The association of calf circumference and all-cause, cardiovascular and cerebrovascular mortality: results from the National Health and Nutrition Examination Surveys

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Abstract

Introduction: Studies on the association between calf circumference (CC) and mortality have been limited. Therefore, we examined the association between CC and all-cause, cardiovascular and cerebrovascular mortality in the present study.

Material and methods: The data were retrieved from the 1999–2006 National Health and Nutritional Examination Surveys (NHANES), composed of 20,214 individuals aged ≥ 18 years with CC being measured. We performed multivariate Cox regression models to examine the associations, then stratified the regression models into subgroups to test for interactions.

Results: Among 20,214 participants, 47.25% were men and the mean age was 45.8 years. In the fully adjusted model, each 1 cm increment in CC was inversely associated with the risk of all-cause mortality (HR = 0.92, 95% CI: 0.90-0.94, $p < 0.0001$) and cardiovascular mortality (HR = 0.90, 95% CI: 0.84–0.97, $p = 0.0056$). Meanwhile, the highest quartile of CC had 50% (HR = 0.50, 95% CI: 0.40–0.64, p trend < 0.001) lower risk of all-cause mortality and 57% (HR = 0.43, 95% CI: 0.21–0.88, p trend = 0.045) lower risk of cardiovascular mortality, compared to the lowest quartile of CC. For cerebrovascular mortality, CC did not have significant associations with mortality.

Conclusions: Our results suggested an independently inverse association between CC and all-cause and cardiovascular mortality.

Key words: anthropometric markers, mortality, NHANES.

Introduction

Cardiovascular and cerebrovascular death remains the leading cause of mortality worldwide [1]. Plentiful factors have been reported to be associated with all-cause and cause-specific mortality, such as high-density lipoprotein cholesterol (HDL-C) [2], serum uric acid and apolipoprotein B (apoB) [3], and lower carbohydrate diets [4]. Another risk factor is the anthropometric index, which may serve as an easy-to-use indicator to iden-

tify the high-risk population. Calf circumference (CC) is an index reflecting lower-limb size, which represents peripheral fat and lean mass. Previous studies indicated that CC was a potential indicator to assess nutritional status and physical function, as well as an important predictor for mortality [5]. In addition, CC is easier to assess than body mass index (BMI) in frail and ill elderly patients, since the measurement of height and weight is often inaccurate or unavailable [6]. There is accumulating evidence to suggest that body composition and fat distribution are important in determining the risk of mortality, whereas global body mass may not be the best predictor [7]. Noticeably, decreased CC mainly reflects muscle loss and nutritional status. Several previous studies have found that increased size of larger limbs was associated with a reduced risk of metabolic disorder or cardiovascular disease [8].

Currently, numerous studies focus on anthropometric markers of abdominal obesity (waist circumference, waist-to-hip ratio, waist-to-height ratio) and the long-term health [9, 10], but it is unclear whether a marker of body composition other than abdominal obesity, namely CC, is another important indicator. To address this research gap, we have conducted this study using data from the National Health and Nutritional Examination Surveys (NHANES) population.

Material and methods

Study population

In the present study, we used publicly available data from NHANES. The study methods and procedures for data collection have been described in detail elsewhere [11]. The current study was based on the analysis of NHANES data collected from 1999 to 2006 (N = 41,474). We selected participants aged ≥ 18 years (n = 22,624), and excluded participants who had missing data on calf circumference (n = 2,389) or mortality (n = 21), making a final sample of 20,214 eligible participants. The selection of the study cohort is presented in Figure 1. The ethics approval for NHANES was obtained by the Institutional Review Board of the Centers for Disease Control and Prevention.

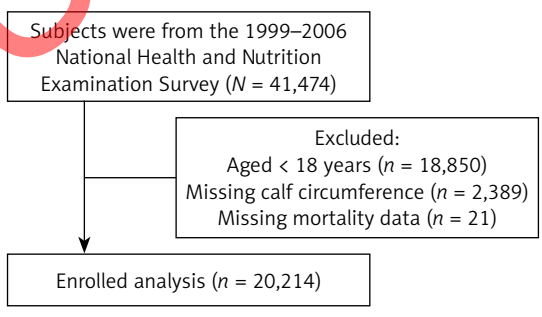

Figure 1. Procedure of selecting participants

Written informed consent was obtained from all participants.

Data collection

Demographic data (age, sex, race), results from physical examination and laboratory tests (systolic blood pressure (SBP), BMI, diastolic blood pressure (DBP), fasting blood glucose, total cholesterol (TC), triglyceride, HDL-C, low-density lipoprotein-cholesterol (LDL-C), estimated glomerular filtration rate (eGFR)), medical history (hypertension, diabetes, cardiovascular diseases), and prescription medication information (anti-hypertensive drugs, anti-diabetes drugs) were retrieved from the NHANES data. Cigarette smoking status was categorized as smoker, ex-smoker or non-smoker. eGFR was calculated by the Modification of Diet in Renal Disease (MDRD) formula [12]. To measure CC, technicians slid the measuring tape up and down the calf in order to find the widest point for accurate measurement. Hypertension was classified by the presence of SBP ≥ 130 mm Hg and/or DBP ≥ 80 mm Hg, and/or currently use of anti-hypertension medication [13]. Diabetes was based on the self-reported history of diabetes or the presence of any one of the following criteria: 1) fasting glucose ≥ 126 mg/dl; 2) non-fasting glucose ≥ 200 mg/dl; 3) Hb_{A1c} ≥ 6.5%; 4) taking medication to lower blood glucose; or 5) consuming insulin [14]. Body mass index was calculated as weight in kilograms divided by squared height in meters (kg/m^2). Obesity was defined as BMI ≥ 30 kg/m^2, overweight was defined as BMI ≥ 25 kg/m^2, normal weight was defined as 18.5 kg/m^2 ≤ BMI < 25 kg/m^2, and underweight was defined as BMI < 18.5 kg/m^2 [15].

Outcome

The anonymized data of NHANES 1999–2006 participants were linked to longitudinal medicare and mortality data. Data on survival status were collected from the date of survey participation until 31 December 2015. Outcomes of our study were all-cause mortality, mortality due to cardiovascular diseases (I00–I09, I11, I13, I20–I51), and cerebrovascular diseases (I60–I69). The cause of death was determined using the 10th revision of the International Classification of Diseases (ICD-10).

Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD), whereas categorical variables were presented as numbers with corresponding percentages. CC was divided into quartiles (Q1-Q4). Baseline characteristics were summarized based on CC quartiles. The Kruskal-Wallis H, one-way ANOVA and χ^2 tests were applied to determine whether the subgroup difference was significant.

Multivariate Cox regression was performed to assess the association between CC and the risk of all-cause, cardiovascular and cerebrovascular mortality. CC was treated as both continuous (per 1 cm increment) and categorical variables (Q1–Q4) and was put into separate models. We computed three regression models which were adjusted for different sets of confounders. The crude model only included CC. Model 1 was further adjusted for age, gender and BMI. Meanwhile, Model 2 was adjusted for age, gender , BMI, SBP, TC, HDL-C, use of antihypertensive drugs and anti-diabetic drugs, eGFR, alcohol drinking, serum albumin, smoking status, race; history of diabetes, hypertension or cardiovascular diseases. The results were reported as the hazard ratio (HR) with 95% confidence interval (CI).

To test the robustness of our results, we further stratified the regression models into subgroups and tested for the interaction. The cohort was divided into groups based on gender, age, hypertension diabetes, BMI, SBP and smoking status. When analysis a subgroup variable, age, gender, BMI, SBP, TC, HDL-C, use of antihypertensive drugs and anti-diabetic drugs, eGFR, alcohol drinking, smoking status, race, history diabetes, hypertension or cardiovascular diseases were all adjusted except the variable itself. The Kaplan-Meier analysis was conducted to compare the difference in survival rates by CC quartiles, and the intergroup differences were estimated by the log-rank test. Cubic spline models were used to estimate the HRs for mortality associated with increasing CC. A two-sided p value < 0.05 was considered statistically significant. Data management and analyses were performed using the statistical software package R version 3.32 (http://www.R-project.org, The R Foundation, Vienna, Austria).

Results

Baseline characteristics

Table I summarizes the characteristics of participants based on CC quartiles. Overall, 20,214 participants were included, with a mean age of 45.8 years; 47.75% were men. During the follow-up period of 11.82 years, 3655 deaths were recorded, including 466 cardiovascular disease deaths and 152 cerebrovascular disease deaths. Participants with the highest quartile of CC had the lowest proportion of all-cause (11.25%), cardiovascular (1.36%) and cerebrovascular mortality (0.37%). All variables were significantly different by quartiles (all p < 0.05).

Relationships between CC and all-cause, cardiovascular and cerebrovascular disease mortality

Results from Cox regression models are shown in Table II. When CC was expressed as a continuous variable, each 1 cm increment of CC was inversely associated with all-cause mortality. The corresponding HR was 0.90 (95% CI: 0.90–0.91, p < 0.0001) in the crude model, 0.91 (95% CI: 0.90–0.92, p < 0.0001) in Model 1 and increased CC was still significantly associated with lower risk of all-cause mortality in Model 2 (HR = 0.92, 95% CI: 0.90–0.94, p < 0.0001). Regarding cardiovascular death, it showed a similar pattern: CC was significantly associated with cardiovascular mortality in Model 2 (HR = 0.90, 95% CI: 0.84–0.97, p = 0.0056). For cerebrovascular death, a significant association was found in the crude model and Model 1, but not Model 2.

When CC was expressed as a categorical variable, the risk of all-cause mortality was significantly lower for participants with the highest quartile of CC in Model 2 (HR = 0.50, 95% CI: 0.40–0.64, p trend < 0.001) when using the lowest quartile as the referent. Similarly, the highest quartile of CC was significantly associated with a lower risk of cardiovascular mortality in Model 2 (Q4: HR = 0.43, 95% CI: 0.21–0.88, p trend = 0.045). The calf circumference was not associated with cerebrovascular mortality when treated as a categorical variable.

In Figure 2, the Kaplan-Meier survival curves plotting quartiles of CC showed that the rates of all-cause and cardiovascular death were statistically significantly different by CC quartiles (both log rank: p < 0.001). Figure 3 demonstrates the cubic spline models estimating the HRs for all-cause and cause-specific mortality associated with increasing CC.

Subgroup analysis

Table III summarizes the association between CC and mortality in subgroups. Among all the subgroups, only BMI significantly modified the associations between CC and mortality risk. The HR of all-cause mortality was 0.80 (95% CI: 0.79–0.82) in the subgroup with BMI < 25 kg/m^2, which was significantly lower than in subjects with BMI ≥ 25 kg/m^2 (HR = 0.88; 95% CI: 0.87–0.89) (p for interaction < 0.0001). A similar pattern was also found for the association between CC and cardiovascular mortality. For the subgroup with BMI < 25 kg/m^2, the HR was 0.74 (95% CI: 0.70–0.78) and when BMI ≥ 25 kg/m^2, the HR was 0.88 (95% CI: 0.85–0.91) (p for interaction = 0.0005).

Discussion

The current study investigated the association between CC and all-cause, cardiovascular and cerebrovascular mortality. We found that CC was inversely associated with all-cause and cardiovascular mortality. For every 1 cm increment in CC,

Table I. Baseline characteristics of participant patients

Parameter	Total	Q1: < 35.20 cm	Q2: 35.20–37.70 cm	Q3: 37.70–40.70 cm	Q4: ≥ 40.70 cm	*P*-value
Number	20214	4923	4982	5178	5131	
Age [years]	45.80 ±20.21	48.96 ±23.25	46.27 ±20.80	45.27 ±18.84	42.83 ±17.11	< 0.001
Male, *n* (%)	9652 (47.75)	1849 (37.56)	2365 (47.47)	2826 (54.58)	2612 (50.91)	< 0.001
Drinking [g]	8.64 ±27.74	7.59 ±28.73	8.82 ±27.70	9.84 ±27.81	8.26 ±26.69	< 0.001
Smoking status, *n* (%):						< 0.001
Non-smoker	9351 (51.83)	2151 (50.60)	2249 (51.10)	2447 (51.87)	2504 (53.61)	
Ex-smoker	4745 (26.30)	1005 (23.64)	1179 (26.79)	1306 (27.68)	1255 (26.87)	
Current smoker	3945 (21.87)	1095 (25.76)	973 (22.11)	965 (20.45)	912 (19.52)	
Race, *n* (%):						< 0.001
Black	4282 (21.18)	840 (17.06)	965 (19.37)	1070 (20.66)	1407 (27.42)	
Mexican American	4743 (23.46)	1521 (30.90)	1317 (26.44)	1143 (22.07)	762 (14.85)	
Other Hispanic	831 (4.11)	242 (4.92)	230 (4.62)	205 (3.96)	154 (3.00)	
White	9588 (47.43)	2073 (42.11)	2297 (46.11)	2568 (49.59)	2650 (51.65)	
Other race	770 (3.81)	247 (5.02)	173 (3.47)	192 (3.71)	158 (3.08)	
BMI [kg/m^2]	28.11 ±6.33	22.73 ±3.37	25.70 ±3.48	28.61 ±3.81	35.03 ±6.26	< 0.001
SBP [mm Hg]	118.01 ±14.82	116.07 ±16.61	116.91 ±14.61	118.41 ±14.18	120.38 ±13.55	< 0.001
DBP [mm Hg]	68.75 ±13.02	66.51 ±13.44	67.89 ±12.80	69.33 ±12.76	70.99 ±12.73	< 0.001
FBG [mg/dl]	103.30 ±34.67	102.49 ±37.20	102.71 ±35.86	102.25 ±32.91	105.72 ±32.56	0.001
TC [mg/dl]	199.11 ±43.86	196.86 ±44.74	198.16 ±44.74	201.54 ±43.88	199.66 ±41.97	< 0.001
HDL-C [mg/dl]	52.59 ±15.68	56.80 ±16.67	53.92 ±15.73	51.37 ±15.20	48.28 ±13.72	< 0.001
TG [mg/dl]	144.87 ±126.33	131.62 ±101.90	137.86 ±128.59	150.28 ±117.58	158.69 ±149.86	< 0.001
LDL-C [mg/dl]	117.21 ±36.48	115.14 ±39.30	115.17 ±36.03	119.58 ±36.06	118.72 ±34.33	< 0.001
eGFR [ml/min/1.73m^2]	94.03 ±34.29	97.77 ±41.08	93.57 ±32.55	92.19 ±31.40	92.85 ±31.38	< 0.001
Hypertension, *n* (%)	6620 (32.89)	1534 (31.38)	1500 (30.29)	1643 (31.79)	1943 (37.96)	< 0.001
Cardiovascular diseases, *n* (%)	756 (4.21)	216 (5.12)	187 (4.26)	199 (4.23)	154 (3.31)	< 0.001
Diabetes, *n* (%)	2377 (11.83)	593 (12.10)	524 (10.58)	576 (11.18)	684 (13.42)	< 0.001
Antihypertensive drugs, *n* (%)	3934 (19.46)	989 (20.09)	938 (18.83)	948 (18.31)	1059 (20.64)	0.010
Anti-diabetic drugs, *n* (%)	1175 (5.81)	300 (6.09)	253 (5.08)	287 (5.54)	335 (6.53)	0.011
All-cause mortality, *n* (%)	3655 (18.08)	1394 (28.32)	920 (18.47)	764 (14.75)	577 (11.25)	< 0.001
Cardiovascular mortality, *n* (%)	466 (2.31)	212 (4.31)	97 (1.95)	87 (1.68)	70 (1.36)	< 0.001
Cerebrovascular mortality, *n* (%)	152 (0.75)	66 (1.34)	42 (0.84)	25 (0.48)	19 (0.37)	< 0.001

Values are mean ± SD or number of patients (%). Q – quartile, BMI – body mass index, SBP – systolic blood pressure, DBP – diastolic blood pressure, FBG – fasting blood glucose, TC – total cholesterol, HDL-C – high-density lipoprotein cholesterol, LDL-C – low-density lipoprotein cholesterol, TG – triglyceride, eGFR – estimated glomerular filtration rate.

Table II. Cox regression analysis for all-cause, cardiovascular and cerebrovascular disease mortality

Exposure	Non-adjusted HR (95% CI), *p*-value	Model 1 HR (95% CI), *p*-value	Model 2 HR (95% CI), *p*-value
All-cause mortality			
Calf circumference (per 1 cm increment)	0.90 (0.90, 0.91), < 0.0001	0.91 (0.90, 0.92), < 0.0001	0.92 (0.90, 0.94), < 0.0001
Calf circumference groups:			
Q1	1.0	1.0	1.0
Q2	0.61 (0.56, 0.67), < 0.0001	0.66 (0.61, 0.73), < 0.0001	0.70 (0.60, 0.81), < 0.0001
Q3	0.48 (0.44, 0.53), < 0.0001	0.57 (0.51, 0.63), < 0.0001	0.64 (0.54, 0.75), < 0.0001
Q4	0.36 (0.33, 0.40), < 0.0001	0.49 (0.43, 0.57), < 0.0001	0.50 (0.40, 0.64), < 0.0001
P for trend	< 0.001	< 0.001	< 0.001
Cardiovascular mortality			
Calf circumference (per 1 cm increment)	0.88 (0.86, 0.90), < 0.0001	0.87 (0.84, 0.91), < 0.0001	0.90 (0.84, 0.97), 0.0056
Calf circumference groups:			
Q1	1.0	1.0	1.0
Q2	0.43 (0.34, 0.54), < 0.0001	0.48 (0.37, 0.62), < 0.0001	0.34 (0.21, 0.56), < 0.0001
Q3	0.36 (0.28, 0.47), < 0.0001	0.44 (0.33, 0.60), < 0.0001	0.38 (0.22, 0.64), 0.0003
Q4	0.29 (0.22, 0.38), < 0.0001	0.41 (0.28, 0.62), < 0.0001	0.43 (0.21, 0.88), 0.0205
P for trend	< 0.001	< 0.001	0.045
Cerebrovascular mortality			
Calf circumference (per 1 cm increment)	0.86 (0.83, 0.90), < 0.0001	0.90 (0.84, 0.96), 0.0028	0.91 (0.80, 1.03), 0.1201
Calf circumference groups:			
Q1	1.0	1.0	1.0
Q2	0.59 (0.40, 0.88), 0.0085	0.76 (0.49, 1.17), 0.2118	0.64 (0.28, 1.46), 0.2893
Q3	0.34 (0.21, 0.53), < 0.0001	0.55 (0.32, 0.94), 0.0293	0.89 (0.37, 2.16), 0.8052
Q4	0.25 (0.15, 0.42), < 0.0001	0.52 (0.25, 1.10), 0.0862	0.70 (0.19, 2.56), 0.5943
P for trend	< 0.001	0.377	0.602

Non-adjusted adjusted for none. Model 1 was adjusted for age, gender and BMI. Model 2 was adjusted for age, gender, BMI, SBP, TC, HDL-C, antihypertensive drugs, anti-diabetic drugs, eGFR, drinking, serum albumin, smoking status, race, diabetes, hypertension, cardiovascular diseases. Q – quartile, HR – hazard ratio, CI – confidence interval.

there was an 8% reduction in the risk of all-cause mortality and a 10% reduction for cardiovascular mortality. For subjects with the highest quartile of CC (≥ 40.70 cm), there was a 50% reduction in the risk of all-cause mortality, and 57% reduction in the risk of cardiovascular mortality.

The calf circumference is an indicator that is simple, non-invasive and easy to obtain in routine clinical practice. However, evaluation of the potential of CC to predict mortality is limited. Previous studies have revealed that CC was closely related to lean muscle mass [16], but the relationship between CC and cause-specific mortality has not been investigated in detail. Prior studies mainly investigated CC among elderly and fragile patients, and found that low CC was suggested to be an indicator of malnutrition in the elderly population [17, 18]. In contrast, a study reported that CC was not an independent predictor of mortality risk after adjusting for other prognostic factors in older patients with cardiovascular disease [19]. The present study focused on the general population and included relatively young and healthy individuals. The results of this study suggested that the usage of CC might be applied to a larger population scale.

Regarding the subgroup analysis, the relationships between CC and mortality differed according to BMI. The calf circumference had a stronger inverse association with mortality among participants with BMI < 25 kg/m^2. This is consistent with the well-established theory that BMI is an independent risk factor for mortality [20], which might weaken the protective effects of increased CC. Also, a study conducted among 160 patients aged ≥ 65 years revealed CC to be a better indicator than BMI in predicting mortality [21]. The calf circumference is potentially a protective factor for mortality, particular for those with lower BMI.

The underlying mechanism of CC relating to all-cause and cardiovascular mortality has not been fully investigated, but several potential mecha-

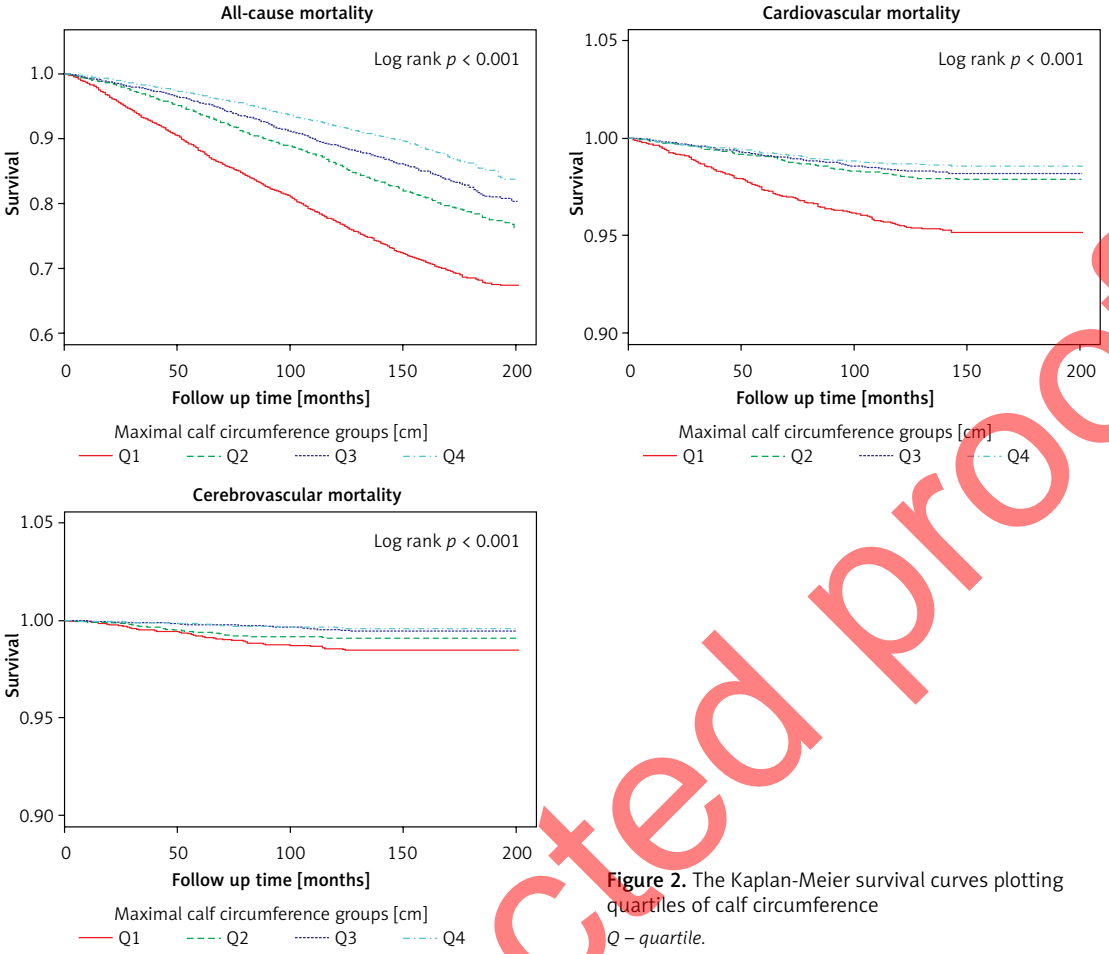

Figure 2. The Kaplan-Meier survival curves plotting quartiles of calf circumference

Q – quartile.

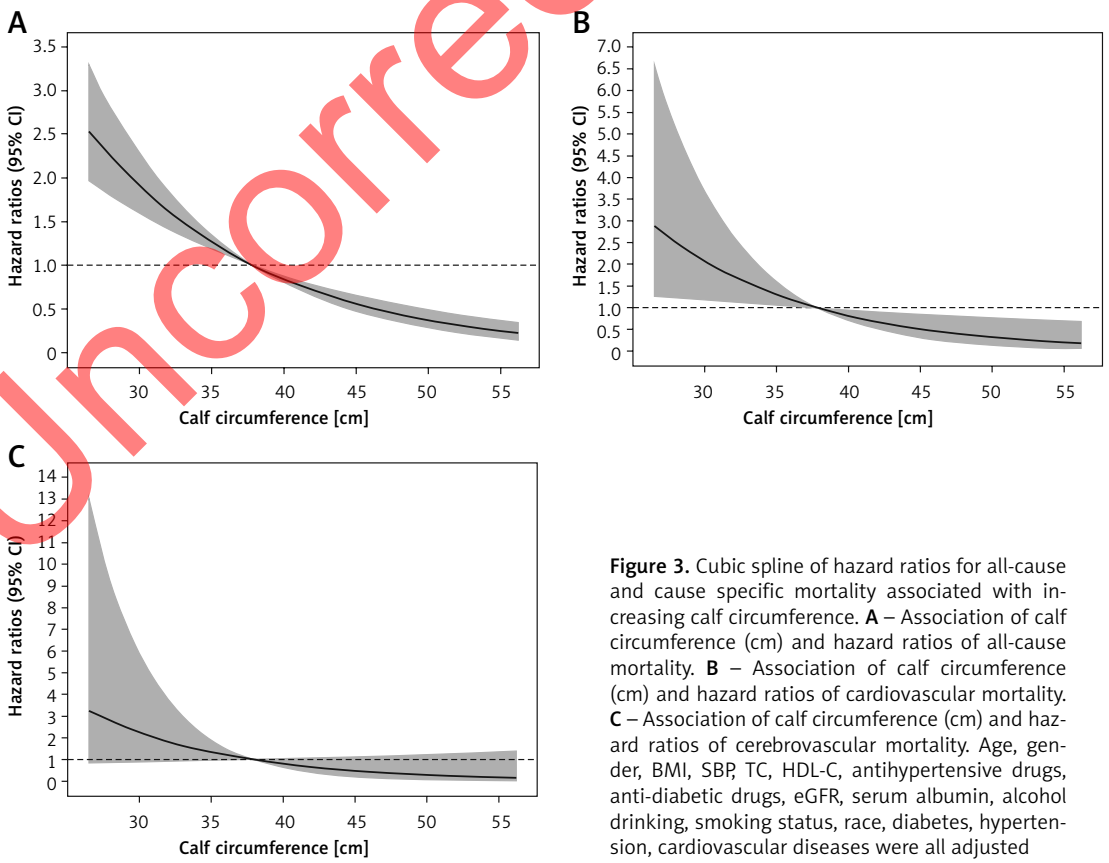

Figure 3. Cubic spline of hazard ratios for all-cause and cause specific mortality associated with increasing calf circumference. **A** – Association of calf circumference (cm) and hazard ratios of all-cause mortality. **B** – Association of calf circumference (cm) and hazard ratios of cardiovascular mortality. **C** – Association of calf circumference (cm) and hazard ratios of cerebrovascular mortality. Age, gender, BMI, SBP, TC, HDL-C, antihypertensive drugs, anti-diabetic drugs, eGFR, serum albumin, alcohol drinking, smoking status, race, diabetes, hypertension, cardiovascular diseases were all adjusted

Table III. Subgroup analysis for calf circumference with all-cause and cardiovascular mortality

Parameter	All-cause mortality			Cardiovascular mortality	
	Number	HR (95% CI), *p*-value	*P* interaction	HR (95% CI), *p*-value	*P* interaction
Gender:			0.1219		0.0829
Male	9652	0.89 (0.88, 0.90), < 0.0001		0.87 (0.84, 0.90), < 0.0001	
Female	10562	0.90 (0.89, 0.91), < 0.0001		0.86 (0.83, 0.89), < 0.0001	
Age:			0.6140		0.5837
< 50	11856	0.96 (0.94, 0.98), < 0.0001		0.99 (0.92, 1.08), 0.8686	
≥ 50	8358	0.91 (0.90, 0.92), < 0.0001		0.89 (0.87, 0.91), < 0.0001	
Diabetes:			0.2294		0.4573
No	17978	0.89 (0.88, 0.90), < 0.0001		0.88 (0.85, 0.90), < 0.0001	
Yes	2080	0.92 (0.91, 0.94), < 0.0001		0.88 (0.84, 0.92), < 0.0001	
Hypertension:			0.0769		0.1296
No	14210	0.88 (0.87, 0.90), < 0.0001		0.79 (0.76, 0.82), < 0.0001	
Yes	5914	0.90 (0.89, 0.91), < 0.0001		0.90 (0.88, 0.93), < 0.0001	
BMI:			< 0.0001		0.0005
< 25	6888	0.80 (0.79, 0.82), < 0.0001		0.74 (0.70, 0.78), < 0.0001	
≥ 25	13122	0.88 (0.87, 0.89), < 0.0001		0.88 (0.85, 0.91), < 0.0001	
SBP:			0.8037		0.6892
< 140	15470	0.92 (0.91, 0.93), < 0.0001		0.89 (0.86, 0.92), < 0.0001	
≥ 140	612	0.90 (0.86, 0.93), < 0.0001		0.86 (0.78, 0.94), 0.0012	
Smoking:			0.9880		0.1757
Non-smoker	9351	0.90 (0.88, 0.91), < 0.0001		0.88 (0.85, 0.91), < 0.0001	
Ex-smoker	4745	0.89 (0.87, 0.90), < 0.0001		0.85 (0.82, 0.89), < 0.0001	
Current smoker	3945	0.90 (0.88, 0.92), < 0.0001		0.87 (0.82, 0.92), < 0.0001	

When analyzing a subgroup variable, age, gender, BMI, SBP, TC, HDL-C, antihypertensive drugs, anti-diabetic drugs, eGFR, serum albumin, drinking, smoking status, race, diabetes, hypertension, cardiovascular diseases were all adjusted except the variable itself. HR – hazard ratio, CI – confidence interval, BMI – body mass index, SBP – systolic blood pressure.

nisms have been proposed. The calf circumference is a marker of peripheral subcutaneous fat, besides lean mass [22]. Several studies have suggested that the association of adiposity distribution with mortality might be partially explained by inflammation [23]. A study revealed that a larger leg fat mass was related to lower fasting and postprandial glucose levels [8]. Some other previous studies showed that a greater CC might have an antiatherogenic effect [24, 25]. For example, a larger CC reduces the frequency of carotid plaques, which give a plausible reason for a lower risk for cardiovascular mortality [25]. A few studies suggested that peripheral fat mass could protect against unstable glucose and lipid metabolites, which in turn reduce adverse effect of fat on cardiometabolic risk [26]. Some other studies implied that polymorphisms were associated with hypertension and, consequently, with a higher risk of cardiovascular mortality [27]. Similarly, CC might also be affected by genetic composition. These results may explain the protective role of a greater CC in all-cause and cardiovascular mortality.

Further prospective studies are expected to elucidate the link between CC and mortality among the general population with various demographics, and to reveal the underlying mechanism between CC and mortality. There were several limitations of our study. First, the CC values varied according to whether the participant was standing or lying. Second, we did not obtain the status of chronic heart failure and chronic kidney disease. Third, some data were self-reported and might be subject to recall bias. Fourth, more sophisticated anthropometric measurements such as dual energy X-ray absorptiometry were not available in this study. Fifth, the optimal cut-off values of CC were calculated from the NHANES data, which mainly represent US citizens. Replication studies are required in an external population.

In conclusion, CC was inversely associated with the risk of all-cause and cardiovascular mortality. CC had a more significant protective effect on those with BMI < 25 kg/m^2.

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Conflict of interest

The authors declare no conflict of interest.

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