Nutrition, Metabolism & Cardiovascular Diseases (2022) **32**, 2830–2838

Available online at www.sciencedirect.com

Nutrition, Metabolism & Cardiovascular Diseases

journal homepage: www.elsevier.com/locate/nmcd

Neck circumference for predicting the occurrence of future cardiovascular events: A 7.6-year longitudinal study

Tingting Hu [1], Yun Shen [1], Weijie Cao, Yiting Xu, Yufei Wang, Xiaojing Ma **, Yuqian Bao*

Department of Endocrinology and Metabolism, Shanghai Jiao Tong University School of Medicine Affiliated Sixth People's Hospital; Shanghai Clinical Center for Diabetes; Shanghai Key Clinical Center for Metabolic Disease; Shanghai Diabetes Institute; Shanghai Key Laboratory of Diabetes Mellitus, Shanghai 200233, China

Received 19 May 2022; received in revised form 11 August 2022; accepted 29 August 2022
Handling Editor: A. Siani
Available online 6 September 2022

KEYWORDS
Cardiovascular event;
Neck circumference;
Longitudinal study

Abstract *Background & aims:* This study aimed to investigate whether neck circumference (NC) could be used to predict future cardiovascular (CV) events in a community-based Chinese cohort.
Methods and results: We enrolled 1435 participants aged 50–80 years (men, 43.62%) from communities in Shanghai. High NC was defined as NC $\geq$ 38.5 cm in men and NC $\geq$ 34.5 cm in women. Kaplan-Meier analysis and Cox proportional hazards regression were performed to explore the association between NC and CV events. During a mean follow-up period of 7.6 years, 148 CV events (10.31%) occurred. The incidence of CV events was higher in men than in women (83 (13.26%) vs. 65 (8.03%), $P = 0.002$). Multivariable-adjusted Cox regression analysis showed that for every 1-SD increase in NC in the whole population, the hazard ratio (HR) of CV events was 1.45 (95% confidence interval [CI], 1.15–1.83). The dose-response association between NC and CV events was significant in men (HR, 1.37, 95% CI, 1.10–1.71) but not in women (HR, 1.19, 95% CI, 0.94–1.52). In comparison with participants showing low baseline NC, those with high baseline NC showed a significantly higher risk of CV events (HR, 1.59, 95% CI, 1.14–2.22). Further stratified by sex, the positive association remained significant in men (HR, 1.90, 95% CI, 1.21–2.98) but not in women (HR, 1.25, 95% CI, 0.75–2.07).
Conclusion: NC was significantly associated with the risk of future CV events in middle-aged and elderly populations in the community and was a better predictor in men.

List of acronyms: Neck circumference, (NC); Cardiovascular, (CV); Hazard ratio, (HR); Confidence interval, (CI); Cardiovascular disease, (CVD); Global burden of disease, (GBD); Fasting plasma glucose, (FPG); Ischemic heart disease, (IHD); International classification of Diseases-10, (ICD-10); Waist circumference, (WC); Body mass index, (BMI); Fasting insulin, (FINS); Glycated hemoglobin, (HbA_{1c}); 2-h blood glucose, (2hPG); Total cholesterol, (TC); Triglyceride, (TG); High-density lipoprotein cholesterol, (HDL-C); Low-density lipoprotein cholesterol, (LDL-C); Homeostasis model-assessed insulin resistance index, (HOMA-IR); Magnetic resonance imaging, (MRI).

* Corresponding author. Department of Endocrinology and Metabolism, Shanghai Jiao Tong University School of Medicine Affiliated Sixth People's Hospital, 600 Yishan Road, Shanghai 200233, China.
** Corresponding author. Department of Endocrinology and Metabolism, Shanghai Jiao Tong University School of Medicine Affiliated Sixth People's Hospital, 600 Yishan Road, Shanghai 200233, China.
E-mail addresses: maxiaojing@sjtu.edu.cn (X. Ma), yqbao@sjtu.edu.cn (Y. Bao).
[1] These two authors contributed equally to this work.

https://doi.org/10.1016/j.numecd.2022.08.023

1. Introduction

Cardiovascular disease (CVD) is a major global health concern. According to the 2020 Global Burden of Disease (GBD) data, the total number of patients with CVD has doubled from 271 million in 1990 to 523 million in 2019, and CVD has become the disease with the highest disability and mortality rates [1]. According to the summary of the China Cardiovascular Health and Disease Report 2020, the incidence of CVD continues to rise, and the number of patients with CVD reached 330 million by 2020. Since 2006, cardiovascular (CV) mortality in China has always ranked first, with 2 out of every 5 deaths due to CVD [2]. A national population-based survey of 74,726 Chinese adults showed that only 1.06% of Chinese adults had ideal CV health status [3].

Obesity has been confirmed to be closely related to a variety of CVD risk factors such as hypertension, type 2 diabetes, and dyslipidemia [4,5]. Obesity has also been related to the occurrence of CV events [6]. The adipose tissue of the trunk is a unique fat depot. In comparison with systemic obesity, excessive accumulation of fat in this region can confer an additional risk of energy imbalance and is independently associated with metabolic abnormalities [7,8]. Neck circumference (NC) is a simple anthropometric parameter that reflects the subcutaneous fat content of the trunk and has the advantages of extremely low cost, high operability, and good repeatability [9]. Previous studies have demonstrated that NC is closely related to CVD risk factors such as subclinical atherosclerosis and metabolic syndrome [10,11], but results of current studies on the relationship between NC and CV events are still inconsistent. A cohort study of 3009 patients with type 2 diabetes revealed that patients with high NC had a significantly increased risk of CV events [12]. However, in the Jackson Heart Study of 5290 subjects, after adjustment for all factors, no independent association was observed between NC and the risk of all-cause mortality, stroke, myocardial infarction, and heart failure for hospitalization [13]. There is still a lack of prospective studies on the predictive ability of NC for CV events in the Chinese community-based population. Thus, this study aimed to explore the predictive ability of NC for CV events in a middle-aged and elderly cohort in Chinese communities.

2. Methods

2.1. Study population

The study participants were recruited from communities in Shanghai from October 2013 to October 2014. All participants received standardized questionnaires and underwent physical examinations and laboratory measurements. The contents of the questionnaires included the history of current and past diseases, medication, family diseases, and personal habits [14]. All participants signed informed consent before participating in the study. This study was approved by the Ethics Committee of the Sixth People's Hospital affiliated to Shanghai Jiao Tong University School of Medicine.

Participants with validated history of malignant tumors, thyroid dysfunction or hyperthyroidism or hypothyroidism, CV or cerebrovascular diseases, severe liver or kidney dysfunction, treatment with steroids or thyroxine, or premenopausal status were excluded at baseline. Follow-up assessments were conducted from October 2021 to February 2022 by phone calls or through electronic medical records, with a mean follow-up period of 7.6 $\pm$ 0.6 years. During the follow-up period, 33 people died due to non-CV events, 358 people were lost to follow-up due to relocation, and 1435 participants aged 50–80 years (mean age: 60.1 $\pm$ 5.1 years) were eventually included in this study, with a follow-up response rate of 80.39% (Fig. 1). No significant differences were observed in the baseline clinical characteristics between the enrolled and lost participants, except for fasting plasma glucose (FPG) level and education attainment (both $P < 0.05$; other variables, $P > 0.05$).

2.2. Outcomes

The primary outcome of this study was the first occurrence of CV events, defined as a composite of ischemic heart disease (IHD) and cerebrovascular events. IHD included cardiac death, myocardial infarction, unstable angina pectoris, hospitalization for heart failure, and coronary revascularization. Cerebrovascular events included ischemic stroke or death due to a cerebrovascular event. Information on the clinical outcomes was collected via telephone and medical information. Subsequently, event information in the medical records was further confirmed by a trained physician and classified using the International Classification of Diseases (ICD-10) codes, and CV events were coded from I00 to I99. Self-reported events showed substantial-to-excellent agreement with medical records (Kappa statistics: 0.94–0.99).

2.3. Baseline anthropometric and laboratory measurements

At baseline, all participants underwent a physical examination, which included measurements of height, weight, NC, waist circumference (WC), and blood pressure. For the NC measurements, participants stood upright with their heads in a horizontal position. The upper edge of the tape was positioned just below the protrusion of the thyroid cartilage and perpendicular to the long axis of the neck (avoiding skin compression). WC was measured at the horizontal position of the mid-axillary line between the lower edge of the costal arch and the midpoint of the iliac crest. According to our previous study, high NC was defined as NC $\geq$ 38.5 cm in men and $\geq$ 34.5 cm in women [15]. Body mass index (BMI) = weight (kg)/height^2 (m^2).

Fasting blood samples were collected from each participant at baseline. Participants with no history of diabetes underwent a 75 g oral glucose tolerance test, and those with a history of diabetes received a 100 g steamed

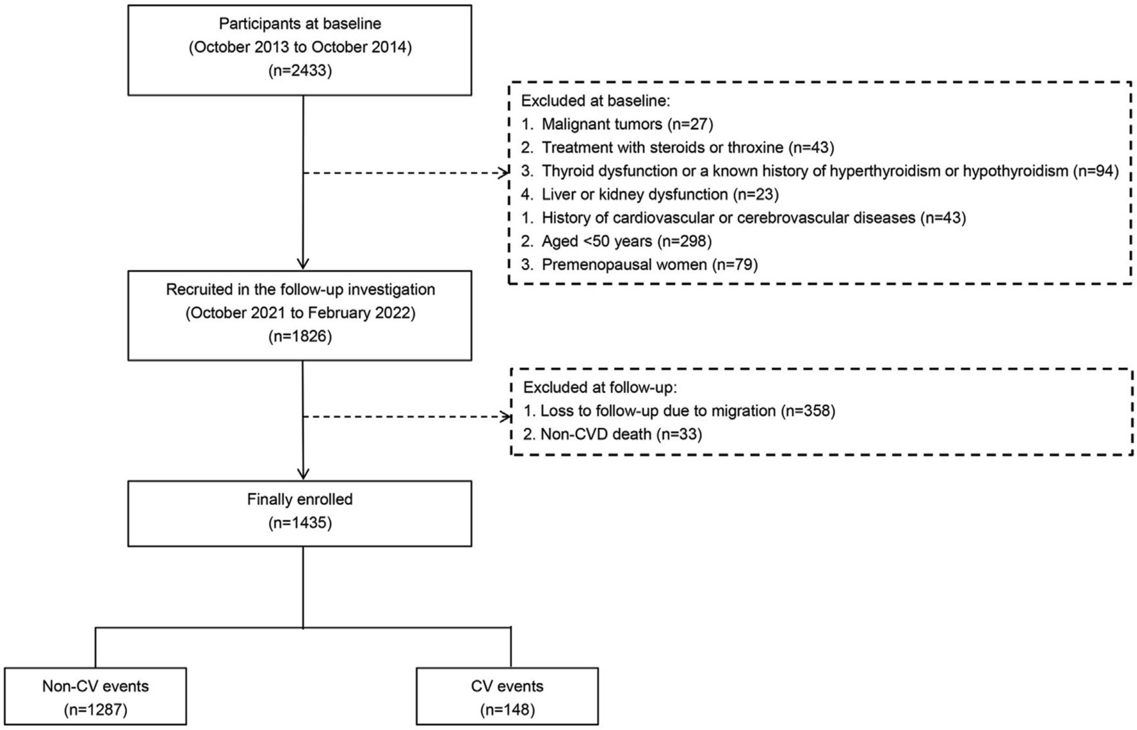

Figure 1 Flowchart of the study population.

bread meal instead. In this study, blood routine along with measurements of FPG, fasting insulin (FINS), glycated hemoglobin (HbA_{1c}), 2-h blood glucose (2hPG), total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) levels were performed. All laboratory tests were performed according to previously described standardized methods [14]. Homeostasis model-assessed insulin resistance index (HOMA-IR) was calculated as FINS (mU/L) $\times$ FPG (mmol/L)/22.5 [16].

2.4. Definitions

Participants in this study who smoked at least one cigarette per day for more than six months at the baseline were defined as current smokers [17]. Hypertension was diagnosed as systolic blood pressure $\geq$ 140 mmHg, and/or diastolic blood pressure $\geq$ 90 mmHg, and/or use of antihypertensive medications according to the ESC/ESH (European Society of Cardiology/European Society of Hypertension) guidelines 2018 criteria [18]. On the basis of ESC 2019 guidelines, diabetes was identified by FPG $\geq$ 7.0 mmol/L, and/or 2hPG $\geq$ 11.1 mmol/L, and/or $HbA_{1c} \geq 6.5\%$, and/or a previous diagnosis of diabetes [19]. Dyslipidemia, based on ESC/EAS (European Atherosclerosis Society) 2019 guidelines, was diagnosed when one of the following criteria was met: (1) TC $\geq$ 5.2 mmol/L (200 mg/dl), (2) TG $\geq$ 1.7 mmol/L (150 mg/dl), and (3) the use of lipid-lowering drugs [20]. WC $\geq$ 90 cm in men or $\geq$ 85 cm in women was considered to indicate abdominal obesity, according to the Chinese Guidelines for the Prevention and Treatment of Type 2 Diabetes (2020 Edition) [21]. On the basis of the World Health Organization 2000 criteria, BMI was categorized as underweight/normal weight (BMI $<$ 25 kg/m^2), overweight (BMI $\geq$ 25 kg/m^2), and obesity (BMI $\geq$ 30 kg/m^2) [22].

2.5. Statistical analyses

Normally distributed data, skewed data, and categorical variables were presented as mean $\pm$ standard deviation, median and interquartile range, frequencies and percentages, respectively. Intergroup comparisons were conducted using Student's t-tests for normally distributed data, Wilcoxon rank-sum test for skewed data, and Chi-square test for categorical variables. Kaplan-Meier analysis with log-rank test was used to assess the cumulative incidence of CV events between different NC groups by the follow-up time. The Cox proportional hazards model was applied to assess the effects of NC on CV events. This study also explored a potential nonlinear relationship between NC and CV events using restricted cubic splines. Sensitivity analysis was performed by excluding current smokers, participants with events during the first year of follow-up, or aged $\geq$ 75 years [23]. We used R 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria) for analysis. A two-tailed $P < 0.05$ was considered statistically significant.

Table 1 Baseline characteristics of participants according to the development of CV events at follow-up.

Variables		Total	Non-CV events	CV events
Men/Women (n)		626/809	543/744	83/65[b]
Age (years)		60.1 ± 5.1	59.9 ± 5.0	61.5 ± 5.2[b]
BMI (kg/m^2)		24.1 ± 3.2	24.0 ± 3.1	25.4 ± 3.6[b]
NC (cm)	Men	38.0 ± 2.3	37.9 ± 2.2	38.9 ± 2.6[b]
	Women	33.7 ± 2.0	33.6 ± 2.0	34.3 ± 2.1[a]
WC (cm)	Men	87.7 ± 8.8	87.3 ± 8.6	90.6 ± 9.4[b]
	Women	82.0 ± 8.9	81.7 ± 8.8	85.3 ± 9.2[b]
SBP (mmHg)		131 (120–146)	130 (120–144)	142 (127–155)[b]
DBP (mmHg)		80 (73–86)	80 (73–86)	82 (75–90)[b]
FPG (mmol/L)		5.26 (4.91–5.79)	5.25 (4.91–5.74)	5.46 (4.93–6.32)[b]
2hPG (mmol/L)		7.41 (6.03–9.64)	7.33 (5.99–9.52)	8.62 (6.40–11.5)[b]
HbA$_{1c}$ (%)		5.70 (5.40–6.00)	5.70 (5.40–5.95)	5.80 (5.50–6.40)[b]
FINS (mU/L)		8.00 (5.72–11.41)	7.94 (5.67–11.20)	9.05 (6.41–13.67)[b]
HOMA-IR		1.95 (1.31–2.96)	1.91 (1.29–2.88)	2.30 (1.53–3.48)[b]
TC (mmol/L)		5.11 (4.53–5.75)	5.10 (4.53–5.74)	5.17 (4.54–5.77)
TG (mmol/L)		1.36 (0.95–1.93)	1.35 (0.94–1.88)	1.57 (1.14–2.25)[b]
HDL-C (mmoll/L)		1.29 (1.10–1.57)	1.30 (1.11–1.59)	1.24 (1.04–1.45)[b]
LDL-C (mmol/L)		3.14 (2.64–3.66)	3.14 (2.63–3.66)	3.20 (2.67–3.69)
Beyond high school education, n (%)		883 (61.53%)	794 (61.69%)	89 (60.14%)
Current smoker, n (%)		316 (22.02%)	279 (21.68%)	37 (25.00%)
Family history of CVD, n (%)		494 (34.43%)	432 (33.57%)	62 (41.89%)
Overweight or obesity, n (%)		515 (35.89%)	439 (34.11%)	76 (51.35%)[b]
Diabetes, n (%)		304 (21.18%)	251 (19.50%)	53 (35.81%)[b]
Hypertension, n (%)		729 (50.80%)	626 (48.64%)	103 (69.59%)[b]
Dyslipidemia, n (%)		939 (65.44%)	834 (64.80%)	105 (70.95%)
Use of antidiabetic agents, n (%)		134 (9.34%)	106 (8.24%)	28 (18.92%)[b]
Use of antihypertensive agents, n (%)		403 (28.08%)	341 (26.50%)	62 (41.89%)[b]
Use of lipid-lowering agents, n (%)		176 (12.26%)	152 (11.81%)	24 (16.22%)

Abbreviation: CV events, cardiovascular events; BMI, body mass index; WC, waist circumference; NC, neck circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; 2hPG, 2h plasma glucose; HbA$_{1c}$, glycated hemoglobin A$_{1c}$; FINS, fasting insulin; HOMA-IR, homeostasis model assessment-insulin resistance index; TC, total cholesterol; TG, triglyceride; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; CVD, cardiovascular disease.

[a] $P < 0.05$, variables in participants with CV events vs. variables in participants without CV events.

[b] $P < 0.01$, variables in participants with CV events vs. variables in participants without CV events.

3. Results

3.1. Baseline clinical characteristics of the study participants

A total of 1435 participants (626 men and 809 women) aged 50–80 years (mean 60.1 ± 5.1 years) who completed follow-up were included. The mean NCs for total population, men and women were 35.6 ± 3.1 cm, 38.0 ± 2.3 cm and 33.7 ± 2.0 cm, respectively. During a mean follow-up period of 7.6 years, 148 CV events (10.31%) occurred, including 62 IHD and 86 cerebrovascular events. The incidence of CV events was higher in men than in women (83 (13.26%) vs. 65 (8.03%), $P = 0.002$). Participants were further divided into non-CV event and CV event groups depending on the occurrence of CV events during follow-up. The baseline characteristics of the study participants are presented in Table 1. In comparison with the non-CV event group, BMI, NC, WC, blood pressure, FPG, 2hPG, HbA$_{1c}$, FINS, HOMA-IR, and TG were significantly higher (all $P < 0.05$) in the CV event group, while HDL-C level was significantly lower ($P = 0.006$). The proportions of overweight/obesity, diabetes, hypertension, antidiabetic therapy, and antihypertensive therapy in the CV event group were significantly higher than those in the non-CV event group (all $P < 0.05$). However, the two groups showed no significant differences in the proportion of education attainment, smoking status, family history of CVD, dyslipidemia, and lipid-lowering treatment (all $P > 0.05$).

3.2. The predictive ability of NC for CV events

The Kaplan-Meier analysis was used to determine the predictive ability of NC for CV events in middle-aged and elderly populations (Fig. 2). The results showed that the sex-adjusted cumulative incidence of CV events in participants with high NC was significantly higher than that in those with low NC in the whole population ($P < 0.001$). When stratified by sex, the association remained positive in men ($P < 0.001$) but became marginally significant in women ($P = 0.05$). Moreover, there was no evidence of nonlinear associations between NC and the risk of CV events through the restricted cubic spline analysis (all P for nonlinearity >0.05).

As shown in Table 2, increasing continuous NC was associated with a higher risk of CV events after multivariate adjustment (hazard ratio [HR], 1.45, 95% confidence interval [CI], 1.15–1.83). When stratified by sex, the dose-

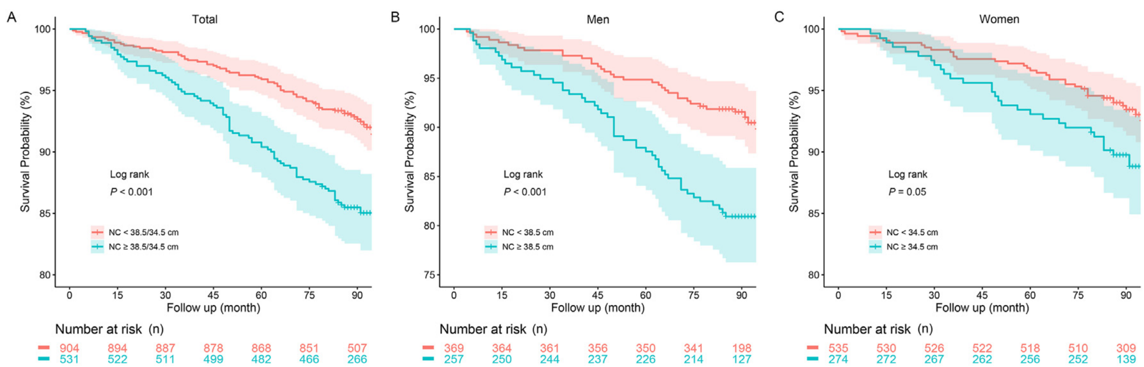

Figure 2 Cumulative curves for the incidence of cardiovascular events in total population (A), men (B) and women (C). The red line represents the number of participants with high NC. The blue line represents the number of participants with low NC.

response association still existed in men (HR, 1.37, 95% CI, 1.10–1.71); however, the effect approached significance in women (HR, 1.19, 95% CI, 0.94–1.52). Cox regression analyses showed that (Table 2) those with high NC had a 59% increased risk of CV events than those with low NC (HR, 1.59, 95% CI, 1.14–2.22). The risk of CV events in men with high NC was markedly increased (HR, 1.90, 95% CI, 1.21–2.98), while the effect was substantially diminished in women (HR, 1.25, 95% CI, 0.75–2.07).

To further verify the association between NC and the risk of CV events, sensitivity analysis was conducted by excluding current smokers, participants who had events during the first year of follow-up, or aged $\geq$ 75 years. The results showed that increasing NC was positively associated with the occurrence of CV events in the total population and men (all $P < 0.05$), while not in women. Among nonsmokers, those with high NC had a 46% (HR, 1.46, 95% CI, 1.11–1.91) increased risk of CV events in the total population. Stratified by sex, the HRs of CV events in men and women with high NC were 1.59 (95% CI 1.13–2.24) and 1.19 (95% CI 0.93–1.52), respectively. Similar results were observed when excluding participants who had events during the first year of follow-up (total population: HR 1.67 95% CI 1.18–2.37; men: HR 1.95, 95% CI 1.21–3.14; women: HR 1.35, 95% CI 0.80–2.29), or aged $\geq$75 years (total population: HR 1.58 95% CI 1.13–2.20; men: HR 1.91, 95% CI 1.22–3.00; women: HR 1.21, 95% CI 0.73–2.01).

3.3. Association between NC and the risk of IHD or cerebrovascular events

Among 148 CV events, 62 were IHD, with 39 occurred in men and 23 in women. Association of NC with IHD was similar to the association with CV events, with multivariate-adjusted HRs of 2.19 (95% CI, 1.30–3.70) in the whole population, 3.78 (95% CI, 1.84–7.75) in men, and 0.99 (95% CI, 0.42–2.31) in women compared to participants with low NC (Table 3). Among 148 CV events, 86 were cerebrovascular events, of which 44 occurred in men and 42 in women. No significant association was observed between NC and cerebrovascular events in the whole population, men and women (all $P > 0.05$).

Table 2 Multivariate Cox proportional-hazards analysis showing hazard ratios of NC with CV events.

Variables	Per 1 SD[b] increase	Low NC[c]	High NC[d]
Total[a]			
Events/Participants, n	148/1435	70/904	78/531
Model 1	1.69 (1.35, 2.11)	1.00	1.90 (1.38, 2.63)
Model 2	1.45 (1.15, 1.83)	1.00	1.59 (1.14, 2.22)
Men			
Events/Participants, n	83/626	34/369	49/257
Model 1	1.52 (1.23, 1.87)	1.00	2.20 (1.42, 3.41)
Model 2	1.37 (1.10, 1.71)	1.00	1.90 (1.21, 2.98)
Women			
Events/Participants, n	65/809	36/535	29/274
Model 1	1.35 (1.07, 1.69)	1.00	1.59 (0.97, 2.59)
Model 2	1.19 (0.94, 1.52)	1.00	1.25 (0.75, 2.07)

Model 1, adjusted for age.
Model 2, adjusted for age, smoking status, education attainment, family history of CVD, diabetes, hypertension, and dyslipidemia.
Abbreviation: NC, neck circumference; CV events, cardiovascular events; CVD, cardiovascular disease.
[a] For the total population, models were further adjusted for sex.
[b] 1 SD: for total population 3.1 cm; men 2.3 cm; women 2.0 cm.
[c] Low NC, NC $<$ 38.5 cm for men and NC $<$ 34.5 cm for women.
[d] High NC, NC $\geq$ 38.5 c for men and NC $\geq$ 34.5 cm for women.

Table 3 The association between NC and the risk of IHD or cerebrovascular events.

Variables	IHD			Cerebrovascular events		
	Per 1 SD[b] increase	Low NC[c]	High NC[d]	Per 1 SD[b] increase	Low NC[c]	High NC[d]
Total[a]						
Events/Participants, n	62/1435	24/904	38/531	86/1435	46/904	40/531
Model 1	1.97 (1.42, 2.74)	1.00	2.62 (1.57, 4.37)	1.45 (1.08, 1.94)	1.00	1.47 (0.96, 2.24)
Model 2	1.65 (1.17, 2.32)	1.00	2.19 (1.30, 3.70)	1.28 (0.94, 1.74)	1.00	1.25 (0.81, 1.94)
Men						
Events/Participants, n	39/626	11/369	28/257	44/626	23/369	21/257
Model 1	1.77 (1.32, 2.37)	1.00	3.84 (1.91, 7.71)	1.26 (0.94, 1.70)	1.00	1.34 (0.74, 2.42)
Model 2	1.68 (1.23, 2.28)	1.00	3.78 (1.84, 7.75)	1.09 (0.80, 1.50)	1.00	1.07 (0.58, 1.95)
Women						
Events/Participants, n	23/809	13/535	10/274	42/809	23/535	19/274
Model 1	1.35 (0.92, 1.99)	1.00	1.46 (0.64, 3.34)	1.33 (1.00, 1.77)	1.00	1.62 (0.88, 2.98)
Model 2	1.08 (0.72, 1.64)	1.00	0.99 (0.42, 2.31)	1.26 (0.93, 1.69)	1.00	1.42 (0.76, 2.67)

Model 1, adjusted for age.
Model 2, adjusted for age, smoking status, education attainment, family history of CVD, diabetes, hypertension, and dyslipidemia.
Abbreviation: NC, neck circumference, IHD, ischemic heart disease; CVD, cardiovascular disease.
[a] For the total popula[a]ion, models were further adjusted for sex.
[b] 1SD: for total popultion 3.1 cm; men 2.3 cm; women 2.0 cm.
[c] Low NC, NC $<$ 38.5 cm for men and NC $<$ 34.5 cm for women.
[d] High NC, NC $\geq$ 38.5 cm for men and NC $\geq$ 34.5 cm for women.

3.4. Comparison of the effects of NC, BMI, and WC in identifying CV events

As shown in Fig. 3, during a mean follow-up period of 7.6 years, 148 CV events occurred in total. Participants with high baseline NC, BMI $\geq$25 kg/m^2, high baseline WC experienced 78, 76, and 80 CV events, respectively. No significant difference was observed between the predictive rates of high baseline NC and baseline BMI $\geq$25 kg/m^2 (52.70% vs. 51.35%, $P > 0.05$). In addition, the predictive rates of CV events in participants with high NC and WC showed no statistical difference (52.70% vs. 54.05%, $P > 0.05$).

A total of 83 CV events occurred in men. Among which, 49, 46, and 48 CV events occurred in those with baseline high NC, BMI $\geq$25 kg/m^2, and high WC, respectively. No

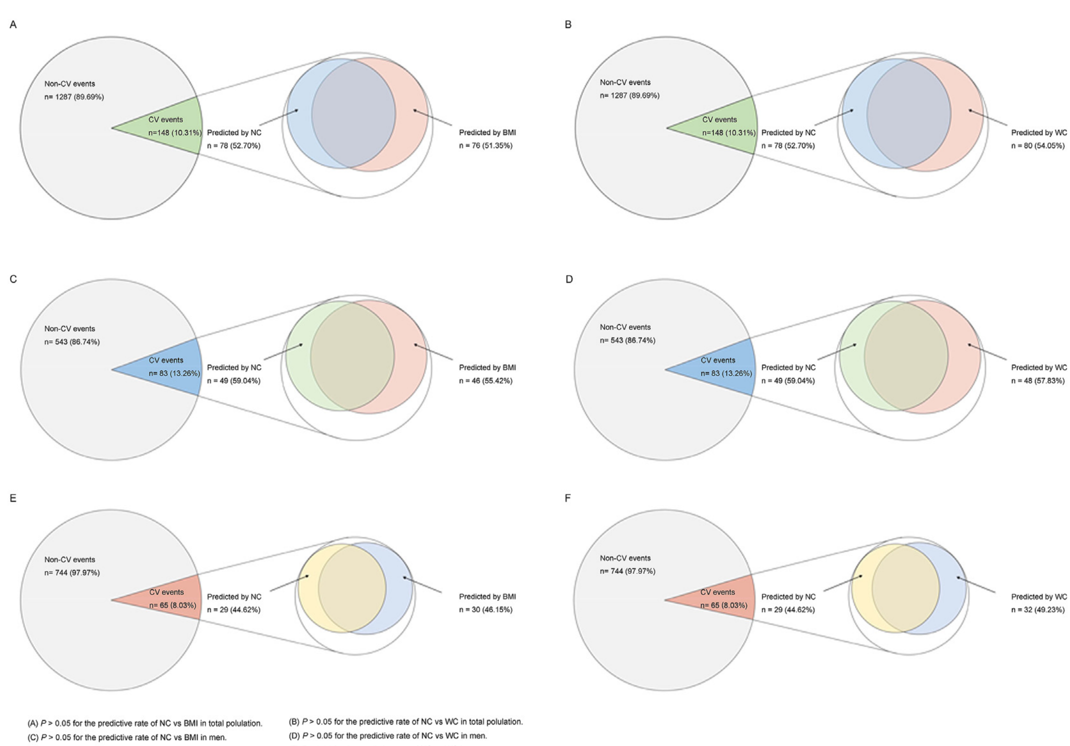

Figure 3 Comparison of predictive ability for cardiovascular events using NC, BMI, and WC cutoff in men and women.

significant differences in predictive ability were observed between baseline high NC and BMI $\geq$25 kg/m^2 (59.04% vs. 55.42%, $P > 0.05$) or baseline high NC and WC (59.04% vs. 57.83%, $P > 0.05$) in men. Similarly, among 65 women with CV events, 29 CV events occurred in those with baseline high NC, 30 CV events occurred in those with baseline BMI $\geq$25 kg/m^2, and 32 CV events occurred in those with baseline high WC. The predictive rates of high baseline NC and BMI $\geq$25 kg/m^2 (44.62% vs. 46.15%, $P > 0.05$) or baseline high NC and WC (44.62% vs. 49.23%, $P > 0.05$) showed no difference.

4. Discussion

To the best of our knowledge, this is the first prospective study to evaluate the ability of NC to predict CV events in the middle-aged and elderly Chinese population. We found that individuals with high NC showed a 1.59-fold higher risk of developing CV events than those with low NC for the next 7.6 years, and the ability of NC to predict IHD was better. The findings also revealed that the predictive ability of NC for CV events was better in men and was comparable to that of BMI or WC.

The global obesity epidemic is now well established, with a nearly doubling increase in prevalence between 1980 and 2015 and a continuous increase in most countries [4]. In addition to promoting the development of CVD, obesity also contributes to adverse clinical outcomes [24,25]. BMI is the most commonly used indicator of obesity. However, several studies have suggested that people with similar BMI may have different body fat distribution and, therefore, different CVD risks [26]. WC, an indicator of central obesity, has been used in the diagnosis of metabolic syndrome and correlates well with CV events [27]. However, some confounding factors, such as the measurement location, breathing rate, and food intake, affect the accuracy of measurement to a certain extent [28]. Therefore, the identification of other simple measures that reflect obesity and fat distribution may help to better predict the occurrence of CV events in more dimensions.

NC is a new measurement index that is simple, saves time, has little variability, and can reflect upper-body fat content [9]. Emerging evidence has supported the link between NC and multiple CV risk factors such as diabetes, hypertension, and subclinical atherosclerosis [29,30]. A cross-section study, conducted in 4152 participants aged 35–74 years, demonstrated that NC was closely correlated with common carotid intima-media thickness [31]. Furthermore, the SCORE risk model was used to estimate fatal atherosclerotic CVD events based on prospective European trials and well recommended by the ESC. Asil et al. conducted a cross-section study involving 232 patients who applied to cardiology clinic with CVD risk factors, and found that NC was closely associated with 10-year CVD mortality in SCORE risk. Moreover, NC was discovered to have the strongest correlation with SCORE risk when compared to BMI and WC, indicating its potential in clinical practice [32]. Recently, several longitudinal studies have explored the relationship between NC and CV events. In a follow-up study of 3299 patients with type 2 diabetes, Yang et al. [33] reported that patients with baseline high NC (NC $\geq$ 75%) had a higher risk of CV events than patients with low NC. Another study of 12,151 patients with high CVD risks who presented to a cardiology department showed that those in the upper tertile of baseline NC had a higher risk of developing long-term CV events than those in the lower tertile [34]. However, there is still a lack of longitudinal studies on the relationship between NC and CV events in Chinese communities. Accordingly, we conducted our prospective study in middle-aged and elderly residents, and NC cutoff point was derived from our previous community-based study [15]. We found a 59% increased risk of CV events in subjects with baseline high NC after a mean follow-up of 7.6 years, which was consistent with the findings of the previous two studies.

However, not all prospective studies have shown a significant correlation between NC and CV events. The Jackson Heart Study conducted an 11-year follow-up of 5290 participants from American communities and found no significant association in the fully adjusted model [13]. Such inconsistencies between studies may be attributable to differences in primary outcomes. Our study focused on the joint effects of clinical events, including IHD and cerebrovascular events, while the Jackson Heart Study focused on the “net effect” of NC on cardiac death, myocardial infarction, heart failure, and stroke. Age, which is an important risk factor for CVD, may be another reason for these inconsistencies. In comparison with the Jackson Heart cohort, our participants were middle-aged and elderly with higher average age (60.1 $\pm$ 5.1 years vs. 55.4 $\pm$ 12.8 years).

Recent studies have revealed that NC is associated with local body fat, especially visceral fat accumulation [35]. Our previous study in 1943 Chinese community residents demonstrated that NC had similar efficacy as WC as a powerful marker of visceral fat content as determined by magnetic resonance imaging (MRI) [15]. To verify whether NC had the same capacity for predicting the risk of CV events as BMI or WC, we compared the predictive ability of baseline high NC, BMI $\geq$25 kg/m^2, and high WC for CV events in the total population, men and women, and found no differences. Our findings showed that NC had similar capacity for identifying CV events as BMI or WC. In addition, our study explored whether the predictive ability of NC for CV events showed a significant sex-related difference. A sex-based stratified analysis found that the predictive ability of NC was greater in men, which might be attributed to the differences in the onset of CV events between men and women. A global case-control study conducted in 52 countries demonstrated that acute myocardial infarction occurred 5–10 years earlier in men than in women across all regions [36]. Considering the similar age distribution between men and women in our data, increasing the follow-up time may better reflect the long-term relationship between NC and CV events in women.

The mechanisms underlying the association of NC with the development of CVD remain unclear. Some studies have suggested that dysfunction of neck adipose tissue may be involved in the pathogenesis of CVD. In addition to serving as a support for the vessel wall, neck adipose tissue is also an important perivascular adipose tissue. Abnormal function of perivascular adipose tissue could trigger an inflammatory response, promote oxidative stress, reduce the production of adipocyte-derived relaxing factors (ADRFs), and increase the activation of cytokines and chemokines [37,38]. All of these factors may link dysfunctional perivascular fat to metabolic disorders such as atherosclerosis, hypertension, and diabetes and ultimately contribute to the occurrence of CV events.

This study had several limitations. First, this was a single-center study that included only community-based population in Shanghai, potentially causing some selection bias. Further studies are required to confirm these findings in population from different regions and ethnic groups. Second, lifestyle variables were not included in the analysis and will be supplemented in the future.

In conclusion, this prospective cohort study based on the middle-aged and elderly population in Chinese communities revealed a significant and positive role of NC in CV events, especially IHD. The predictive ability of NC was better in men than that in women.

Acknowledgements

This work was supported by grant from Shanghai Municipal Science and Technology Commission Medical Guide Project (19411964300).

References

[1] Roth Gregory A, Mensah George A, Johnson Catherine O, Addolorato G, Ammirati E, Baddour Larry M, et al. Global burden of cardiovascular diseases and risk factors, 1990-2019. J Am Coll Cardiol 2020;76(25):2982−3021.
[2] The Writing Committee of the Report on Cardiovascular Health and Diseases in China. Key points of report on cardiovascular health and diseases in China 2020. Chin J Cardiovas Rev 2021;19(7):582−90.
[3] Zhang M, Shi Y, Shi O, Zhao Z, Zhang X, Li C, et al. Geographical variations in cardiovascular health in China: a nationwide population-based survey of 74,726 adults. Lancet Reg Health West Pac 2020;3:100033.
[4] Powell-Wiley TM, Poirier P, Burke LE, Després JP, Gordon-Larsen P, Lavie CJ, et al. Obesity and cardiovascular disease: a scientific statement from the American Heart Association. Circulation 2021; 143(21):e984−1010.
[5] Moore KJ, Shah R. Introduction to the obesity, metabolic syndrome, and CVD compendium. Circ Res 2020;126(11):1475−6.
[6] Kim MS, Kim WJ, Khera AV, Kim JY, Yon DK, Lee SW, et al. Association between adiposity and cardiovascular outcomes: an umbrella review and meta-analysis of observational and Mendelian randomization studies. Eur Heart J 2021;42(34):3388−403.
[7] Lee JJ, Pedley A, Therkelsen KE, Hoffmann U, Massaro JM, Levy D, et al. Upper body subcutaneous fat is associated with cardiometabolic risk factors. Am J Med 2017;130(8):958−66.
[8] Youssef S, Nelder M, Sun G. The association of upper body obesity with insulin resistance in the Newfoundland population. Int J Environ Res Publ Health 2021;18(11):5858.
[9] Yang GR, Yuan SY, Fu HJ, Wan G, Zhu LX, Bu XL, et al. Neck circumference positively related with central obesity, overweight, and metabolic syndrome in Chinese subjects with type 2 diabetes: Beijing Community Diabetes Study 4. Diabetes Care 2010;33(11): 2465−7.
[10] Xu Y, Jian C, Ma X, Shen Y, Wang Y, Bao Y. Comparison of neck and waist circumferences for identifying subclinical atherosclerosis in a community-based population. Diabetes Metab Res Rev 2021; 37(5):e3382.
[11] Kim KY, Moon HR, Yun JM. Neck Circumference as a predictor of metabolic syndrome in Koreans: a cross-sectional study. Nutrients 2021;13(9):3029.
[12] Yang GR, Yuan MX, Wan G, Zhang XL, Fu HJ, Yuan SY, et al. Association between neck circumference and the occurrence of cardiovascular events in type 2 diabetes: Beijing Community Diabetes Study 20 (BCDS-20). BioMed Res Int 2019:4242304.
[13] Pumill CA, Bush CG, Greiner MA, Hall ME, Dunlay SM, Correa A, et al. Neck circumference and cardiovascular outcomes: insights from the Jackson Heart Study. Am Heart J 2019;212:72−9.
[14] Xu Y, Ma X, Pan X, He X, Wang Y, Bao Y. Serum adipocyte fatty acid-binding protein levels: an indicator of non-alcoholic fatty liver disease in Chinese individuals. Liver Int 2019;39(3): 568−74.
[15] Luo Y, Ma X, Shen Y, Xu Y, Xiong Q, Zhang X, et al. Neck circumference as an effective measure for identifying cardio-metabolic syndrome: a comparison with waist circumference. Endocrine 2017;55(3):822−30.
[16] Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28(7):412−9.
[17] Yang G, Fan L, Tan J, Qi G, Zhang Y, Samet JM, et al. Smoking in China: findings of the 1996 national prevalence survey. JAMA 1999;282(13):1247−53.
[18] Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al. ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J 2018;39(33):3021−104.
[19] Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, et al. ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J 2020;41(2):255−323.
[20] Mach F, Baigent C, Catapano AL, Koskinas KC, Manuela Casula, Lina Badimon, et al. ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J 2020;41(1):111−88.
[21] Chinese Diabetes Society. Chinese guideline for the prevention and treatment of type 2 diabetes mellitus (2020 edition). Chin J Diabetes Mellitus 2021;13(4):315−409.
[22] WHO. Obesity. Preventing and managing the global epidemic. World Health Organ Tech Rep Ser 2000;894:i−253.
[23] Xing Z, Peng Z, Wang X, Zhu Z, Pei J, Hu X, et al. Waist circumference is associated with major adverse cardiovascular events in male but not female patients with type-2 diabetes mellitus. Cardiovasc Diabetol 2020;19(1):39.
[24] Lyall DM, Celis-Morales C, Ward J, Iliodromiti S, Anderson JJ, Gill JMR, et al. Association of body mass index with cardiometabolic disease in the UK Biobank: a Mendelian randomization study. JAMA Cardiol 2017;2(8):882−9.
[25] Bhaskaran K, dos-Santos-Silva I, Leon DA, Douglas IJ, Smeeth L. Association of BMI with overall and cause-specific mortality: a population-based cohort study of 3.6 million adults in the UK. Lancet Diabetes Endocrinol 2018;6(12):944−53.
[26] Eckel N, Li Y, Kuxhaus O, Stefan N, Hu FB, Schulze MB. Transition from metabolic healthy to unhealthy phenotypes and association with cardiovascular disease risk across BMI categories in 90,257 women (the Nurses' Health Study): 30 year follow-up from a prospective cohort study. Lancet Diabetes Endocrinol 2018;6(9): 714−24.
[27] Cho JH, Rhee EJ, Park SE, Kwon H, Jung JH, Han KD, et al. The risk of myocardial infarction and ischemic stroke according to waist circumference in 21,749,261 Korean adults: a nationwide population-based study. Diabetes Metab J 2019;43(2):206−21.
[28] Agarwal SK, Misra A, Aggarwal P, Bardia A, Goel R, Vikram NK, et al. Waist circumference measurement by site, posture, respiratory phase, and meal time: implications for methodology. Obesity 2009;17(5):1056−61.
[29] Li HX, Zhang F, Zhao D, Xin Z, Guo SQ, Wang SM, et al. Neck circumference as a measure of neck fat and abdominal visceral fat in Chinese adults. BMC Publ Health 2014;14:311.

[30] Fantin F, Comellato G, Rossi AP, Grison E, Zoico E, Mazzali G, Zamboni M. Relationship between neck circumference, insulin resistance and arterial stiffness in overweight and obese subjects. Eur J Prev Cardiol 2017;24(14):1532–40.
[31] Baena CP, Lotufo PA, Santos IS, Goulart AC, Bittencourt MS, Duncan BB, et al. Neck circumference is associated with carotid intimal-media thickness but not with coronary artery calcium: results from the ELSA-Brasil. Nutr Metabol Cardiovasc Dis 2016; 26(3):216–22.
[32] Asil S, Murat E, Taşkan H, Barış VÖ, Görmel S, Yaşar S, et al. Relationship between cardiovascular disease risk and neck circumference shown in the systematic coronary risk estimation (SCORE) risk model. Int J Environ Res Publ Health 2021;18(20): 10763.
[33] Yang GR, Yuan MX, Wan G, Zhang XL, Fu HJ, Yuan SY, et al. Neck circumference and waist circumference associated with cardiovascular events in type 2 diabetes (Beijing Community Diabetes Study 23). Sci Rep 2021;11(1):9491.
[34] Dai Y, Wan X, Li X, Jin E, Li X. Neck circumference and future cardiovascular events in a high-risk population - a prospective cohort study. Lipids Health Dis 2016;15:46.
[35] Arias Téllez MJ, Acosta FM, Sanchez-Delgado G, et al. Association of neck circumference with anthropometric indicators and body composition measured by DXA in young Spanish adults. Nutrients 2020;12(2):514.
[36] Walli-Attaei M, Joseph P, Rosengren A, Chow CK, Rangarajan S, Lear SA, et al. Variations between women and men in risk factors, treatments, cardiovascular disease incidence, and death in 27 high-income, middle-income, and low-income countries (PURE): a prospective cohort study. Lancet 2020;396(10244):97–109.
[37] Pandzic Jaksic V, Grizelj D, Livun A, Boscic D, Ajduk M, Kusec R, et al. Neck adipose tissue - tying ties in metabolic disorders. Horm Mol Biol Clin Invest 2018;33(2).
[38] Nosalski R, Guzik TJ. Perivascular adipose tissue inflammation in vascular disease. Br J Pharmacol 2017;174(20):3496–513.