Endocrine Journal 2022, **69** (7), 809-818

ORIGINAL

Neck circumference is independently associated with metabolic syndrome in women with polycystic ovary syndrome

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Abstract. Recent compelling evidence has shown that neck circumference (NC), as a reliable and convenient anthropometric index, has better predictive values of hyperuricemia and insulin resistance in women with polycystic ovary syndrome (PCOS) compared with traditional anthropometric measurements. Since both PCOS and metabolic syndrome (MetS) share similar characteristics and affect long-term health of women, we conducted this cross-sectional study to explore the correlation of NC with MetS and metabolic risk factors. Anthropometric parameters, blood pressure, glycemic and lipid profile of 633 PCOS and 2,172 non-PCOS women from January 2018 to June 2021 were analyzed. The results showed that the prevalence of MetS was 28.0% and 9.4% in PCOS and non-PCOS women, respectively. The prevalence of MetS, hypertention, obesity, central obesity, hyperglycemia and dyslipidaemia was also significantly higher in both PCOS and non-PCOS women with larger NC. Additionally, logistic regression analysis showed that PCOS women in the highest quartile of NC had the highest prevalence of MetS (RR = 9.94, 95%CI: 2.41–40.99) after adjusting for confounding factors, while the association between NC and MetS was much attenuated after adjusting for confounding factors in non-PCOS women. Furthermore, we also identified that the optimal NC cutoff value was 33 cm in PCOS women for the prediction of MetS. The potential mechanism could be attributed to the increased release of adipokines and excessive free fatty acids release from subcutaneous adipose tissue, which consequently precipitate the development of MetS. In conclusion, NC was found to be positively and independently correlated with the prevalence of MetS.

Key words: Neck circumference, Anthropometric measurement, Polycystic ovary syndrome, Metabolic syndrome, Metabolic risk factor

POLYCYSTIC OVARY SYNDROME (PCOS) is one of the most common reproductive endocrinopathies. It is characterized by hyperandrogenism, chronic anovulation, and polycystic ovarian morphology and affects 4%–21% of women of reproductive age [1]. PCOS not only leads to reproductive dysfunction in women of childbearing age but is also closely related to the incidence and development of a variety of diseases, including impaired glucose tolerance, type 2 diabetes, non-alcoholic fatty liver disease, obstructive sleep apnea syndrome, cardiovascular and cerebrovascular diseases [2, 3]. Thus far, the pathogenesis of metabolic changes in women with PCOS has not yet been fully elucidated, making it more difficult to perform intervention at the metabolic level.

Metabolic syndrome (MetS) is a collection of metabolic disorders including obesity, glucose intolerance, dyslipidaemia, and hypertension, that are associated with an increased risk of cardiovascular diseases [4]. It has been reported that MetS occurs more than thrice as frequently in women with PCOS than in women without PCOS [5]. PCOS women with MetS have a lower cumulative live birth rate than women without MetS, which indicates a vicious cycle between abnormal metabolism and lowered female fecundity [6]. The etiologies of MetS include central obesity and insulin resistance, and central obesity is one of the criteria for the diagnosis of

Submitted Dec. 15, 2021; Accepted Jan. 25, 2022 as EJ21-0761
Released online in J-STAGE as advance publication Feb. 16, 2022
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metabolic syndrome [7]. In clinical practice, waist circumference has been used as an evaluation index for central obesity [8]. However, waist circumference is not always accurate when measured postprandially or with heavy clothes. Additionally, in order to make a definite diagnosis of MetS, patients need to undergo a series of examinations including blood drawing, blood pressure measurement and anthropometric measurement, which are known to be time-consuming, technically demanding as well as labor intensive [9]. Therefore, it is of great necessity to find a simple and reliable method to identify MetS in the early stage.

Neck circumference (NC) has been well acknowledged as a convenient anthropometric index that reflects subcutaneous fat tissue of the upper body [10]. Studies have demonstrated that a larger NC is closely related to abnormal glycolipid metabolism and a higher incidence of MetS due to increased release of adipokines and excessive free fatty acid release from subcutaneous adipose tissue [11]. It has been reported that in the general female population, NC can predict MetS beyond the classical anthropometric parameters [12]. Since women with PCOS are more susceptible to metabolic abnormalities, compelling evidence has shown that NC was also closely associated with serum uric acid and insulin resistance in women with PCOS [13, 14]. A recent study conducted in 200 Bangladeshi women found that in women with PCOS, NC may be a convenient method for assessing MetS [15]. However, studies focusing on the association between NC and MetS with large sample sizes in women with or without PCOS are scarce. Therefore, this study was conducted to investigate the correlation of NC with MetS and metabolic risk factors and to compare the predictive value of NC for MetS in women with or without PCOS.

Patients and Methods

Participants

This is a retrospective cross-sectional study that initially enrolled 4,881 women at the reproductive center of the First Affiliated Hospital of Wenzhou Medical University from January 2018 to June 2021. The exclusion criteria were women with a history of neck surgery (n = 66), neck malformation (n = 10), thyroid dysfunction (n = 210), congenital adrenal hyperplasia (n = 21), Cushing's syndrome (n = 19), androgen-secreting neoplasms (n = 6), malignant tumor (n = 24), tuberculosis (n = 36), regular oral contraceptives (n = 189), oral glucocorticoids (n = 47), any antidiabetic treatment (n = 95), women with poor ovarian reserve or premature ovarian failure (n = 956), or incomplete information for laboratory or anthropometric parameters (n = 397). Finally, a total of 2,805 women were included for further analysis, of which 633 women were diagnosed with PCOS. This study was approved by the Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University (2021N07). Written informed consent for the whole procedure was obtained from all participating patients.

Definitions

Before making a proper diagnosis of PCOS, endocrinopathies that mimic PCOS should be ruled out first, as listed in the exclusion criteria above. The diagnostic criteria included two out of three following features according to the 2003 Rotterdam diagnostic criteria [16]: (1) menstrual abnormalities, including oligomenorrhea or amenorrhea; (2) clinical and/or biochemical hyperandrogenism, including hirsutism (Ferriman-Galwey score >6) or testosterone concentration >2.81 nmol/L; and (3) polycystic ovarian morphology under B-ultrasound as indicated by the number of follicles with a diameter of 2–9 mm ≥12 and/or ovarian volume ≥10 mL on abdominal ultrasound (3–5 mHz) or transvaginal (frequencies of transducer: 5–7 mHz). The definition of MetS adopted in this study was promulgated by the International Diabetes Federation (IDF)—the IDF criteria. According to the IDF definition of MetS, at least three of the following factors should be included to diagnose the MetS: (1) central obesity based on waist circumference (WC ≥80 cm for women in a Chinese population) [17]; (2) increased triglycerides (TG ≥1.69 mmol/L); (3) decreased high-density lipoprotein (HDL <1.29 mmol/L for women); (4) high blood pressure (systolic blood pressure ≥130 or diastolic blood pressure ≥85 mmHg); (5) hyperglycemia (fasting blood glucose ≥5.60 mmol/L) [18]. The prevalence of MetS was calculated as the number of patients diagnosed with MetS divided by the total number of PCOS or non-PCOS women recruited in the study. Obesity was defined as a body mass index (BMI) ≥25 kg/m^2 according to the Asian BMI criteria [19]. Hypertension was diagnosed as systolic blood pressure (SBP) ≥140 mmHg or diastolic blood pressure (DBP) ≥90 mmHg, or use of any antihypertensive medication within 2 weeks [20]. Dyslipidaemia was defined as total cholesterol (TC) ≥6.22 mmol/L or triglycerides (TG) ≥2.26 mmol/L or high-density lipoprotein (HDL) <1.04 mmol/L, or low-density lipoprotein (LDL) ≥4.14 mmol/L, according to the National Cholesterol Education Program [21]. Insulin resistance and β-cell function were estimated by the homeostasis model assessment of insulin resistance (HOMA-IR; calculated as FBG (mmol/L) × fasting insulin (FINS, mIU/L)/ 22.5) and HOMA of β-cell function (HOMA-β, calculated as (20 × FINS)/(FBG-3.5)) index, respectively.

Anthropometric and laboratory measurements

The anthropometric measurements include BMI, NC, WC, hip circumference (HC), waist to hip ratio (WHR), which were taken after an overnight fast with standing upright and shoulders relaxed position. Neck circumference was measured using a measuring tape at the level of the thyroid cartilage [22]. BMI was calculated as the body weight in kilograms divided by the height in meters squared [23]. WC was measured at the midpoint between the iliac crest and the lowest rib, and HC was measured at the level of maximum extension of the hip [24]. All the anthropometric measurements were completed by one nurse who had received training to ensure the reliability of data in our center. Blood pressure was measured with an electronic sphygmomanometer after 10 min rest in the sitting position. Hormonal and metabolic parameters were obtained by analyzing the fasting blood samples after an overnight fast of at least 8 hours during the menstrual period. The assay methods of hormonal and metabolic parameters have been detailed in a previous study [25]. The intra-assay variation was less than 10% and the inter-assay variation was less than 10% for all the assay methods.

Statistical analysis

The data were evaluated by SPSS 23.0 software (IBM Corporation) and MedCalc Application 19.0.4 software. Patients with or without PCOS were grouped into four frequency groups according to neck circumference, respectively. The value lied below the 25 percent of the bottom value was denoted by quartile (Q1). The other three quartiles were respectively denoted as Q2, Q3, and Q4. Demographic and laboratory variables with a skewed distribution were presented as the medians (interquartile ranges), otherwise were presented as mean ± standard deviation. Skewness and kurtosis tests for normality were performed and the results showed that the levels of basal LH, E2 and T, LH/FSH ratio, AMH, FINS, HOMA-IR, HOMA-β, LDL, and TG were non-normally distributed. For continuous variables, *p* values for trends across quartiles were calculated by linear regression analysis. Data with skewed distributions were logarithmically transformed prior to linear regression analysis. Logistic regression analysis was performed to obtain the odds ratios and 95% confidence interval (CI) of NC for metabolic syndrome based on quartiles of NC. Model 1 was unadjusted. In model 2, adjusted variables included age, SBP, and DBP. In model 3, BMI, HC, LH/FSH ratio (log-transformmed), TG (log-transformmed), HDL and HOMA-IR (log-transformmed) were further adjusted. Logistic regression analysis was performed to obtain the prevalence ratios for each metabolic risk factors (hypertension, obesity, central obesity, hyperglycemia and dyslipidaemia) based on quartiles of NC after adjusting for relevant variables. Meanwhile, *p* values for trends across the quartiles were calculated by the Cochran–Mantel–Haenszel method. Receiver operating characteristic (ROC) curves were used to compare the predictive ability of NC, BMI, HC and WHR for MetS by calculating the area under the curve (AUC). The Youden index, defined as sensitivity + specificity – 1, was calculated to identify the optimal cutoff points. The specificity and sensitivity of NC, BMI, HC and WHR as well as the positive and negative predictive values were calculated for each cutoff point in the sample. All *p* values lower than 0.05 were considered statistically significant.

Results

Baseline characteristics according to the quartiles of neck circumference in PCOS

The general demographic, anthropometric information and metabolic characteristics in PCOS women according to the quartiles of NC were described in Table 1. The ranges of NC in Q1, Q2, Q3 and Q4 were <31.0 cm (*n* = 200), 31.0–33.0 cm (*n* = 189), 33.0 cm–35.0 cm (*n* = 150), and >35.0 cm (*n* = 94). Subjects with larger NC showed elevated levels of BMI, NC, WC, HC, WHR, SBP, DBP, basal T, FBG, FINS, HOMA-IR, HOMA-β, TG, LDL, but lower levels of HDL. No significant differences were observed between the quartiles of age, the number of current smoker, LH/FSH ratio and the level of basal LH, basal FSH, basal E2, AMH and TC.

The baseline characteristics in non-PCOS women were described in Table 2. The ranges of NC in Q1, Q2, Q3 and Q4 were <30.0 cm (*n* = 840), 30.0–31.0 cm (*n* = 405), 31.0 cm–33.0 cm (*n* = 551), and >33.0 cm (*n* = 376). Subjects with larger NC showed elevated levels of age, BMI, NC, WC, HC, WHR, SBP, DBP, basal FSH, basal E2, FBG, FINS, HOMA-IR, HOMA-β, TG, LDL, but lower levels of basal LH, LH/FSH ratio, basal T, AMH and the number of current smoker. No significant differences were observed between the quartiles of FBG, FINS, HOMA-IR, HOMA-β, TC, TG, HDL and LDL.

Percentages of MetS and metabolic risk factors across the quartiles of NC in PCOS and non-PCOS

Of the 633 subjects with PCOS, 177 (28.0%) were diagnosed with MetS. Hypertension was diagnosed in 32 women (5.1%). Obesity and central obesity were diagnosed in 210 (33.2%) and 311 women (49.1%), respectively. Hyperglycemia was found in 125 (19.8%) women. Dyslipidaemia was detected in 140 women (22.1%). The prevalence of MetS and the percentages of metabolic risk factors, including hypertension, obesity, central obesity, hyperglycemia, and dyslipidaemia in women with PCOS

Table 1 Baseline characteristics according to quartiles of neck circumference in PCOS

Variables	Quartiles of NC				*p* for trend
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	
	200	189	150	94	
Age (year)	28.61 ± 3.68	30.27 ± 3.80	29.52 ± 3.77	30.25 ± 3.47	0.23
Current smoker (*n*, %)	2 (1.0%)	4 (2.1%)	2 (1.3%)	1 (1.1%)	0.99
History of DM (*n*, %)	0 (0.0%)	1 (0.5%)	3 (2.0%)	6 (6.4%)	<0.001
BMI (kg/m^2)	20.64 ± 2.29	23.33 ± 2.41	25.84 ± 3.01	27.72 ± 2.91	<0.001
NC (cm)	29.98 ± 0.99	32.47 ± 0.50	34.53 ± 0.50	37.20 ± 1.48	<0.001
WC (cm)	71.39 ± 6.21	78.79 ± 6.81	85.87 ± 7.29	91.51 ± 7.80	<0.001
HC (cm)	87.63 ± 5.12	92.79 ± 5.10	98.79 ± 5.63	101.71 ± 7.13	<0.001
WHR	0.81 ± 0.06	0.85 ± 0.06	0.87 ± 0.06	0.90 ± 0.05	<0.001
SBP (mmHg)	107.12 ± 10.57	112.26 ± 11.21	116.57 ± 12.70	122.20 ± 12.60	<0.001
DBP (mmHg)	71.46 ± 7.62	75.21 ± 8.36	77.23 ± 9.52	80.99 ± 10.00	<0.001
Basal LH (IU/L)	7.20 (5.19–10.76)	6.56 (4.46–9.63)	6.59 (4.40–10.89)	6.41 (3.88–9.65)	0.07
Basal FSH (IU/L)	7.15 ± 2.88	6.95 ± 1.74	6.55 ± 1.74	6.70 ± 1.50	0.07
LH/FSH ratio	1.09 (0.76–1.60)	0.98 (0.68–1.38)	1.04 (0.72–1.53)	1.03 (0.59–1.40)	0.14
Basal E2 (pmol/L)	174.00 (114.00–241.00)	177.00 (121.00–225.50)	172.00 (117.00–209.00)	159.30 (130.00–192.00)	0.35
Basal T (nmol/L)	1.84 (1.39–2.45)	2.02 (1.61–2.53)	2.08 (1.59–2.62)	2.11 (1.60–2.67)	0.03
AMH (ng/mL)	7.91 (6.16–11.61)	8.34 (6.54–11.33)	8.60 (5.94–10.74)	7.80 (5.57–11.02)	0.38
FBG (mmol/L)	5.10 ± 0.39	5.20 ± 0.49	5.43 ± 1.00	5.64 ± 1.99	<0.001
FINS (mIU/L)	8.32 (5.78–11.08)	11.21 (7.72–14.18)	14.50 (10.19–22.61)	16.30 (12.51–22.86)	<0.001
HOMA-IR	1.80 (1.31–2.55)	2.59 (1.77–3.43)	3.36 (2.44–5.70)	3.90 (2.85–6.10)	<0.001
HOMA-β	100.18 (75.09–143.99)	129.22 (94.46–182.33)	172.08 (114.41–235.46)	198.64 (137.26–264.84)	0.01
TC (mmol/L)	4.88 ± 0.85	5.05 ± 1.00	4.96 ± 0.99	5.07 ± 0.93	0.21
TG (mmol/L)	1.04 (0.74–1.38)	1.33 (0.90–1.97)	1.47 (1.00–2.09)	1.72 (1.26–2.31)	<0.001
HDL (mmol/L)	1.49 ± 0.33	1.35 ± 0.30	1.22 ± 0.27	1.14 ± 0.20	<0.001
LDL (mmol/L)	2.70 (2.23–3.08)	2.83 (2.40–3.40)	2.89 (2.46–3.52)	2.95 (2.48–3.50)	0.003

Note: DM, diabetes mellitus; BMI, body mass index; NC, neck circumference; WC, waist circumference; HC, hip circumference; WHR, waist to hip ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; LH, luteinizing hormone; FSH, follicle stimulating hormone; E2, estradiol; T, testosterone; AMH, anti-mullerian hormone; FBG, fasting plasma glucose; FINS, fasting insulin; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-β, homeostasis model assessment of β cell function; TC, total cholesterol; TG, triglycerides; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

were shown in Fig. 1A. The prevalence of MetS from Q1 to Q4 was 5.0%, 19.0%, 47.3% and 63.8%, respectively.

In 2,172 women without PCOS, the prevalence of MetS was 9.4%. Hypertension, obesity, central obesity, hyperglycemia, and dyslipidaemia were diagnosed in 45 (2.1%), 279 (12.8%), 518 (23.8%), 226 (10.4%) and 312 (14.4%) women, respectively. The prevalence of MetS and the percentages of metabolic risk factors in non-PCOS were shown in Fig. 1B. The prevalence of MetS from Q1 to Q4 was 1.5%, 5.4%, 11.4% and 28.5%, respectively.

More specifically, there exhibited a growing tendency in the percentage of hypertension, obesity, central obesity, hyperglycemia and dyslipidaemia consistent with the elevation of NC in both PCOS and non-PCOS women (*p* for trend <0.001).

Prevalence ratios for MetS based on the quartiles of NC in PCOS

The prevalence ratios for MetS and metabolic risk factors based on the quartiles of NC in PCOS and non-PCOS were shown in Table 3. In both women with PCOS or without PCOS, the prevalence ratio of MetS increased significantly, ranging from the lowest quartile

Table 2 Baseline characteristics according to quartiles of neck circumference in non-PCOS

Variables	Quartiles of NC				*p* for trend
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	
	840	405	551	376	
Age (year)	29.39 ± 3.02	29.81 ± 2.76	29.58 ± 2.90	30.19 ± 2.98	<0.001
Current smoker (*n*, %)	27 (3.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	<0.001
History of DM (*n*, %)	1 (0.1%)	0 (0.0%)	1 (0.2%)	3 (0.8%)	0.05
BMI (kg/m^2)	19.87 ± 2.08	21.21 ± 2.07	22.53 ± 2.52	25.10 ± 3.33	<0.001
NC (cm)	29.21 ± 0.88	31.00	32.38 ± 0.48	35.33 ± 1.64	<0.001
WC (cm)	68.42 ± 5.35	73.16 ± 5.57	77.03 ± 6.82	83.59 ± 8.82	<0.001
HC (cm)	85.88 ± 4.58	89.67 ± 4.90	92.54 ± 5.64	97.82 ± 7.20	<0.001
WHR	0.80 ± 0.05	0.82 ± 0.05	0.83 ± 0.06	0.85 ± 0.06	<0.001
SBP (mmHg)	106.35 ± 10.58	108.62 ± 10.45	110.42 ± 11.40	114.07 ± 11.94	<0.001
DBP (mmHg)	71.37 ± 7.52	72.21 ± 7.56	73.07 ± 8.17	75.55 ± 8.48	<0.001
Basal LH (IU/L)	4.87 (3.50–6.77)	4.51 (3.35–5.74)	4.10 (3.08–5.43)	3.86 (2.87–5.22)	<0.001
Basal FSH (IU/L)	7.36 ± 1.77	7.65 ± 1.79	8.02 ± 2.43	8.37 ± 2.46	<0.001
LH/FSH ratio	0.67 (0.50–0.90)	0.59 (0.45–0.78)	0.52 (0.39–0.68)	0.47 (0.35–0.63)	<0.001
Basal E2 (pmol/L)	161.00 (118.00–218.00)	169.00 (122.00–227.30)	169.00 (122.00–226.00)	190.00 (136.75–258.25)	<0.001
Basal T (nmol/L)	1.60 (1.26–1.99)	1.41 (1.09–1.87)	1.38 (0.96–1.84)	1.39 (0.99–1.74)	<0.001
AMH (ng/mL)	5.36 (4.63–6.28)	3.47 (3.23–3.72)	2.42 (2.15–2.68)	1.49 (1.27–1.67)	<0.001
FBG (mmol/L)	5.18 ± 0.49	5.19 ± 0.56	5.19 ± 0.50	5.20 ± 0.79	0.62
FINS (mIU/L)	2.64 (1.89–3.68)	2.43 (1.71–3.38)	2.51 (1.71–3.62)	2.43 (1.68–3.83)	0.64
HOMA-IR	0.58 (0.42–0.90)	0.56 (0.38–0.79)	0.58 (0.38–0.84)	0.56 (0.37–0.94)	0.53
HOMA-β	24.39 (17.66–34.01)	23.11 (16.61–33.89)	23.14 (16.83–32.99)	21.70 (16.00–33.99)	0.92
TC (mmol/L)	4.66 ± 0.84	4.72 ± 0.96	4.66 ± 0.81	4.61 ± 0.86	0.39
TG (mmol/L)	0.99 (0.74–1.38)	1.00 (0.78–1.42)	0.98 (0.74–1.45)	0.99 (0.72–1.41)	0.69
HDL (mmol/L)	1.39 ± 0.29	1.42 ± 0.33	1.38 ± 0.28	1.39 ± 0.29	0.73
LDL (mmol/L)	2.16 (2.54–3.03)	2.51 (2.12–2.95)	2.54 (2.17–2.96)	2.50 (2.08–2.96)	0.20

Note: DM, diabetes mellitus; BMI, body mass index; NC, neck circumference; WC, waist circumference; HC, hip circumference; WHR, waist to hip ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; LH, luteinizing hormone; FSH, follicle stimulating hormone; E2, estradiol; T, testosterone; AMH, anti-mullerian hormone; FBG, fasting plasma glucose; FINS, fasting insulin; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-β, homeostasis model assessment of β cell function; TC, total cholesterol; TG, triglycerides; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

of NC to the highest. Compared with the lowest quartile, women with PCOS in the highest quartile of NC showed the highest prevalence ratio of MetS (OR = 33.53, 95% CI: 15.64–71.87). After adjusting for traditional confounding factors of age, SBP and DBP (model 2), the ORs for the prevalence of MetS, as compared with the lowest quartile, were 3.14 (95% CI, 1.47–6.70) for Q2, 11.29 (95% CI, 5.41–23.57) for Q3, and 15.99 (95% CI, 7.20–35.53) for Q4, respectively (*p* for trend <0.001). Following further adjustment for BMI, HC, LH/FSH ratio (log-transformmed), TG (log-transformmed), HDL and HOMA-IR (log-transformmed) (model 3), an 123%, 723%, and 894% increase in prevalence ratios for MetS was found in the second, third and fourth quartiles, respectively, compared with those in the first one (*p* for trend <0.001). Likewise, women without PCOS showed similar trend of the prevalence ratio for MetS in model 1 and model 2 as in women with PCOS (*p* for trend <0.001). However, after further adjustment in model 3, there were no significant differences in the prevalence ratio of MetS in Q2, Q3 and Q4 when compared with Q1 (*p* for trend = 0.01).

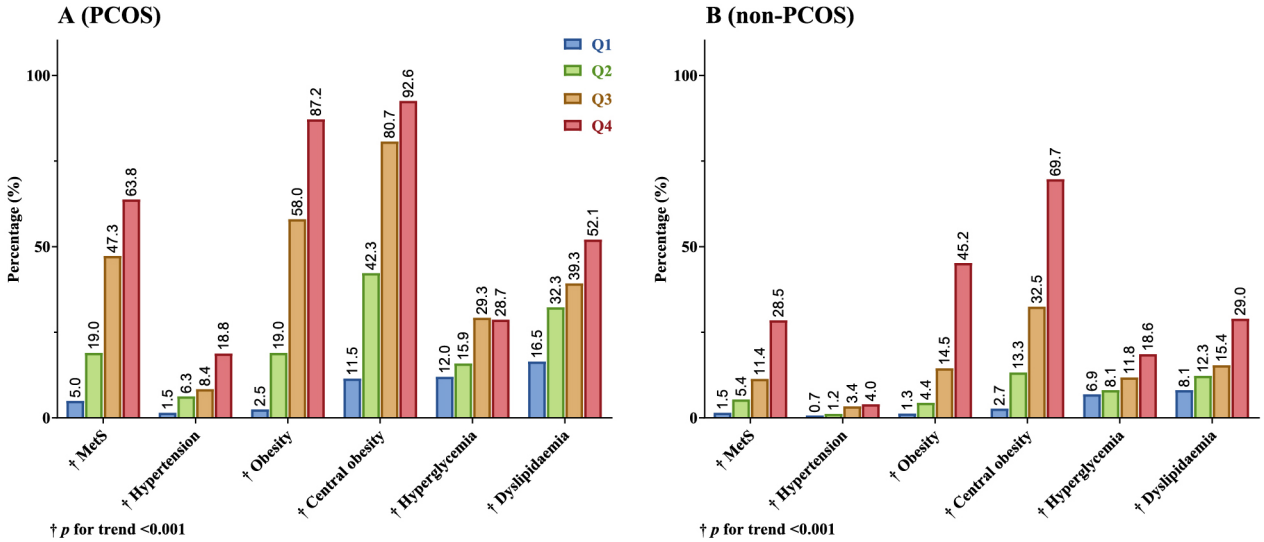

Fig. 1 Percentage of MetS and metabolic risk factors across the quartiles of NC in PCOS and non-PCOS

Table 3 Prevalence ratios for MetS based on the quartiles of NC

	Quartiles of NC				*p* for trend
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	
MetS in PCOS					
Model 1	1.00 (Reference)	4.47 (2.15–9.30)	17.08 (8.38–34.81)	33.53 (15.64–71.87)	<0.001
Model 2	1.00 (Reference)	3.14 (1.47–6.70)	11.29 (5.41–23.57)	15.99 (7.20–35.53)	<0.001
Model 3	1.00 (Reference)	2.23 (0.68–7.35)	8.23 (2.35–28.81)	9.94 (2.41–40.99)	<0.001
MetS in non-PCOS					
Model 1	1.00 (Reference)	3.65 (1.82–7.33)	8.21 (4.47–15.08)	25.03 (14.00–45.74)	<0.001
Model 2	1.00 (Reference)	3.39 (1.67–6.90)	6.76 (3.63–12.59)	17.25 (9.39–31.68)	<0.001
Model 3	1.00 (Reference)	2.54 (0.70–9.28)	2.46 (0.73–8.26)	3.23 (0.88–11.87)	0.10

Note: Model 1 was unadjusted. Model 2 was adjusted for age, SBP, and DBP. Model 3 was further adjusted for BMI, HC, LH/FSH ratio (log-transformmed), TG (log-transformmed), HDL and HOMA-IR (log-transformmed). NC, neck circumference; SBP, systolic pressure; DBP, diastolic pressure; BMI, body mass index; HC, hip circumference; TG, triglycerides; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; CI, confidence interval; OR, odds ratio.

The ROC curves of NC and other anthropometric parameters for MetS

The ROC curves constructed to compare the predictive values of NC and other anthropometric indices for MetS were shown in Fig. 2. In women with PCOS, an NC of ≥33 cm were the best values of combined sensitivity and specificity in identifying MetS in women with PCOS (Fig. 2A). The AUC (95% CI) for NC was 0.81 (0.78–0.84), which was significantly larger than that for HC ($p < 0.001$), with the AUC (95% CI) of 0.74 (0.70–0.77). The AUCs of NC in identifying MetS were higher than those of BMI and WHR. However, there were no significant differences between those AUCs.

The different cutoff points, sensitivities, specificities, positive and negative predictive values of NC, BMI, HC and WHR are shown in Table 4. The optimal cutoff points of NC, BMI, HC and WHR in predicting MetS were 33.0 cm (Youden index = 0.49), 23.81 kg/m^2 (Youden index = 0.51), 90.0 cm (Youden index = 0.39) and 0.86 cm (Youden index = 0.47), respectively. The specificity (SP) and positive predictive value (PPV) of NC were 75.22% and 53.69%, which were comparatively higher than those of BMI (SP: 67.32%; PPV: 49.83%), HC (SP: 46.93%; PPV: 40.24%) and WHR (SP: 66.01%; PPV: 47.98%).

In non-PCOS women, the AUC of BMI was 0.85 (0.83–0.86), which was significantly larger than that of NC, HC and WHR ($p < 0.001$). The optimal cutoff points of NC, BMI, HC and WHR in predicting MetS were 31.0 cm (Youden index = 0.44), 22.77 kg/m^2 (Youden index = 0.59), 93.0 cm (Youden index = 0.47) and 0.84 cm (Youden index = 0.48), respectively. The Youden index

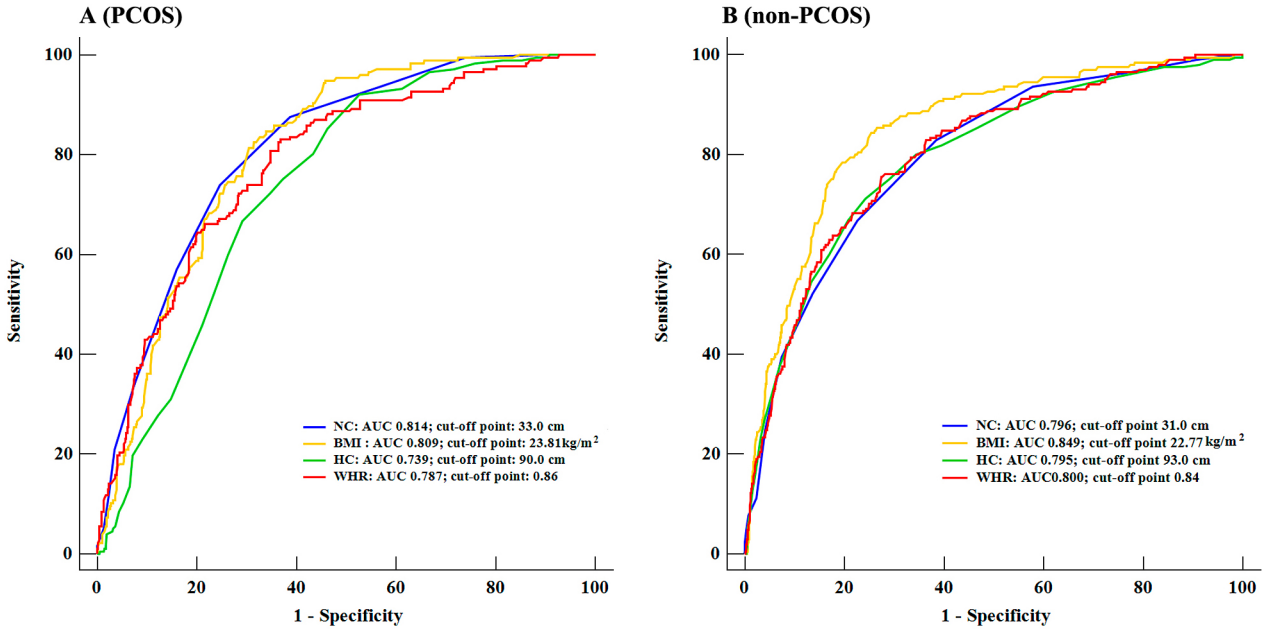

Fig. 2 Receiver operating characteristic curves for the detection of MetS using NC, BMI, HC and WHR
Abbreviations: NC, neck circumference; BMI, body mass index; HC, hip circumference; WHR, waist to hip ratio

Table 4 AUC, cutoff points, sensitivities, specificities, positive and negative predictive values of anthropometric measures for MetS

Variables	AUC	Cut-off points	Youden Index	SE (95% CI)	SP (95% CI)	PPV (%)	NPV (%)
PCOS							
NC (cm)	0.813	33.00	0.49	74.01 (66.90–80.30)	75.22 (71.00–79.10)	53.69	88.18
BMI (kg/m^2)	0.808*	23.81	0.51	83.62 (77.30–88.70)	67.32 (62.80–71.60)	49.83	91.37
HC (cm)	0.740	90.00	0.39	92.09 (87.10–95.60)	46.93 (42.30–51.60)	40.24	93.86
WHR	0.789	0.86	0.47	80.79 (72.40–86.30)	66.01 (61.50–70.30)	47.98	89.85
Non-PCOS							
NC (cm)	0.796	31.00	0.44	82.93 (77.10–87.80)	61.51 (59.30–63.70)	18.34	97.19
BMI (kg/m^2)	0.849$^{\#}$	22.77	0.59	84.39 (78.70–89.10)	74.58 (72.60–76.50)	25.71	97.86
HC (cm)	0.795	93.00	0.47	71.22 (64.50–77.30)	75.70 (73.70–77.60)	23.40	96.19
WHR	0.800	0.84	0.48	75.61 (69.10–81.30)	72.55 (70.50–74.50)	22.31	96.61

Note: *, compared with the AUC of HC, $p < 0.001$; $^{\#}$, compared with the AUC of NC, HC, and WHR, $p < 0.001$.
NC, neck circumference; BMI, body mass index; HC, hip circumference; WHR, waist to hip ratio; AUC, area under the curve; 95% CI, 95% confidence interval; SE, sensitivity; SP, specificity; PPV, positive predictive value; NPV, negative predictive value

of NC was the lowest compared with BMI, HC and WHR. All the anthropometric parameters showed high negative predictive value and low positive predictive value.

Discussion

The current cross-sectional study revealed that compared with women without PCOS, NC was strongly and independently associated with MetS in women with PCOS. The incidence of MetS and metabolic risk factors in women with PCOS was also much higher than that in women without PCOS. Additionally, NC was significantly associated with risk factors for MetS in both women with or without PCOS, which contributed to predicting the likelihood of metabolic risk factors in women with PCOS.

With a higher prevalence of obesity, insulin resistance and dyslipidemia, women with PCOS are more susceptible to MetS than women without PCOS. Studies have shown that the prevalence of MetS in women with PCOS was approximately 27.2%, which was almost twofold higher than that in age-matched women in the general population [26]. In this study, the prevalence of MetS in women with PCOS (28%) was almost threefold higher than that in women without PCOS (9.4%), which

indicates a significantly higher prevalence of MetS in women with PCOS. Therefore, it is of great importance to find a simple and reliable screening method for early recognition for the initiation of timely precautions in high-risk populations during symptomless periods.

Various simple anthropometric indices, including waist circumference, body mass index, hip circumference, and waist-to-hip ratio, are widely applied in clinical practice as markers that reflect obesity or central obesity and predict cardiovascular risks. Neck circumference can reflect the ectopic fat deposition in the upper body and has been applied in determining the degree of obesity and obesity-related metabolic disorders, including cardiovascular diseases and insulin resistance [27, 28]. NC measurement is reported to be more strongly associated with MetS and cardiovascular risk factors than other anthropometric parameters and can be regarded as an independent predictor for MetS [29]. Although many studies have reported that NC is related to the risk of hypertension, hyperglycemia, obesity, central obesity and dyslipidemia, these studies did not adjust for relevant variables and failed to explore the independent correlation between NC and each metabolic risk factor [30, 31].

In the current study, the prevalence of MetS and metabolic risk factors in women with PCOS was increased significantly from the lowest quartile to the highest quartile of NC. Even after adjusting for confounding factors, NC was still independently correlated with MetS, which indicates that ectopic fat deposition might play a critical role in the development of MetS in women with PCOS. Although the Youden index was highest for BMI, we compared the ROC curves among those variables and found that there were no significant differences between BMI and NC. Additionally, NC is easy to measure and will not be affected postprandially or by clothing, which indicates that NC might possess predictive value for MetS in women with PCOS. In women without PCOS, there were also increasing trends for the prevalence of MetS and metabolic risk factors from the lowest quartile to the highest. However, the association between MetS and NC was much attenuated after adjusting for various confounding factors, suggesting that NC might not be an independent parameter when determining MetS in those women. Moreover, the ROC analysis in women without PCOS showed that BMI might be the optimal parameter when determining MetS. Since WC has been included in the diagnostic criteria of MetS, we did not compare the predictive ability between NC and WC due to inevitable bias. Interestingly, we identified that the optimal NC cutoff value was 33.0 cm (sensitivity: 74.0%; specificity: 75.2%) in women with PCOS for the prediction of MetS. This value is comparatively smaller than that in women with PCOS from Bangladesh (34.25 cm; sensitivity: 63.0%; specificity: 64.0%). Such a difference could be attributed to the difference in ethnicity and dietary culture, and the cutoff value in this study might be more applicable for women from East Asia.

Several potential mechanisms contribute to the high prevalence of MetS in women with PCOS with larger NCs. First, it has been reported that obstructive sleep apnea (OSA) is 5 to 30 times more likely to be present in women with PCOS, and the prevalence of metabolic syndrome is 6 to 9 times higher in individuals with OSA than in the general population [32]. Hypoxemia, one of the most typical characteristics of OSA, increases the release of adipokines from adipose tissue. Thus, it contributes to a collection of metabolic abnormalities, including decreased glucose tolerance and insulin sensitivity. Second, recent compelling evidence indicates that NC is independently associated with hyperuricemia in women with PCOS, and elevated serum uric acid levels have been well acknowledged as a risk factor for metabolic risk factors [25]. Third, it has been demonstrated that NC is a reliable indicator for insulin resistance in women with PCOS [13]. Insulin resistance, although it has not been included in the diagnostic criteria of metabolic syndrome, is a central factor in the pathogenesis of both MetS and PCOS [33]. In addition, increasing evidence has shown that the variation in NC directly reflects subcutaneous adipose deposition, from which more than 60% of free fatty acids (FFAs) are released [34]. Excessive FFAs have emerged as a major cause of insulin resistance in insulin target organs, which consequently advances the development of MetS [35].

To the best of our knowledge, this study comprehensively assessed the correlations between NC and MetS and metabolic risk factors in both women with PCOS and without PCOS. The strengths of our study lie in the complete and validated metabolic data, as well as the standardized measurement of NC. Moreover, the inter-observer differences in measurement are small in NC, which makes our findings easily and stably applicable to clinical practice. Most infertile women with PCOS tend to neglect the importance of long-term management of PCOS after conception by assisted reproductive technology. However, several limitations should be taken into consideration. First, the single-center retrospective design of this study limits its ability to interpret the causality of associations. Second, selection bias could not be excluded since all the participants were infertile women seeking ART treatment in our reproductive center. Thus, we failed to assess the association of NC and MetS in women who conceived naturally. Thus, prospectively designed studies on a larger scale should be conducted to strengthen our findings.

In summary, we found that NC was positively and independently correlated with the prevalence of MetS in women with PCOS. The best cutoff value of NC for detecting MetS was 33.0 cm, with a comparable predictive value with BMI. Therefore, as a simple, stable and highly reproducible measuring method, more prospectively designed studies are needed to establish clinical utility in the routine clinical assessment and long-term management of women with PCOS.

Acknowledgements

This work was supported by Natural Science Foundation of Zhejiang Province (LGD21H070001), Health Department of Zhejiang province (2021KY785) and Wenzhou Municipal Science and Technology Bureau Foundation of Wenzhou, Zhejiang, China (Y2020517).

We would like to thank all the doctors, nurses and laboratory staffs at the Reproductive Medicine Center of the First Affiliated Hospital of Wenzhou Medical University for providing all the necessary information required for this study.

Disclosure

None of the authors have any potential conflicts of interest associated with this research.

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