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ORIGINAL CONTRIBUTION

Principal component 1 score calculated from metabolic syndrome diagnostic parameters is a possible marker for the development of metabolic syndrome in middle-aged Japanese men without treatment for metabolic diseases

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Abstract
Purpose The risk of metabolic syndrome (MetS) is assessed based on the presence of risk factors that include dyslipidemia, hyperglycemia, hypertension and obesity. In this study, we assessed the risk of MetS using principle component (PC) analysis of MetS diagnostic parameters and examined whether the resulting eigenvalues are associated with the circulating concentrations of inflammatory cytokines [interleukin (IL)-1β and IL-6] and a marker for insulin sensitivity (adiponectin) in middle-aged Japanese men without treatment for metabolic diseases.
Materials We conducted a cross-sectional study of 308 Japanese men without treatment for metabolic diseases aged 40–69 years who participated in health checkups in Japan. We calculated the PC1 score from the following MetS diagnostic parameters: body mass index (BMI), fasting blood glucose, diastolic blood pressure, triacylglycerol and high-density lipoprotein cholesterol. We compared the relationship between PC1 scores and other clinical parameters, including IL-1β, IL-6 and adiponectin, by Spearman's rank correlation coefficient analyses and Jonckheere–Terpstra test.
Results The associations for most clinical parameters were higher with the PC1 score than with other MetS diagnostic parameters. Homeostasis model assessment–insulin resistance, an index of insulin resistance, showed stronger associations with PC1 score than with MetS diagnostic parameters. Significant associations for IL-1β, IL-6 and adiponectin were observed with the PC1 score, BMI and triacylglycerol; these associations were higher with the PC1 score than with BMI and triacylglycerol.
Conclusions The present results show that the PC1 score is closely associated with parameters of MetS, inflammation and insulin resistance.

Keywords MetS · Principal component analysis · Inflammation · Insulin resistance · Japanese men without treatment for metabolic diseases

Introduction

Metabolic abnormalities such as hyperglycemia and dyslipidemia are associated with the development of diabetes and related complications such as hypertension, and cardiovascular and microvascular diseases [1–3]. In particular, recent studies have demonstrated that the accumulation of fat, particularly visceral fat, contributes to the development and progression of these diseases [4, 5]. Increased accumulation of fat causes lipid abnormalities and subsequently diabetes, hyperglycemia, hypertension and related complications. The resulting syndrome, metabolic syndrome (MetS), is caused by hyperglycemia, hypertension and dyslipidemia and is frequently accompanied by overweight/obesity. Many studies in Western countries and in

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Japan have reported an increased risk for the development and progression of diabetes, as well as microvascular and cardiovascular diseases (CVD), in obese/overweight individuals with several MetS-related abnormalities [6–8]. Based on the results observed in these epidemiological studies, MetS is defined as the presence of hypertension, dyslipidemia [triacylglycerol and/or high-density lipoprotein (HDL) cholesterol], hyperglycemia and overweight [7]. However, it is difficult to predict the risk for the development and progression of MetS, and its related complications, using these parameters alone because different values for each parameter carry different levels of risk. Furthermore, it is unlikely that these differential values can be consolidated into a single value representing the risk for these diseases.

To overcome this problem, several epidemiological studies have used factor analysis-based methods, such as principal component (PC) analysis, to combine MetS diagnostic parameters (i.e., hyperglycemia, hypertension, dyslipidemia and overweight) into a single factor. In studies performed in Western countries, the combined parameters derived from such analyses were associated with MetS-related parameters rather than the individual parameters [9–12], although similar studies have not yet been conducted in Japan. These results suggest that the outcomes of factor analysis could be useful markers for the risk of developing MetS and related complications in individuals and in populations. However, this supposition has not been evaluated in any study.

Recent studies have demonstrated that the major cause of these metabolic diseases and related complications is the production of inflammatory cytokines such as interleukin (IL)-1β, IL-6, IL-12, IL-18 and tumor necrosis factor (TNF)-α by leukocytes and other tissues [13–15]. These cytokines stimulate macrophage infiltration into the vascular endothelium and increase the risk of atherosclerosis [16, 17]. In particular, IL-1β and IL-6 seem to be very important for predicting the risk of inflammation and the onset of obesity and diabetes. Indeed, several studies in Western countries and in Japan, including our own studies, have demonstrated that circulating IL-1β and IL-6 concentrations are positively associated with moderate glucose intolerance, overweight and type 2 diabetes [13, 18–22]. In addition, many recent studies have suggested that adiponectin, an adipose tissue-secreted cytokine that enhances insulin sensitivity in skeletal muscle, adipose tissue and liver [23, 24], is a putative marker for the development of MetS and related complications. This is because circulating adiponectin concentrations are negatively associated with metabolic parameters such as fasting glucose, triacylglycerol, total cholesterol and low-density lipoprotein cholesterol concentrations and positively associated with HDL cholesterol concentrations [25–30]. Thus, it seems likely that the combination of MetS diagnostic parameters derived by factor analysis is positively associated with circulating IL-1β and IL-6 concentrations and negatively associated with circulating adiponectin concentrations.

Therefore, in the present study, we used principle component analysis to create a single parameter from a group of MetS diagnostic parameters and evaluated its association with other clinical parameters, including IL-1β, IL-6 and adiponectin levels in 308 Japanese men without treatment for metabolic diseases who were not taking medications for any metabolic diseases.

Subjects and methods

Study population

We conducted a cross-sectional study of 308 Japanese men without treatment for metabolic diseases aged 40–69 years (mean $\pm$ SD, 58.6 $\pm$ 7.7 years) who participated in health checkups offered by the city government of Izunokuni (Shizuoka Prefecture, Japan) between June 2005 and September 2005. Anthropometric data and blood samples were collected from each participant by trained medical staff. The participants were also asked about their smoking status and self-reported physical activity. Smoking status was classified as never, past or current. Self-reported physical activity was classified as none, once weekly, 2–3 times/week or every day. We excluded people who were being treated for stroke, hypertension, cardiac disease, diabetes, hyperlipidemia, liver disease, kidney disease or gout. Thus, we regarded the population as Japanese men without treatment for metabolic diseases. All subjects gave informed consent for the use of their personal information in this study. The study protocol was approved by the Ethics Committee of the University of Shizuoka (Shizuoka, Japan).

Measurements

The subjects underwent an overnight fast starting at the latest 21:00 h on the day before the health checkup, and blood samples were collected between 08:30 and 09:00 h on the day of the health checkup. Thus, all subjects fasted for at least 11.5 h before blood collection. Other parameters, including height, weight, waist circumference and blood pressure, were measured at the health checkup between 09:00 and 11:00 h. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Blood biochemical parameters were measured on a JCA-BM2250 analyzer using specific kits for fasting plasma glucose (quick auto neo GLU-HK; Shino-Test Co., Ltd, Tokyo, Japan), and serum triacylglycerol

(detaminar-TGII; Kyowa Medex Co., Ltd, Tokyo, Japan), total cholesterol (detaminar-TCII, Kyowa Medex Co., Ltd), HDL cholesterol (metabolead HDL-C, Kyowa Medex Co., Ltd), aspartate aminotransferase (AST) (quick auto neo AST; Shino-Test Co., Ltd), alanine aminotransferase (ALT) (quick auto neo ALT; Shino-Test Co., Ltd) and γ-glutamyl-transpeptidase (GTP) (quick auto neo γ-GT; Shino-Test Co., Ltd). Plasma samples were kept at -80 °C until assayed. Plasma insulin levels were measured using a solid-phase two-site enzyme immunoassay (Mercodia Ultrasensitive Insulin ELISA Kit; Mercodia, Uppsala, Sweden). Plasma total adiponectin (Adiponectin ELISA Kit; Otsuka Pharmaceutical Co., Tokyo, Japan), IL-1β (Quantikine IL-1β; R&D Systems, Oxford, UK) and IL-6 (Quantikine IL-6; R&D Systems) levels were measured by enzyme-linked immunosorbent assays. All assays were performed according to the manufacturers' instructions, and the concentrations were determined based on standard curves calculated from several dilutions of each recombinant protein. The mean intra-assay and inter-assay coefficients of variation for the insulin, total adiponectin, IL-1β and IL-6 assays are less than 5%. Homeostasis model assessment–insulin resistance (HOMA-IR) was determined using the formula: fasting blood glucose (mg/100 mL) $\times$ fasting plasma insulin (mU/L)/405.

Statistical analysis

The clinical and biochemical data of the subjects are presented as means $\pm$ standard deviation (SD). PC analysis was performed using BMI, diastolic blood pressure, fasting blood glucose, triacylglycerol and HDL cholesterol to calculate the PC scores. Spearman's rank correlation coefficient analyses were used to calculate correlations for all subjects. The Jonckheere–Terpstra test was used to calculate correlations of MetS diagnostic parameters with HOMA-IR, IL-1β, IL-6 and adiponectin among tertiles of MetS diagnostic parameters. For all analyses, a value of $P < 0.05$ was considered significant. All statistical analyses were performed using Excel Statistics 2008 (Social Survey Research Information Co., Ltd., Tokyo, Japan).

Results

The study subjects were all Japanese men without treatment for metabolic diseases who ranged in age from 40 to 69 years (mean $\pm$ SD, 58.6 $\pm$ 7.7 years). The characteristics of the subjects are shown in Table 1.

We performed PC analysis using the specified MetS diagnostic parameters (i.e., BMI, diastolic blood pressure, fasting blood glucose, triacylglycerol and HDL cholesterol). We used BMI as an index of overweight instead of waist circumference because waist circumference shows inter-investigator differences. We did not include systolic blood pressure or total cholesterol in the PC analysis because these parameters are closely associated with diastolic blood pressure and HDL cholesterol, respectively, and multiple classification analysis may be biased if multiple parameters showing collinearity are loaded together. We extracted two PCs, PC1 and PC2, which explained 36.6 and 21.9% of the characteristics of the population, respectively. The eigenvalues for PC1 and PC2, as combined MetS diagnostic parameters, are presented in Table 2.

Next, we investigated the correlations between the individual PC scores (i.e., PC1 and PC2) or individual MetS diagnostic parameters, with clinical parameters, including IL-1β, IL-6 and adiponectin, using Spearman's correlation coefficient analyses. The PC1 score, but less so the PC2 score, was associated with most of the parameters evaluated. The PC1 score was positively associated with BMI, waist circumference, systolic blood pressure, diastolic blood pressure, fasting blood pressure, total cholesterol, triacylglycerol, AST, ALT, γ-GTP, insulin, HOMA-IR, IL-1β and IL-6, and it was negatively associated with HDL cholesterol and adiponectin. Overall, the PC1 and PC2 scores were significantly associated with 15 and 10 parameters, respectively. BMI, diastolic blood pressure, fasting blood glucose, triacylglycerol and HDL cholesterol were significantly associated with 16, 12, 13, 15 and 12 parameters, respectively. The number of factors associated with the PC1 score, BMI and triacylglycerol was similar, but the strength of associations of systolic blood pressure, diastolic blood pressure, fasting blood glucose, HDL cholesterol, AST, ALT, γ-GTP, insulin, HOMA-IR, IL-1β, IL-6 and adiponectin was greater with the PC1 score than with BMI and triacylglycerol (Table 3).

Next, we used the Jonckheere–Terpstra test to determine whether HOMA-IR, IL-1β, IL-6 and adiponectin concentrations differed among tertiles of PC1 and MetS diagnostic parameters. Positive trends for HOMA-IR were observed across tertiles of PC1, BMI, diastolic blood pressure, fasting blood glucose and triacylglycerol, and a negative trend was observed across HDL cholesterol tertiles. Positive trends for IL-1β were observed across tertiles of PC1, BMI, fasting blood glucose and triacylglycerol, and a negative trend was observed across HDL cholesterol tertiles. Positive trends for IL-6 were observed across tertiles of PC1, BMI, diastolic blood pressure, fasting blood glucose and triacylglycerol, and a negative trend was observed across HDL cholesterol tertiles. Negative trends for adiponectin were observed across tertiles of PC1, BMI, diastolic blood pressure and triacylglycerol, and a positive trend was observed across HDL cholesterol tertiles (Table 4). Overall, the PC1 score was more frequently

Table 1 Physical, clinical and lifestyle characteristics

Characteristics	Category	Means ± SD or percentage	N
Age (years)		58.6 ± 7.7	308
BMI (kg/m^2)		23.2 ± 2.9	308
Waist circumference (cm)		84.4 ± 7.7	298
Smoking			
Number of cigarettes (number/day)		12.1 ± 11.9	284
Duration of smoking (years)		15.8 ± 16.1	284
Self-reported physical activity	Every day	19.1%	59
	2–3 times per week	16.2%	50
	Once per week	10.7%	33
	Never	45.1%	139
	Unknown	8.8%	27
Alcohol intake (g/day)		30.5 ± 38.0	307
Energy intake (kcal/day)		2,156.0 ± 523.2	295
Systolic blood pressure (mmHg)		126.8 ± 17.0	308
Diastolic blood pressure (mmHg)		76.9 ± 12.0	308
Fasting blood glucose (mg/dL)		103.2 ± 23.3	308
Total cholesterol (mg/dL)		196.9 ± 31.9	308
Triacylglycerol (mg/dL)		134.1 ± 124.2	308
HDL cholesterol (mg/dL)		54.7 ± 15.2	308
AST (U/L)		23.4 ± 10.5	308
ALT (U/L)		24.2 ± 14.0	308
γ-GTP (U/L)		42.1 ± 76.0	308
Creatinine (mg/dL)		0.80 ± 0.11	308
Insulin (mU/L)		5.17 ± 6.23	295
HOMA-IR		1.40 ± 2.06	295
IL-1β (pg/mL)		1.70 ± 2.61	308
IL-6 (pg/mL)		3.41 ± 3.29	308
Adiponectin (μg/mL)		5.51 ± 3.00	277

BMI body mass index, *HDL cholesterol* high-density lipoprotein cholesterol, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase; *γ-GTP* γ-glutamyl-transpeptidase, *HOMA-IR* homeostasis model assessment–insulin resistance, *IL* interleukin

Table 2 Eigenvalues of PC analysis of MetS diagnostic parameters in 308 middle-aged men

Variable	PC1 (36.6%)	PC2 (21.9%)
BMI (kg/m^2)	0.599	0.517
Diastolic blood pressure (mmHg)	0.468	0.694
Fasting blood glucose (mg/dL)	0.643	−0.219
Triacylglycerol (mg/dL)	0.728	−0.477
HDL cholesterol (mg/dL)	−0.554	0.265

BMI body mass index, *HDL* cholesterol, high-density lipoprotein cholesterol

associated with cytokine concentrations than with MetS diagnostic parameters.

Discussion

In the present study, we examined the associations between the scores derived from PC analysis of MetS diagnostic parameters and clinical parameters, including IL-1β, IL-6 and adiponectin, in Japanese middle-aged men. From PC analysis using BMI, diastolic blood pressure, fasting blood glucose, HDL cholesterol and triacylglycerol, we extracted two PC scores, PC1 and PC2, which explained the characteristics of 36.6 and 21.9% of the study population, respectively. In this study, we focused on the PC1 score because this score was more strongly associated with metabolic risk factors than was the PC2 score in this population. Interestingly, we found that the PC1 score was not only strongly associated with the MetS diagnostic parameters included as variables in PC analysis, but also with other parameters such as liver injury markers. In addition, the associations with insulin and HOMA-IR were stronger with the PC1 score than with individual MetS diagnostic parameters. Similar findings from studies performed in Western countries have already been reported [9–12], and our study is the first to demonstrate this in Japan. Furthermore, the associations with metabolic risk factors were stronger with the PC1 score than with individual MetS diagnostic parameters. These results suggest that the PC1 score derived from the MetS diagnostic

Table 3 Correlations between principal components or MetS diagnostic parameters, and subject characteristics

	PC1 score	PC2 score	BMI	Diastolic blood pressure	Fasting blood glucose	Triacylglycerol	HDL cholesterol
PC1 score		0.333***	0.705***	0.513***	0.413***	0.643***	−0.609***
Age (years)	0.053	–	−0.033	0.074	0.175**	−0.018	0.028
BMI (kg/m^2)	0.705***	0.567***	–	0.298***	0.211***	0.297***	−0.266***
Waist circumference (cm)	0.646***	0.405***	0.786***	0.252***	0.176**	0.339***	−0.310***
Systolic blood pressure (mmHg)	0.442***	0.576***	0.291***	0.735***	0.242***	0.146*	−0.040
Diastolic blood pressure (mmHg)	0.513***	0.744***	0.298***	–	0.204***	0.173**	−0.046
Fasting blood glucose (mg/dL)	0.413***	0.061	0.211***	0.204***	–	0.105	−0.040
Total cholesterol (mg/dL)	0.087	0.089	0.122*	0.085	0.100	0.234***	0.232***
Triacylglycerol (mg/dL)	0.643***	−0.125*	0.297***	0.173**	0.105	–	−0.464***
HDL cholesterol (mg/dL)	−0.609***	0.210***	−0.266***	−0.046	−0.040	−0.464***	–
AST (U/L)	0.188***	0.038	0.139*	0.028	0.208***	0.149**	−0.053
ALT (U/L)	0.408***	0.111	0.357***	0.072	0.176**	0.303***	−0.225***
γ-GTP (U/L)	0.351***	0.091	0.203***	0.206***	0.349***	0.356***	−0.119*
Creatinine (mg/dL)	0.077	0.117*	0.074	0.128*	−0.034	0.013	−0.062
Insulin (mU/L)	0.585***	0.208***	0.563***	0.232***	0.282***	0.365***	−0.370***
HOMA-IR	0.622***	0.200***	0.563***	0.251***	0.424***	0.368***	−0.346***
IL-1β (pg/mL)	0.241***	0.062	0.181**	0.081	0.335***	0.158**	−0.147**
IL-6 (pg/mL)	0.221***	0.078	0.133*	0.159**	0.297***	0.122*	−0.111
Adiponectin (μg/mL)	−0.283***	−0.112	−0.272***	−0.104	−0.015	−0.204***	0.153*
Smoking							
Number of cigarettes (number/day)	0.026	0.017	0.049	−0.016	−0.028	0.044	−0.014
Duration of smoking (years)	0.010	−0.032	−0.012	−0.007	−0.047	0.053	−0.046
Self-reported physical activity[a]	0.001	−0.087	−0.065	−0.054	−0.104	0.052	−0.036
Alcohol intake (g/day)	−0.031	0.122	−0.031	0.142*	0.070	0.020	0.246***
Energy intake (kcal/day)	0.014	0.088	0.024	0.077	0.061	0.068	0.113

BMI body mass index, *HDL cholesterol* high-density lipoprotein cholesterol, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *γ-GTP* γ-glutamyl-transpeptidase, *HOMA-IR* homeostasis model assessment–insulin resistance, *IL* interleukin

Spearman's correlation coefficients (*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$) were calculated for all subjects

[a] Self-reported physical activity: 1 = everyday, 2 = 2–3 times per week, 3 = once per week or 4 = never

parameters is an index of metabolic abnormalities, particularly insulin resistance without determining HOMA-IR, in Japanese men without treatment for metabolic diseases.

Although we have demonstrated that the PC1 score is strongly associated with several metabolic risk factors, it is still unclear whether the PC1 score is associated with the risk for the development or progression of MetS and related complications. Several recent studies have demonstrated that higher IL-1β and IL-6 concentrations and lower adiponectin concentrations are associated with the development and progression of overweight, diabetes, MetS and related complications [13, 16–22]. In addition, a recent cohort study in the US demonstrated that healthy individuals with higher IL-6 concentrations had a higher subsequent incidence of heart failure than did individuals with lower IL-6 concentrations [31]. Similarly, another study showed that lower adiponectin concentrations in healthy subjects were associated with a higher subsequent incidence of diabetes [32]. Thus, we investigated the associations between the PC1 score and the circulating concentrations of IL-1β, IL-6 and adiponectin in this population of Japanese men. Surprisingly, the PC1 score was strongly and positively associated with IL-1β and IL-6 concentrations and negatively associated with adiponectin concentrations. Among the PC1 and MetS diagnostic parameters (e.g., BMI and triacylglycerol) that are associated with the levels of these proteins, the association was strongest with the PC1 score than with the individual MetS

Table 4 Correlations between PC1 or metabolic diagnostic parameters and cytokine concentrations

PC1	Low (102) −2.943 to −0.538	Middle (103) −0.537 to 0.333	High (103) 0.349–12.22	*P* for trend
HOMA-IR[a]	0.71±0.91	1.38±2.06	2.09±2.56	<0.001
IL-1β (pg/mL)	0.97±1.83	1.88±2.64	2.24±3.04	0.001
IL-6 (pg/mL)	2.56±2.73	3.62±3.31	4.04±3.57	<0.001
Adiponectin (μg/mL)	6.80±3.74	5.29±2.47	4.54±2.13	<0.001
BMI	Low (103) 15.5–21.9	Middle (103) 22.0–24.3	High (102) 24.4–32.0	*P* for trend
HOMA-IR[a]	0.68±0.85	1.12±1.08	2.38±3.03	<0.001
IL-1β (pg/mL)	1.43±2.39	1.32±2.16	2.35±3.07	0.004
IL-6 (pg/mL)	3.01±3.11	3.01±2.87	4.22±3.67	0.007
Adiponectin (μg/mL)	6.74±3.42	4.98±2.80	4.78±2.20	<0.001
Diastolic blood pressure	Low (101) 46–70	Middle (110) 71–80	High (97) 81–130	*P* for trend
HOMA-IR[a]	1.25±1.69	1.18±1.70	1.81±2.63	<0.001
IL-1β (pg/mL)	1.67±2.69	1.86±2.51	1.54±2.61	0.564
IL-6 (pg/mL)	3.12±3.73	3.68±3.15	3.41±2.89	0.019
Adiponectin (μg/mL)	5.80±2.98	5.71±3.31	4.95±2.45	0.035
Fasting blood glucose	Low (99) 70–94	Middle (102) 95–103	High (107) 104–359	*P* for trend
HOMA-IR[a]	0.76±0.62	1.38±2.01	2.02±2.71	<0.001
IL-1β (pg/mL)	0.77±1.76	1.54±2.45	2.71±3.02	<0.001
IL-6 (pg/mL)	2.46±2.87	3.04±2.84	4.65±3.64	<0.001
Adiponectin (μg/mL)	5.39±2.80	5.41±2.63	5.70±3.41	0.475
Triacylglycerol	Low (103) 30–84	Middle (103) 85–135	High (102) 136–1442	*P* for trend
HOMA-IR[a]	0.91±1.06	1.30±1.83	2.00±2.77	<0.001
IL-1β (pg/mL)	1.23±2.19	2.11±2.89	1.75±2.62	0.010
IL-6 (pg/mL)	2.82±2.96	3.84±3.40	3.57±3.39	0.026
Adiponectin (μg/mL)	6.50±3.71	5.22±2.58	4.80±2.17	<0.001
HDL cholesterol	Low (106) 22–47	Middle (102) 48–58	High (100) 59–127	*P* for trend
HOMA-IR[a]	1.79±2.50	1.36±1.65	1.00±1.80	<0.001
IL-1β (pg/mL)	2.25±2.96	1.64±2.62	1.17±2.01	0.007
IL-6 (pg/mL)	4.05±3.95	3.28±3.04	2.86±2.55	0.052
Adiponectin (μg/mL)	4.93±2.17	5.32±2.71	6.42±3.80	0.008

P values for trends were calculated using the Jonckheere–Terpstra test among the three groups

BMI body mass index, *HDL* cholesterol, high-density lipoprotein cholesterol, *HOMA-IR* homeostasis model assessment–insulin resistance *IL* interleukin

[a] HOMA-IR = Fasting blood glucose × fasting insulin/405

diagnostic parameters. Because the higher concentrations of IL-1β and IL-6 and the lower adiponectin concentrations are directly and mechanistically linked with the development of cardiovascular and microvascular diseases, as well as diabetes, it seems likely that the PC1 score is associated with the risk of the development and progression of MetS and related complications. Thus, cohort studies are needed to examine whether the future incidence of diabetes, hypertension, and cardiovascular and microvascular diseases is higher among subjects without metabolic diseases

with higher PC1 scores, higher IL-1β and IL-6 concentrations, and lower adiponectin concentrations.

It should be noted that the strength of the associations with IL-1β and IL-6 was weaker for the PC1 score than for fasting blood glucose, while adiponectin concentrations were not associated with fasting blood glucose levels. Our previous studies showed that the circulating IL-1β and IL-6 concentrations are positively associated with fasting blood glucose concentrations in non-overweight and overweight Japanese men without treatment for metabolic diseases [21]. Notably, the concentrations of these cytokines were associated with overweight in studies performed in Western countries [13, 18, 19, 22]. However, plasma IL-6 concentrations were not associated with HOMA-IR, a marker for insulin resistance, in another study of non-overweight Japanese people with type 2 diabetes [33]. Japanese people tend to be relatively lean and often develop diabetes in the absence of overweight or obesity. Thus, the stronger associations of these cytokines with fasting blood glucose than with the PC1 score may be because hyperglycemia contributes to the increases in the circulating concentrations of these cytokines. These findings suggest that higher fasting glucose concentrations, even if they are within the specified range, in the absence of overweight, hypertension and lipid abnormalities, play a critical role in the development and progression of metabolic diseases and related complications, particularly in Japanese individuals. However, it was already demonstrated in Japan that subjects with an increased number of MetS diagnostic parameters exceeding the criteria were at greater risk for CVD and death [34–36]. It was also reported in Japan that subjects with an increased number of MetS diagnostic parameters exceeding the criteria, and who had elevated blood glucose concentrations or type 2 diabetes, were at greater risk of CVD and death than normoglycemic or non-diabetic individuals [37–39]. Thus, elevated fasting blood glucose concentrations in combination with other MetS parameters and/or the PC1 value may greatly increase the risk of CVD and death. This may be due to lipid abnormalities and elevated circulating cytokine (IL-1β and IL-6) concentrations caused by increased fasting blood glucose concentrations. Studies are needed to examine whether subjects with a PC1 score with higher cytokine and fasting blood glucose concentrations are at increased risk for CVD in Japan and other Asian and Western countries.

In summary, in our middle-aged Japanese men without treatment for metabolic diseases, the PC1 score is closely associated with markers of MetS, inflammation and insulin resistance. The results of this study suggest that the PC1 score derived from factor analysis of MetS diagnostic parameters is a possible marker for the development of MetS and related complications in Japanese middle-aged men without treatment for metabolic diseases.

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Conflict of interest The authors declare no conflict of interest.

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