

# AMCoR

Asahikawa Medical University Repository <http://amcor.asahikawa-med.ac.jp/>

Hypertension Research (2006.08) 29巻8号:589～596.

Metabolic Syndrome, C-Reactive Protein and Increased Arterial Stiffness  
in Japanese Subjects  
(日本人におけるメタボリックシンドローム、C反応性蛋白及び動脈硬化進展)

Saijo Yasuaki, Yoshioka Eiji, Fukui Tomonori, Kawaharada  
Mariko, Kishi Reiko

# **The Metabolic Syndrome, C-reactive Protein and Increased Arterial Stiffness in Japanese subjects**

---

**Yasuaki SAIJO\*, Eiji YOSHIOKA, Tomonori FUKUI, Mariko KAWAHARADA, Reiko  
KISHI**

Department of Public Health, Hokkaido University Graduate School of Medicine, Kita 15, Nishi 7,  
Kita-ku, Sapporo 060-8638, Japan

\* Department of Health Science, Asahikawa Medical College, Midorigaoka, E2-1-1-1, Asahikawa,  
Hokkaido 078-8510, Japan

Short running head: The metabolic syndrome, C-reactive protein and arterial stiffness

Grant: This work was supported in part by a Grant-in-Aid for Young Scientists from the Ministry  
of Education, Culture, Sports, Science and Technology of Japan and a Grant-in-Aid for Scientific  
Research from the Ministry of Health, Labour and Welfare of Japan.

Total number of tables: 2

Total number of figures: 3

Address for Reprints: Yasuaki Saijo, M.D., Ph.D., Department of Health Science, Asahikawa  
Medical College, Midorigaoka, E2-1-1-1, Asahikawa, Hokkaido 078-8510, Japan

E-mail: [y-saijo@asahikawa-med.ac.jp](mailto:y-saijo@asahikawa-med.ac.jp)

Telephone: +81 166 68 2402

Fax: +81 166 68 2409

## **Abstract**

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 3412 men and 854 women. Adjusted mean values of baPWV in men with 0, 1, 2, and  $\geq 3$  components were 1309, 1372, 1422, and 1462 cm/sec, respectively (p for trend  $<0.001$ ). Adjusted mean values of baPWV in women with 0, 1, 2, and  $\geq 3$  components were 1212, 1292, 1357, and 1391 cm/sec, respectively (p for trend  $<0.001$ ). Adjusted geometric mean concentrations of CRP in men with 0, 1, 2, and  $\geq 3$  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  $\geq 3$  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.

**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 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.

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 (8229 men and 2194 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 3907 men and 1044 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 ( $<0.9$ , 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 ex-smokers. Drinkers were defined as those who consumed alcohol once a week or more. With regard to leisure-time exercise (with perspiration), subjects were categorized as exercising “rarely or never”, or “ $\geq 1$  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<sup>2</sup>).

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 high density lipoprotein cholesterol (HDL-C) 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, Georgia. 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  $\geq 150$  mg/dL, (2) HDL cholesterol  $< 40$  mg/dL for men and  $< 50$  mg/dL for women, (3) blood pressure  $\geq 135/85$  mmHg, (4) fasting glucose  $> 110$  mg/dL, and (5) BMI  $> 25$  (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 ankle brachial index (ABI) were measured using a pulse-wave velocimeter concurrently with PWV measurement. ABI is the ratio of ankle systolic blood pressure to brachial systolic blood pressure, 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 males and females. The subjects were categorized according to the number of MS components present: 0, 1, 2, and  $\geq 3$  for men and women. The data are presented as the mean  $\pm$  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, heart rate, TC, UA, smoking status (smoker/nonsmoker), alcohol consumption

(drinker/rarely or never), frequency of exercise ( $\geq 1$ /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-transformed 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 ( $\geq 0.090$  mg/dL for men and  $\geq 0.053$  mg/dL for women). The subjects were classified as having 0, 1 to 2, and  $\geq 3$  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, IL).

## Results

Characteristics of the groups according to the number of MS components are shown in Table 1 for males and Table 2 for females. In male subjects, age, BMI, HR, systolic blood pressure (SBP), diastolic blood pressure (DBP), TC, TG, HDL-C, 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 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  $\geq 3$  components were 1309, 1372, 1422, and 1462 cm/sec, respectively (p for trend  $<0.001$ ). Adjusted mean values of baPWV in women with 0, 1, 2, and  $\geq 3$  components were 1212, 1292, 1357, and 1391 cm/sec, 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  $\geq 3$  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  $\geq 3$  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 the top quartile ( $\geq 0.090$  mg/dL for men and  $\geq 0.053$  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, combining 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- $\alpha$  (25) as proinflammatory cytokines. The synthesis of CRP, mostly under the control of IL-6 (26) and TNF- $\alpha$ , 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- $\alpha$  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=5752; male) (36). In this study, the number of male subjects was relatively small (n=3512), 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 CVD 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 circumference 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 AHA/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 systolic blood pressure 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 regression 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.



## **Acknowledgments**

We thank Mr. Manabu Shojiguchi, Mr. Hiroyuki Arizuka, Ms. Toyoko Enomoto, Mr. Takanori Mogi, Mr. Naoto Sasaki, Mr. Takeshi Tsuda, Ms. Tomoko Arihara, Dr. Toshiyuki Hayashi, Ms. Chizuko Sato, and Dr. Takehito Nakabayashi for their excellent assistance with data collection, and Ms. Akemi Onodera, Ms. Maki Fukushima, and Ms. Aki Yasuike for their assistance with the baPWV measurement.

## References

1. Isomaa B, Almgren P, Tuomi T, *et al.* Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care* 2001; **24**: 683-9.
2. Lakka HM, Laaksonen DE, Lakka TA, *et al.* The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. *JAMA* 2002; **288**: 2709-16.
3. Malik S, Wong ND, Franklin SS, *et al.* Impact of the metabolic syndrome on mortality from coronary heart disease, cardiovascular disease, and all causes in United States adults. *Circulation* 2004 ;**110**: 1245-50.
4. Ishizaka N, Ishizaka Y, Toda E, Hashimoto H, Nagai R, Yamakado M. Hypertension is the most common component of metabolic syndrome and the greatest contributor to carotid arteriosclerosis in apparently healthy Japanese individuals. *Hypertens Res* 2005 ; **28**: 27-34.
5. Takeuchi H, Saitoh S, Takagi S, *et al.* Metabolic syndrome and cardiac disease in Japanese men: applicability of the concept of metabolic syndrome defined by the National Cholesterol Education Program-Adult Treatment Panel III to Japanese men--the Tanno and Sobetsu Study. *Hypertens Res* 2005; **28**: 203-8.
6. Fernandez-Real JM, Ricart W. Insulin resistance and chronic cardiovascular inflammatory syndrome. *Endocr Rev* 2003; **24**: 278-301.
7. Lemieux I, Pascot A, Prud'homme D, *et al.* Elevated C-reactive protein: another component

of the atherothrombotic profile of abdominal obesity. *Arterioscler Thromb Vasc Biol* 2001; **21**: 961-7.

8. Saijo Y, Kiyota N, Kawasaki Y, *et al.* Relationship between C-reactive protein and visceral adipose tissue in healthy Japanese subjects. *Diabetes Obes Metab* 2004; **6**: 249-58.
9. Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. *N Engl J Med* 2000; **342**: 836-843.
10. Koenig W, Sund M, Frohlich M, *et al.* C-reactive protein, a sensitive marker of inflammation, predicts future risk of coronary heart disease in initially healthy middle-aged men: results from the MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) Augsburg Cohort Study, 1984 to 1992. *Circulation* 1999; **99**: 237-242.
11. Danesh J, Whincup P, Walker M, *et al.* Low grade inflammation and coronary heart disease: prospective study and updated meta-analyses. *BMJ* 2000; **321**: 199-204.
12. Ridker PM, Rifai N, Rose L, Buring JE, Cook NR. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. *N Engl J Med* 2002; **347**: 1557-65.
13. Ridker PM, Buring JE, Cook NR, Rifai N. C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events: an 8-year follow-up of 14 719 initially healthy

- American women. *Circulation* 2003; **107**: 391-7.
14. Rutter MK, Meigs JB, Sullivan LM, D'Agostino RB Sr, Wilson PW. C-reactive protein, the metabolic syndrome, and prediction of cardiovascular events in the Framingham Offspring Study. *Circulation* 2004; **110**: 380-5.
  15. Lehmann ED. Clinical value of aortic pulse-wave velocity measurement. *Lancet* 1999; **354**: 528-9.
  16. Asmar R, Benetos A, Topouchian J, *et al.* Assessment of arterial distensibility by automatic pulse wave velocity measurement. Validation and clinical application studies. *Hypertension* 1995; **26**: 485-90.
  17. Laurent S, Katsahian S, Fassot C, *et al.* Aortic stiffness is an independent predictor of fatal stroke in essential hypertension. *Stroke* 2003; **34**: 1203-6.
  18. Laurent S, Boutouyrie P, Asmar R, *et al.* Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. *Hypertension* 2001; **37**:1236-41.
  19. Guerin AP, Blacher J, Pannier B, Marchais SJ, Safar ME, London GM. Impact of aortic stiffness attenuation on survival of patients in end-stage renal failure. *Circulation* 2001; **103**: 987-92.
  20. Grundy SM, Cleeman JI, Merz CN, *et al.* Implications of recent clinical trials for the

National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation* 2004; **110**: 227-39.

21. Examination Committee of Criteria for 'Obesity Disease' in Japan; Japan Society for the Study of Obesity. New criteria for 'obesity disease' in Japan. *Circ J* 2002 ; 66: 987-92
22. Yamashina A, Tomiyama H, Takeda K, *et al.* Validity, reproducibility, and clinical significance of noninvasive brachial-ankle pulse wave velocity measurement. *Hypertens Res* 2002; **25**: 359-64.
23. Tomiyama H, Yamashina A, Arai T, *et al.* Influences of age and gender on results of noninvasive brachial-ankle pulse wave velocity measurement—a survey of 12517 subjects. *Atherosclerosis* 2003; **166**: 303-9.
24. Purohit A, Ghilchik MW, Duncan L, *et al.* Aromatase activity and interleukin-6 production by normal and malignant breast tissues. *J Clin Endocrinol Metab* 1995; **80**: 3052-8.
25. Hotamisligil GS, Arner P, Caro JF, Atkinson RL, Spiegelman BM. Increased adipose tissue expression of tumor necrosis factor-alpha in human obesity and insulin resistance. *J Clin Invest* 1995; **95**: 2409-15
26. Heinrich PC, Castell JV, Andus T. Interleukin-6 and the acute phase response. *Biochem J* 1990; **265**: 621-36.
27. Festa A, D'Agostino R Jr, Howard G, Mykkanen L, Tracy RP, Haffner SM. Chronic

subclinical inflammation as part of the insulin resistance syndrome: the Insulin Resistance Atherosclerosis Study (IRAS). *Circulation* 2000; **102**: 42-7.

28. Warren RS, Starnes HF Jr, Gabilove JL, Oettgen HF, Brennan MF. The acute metabolic effects of tumor necrosis factor administration in humans. *Arch Surg* 1987; **122**: 1396-400.
29. Wu T, Dorn JP, Donahue RP, Sempos CT, Trevisan M. Associations of serum C-reactive protein with fasting insulin, glucose, and glycosylated hemoglobin: the Third National Health and Nutrition Examination Survey, 1988-1994. *Am J Epidemiol* 2002; **155**: 65-71.
30. Aronson D, Bartha P, Zinder O, *et al.* Association between fasting glucose and C-reactive protein in middle-aged subjects. *Diabet Med* 2004; **21**: 39-44.
31. Morohoshi M, Fujisawa K, Uchimura I, Numano F. Glucose-dependent interleukin 6 and tumor necrosis factor production by human peripheral blood monocytes in vitro. *Diabetes* 1996; **45**: 954-9.
32. Guha M, Bai W, Nadler JL, Natarajan R. Molecular mechanisms of tumor necrosis factor alpha gene expression in monocytic cells via hyperglycemia-induced oxidant stress-dependent and -independent pathways. *J Biol Chem* 2000; **275**: 17728-39.
33. Lakoski SG, Cushman M, Palmas W, Blumenthal R, D'Agostino RB Jr, Herrington DM. The relationship between blood pressure and C-reactive protein in the Multi-Ethnic Study of Atherosclerosis (MESA). *J Am Coll Cardiol* 2005; **46**: 1869-74.

34. Piche ME, Lemieux S, Weisnagel SJ, Corneau L, Nadeau A, Bergeron J. Relation of high-sensitivity C-reactive protein, interleukin-6, tumor necrosis factor-alpha, and fibrinogen to abdominal adipose tissue, blood pressure, and cholesterol and triglyceride levels in healthy postmenopausal women. *Am J Cardiol* 2005; **96**: 92-7.
35. Nakanishi N, Suzuki K, Tatara K. Clustered features of the metabolic syndrome and the risk for increased aortic pulse wave velocity in middle-aged Japanese men. *Angiology* 2003; **54**: 551-9.
36. Tomiyama H, Koji Y, Yambe M, *et al.* Elevated C-reactive protein augments increased arterial stiffness in subjects with the metabolic syndrome. *Hypertension* 2005; **45**: 997-1003.
37. Nakanishi N, Shiraishi T, Wada M. Brachial-ankle pulse wave velocity and metabolic syndrome in a Japanese population: the Minoh study. *Hypertens Res* 2005; **28**: 125-31.
38. Wilson PW, Nam BH, Pencina M, D'Agostino RB Sr, Benjamin EJ, O'Donnell CJ. C-reactive protein and risk of cardiovascular disease in men and women from the Framingham Heart Study. *Arch Intern Med* 2005; **165**: 2473-8.
39. Pearson TA, Mensah GA, Alexander RW, *et al.* Markers of inflammation and cardiovascular disease: application to clinical and public health practice: A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation* 2003; **107**: 499-511.

40. Anand SS, Razak F, Yi Q, *et al.* C-reactive protein as a screening test for cardiovascular risk in a multiethnic population. *Arterioscler Thromb Vasc Biol* 2004; **24**:1509-15.
41. Yamada S, Gotoh T, Nakashima Y, *et al.* Distribution of serum C-reactive protein and its association with atherosclerotic risk factors in a Japanese population : Jichi Medical School Cohort Study. *Am J Epidemiol* 2001; **153**: 1183-90.
42. Jilma B, Dirnberger E, Loscher I, *et al.* Menstrual cycle-associated changes in blood levels of interleukin-6, alpha1 acid glycoprotein, and C-reactive protein. *J Lab Clin Med* 1997; **130**: 69-75.
43. Macy EM, Hayes TE, Tracy RP. Variability in the measurement of C-reactive protein in healthy subjects: implications for reference intervals and epidemiological applications *Clin Chem* 1997; **43**: 52-58.
44. Saijo Y, Utsugi M, Yoshioka E, *et al.* Relationships of C-reactive protein, uric acid, and glomerular filtration rate to arterial stiffness in Japanese subjects. *J Hum Hypertens* 2005; **19**: 907-13.



## Figure legends

FIGURE 1 Adjusted mean (SE) 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).

FIGURE 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).

FIGURE 3 Adjusted mean (SE) values of baPWV according to the number of metabolic

syndrome components and according to CRP levels within or without top quartile levels ( $\geq 0.090$  mg/dL for men  $\geq 0.053$  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).

**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=1274)	1 (n=1060)	2 (n=662)	≥3 (n=409)	
Age (y)	46.8 ± 7.1	49.0 ± 6.7	49.6 ± 6.5	49.6 ± 6.0	<0.0001
BMI (kg/m <sup>2</sup> )	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
≥1week	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)	1276 ± 135	1380 ± 187	1448 ± 209	1501 ± 244	<0.0001

Variables are presented as mean±SD, median(interguatile range) for skewed variables, or percentage

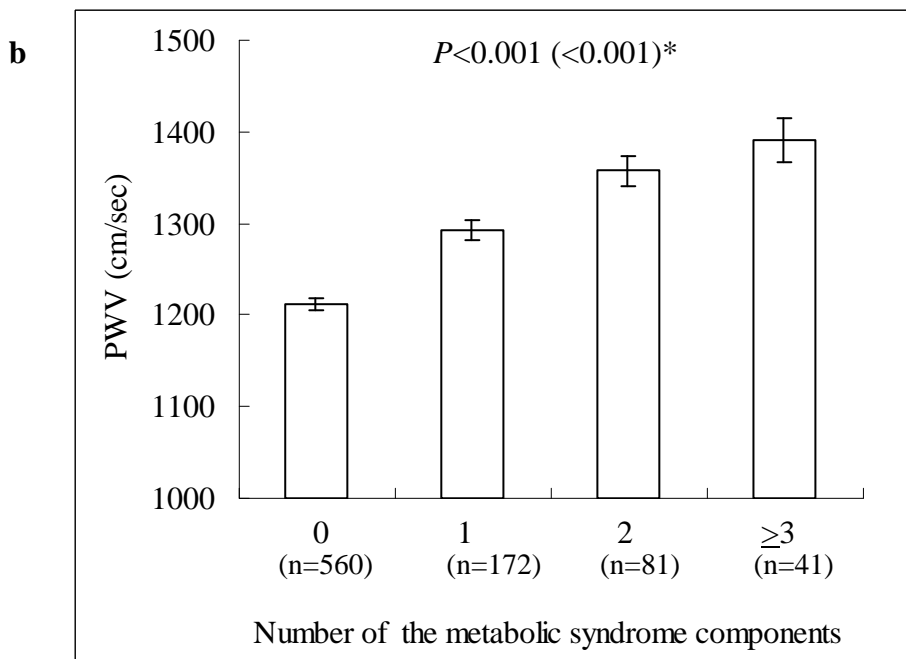
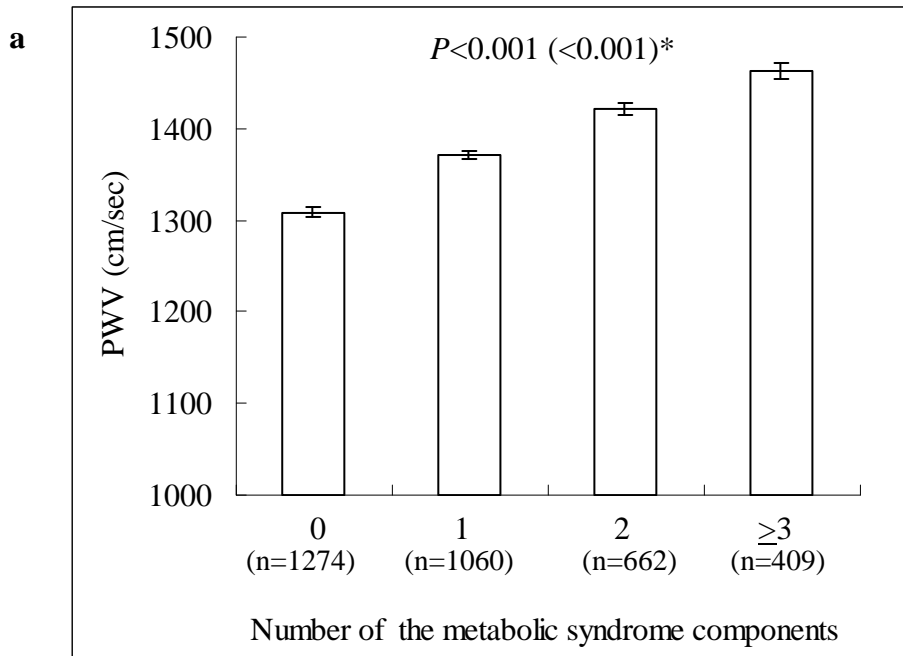
**Table 2.** Characteristics of female subjects according to the number of metabolic syndrome components.

	Number of Metabolic Syndrome Components				p value
	0 (n=560)	1 (n=172)	2 (n=81)	$\geq 3$ (n=41)	
Age (y)	45.3 $\pm$ 7.1	49.1 $\pm$ 6.4	49.8 $\pm$ 6.6	51.5 $\pm$ 5.9	<0.0001
BMI (kg/m <sup>2</sup> )	20.6 $\pm$ 2.1	23.0 $\pm$ 3.3	25.4 $\pm$ 4.2	27.3 $\pm$ 4.0	<0.0001
SBP (mmHg)	108.0 $\pm$ 9.2	123.0 $\pm$ 16.4	128.2 $\pm$ 17.8	140.9 $\pm$ 16.6	<0.0001
DBP (mmHg)	65.4 $\pm$ 7.0	74.7 $\pm$ 11.3	76.8 $\pm$ 10.4	84.7 $\pm$ 9.7	<0.0001
Heart rate (bpm)	58.6 $\pm$ 7.5	60.4 $\pm$ 8.2	61.8 $\pm$ 9.9	65.4 $\pm$ 9.2	<0.0001
Total cholesterol (mg/dL)	204.2 $\pm$ 30.6	212.1 $\pm$ 32.1	221.3 $\pm$ 32.1	222.9 $\pm$ 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 $\pm$ 13.2	68.0 $\pm$ 15.5	56.2 $\pm$ 12.6	51.4 $\pm$ 9.3	<0.0001
Fasting glucose (mg/dL)	85.0 $\pm$ 7.2	90.8 $\pm$ 12.4	97.8 $\pm$ 22.7	113.5 $\pm$ 35.4	<0.0001
Uric acid (mg/dL)	4.3 $\pm$ 0.8	4.7 $\pm$ 1.1	5.1 $\pm$ 1.2	5.3 $\pm$ 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
≥1week	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 (%)	31.8	48.8	56.8	68.3	<0.0001
Postmenopausal					
Current use of hormone-replacement therapy (%)	1.8	3.5	1.2	0.0	0.37
PWV (cm/s)	1191 ± 130	1317 ± 195	1404 ± 221	1478 ± 164	<0.0001

Variables are presented as mean±SD, median (interquartile range) for skewed variables, or percentage.

**Fig. 1.** Adjusted mean (SE) values of baPWV according to the number of metabolic syndrome components.

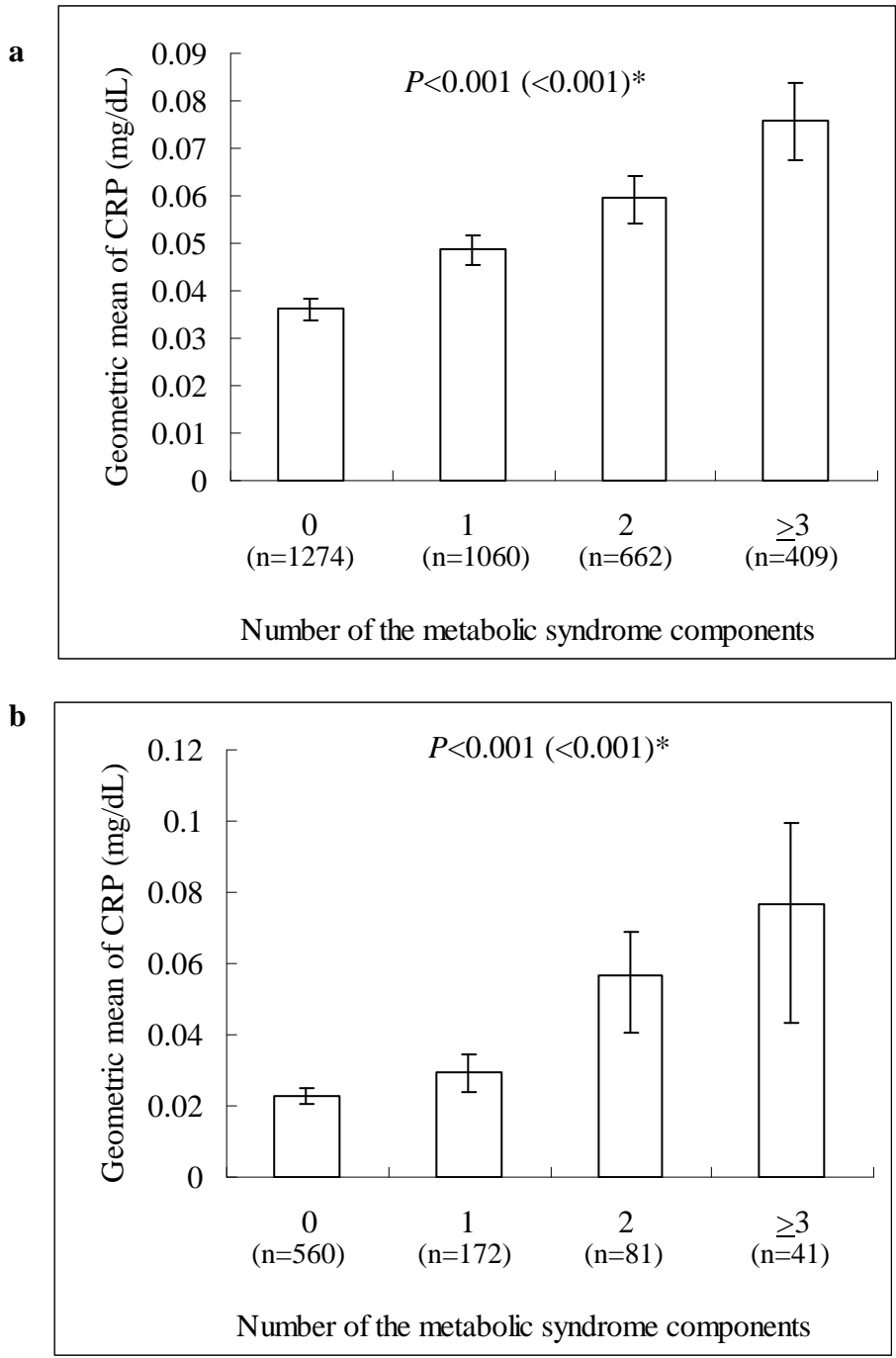


(a) Men: adjusted for age, heart rate, TC, UA, smoking status, alcohol consumption, frequency of exercise, educational attainment and medication for hyperlipidemia. (b) Women: adjusted for age, heart rate, TC, UA, smoking status, alcohol consumption, frequency of exercise, educational attainment, medication for hyperlipidemia and menopausal status.

\**P* value for difference (*P* for trend).



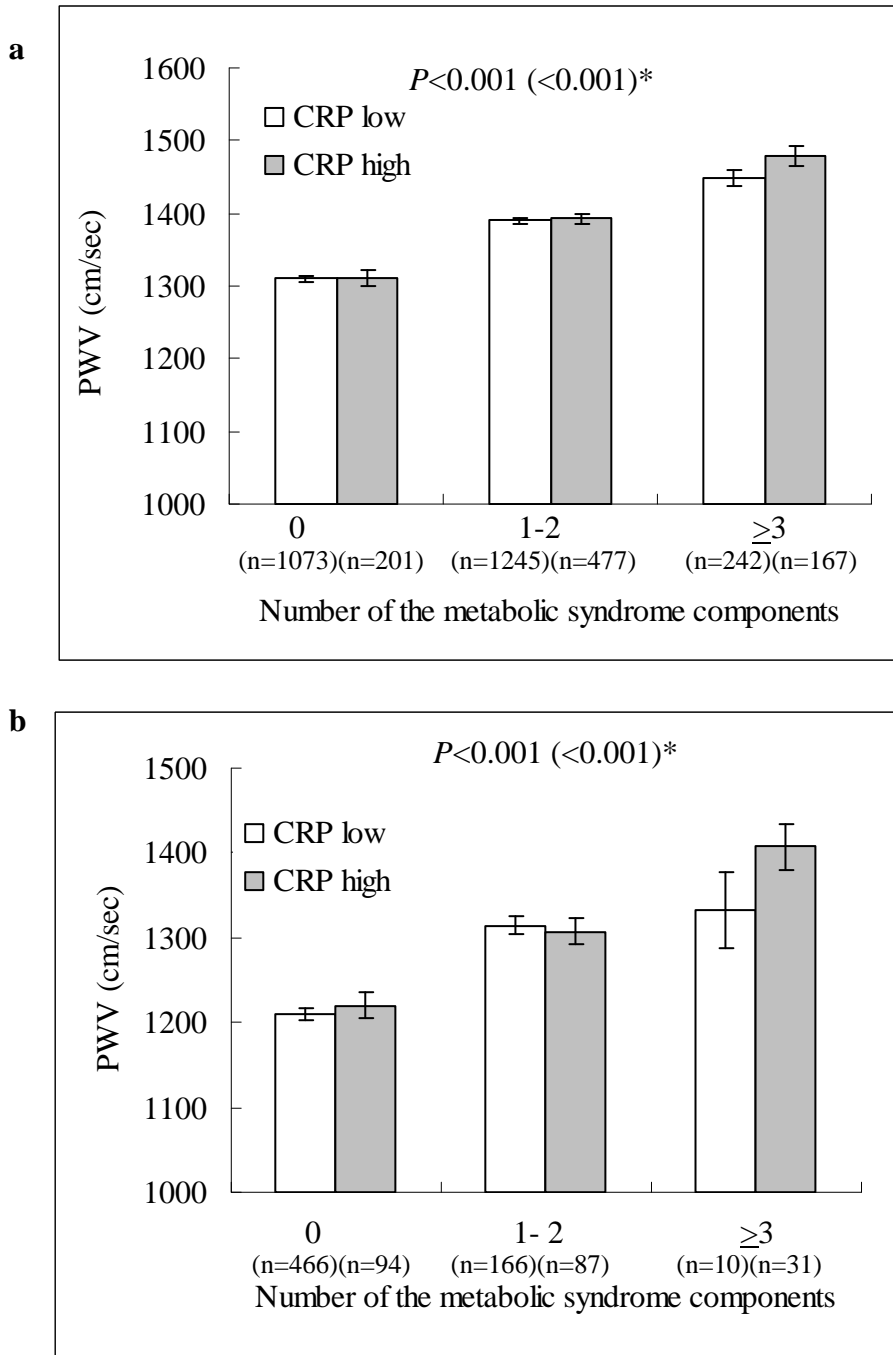
**Fig. 2.** Adjusted geometric mean (95%CI) concentrations of CRP according to the number of metabolic syndrome components.



(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).

**Fig. 3.** Adjusted mean (SE) values of baPWV according to the number of metabolic syndrome components and according to CRP levels within or without top quartile levels ( $\geq 0.090$  mg/dL for men and  $\geq 0.053$  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).

## **Abbreviations**

MS: metabolic syndrome

CRP: C-reactive protein

PWV: pulse wave velocity

baPWV: brachial-ankle pulse wave velocity

BSA: body surface area

BMI: body mass index

TC: total cholesterol

TG: triglycerides

HDL-C: high density lipoprotein cholesterol

UA: uric acid

HR: heart rate

ABI: ankle brachial index

ANOVA: analysis of variance

GLM: general linear model

SBP: systolic blood pressure

DBP: diastolic blood pressure