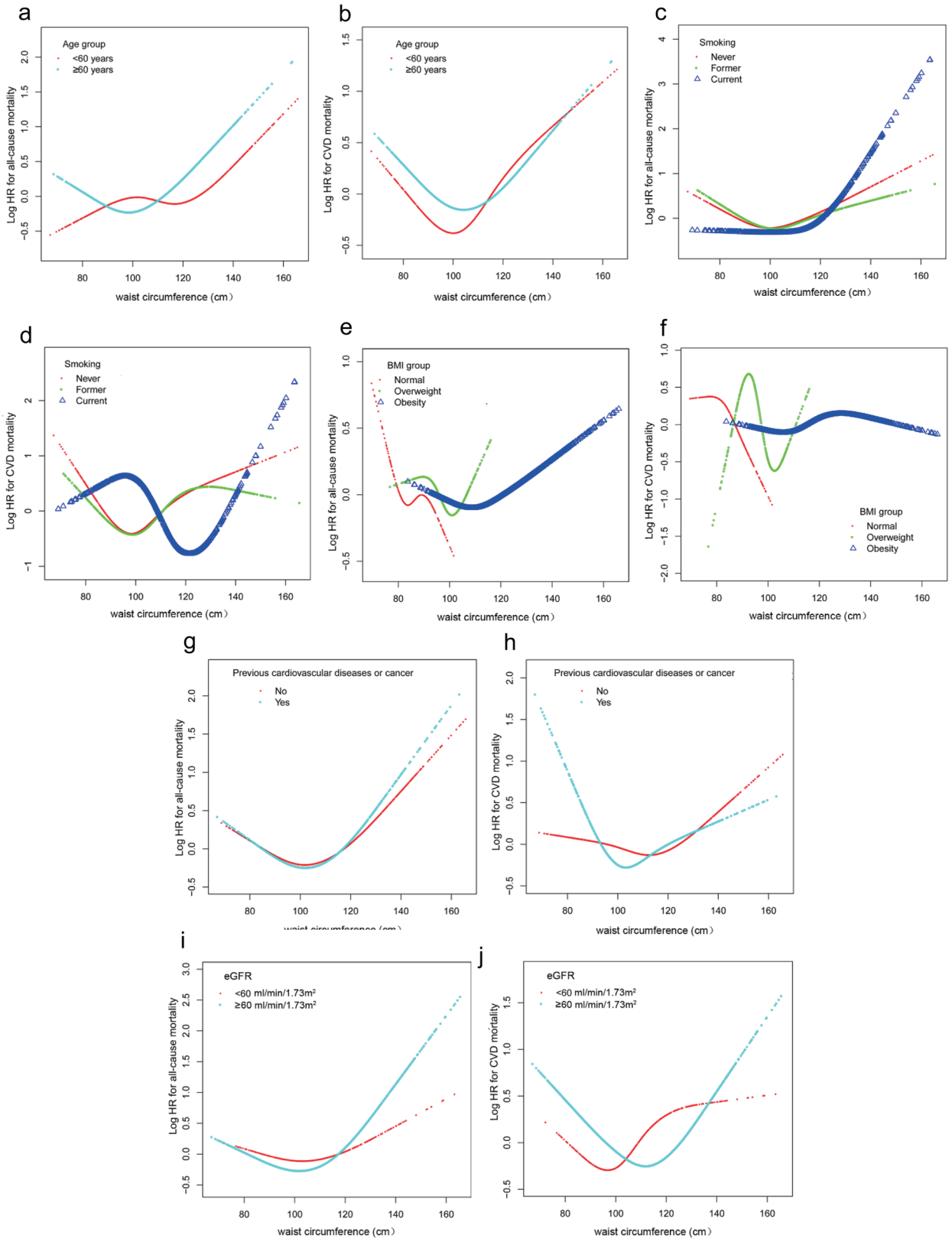

Fig. 3. Spline fitting curves of waist circumference in different subgroups with all-cause (a, c, e, g, i) and CVD (b, d, f, h, j) mortality among women. CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio.

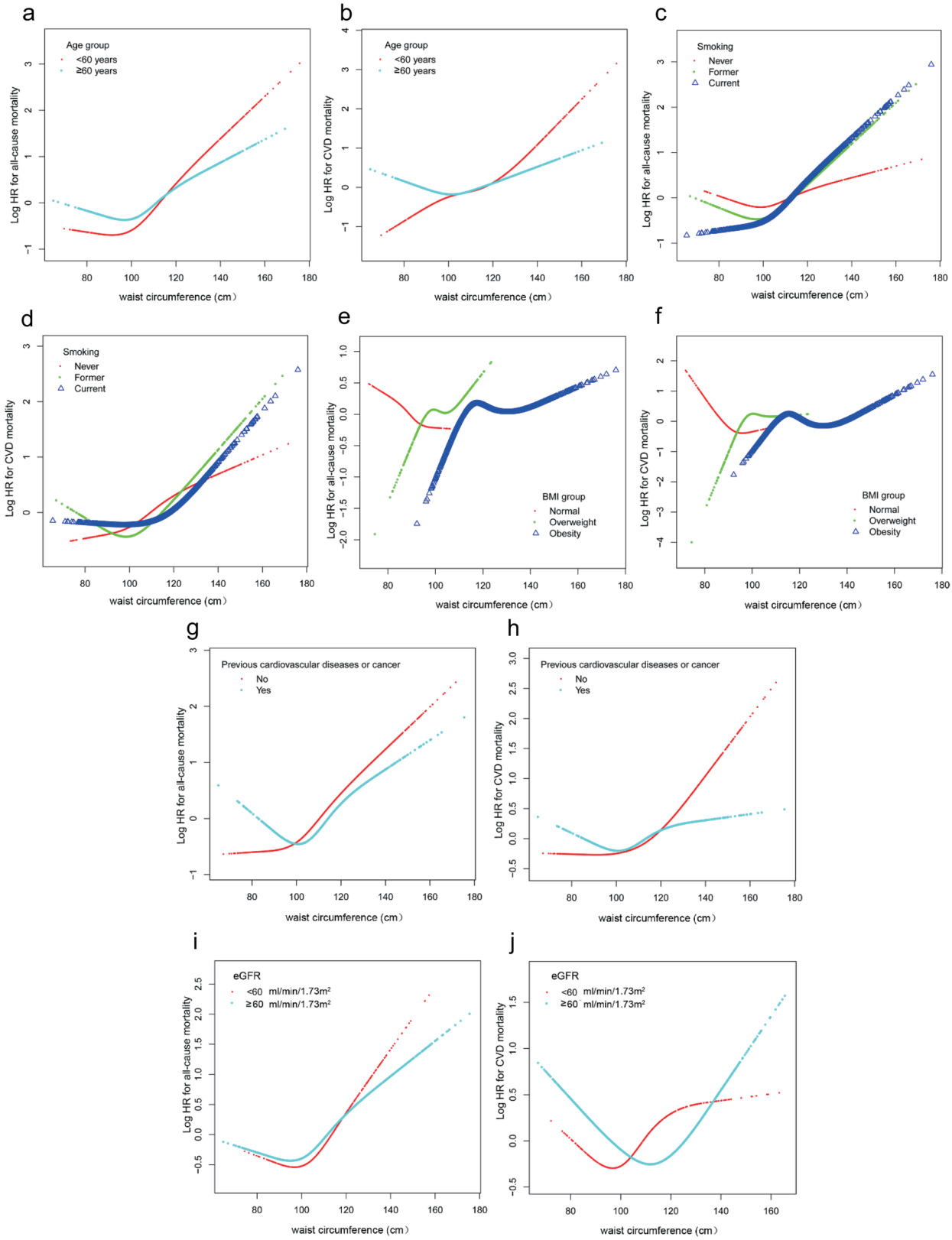

Fig. 4. Spline fitting curves of waist circumference in different subgroups with all-cause (a, c, e, g, i) and CVD (b, d, f, h, j) mortality among men. BMI, body mass index; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio.

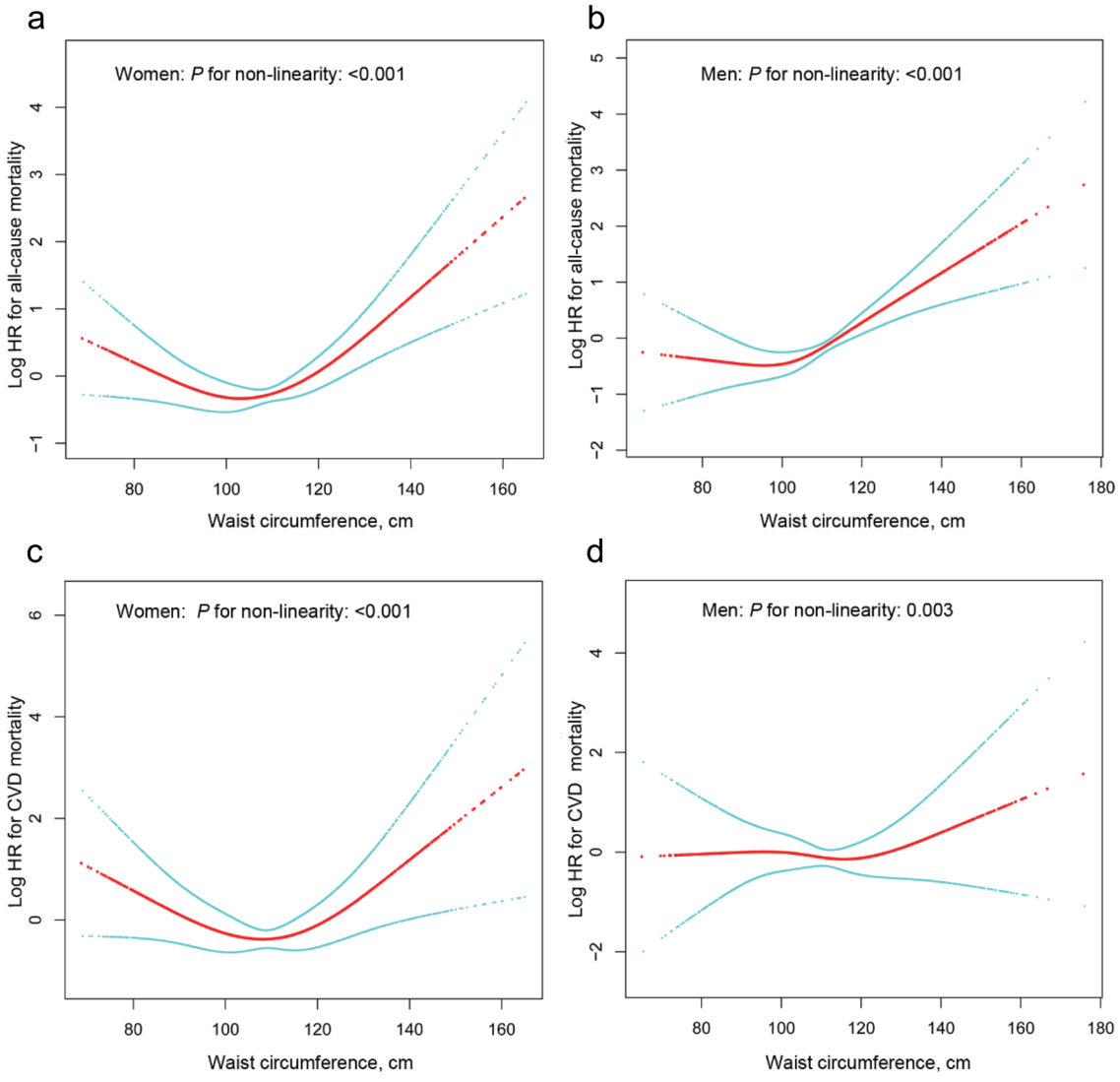

Fig. 5. Nonlinear associations of waist circumference with all-cause and CVD mortality: women (a, c) and men (b, d) with the exclusion of subjects with missing covariates. The solid red line represents the smooth curve fit between WC and mortality. The blue curves are the 95% CIs of the fit. CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; WC, waist circumference.

inversely associated with health risks.[22,27]

After considering the effects of height and weight,[17,19] we conducted subgroup analyses stratified by BMI categories and found that the association between WC and mortality varied across BMI categories, presenting as U-shaped, reverse U-shaped, or even linear patterns. Notably, the negative relationship between WC and mortality was only evident among men with normal BMI, aligning with a Korean study[17] but contradicting a European study.[25] We hypothesize that this "obesity paradox" in the "normal BMI" subgroup may be partly attributed to the loss of beneficial fat, such as muscle mass. Previous studies revealed that smoking may be a modifiable factor influencing the relationship between mortality and BMI.[13,25] Particularly among current smokers, being underweight was more strongly related to elevated mortality risk, which also partly accounts for the "obesity paradox".[13,25] In contrast, when smokers' BMI was adjusted, WC became more strongly and positively associated with mortality.[25] This could be attributed to smokers' tendency to have a more metabolically unfavorable adipose distribution, with a higher likelihood of abdominal obesity compared to non-smokers.[25] Consistent with this, our subgroup analyses indicated that the positive correlation between WC and mortality was more pronounced among current smokers of both genders.

The present study has several strengths. First, to assess if there is a dose-response association between WC and mortality, we treated WC as a categorical variable in addition to a continuous variable, exploring its nonlinear association with mortality. This enabled us to find cohort-distinct WC values linked to the lowest mortality risk in U.S. adults with DM from the NHANES dataset. If a causal relationship could be established, our findings may provide insights for physicians in primary healthcare settings: a lower WC may not always be advantageous for DM patients; in fact, a moderate degree of central obesity might be health-promoting, particularly in female patients. Additionally, we conducted comprehensive analyses across the entire cohort and within subgroups

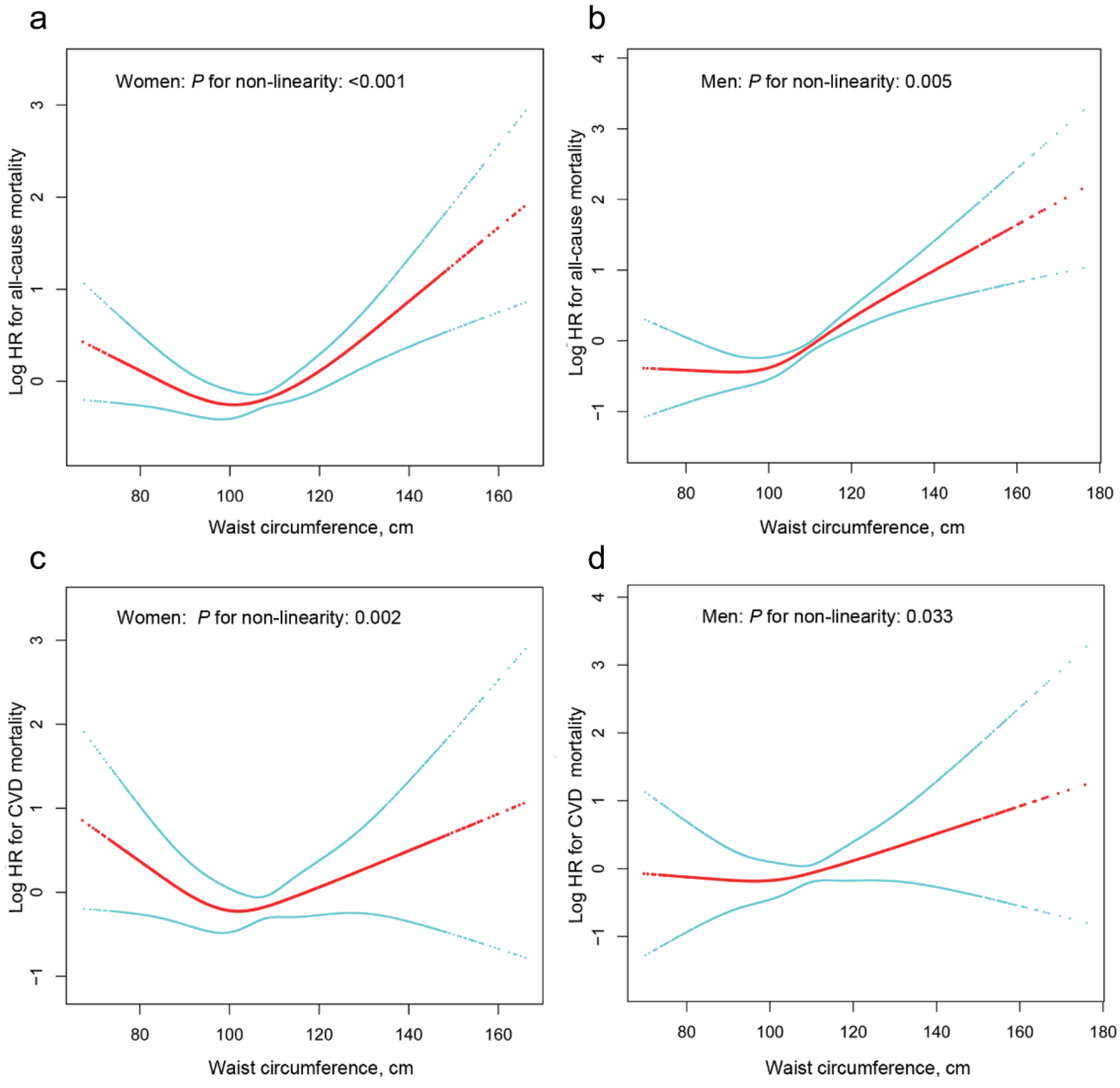

Fig. 6. Nonlinear associations of waist circumference with all-cause and CVD mortality: women (a, c) and men (b, d) with the exclusion of subjects with less than one year of follow-up. The solid red line represents the smooth curve fit between WC and mortality. The blue curves are the 95% CIs of the fit. CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; WC, waist circumference.

where the "obesity paradox" has been previously observed, such as smokers, the elderly, and individuals with prior CVD, cancer, or chronic kidney disease. This strategy allowed us to explore the robustness of the observed associations across different demographic and clinical contexts in DM patients.

Furthermore, this study still has some limitations. First, the baseline WC should not be assumed to have a causal relationship with mortality risk due to the observational nature of this research. Despite efforts to minimize confounding by controlling for various variables, the potential impact of unmeasured confounders cannot be fully ruled out. Additionally, obesity's role as a risk factor for certain comorbidities could introduce collider stratification bias, further complicating the analysis. Second, the shapes of the curves varied among subgroups, suggesting a need for further investigation into these differences. Third, WC and other potential confounders may have been influenced by disease symptoms or treatments, yet these factors were only assessed at baseline, potentially limiting the study's conclusions. Fourth, emerging evidence suggests that waist-to-hip ratio, waist-to-height ratio, and the body shape index may more accurately reflect visceral fat accumulation than WC alone.[22,34,38] These composite anthropometric indices could potentially enhance the predictive accuracy of mortality risk algorithms. However, these indicators were not subjected to further comparative analysis and discussion in this study. Fifth, due to the inclusion criteria and missing data, the representativeness of the U.S. population was not guaranteed. Consequently, NHANES sampling weights were not applied in this analysis. Lastly, as the study population was derived from the NHANES and consisted solely of individuals with DM, the generalizability of the findings to other DM cohorts should be approached with caution.

Conclusions

Baseline WC revealed a U-shaped association with all-cause and

CVD mortality risk in the female diabetic NHANES dataset, while a J-shaped association was observed in males. Whether the WC-related "obesity paradox" genuinely exists or is merely a coincidental artifact requires careful consideration. These findings underscore the necessity for further clinical and mechanistic investigations to elucidate the influence of WC on mortality outcomes.

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Conflict of interest

A preprint version has previously been published.[39] BS has been an Editorial Board Member of *Chronic Metabolic Diseases* since 2024. The other authors have no conflict of interests related to this publication.

Author contributions

Study concept and design (BS, HZ), acquisition of data (BS, HJ, TT, CP), analysis and interpretation of data (XL, YW), drafting of the manuscript (BS, HJ, XS), critical revision of the manuscript for important intellectual content (YL, BS), administrative, technical, or material support (XW, LC), and study supervision (YG, HC). All authors have made significant contributions to this study and have approved the final manuscript.

Ethical statement

The NHANES study adheres to the principles of the Helsinki Declaration (as revised in 2013). The National Center for Health Statistics Ethics Review Board approved the study (approval IDs available at https://www.cdc.gov/nchs/nhanes/irba98.htm) and authorized public use of NHANES data. All participants provided written informed consent.

Data sharing statement

The datasets presented in this study are available from online repositories (http://cdc.gov/nchs/nhanes) or from the corresponding author upon reasonable request.

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