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Incremental significance and sex discrepancies of neck circumference on the odds of ischaemic stroke: a multistage, population-based, cross-sectional study from Northeast China

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ABSTRACT

Objectives Accumulated evidence suggests that neck circumference (NC) is associated with cardiometabolic risk factors. However, limited studies are available regarding the association between NC or height normalised NC (neck-to-height ratio (NHR)) and risk of ischaemic stroke (IS) in the Chinese population. Therefore, we aimed at examining the associations between NC or NHR and odds of IS and exploring the discrepancies between men and women.
Design A multistage cluster cross-sectional study.
Setting A population-based study carried out in Northeast China.
Methods A cross-sectional study was undertaken in Northeast China between September 2017 and March 2019, involving 7236 men and 11 352 women, respectively. The median age of participants was 60.30 years, ranging from 40 to 97 years. The associations between NC or NHR and odds of IS were calculated using multiple logistic regression models. Dose–response relationships were depicted using restricted cubic spline functions. Reclassification analyses were carried out to determine the incremental significance of NC or NHR on the odds of IS.
Results In women, NC and NHR were significantly associated with the odds of IS, independent of traditional risk factors and other anthropometric parameters for obesity. The highest quartile of NC and NHR had a 1.60 (95% CI 1.16 to 2.22)-and 1.72 (95% CI 1.23 to 2.41) times higher odds of IS compared with the lowest quartile. Furthermore, the odds of IS increased by 1.10 (95% CI 1.01 to 1.20) and 1.12 (95% CI 1.02 to 1.22) times per 1 SD increase in NC and NHR, respectively. Reclassification analyses showed that the proportion of correct classification increased by 11.5% (95% CI 2.2% to 20.7%) and 22.8% (95% CI 13.5% to 32.0%) after the addition of NC or NHR into established models, respectively. However, the findings could not be replicated in men.
Conclusion NC and NHR might be promising independent indicators for women IS. Their incremental value in the risk stratification of IS enables the individualised prevention of IS in women.

Strengths and limitations of this study

- A multistage cluster cross-sectional study was conducted to elucidate the association between neck circumference (NC) and odds of ischaemic stroke (IS).
- Sex-specific associations between NC and odds of IS were examined.
- The dose–response relationship between NC and the odds of IS was also explored.
- The cross-sectional study design limited the ability to infer the causal relationship between NC and the odds of IS.

INTRODUCTION

Stroke was the third most common cause of death in China (147.04/100 000 persons), accounting for almost one-fifth of deaths in China and one-third of deaths from stroke worldwide.[1] It was estimated that there were approximately 1.53 million Chinese residents who died of stroke in 2017.[1] According to the national epidemiological survey of stroke in China (NESS-China) study, the northeast region bears the biggest stroke burden in China, with age-standardised incidence and mortality of 365.2/100 000 person-years and 158.5/100 000 person-years, respectively.[2] Ischaemic stroke (IS) accounted for approximately 77.8% of the prevalent stroke in China.[2]

Obesity is a disorder of the energy homeostasis system. It is partly characterised by the limited expandability and dysfunction of adipocytes. Accumulated evidence shows that obesity plays an important role in the pathogenesis of cardiovascular diseases (CVDs), such as hypertension, coronary artery disease and stroke.[3] In clinical practice, body mass index (BMI), waist circumference (WC) and waist-to-hip ratio (WHR) are widely used to assess obesity. However, BMI alone cannot reflect the body fat distribution.[4] Though seemingly easy to perform, WC measurements can vary across operators due to the lack of uniformly accepted protocol.[5] Furthermore, the measurement of WC may be significantly influenced by factors such as stomach fullness, the state of expiration and weather conditions, particularly winter.[6] Lastly, some participants may feel the process of WC measurement distressing, given the need to disrobe and have the tape measure positioned around their central obesity.[7]

By contrast, neck circumference (NC) may be an alternative anthropometric measure for diagnosing obesity, since it may be more consistently measured, time-saving and less invasive to individuals' privacy.[7] Emerging data suggest that NC is associated with cardiometabolic risk factors.[7 8] However, the effects of elevated NC on cardiovascular events remain controversial.[7 9 10] Limited studies are available regarding the association between NC and risk of stroke in the Chinese population. Additionally, though established evidence suggests that height normalised NC (neck-to-height ratio (NHR)) is superior to NC in evaluating the upper-body adipose distribution in patients with obstructive sleep apnoea syndrome,[11] few studies have explored the relationship between NHR and stroke yet.

Therefore, we tried to explore the associations between NC or NHR and the odds of IS using a population-based cross-sectional study from Northeast China and to investigate whether the associations were independent of other obesity indexes such as BMI, WC and WHR. Considering the sex-specific differences in adipose tissue distribution patterns and metabolic control,[12 13] sex discrepancies for the associations were further examined.

METHODS

Study participants

We conducted a cross-sectional study in Northeast China between September 2017 and March 2019. As previously described,[14] we recruited study participants through a multistage, stratified and cluster random sampling strategy. As shown in figure 1, all permanent residents aged ≥40 years were invited to participate in our study (n=22 009), with the exclusion of those who were pregnant or had a mental illness. Of them, 18 796 completed the study, resulting in an effective response rate of 85.4%. After the exclusion of 208 patients who had haemorrhagic stroke, 18 588 participants were eligible for the final analysis, involving 7236 men and 11 352 women, respectively. The median (lower quartile–upper quartile) stroke duration was 3 (1–6) years. Written informed consents were obtained from all participants.

Data collections

As previously described,[15] data collection was performed by a single clinic visit using a self-administered questionnaire

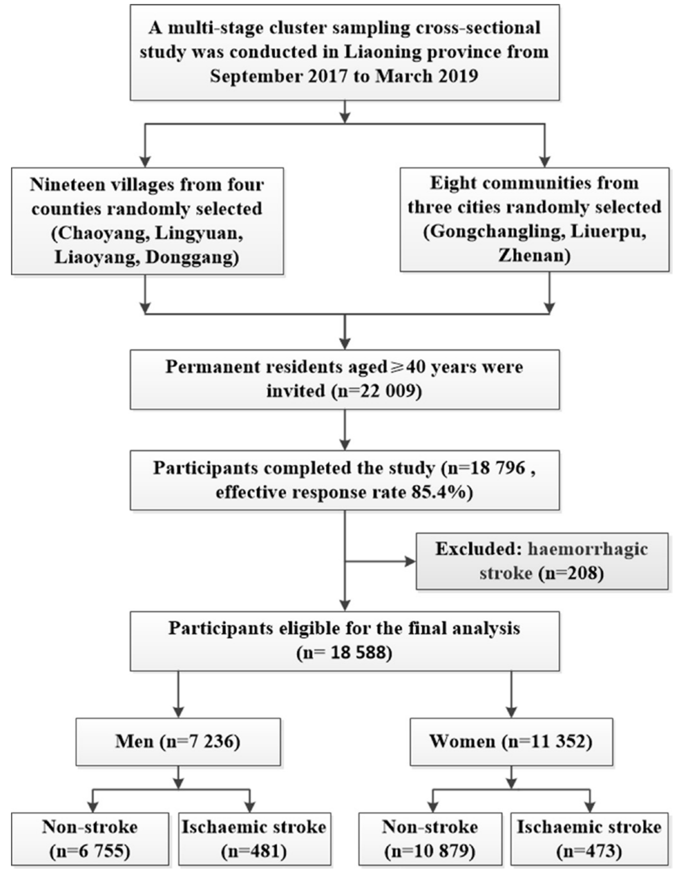

Figure 1 Flowchart for participant selection.

during a face-to-face interview by well-trained investigators. Blood samples were gathered from participants after at least 8 hours of overnight fasting. Laboratory tests of fasting plasma glucose, glycosylated haemoglobin (HbA1c), total cholesterol (TC), triglyceride (TG), serum high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) were performed using an Abbott Diagnostics C800i autoanalyser (Abbott Laboratories, Abbott Park, Illinois, USA) with commercial kits.[14]

Anthropometric measurements

Physical parameters, including height, weight, WC, hip circumference (HC) and NC, were measured to within 0.1 kg and 0.1 cm, as appropriate, with participants wearing lightweight clothes and being barefoot. WC was recorded at the midpoint between the lowest rib and the highest point of the iliac crest. HC was recorded at the level of the greater trochanter. NC was recorded at the level of the lower part of the thyroid cartilage (just below Adam's apple), with the tape placed perpendicular to the long axis of the neck and contacting the skin surface under acceptable pressure. All circumferences were taken using an inelastic tape with the participants standing upright and looking straight forward, having their shoulders relaxed.

BMI was computed as weight (kg) divided by the square of the height (square metre). WHR was computed as

Table 1 Baseline characteristics of the study subjects (nN=18 588)

Variables	Men n=7236 (38.9%) Non-stroke (n=6775)	IS (n=481)	P value	Women n=11 352 (61.1%) Non-stroke (n=10 879)	IS (n=473)	P value
Age (years)	60.93±10.17	66.22±8.88	<0.001	59.39±9.71	66.31±8.02	<0.001
40–49	1027 (15.2)	17 (3.5)	<0.001	1839 (16.9)	10 (2.1)	<0.001
50–59	1909 (28.3)	80 (16.6)		3638 (33.4)	81 (17.1)	
60–69	2475 (36.6)	219 (45.5)		3764 (34.6)	206 (43.6)	
70–79	1109 (16.4)	140 (29.1)		1384 (12.7)	154 (32.6)	
≥80	235 (3.5)	25 (5.2)		251 (2.3)	22 (4.7)	
Education						
Primary school or below	2800 (41.5)	246 (51.1)	<0.001	5764 (53.0)	343 (72.5)	<0.001
Middle school	2915 (43.2)	179 (37.2)		3947 (36.3)	106 (22.4)	
High school or above	1040 (15.4)	56 (11.6)		1168 (10.7)	24 (5.1)	
Ever smoking	4656 (69.0)	343 (70.9)	0.38	874 (8.4)	52 (11.0)	0.02
Current drinking	3731 (55.2)	149 (31.0)	<0.001	1021 (9.4)	18 (3.8)	<0.001
Lack of exercise	703 (10.4)	141 (29.3)	<0.001	1438 (13.2)	139 (29.4)	<0.001
Family history of stroke	1757 (26.0)	208 (43.2)	<0.001	3214 (29.5)	205 (43.3)	<0.001
Hypertension	3841 (56.9)	384 (79.8)	<0.001	5866 (53.9)	404 (85.4)	<0.001
Diabetes	1064 (15.8)	123 (25.7)	<0.001	1811 (16.7)	156 (33.3)	<0.001
AF	95 (1.4)	14 (2.9)	<0.01	90 (0.8)	10 (2.1)	<0.01
SBP (mm Hg)	142.86±21.16	153.56±22.55	<0.001	141.58±23.04	156.91±23.34	<0.001
DBP (mm Hg)	86.86±11.42	89.92±12.11	<0.001	84.02±11.36	88.07±12.50	<0.001
FBG (mmol/L)	6.09±1.73	6.42±2.01	<0.001	6.05±2.02	6.72±2.56	<0.001
HbA1c (%)	5.49±0.94	5.70±1.14	<0.001	5.63±1.13	5.97±1.33	<0.001
TC (mmol/L)	4.95±1.10	4.81±1.03	<0.01	5.22±1.13	5.40±1.23	<0.01
TG (mmol/L)	1.65±1.73	1.55±1.59	0.18	1.70±1.44	2.00±1.36	<0.001
HDL-C (mmol/L)	1.75±0.75	1.71±0.79	0.36	1.79±0.70	1.78±0.81	0.83
LDL-C (mmol/L)	2.46±0.90	2.34±0.88	<0.01	2.62±0.99	2.69±1.19	0.21
Dyslipidaemia	2223 (32.9)	160 (33.4)	0.84	4010 (36.9)	247 (52.7)	<0.001
Lipid-lowering therapy	103 (1.5)	41 (8.5)	<0.001	208 (1.9)	37 (7.8)	<0.001
Anthropometric measurements						
BMI (kg/m^2)	24.35±3.57	24.56±3.35	0.21	24.91±3.66	25.48±3.90	<0.01
Overweight/obesity (≥24.0)	3495 (51.7)	275 (57.3)	0.02	5400 (80.9)	282 (81.5)	0.77
WC (cm)	84.11±10.18	85.77±9.99	<0.01	82.70±9.74	85.69±10.15	<0.001
High WC (M: ≥90.0, W: ≥80.0)	1962 (29.0)	162 (33.7)	0.03	6678 (61.4)	347 (73.4)	<0.001
WHR	0.90±0.07	0.91±0.07	<0.001	0.88±0.08	0.90±0.07	<0.001
High WHR (M: ≥0.90, W: ≥0.80)	3348 (49.6)	284 (59.0)	<0.001	9820 (90.3)	385 (94.5)	<0.01
NC (cm), median (range)	36.75±3.12	37.03±2.81	0.048	33.43±2.75	34.11±2.73	<0.001
Q1 (M: 33.7, ≤34.9; W: 30.5, ≤31.8)	1724 (25.5)	103 (21.4)	0.12	2763 (25.4)	85 (18.0)	<0.001
Q2 (M: 35.9, 35.0–36.5; W: 32.5, 31.9–33.2)	1714 (25.4)	121 (25.2)		2795 (25.7)	105 (22.2)	
Q3 (M: 37.5, 36.6–38.5; W: 34.0, 33.3–35.0)	1736 (25.7)	126 (26.2)		2838 (26.1)	125 (26.4)	
Q4 (M: 40.0, ≥38.6; W: 36.5, ≥35.1)	1581 (23.4)	131 (27.2)		2483 (22.8)	158 (33.4)	
NHR (median, range)	0.221±0.019	0.224±0.017	<0.01	0.214±0.019	0.221±0.018	<0.001
Q1 (M: 0.202, ≤0.209; W: 0.195, ≤0.202)	1682 (24.9)	86 (17.9)	<0.01	2698 (24.8)	67 (14.2)	<0.001
Q2 (M: 0.215, 0.210–0.220; W: 0.208, 0.203–0.213)	1717 (25.4)	123 (25.6)		2769 (25.5)	89 (18.8)	
Q3 (M: 0.226, 0.221–0.232; W: 0.219, 0.214–0.225)	1709 (25.3)	122 (25.4)		2767 (25.4)	119 (25.2)	
Q4 (M: 0.241, ≥0.233; W:0.234, ≥0.226)	1647 (24.4)	150 (31.2)		2645 (24.3)	198 (41.9)	

AF, atrial fibrillation; BMI, body mass index; DBP, diastolic blood pressure; FBG, fasting blood glucose; HbA1c, glycated haemoglobin; HDL-C, high-density lipoprotein cholesterol; IS, ischaemic stroke; LDL-C, low-density lipoprotein cholesterol; M, men; NC, neck circumference; NHR, neck-to-height ratio; Q1–Q4, first quartile to fourth quartile; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride; W, women; WC, waist circumference; WHR, waist-hip ratio; WHR, waist-to-hip ratio.

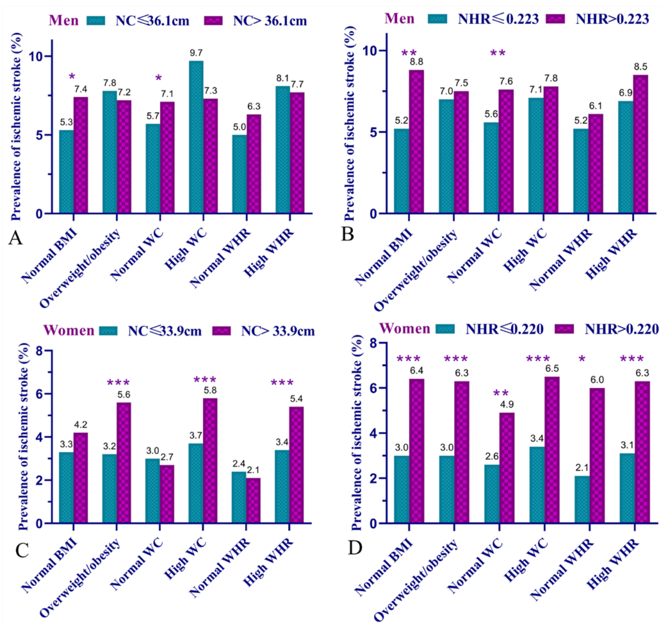

Figure 2 Comparisons of the prevalence of IS between the normal and elevated NC/NHR groups according to different categories of BMI, WC and WHR. (A) NC for men, (B) NHR for men, (C) NC for women and (D) NHR for women. *P<0.05, **P<0.01, ***P<0.001. BMI, body mass index; IS, ischaemic stroke; NC, neck circumference; NHR, neck-to-height ratio; WC, waist circumference; WHR, waist-to-hip ratio.

WC (centimetre) divided by HC (centimetre). NHR was calculated as NC (centimetre) divided by height (centimetre).[3] Overweight/obesity was defined as BMI of ≥24.0 kg/m^2 based on the criteria of Working Group on Obesity in China.[16] High WC was defined as WC of ≥90.0 cm for men and ≥80.0 cm for women, respectively.[17] High WHR was defined as WHR ≥0.90 for men and WHR ≥0.80 for women, respectively.[18 19] To date, there are no uniform cut-offs for both NC and NHR. Participants were divided into NC quartiles according to the following ranges (men/women): ≤34.9/≤31.8, 35.0–36.5/31.9–33.2, 36.6–38.5/33.3–35.0 and ≥38.6/≥35.1 cm. Similarly, participants were divided into NHR quartiles according to the following ranges (men/women): ≤0.209/≤0.202, 0.210–0.220/0.203–0.213, 0.221–0.232/0.214–0.225 and ≥0.233/≥0.226.

Definitions

Participants who self-reported a certain or doubtful history of stroke before the survey were further verified by an experienced neurologist following the recommendations of the WHO.[20] The medical record and CT and/or MRI during the hospital stay were obtained and then carefully reviewed to verify the occurrence of IS.[15] We referred to health insurance data as a supplement.

We defined regular exercise as moderate-intensity exercise or equivalent to walking for at least 30 min and three times/week.[14] Individuals who engaged in moderate and heavy physical labour fulfilled the criteria due to their job. Otherwise, individuals would be considered as having lack of exercise.

Hypertension was defined as an average systolic blood pressure of ≥140 mm Hg or an average diastolic blood pressure of ≥90 mm Hg and/or self-reported use of antihypertensive medications within 2 weeks.[21] Diabetes was diagnosed as FBG of ≥7.0 mmol/L or HbA1c of ≥6.5%, and/or a previous diagnosis of diabetes.[14] Atrial fibrillation (AF) was diagnosed according to the ECG report and/or previous diagnosis of AF. Participants were diagnosed with dyslipidaemia if they met any of the following criteria[22]: TC ≥6.22 mmol/L, TG ≥2.26 mmol/L, LDL-C ≥4.14 mmol/L, HDL-C <1.04 mmol/L or patients who were taking lipid-regulating medications.

Statistical analysis

Continuous variables were expressed as means and SD. Categorical variables were expressed as frequencies and percentages. Student's t-test and χ^2 test were used to compare the between-group differences, respectively. The receiver operating characteristic (ROC) curves were built to assess the performance of different anthropometric measurements to identify the condition of IS. NC and NHR would be dichotomised to compare the difference in IS prevalence between normal and elevated NC or NHR groups stratified by other measures of obesity. The associations between NC or NHR and odds of IS were evaluated using multiple logistic regression models. Additionally, the associations between per 1-SD NC or NHR increase and odds of IS were also examined. The ORs and the corresponding 95% confidence intervals (95% CIs) were presented for logistic regression analyses. Furthermore, dose–response relationships between NC or NHR and odds of IS were depicted using the SAS V.9.4. macro provided by Desquilbet and Mariotti[23] and had been previously applied in one of my previous articles.[24] Both the overall associations and non-linear associations between NC or NHR and odds of IS were examined. If the test for the overall association between NC or NHR and the odds of IS was statistically significant, NC or NHR was significantly associated with IS, regardless of the shape of the associations. Meanwhile, if the test for the non-linear association was also statistically significant, the association was not linear. Otherwise, the association was linear. Lastly, the continuous net reclassification improvement (NRI) index and the integrated discrimination improvement (IDI) index were calculated to assess the incremental significance of NC or NHR in the risk stratification of IS. Missing data were imputed using a multiple imputation strategy. Adjustment for multiplicity in the analyses was performed post hoc with the application of the Benjamini-Hochberg method.

ROC analyses were performed using MedCalc for Windows V.19.5.6 (MedCalc Software, Ostend, Belgium). The dose–response analyses were performed using the SAS software V.9.4. Reclassification analyses were conducted using R software V.3.6.3 (R Foundation for Statistical Computing, Vienna, Austria). All other statistical analyses were conducted using SPSS software V.22.0.

Table 2 Associations between NC or NHR and odds of IS in multiple logistic models after adjusting for confounding factors

Models	OR (95% CI) Q2 vs Q1	Q3 vs Q1	Q4 vs Q1	Per 1 SD increase
Quartile of NC in men				
Model 1	1.19 (0.91 to 1.56)	1.23 (0.94 to 1.60)	1.40 (1.07 to 1.83)	1.09 (1.00 to 1.18)
Model 2	1.26 (0.96 to 1.66)	1.38 (1.05 to 1.81)*	1.71 (1.31 to 2.25)***	1.16 (1.07 to 1.26)**
Model 3	1.19 (0.90 to 1.58)	1.28 (0.97 to 1.70)	1.36 (1.02 to 1.82)	1.08 (0.99 to 1.18)
Model 4	1.13 (0.85 to 1.51)	1.17 (0.86 to 1.59)	1.24 (0.88 to 1.75)	1.04 (0.94 to 1.16)
Quartile of NHR in men				
Model 1	1.38 (1.04 to 1.84)*	1.38 (1.04 to 1.83)*	1.79 (1.36 to 2.34)***	1.14 (1.05 to 1.23)**
Model 2	1.43 (1.08 to 1.90)*	1.39 (1.04 to 1.84)*	1.87 (1.42 to 2.46)***	1.16 (1.07 to 1.25)***
Model 3	1.33 (0.99 to 1.78)	1.19 (0.88 to 1.60)	1.46 (1.09 to 1.95)*	1.07 (0.98 to 1.16)
Model 4	1.27 (0.95 to 1.72)	1.08 (0.79 to 1.47)	1.29 (0.93 to 1.79)	1.02 (0.92 to 1.13)
Quartile of NC in women				
Model 1	1.22 (0.91 to 1.63)	1.43 (1.08 to 1.90)*	2.07 (1.58 to 2.71)***	1.19 (1.11 to 1.27)***
Model 2	1.28 (0.95 to 1.72)	1.56 (1.18 to 2.08)**	2.16 (1.65 to 2.84)***	1.19 (1.11 to 1.28)***
Model 3	1.24 (0.91 to 1.67)	1.30 (0.97 to 1.75)	1.58 (1.19 to 2.11)**	1.10 (1.02 to 1.20)*
Model 4	1.25 (0.91 to 1.70)	1.32 (0.96 to 1.81)	1.60 (1.16 to 2.22)*	1.10 (1.01 to 1.20)*
Quartile of NHR in women				
Model 1	1.29 (0.94 to 1.79)	1.73 (1.28 to 2.35)***	3.01 (2.27 to 4.00)***	1.31 (1.21 to 1.42)***
Model 2	1.26 (0.91 to 1.74)	1.54 (1.14 to 2.10)**	2.42 (1.82 to 3.22)**	1.23 (1.14 to 1.32)***
Model 3	1.09 (0.79 to 1.52)	1.27 (0.92 to 1.73)	1.67 (1.24 to 2.26)**	1.12 (1.03 to 1.21)*
Model 4	1.11 (0.79 to 1.56)	1.28 (0.91 to 1.80)	1.72 (1.23 to 2.41)*	1.12 (1.02 to 1.22)*

Model 1: unadjusted
Model 2: adjusted for age group.
Model 3: adjusted for age group, education level, ever smoking, current drinking, lack of exercise, family history of stroke, hypertension, diabetes, atrial fibrillation and dyslipidaemia.
Model 4: model 3+additionally adjusted for overweight/obesity, high WC and high WHR.
*P<0.05, **P<0.01, ***P<0.001.
IS, ischaemic stroke; NC, neck circumference; NHR, neck-to-height ratio; Q1–Q4, first quartile to fourth quartile; WC, waist circumference; WHR, waist-hip ratio. *indicates p<0.05;

Two-tailed p values of <0.05 were considered statistically significant.

Patient and public involvement

It was not appropriate or possible to involve patients or the public in the design, conduct, reporting or dissemination plans of our research.

RESULTS

Characteristics of the study population

There were 18 588 participants eligible for the final analysis, including 7236 men (38.9%) and 11 352 women (61.1%), respectively. The characteristics of the study population are presented in table 1. The NC and NHR levels of patients with IS were higher than those in the participants who did not have a stroke in both men and women populations (NC for men: 37.03 vs 36.75, p=0.048; NC for women: 34.11 vs 33.43, p<0.001; NHR for men: 0.224 vs 0.221, p<0.01; NHR for women: 0.221 vs 0.214, p<0.001). The distribution of NHR quartiles was significantly different between the non-stroke and IS groups regardless of sex (p<0.01 and p<0.001, respectively). Nevertheless, the distribution of NC quartiles between the two groups was merely different in women (p<0.001) but not in men (p=0.12).

ROC analyses

The ROC curves for different anthropometric measurements are shown in online supplemental figure 1). All areas under the curve were statistically significant except for the BMI in the men population (p<0.05). The optimal cut-off values and the corresponding sensitivity/specificity of NC and NHR to determine IS are shown in online supplemental table 1. For men, the optimal NC and NHR cut-offs were 36.1 and 0.223 cm, respectively. As for women, the optimal NC and NHR cut-offs were 33.9 and 0.220 cm, respectively.

Comparisons of the prevalence of IS between the normal and elevated NC or NHR groups according to different categories of BMI, WC and WHR

As shown in figure 2, our results revealed some discrepancies in the prevalence of IS between the normal and elevated NC or NHR groups when the participants were stratified by BMI, WC and WHR. A higher prevalence of

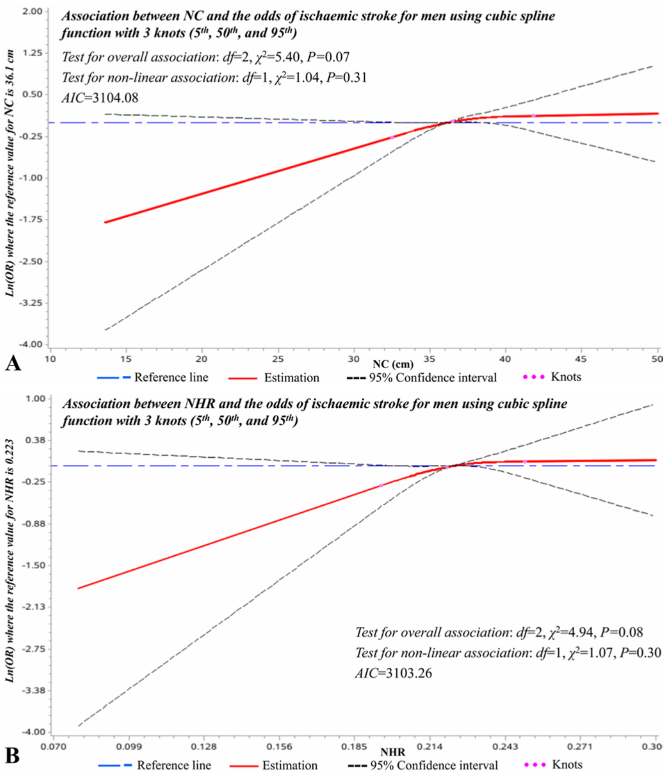

Figure 3 Dose–response associations between NC (A) or NHR (B) and odds of IS for men. Adjusted for age group, education level, ever smoking, current drinking, exercise, family history of stroke, hypertension, diabetes, atrial fibrillation and dyslipidaemia. Y-axis indicates the ln (OR) of IS for any value of NC or NHR compared with the reference value. Dashed lines refer to 95% CIs. AIC, Akaike information criterion; IS, ischaemic stroke; NC, neck circumference; NHR, neck-to-height ratio.

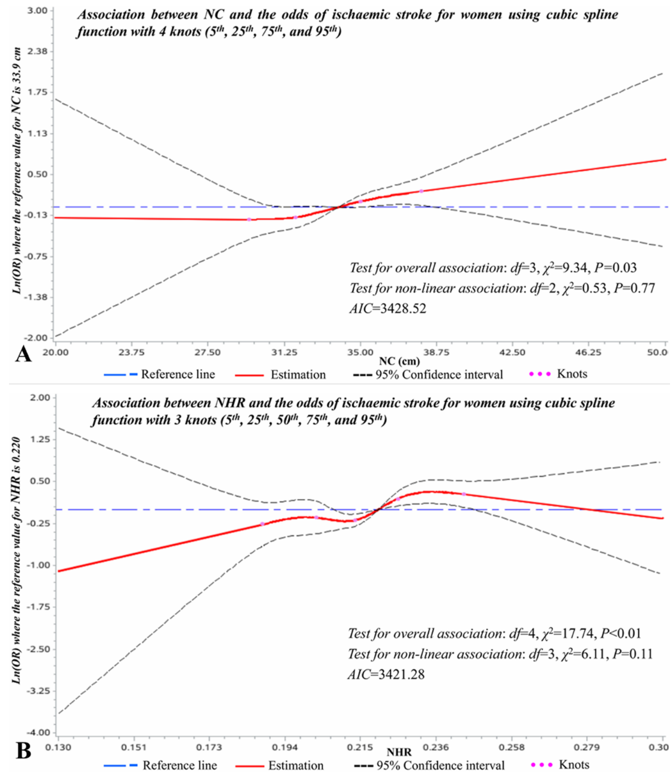

Figure 4 Dose–response associations between NC (A) or NHR (B) and odds of IS for women. Adjusted for age group, education level, ever smoking, current drinking, exercise, family history of stroke, hypertension, diabetes, atrial fibrillation and dyslipidaemia. Y-axis indicates the ln (OR) of IS for any value of NC or NHR compared with the reference value. Dashed lines refer to 95% CIs. AIC, Akaike information criterion; IS, ischaemic stroke; NC, neck circumference; NHR, neck-to-height ratio.

IS was observed in participants with elevated NC or NHR as compared with those with normal NC or NHR in some subgroups.

Associations between NC or NHR and odds of IS in multiple logistic regression models

As shown in table 2, the associations between NC or NHR and odds of IS were explored by gradually adjusting the confounding factors in multiple logistic regression models, in which the first quartile served as the reference category. When fully adjusted for confounding factors, the associations between NC or NHR and odds of IS turned out to be insignificant among men in model 4.

Conversely, the associations between NC or NHR in women persisted even after the full adjustment of the risk factors in model 4. Women in the fourth NC quartile had 1.60 (95% CI 1.16 to 2.22) times higher odds of IS as compared with those in the first NC quartile. The linear trend was also significant, with the odds of IS increasing by 1.10 (95% CI 1.01 to 1.20) times per 1 SD increase of NC. Similarly, women in the fourth NHR quartile had 1.72 (95% CI 1.23 to 2.41) times higher odds of IS as compared with those in the first NHR quartile. The odds of IS increased by 1.12 (95% CI 1.02 to 1.22) times per 1 SD increase of NHR.

Dose–response analyses of the associations between NC or NHR and odds of IS

To further explore the associations between NC or NHR and odds of IS, the dose–response curves were plotted (figures 3 and 4). The dose–response relationships between NC or NHR and the odds of IS did not differ substantially between men and women (all with p>0.05 for non-linear association). However, when evaluating the overall linear associations between exposure and IS, NC and NHR were significant at p<0.05 threshold among women but not among men.

Reclassification analyses

To further evaluate whether NC or NHR has an incremental value in predicting the odds of IS, NRI and IDI were calculated (table 3). Reclassification statistics showed a significant improvement in both NRI (NC: 0.115, 95% CI 0.022 to 0.207, p=0.02; NHR: 0.228, 95% CI 0.135 to 0.320, p<0.001) and IDI (NC: 0.001, 95% CI 0 to 0.002, p=0.03; NHR: 0.003, 95% CI 0.001 to 0.004, p<0.001) for women, which indicated that the predictive power of the model had been improved by the addition of NC or NHR into the established clinical risk factor model. The proportions of correct classification after the addition of NC or NHR increased by 11.0% and 22.2%, respectively. In contrast, no significant improvement was observed in the risk stratification of IS with the addition of NC for men. The NRI but not IDI was statistically significant when adding NHR into the established model for men (p<0.01 and p=0.16, respectively).

DISCUSSION

We found that NC and NHR were independently associated with the prevalence of IS in women, but not men, in a community-dwelling sample of northern Chinese adults. As compared with those in the lowest quartile, women in the highest quartile of NC and NHR had a 1.60 and 1.72 times higher odds of IS, respectively. Furthermore, the odds of IS among women increasing by 1.10 and 1.12 times per 1 SD increase in NC and NHR, respectively. The dose–response relationships between NC or NHR and odds of women IS were linear. The incremental value of NC and NHR on the odds of women IS was further confirmed by reclassification analyses, with the percentages of correct classification increased by 11.5% and 22.8%, respectively. However, our study failed to find any significant association between NC or NHR with the odds of men IS in fully adjusted models.

NC may be a useful tool for screening individuals with obesity,[4 25–27] which was further verified by our data. NC, NHR, BMI, WC and WHR were positively correlated with each other regardless of sex, all with p<0.001 (online supplemental figure 2). Evidence showed that different compartments of body fat were associated with heterogeneous physiological and pathological metabolisms.[28] As mentioned previously, BMI is unable to reflect the characteristics of local fat deposition,[29] while the measurement of central obesity using WC is susceptible to the changes in the body size caused by breathing, diet and lifestyle habits such as drinking alcohol.[30] Therefore, NC, which can be more easily and accurately measured, is a promising proxy to evaluate obesity.[31]

The potential mechanisms linking NC to IS have not been fully understood. Elevated plasma free fatty acids (FFAs) likely provide a basis for the development of insulin resistance, increased very-low-density lipoprotein, high oxidative stress, endothelial dysfunction and other metabolic disorders.[9 31] All damages caused by FFAs might thus contribute to the elevated risk of IS. Upper-body subcutaneous adipose tissue (SAT), typically represented by NC, was the primary source of systemic FFAs.[32] The excess systematic FFAs might partially explain the association between NC and elevated risk of IS. Moreover, two ectopic perivascular fat depots surrounding bilateral carotid vessels were found in a relatively small area of the neck.[33] Their paracrine of adipokines such as leptin, adiponectin and interleukin (IL)-6 might lead to metabolic dysfunction including insulin resistance.[34] The upper-body SAT might also have a direct pathogenic impact on local vasculature.[35] It has been reported that NC was linearly correlated with both the internal and common carotid artery intima–media thickness,[35] which is a surrogate marker of subclinical atherosclerosis and a predictor of stroke outcomes.[36]

Though many studies have tried to clarify the role of NC in the pathogenic process of CVD, most of them were conducted to explore the association between NC and cardiometabolic risk factors.[4 31 34 37] Thus, the associations between NC and cardiometabolic risk factors were well established. However, the relationship between elevated NC and the risk of cardiovascular events remains controversial. The Framingham Study did not find any significant association between NC and incident CVD outcome in multivariable-adjusted models.[9] In contrast, a recent meta-analysis proved that larger NC was associated with an increased risk of coronary artery disease.[10] Limited studies have reported the association between NC and the risk or prognosis of stroke.[7 8 35 38] The conclusions drawn from these studies were inconsistent as well. The difference in races and source of populations might partly account for the discrepancies. The only study from China reported a significant association between NC and the occurrence of major adverse cardiovascular events including stroke.[8] However, it was conducted based on patients with type 2 diabetes rather than the general population. Therefore, the

Table 3 Incremental value of NC or NHR in predicting the probability of IS

Variables	NRI (95% CI)	P value	IDI (95% CI)	P value
Men				
NC	0.027 (−0.064 to 0.118)	0.56	0 (−0.001 to 0.001)	0.46
NHR	0.146 (0.054 to 0.238)	<0.01	0.001 (0 to 0.002)	0.16
Women				
NC	0.115 (0.022 to 0.207)	0.02	0.001 (0 to 0.002)	0.03
NHR	0.228 (0.135 to 0.320)	<0.001	0.003 (0.001 to 0.004)	<0.001

Reclassification indices were calculated for the addition of NC or NHR in the model adjusted for age group, education level, ever smoking, current drinking, lack of exercise, family history of stroke, hypertension, diabetes, atrial fibrillation, dyslipidaemia, overweight/obesity, high WC and high WHR.

IDI, integrated discrimination improvement; IS, ischaemic stroke; NC, neck circumference; NHR, neck-to-height ratio; NRI, net reclassification improvement; WC, waist circumference; WHR, waist-to-hip ratio.

findings of our study should be further verified in different populations.

To the best of our knowledge, our study is the first to report a significant association between NHR and stroke. NHR, a simple index for height-corrected NC, has been previously proved to be a better tool for the assessment of the upper-body adipose distribution than NC in patients with OSA.[11] NC and NHR have been reported to be closely correlated to the severity of OSA.[11 39 40] Moreover, Duarte *et al* even developed a useful and practical tool for OSA screening, with two variables involved (NC and age).[41] As revealed by two prospective cohort studies,[42 43] OSA was independently associated with a 2.0–4.5 times increased risk of IS. In OSA, apnoeic/hypoxemic episodes initiated the release of inflammatory markers (such as IL-1, IL-6, tumour necrosis factor-alpha and interferon-γ), caused oxidative stress and vascular damage, increased aggregation of platelets, and thus lead to stroke.[44] The sympathetic system stimulation that resulted from OSA might also activate the release of catecholamines and increase blood pressure, a well-known risk factor for stroke.[45] Therefore, we speculated that the relationship between NC and odds of stroke might be mediated by OSA. However, the mediating effect of OSA should be further verified by future prospective study.

Interestingly, sex discrepancies were observed for the associations between NC or NHR and odds of IS. Higher NC or NHR was associated with increased odds of IS merely in the women population but not in the men population, after adjusting for confounding factors including BMI, WC and WHR. Sex differences were also found in the Framingham Heart Study, which demonstrated a greater association of NC with cardiometabolic risk factors in women compared with men.[9] The mechanisms accounted for the sex discrepancies are not well understood. According to a previous study, adipose tissue contributed to abnormal FFAs metabolism mainly in two ways: increased hepatic FFAs delivery from visceral adipose tissue (VAT) lipolysis and excess release of FFAs from SAT.[46] It has been suggested that in women, there is a higher percentage of hepatic FFA delivery from VAT than in men.[46] Furthermore, women's SAT is more efficient in storing FFAs than men's.[32 47 48] Similarly, another study showed that neck adiposity was significantly related to OSA severity in women but not in men.[48] This might partially explain sex discrepancies of neck adiposity on the risk of IS. It is worth noting that the prevalence of IS in study participants was higher in men compared with women (6.6% vs 4.1%), which also might account for the sex discrepancies. Our findings should be explained with caution to some extent when generalised to other populations.

LIMITATIONS

Our study has several limitations. First, a single measurement of the NC was unable to accurately quantify the neck fat depots, since the measurement of NC involved both adipose and lean tissue.[34] Second, the cross-sectional study design was unable to infer a causal relationship between NC or NHR with the risk of IS. Third, other confounding factors such as dietary intakes were not taken into consideration, which might result in residual confounding. Fourth, we did not impose strict restrictions on the look-back window of stroke (eg, the stroke should have occurred within the last 5 years). Lastly, well-designed prospective studies with large sample sizes are needed to validate our findings in other populations.

CONCLUSION

In conclusion, NC and NHR were significantly associated with the odds of IS among women, independent of traditional risk factors and other obesity measurements. Furthermore, dose–response analyses showed that the associations were linear. Sex discrepancies did exist for the associations. NC and NHR, two simple and valuable surrogate indicators for obesity, have incremental value in the risk stratification of IS and thus enable individualised prevention of IS in the Chinese women population.

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