*Original Article*

# Metabolic Syndrome, C-Reactive Protein and Increased Arterial Stiffness in Japanese Subjects

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**The aim of this study was to investigate whether the metabolic syndrome (MS) was associated with an elevated level of C-reactive protein (CRP) and increased arterial stiffness, and to clarify whether combined MS and CRP data had a stronger relation to arterial stiffness than did MS data alone. Brachial-ankle pulse wave velocity (baPWV), CRP, and conventional risk factors were evaluated in 3,412 men and 854 women. Adjusted mean values of baPWV in men with 0, 1, 2, and ≥3 components were 1,309, 1,372, 1,422, and 1,462 cm/s, respectively (*p* for trend <0.001). Adjusted mean values of baPWV in women with 0, 1, 2, and ≥3 components were 1,212, 1,292, 1,357, and 1,391 cm/s, respectively (*p* for trend <0.001). Adjusted geometric mean concentrations of CRP in men with 0, 1, 2, and ≥3 components were 0.036, 0.049, 0.059, and 0.076 mg/dl, respectively (*p* for trend <0.001). Adjusted geometric mean concentrations of CRP in women with 0, 1, 2, and ≥3 components were 0.023, 0.030, 0.057, and 0.077 mg/dl, respectively (*p* for trend <0.001). In analyses of adjusted mean values of baPWV according to the number of MS components and according to CRP levels within or without top quartile levels, the *p* value for the trend was significant (<0.001) in both men and women but, in post hoc analyses, comparing high and low CRP levels in each MS component–number group, no significant difference was found. These results suggest that, for prediction of increased arterial stiffness, combining MS and CRP data has little additive effect compared to the use of MS data alone. (*Hypertens Res* 2006; 29: 589–596)**

***Key Words*: C-reactive protein, metabolic syndrome, pulse wave velocity, arterial stiffness**

## Introduction

The metabolic syndrome (MS), a cluster of obesity, hypertension, impaired glucose tolerance, a low high-density lipoproteion (HDL) cholesterol level, and/or hypertriglyceridemia, is associated with a greatly increased risk of cardiovascular disease (*1–5*). There is also an association of MS with inflammation (*6*). Excess adipose tissue mass causes an increased serum level of C-reactive protein (CRP) (*7*, *8*), which is a strong predictor of cardiovascular events (*9–12*). Moreover, it has been reported that, at all levels of severity of MS, the CRP level provides important and independent prognostic information in terms of future cardiovascular risk (*13*). However, another report insisted that combining CRP and MS data added little to overall cardiovascular disease risk prediction (*14*). Therefore, the relationships of MS, CRP, and atherosclerotic disease should be explored in more detail.

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**Table 1. Characteristics of Male Subjects According to the Number of Metabolic Syndrome Components**

| | Number of components of the metabolic syndrome | | | | *p* value |
|---|---|---|---|---|---|
| | 0 ($n$=1,274) | 1 ($n$=1,060) | 2 ($n$=662) | ≥3 ($n$=409) | |
| Age (years) | 46.8±7.1 | 49.0±6.7 | 49.6±6.5 | 49.6±6.0 | <0.0001 |
| BMI (kg/m$^2$) | 22.0±1.8 | 23.8±4.5 | 25.4±2.8 | 27.0±2.7 | <0.0001 |
| SBP (mmHg) | 113.1±8.2 | 124.3±14.3 | 130.7±15.8 | 136.0±15.5 | <0.0001 |
| DBP (mmHg) | 71.1±6.8 | 79.1±10.1 | 83.4±10.8 | 86.5±11.0 | <0.0001 |
| Heart rate (bpm) | 58.3±8.7 | 60.9±9.3 | 62.3±9.5 | 64.6±10.6 | <0.0001 |
| Total cholesterol (mg/dl) | 201.2±30.4 | 207.3±33.1 | 213.2±33.7 | 216.6±37.7 | <0.0001 |
| Triglyceride (mg/dl) | 81 (61–105) | 107 (77–146) | 142 (99–190) | 189 (159–242) | <0.0001 |
| HDL cholesterol (mg/dl) | 61.5±13.4 | 57.2±14.0 | 53.1±13.9 | 46.4±12.1 | <0.0001 |
| Fasting glucose (mg/dl) | 88.7±7.6 | 94.6±16.8 | 99.9±22.7 | 114.7±37.2 | <0.0001 |
| Uric acid (mg/dl) | 5.6±1.1 | 5.9±1.2 | 6.2±1.2 | 6.2±1.2 | <0.0001 |
| CRP (mg/dl) | 0.030 (0.017–0.062) | 0.043 (0.023–0.090) | 0.057 (0.033–0.109) | 0.730 (0.044–0.138) | <0.0001 |
| Current smoker (%) | 48.0 | 47.1 | 53.0 | 56.2 | 0.003 |
| Drinker (%) | 70.6 | 75.5 | 75.2 | 69.9 | 0.015 |
| Frequency of exercise (%) | | | | | |
| Rarely or never | 52.2 | 54.4 | 56.5 | 58.9 | 0.07 |
| ≥1/week | 47.8 | 45.6 | 43.5 | 41.1 | |
| Educational attainment (%) | | | | | |
| High school education or less | 52.7 | 59.1 | 60.0 | 62.8 | <0.001 |
| Medication for | | | | | |
| Hypertension (%) | 0.0 | 8.9 | 19.6 | 23.0 | <0.0001 |
| Hyperlipidemia (%) | 2.1 | 3.4 | 7.4 | 6.8 | <0.0001 |
| Diabetes (%) | 0.0 | 2.3 | 4.1 | 6.7 | <0.0001 |
| PWV (cm/s) | 1,276±135 | 1,380±187 | 1,448±209 | 1,501±244 | <0.0001 |

Variables are presented as mean±SD, median (interquatile range) for skewed variables, or percentage. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein; CRP, C-reactive protein; PWV, pulse wave velocity.

Pulse wave velocity (PWV) is known to be an indicator of arterial stiffness (*15*, *16*), and elevated PWV is associated with development of atherosclerotic diseases (*16–19*). A simple noninvasive automatic method for measurement of brachial-ankle PWV (baPWV) has recently been developed. The technical simplicity and short sampling time of the new method make it more feasible for screening a large population than previous methods such as carotid-femoral PWV.

The aim of this study was to investigate whether MS was associated with elevated CRP and increased arterial stiffness, and to clarify whether combining MS and CRP data would provide more information about arterial stiffness than MS data alone.

## Methods

### Subjects

The subjects were local government employees (8,229 men and 2,194 women) aged 35 years or more who had their annual health checkup during the period from April 2003 through March 2004. We used a self-administered questionnaire including items on clinical history, family history, smoking, alcohol consumption, educational status, frequency of exercise, menopausal status and hormone-replacement therapy. The questionnaire was distributed to the subjects in advance of their annual health checkup, and was collected at the checkup. Answers to the questionnaire and written informed consent to view health checkup data were obtained from 3,907 men and 1,044 women (response rate: men 47.5%, women 47.6%). A total of 685 subjects (495 men, 190 women) were excluded for the following reasons: past history of coronary disease or stroke ($n$=136; 124 men, 12 women), low ankle/brachial pressure index (ABI) (<0.9, $n$= 12; 11 men, 1 woman), PWV not measured ($n$=600; 416 men, 184 women), or blood samples not analyzed ($n$=3; 3 women).

This study was conducted with all the subjects' written informed consent and approved by the institutional ethical board for epidemiological studies of Hokkaido University Graduate School of Medicine.

### Data Collection

Subjects were classified as either current smokers or nonsmokers, with the latter group including both never- and exsmokers. Drinkers were defined as those who consumed alco-

**Table 2. Characteristics of Female Subjects According to the Number of Metabolic Syndrome Components**

| | Number of metabolic syndrome components | | | | *p* value |
|---|---|---|---|---|---|
| | 0 | 1 | 2 | ≥3 | |
| | (*n*=560) | (*n*=172) | (*n*=81) | (*n*=41) | |
| Age (years) | 45.3±7.1 | 49.1±6.4 | 49.8±6.6 | 51.5±5.9 | <0.0001 |
| BMI (kg/m$^2$) | 20.6±2.1 | 23.0±3.3 | 25.4±4.2 | 27.3±4.0 | <0.0001 |
| SBP (mmHg) | 108.0±9.2 | 123.0±16.4 | 128.2±17.8 | 140.9±16.6 | <0.0001 |
| DBP (mmHg) | 65.4±7.0 | 74.7±11.3 | 76.8±10.4 | 84.7±9.7 | <0.0001 |
| Heart rate (bpm) | 58.6±7.5 | 60.4±8.2 | 61.8±9.9 | 65.4±9.2 | <0.0001 |
| Total cholesterol (mg/dl) | 204.2±30.6 | 212.1±32.1 | 221.3±32.1 | 222.9±39.7 | <0.0001 |
| Triglycerides (mg/dl) | 59 (46–78) | 76 (55–100) | 125 (83–175) | 166 (92–196) | <0.0001 |
| HDL cholesterol (mg/dl) | 73.5±13.2 | 68.0±15.5 | 56.2±12.6 | 51.4±9.3 | <0.0001 |
| Fasting glucose (mg/dl) | 85.0±7.2 | 90.8±12.4 | 97.8±22.7 | 113.5±35.4 | <0.0001 |
| Uric acid (mg/dl) | 4.3±0.8 | 4.7±1.1 | 5.1±1.2 | 5.3±1.3 | <0.0001 |
| CRP (mg/dl) | 0.020 (0.010–0.038) | 0.030 (0.018–0.056) | 0.054 (0.036–0.138) | 0.111 (0.057–0.222) | <0.0001 |
| Current smoker (%) | 24.5 | 27.3 | 18.5 | 19.5 | 0.42 |
| Drinker (%) | 53.6 | 51.2 | 50.6 | 53.6 | 0.92 |
| Frequency of exercise (%) | | | | | |
| Rarely or never | 66.8 | 65.7 | 69.1 | 78.0 | 0.47 |
| ≥1/week | 33.2 | 34.3 | 31.0 | 22.0 | |
| Educational attainment (%) | | | | | |
| High school education or less | 39.6 | 51.7 | 49.4 | 58.5 | <0.01 |
| Medication for | | | | | |
| Hypertension (%) | 0.0 | 7.0 | 9.9 | 41.5 | <0.0001 |
| Hyperlipidemia (%) | 2.9 | 5.2 | 7.4 | 22.0 | <0.0001 |
| Diabetes (%) | 0.0 | 1.2 | 2.5 | 9.8 | <0.0001 |
| Menopausal status (%) | | | | | |
| Postmenopausal | 31.8 | 48.8 | 56.8 | 68.3 | <0.0001 |
| Current use of hormone-replacement therapy (%) | 1.8 | 3.5 | 1.2 | 0.0 | 0.37 |
| PWV (cm/s) | 1,191±130 | 1,317±195 | 1,404±221 | 1,478±164 | <0.0001 |

Variables are presented as mean±SD, median (interquartile range) for skewed variables, or percentage. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein; CRP, C-reactive protein; PWV, pulse wave velocity.

hol once a week or more. With regard to leisure-time exercise (with perspiration), subjects were categorized as exercising "rarely or never," or "≥1 per week." Finally, two groups were used to categorize subjects according to their educational attainment: "high school education or less" and "more than high school education."

Anthropometric measures (height, body weight, and waist and hip circumferences) were recorded by a standardized protocol. The body mass index (BMI) was calculated as weight (kg)/height (m)$^2$.

Blood samples were drawn from the antecubital vein of the seated subject with minimal tourniquet use after a 12-h fast. Specimens were collected in siliconized glass vacuum tubes containing sodium fluoride for blood glucose, and no additives for serum.

Total cholesterol (TC) levels were measured by an enzymatic method (Wako, Osaka, Japan). The triglyceride (TG) levels were measured by an enzymatic method (Daiichi Pure Chemicals, Tokyo, Japan), the HDL cholesterol level by a direct method (Daiichi Pure Chemicals), uric acid (UA) by an enzymatic method (Daiichi Pure Chemicals), creatinine by an enzymatic method (Kanto Kagaku, Tokyo, Japan), and blood glucose by an amperometric method (Arkray, Kyoto, Japan).

CRP was measured by nephelometry, with a latex particle–enhanced immunoassay (N Latex CRP II; Dade Behring, Tokyo, Japan). The assay could detect 0.004 mg/dl of CRP. Undetectable CRP values were recorded as 0.002 mg/dl.

All blood variables except for CRP were measured at Daiichi Clinical Laboratories, Inc. (Sapporo, Japan), a commercial hematology laboratory, where the measurements of TC and HDL cholesterol were all standardized by the Lipid Standardization Program of the Centers for the Disease Control and Prevention, Atlanta, USA. CRP was measured at Mitsubishi Kagaku Bio-Clinical Laboratories, Inc. (Tokyo, Japan), a commercial hematology laboratory.

We used a modified version of the National Cholesterol

Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Pressure (Adult Treatment Panel III) (*20*), and subjects with three or more of the following attributes were typically defined as having MS: 1) triglycerides ≥150 mg/dl, 2) HDL cholesterol <40 mg/dl for men and <50 mg/dl for women, 3) blood pressure ≥135/85 mmHg, 4) fasting glucose >110 mg/dl, and 5) BMI >25 kg/m$^2$ (*21*) (the waist circumference was not available in this study). In addition, subjects met the criteria for high blood pressure or high fasting blood glucose if they were currently using medications for hypertension or diabetes.

baPWV was measured using a volume-plethysmographic apparatus (Form PWV/AVI; model BP-203RPEII, Colin Co., Komaki, Japan) (*22*, *23*). This device records the phonocardiogram, electrocardiogram, and volume pulse form and arterial blood pressure at both the left and right brachia and ankles. baPWV was calculated by time-phase analysis between right brachial and volume waveforms at both ankles. Blood pressure, heart rate (HR), and the ABI were measured using a pulse-wave velocimeter concurrently with PWV measurement. ABI is the ratio of ankle systolic blood pressure (SBP) to brachial SBP, and right and left ABIs were measured simultaneously. In all the studies, baPWV was obtained after an at least 5-min rest.

## Statistical Analysis

All analyses were performed separately for men and women. The subjects were categorized according to the number of MS components present: 0, 1, 2, and ≥3 for men and women. The data are presented as the mean±SD or median values (and interquartile range) for variables with a skewed distribution or percentages, and the data were compared among groups using analysis of variance (ANOVA), the Kruskal-Wallis test, or the $\chi^2$-test. The mean PWVs were compared among the groups using general linear model (GLM) univariate analyses adjusted for age, HR, TC, UA, smoking status (smoker/nonsmoker), alcohol consumption (drinker/rarely or never), frequency of exercise (≥1/week/rarely or never), educational attainment (high school education or less/more than high school education), and medication for hyperlipidemia for men, and all of these variables plus menopausal status for women. Then, because of its skewed distribution, the mean log-transferred CRP was compared among the groups, using GLM univariate analyses adjusted for the variables cited above.

Next, CRP was divided into quartiles, and the top quartile of CRP was defined as high CRP (≥0.090 mg/dl for men and ≥0.053 mg/dl for women). The subjects were classified as having 0, 1–2, and ≥3 components of the syndrome, and each group was divided into those with and without high CRP. The mean PWV was compared among the groups using GLM univariate analyses adjusted for the variables cited above.

*p*-values <0.05 were considered to be statistically significant. All analyses were conducted using the SPSS software package Version 12 for Windows (SPSS Inc., Chicago, USA).

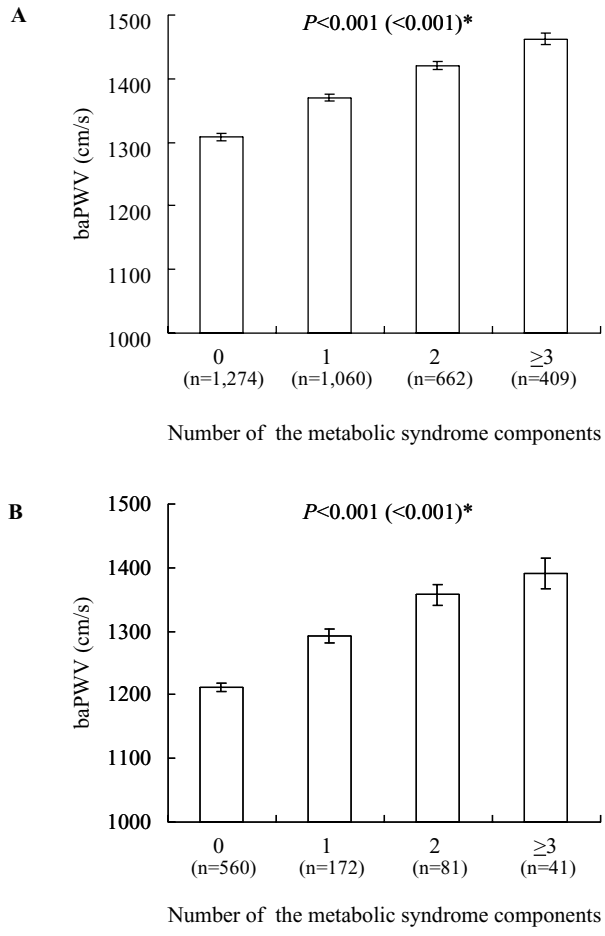


**Fig. 1.** *Adjusted mean±SEM values of baPWV according to the number of metabolic syndrome components. A: Men: adjusted for age, heart rate, TC, UA, smoking status, alcohol consumption, frequency of exercise, educational attainment and medication for hyperlipidemia. B: Women: adjusted for age, heart rate, TC, UA, smoking status, alcohol consumption, frequency of exercise, educational attainment, medication for hyperlipidemia and menopausal status.* *p *value for difference (*p *for trend).*

## Results

Characteristics of the groups according to the number of MS components are shown in Table 1 for men and Table 2 for women. In male subjects, age, BMI, HR, SBP, diastolic blood pressure (DBP), TC, TG, HDL cholesterol, UA, CRP, smoking, drinking, education, medication for hypertension, medication for hyperlipidemia, medication for diabetes and PWV were significantly different among the groups. In female subjects, all of the above-cited variables except for smoking and

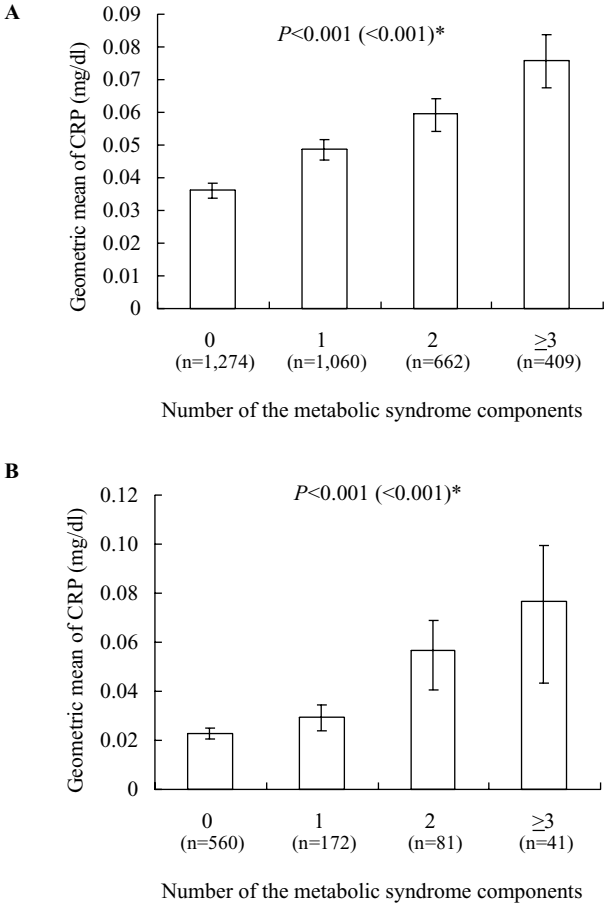


**Fig. 2.** *Adjusted geometric mean (95% CI) concentrations of CRP according to the number of metabolic syndrome components. A: Men: adjusted for age, TC, UA, smoking status, alcohol consumption, frequency of exercise, educational attainment and medication for hyperlipidemia. B: Women: adjusted for age, heart rate, TC, UA, smoking status, alcohol consumption, frequency of exercise, educational attainment, medication for hyperlipidemia and menopausal status.* *p *value for difference (*p *for trend).*

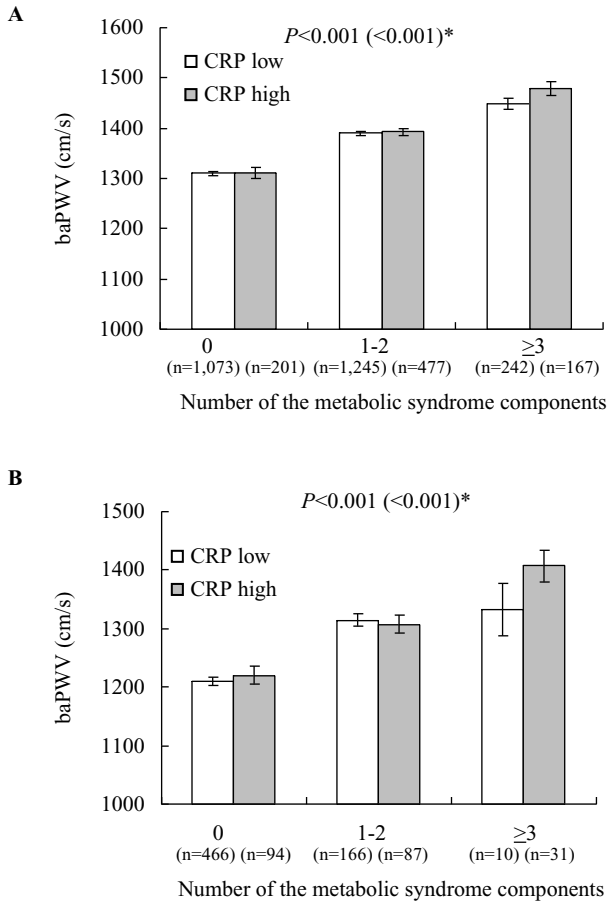


**Fig. 3.** *Adjusted mean±SEM values of baPWV according to the number of metabolic syndrome components and according to CRP levels within or without top quartile levels (≥0.090 mg/dl for men, ≥0.053 mg/dl for women). A: Men: adjusted for age, heart rate, TC, UA, smoking status, alcohol consumption, frequency of exercise, educational attainment and medication for hyperlipidemia. B: Women: adjusted for age, heart rate, TC, UA, smoking status, alcohol consumption, frequency of exercise, educational attainment, medication for hyperlipidemia and menopausal status.* *p *value for difference (*p *for trend).*

drinking were significantly different among the groups.

Figure 1 shows the adjusted mean values of baPWV according to the number of MS components. Adjusted mean values of baPWV in men with 0, 1, 2, and ≥3 components were 1,309, 1,372, 1,422, and 1,462 cm/s, respectively ($p$ for trend <0.001). Adjusted mean values of baPWV in women with 0, 1, 2, and ≥3 components were 1,212, 1,292, 1,357, and 1,391 cm/s, respectively ($p$ for trend <0.001).

Figure 2 shows the adjusted geometric mean concentrations of CRP according to the number of MS components. Adjusted geometric mean concentrations of CRP in men with 0, 1, 2, and ≥3 components were 0.036, 0.049, 0.059, and 0.076 mg/dl, respectively ($p$ for trend <0.001). Adjusted geometric mean concentrations of CRP in women with 0, 1, 2, and ≥3 components were 0.023, 0.030, 0.057, and 0.077 mg/dl, respectively ($p$ for trend <0.001).

Figure 3 shows the adjusted mean values of baPWV according to the number of MS components and according to CRP levels within and without top quartile levels (≥0.090 mg/dl for men and ≥0.053 mg/dl for women). The $p$ value for the trend was significant (<0.001) in both men and women, but, in post hoc analyses, comparing high and low CRP levels in each MS component–number group, no significant difference was found.

## Discussion

In this study, baPWV and CRP were significantly associated with the number of MS components. However, combing MS and CRP data had little additive effect on the prediction of increased baPWV compared to the use of MS data alone.

In previous reports (*7*, *8*), CRP was significantly related to obesity, a component of MS. Adipose tissue secreted IL-6 (*24*) and TNF-α (*25*) as proinflammatory cytokines. The synthesis of CRP, mostly under the control of IL-6 (*26*) and TNF-α, can stimulate the production of CRP (*27*), which is significantly associated with glucose metabolism after controlling for BMI (*28–30*). Experimentally, hyperglycemia causes IL-6 and TNF-α release from monocytes (*31*, *32*). Furthermore, after controlling for BMI, CRP is associated with hypertension (*33*). Piche *et al*. have reported that, even after adjustment for visceral adipose tissue, CRP is related to insulin sensitivity and blood pressure, but is not related to a higher triglyceride level and low HDL cholesterol (*34*). Thus, the main MS components that influence the CRP level may be visceral obesity, hyperglycemia, and hypertension.

Several studies have reported a significant association between MS and arterial stiffness evaluated by PWV (*35–37*). Tomiyama *et al*. reported that PWV was significantly higher in MS subjects with elevated CRP than in those without it in a large study ($n$=5,752; men) (*36*). In this study, the number of male subjects was relatively small ($n$=3,512), and that of female subjects was smaller still ($n$=824), and these sample sizes may have diminished the statistical power of the analysis.

As previously mentioned, Ridker *et al*. reported that, at all levels of severity of MS, CRP added important and independent prognostic information in terms of future cardiovascular risk (*13*). However, another report insisted that combining CRP and MS data added little to overall cardiovascular disease risk prediction (*14*). Moreover, it has been reported that, for prediction of future major cardiovascular disease and major coronary heart disease, elevated CRP provides no further prognostic information beyond traditional risk factors (*38*). Indeed, as we previously reported, CRP was significantly related to PWV even after adjustment for conventional risk factors, but its predictive benefit for increased arterial stiffness might be rather small.

The present study has several limitations. The significance of baPWV for the prediction of cardiovascular events has not been reported. However, the validity and reliability of the methods used to measure baPWV have been established (*22*). Because waist circumstance was not available in this study, we used a modified version of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Pressure (Adult Treatment Panel III) (*20*). The American Heart Association (AHA)/Centers for Disease Control and Prevention (CDC) Scientific Statement recommends that the optimal cutoff point of CRP be 0.3 mg/dl based on cardiovascular disease event risk in cohort studies (*39*). But CRP varies substantially between people of different ethnic origins (*40*), and Japanese have lower CRP levels than Westerners (*8*, *41*). Additionally, the cutoff point of CRP for the prediction of cardiovascular disease events in Japanese has not been established. Therefore, in this study, CRP was divided into quartiles, and the top quartile of CRP was defined as high CRP. Jilma *et al*. (*42*) reported observing menstrual cycle–associated changes in the blood levels of CRP. But short-term fluctuations of CRP levels are infrequent (*43*), and most reports of the relationship between CRP and cardiovascular risk have not involved adjustments for the menstrual cycle. In our study, therefore, we did not ask our subjects about their menstrual cycle.

Because the definition of MS includes an increased blood pressure level, blood pressure adjustment was not used in our analysis of the adjusted mean baPWV. When SBP adjustment was added to the analysis, the significant differences disappeared (data not shown). Blood pressure was a contributing factor to baPWV, and we previously reported a relationship between blood pressure and baPWV based on multiple repression analysis (*44*). Additional studies with large sample sizes will be needed to examine the relation between blood pressure and baPWV in MS patients.

In summary, baPWV and CRP were significantly associated with the number of MS components. However, for prediction of increased arterial stiffness, combining MS and CRP data had little additive effect compared to the use of MS data alone.

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