Fasting triglycerides and glucose index is more suitable for the identification of metabolically unhealthy individuals in the Chinese adult population: A nationwide study

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Keywords

Insulin resistance, Metabolically unhealthy, Triglycerides and glucose index

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ABSTRACT

Aims/Introduction: Metabolic unhealth can be defined by the components of metabolic syndrome, which is closely connected to insulin resistance. We aimed to determine a simple index to identify metabolic unhealth in the Chinese adult population.

Materials and Methods: A total of 30,291 individuals were screened from the China National Diabetes and Metabolic Disorders Study carried out from June 2007 to May 2008. Metabolic unhealth was defined using components of metabolic syndrome, except waist circumference. We compared the three surrogate indices of insulin resistance: the product of fasting triglycerides and glucose (TyG), triglycerides divided by high-density lipoprotein cholesterol and the metabolic score for insulin resistance for the evaluation of metabolic status.

Results: All indices had high sensitivity and specificity for the identification of metabolic unhealth, especially the TyG index with an area under the curve of 0.863 for men and 0.867 for women. Participants were divided into subgroups for further analysis. The TyG index also showed high diagnostic values, especially for younger individuals and men with normal waist circumference. Sex-specific cut-offs for three indices were also used to define metabolic unhealth. The TyG index showed the highest agreement with κ values of 0.603 and 0.605 for men and women between the components of metabolic syndrome and three indices.

Conclusions: We propose that the TyG index, just read in one blood laboratory test report, is simpler and more suitable for the identification of metabolically unhealthy individuals as well as who have high risk of cardiometabolic diseases of the Chinese adult population.

INTRODUCTION

Obesity is a strong risk factor for a series of cardiometabolic diseases worldwide, such as diabetes, hypertension and metabolic syndrome (MetS).¹ Body mass index (BMI) is the most widely used indicator of obesity, although it might not accurately evaluate the degree of fat accumulation.² Interestingly, not all obese individuals show the aggregation of metabolic and cardiovascular risk factors. In addition, not all lean individuals present with a healthy metabolic and disease-free phenotype.³ Therefore, two subgroups of obesity have received increasing interest in recent years: metabolically unhealthy normal weight individuals and metabolically healthy obese individuals. The former present with insulin resistance (IR) and/or hyperinsulinemia, hypertriglyceridemia or hypertension, and have a high risk of cardiovascular disease and type 2 diabetes mellitus.^{4–9} The latter group shows high insulin sensitivity, a lower level of fat accumulation associated with metabolic abnormalities, and a low prevalence of hypertension, hyperlipidemia and hyperglycemia.^{3,10–12} However,

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© 2018 The Authors. Journal of Diabetes Investigation published by Asian Association for the Study of Diabetes (AASD) and John Wiley & Sons Australia, Ltd This is an open access article under the terms of the Greative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes. there is a lack of a consensus on the definition of metabolic unhealth. The components of MetS are used to define metabolic abnormalities in most studies,^{13–17} and it is reported that metabolically healthy and metabolically unhealthy phenotypes can be present in any individual independent of BMI.¹⁸ MetS appears to be caused by a complex array of cross-connected mechanisms, and IR seems to play an important role.^{19,20} Direct estimation of individual IR demands diagnostic tests that have considerably high costs and low availability for epidemiological use.²¹ Therefore, it is necessary to determine a simple diagnostic criterion to identify individuals in the early stages of metabolic abnormality and with a high risk of cardiometabolic diseases to intervene as early as possible. Because of this connection, we hypothesize that metabolic abnormalities can be assessed based on the degree of IR.

The homeostasis model assessment for insulin resistance (HOMA-IR) index is the most widely used to evaluate the degree of IR.²² Because insulin testing is expensive, the product of fasting triglycerides (TG) and glucose (TyG) has been utilized as an alternative for estimating IR.²³ Furthermore, the plasma concentration ratio of TG/HDL, TG divided by high-density lipoprotein cholesterol (HDL-C), has been suggested as a useful surrogate index of insulin action.^{24,25} In addition, the metabolic score for IR (METS-IR) has been reported as a novel index for the evaluation of cardiometabolic risk in healthy and at-risk individuals, and as a promising tool for screening insulin sensitivity.²⁶

Previous studies have shown that only HOMA-IR and TyG are involved in identifying metabolically unhealthy individuals. Wildman et al. used the modified criteria of MetS to replace waist circumference (WC) combined with IR status defined by HOMA-IR to identify metabolically healthy or unhealthy individuals,17,27 and this definition is now used widely.16,18 Furthermore, Korean studies²⁸⁻³⁰ have shown that the TyG index is a useful marker for the identification of individuals with metabolic disorders. However, the value of the degree of IR as an index of metabolic abnormalities in the Chinese population remains to be established. Therefore, in the current study, we aim to compare the three common surrogate indices of IR (TyG, TG/HDL and METS-IR) for the evaluation of metabolic status in the Chinese adult population. Based on our analyses, we propose a simpler and more suitable index for the identification of metabolically unhealthy individuals in the Chinese adult population.

METHODS

Participants

Data were obtained from the China National Diabetes and Metabolic Disorders Study, a nationwide population-based cross-sectional survey carried out from June 2007 to May 2008. Participants were residents aged >20 years using a multistage stratified sampling method. The final response rate was 87.3%, with a total of 46,239 participants from 17 study group field centers completed the survey. The details of the study have been described elsewhere.31-36 Complete data were not available for all participants. For that reason, we screened participants by BMI, WC, fasting plasma glucose, fasting plasma insulin, systolic blood pressure, diastolic blood pressure, serum TG, serum HDL-C and serum low-density lipoprotein cholesterol. A total of 37,122 individuals (14,579 men and 22,543 women) were screened further. Individuals might present with normal blood glucose, serum lipid and blood pressure levels after treatment for hyperglycemia, hypertension or hyperlipidemia; and a census-linked cohort study with up to 32 years of follow up showed that the increased mortality risk for underweight people is mainly as a result of an increased mortality risk from external causes - not cancer, or cardiovascular or respiratory diseases.37 Therefore, a total of 6,831 individuals were excluded because they were taking medication to treat hyperglycemia, hypertension or hyperlipidemia, and a BMI <18.5. However, individuals with known hyperglycemia (hypertension, hyperlipidemia), but not taking medication were included in the present study, because they were newly diagnosed patients, and the indices of the study were suitable for these people. After all exclusion criteria were applied, a total of 30,291 individuals (11,984 men and 18,307 women) were enrolled in the study. The China National Diabetes and Metabolic Disorders Study was approved by the institutional review boards of 17 participant centers. Written informed consent was obtained from each participant before data collection. Institutional review board approvals covered every participant in the study.

Data Collection

Standardized questionnaires were used to collect demographic characteristics, personal medical history, family history of diseases and lifestyle risk factors. Cigarette smoking was defined as having smoked >100 cigarettes during the participant's lifetime. If an ex-smoker had smoked >100 cigarettes, he/she was classified as a smoker. Alcohol drinking was defined as the consumption of at least 30 g of alcohol per week for \geq 1 year. Physical activity was defined as participation in moderate or vigorous activity for a period of \geq 30 min at least 3 days per week. Socioeconomic status, educational level, occupation and income were also recorded.

For the collection of anthropometric data, participants were required to remove shoes and socks, and wear light clothing for the measurement of bodyweight, height (BMI = bodyweight [kg] / body height $[m]^2$) and body fat content (measured by bioelectric impedance analysis; Tanita, Tokyo, Japan). WC was measured at the mid-point between the costal margin and the iliac crest. Blood pressure was measured using a standardized mercury sphygmomanometer in the sitting position after at least 5 min of rest. Two consecutive readings of blood pressure were taken on the same arm and the mean of the two measures was used for analysis.

After at least 8 h of overnight fasting, participants without a history of diabetes were subjected to a 75-g oral glucose tolerance test, whereas those with a history of diabetes were subjected to the steamed bread meal test for safety reasons that contained approximately 80 g of complex carbohydrates. Plasma glucose, TG, HDL-C, low-density lipoprotein cholesterol, total cholesterol and uric acid were analyzed enzymatically using an automated biochemical analyzer (MOD-ULAR-000GS; Roche, Basel, Switzerland). All laboratory measurements complied with the requirements of a standardization and certification program.³⁴

Definitions

All participants were divided into three groups using BMI for Chinese men and women as the criteria³⁸: normal weight (BMI 18.5–23.9 kg/m²), overweight (BMI 24.0–27.9 kg/m²) and obese (BMI \geq 28.0 kg/m²). According to the Chinese criterion of central obesity, we defined increased WC as >90 cm in men and >85 cm in women.

Participants were diagnosed with MetS based on the presence of more than three of the following criteria defined by the harmonized International Diabetes Federation²⁷: (i) hyperglycemia (fasting blood glucose levels \geq 100 mg/dL [5.60 mmol/L] or drugs for diabetes); (ii) hypertension (systolic blood pressure \geq 130 mmHg and/or diastolic blood pressure \geq 85 mmHg and/or treatment to reduce blood pressure); (iii) hypertriglyceridemia (fasting plasma triglyceride levels \geq 1.69 mmol/L [150 mg/dL] or treatment); (iv) HDL-C <40 mg/dL (1.04 mmol/L) for men and 50 mg/dL (1.30 mmol/L) for women; and (v) central obesity (or visceral obesity, WC >85 cm in men and >80 cm in women).

Participants were classified according to metabolic status based on the four metabolic parameters,^{13,15,39} also used in other studies: elevated blood pressure, impaired fasting glucose or diabetes, low HDL-C concentration and hypertriglyceridemia. The metabolically healthy state was defined as the presence of none or one of the metabolic factors, whereas the metabolically unhealthy state was defined as the presence of two or more metabolic factors.

The TyG was calculated as Ln [fasting triglycerides (mg/ dL) × fasting glucose (mg/dL) / 2].^{23,40} The TG/HDL was defined as TG divided by HDL-C.²⁴ The METS-IR was defined as Ln [$(2 \times fasting glucose) + TG$] × BMI) / (Ln[HDL-C]).²⁶

Statistical Analysis

All data were analyzed using SPSS 20.0 (SPSS Inc., Chicago, IL, USA). Quantitative data were expressed as the mean \pm standard deviation. Two-sample comparisons were carried out using *t*-tests for normally distributed measurement data, whereas non-normal distributed continuous variables were compared using the Mann–Whitney *U*-test. Categorical variables were expressed as the number of total cases (*n*) and percentages (%), and compared using the χ^2 -test. Receiver operating characteristic (ROC) curves were used to analyze the diagnostic value of IR surrogate indices for metabolically healthy or unhealthy status, and to determine the optimal cut-offs. The diagnostic value of all indices was compared by the *Z*-test. The highest Youden's Index

was used to determine the optimal diagnostic cut-off. All analysis of ROC curves was carried out using MedCalc Statistical Software version 15.8 (MedCalc Software bvba, Ostend, Belgium). Diagnostic concordance between the components of MetS (except WC) and the TyG index was estimated using κ values. P < 0.05 was considered to show statistical significance.

RESULTS

In total, 30,291 participants (11,984 men and 18,307 women) were enrolled in the present study, with a mean age of 43.26 ± 13.66 years (range 20–99 years). The demographic and clinical characteristics of the study participants are shown in Table 1.

The ROC curve analyses confirmed the value of TyG, METS-IR and TG/HDL in identifying metabolic unhealth. As shown in Figure 1 and Table 2, all of the indices had high sensitivity and specificity for the identification of metabolic unhealth, with an area under the curve (AUC) for TyG (men 0.863, 95% confidence interval [CI] 0.857–0.869; women 0.867, 95% CI 0.862–0.872), METS-IR (men 0.810, 95% CI 0.803–0.817; women 0.805, 95% CI 0.799–0.810) and TG/HDL (men 0.841, 95% CI 0.834–0.848; women 0.857, 95% CI 0.852–0.862). The TyG index had the best diagnostic value of those indices for metabolically unhealthy individuals.

Based on our preliminary findings, we selected the TyG index for further analysis. Participants were separated into two or three subgroups according to BMI (normal weight, overweight and obesity) and WC (normal and increased). The AUCs (95% CIs) showed no significant difference in BMI subgroups both men and women in any of the groups (Figure 2 and Figure 3). The same results have been observed in WC subgroups of women. For men, however, the AUCs of individuals with normal WC (0.857, 95% CI 0.849-0.864) were higher than those with increased WC (0.839, 95% CI 0.826-0.851; Figure 2). Furthermore, participants were divided into five age groups (participants aged 20-30, 31-40, 41-50, 51-60 and >60 years). We found that the AUCs (95% CIs) of age groups 20-30 years and 31-40 years outperformed other age groups for both men and women (Figures 2,3). Furthermore, the cutoffs of TyG index for all groups varied from 8.72 to 8.84.

Therefore, the sex-specific thresholds for the TyG index (men 8.81, women 8.73), METS-IR (men 37.67, women 34.99) and TG/HDL (men 1.32, women 1.09; Table 2) were used to classify participants as metabolically healthy or metabolically unhealthy. Kappa statistics for the agreement of metabolically unhealthy individuals between the components of MetS (except WC) and all indices are shown in Table 3. The κ values of men and women were 0.603 and 0.605 with the highest agreement among three indices.

DISCUSSION

The present study was a nationwide survey carried out in China with a large sample size to ensure that the results are representative of this population. In this cross-sectional study, we directly

Variable	Overall ($n = 30291$)	Men ($n = 11984$)	Women ($n = 18307$)	P-value	
Age (years)	43.26 ± 13.66	43.39 ± 12.44	43.34 ± 12.94	0.399	
Age 1, n (%)	5460 (18.0)	2451 (20.5)	3009 (16.4)		
Age 2, n (%)	7889 (26.0)	2934 (24.5)	4955 (27.1)		
Age 3, n (%)	8159 (26.9)	2996 (25.0)	5163 (28.2)		
Age 4, n (%)	5581 (18.4)	2149 (17.9)	3432 (18.7)		
Age 5, n (%)	3202 (10.6)	1454 (12.1)	1748 (9.5)		
WC, cm	85.28 ± 10.2	79.15 ± 9.58	81.58 ± 10.28	< 0.0001	
Increased WC, n (%)	7938 (26.2)	3483 (29.1)	4455 (24.3)	< 0.0001	
Body mass index, kg/m²	24.48 ± 3.45	23.87 ± 3.35	24.11 ± 3.4	< 0.0001	
Normal weight, n (%)	15937 (52.6)	5657 (47.2)	10280 (56.2)		
Overweight, n (%)	10243 (33.8)	4422 (36.9)	5821 (31.8)		
Obese, n (%)	4111 (13.6)	1905 (15.9)	2206 (12.1)		
FPG, mmol/L	5.28 ± 1.2	5.19 ± 1.08	5.23 ± 1.13	< 0.0001	
2-h PG, mmol/L	6.5 ± 2.8	6.54 ± 2.53	6.52 ± 2.64	0.293	
Fasting plasma insulin (µIU/L)	8.53 ± 6.35	8.34 ± 5.94	8.41 ± 6.11	0.009	
Cholesterol (mmol/L)	4.69 ± 0.96	4.66 ± 0.98	4.67 ± 0.97	0.011	
Triglyceride (mmol/L)	1.7 ± 1.24	1.37 ± 0.92	1.5 ± 1.07	< 0.0001	
HDL-C (mmol/L)	1.27 ± 0.33	1.37 ± 0.33	1.33 ± 0.34	< 0.0001	
LDL-C (mmol/L)	2.76 ± 0.83	2.71 ± 0.83	2.73 ± 0.83	< 0.0001	
Systolic blood pressure (mmHg)	123.08 ± 17.06	117.71 ± 17.39	119.84 ± 17.45	< 0.0001	
Diastolic blood pressure (mmHg)	79.73 ± 10.86	75.79 ± 10.18	77.35 ± 10.63	< 0.0001	
TyG	8.68 ± 0.63	8.48 ± 0.58	8.56 ± 0.61	< 0.0001	
METS-IR	36.96 ± 7.08	34.73 ± 6.31	35.61 ± 6.71	< 0.0001	
TG/HDL	1.5 ± 1.41	1.11 ± 0.96	1.26 ± 1.18	< 0.0001	
Alcohol drinking, <i>n</i> (%)	6158 (20.3)	5337 (44.5)	821 (4.5)	< 0.0001	
Cigarette smoking, n (%)	6276 (20.7)	5750 (48.0)	526 (2.9)	< 0.0001	
Physical activity, n (%)	10042 (33.2)	4021 (33.6)	6021 (32.9)	0.235	
Metabolically unhealthy, n (%)	10148 (33.5)	4435 (37.0)	5713 (11.5)	< 0.0001	
Elevated blood pressure, n (%)	8344 (27.5)	4100 (34.2)	4244 (23.2)	< 0.0001	
Impaired fasting glucose , n (%)	7520 (24.8)	3280 (27.4)	4240 (23.2)	< 0.0001	
Low HDL-C, n (%)	10814 (35.7)	2999 (25.0)	7815 (42.7)	< 0.0001	
Hypertriglyceridemia, n (%)	8496 (28.0)	4309 (36.0)	4187 (22.9)	< 0.0001	

Data are expressed as mean \pm standard deviation, median (interquartile range) or *n* (%). Student's *t*-test for continuous variables, Mann–Whitney *U*-test for abnormally distributed data, and χ^2 -test for categorical variables. Age 1, 2, 3, 4 and 5: participants aged 20–30, 31–40, 41–50, 51–60 and >60 years. 2-h PG, 2-h postprandial plasma glucose; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; WC, waist circumference.

compared three surrogate indices of IR (TyG, TG/HDL and METS-IR) on their diagnostic accuracy of metabolically unhealthy individuals. Overall, we found that the TyG index outperformed other indices with the highest sensitivity and specificity and the largest AUCs (95% CIs) for the identification of metabolic unhealth. In a subgroup analysis, the TyG index also showed high AUCs and diagnostic values, especially for younger individuals and men with normal WC. Therefore, the clinical application of the TyG index is suitable for all people.

Currently, there is still no universal consensus on the definition of metabolic status. The components of MetS are used to define metabolic disorders in many studies or are combined with HOMA-IR and C-reactive protein.^{13–17} Multiple versions of diagnostic criteria for MetS have been proposed during its evolution, such as the criteria from the American Heart Association/National Heart, Lung and Blood Institute (revised Adult Treatment Panel III),⁴¹ International Diabetes Federation⁴² and Joint Interim Statement of the International Diabetes Federation Task Force on Epidemiology and Prevention.²⁷ The Adult Treatment Panel III and International Diabetes Federation criteria have the same cut-offs of WC (90 cm for Chinese men and 80 cm for Chinese women) for central obesity, but the Joint Interim Statement of the International Diabetes Federation Task Force on Epidemiology and Prevention criterion meets Chinese cut-offs for central obesity with WC >85 cm for men and >80 cm for women. All criteria, however, have the same values and conditions for other components of MetS. Furthermore, the components of MetS (except WC) are widely utilized in clinical settings.^{13,15,39} To ensure that the present findings were applicable to more populations, participants were classified according to metabolic status based on the four widely utilized metabolic parameters.

In addition, IR is a hallmark of obesity, diabetes and cardiovascular diseases, and leads to many of the abnormalities associated with MetS.^{19,20} Because testing for insulin sensitivity is expensive, the use of surrogate markers to assess insulin resistance might help to maximize medical resources, while minimizing costs and inconvenient side-effects for both clinical practice and epidemiological purposes. Thus, one of the notable advantages of the current study is that we compared the

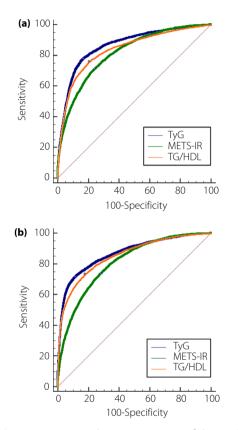


Figure 1 | Receiver operating characteristic curves of the product of fasting triglycerides and glucose (TyG), the metabolic score for insulin resistance (METS-IR) and the triglycerides divided by high-density lipoprotein cholesterol (TG/HDL) index for predicting metabolic unhealth of (a) men and (b) women. [Colour figure can be viewed at wileyonlinelibrary.com]

diagnostic capacity of the IR surrogates, TyG, TG/HDL and METS-IR, for identifying metabolically unhealthy individuals. The elements of all indices are significant components or highly correlated with the definition of metabolic unhealth in the present study. Although the TyG index is determined on the basis of just two parameters of easily obtained routine clinical laboratory data, it had the highest value for the identification of metabolically unhealthy individuals. Interestingly, although MetS-IR is determined on the basis of four parameters connected closely with metabolic disorders for Mexican individuals, the value of this index for the identification of metabolic unhealth was unremarkable, possibly because of racial and population differences, such as BMI and WC. Furthermore, in Figure 1, the curve of the TyG index was similar to the TG/HDL, except for the area nearing the cut-off. In Table 2, however, the AUCs (95% CIs) of the TyG index was significantly larger than the TG/HDL (P < 0.0001).

The TyG index was first reported as a surrogate of HOMA-IR for identifying IR in apparently healthy individuals in 2008.²³ Subsequently, Fernando *et al.* compared the TyG index with the euglycemic-hyperinsulinemic clamp test, and suggested that TyG could be useful for the identification of individuals with decreased insulin sensitivity in 2010.⁴⁰ A series of cohort and cross-sectional studies confirmed a strong correlation between the TyG index and IR,⁴³ type 2 diabetes mellitus,^{30,44–46} MetS,⁴⁷ hypertension,⁴⁸ cardiovascular events⁴⁹ and fatty liver^{50–52} both in China and elsewhere. Published studies have shown that the TyG index is helpful for the prediction and early identification of individuals at high risk of cardiometabolic diseases.

A Korean study by Lee *et al.*²⁹ published in 2014 was the first to show that the TyG index is a useful marker for the identification of individuals with distinct metabolic characteristics within similar BMI ranges. In that study, "metabolic obesity" was defined as those individuals falling into the highest HOMA-IR quartile, and they selected non-diabetic participants for further analysis. Another study²⁸ also showed that TyG is a simple diagnostic criterion for the identification of individuals with a higher risk of metabolic diseases in non-diabetic and normal weight individuals. That study used ROC analysis to determine the cut-off value of the TyG index (8.82 for men and 8.73 for women) for the identification of metabolically

Table 2 | Comparison of receiver operating characteristic curves for predicting metabolic unhealth of men and women

	Men					Women						
	Cutoff	Sensitivity	Specificity	AUC 95% CI		P-value	Cutoff	Sensitivity	Specificity	AUC	95% CI	P-value
TyG MFTS-IR	8.81 37.67	77.47 70.76	83.55 76.00	0.863 0.810	0.857–0.869 0.803–0.817	<0.0001	8.73 34.99	71.49 73.39	88.57 72.08	0.867 0.805	0.862–0.872 0.799–0.810	< 0.0001
TG/HDL	1.32	75.63	79.84	0.841	0.834-0.848	< 0.0001	1.09	73.22	82.44	0.857	0.852-0.862	< 0.0001

P-value, in comparison with the reference index (the product of fasting triglycerides and glucose [TyG]). AUC, the area under the curve values; METS-IR, the metabolic score for insulin resistance index; TG/HDL, the triglycerides divided by high-density lipoprotein cholesterol index.

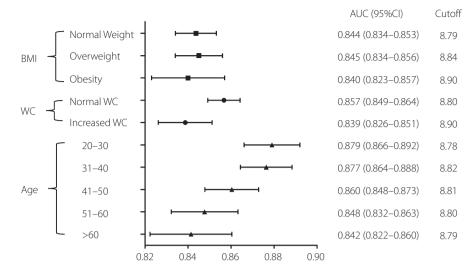


Figure 2 | Comparison of area under the curve (AUC) of receiver operating characteristic curves of the product of fasting triglycerides and glucose (TyG) index for diagnosing metabolic unhealth among body mass index (BMI), waist circumference (WC) and age subgroups in men. BMI: normal weight (18.5–23.9 kg/m²), overweight (24.0–27.9 kg/m²) and obesity (\geq 28.0 kg/m²); WC: normal (\leq 90 cm), increased (>90 cm).

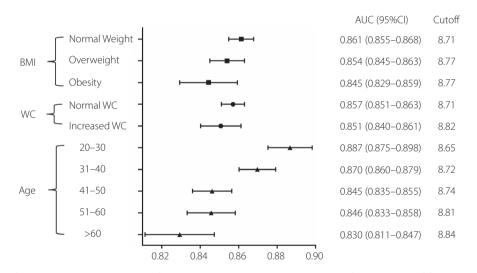


Figure 3 | Comparison of area under the curve (AUC) of receiver operating characteristic curves of the product of fasting triglycerides and glucose (TyG) index for diagnosing metabolic unhealth among body mass index (BMI), waist circumference (WC) and age subgroups in women. BMI: normal weight (18.5–23.9 kg/m²), overweight (24.0–27.9 kg/m²) and obesity (≥28.0 kg/m²); WC: normal (≤85 cm), increased (>85 cm).

obese individuals defined by MetS. The resultant cut-off was almost equal to the one determined in our current study (men 8.81; women 8.73; Table 2). Furthermore, Lee *et al.*⁵² suggested that the predictive value of the TyG index for diabetes was comparable with the predictive value of metabolic health, which was defined by the components of MetS and HOMA-IR (>90th percentile). The main difference in these studies was the definition of metabolic unhealth, which we defined according to the components of MetS (except WC).^{13,15,39} Although the risk and prevalence of metabolically unhealthy individuals

varies considerably according to the criteria used,^{15,16} both metabolically healthy and unhealthy obese patients carried an elevated risk of mortality. These findings show that BMI still plays an important role in metabolically unhealthy individuals, especially in populations with higher BMI. A difference also exists, however, in population selection, and we considered only participants not taking medication for hyperglycemia, hypertension or hyperlipidemia, and a BMI \geq 18.5. In fact, there were 3,775 (10.1% of 37,122 total participants) participants with diabetes, but just 1,278 (33.9% of participants with diabetes)

	ТуG						TG/HDL					METS-IR						
	Men (>8.81), <i>n</i>		Women (>8.73), <i>n</i>		Men (>1.32), <i>n</i>		Women (>1.09), <i>n</i>		Men (>37.67), <i>n</i>		Women (>34.99), <i>n</i>							
	_	+	Total	_	+	Total	_	+	Total	_	+	Total	_	+	Total	_	+	Total
MU (n)																		
	6318	1231	7549	11131	1463	12594	6036	1513	7549	10347	2247	12594	5737	1812	7549	9073	3521	12594
_																		
+	1011	3424	4435	1621	4092	5713	1095	3340	4435	1516	4197	5713	1297	3138	4435	1519	4194	5713
Total	7329	4655	11984	12752	5555	18307	7131	4853	11984	11863	6444	18307	7034	4950	11984	10592	7715	18307
κ value	0.603 0.605				0.5	542		0.537		0.457		0.415						
P-value	<0.0001		<0.0001		< 0.0001		< 0.0001		< 0.0001		< 0.0001							

Table 3 | Agreement (κ value) between the components of metabolic syndrome (except waist circumference) and the cut-offs of indices for the diagnosis of metabolic unhealthy individuals

MU, metabolically unhealthy.

admitted that they had diabetes and received treatment (data not shown). It was noteworthy that nearly two-thirds of the participants were unaware of their abnormal metabolism for glucose, and these individuals attracted our attention.

The current study was a well-designed population-based survey with a large number of participants representing the general Chinese population. Nevertheless, some limitations should be acknowledged. First, we did not establish the causal relationship or clinical outcomes associated with the TyG index and metabolic status to determine whether or not the TyG index is a suitable predictive marker of cardiometabolic diseases. Second, the menopausal status of women was not determined in the survey. We were, therefore, unable to analyze the differences between pre- and post-menopausal populations. Third, misclassification of participants was possible, because we used just four components of MetS to define previously confirmed metabolically unhealthy status.^{13,15,39} Finally, because all participants in the present study were Chinese men and women, the applicability of our findings to other ethnic groups is uncertain.

In conclusion, by comparing common surrogate indices of IR, we provide evidence supporting the use of the TyG index to identify metabolically unhealthy individuals. Therefore, we propose that the TyG index is simpler and more suitable for the identification of metabolically unhealthy individuals and those who have a high risk of cardiometabolic diseases in the Chinese adult population.

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DISCLOSURE

The authors declare no conflict of interest.

REFERENCES

- 1. Mendis S, Davis S, Norrving B. Organizational update: the world health organization global status report on noncommunicable diseases 2014; one more landmark step in the combat against stroke and vascular disease. *Stroke* 2015; 46: e121–e122.
- 2. Oliveros E, Somers VK, Sochor O, *et al*. The concept of normal weight obesity. *Prog Cardiovasc Dis* 2014; 56: 426–433.
- 3. Karelis AD, St-Pierre DH, *et al.* Metabolic and body composition factors in subgroups of obesity: what do we know? *J Clin Endocrinol Metab* 2004; 89: 2569–2575.
- 4. Conus F, Rabasa-Lhoret R, Peronnet F. Characteristics of metabolically obese normal-weight (MONW) subjects. *Appl Physiol Nutr Metab* 2007; 32: 4–12.
- 5. Conus F, Allison DB, Rabasa-Lhoret R, *et al.* Metabolic and behavioral characteristics of metabolically obese but normal-weight women. *J Clin Endocrinol Metab* 2004; 89: 5013–5020.
- 6. Ruderman NB, Berchtold P, Schneider S. Obesity-associated disorders in normal-weight individuals: some speculations. *Int J Obes* 1982; 6(Suppl 1): 151–157.
- 7. Dvorak RV, DeNino WF, Ades PA, *et al.* Phenotypic characteristics associated with insulin resistance in metabolically obese but normal-weight young women. *Diabetes* 1999; 48: 2210–2214.
- 8. Ruderman NB, Schneider SH, Berchtold P. The, "metabolically-obese", normal-weight individual. *Am J Clin Nutr* 1981; 34: 1617–1621.
- 9. Ruderman N, Chisholm D, Pi-Sunyer X, *et al.* The metabolically obese, normal-weight individual revisited. *Diabetes* 1998; 47: 699–713.
- 10. Navarro E, Funtikova AN, Fito M, *et al.* Can metabolically healthy obesity be explained by diet, genetics, and inflammation? *Mol Nutr Food Res* 2015; 59: 75–93.
- 11. Karelis AD, Faraj M, Bastard JP, *et al*. The metabolically healthy but obese individual presents a favorable inflammation profile. *J Clin Endocrinol Metab* 2005; 90: 4145–4150.

- 12. Brochu M, Tchernof A, Dionne IJ, *et al.* What are the physical characteristics associated with a normal metabolic profile despite a high level of obesity in postmenopausal women? *J Clin Endocrinol Metab* 2001; 86: 1020–1025.
- 13. Hashimoto Y, Tanaka M, Okada H, *et al.* Metabolically healthy obesity and risk of incident CKD. *Clin J Am Soc Nephrol* 2015; 10: 578–583.
- 14. Okamura T, Hashimoto Y, Hamaguchi M, *et al.* Metabolically healthy obesity and risk of leukoaraiosis; a population based cross-sectional study. *Endocr J* 2018; 65: 669–675.
- Hinnouho GM, Czernichow S, Dugravot A, et al. Metabolically healthy obesity and risk of mortality: does the definition of metabolic health matter? *Diabetes Care* 2013; 36: 2294–2300.
- 16. Velho S, Paccaud F, Waeber G, *et al.* Metabolically healthy obesity: different prevalences using different criteria. *Eur J Clin Nutr* 2010; 64: 1043–1051.
- 17. Wildman RP, Muntner P, Reynolds K, *et al.* The obese without cardiometabolic risk factor clustering and the normal weight with cardiometabolic risk factor clustering: prevalence and correlates of 2 phenotypes among the US population (NHANES 1999-2004). *Arch Intern Med* 2008; 168: 1617–1624.
- 18. Torres-Castillo N, Campos-Perez W, Gonzalez-Becerra K, *et al.* Waist circumference is an anthropometric parameter that identifies women with metabolically unhealthy phenotypes. *Nutrients* 2018; 10: 447.
- 19. Bagby SP. Obesity-initiated metabolic syndrome and the kidney: a recipe for chronic kidney disease? *J Am Soc Nephrol* 2004; 15: 2775–2791.
- 20. Bonora BM, Marescotti M, Marcuzzo G, *et al.* Synergistic interactions among metabolic syndrome components and homeostasis model assessment of insulin resistance in a middle-aged general population over time. *Metab Syndr Relat D* 2015; 13: 171–178.
- 21. Singh B, Saxena A. Surrogate markers of insulin resistance: a review. *World J Diabetes* 2010; 1: 36–47.
- 22. Matthews DR, Hosker JP, Rudenski AS, *et al.* Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985; 28: 412–419.
- 23. Simental-Mendía LE, Rodríguez-Morán M, Guerrero-Romero F. The product of fasting glucose and triglycerides as surrogate for identifying insulin resistance in apparently healthy subjects. *Metab Syndr Relat D* 2008; 6: 299–304.
- 24. Abbasi F, Reaven GM. Comparison of two methods using plasma triglyceride concentration as a surrogate estimate of insulin action in nondiabetic subjects: triglycerides x glucose versus triglyceride/high-density lipoprotein cholesterol. *Metabolism* 2011; 60: 1673–1676.
- 25. McLaughlin T, Reaven G, Abbasi F, *et al.* Is there a simple way to identify insulin-resistant individuals at increased risk of cardiovascular disease? *Am J Cardiol* 2005; 96: 399–404.

- 26. Bello-Chavolla OY, Almeda-Valdes P, Gomez-Velasco D, *et al.* METS-IR, a novel score to evaluate insulin sensitivity, is predictive of visceral adiposity and incident type 2 diabetes. *Eur J Endocrinol* 2018; 178: 533–544.
- 27. Alberti KGMM, Eckel RH, Grundy SM, *et al.* Harmonizing the Metabolic Syndrome: a Joint Interim Statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation* 2009; 120: 1640–1645.
- 28. Lee S, Han K, Yang HK, *et al.* A novel criterion for identifying metabolically obese but normal weight individuals using the product of triglycerides and glucose. *Nutr Diabetes* 2015; 5: e149–e149.
- 29. Lee S, Han K, Yang HK, *et al.* Identifying subgroups of obesity using the product of triglycerides and glucose: the Korea National Health and Nutrition Examination Survey, 2008-2010. *Clin Endocrinol* 2015; 82: 213–220.
- 30. Lee DY, Lee ES, Kim JH, *et al.* Predictive value of triglyceride glucose index for the risk of incident diabetes: a 4-year retrospective longitudinal study. *PLoS ONE* 2016; 11: e0163465.
- Jia A, Xu S, Ming J, *et al.* Body fat percentage cutoffs for risk of cardiometabolic abnormalities in the Chinese adult population: a nationwide study. *Eur J Clin Nutr* 2018; 72: 728–735.
- 32. Xu S, Gao B, Xing Y, *et al.* Gender differences in the prevalence and development of metabolic syndrome in Chinese population with abdominal obesity. *PLoS ONE* 2013; 8: e78270.
- 33. Ming J, Xu S, Yang C, *et al.* Metabolic syndrome and chronic kidney disease in general Chinese adults: results from the 2007–08 China National Diabetes and Metabolic Disorders Study. *Clin Chim Acta* 2014; 430: 115–120.
- 34. Yang W, Lu J, Weng J, *et al.* Prevalence of diabetes among men and women in China. *New Engl J Med* 2010; 362: 1090–1101.
- 35. Xing Y, Xu S, Jia A, *et al.* Recommendations for revision of Chinese diagnostic criteria for metabolic syndrome: a nationwide study. *J Diabetes.* 2018; 10: 232–239.
- 36. Xu S, Ming J, Xing Y, *et al.* Regional differences in diabetes prevalence and awareness between coastal and interior provinces in China: a population-based cross-sectional study. *BMC Public Health* 2013; 13: 299.
- 37. Roh L, Braun J, Chiolero A, *et al.* Mortality risk associated with underweight: a census-linked cohort of 31,578 individuals with up to 32 years of follow-up. *BMC Public Health* 2014; 14: 371.
- 38. Zhou B. Predictive values of body mass index and waist circumference to risk factors of related diseases in Chinese

adult population. *Zhonghua Liu Xing Bing Xue Za Zhi* 2002; 23: 5–10.

- 39. Hashimoto Y, Hamaguchi M, Fukuda T, *et al.* Fatty liver as a risk factor for progression from metabolically healthy to metabolically abnormal in non-overweight individuals. *Endocrine* 2017; 57: 89–97.
- 40. Guerrero-Romero F, Simental-Mendía LE, González-Ortiz M, *et al.* The product of triglycerides and glucose, a simple measure of insulin sensitivity. comparison with the euglycemic-hyperinsulinemic clamp. *J Clin Endocrinol Metab* 2010; 95: 3347–3351.
- 41. Grundy SM, Brewer HJ, Cleeman JI, *et al.* Definition of metabolic syndrome: report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. *Arterioscler Thromb Vasc Biol* 2004; 24: e13–e18.
- 42. Alberti KG, Zimmet P, Shaw J. Metabolic syndrome–a new world-wide definition. A Consensus Statement from the International Diabetes Federation. *Diabet Med* 2006; 23: 469–480.
- 43. Mazidi M, Kengne A, Katsiki N, *et al.* Lipid accumulation product and triglycerides/glucose index are useful predictors of insulin resistance. *J Diabetes Complicat* 2018; 32: 266–270.
- 44. Zhang M, Wang B, Liu Y, *et al.* Cumulative increased risk of incident type 2 diabetes mellitus with increasing triglyceride glucose index in normal-weight people: the Rural Chinese Cohort Study. *Cardiovasc Diabetol* 2017; 16: 30.

- 45. Wang B, Zhang M, Liu Y, *et al.* Utility of three novel insulin resistance-related lipid indices for predicting type 2 diabetes mellitus among people with normal fasting glucose in rural China. *J Diabetes* 2018; 10: 641–652.
- 46. Lee SH, Kwon HS, Park YM, *et al.* Predicting the development of diabetes using the product of triglycerides and glucose: the Chungju Metabolic Disease Cohort (CMC) study. *PLoS ONE* 2014; 9: e90430.
- 47. Li R, Li Q, Cui M, *et al.* Clinical surrogate markers for predicting metabolic syndrome in middle-aged and elderly Chinese. *J Diabetes Investig* 2018; 9: 411–418.
- 48. Zheng R, Mao Y. Triglyceride and glucose (TyG) index as a predictor of incident hypertension: a 9-year longitudinal population-based study. *Lipids Health Dis* 2017; 16: 175.
- 49. Sánchez-Íñigo L, Navarro-González D, Fernández-Montero A, *et al.* The TyG index may predict the development of cardiovascular events. *Eur J Clin Invest* 2016; 46: 189–197.
- 50. Cazzo E, Jimenez LS, Gestic MA, *et al.* Type 2 diabetes mellitus and simple glucose metabolism parameters may reliably predict nonalcoholic fatty liver disease features. *Obes Surg* 2018; 28: 187–194.
- 51. Zhang S, Du T, Zhang J, *et al.* The triglyceride and glucose index (TyG) is an effective biomarker to identify nonalcoholic fatty liver disease. *Lipids Health Dis* 2017; 16: 15.
- 52. Yang H, Chen G, Song C, *et al.* A novel index including SNPs for the screening of nonalcoholic fatty liver disease among elder Chinese. *Medicine* 2018; 97: e0272.