Original Article

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

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Results of a 6-year follow-up study were used to determine whether the concept of and the criteria for metabolic syndrome as defined by the National Cholesterol Education Program–Adult Treatment Panel III (NCEP-ATP III) can be applied to Japanese men for prediction of the occurrence of cardiac disease. The subjects were 808 men who underwent mass health check-ups in 1993 and who were not on medication for hypertension, diabetes or hyperlipidemia. Individuals who had hypertriglyceridemia, hypo-high density lipoprotein (HDL) cholesterolemia, high blood pressure, and/or high fasting plasma glucose levels were identified on the basis of the NCEP-ATP III criteria. Not in conformity with the NCEP-ATP III, however, a cut-off value of 85 cm was used for waist girth as an indicator of abdominal obesity. The subjects who had 3 or more risk factors were judged as having metabolic syndrome. The proportion of subjects having metabolic syndrome was 25.3%. In the 6-year follow-up study, cardiac disease occurred in 11.7% of the subjects in the metabolic syndrome group and in 6.7% of the subjects in the non-metabolic syndrome group. Results of regression analysis using Cox's proportional hazards model showed that subjects in the metabolic syndrome group had a 2.2-times greater risk of developing cardiac disease than did subjects in the non-metabolic syndrome group. The concept of metabolic syndrome as defined in the NCEP-ATP III was therefore considered to be useful for predicting the occurrence of cardiac disease in Japanese men. (*Hypertens Res* 2005; 28: 203–208)

***Key Words*: metabolic syndrome, National Cholesterol Education Program–Adult Treatment Panel III, insulin resistance, prognosis**

Introduction

The third revision of the Adult Treatment Panel (ATP III) (*1*) is a guideline for cholesterol testing and management in the United States published by the National Cholesterol Education Program (NCEP) in 2001. The NCEP-ATP III emphasizes, in addition to the importance of cholesterol control, the importance of other risk factors for development of cardiovascular diseases, especially coronary heart disease, and proposes that concurrence of risk factors in individuals be designated as metabolic syndrome. This indicates that rigid control of the serum cholesterol level alone cannot completely prevent the occurrence of coronary heart diseases and

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Table 1. Characteristics of Subjects with and without Metabolic Syndrome at Baseline (1993)

	Subjects with metabolic syndrome (n=197)	Subjects without metabolic syndrome (n=583)	p
Age (years)	61.8±11.2	59.8±12.1	0.050
BMI (kg/m^2)	25.2±2.9	22.5±2.8	<0.001
Waist (cm)	89.9±6.8	80.5±8.6	<0.001
SBP (mmHg)	140.6±14.4	131.3±18.5	<0.001
DBP (mmHg)	84.8±8.2	80.0±9.1	<0.001
T-cho (mg/dl)	192.8±34.1	184.8±30.4	0.004
HDL (mg/dl)	45.4±13.6	57.2±13.3	<0.001
TG (mg/dl)	211.1±99.2	124.3±64.3	<0.001
FPG (mg/dl)	103.5±25.7	90.7±15.2	<0.001

BMI, body mass index; Waist, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; T-cho, total cholesterol level; HDL, high density lipoprotein-cholesterol level; LDL, low density lipoprotein-cholesterol level; TG, triglyceride level; FPG, fasting plasma glucose. Values are means±SDs.

that risk factors other than low density lipoprotein (LDL)-cholesterol and their concurrence in individuals are crucial to the development of coronary heart diseases.

In the NCEP-ATP III, metabolic syndrome in men is defined as the coexistence in an individual of at least three of the following: 1) waist girth over 102 cm, 2) serum triglyceride level over 150 mg/dl, 3) serum high density lipoprotein (HDL)-cholesterol level below 40 mg/dl, 4) systolic blood pressure (SBP) over 130 mmHg and/or diastolic blood pressure (DBP) over 85 mmHg, and 5) fasting plasma glucose level over 110 mg/dl. The existence of insulin resistance seems to underlie metabolic syndrome. We previously reported that the existence of insulin resistance contributes to the development of metabolic syndrome in Japanese men (*2*–*4*). In Japanese people with a genetic predisposition to low mean serum cholesterol levels, insulin resistance is relatively more influential than the other risk factors for cardiovascular diseases, including coronary heart disease (*4*, *5*). The designation of metabolic syndrome in the NCEP-ATP III appears to be useful for prevention of arteriosclerotic diseases in Japanese people as in the United States. However, to our knowledge, there has been no report on the association between metabolic syndrome and cardiac diseases in Japanese people.

The aim of this study was to determine whether the concept of and the criteria for metabolic syndrome proposed by the NCEP-ATP III can be applied to Japanese men to predict onset of cardiac diseases and whether the criterion of three or more risk factors for the diagnosis of metabolic syndrome is a reasonable one on the basis of the results of a 6-year follow-up study.

Methods

The subjects were 808 men who underwent health examinations in the towns of Tanno and Sobetsu in Hokkaido, Japan (*6*) and who were not receiving treatment for hypertension, diabetes or hyperlipidemia. The mean age of the subjects was 60.3±11.9 years. Information on medication being taken by the subjects was obtained through questionnaires distributed by a health nurse. Informed consent for inclusion in this study was obtained from all subjects. Blood samples were collected early in the morning from subjects more than 10 h after the last dietary intake. The plasma level of glucose (determined by the glucose-oxidize electrode method), and the serum total cholesterol (cholesterol-oxidize–dimethoxy-anilinehydroxy-3-sulfopropyl [DAOS] method), serum HDL-cholesterol (dextran-sulfate magnesium-hydrochloride precipitation method) and serum triglyceride levels (glycerol-3-phosphate-oxidize–DAOS method) were measured. Waist girth was measured (*7*) after expiration at the level of the navel by the same technician. Blood pressure was measured twice in the sitting position using a mercury sphygmomanometer (the first phase of Korotkoff's sound was taken as the SBP and the fifth phase was taken as the DBP). The average of the two measurements was used for analysis.

Subjects having one or more of the following criteria for metabolic syndrome in the NCEP-ATP III were identified: serum triglyceride level over 150 mg/dl (hypertriglyceridemia [HTG]), serum HDL-cholesterol level below 40 mg/dl (low-HDL cholesterolemia [LHDL]), SBP over 130 mmHg and/or DBP over 85 mmHg (high blood pressure [HBP]), fasting plasma glucose level over 110 mg/dl (high fasting plasma glucose level [HFPG]), and waist girth over 85 cm (abdominal obesity [AO]). The criterion for abdominal obesity defined by the NCEP-ATP III is waist girth over 102 cm. Of the 808 subjects in the present study, only 17 (2.7%) fulfilled this criterion (waist girth over 102 cm). We therefore used waist girth over 85 cm, which is the criterion for obesity of visceral fat type of the Japan Society for the Study of Obesity (*7*, *8*), as the criterion for AO. Subjects who had 3 or more of the risk factors were judged as having metabolic syndrome (MS group), and subjects who had 2 or less risk factors were judged as not having metabolic syndrome (non-MS group). Twenty-eight men for whom data on waist circumference or

Table 2. Characteristics of Subjects with and Subjects without Cardiac Disease at Baseline (1993)

	Subjects with cardiac disease (n=49)	Subjects without cardiac disease (n=566)	p
Age (years)	64.6±7.4	61.6±10.6	0.014
BMI (kg/m^2)	23.3±3.2	23.2±4.2	0.727
Waist (cm)	85.0±9.8	82.6±9.3	0.104
SBP (mmHg)	136.5±17.6	134.3±18.1	0.399
DBP (mmHg)	81.6±8.1	81.7±9.3	0.944
T-cho (mg/dl)	181.4±31.9	187.0±31.1	0.240
HDL (mg/dl)	53.6±14.9	54.6±14.4	0.676
TG (mg/dl)	139.0±62.2	144.3±85.2	0.584
FPG (mg/dl)	95.8±20.9	93.5±17.9	0.446

Abbreviations are the same as in Table 1. Cardiac diseases are angina pectoris, myocardial infarction, heart failure and death from such cardiac diseases. Values are means±SDs.

on biochemical measures included in the definition of MS were missing were excluded, leaving 780 men for analysis.

The subjects were followed up for 6 years. The end-point was the occurrence of cardiac diseases, including angina pectoris, myocardial infarction, and heart failure, or death from such cardiac diseases. Occurrence of cardiac diseases was determined by interviews with the subjects and their families, notification from district health nurses, and distribution of questionnaires to family doctors who had treated subjects with cardiac disease. Diagnosis of cardiac disease was made from clinical symptoms and results of laboratory examinations such as ECG, chest X-ray photograph (XP) and blood tests. Diagnosis of coronary heart disease was made on the basis of the criteria of the MONICA project (available from: http://www.ktl.fi/publications/monica/manual/index.htm). The incidence of cardiac diseases during the 6-year period was compared between the MS group and the non-MS group. Moreover, the incidences of cardiac diseases in subjects who had 2 or more risk factors (2, 3, 4 or 5 risk factors) and in subjects who had 4 or more risk factors (4 or 5 risk factors) in the first year were compared with the incidences in subjects who had less than 2 risk factors (0 or 1 risk factor) and in subjects who had less than 4 risk factors (1, 2 or 3 risk factors), respectively. Follow-up was started in August 1993 and completed in August 1999.

The Japanese Windows Edition of the Statistical Package for Social Science (SPSS) Ver. 11 was used for statistical analysis. All numerical values are expressed as the means±SD. The unpaired t-test was used for examination of intergroup differences. For analysis of factors determining prognosis, Cox's proportional hazards model was used. A p-value less than 0.05 was considered statistically significant.

Results

The mean age of all subjects was 60.3±11.9 years, the mean body weight was 61.3±9.8 kg, the mean body mass index (BMI) was 23.1±3.0 kg/m^2 and the mean waist girth was 82.8±9.2 cm. The mean SBP and DBP were 133.7±18.0 mmHg and 81.2±9.1 mmHg, respectively, and the mean plasma levels of total cholesterol, HDL-cholesterol, triglyceride and fasting blood glucose were 186.8±31.6 mg/dl, 54.3±14.4 mg/dl, 146.2±83.6 mg/dl and 94.1±19.3 mg/dl, respectively.

The proportions of subjects with AO, HTG, LHDL, HBP and HFPG were 43.1%, 35.7%, 16.5%, 59.4% and 13.8%, respectively. The proportions of subjects without risk factors was 18.1%, and the proportions of subjects with 1, 2, 3, 4 and 5 risk factors were 29.7%, 26.9%, 17.5%, 6.8% and 1.0%, respectively. The proportionsof subjects with 2 or more, 3 or more and 4 or more risk factors were 52.2%, 25.3% and 7.8%, respectively. Subjects who had 3 or more risk factors were assigned to the MS group.

Table 1 compares the profiles of subjects in the MS group with those of subjects in the non-MS group (*i.e.*, subjects with two or less risk factors). There were no significant differences between the two groups in age. The values of BMI, waist girth and blood pressure and the levels of total cholesterol, triglycerides and fasting plasma glucose were significantly higher in the MS group. The HDL-cholesterol level was significantly lower in the MS group.

During the follow-up study, from 1993 to 1999, 193 subjects dropped out. There was no significant difference between the subjects who dropped out and the remaining subjects in terms of the proportion of subjects with metabolic syndrome. The remaining 615 subjects were followed for a mean period of 4.8 years. Cardiac disease occurred in 49 subjects (angina pectoris occurred in 30 subjects, myocardial infarction in 15 subjects and heart failure in 4 subjects), or 31 subjects in the non-MS group and 18 subjects in the MS group.Thirty-two of the subjects with 2 or more risk factors and four of the subjects with 4 or more risk factors developed cardiac disease. Table 2 shows a comparison of clinical characteristics at baseline between subjects with and those without cardiac disease. There were no significant differences between the two groups in the values of BMI, waist girth or

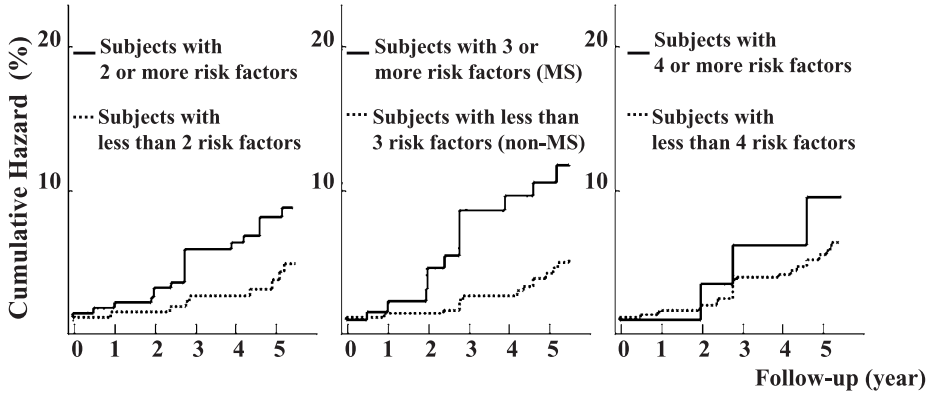

Fig. 1. *Kaplan-Meier hazard curves for onset of cardiac disease. The relative risk in the MS group was 2.23 (95% CI: 1.14–4.34,* p*=0.019)-times higher than that in the non-MS group. The risk in the subjects with 2 or more risk factors relative to the risk in the subjects with less than 2 risk factors was 1.43 (0.73–2.81,* p*=0.301). The risk in the subjects with 4 or more risk factors relative to the risk in the subjects with less than 4 risk factors was 1.74 (0.61–4.93,* p*=0.299). Relative risk was determined by Cox's proportional hazards model adjusted for age, smoking and total cholesterol.*

blood pressure or in the levels of total cholesterol, triglycerides, fasting plasma glucose and HDL-cholesterol. The Kaplan-Meier hazard curve showed that the incidence of cardiac diseases was significantly higher in the MS group than in the non-MS group during the follow-up study (Fig. 1). The relative risk of occurrence of cardiac diseases in the MS group was 2.23 (95% confidence interval [CI]: 1.14–4.34; $p=0.019$)-times higher than that in the non-MS group according to the results of analysis using Cox's proportional hazards model adjusted for age, smoking and total cholesterol. The risks of occurrence of cardiac diseases in the subjects with 2 or more risk factors and in those with 4 or more risk factors relative to the risks in the subjects with less than 2 risk factors and in those with less than 4 risk factors were 1.43 (0.73–2.81, $p=0.301$) and 1.74 (0.61–4.93, $p=0.299$), respectively (Table 3).

Discussion

Hyperlipidemia, hypertension, disorders in glucose tolerance, and obesity are well-known risk factors for cardiovascular diseases. It was clarified by epidemiological studies in the 1990s that even if the risks of individual factors were not serious, the probability of the occurrence of ischemic cardiac diseases would increase when many risk factors coexisted in an individual (*9*–*16*). The clinical findings for metabolic syndrome as defined by the NCEP-ATP III reflect this state. The definition of metabolic syndrome by NCEP-ATP III emphasizes the importance of abdominal obesity and includes in the diagnostic criteria mild risk factors such as blood pressure at high levels within the normal range and hyperglycemia under a fasting condition. The diagnostic criteria for individual risk factors are shown more clearly in the criteria of metabolic syndrome as defined by NCEP-ATP III. High blood pressure and hyperglycemia are defined as risk factors in MS, even though in general they are less severe conditions than hypertension or diabetes as defined in the Sixth Report of the Joint National Committee (JNC VI) (*17*), or by the criteria of the World Health Organization-International Society of Hypertension (WHO/ISH) (*18*), the World Health Organization (WHO) (*19*), or the American Diabetes Association (ADA) (*20*) . This indicates that the concurrence of mild risk factors is crucial for the development of arteriosclerosis in the concept of metabolic syndrome.

In the present study, the criteria for metabolic syndrome in the NCEP-ATP III were applied to Japanese men with the modification that 85 cm instead of 102 cm was used for the cut-off value of waist girth for AO. Using the original NCEP-ATP III criteria, only 2.7% of the present subjects fulfilled the criterion of waist girth over 102 cm, and the prevalence of the metabolic syndrome was 12%. We therefore used as the criterion for AO waist girth over 85 cm, which is the criterion of the Japan Society for the Study of Obesity (*7*, *8*) for obesity of visceral fat type. Waist girth of 85 cm in Japanese men is known to correspond to an area occupied by visceral fat of 100 cm^2 in transverse CT images at the level of the navel (*8*). The incidences of hypertension, diabetes, hyperlipidemia and diseases of the circulatory organs are high in men in whom the area of visceral fat exceeds 100 cm^2 in transverse CT images (*8*, *21*). An increase in the amount of visceral fat, which causes abdominal obesity, tends to induce insulin resistance and is associated with arteriosclerosis (*8*, *21*, *22*). Measurement of waist girth is a simple but apparently useful method for diagnosing abdominal obesity. In Asians, decreasing the criterion of waist circumference increased the prevalence of the metabolic syndrome. When the criterion of waist

Table 3. Hazard Ratio for Occurrence of Cardiac Diseases According to the Results of Cox's Proportional Hazards Model Adjusted for Age, Smoking and Total Cholesterol

Subjects	Hazard ratio (95% confidence interval)
With 2 or more risk factors†	1.43 (0.73–2.81)
With 3 or more risk factors (MS)††	2.23 (1.14–4.34)*
With 4 or more risk factors†††	1.74 (0.61–4.93)

*$p<0.05$. †The risk of occurrence of cardiac diseases in the subjects with 2 or more risk factors relative to the risk in those with less than 2 risk factors. ††The risk in the MS group relative to the risk in the non-MS group. †††The risk in the subjects with 4 or more risk factors relative to the risk in those with less than 4 risk factors.

circumference was decreased from 102 cm to 90 cm, the prevalence of the metabolic syndrome increased 13% to 21% in the Singapore male population (*23*), and 16% to 29% in the Korean male population (*24*). This suggests that NCEP-ATP III criteria may underestimate the population at risk in the Asian population. There is thus need of a new abdominal obesity criterion for metabolic syndrome that is suitable for the Japanese population.

Lakka *et al*. (*25*) reported in 2002 that the risk of mortality from coronary heart diseases was higher in individuals with metabolic syndrome in the ordinary Finnish male population that included subjects who were receiving treatment for hypertension or hyperlipidemia, and they emphasized the importance of prevention of development of metabolic syndrome and the importance of its diagnosis and therapy in an early stage. In the present study, in the subjects who were not receiving treatment for hypertension, diabetes or hyperlipidemia, the relative risk of mortality and morbidity from cardiac disease in the metabolic syndrome group, even after adjusting for age, smoking and total cholesterol, was 2.2-times greater than that in the non-metabolic syndrome group.

On the other hand, there were no significant differences between cardiac disease mortality/morbidity in the subjects with 2 or more risk factors and those with less than 2 risk factors or between cardiac disease mortality/morbidity in the subjects with 4 or more risk factors and those with less than 4 risk factors. This indicates that the NCEP-ATP III criterion for metabolic syndrome, *i.e.*, the presence of 3 or more risk factors, is reasonable for predicting cardiac disease in the Japanese population.

Our results indicate that the concept of metabolic syndrome defined by the NCEP-ATP III is useful for prediction of onset of cardiac disease in Japanese men.

The concept of metabolic syndrome seems to be strategically important for prevention of arteriosclerotic diseases in Japan as well as in the United States, Finland or other countries, because individuals with metabolic syndrome can be easily identified according to the criteria. It is important to control risk factors for cardiovascular diseases, such as lipid metabolic disorders, high blood pressure, disorders in glucose tolerance, and obesity, in persons with metabolic syndrome (*i.e.*, in persons having three or more of these risk factors), even if the risk of each factor is not serious. A strategy for the control of these risk factors is therefore needed.

References

1. National Cholesterol Education Program: Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 2001; **285**: 2486–2497.
2. Ohnishi H, Saitoh S, Ura N, *et al*: Relationship between insulin resistance and accumulation of coronary risk factors. *Diabetes, Obes Metab* 2002; **4**: 388–393.
3. Takeuchi H, Saitoh S, Takagi S, *et al*: Metabolic syndrome and insulin resistance in Japanese males—Tanno-Soubestu study. *J Jpn Diab Soc* 2003; **46**: 739–744.
4. Murakami H, Ura N, Furuhashi M, Higashiura K, Miura T, Shimamoto K: Role of adiponectin in insulin-resistant hypertension and atherosclerosis. *Hypertens Res* 2003; **26**: 705–710.
5. Hirose H, Saito I, Kawabe H, Saruta T: Insulin resistance and hypertension: seven-year follow-up study in middle-aged Japanese men (the KEIO Study) . *Hypertens Res* 2003; **26**: 795–800.
6. Takagi S, Saitoh S, Nakano M, *et al*: Relationship between blood pressure level and mortality rate: an 18-year study conducted in two rural communities in Japan. *J Hypertens* 2000; **18**: 143–148.
7. Matsuzawa Y: The new diagnostic criteria of obesity. *J Jpn Soc Stud Obes* 2000; **6**: 18–28.
8. 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**: 987–992.
9. Ruige JB, Assendelft WJJ, Dekker JM, Kostense PJ, Heine RJ, Bouter LM: Insulin and risk of cardiovascular disease. A meta-analysis. *Circulation* 1998; **97**: 996–1001.
10. Lempiainen P, Mykkanen L, Pyorala K, Laakso M, Kuusisto J: Insulin resistance syndrome predicts coronary heart disease events in elderly nondiabetic men. *Circulation* 1999; **100**: 123–128.
11. Nakamura T, Tsubono Y, Kameda K, *et al*: Magnitude of sustained multiple risk factors for ischemic heart disease in Japanese employees: a case-control study. *Jpn Circ J* 2001; **65**: 11–17.
12. Reaven GM: Role of insulin resistance in human disease. *Diabetes* 1988; **37**:1595–1607.
13. Kaplan NM: The deadly quartet: Upper-body obesity, glucose intolerance, hypertriglyceridemia, and hypertension. *Arch Intern Med* 1989; **149**: 1514–1520.
14. DeFronzo RA, Ferranni E: Insulin resistance: a multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. *Diabetes Care* 1991; **14**: 173–194.
15. Zimmet P, Alberti KGMM, Shaw J: Global and societal

implications of the diabetes epidemic. *Nature* 2001; **414**: 782–787.
16. Tozawa M, Iseki K, Iseki C, *et al*: Impact of multiple risk factor clustering on the elevation of blood pressure. *Hypertens Res* 2002; **25**: 811–816.
17. Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Arch Intern Med* 1997; **157**: 2413–2446.
18. Guidelines Subcommittee: 1999 World Health Organization–International Society of Hypertension Guidelines for the Management of Hypertension. *J Hypertens* 1999; **17**: 151–183.
19. Alberti KG, Zimmet PZ: Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med* 1998; **15**: 539–553.
20. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 1997; **20**: 1183–1197.
21. Nakamura T, Tokunaga K, Shimomura I, *et al*: Contribution of visceral fat accumulation to the development of coronary artery disease in non-obese men. *Atherosclerosis* 1994; **107**: 239–246.
22. Nishina M, Kikuchi T, Yamazaki H, Kameda K, Hiura M, Uchiyama M: Relationship among systolic blood pressure, serum insulin and leptin, and visceral fat accumulation in obese children. *Hypertens Res* 2003; **26**: 281–288.
23. Tan CE, Ma S, Wai D, Chew SK, Tai ES: Can we apply the National Cholesterol Education Program adult treatment panel definition of the metabolic syndrome to Asians? *Diabetes Care* 2004; **27**: 1182–1186.
24. Oh JY, Hong YS, Sung YA, Barrett-Connor E: Prevalence and factor analysis of metabolic syndrome in an urban Korean population. *Diabetes Care* 2004; **27**: 2027–2032.
25. Lakka HM, Laaksonen DE, Lakka TA, *et al*: The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. *JAMA* 2002; **288**: 2709–2716.