Association between insulin resistance and metabolic syndrome risk factors in Japanese

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ABSTRACT

Aims/Introduction: It is important to identify individuals at risk of metabolic syndrome (MetS), namely those with insulin resistance. Therefore, the aim of the present study was to find anthropometric and metabolic parameters that can better predict insulin resistance.

Subjects and Methods: We selected 3899 individuals (2058 men and 1841 women), excluding those with fasting plasma glucose (FPG) ≥126 mg/dL, on medication for hypertension, dyslipidemia or diabetes, and those with a history of advanced macrovascular disease. Using multivariate analyses, we selected components for obesity, lipids, and blood pressure based on the strength of their association with the homeostasis model assessment of insulin resistance (HOMA-IR).

Results: In multiple linear regression analysis, body mass index (BMI), waist circumference (WC), triglycerides (TG), high-density lipoprotein–cholesterol (HDL-C), and systolic blood pressure (SBP) were selected in men and women, and the effect of BMI on HOMA-IR outweighed that of WC. In multiple logistic regression analysis, BMI, TG, and SBP were significantly associated with HOMA-IR ≥2.5 in both genders, but WC and HDL-C were only selected in men. Combinations of BMI, TG, SBP, and FPG showed higher HOMA-IR values than those of the existing MetS components, considered useful for the identification of individual with higher insulin resistance.

Conclusions: Body mass index, TG and SBP were selected as components significantly related to insulin resistance. The selected components were fundamentally adherent to the existing MetS criteria, the only difference being the measure of obesity, in which a stronger association with insulin resistance was observed for BMI than WC. (J Diabetes Invest, doi: 10.1111/j.2040-1124.2011.00162.x, 2012)

KEY WORDS: HOMA-IR, Insulin resistance, Metabolic syndrome

INTRODUCTION

Increased insulin resistance as a result of unhealthy lifestyles and obesity likely contributes to the increased incidence of metabolic abnormalities and, consequently, the development of metabolic syndrome (MetS)[1,2]. Currently, a diagnosis of MetS is made using four components: (i) waist circumference (WC), according to population- and country-specific criteria, is used to define abdominal obesity; (ii) fasting plasma glucose (FPG) is used to define hyperglycemia; (iii) systolic and diastolic blood pressure (SBP and DBP, respectively) are used to define hypertension; and (iv) triglycerides (TG) and high-density lipoprotein–cholesterol (HDL-C) are used separately[3–6] or in combination[7] to define dyslipidemia. From the preventive point of view, it is important to identify individuals at risk of MetS, namely those with insulin resistance. However, it is unclear whether insulin resistance is predictable using these parameters.

The homeostasis model assessment of insulin resistance (HOMA-IR) is a useful model for assessing insulin resistance[8,9]. It requires only a single measurement of FPG and immunoreactive insulin (IRI) and is considered an alternative to euglycemic hyperinsulinemic glucose clamp, the gold standard method that is both costly and invasive. However, insulin measurement remains expensive and difficult to perform in some health care settings. It would be of clinical use if there was a predictive tool for the presence of insulin resistance that did not require measurement of IRI.

In the present study, we focused on insulin resistance, which contributes to the clustering of borderline risk factors in the early stage of MetS, and aimed to find anthropometric and metabolic parameters that can better predict insulin resistance. To this end, we excluded individuals with FPG ≥126 mg/dL, on medication for hypertension, dyslipidemia or diabetes, and those with a history of advanced macrovascular disease from our analyses. Here, we selected components that exhibited significant correlations with HOMA-IR by multivariate analyses and compared the selected components with those used to diagnose MetS.

SUBJECTS AND METHODS

Study Population

Of the 4907 people who first underwent annual health checks at the Health Evaluation and Promotion Center at Tokai University Hachioji Hospital between April 2007 and January 2010, 3899 (2058 men and 1841 women) were sequentially enrolled in the present cross-sectional study. The following individuals were

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excluded: 18 without a complete set of measurements; 109 with FPG ≥126 mg/dL; 797 on medication for hypertension, dyslipidemia, or diabetes; and 84 with a history of cerebrovascular disease, chronic renal failure or cardiovascular disease (CVD). The medical history was obtained using a self-administered questionnaire and interview by nurses, asking whether the individual had been diagnosed as having a cerebrovascular disease (e.g. cerebral hemorrhage, cerebral infarction), chronic renal failure or CVD (e.g. angina, myocardial infarction), or whether the subject had been treated for any of these diseases. Verbal consent was obtained from the subjects to use anonymous health records for analysis. The present study was designed in compliance with the ethics regulations outlined in the Helsinki Declaration and the privacy of participants was protected by unlinkable anonymization.

Definitions of MetS and Insulin Resistance

Anthropometric measurements were performed and blood samples were obtained after overnight fasting. All measurements were included in the routine health check examinations. The WC was assessed at the end of expiration, measuring the minimum circumference at the level of the umbilicus to the nearest 0.1 cm. Blood pressure was measured on the right upper arm with the subject in a sitting position. Serum lipid levels were measured enzymatically. Fasting serum IRI was measured by fluorescence-enzyme immunoassay (ST AIA-PACK IRI; Toso, Tokyo, Japan). Intra- and interassay coefficients of variation were 1.4–2.3% and 2.6–4.6%, respectively, and cross-reactivity with proinsulin molecules was 2.0%. The HOMA-IR was calculated as follows[8]: FPG (mg/dL) × IRI (μU/mL)/405. In the present study, HOMA-IR ≥2.5 was taken to indicate insulin resistance, based on the HOMA-IR reference intervals that we recently determined following the stringent C28-A3 document from the Clinical and Laboratory Standards Institute (CLSI) using 2153 healthy Japanese individuals[10]. In addition, HOMA-IR ≥2.5 is considered to indicate insulin resistance in Asians[11–15]. The following cut-off values were used according to the latest global definition of MetS[6]: WC ≥85 cm for men and ≥90 cm for women; FPG ≥100 mg/dL; TG ≥150 mg/dL; HDL-C <40 mg/dL for men and <50 mg/dL for women; and SBP ≥130 mmHg and/or DBP ≥85 mmHg. A cut-off value of ≥25 kg/m^2 was set for BMI[16].

Statistical Analysis

Data are expressed as the mean ± SD or mean ± SE. All statistical analyses were performed using SPSS version 18.0 (SPSS Inc., Chicago, IL, USA). Normality was examined using the Kolmogorov–Smirnov test. Because no variables were normally distributed, log-transformed values were used to determine statistical significance. Log-transformed values appeared more normally distributed in the histograms, although normality was still rejected statistically. The significance of comparisons between the non-insulin-resistant (HOMA-IR <2.5) group and the insulin-resistant (HOMA-IR ≥2.5) group was determined by Student's *t*-test. Pearson's correlation coefficient was calculated as a measure of association. The odds ratio (OR) and 95% confidence interval (CI) for HOMA-IR ≥2.5 were calculated using the non-insulin-resistant group as the reference. Multiple linear regression analysis was performed to find significant determinants of HOMA-IR, including BMI, WC, TG, HDL-C, SBP, and DBP with or without FPG as independent variables. We then performed multiple logistic regression analysis to calculate the ORs for HOMA-IR ≥2.5 using the non-insulin-resistant group as the reference and including the same variables as used in the multiple linear regression analysis. Variable selection in the multiple linear and logistic regression analyses was made by a stepwise procedure. Statistical significance for comparisons of HOMA-IR values among the groups with different numbers of components was determined using analysis of variance (ANOVA) and Scheffé's multiple comparison tests. All P values were two-tailed and $P < 0.05$ was considered significant.

RESULTS

The clinical characteristics of the individuals examined in the present study are given in Table 1: 15.6% of men ($n = 321$) and 8.4% of women ($n = 154$) were in the insulin-resistant (HOMA-IR ≥2.5) group. Furthermore, HDL-C was significantly lower and all other MetS components were significantly higher in the insulin-resistant group for both men and women. No significant association between HOMA-IR and age was observed in men ($r = -0.035$; $P = 0.11$) and the degree of correlation was negligible in women, although the correlation between HOMA-IR and age was significant ($r = 0.074$; $P < 0.01$; Figure 1). There was a significant correlation ($P < 0.01$) between HOMA-IR and all the variables (Figure 1). In both men and women, BMI, WC, and FPG showed correlation coefficients ≥0.4 and the degree of correlation with HOMA-IR was comparable between BMI and WC (Figure 1). In univariate analysis, the ORs of BMI and WC for HOMA-IR ≥2.5 were similar and were higher than those for the other components, although the ORs were significantly increased for all the MetS components (Table 2).

Tables 3 and 4 show the results of multivariate analyses including BMI, WC, TG, HDL-C, SBP, and DBP as independent variables. Stepwise multiple linear regression analysis was performed to find significant determinants for HOMA-IR (Table 3). Although BMI, WC, TG, HDL-C, and SBP were selected, DBP was excluded in both men and women. The standardized regression coefficients for BMI exceeded those for WC in both genders. The addition of FPG into the multiple linear regression analysis gave the same result (Table S1 available as an accessory publication to this paper). It was suggested that the effect of BMI on HOMA-IR was dominant compared with WC. We performed multiple logistic regression analysis for insulin resistance and found that BMI, TG, and SBP were significantly associated with HOMA-IR ≥2.5 in both genders (Table 4). In contrast, WC and HDL-C were only associated in men and DBP was not associated in either gender. The OR of BMI for HOMA-IR ≥2.5 was higher than that of WC in men. The addition of FPG into the multiple logistic regression analysis also gave the same result (Table S2).

Table 1 | Comparison of clinical characteristics between non-insulin-resistant (HOMA-IR <2.5) and insulin-resistant (HOMA-IR ≥2.5) groups

	Men				Women			
	HOMA-IR				HOMA-IR			
	Total	<2.5	≥2.5	*P*	Total	<2.5	≥2.5	*P*
n	2058	1737	321		1841	1687	154	
Age (years)	47.9 ± 11.5	47.9 ± 11.7	47.9 ± 10.8	0.701	47.7 ± 11.2	47.4 ± 11.1	50.4 ± 11.7	0.003
BMI (kg/m^2)	23.6 ± 3.1	23.0 ± 2.6	26.9 ± 3.4	<0.001	21.6 ± 3.0	21.2 ± 2.6	25.4 ± 4.2	<0.001
WC (cm)	84.4 ± 8.5	82.8 ± 7.4	93.3 ± 8.5	<0.001	78.0 ± 8.8	77.1 ± 8.1	87.6 ± 10.4	<0.001
FPG (mg/dL)	99.3 ± 8.5	98.4 ± 8.0	105.0 ± 8.7	<0.001	94.2 ± 8.0	93.3 ± 8.1	103.2 ± 9.6	<0.001
FIRI (μU/mL)	6.4 ± 4.1	5.0 ± 2.1	13.7 ± 4.6	<0.001	5.6 ± 3.7	4.9 ± 2.0	13.9 ± 6.7	<0.001
HOMA-IR	1.6 ± 1.1	1.2 ± 0.5	3.6 ± 1.3	<0.001	1.3 ± 1.0	1.1 ± 0.5	3.5 ± 1.7	<0.001
TG (mg/dL)	121.7 ± 80.6	112.4 ± 74.7	172.3 ± 91.8	<0.001	77.9 ± 40.4	74.4 ± 36.9	116.5 ± 54.2	<0.001
HDL-C (mg/dL)	58.0 ± 14.1	59.5 ± 14.1	49.5 ± 10.6	<0.001	72.6 ± 16.2	73.4 ± 16.0	64.3 ± 16.4	<0.001
SBP (mmHg)	117.7 ± 16.1	116.1 ± 15.6	126.3 ± 16.4	<0.001	112.4 ± 17.0	111.1 ± 15.9	127.0 ± 20.8	<0.001
DBP (mmHg)	75.7 ± 12.2	74.6 ± 12.0	81.4 ± 12.0	<0.001	69.6 ± 11.5	69.0 ± 11.1	76.8 ± 13.2	<0.001

Data are mean ± SD. HOMA-IR, the homeostasis model assessment of insulin resistance; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; FIRI, fasting immunoreactive insulin; TG, triglyceride; HDL-C, high-density lipoprotein–cholesterol.

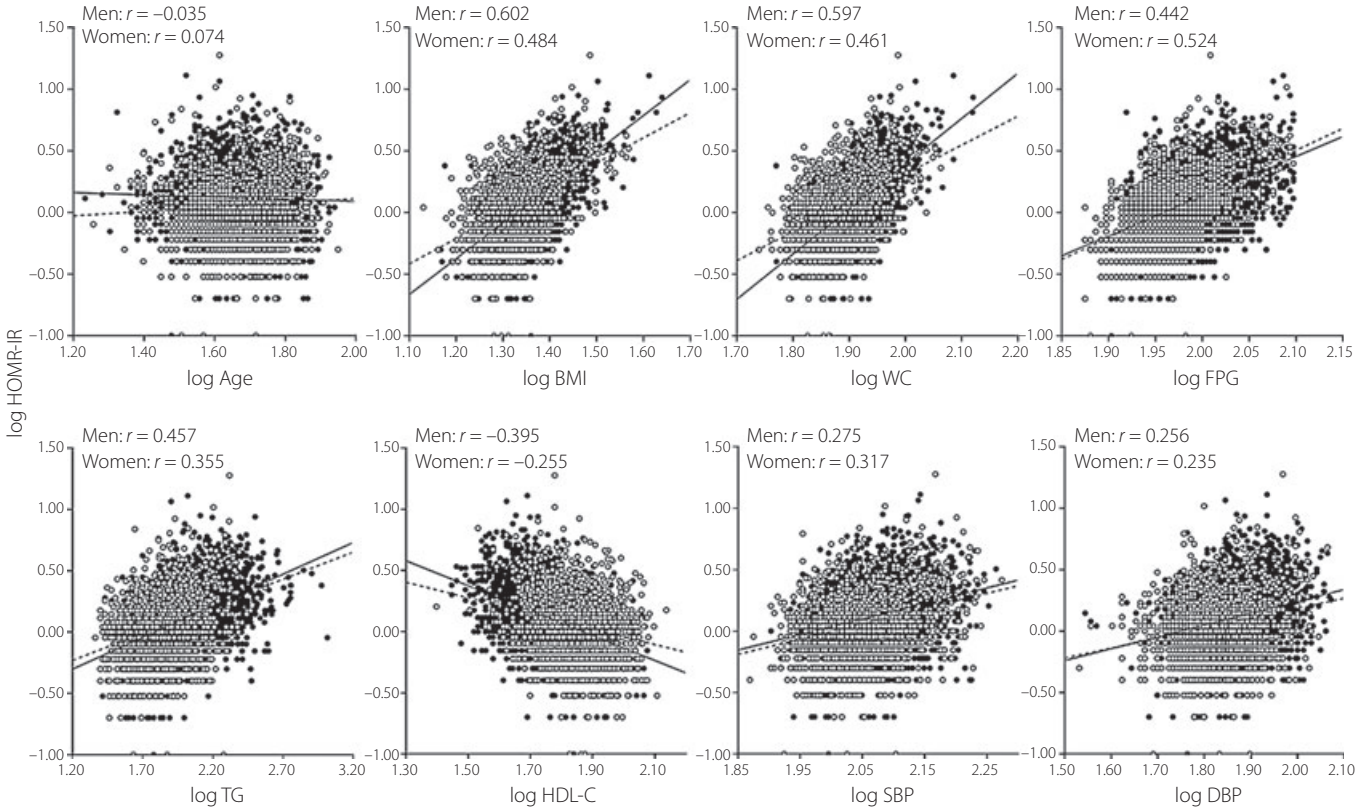

Figure 1 | Correlation between HOMA-IR and various variables in men (●; —) and women (○; - - - - -). Log-transformed values were used in the figures. There was a significant correlation ($P < 0.01$) between HOMA-IR and all the variables, except for age in men ($P = 0.11$). HOMA-IR, the homeostasis model assessment of insulin resistance; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; TG, triglyceride; HDL-C, high-density lipoprotein–cholesterol.

Multivariate analyses suggested that BMI, TG, and SBP were factors related to insulin resistance in both genders. We next examined HOMA-IR values stratified by the numbers of the four components (BMI, FPG, SBP, and TG) in comparison with those of MetS components (WC, FPG, SBP/DBP, TG, and HDL-C; Table 5). In both cases, average HOMA-IR values increased

Table 2 | Univariate analysis: odds ratios and 95% confidence intervals for insulin resistance

	Men			Women		
	OR	95% CI	*P*	OR	95% CI	*P*
BMI ≥25 kg/m^2	9.322	7.123–12.200	<0.001	9.480	6.615–13.588	<0.001
WC*	10.198	7.313–14.220	<0.001	9.313	6.395–13.563	<0.001
FPG ≥100 mg/dL	4.101	3.154–5.334	<0.001	6.519	4.620–9.198	<0.001
TG ≥150 mg/dL	4.519	3.523–5.796	<0.001	6.797	4.394–10.514	<0.001
HDL-C†	3.706	2.574–5.335	<0.001	3.644	2.289–5.801	<0.001
SBP ≥130 mmHg	2.868	2.222–3.702	<0.001	5.470	3.862–7.747	<0.001
DBP ≥85 mmHg	2.750	2.134–3.543	<0.001	4.286	2.905–6.325	<0.001

*The cut-off values for waist circumference (WC) were ≥85 cm for men and ≥90 cm for women. †The cut-off values for high-density lipoprotein–cholesterol (HDL-C) were <40 mg/dL for men and <50 mg/dL for women. OR, odds ratio; CI, confidence interval; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; TG, triglyceride; HDL-C, high-density lipoprotein–cholesterol.

Table 3 | Multiple linear regression analysis for HOMA-IR

	Men			Women		
	Standardized regression coefficient	*t*	*P*	Standardized regression coefficient	*t*	*P*
BMI	0.275	7.879	<0.001	0.264	7.681	<0.001
WC	0.196	5.551	<0.001	0.122	7.613	<0.001
TG	0.197	10.315	<0.001	0.168	7.311	<0.001
HDL-C	−0.123	−6.430	<0.001	−0.065	−2.967	0.003
SBP	0.089	5.675	<0.001	0.154	7.311	<0.001
DBP						

Variable selection was made by a stepwise procedure. BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglyceride; HDL-C, high-density lipoprotein–cholesterol.

significantly along as the numbers of components increased, and there were significant differences ($P < 0.01$) among all groups by Scheffé's multiple comparison tests. However, combinations of the selected components showed higher HOMA-IR values than those of the existing MetS components and both men and women with three or more of the four components had average HOMA-IR values >2.5.

Table 5 | HOMA-IR values stratified according to the number of the four components identified in the present study (BMI, FPG, SBP and TG) in comparison with (b) that of the metabolic syndrome components (WC, FPG, SBP/DBP, TG, and HDL-C)

	Men			Women		
	n	HOMA-IR		*n*	HOMA-IR	
		Mean ± SE	≥2.5		Mean ± SE	≥2.5
(a) No. components identified in the present study (BMI, FPG, SBP, TG)						
0	682	0.98 ± 0.02	0.9%	1157	1.04 ± 0.01	2.0%
1	645	1.44 ± 0.03	9.8%	437	1.51 ± 0.04	9.4%
2	436	1.98 ± 0.05	24.5%	179	2.06 ± 0.09	26.8%
3	231	2.60 ± 0.10	43.3%	56	3.10 ± 0.21	64.3%
4	64	3.39 ± 0.21	70.3%	12	4.38 ± 1.43	50.0%
(b) No. MetS components						
0	541	0.92 ± 0.02	0.2%	1097	1.04 ± 0.02	1.7%
1	561	1.31 ± 0.03	6.4%	466	1.46 ± 0.04	9.0%
2	506	1.79 ± 0.04	18.4%	185	1.99 ± 0.08	23.8%
3	301	2.34 ± 0.08	35.5%	72	2.58 ± 0.16	47.2%
≥4	149	2.89 ± 0.12	56.4%	21	4.10 ± 0.82	71.4%

There were significant differences ($P < 0.01$) among the all groups by Scheffé's multiple comparison tests. SE, standard error; BMI, body mass index; SBP, systolic blood pressure; TG, triglyceride; FPG, fasting plasma glucose; MetS, metabolic syndrome.

Table 4 | Multiple logistic regression analysis: odds ratios and 95% confidence intervals for insulin resistance

	Men					Women				
	Regression coefficient	SE	OR	95% CI	*P*	Regression coefficient	SE	OR	95% CI	*P*
BMI	0.163	0.048	1.178	1.072–1.293	<0.001	0.302	0.029	1.353	1.278–1.433	<0.001
WC	0.089	0.018	1.093	1.054–1.133	<0.001					
TG	0.003	0.001	1.003	1.001–1.005	<0.001	0.010	0.002	1.010	1.007–1.014	<0.001
HDL-C	−0.033	0.007	0.967	0.954–0.980	<0.001					
SBP	0.023	0.004	1.023	1.014–1.032	<0.001	0.030	0.005	1.030	1.020–1.041	<0.001
DBP										

Variable selection was made by a stepwise procedure. SE, standard error; OR, odds ratio; CI, confidence interval; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglyceride; HDL-C, high-density lipoprotein–cholesterol.

DISCUSSION

In the present study, the association between insulin resistance and MetS risk factors was examined and BMI, TG, and SBP were found to be factors related to insulin resistance in both genders by multivariate analyses.

From the preventive point of view, we focused on the early stage of MetS in which insulin resistance contributes to the clustering of borderline metabolic risk factors. For this purpose, we considered it important to appropriately select reference individuals. We excluded from analysis those individuals with FPG ≥126 mg/dL and on medication for hypertension, dyslipidemia, or diabetes, because these diseases are already known to be CVD risk factors. Another reason for this exclusion was that inclusion of individuals on treatment, particularly patients with diabetes, may make it difficult to interpret the contribution of insulin resistance to the pathophysiology of MetS[17]. We also decided that those who had a history of cerebrovascular disease, chronic renal failure, or CVD were inappropriate for inclusion in the analyses because our aim was to diagnose MetS in the pre-atherogenic stage.

We primarily excluded FPG from the analyses because FPG is used to calculate HOMA-IR and shows relatively higher correlation with HOMA-IR ($r = 0.442$ for men and $r = 0.524$ for women). Prior to the analysis, we confirmed that the influence of age on insulin resistance was clinically negligible. Previous studies in other ethnic populations have found that insulin resistance is closely associated with aging[18–20] and age-related insulin resistance may be likely related to changes in adiposity rather than being an inevitable consequence of aging[18,20]. In Japanese individuals without diabetes, there has been no report showing that insulin resistance increases with age. Moreover, we have recently reported that no age-related change in HOMA-IR was observed with advancing age in Japanese individuals[21]. Furthermore, because our aim was to find anthropometric and metabolic parameters related to HOMA-IR and to compare the selected components with those used to diagnose MetS, we did not include age in the multivariate analyses.

In terms of anthropometric measures of obesity, we directly compared BMI and WC. In univariate analysis, BMI and WC were comparably associated with insulin resistance. Previously, we have examined the diagnostic capability of BMI and WC in predicting HOMA-IR ≥2.5 using receiver operating characteristic (ROC) analysis and reported that the area under the curve and 95% confidence intervals (CI) were similar between WC and BMI[22], compatible with the results obtained with univariate analysis. However, the effect of BMI on HOMA-IR outweighed that of WC in multivariate analyses. These findings suggest that BMI is superior to WC for the prediction of insulin resistance when the interrelations among the components are taken into consideration. This discrepancy may arise in part from the validity of the currently used cut-off values for the prediction of insulin resistance. We have found previously that there are gender differences in BMI cut-off values (25 kg/m^2 for men and 23 kg/m^2 for women), as well as those of WC (88 cm for men and 82 cm for women), in predicting HOMA-IR ≥2.5 using ROC analysis[22]. When insulin resistance is targeted, the specific cut-off values for BMI and WC may need to be established. As long as the current cut-off values are used, we propose that BMI may be superior to WC for the prediction of insulin resistance.

Regarding hypertension, only SBP was selected as a component related to insulin resistance. This probably results from multicollinearity. When a set of variables is highly correlated with each other, only one of them can explain the model. Because the correlation between SBP and DBP was high ($r = 0.827$ in men and $r = 0.759$ in women), individuals with high SBP are likely to have high DBP and therefore only SBP can represent the measure of hypertension. The association between insulin resistance and hypertension is less tight among the other MetS components[5,23].

For the measure of dyslipidemia, there was a gender difference in multivariate analyses: both TG and HDL-C were selected in men, but only TG was selected in women. Generally, HDL-C is higher in women, but the prevalence of low HDL-C was similar between men and women: 6.5% of our female subjects had HDL-C <50 mg/dL compared with 6.9% of men who had HDL-C <40 mg/dL. Although the Japanese criteria require elevated TG and/or reduced HDL-C for dyslipidemia[7], other definitions count TG and HDL-C as separate components[3–6]. It remains inconclusive from our study whether TG and HDL-C should be counted separately for association with insulin resistance.

Finally, to confirm whether the multiplicity of the risk factors could be attributed to enhanced insulin resistance, HOMA-IR values stratified by numbers of the four components (BMI, FPG, SBP, and TG) in comparison with those of MetS components (WC, FPG, SBP/DBP, TG, and HDL-C) were examined. Combinations of the selected components were found to show higher HOMA-IR values than those of the existing MetS components, suggesting that the use of the four components (BMI, FPG, SBP, and TG) may be better to identify individuals with higher insulin resistance.

Because of the cross-sectional nature of the present study, the cause–effect relationship of our findings is unclear and a prospective study is required. Another limitation of the present study is that we used HOMA-IR as an index of insulin resistance, which reflects the balance between hepatic glucose output and insulin secretion in the basal state and sometimes fails to show a close relationship with whole-body insulin resistance assessed by euglycemic clamp, especially in subjects with high FPG levels[9,24]. In addition, the superiority of BMI to WC may not be evaluated by the comparison of their ORs in 1-unit increments in multiple logistic regression analysis, although it is unknown how many units are incremented for WC to correspond to a 1-unit increment of BMI in association with insulin resistance (HOMA-IR ≥2.5).

In conclusion, the present study has shown that BMI, TG, and SBP are selected as components significantly related to insulin resistance in Japanese. The selected components were fundamentally adherent to the existing MetS criteria, except for the measure of obesity, for which we found that BMI had a stronger association with insulin resistance than did WC. The combination of BMI, FPG, SBP, and TG is expected to be a predictive tool for insulin resistance, the precision of which requires further validation.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1 | Multiple linear regression analysis for HOMA-IR including FPG
Table S2 | Multiple logistic regression analysis including FPG: odds ratios and 95% confidence intervals for insulin resistance

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