Received: 15 March 2019 | Revised: 25 April 2019 | Accepted: 6 May 2019

DOI: 10.1111/jch.13587

ORIGINAL PAPER

WILEY

Adiposity measures and pre-diabetes or diabetes in adults with hypertension in Singapore polyclinics

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Funding information
SingHypertension was supported by research funds from Clinician Scientist Award to Prof. Tazeen H Jafar from National Medical Research Council. Dr Yeli Wang and Dr Chandrika Ramakrishnan were supported by grant from the Tanoto Initiative for Diabetes Research. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Abstract

Identification of hypertensive patients with pre-diabetes or diabetes is important for timely prevention of complications including vascular disease. We aimed to compare the association and discrimination of central obesity measures (waist circumference [WC] and waist-to-height ratio [WHtR]) with generalized obesity measure (body mass index [BMI]) in relation to pre-diabetes and diabetes among a group of Asian hypertensive patients for the first time. We used the baseline data of 925 subjects aged 40 years or older with uncontrolled hypertension recruited at eight primary care clinics in Singapore. Information on height, weight, WC, fasting blood glucose, and hemoglobin A1c (HbA1c) was collected. Pre-diabetes or diabetes was defined as having reported physician-diagnosed diabetes or taking anti-diabetes medication, fasting blood glucose ≥ 5.6 mmol/dL or HbA1c ≥ 5.7%. Among 925 subjects, 495 (53.5%) had pre-diabetes or diabetes. In logistic regression models, BMI was not associated with pre-diabetes or diabetes after adjusting for WC or WHtR, while a positive association remained with both WC and WHtR after adjustment of BMI. Both WC and WHtR had significantly better discrimination than BMI (respective area under ROC curve: 0.63 for WC, 0.63 for WHtR, and 0.60 for BMI; $P = 0.019$), and adding WC or WHtR on top of BMI further correctly reclassified 42.7% and 38.7% hypertensive patients to the right risk group of pre-diabetes or diabetes indicated by net reclassification improvement. However, WHtR was not superior to WC. In conclusion, our results suggested that central obesity has stronger association with and better discrimination for pre-diabetes or diabetes than generalized obesity.

1 | INTRODUCTION

The global burden of hypertension and diabetes is rising. About 1 billion people suffer from hypertension globally,[1] and many individuals have co-existing diabetes.[2] According to the International Diabetes Federation, around 425 million people were diagnosed with diabetes worldwide in 2017, and at least 352 million people had pre-diabetes, who were at high risk of developing diabetes in the subsequent years.[3] Diabetes increases the risk of complications from microvascular disease (kidneys, eyes, limbs, and microvascular cardiac) and macrovascular disease (coronary atherosclerotic vascular, cerebrovascular, and peripheral vascular systems),[4] and patients with both hypertension and diabetes could have a 2-fold risk of developing cardiovascular disease (CVD) compared to hypertensive patients without diabetes.[5] Thus, early identification of hypertensive patients with pre-diabetes or diabetes could expedite timely intervention for the prevention of CVD risk.

Generalized obesity and central obesity are major modifiable risk factors for pre-diabetes or diabetes. Landmark clinical trials have shown that lifestyle intervention focused on weight loss could delay

or prevent the onset of diabetes among high-risk individuals.[6-12] The American Diabetes Association suggests that hypertensive patients who are overweight or obese (defined by body mass index [BMI] ≥ 25 kg/m^2 or ≥23 kg/m^2 in Asian Americans) should be tested for pre-diabetes and risk for future diabetes.[13] However, the examination of the NHANES data from 1988 to 2012 has shown that the US nationally representative prevalence of pre-diabetes and central obesity (indicated by waist circumference [WC] and waist-to-height ratio [WHtR]) has substantially increased among individuals within a healthy BMI range (18.5-<25 kg/m^2).[14] Likewise, in a nationwide sample of Chinese adults with BMI < 25 kg/m^2, WC has shown to be statistically associated with higher risk of pre-diabetes or diabetes.[15] Nevertheless, previous studies comparing central obesity with generalized obesity have been mostly conducted in general populations[16-25] or outpatient clinic,[26] while the evidence among hypertensive patients is scarce. In addition, compared to Caucasians, Asians develop diabetes at lower BMIs[27] and are more likely to have lower β-cell function and develop insulin resistance.[28] Considering this potential biological difference between Asians and Caucasians, it is important to compare the adiposity measures in a hypertensive population in Asia, which is likely to be meaningful from a public health perspective. However, there is scarcity of literature in Asian hypertensive patients on the relationship of adiposity measures with broader outcome of both pre-diabetes and diabetes.

Therefore, we used data on patients with uncontrolled hypertension to examine the performance of different adiposity measures (BMI, WC, and WHtR) in the identification of pre-diabetes and diabetes. We compared the multivariate-adjusted associations between adiposity measures with pre-diabetes or diabetes and examined the predictive performance of these measures by using both C-statistics and net reclassification improvement (NRI) statistics. In addition, we explored the optimal threshold associated with each measure to aid clinical practice.

2 | METHODS

2.1 | Study population

The SingHypertension study is a cluster randomized controlled trial in 8 primary care clinics in the multi-ethnic Singapore evaluating the effect of a multicomponent intervention compared to usual care in lowering blood pressure over 2 years, where the major ethnic groups are Chinese, Malay, and Indian.[29] In brief, 1,010 participants aged 40 years or older with diagnosed hypertension and uncontrolled blood pressure (systolic blood pressure [SBP] ≥140 mm Hg or diastolic blood pressure [DBP] ≥90 mm Hg) were recruited between January 2017 and April 2018 from 8 polyclinics, which provided subsidized primary care to all Singaporeans and permanent residents. The current study used the cross-sectional data from the baseline interview. A total of 73 participants were excluded (consent withdrawn [n = 35], administrative restructuring of clinics [n = 10], physician screening failure [n = 25], and protocol deviation [n = 3]), leaving 937 participants enrolled in the current study. We further excluded 12 participants who had extreme adiposity levels defined by over 3 standard deviation from the mean value (n = 7 for BMI, n = 2 for WC, and n = 3 for WHtR); thus, the final sample size for the current analysis was 925 participants. The flowchart of the current study design is shown in Figure S1.

2.2 | Assessment of exposures, covariates, and outcome

Research staff were rigorously trained in assessments of height, weight, and WC with strict criteria for reproducibility measures. The intra-class correlation coefficients were 0.99 for height, 0.99 for weight, and 0.97 for WC.

At baseline visits, the trained research staff at each polyclinic measured the blood pressure (BP) and anthropometry measurements (height, weight, and WC) for each participant after obtaining the informed consent. For each participant with a sitting position and had rested for at least 5 minutes, BP was measured three times with 3-minute intervals using an automated device (Omron HEM-7130), and the average of the last two BP readings was used for the current analysis. The BP device comes with arm cuffs of three different sizes (small [arm circumference < 23 cm], standard [arm circumference 23-<33 cm], and large [arm circumference ≥ 23 cm]). To select the right cuff size, the trained research staff measured the circumference of the midarm, which is the midpoint between the shoulder and elbow. The BP measurements were conducted during the first half of the day (before 3 PM) to avoid nocturnal dipping of BP. In addition, participants wore light clothes and removed shoes for the measurements of weight (using Tanita HS 302 Solar digital scale) and height (using the stadiometer). Following the World Health Organization (WHO) protocol for measuring WC, participants removed any jackets or tight clothing (ie, belt) around the waist, and natural WC was measured by a standard clinic measuring tape at the approximate midpoint between the lower margin of the last palpable rib and the top of the iliac crest.

In addition, the trained research staff conducted a face-to-face interview with each participant using structured questionnaires to collect information on demographics, socio-demographics (age, gender, ethnicity, education, employment status, and whether owning a house), personal and family medical history (heart disease, diabetes and stroke), medication adherence, smoking status, physical activity levels, and dietary habits. Smoking status was evaluated using questions adapted from WHO Tobacco Questions for Surveys,[30] and physical activity levels were measured using the International Physical Activity Questionnaire (IPAQ) 9-item short form.[31] Self-reported medication adherence was defined as the percentage of patients reporting using the medications among those who were prescribed medications by doctors at the time of interview. Moreover, at the time of recruitment, each participant also received a panel test in the polyclinics at a subsidized cost, and the measurements included fasting blood glucose, hemoglobin A1c (HbA1c), and lipids (serum total cholesterol [TC], HDL cholesterol [HDL-C], LDL cholesterol [LDL-C]). Glucose levels

were measured on the Roche Cobas c702 automated chemistry using Roche Diagnostics Glucose reagent. BMI was calculated as weight (kg)/(height [m])^2, and WHtR was calculated as WC (cm)/height (cm).

Pre-diabetes was defined as meeting one of the three criteria: (a) had fasting blood glucose between 5.6 and <7.0 mmol/dL and (b) had HbA1c levels between 5.7% and <6.5%.[13] Diabetes was defined as: (a) reported physician-diagnosed diabetes or taking anti-diabetes medications, (b) had fasting blood glucose ≥7.0 mmol/dL, or (c) had HbA1c levels ≥ 6.5%.[13] The thresholds of blood tests were based on 2018 ADA recommendations on diagnosis of pre-diabetes and diabetes.[13]

2.3 | Statistical analysis

Demographic, lifestyle, and clinical characteristics between subjects with and without pre-diabetes or diabetes were compared using Student *t* test (continuous variables) and chi-square test (categorical variables). Pearson correlation coefficients were calculated between BMI, WC, WHtR, TG, HDL-C, LDL-C, TC, SBP, and DBP (all had normal distribution).

Participants were divided into quartiles according to the gender-specific distribution of each adiposity measure (BMI, WC, and WHtR). Using the first quartile as the reference group, logistic regression models were used to calculate the odds ratio (OR) and 95% CI of pre-diabetes or diabetes for the second to fourth quartiles of each adiposity measure. In addition, baseline clinics were treated as the clustering factor in all models. Restricted cubic spline analysis was used to examine the linearity of the crude association between each adiposity measure (with 4 knots at 5%, 35%, 65%, and 95%) and the odds of pre-diabetes or diabetes. We used several models to adjust for various potential confounding factors, which were chosen based on both clinical and statistical significance. Model 1 included demographic factors such as age (years), gender, and ethnicity (Chinese, Malay, Indian, others). Model 2 additionally adjusted for medical history and lifestyle factors including SBP (quartiles), DBP (quartiles), family history of stroke (yes, no), family history of heart disease (yes, no), smoking status (never smokers, past or current smokers), physical activity levels (moderate activity <150 min/wk and vigorous activity <75 min/wk, moderate activity ≥150 min/wk or vigorous activity ≥75 min/wk), dietary habits (dining at hawker center, never dining at hawker center), and dietary quality (eating uncooked vegetables <4 times/mo and eating fruits <4 times/wk, eating uncooked vegetables ≥4 times/mo or eating fruits ≥4 times/wk). In model 3, we further adjusted for blood biomarkers such as TC, HDL-C, LDL-C, and TG (all in quartiles). Subsequently, we examined whether the association between pre-diabetes or diabetes risk and BMI was independent of WC or WHtR, and whether that of WC and WHtR was independent of BMI by further including the corresponding adiposity measures in the logistic regression models. To test the robustness of the results, in sensitivity analyses, we repeated the above-mentioned analyses among subgroup participants with worse lipid levels (TG ≥ 1.7 mmol/L and/or HDL-C < 1.04 mmol/L in men and < 1.30 mmol/L in women) and examined the association between adiposity measures and diabetes risk.

Subsequently, we evaluated the discrimination of the adiposity measures for pre-diabetes or diabetes. The discrimination among different adiposity measures was compared by C-statistics using DeLong's method.[32] Youden index from ROC analysis, where the sum of the associated sensitivity and specificity minus one reached the maximum value, was applied to explore the optimal threshold of each adiposity measure in men and women separately. In addition, we used continuous NRI to evaluate the incremental improvements in risk predictions of adding WC/WHtR on top of BMI,[33] which assesses the net percentage of patients with pre-diabetes or diabetes correctly assigned to a higher predicted risk, as well as persons without pre-diabetes or diabetes correctly assigned to a lower risk. Moreover, the model fitness was assessed by Akaike information criteria, where a lower value indicated better model fit.

Moreover, we evaluated the diabetes management among participants with diagnosed diabetes in this hypertensive population. Among people with diabetes, we calculated the percentage of uncontrolled blood pressure and blood glucose (HbA1c ≥ 7.0%), as well as medication adherence (anti-hypertension and anti-diabetes medications). We used Stata version 14.0 (Stata Corp) and SAS version 9.4 (SAS Institute, Inc) for the analyses, where we considered two-sided *P* value < 0.05 to be statistically significant.

3 | RESULTS

In the current study comprising 925 hypertensive participants, the mean age was 64.7 years and more than half of the subjects had pre-diabetes or diabetes (n = 495; 53.5%). Compared with their counterparts without pre-diabetes or diabetes, those with the condition were more likely to be Malays or Indians, less likely to do physical activity, more likely to be currently working and had higher levels of all adiposity measures (BMI, WC, and WHtR). In addition, participants with pre-diabetes or diabetes compared to those without had lower DBP and were less likely to have family history of stroke (Table 1). In addition, the distribution of baseline characteristics according to the sex-specific quartiles of adiposity measures is shown in Tables S1-S3.

BMI, WC, and WHtR were highly interrelated (correlation coefficients ranged from 0.74 to 0.89, $P < 0.001$), while their correlations with other variables such as lipids were much weaker (Table S4). Among the three adiposity measures, WC had the strongest correlation with SBP ($r = -0.09$; $P = 0.07$) and DBP ($r = 0.17$; $P < 0.001$). In the crude model, spline analysis suggested a linear association between all three adiposity measures and the odds of pre-diabetes or diabetes (all *P* for nonlinearity >0.05; Figure S2). The multivariable analyses are shown in Table 2. After adjusting for demographics, lifestyle, and dietary habits, participants in the highest vs lowest quartile of BMI were associated with a 2.3-fold increased odds of pre-diabetes or diabetes in model 3 (OR comparing 4th vs 1st quartile: 2.33; 95% CI: 1.40-3.88; *P*-trend = 0.007). However, the positive association attenuated to null after further adjustment for either

TABLE 1 Demographic, lifestyle, and clinical characteristics of participants with and without pre-diabetes or diabetes[a]

	With pre-diabetes or diabetes (n = 495)	Without pre-diabetes or diabetes (n = 430)	*P*-value[b]
Age (y)	64.7 (9.56)	64.6 (10.0)	0.85
Gender (Female, %)	229 (46.3)	226 (52.6)	0.06
Ethnicity (%)			
Chinese	338 (68.3)	348 (80.9)	<0.001
Malay	73 (14.8)	46 (10.7)	
Indian	68 (13.7)	19 (4.42)	
Others	16 (3.23)	17 (3.95)	
Height (cm)	161 (8.81)	160 (9.22)	0.11
Weight (kg)	70.7 (14.3)	66.1 (13.3)	<0.001
BMI (kg/m^2)			
Normal/underweight (<23)	83 (16.8)	126 (29.3)	<0.001
Overweight (23-<27.5)	219 (44.2)	172 (40.0)	
Obese (≥27.5)	193 (39.0)	132 (30.7)	
Waist circumference (cm)			
Desirable (Men < 90, women < 80)	100 (20.2)	161 (37.4)	<0.001
High (Men 90-<102, women 80-<88)	195 (39.4)	156 (36.3)	
Very high (Men ≥ 102, women ≥ 88)	200 (40.4)	113 (26.3)	
Waist-to-height ratio	0.58 (0.06)	0.55 (0.07)	<0.001
Education levels (%)			
No education	20 (4.72)	28 (5.74)	0.18
Primary school	89 (21.0)	116 (23.8)	
Secondary school	177 (41.8)	217 (44.5)	
Post-secondary education	138 (32.6)	127 (26.0)	
Employment status (yes, %)	226 (52.6)	225 (45.5)	0.031
Own house (yes, %)	423 (85.5)	362 (84.2)	0.59
Systolic blood pressure (mm Hg)	149 (13.5)	150 (12.5)	0.48
Diastolic blood pressure (mm Hg)	87.6 (9.49)	89.1 (10.0)	0.016
Self-reported heart disease (%)	53 (10.7)	41 (9.53)	0.56
Self-reported stroke (%)	21 (4.24)	14 (3.26)	0.43
Chronic kidney disease[c] (%)	75 (15.2)	51 (11.9)	0.15
Family history of heart disease (%)	86 (17.4)	56 (13.0)	0.07
Family history of stroke (%)	86 (17.4)	108 (25.1)	0.004
Taking any medications (%)	471 (95.2)	403 (93.7)	0.34
Cigarette smoking (%)			
Never smokers	118 (23.8)	81 (18.8)	0.06
Former or current smokers	377 (76.2)	349 (81.2)	
Physical activity			
No	336 (67.9)	259 (60.2)	0.015
Yes	159 (32.1)	171 (39.8)	
Dietary habits			
Dining at Hawker center	203 (41.0)	200 (46.6)	0.09
Never Dining at Hawker center	292 (59.0)	229 (53.4)	
Dietary quality[d]			
Poor	88 (17.8)	82 (19.1)	0.61
Good	407 (82.2)	348 (80.9)	

(Continues)

TABLE 1 (Continued)

	With pre-diabetes or diabetes (n = 495)	Without pre-diabetes or diabetes (n = 430)	*P*-value[b]
Total cholesterol, mmol/L	4.47 (0.92)	4.88 (0.86)	<0.001
LDL cholesterol, mmol/L	2.42 (0.81)	2.70 (0.76)	<0.001
HDL cholesterol, mmol/L	1.34 (0.38)	1.55 (0.45)	<0.001
Triglyceride, mmol/L	1.56 (0.84)	1.38 (0.64)	<0.001
Fasting plasma glucose, mmol/dL	6.85 (1.89)	5.03 (0.32)	<0.001

[a]Data are expressed as mean (SD) for continuous variables, and n (percentage) for categorical variables. Participants with pre-diabetes or diabetes met one of the three criteria: (a) self-reported physician-diagnosed or taking diabetes medications; (b) fasting plasma glucose levels ≥5.6 mmol/dL; and 3) hemoglobin A1c ≥ 5.7%.
[b]*P* values based on student *t* test for continuous variables, and chi-square test for categorical variables.
[c]Chronic kidney disease was defined as having either estimated glomerular filtration rate <60 mL/min/1.73 m^2 calculated using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation or albuminuria ≥30 mg/g.
[d]Poor dietary quality was defined as eating uncooked vegetables <4 times/mo and eating fruits <4 times/wk; good dietary quality was defined as eating uncooked vegetables ≥4 times/mo or eating fruits ≥4 times/wk.

WC (OR comparing 4th vs 1st quartile: 1.15; 95% CI: 0.42-3.18; *P*-trend = 0.93) or WHtR (OR comparing 4th vs 1st quartile: 1.18; 95% CI: 0.50-2.78; *P*-trend = 0.61). The variance inflation factor (VIF) was 2.71 for BMI and 2.69 for WC when including them in the same model, indicating that the collinearity is not likely to exist between BMI and WC. On the contrary, WC and WHtR remained a strong and dose-dependent association with the odds of pre-diabetes or diabetes independent of BMI. In the final model with adjustment of BMI, the respective OR comparing the extreme quartile of WC and WHtR was 2.71 (95% CI 1.13-6.50; *P*-trend = 0.001) and 2.45 (95% CI 1.29-4.64; *P*-trend = 0.003).

In sensitivity analyses, the association between each adiposity measure and the odds of diabetes remained similar to the main analyses (Tables S5 and S6). When comparing the highest vs lowest quartile in the fully adjusted model, BMI was not associated with the odds of diabetes, while higher WC (OR comparing 4th vs 1st quartile: 3.94; 95% CI: 1.91-8.12; *P*-trend = 0.001) and WHtR (OR comparing 4th vs 1st quartile: 3.02; 95% CI: 1.09-8.36; *P*-trend = 0.036) were strongly associated with higher odds of diabetes (Table S5). Likewise, among participants with worse lipid profile, BMI was not associated with the odds of pre-diabetes or diabetes, while WC and WHtR were positively associated with the odds of pre-diabetes or diabetes (Table S6). In addition, when stratifying participants with and without pre-diabetes and diabetes by lower and higher levels of BMI and WC (< vs ≥ respective median values), we found that among participants with pre-diabetes and diabetes, the number of those with both higher WC (≥median levels, 94 cm in men and 88 cm in women) and lower BMI (<median levels, 26.2 kg/m^2 in men and 26.0 kg/m^2 in women) levels was higher than the number of those with higher BMI but lower WC levels (n = 56 [11.3%] vs 36 [7.27%]). Among people without pre-diabetes or diabetes, the number of those with higher BMI and lower WC levels was slightly higher than the number of those with higher WC and lower BMI levels (n = 39 [9.07%] vs 36 [8.37%]; Table S7). The results further supported the finding from the multivariable logistic regression models that WC may be more closely related to pre-diabetes and diabetes than BMI.

In regard to predictive utility, continuous WC and WHtR had statistically better estimates of discrimination (AUC [95% CI]: 0.63 [0.60-0.67] for WC, 0.63 [0.59-0.66] for WHtR vs 0.60 [0.56-0.63] for BMI; *P* = 0.019) (Table 3). Adding dichotomized WC or WHtR (< vs ≥ optimal threshold identified by Youden Index) on top of BMI dichotomized by ADA recommendation (< vs ≥23 kg/m^2) or Youden Index (< vs ≥24.4 kg/m^2) resulted in significant gains in NRIs (42.7% [95% CI: 29.8%-55.7%] for WC, 38.7% [25.8%-51.6%] for WHtR; Table 3 and Table S8). Thus, WC and WHtR demonstrated superior clinical utility than BMI for the identification of people with pre-diabetes or diabetes in the current population. In addition, the observation that WC had similar AUC and slightly higher NRI than WHtR suggested that WHtR is not better than WC, and WC alone is a simple and useful clinical tool. The optimal threshold of WC was 91.5 cm in men and 83.0 cm in women for identifying the odds of pre-diabetes or diabetes, and the associated sensitivity was 69.6% and 82.5%, respectively (Table 3).

We evaluated the medication adherence in the study population with diabetes. Among 284 participants with diagnosed diabetes, 82.0% participants reported adherence to anti-diabetes medications, and 71.8% used oral medications only. However, 62.3% had poorly controlled blood glucose levels (HbA1c ≥ 7.0%; Table S9). In addition, 276 (98.6%) participants reported adherence to anti-hypertensive medications, with majority using 1 or 2 medications (42.3% and 35.9%, respectively), and 19.4% participants had poor control of blood pressure (systolic blood pressure ≥ 160 mm Hg or diastolic blood pressure ≥ 100 mm Hg; Table S9).

4 | DISCUSSION

In this Asian population with uncontrolled hypertension, we found that central obesity measures including WC and WHtR both had a strong and independent relation with pre-diabetes or diabetes after adjusting for BMI, while BMI lost its significance after adjustment for central obesity. In addition, both WC and WHtR had better

TABLE 2 Odds ratios (95% confidence intervals) for pre-diabetes or diabetes according to quartiles of adiposity measures[a]

	Quartiles of adiposity measures				*P* for trend[b]	Per 1 SD increment
	Q1	Q2	Q3	Q4		
BMI						
Median (range)	21.9 (14.6-23.2)	24.7 (23.3-26.0)	27.3 (26.1-29.1)	31.7 (29.2-42.0)		
Cases/controls	94/136	125/107	127/105	149/82		
Model 1[c]	1.00	1.75 (1.30-2.37)	1.77 (1.10-2.83)	2.78 (1.54-5.02)	0.002	1.46 (1.16-1.84)
Model 2[d]	1.00	1.81 (1.30-2.53)	1.85 (1.12-3.04)	2.87 (1.56-5.27)	0.001	1.45 (1.17-1.81)
Model 3[e]	1.00	1.65 (1.22-2.24)	1.60 (0.92-2.78)	2.33 (1.40-3.88)	0.007	1.35 (1.12-1.62)
Model 3[e] + WC	1.00	1.33 (0.83-2.11)	1.02 (0.42-2.45)	1.15 (0.42-3.18)	0.93	1.05 (0.80-1.40)
Model 3[e] + WHtR	1.00	1.33 (0.88-2.01)	1.02 (0.47-2.19)	1.18 (0.50-2.78)	0.61	1.07 (0.84-1.36)
WC						
Median (range)	79.0 (58.0-84.0)	87.5 (84.3-90.5)	95.0 (91.0-99.0)	104.0 (99.2-125.5)		
Cases/controls	89/145	118/108	138/101	150/76		
Model 1[c]	1.00	1.97 (1.21-3.22)	2.49 (1.71-3.63)	3.27 (2.20-4.84)	<0.001	1.64 (1.35-1.99)
Model 2[d]	1.00	2.12 (1.29-3.48)	2.73 (1.88-3.95)	3.40 (2.37-4.88)	<0.001	1.67 (1.38-2.03)
Model 3[e]	1.00	1.98 (1.25-3.14)	2.44 (1.74-3.42)	2.81 (1.88-4.22)	<0.001	1.56 (1.30-1.86)
Model 3[e] + BMI	1.00	1.86 (1.07-3.58)	2.38 (1.25-4.52)	2.71 (1.13-6.50)	0.001	1.60 (1.20-2.13)
WHtR						
Median (range)	0.50 (0.38-0.52)	0.55 (0.53-0.57)	0.59 (0.57-0.61)	0.65 (0.61-0.78)		
Cases/controls	89/141	119/114	127/103	160/72		
Model 1[c]	1.00	1.65 (1.22-2.23)	1.96 (1.51-2.54)	3.17 (2.13-4.72)	<0.001	1.56 (1.31-1.87)
Model 2[d]	1.00	1.72 (1.31-2.26)	2.11 (1.64-2.70)	3.27 (2.25-4.74)	<0.001	1.59 (1.33-1.89)
Model 3[e]	1.00	1.55 (1.20-1.98)	1.91 (1.51-2.41)	2.58 (1.87-3.57)	<0.001	1.48 (1.26-1.74)
Model 3[e] + BMI	1.00	1.52 (1.03-2.25)	1.84 (1.32-2.57)	2.45 (1.29-4.64)	0.003	1.52 (1.22-1.90)

Abbreviations: BMI, body mass index; SD, standard deviation; WC, waist circumference; WHtR, waist-to-height ratio.

[a]Logistic regression analysis was used to compute the odds ratios of adiposity measures treating baseline clinics as the clustering factor. Participants with pre-diabetes or diabetes met one of the three criteria: (a) self-reported physician-diagnosed or taking diabetes medications; (b) fasting plasma glucose levels ≥5.6 mmol/dL; and (c) hemoglobin A1c ≥ 5.7%.

[b]Linear trend was tested by using the median level of each quartile of adiposity measure.

[c]Model 1: adjusted for age (y), gender, and ethnicity (Chinese, Malay, Indian, mixed, others).

[d]Model 2: Model 1 plus adjusted for diastolic blood pressure (quartiles), family history of stroke (yes, no), family history of heart disease (yes, no), employment status (yes, no), smoking status (never smokers, past or current smokers), physical activity (no, yes), dietary habits (dining at hawker center, never dining at hawker center) and dietary quality (eating uncooked vegetables < 4 times/mo and eating fruits < 4 times/wk, eating uncooked vegetables ≥ 4 times/mo or eating fruits ≥ 4 times/wk).

[e]Model 3: Model 2 plus adjusted for total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides (all in quartiles).

discrimination than BMI, and adding WC or WHtR on top of BMI further reclassified 42.7% and 38.7% hypertensive patients to the right risk group of pre-diabetes or diabetes. However, WHtR is not superior to WC, suggesting that WC alone is the best pre-screening tool for pre-diabetes or diabetes in this population. Our results implied that measuring WC in addition to BMI in clinics could provide incremental benefits in the identification of Asian hypertensive patients with pre-diabetes or diabetes.

In 2018, the American Diabetes Association (ADA) suggested to screen hypertensive patients with BMI ≥23 kg/m^2 among Asian Americans. However, our results implied that WC could be a better tool than the BMI-based screening in the current Asian population with hypertension. Consistent with our findings, the largest prospective study in China (Kadoorie Biobank) among ~0.5 million participants also showed a stronger association with WC compared to BMI.[16] The differences of AUCs for WC (0.63) and WHtR (0.63) compared to BMI (0.60) were small in the current study. Similarly, prior studies among general populations with outcome of pre-diabetes or diabetes also showed small improvements in AUC values for WC/WHtR compared to BMI.[17-25] The small difference may be due to the limitation of AUC of being insensitive to model improvement, which has shown only a small increment when adding an important risk factor to the model.[34] Thus, we further applied NRI as a complementary method and found that on top of BMI, WC and WHtR additionally reclassified 42.7% and 38.7% individuals to the correct risk category of pre-diabetes or diabetes, thus demonstrating superior clinical efficiency of WC and WHtR over BMI.

TABLE 3 Summary statistics to assess adiposity measures in discrimination of pre-diabetes or diabetes (n = 925)

Variable	Thresholds	Sensitivity	Specificity	Discrimination (AUC [95% CI])[a]	Calibration (AIC)	NRI (95% CI)[b] over BMI 23 kg/m^2	NRI (95% CI)[b] over BMI 24.4 kg/m^2
Body mass index (kg/m^2)							
Men	23.0[c]	82.7%	27.5%	0.60 (0.56-0.63)	1257		
Women	23.0[c]	83.8%	31.0%				
Men	24.4[d]	72.2%	46.1%				
Women	24.4[d]	74.7%	43.4%				
Waist circumference (cm)							
Men	91.5[d]	69.6%	54.4%	0.63 (0.60-0.67)[e]	1230	42.7% (29.8%-55.7%)	42.7% (29.8%-55.7%)
Women	83.0[d]	82.5%	38.1%				
Waist-to-height ratio							
Men	0.54[d]	75.2%	47.6%	0.63 (0.59-0.66)[e]	1236	38.7% (25.8%-51.6%)	38.7% (25.8%-51.6%)
Women	0.55[d]	73.4%	45.6%				

Abbreviations: AIC, Akaike information criteria; AUC, area under receiver operating characteristics curve; CI, confidence interval; NRI, net reclassification improvement.

[a]AUC was calculated using the continuous variables of body mass index, waist circumference, and waist-to-height ratio.

[b]NRI was assessed by adding the binary variables of waist circumference and waist-to-height ratio (< vs ≥ respective threshold) on top of binary body mass index (< vs ≥23 kg/m^2 or < vs ≥24.4 kg/m^2).

[c]Equal to or above the threshold was defined as overweight for Asian Americans by American Diabetes Association.

[d]The optimal thresholds were identified based on the Youden Index, where sensitivity + specificity-1 reached maximum.

[e]The higher AUCs of waist circumference and waist-to-height ratio compared to body mass index were statistically significant (P = 0.019).

The optimal threshold of WC identified in the current hypertensive population (91.5 cm for men and 83.0 cm for women) was higher than that identified in other Asian studies among general populations (85-86.1 cm for men and 77.5-80 cm for women),[17,18] and this observation was consistent with the finding that central obesity is correlated with blood pressure elevation.[35] In addition, the optimal WC threshold in the current population was substantially lower than that identified in a US study comprising of Caucasians and African Americans (99.1-99.4 cm in men and 91.9-96.8 cm in women)[36] and may suggest the ethnic difference in propensity to cardiometabolic risk for the same level of central obesity. Similarly, a recent prospective study among 136 112 postmenopausal women in the United States has reported that the superiority of WC for diabetes prediction compared to other anthropometric measures was only observed in Asian women but not in African American women.[37] Although the underlying mechanism behind the observed ethnic difference is not clear, previous studies observed ethnic variation in mediators of cardiometabolic risk including adipokines[38] or glucose levels,[39] which may account for the potential ethnic heterogeneity. Furthermore, the sensitivity associated with the optimal threshold of WC (69.6% for men and 82.5% for women) was comparable to those reported in the previous studies (50.2%-77.0% for men and 60.0%-77.1% for women),[17,18,36] thus further indicated the usefulness of WC in the current population.

The underlying mechanism behind the relationship between central obesity and impaired glucose levels may be via the role of abdominal fat as a marker of increased ectopic fat, which is the driver of metabolic complications and the predictor of future development of diabetes.[40] The accumulation of fat storage begins at subcutaneous sites; after subcutaneous fat reaches its maximum size, extra triglycerides will spill over to visceral or ectopic (non-adipose tissue sites such as the liver or pancreas) sites for storage.[41-43] Increased visceral/abdominal fat is considered as a marker of increased ectopic fat,[44] and the large prospective studies found that ectopic fat, rather than subcutaneous fat, is key to metabolic abnormality and subsequent development of diabetes.[40,45] Further studies are needed to elucidate these mechanisms behind central obesity and pre-diabetes or diabetes.

Our study had some important clinical implications. First, WC is not routinely assessed in the polyclinics in Singapore, or most clinics in Asia. A simple measurement of WC can be readily carried out with a tape in both the clinic and community settings, and nurses can be trained in standardized measurements of WC as we have demonstrated. Hence, WC could be used as a pre-screening tool to alert health care providers about patients at high risk of pre-diabetes or diabetes. It is likely to offer incremental value to BMI measurements in terms of identifying Asian hypertensive patients with pre-diabetes or diabetes. In fact, from a health system perspective, using a pre-screening tool is likely to decrease the number of people required for blood tests and could offer practical solutions for remote settings and populations. Second, since hypertensive patients with pre-diabetes or diabetes are at high risk of developing cardiovascular disease,[5] such a pre-screening tool among hypertensive patients is very important for clinicians to choose the appropriate therapies and intervention programs to prevent the cardiovascular outcomes. Although the causal relationship cannot be determined

in the cross-sectional study, landmark clinical trials have shown that central obesity is a modifiable risk factor for diabetes.[6-12] Of note, Diabetes Prevention Program has shown that weight loss is so far the most important contributor to diabetes prevention.[6,7] In addition, we found that 62.3% of hypertensive patients with diabetes had poor control of blood glucose levels (HbA1c ≥ 7.0%). These findings underscore that future intervention programs need to evaluate drug adherence and lifestyle modifications with focus on decreasing WC in these patients at high risk of vascular complications. Thus, our findings have significant clinical and public health implications for using WC in hypertensive adults as the pre-screening tool for pre-diabetes and diabetes, and as a risk stratification tool for CVD in community outreach settings in Singapore and probably other Asian countries. In addition, we have found that WC had the strongest correlation with SBP and DBP among the three adiposity measures, which indicates the potential role of WC to identify the presence of uncontrolled hypertension as well. Consistently, a prior study in Brazil also found that hypertension was only associated with abdominal adiposity but not with BMI.[46] However, since the evidence regarding this topic is scarce, future studies are warranted to examine this issue.

However, some limitations merit consideration. First, the AUC values of all adiposity measures were smaller than 0.7 in the present study, thus indicating modest discrimination performance. Second, the current study did not have information on all anthropometric measures (eg, hip circumference) and thus cannot compare with other adiposity measures (eg, waist-to-hip ratio); however, previous studies have shown that WC was more closely related to the level of abdominal visceral adipose tissue than the waist-to-hip ratio,[47] and waist-to-hip ratio had smaller or at best similar discrimination compared to WC for the identification of people with pre-diabetes or diabetes.[17,19-22,36] In addition, the majority of the participants in the current study were Chinese (n = 686; 74.2%), and a small percentage were Malay (n = 119; 12.9%) and Indian (n = 87; 9.4%). Due to the small numbers for Malay and Indian, we lack power to perform stratified analysis to explore the performance of the adiposity measures among Malays and Indians. Therefore, further studies with larger sample size are warranted to validate our results and explore the optimal threshold in other ethnic groups.

5 | CONCLUSIONS

In conclusion, our results based on multi-ethnic population in primary care clinics in Asia show that compared to generalized obesity measured by BMI, central obesity measured by WC had stronger association with and better discrimination for pre-diabetes and diabetes. Our findings suggest that WC could be measured in addition to BMI to provide incremental benefit in the identification of Asian hypertensive patients with pre-diabetes or diabetes. Future studies are warranted to evaluate the clinical and cost effectiveness of WC that integrates in the primary care setting in Singapore and other Asian countries.

ACKNOWLEDGMENTS

The authors would like to thank Ms. Patricia T. Kin and Ms. Caris Yang Thong Tan from the Department of Research in SingHealth Polyclinics. The authors would also like to thank all site principal investigators (Dr. Paul Goh, Dr. Peter Moey, Dr. Joanne Hui Min Quah, Dr. Siew Wai Hwang, Dr. Juliana Bahadin, Dr. Anandan Gerard Thiagarajah, Dr. Jason Chan, Dr. Gary Kang, and Dr. Agnes Koong), participants, and all administrative and support staff involved with the study at recruiting polyclinics.

CONFLICT OF INTEREST

None.

AUTHORS' CONTRIBUTIONS

THJ conceived the study idea, designed the study and directed the overall conduct of the study; NCT contributed to protocol implementation and data acquisition; CR contributed to project management; RMS assisted data management; YW and RMS conducted the final analysis. YW wrote the first and final drafts. All authors provided critical comments, and approved the final version.

DATA ACCESSIBILITY

Data are available on reasonable request from THJ subject to approval by SingHypertension IRB.

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Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Wang Y, Shirore RM, Ramakrishnan C, Tan NC, Jafar TH. Adiposity measures and pre-diabetes or diabetes in adults with hypertension in Singapore polyclinics. *J Clin Hypertens*. 2019;21:953–962. https://doi.org/10.1111/jch.13587