Cigarette Smoking and the Risk of the Metabolic Syndrome in Middle-Aged Japanese Male Office Workers

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Abstract: To examine the association between cigarette smoking and the risk of the metabolic syndrome (MS), 3,649 Japanese male office workers aged 35–59 yr who did not have a history of cardiovascular disease were enrolled in this study. 2,994 men without the MS at entry were followed up over a 7-yr period. A modified National Cholesterol Education Program definition with body mass index instead of waist circumference was used for the MS. With adjustment for age, family history of diabetes, alcohol intake, and regular physical activity, the odds ratios of the MS were 1.0 (referent), 1.30 (95% confidence interval (CI), 1.00–1.68), 1.07 (95% CI, 0.82–1.39), 1.17 (95% CI, 0.88–1.56), and 1.66 (95% CI, 1.24–2.20) for never smokers, ex-smokers, and those who smoked 1–20 cigarettes/d, 21–30 cigarettes/d, and ≥ 31 cigarettes/d, respectively (P for trend for current smokers only = 0.006). As for the risk of developing the MS, the respective multivariate-adjusted hazard ratios of developing the MS were 1.0 (referent), 1.43 (95% CI, 1.14–1.79), 1.14 (95% CI, 0.91–1.44), 1.45 (95% CI, 1.14–1.84), and 1.59 (95% CI, 1.24–2.05) (P for trend for current smokers only = 0.001). Among men without the MS at entry, body weight gain over 7 yr, compared with never smokers, was significantly higher in smokers who quit smoking. It is important for the prevention of the MS not only to quit smoking but also to prevent weight gain after smoking cessation.

Key words: Cigarette smoking, Smoking cessation, Metabolic syndrome, Cardiovascular risk factor, Weight gain, Japanese men

Introduction

Smoking is a major risk factor for coronary heart disease (CHD), with a dose-response correlation between CHD morbidity and mortality and the number of cigarettes smoked¹⁾. Several studies have shown that smoking induces insulin resistance or hyperinsulinemia and leads to type 2 diabetes^{2–5)}. Increased insulin resistance may underlie the clustering of the metabolic and hemodynamic abnormalities that have potent atherosclerotic properties, designated metabolic syndrome (MS)^{6, 7)}. Thus, the MS may account for the observed link between smoking and atherosclerotic

disorders⁸⁾.

The Adult Treatment Panel III of the National Cholesterol Education Program (NCEP) recently proposed a definition of the MS to aid identification of individuals at risk for both CHD and type 2 diabetes⁹⁾. The definition incorporates thresholds for five easily measured variables linked to insulin resistance: waist circumference, triglyceride level, high-density lipoprotein (HDL) cholesterol level, fasting plasma glucose level, and blood pressure. To the best of our knowledge, however, no studies have examined the association between cigarette smoking and the MS defined by the NCEP criteria. Using a modified NCEP criteria with body mass index (BMI) instead of waist circumference, we examined the association of cigarette smoking with the

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prevalence of the MS in Japanese male office workers, and performed a longitudinal study to prospectively examine the association of cigarette smoking with the development of the MS.

Methods

Subjects and study design

The study was conducted among employees of Company A, one of the largest building contractors in Japan. A total of 3,649 Japanese male office workers aged 35–59 yr with no prior history of CHD or stroke participated in cardiovascular risk surveys in May 1994. All the participants were white-collar workers, and most were professionals. This study was conducted in accordance with the principles set out in the Declaration of Helsinki 1975, as revised in 1993. The study design was approved by the ethical committee of the Japan Labor and Welfare Association. Only the field data set, which excluded the private information such as name and insurance number, was used for the study. All participants were informed of the nature of the screening and all signed the questionnaire.

Of 3,694 potential participants, 586 (16.1%) were identified to have the MS at the initial examination. The remaining 3,063 men constituted the MS-free cohort, and were re-examined over 7 successive years until May 2001. We also excluded 69 men who did not participate in consecutive annual health examinations during the follow-up. The final study cohort for analysis therefore consisted of 2,994 men. Men in whom the MS was found during repeated surveys through May 2001 were defined as incidental cases of the MS.

Annual health examinations at study entry included medical history, physical examination, a questionnaire on health-related behavior, anthropometric measurements, and biochemical measurements. The participants were asked to fast for at least 8 h and to avoid heavy physical activity for more than 2 h before the examinations. Medical history and use of prescription drugs were assessed by the examining physicians. A family history of diabetes was defined as having a mother, father, sister, or brother with diagnosed diabetes. As for health-related behavior, data on smoking status, alcohol intake, and regular physical activity were obtained by interview. The questionnaire asked about smoking habits (never, past, or current smoker); past or current smokers were asked about the number of cigarettes smoked per day and the duration of smoking in years. Current smokers were subdivided into three groups by the daily number of cigarettes smoked: 1–20 cigarettes/d, 21–30

cigarettes/d, and ≥ 31 cigarettes/d. The questions about alcohol intake included items about the type of alcoholic beverage, the frequency on a weekly basis of alcohol consumption, and the usual amount consumed daily. Weekly alcohol intake was calculated and then converted to daily alcohol consumption (grams of ethanol per day) by using standard Japanese tables. Participants were asked about the type and frequency on weekly basis of leisure-time physical activity. Physical exercise was defined as participation in any physical activity, such as jogging, cycling, swimming or tennis, that was performed long enough to cause sweating. BMI, calculated as weight divided by the square of height in meters, was used as an index of relative weight. After a 5-min rest in a quiet room, systolic and diastolic blood pressures were measured on the right arm by using a standard mercury sphygmomanometer. Blood samples were drawn from an antecubital vein. Serum HDL cholesterol level and triglyceride level and fasting plasma glucose level were determined according to standard laboratory procedures^{10, 11}. The five variables of the MS (blood pressure, BMI, HDL cholesterol, triglycerides, and fasting glucose) were measured at annual health examinations in May from 1995 to 2001. Quality control of the laboratory was internal, and the coefficients of variation within assays for serum triglycerides and HDL cholesterol and plasma glucose were no more than 3% between 1994 and 2001. Data on smoking status were also obtained by interview at annual health examinations from 1995 to 2001.

The five thresholds used were BMI ≥ 25 , proposed by the Japan Society for the Study of Obesity¹², systolic blood pressure ≥ 130 mm Hg and/or diastolic blood pressure ≥ 85 mm Hg, triglyceride level ≥ 1.69 mmol/l, HDL cholesterol level < 1.03 (men) and < 1.29 (women) mmol/l, and fasting glucose level ≥ 6.1 mmol/l⁹. Individuals met the criteria for high blood pressure or high fasting glucose level if they were currently using blood pressure medications or hypoglycemic diabetes control. Individuals were classified as having the MS if they fulfilled three or more of the criteria.

Statistical analyses

The chi-square test and unpaired *t* test were used to analyze the statistical differences among characteristics of the study participants at enrollment in relation to the MS. Logistic regression was used to estimate the odds of the MS in each smoking category. For each participant, person-years of follow-up were calculated from the date of enrollment to the date of the first incidence of the development of the MS or the date of the last follow-up, whichever came first. Cox's proportional hazards models were used to evaluate the

Table 1. Baseline characteristics of 3,649 Japanese male office workers fulfilling metabolic syndrome criteria

Characteristic	Metabolic syndrome		P value
	Present n=586 (16.1%)	Absent n=3,063 (83.9%)	
Age, yr	48.5 ± 6.0	47.1 ± 6.3	<0.001
Family history of diabetes, %	11.3	8.7	0.044
Current drinkers, %	82.8	85.4	0.106
Smoking status, %			
Never-smokers	25.3	30.7	0.002
Ex-smokers	22.0	19.6	
Current smokers (cigarettes/d)			
1–20	19.5	21.6	
21–30	16.0	15.9	
≥31	17.2	12.2	
Regular physical activity at least once a week, %	51.0	53.3	0.302
Body mass index, kg/m ²	26.1 ± 2.6	23.0 ± 2.4	N/A
Systolic blood pressure, mmHg	138.3 ± 14.2	126.4 ± 14.7	N/A
Diastolic blood pressure, mmHg	85.2 ± 10.7	77.0 ± 10.7	N/A
Medication for hypertension, %	16.2	4.8	N/A
Fasting plasma glucose, mmol/L	5.85 ± 1.46	5.09 ± 0.69	N/A
Medication for diabetes, %	6.7	1.5	N/A
Triglycerides, mmol/L	2.86 ± 1.89	1.27 ± 0.80	N/A
High-density lipoprotein cholesterol, mmol/L	1.13 ± 0.26	1.44 ± 0.32	N/A

Data are means ± SD unless indicated otherwise. N/A, not applicable because criteria for selection of cases is based on these parameters.

association between smoking status and development of the MS. To examine the association of cigarette smoking with body weight trend over a 7-yr period, we used a simple linear regression model. Each individual's eight body weight values were regressed on the time of survey. The slope coefficient of this model was used to represent an individual's body weight trend. Differences in mean values of body weight change over 7 yr among categories of smoking status were tested by a generalized linear model analysis. Logistic regression was used to estimate the odds of body weight gain of ≥5 kg at study end in each smoking category. In the multivariate analyses, data were adjusted for age, family history of diabetes, alcohol intake, and physical activity at study entry. Potential confounding factors, except for age, were treated as categorical variables: family history of diabetes (no or yes); alcohol consumption (graded as 1 [none] or as quartile 1 [grade 2] to quartile 4 [grade 5] for drinkers); and regular physical exercise (graded from 1 to 3 [hardly ever, once a week, or twice or more a week]). The linear trend in odds ratios and hazard ratios across increasing categories of smoking for current smokers only was evaluated using the likelihood ratio test for trend. The median value of cigarettes/d for each smoking category was used for the

analyses: none for never smokers, 15 cigarettes/d for those who smoked 1–20 cigarettes/d, 25 cigarettes/d for those who smoked 21–30 cigarettes/d, and 40 cigarettes/d for those who smoked ≥31 cigarettes/d.

Data were analyzed by using the SPSS/PC statistical package (SPSS, Chicago, IL). All reported P values are two-tailed, and those less than 0.05 were considered to be statistically significant.

Results

As defined by the modified NCEP criteria, 586 men (16.1%) had the MS at baseline assessment. The characteristics of those with and those without the syndrome are shown in Table 1. Mean age and the percentage of participants with a family history of diabetes were significantly higher in those with the MS than those without. The percentages of those who never smoked and smoked ≥31 cigarettes/d were lower and higher in those with the MS than those without, respectively.

Table 2 shows the risk of prevalence of the MS in relation to smoking status. With adjustment for age, family history of diabetes, alcohol intake, and regular physical activity,

Table 2. The risk of prevalence of the metabolic syndrome among 3,649 Japanese male office workers, according to smoking status

	Never smokers (n=1088)	Ex-smokers (n=728)	Current smokers (cigarettes/d)			P-value for trend*
			1–20 (n=776)	21–30 (n=582)	≥31 (n=475)	
Cases, <i>n</i>	148	129	114	94	101	
Prevalence, %	13.6	17.7	14.7	16.2	21.3	
Age-adjusted odds ratio (95% CI)	1.00 (referent)	1.32 (1.02, 1.71)	1.09 (0.84, 1.42)	1.20 (0.91, 1.59)	1.73 (1.31, 2.29)	0.002
Multivariate-adjusted odds ratio [†] (95% CI)	1.00 (referent)	1.30 (1.00, 1.68)	1.07 (0.82, 1.39)	1.17 (0.88, 1.56)	1.66 (1.24, 2.20)	0.006

CI indicates confidence interval. *The test for trend is calculated across increasing categories of smoking for current smokers only. [†]Adjusted for age, family history of diabetes, alcohol intake, and regular physical activity.

Table 3. The risk of incidence of the metabolic syndrome among 2,994 Japanese male office workers without the metabolic syndrome during 7 yr of follow-up, according to smoking status at study entry

	Never smokers (n=915)	Ex-smokers (n=585)	Current smokers (cigarettes/d)			P-value for trend*
			1–20 (n=652)	21–30 (n=473)	≥31 (n=369)	
Cases, <i>n</i>	160	143	131	118	104	
Person-years	5,344	3,272	3,713	2,578	2,047	
Rate per 1,000 person-years	29.9	43.7	35.3	45.8	50.8	
Age-adjusted hazard ratio (95% CI)	1.00 (referent)	1.43 (1.14, 1.79)	1.17 (0.93, 1.48)	1.50 (1.18, 1.90)	1.66 (1.30, 2.12)	<0.001
Multivariate-adjusted hazard ratio [†] (95% CI)	1.00 (referent)	1.43 (1.14, 1.79)	1.14 (0.91, 1.44)	1.45 (1.14, 1.84)	1.59 (1.24, 2.05)	0.001

CI indicates confidence interval. *The test for trend is calculated across increasing categories of smoking for current smokers only. [†]Adjusted for age, family history of diabetes, alcohol intake, and regular physical activity at study entry.

the odds ratios of the MS, compared with never smokers, were 1.30 (95% confidence interval (CI), 1.00–1.68) for ever-smokers, 1.07 (95% CI, 0.82–1.39) for those who smoked 1–20 cigarettes/d, 1.17 (95% CI, 0.88–1.56) for those who smoked 21–30 cigarettes/d, and 1.66 (95% CI, 1.24–2.20) for those who smoked ≥31 cigarettes/d (P for trend for current smokers only=0.006).

Table 3 shows the risk of developing the MS during 7 yr of follow-up in relation to smoking status at study entry. With adjustment for age, family history of diabetes, alcohol intake, and regular physical activity, the hazard ratios of developing the MS, compared with never smokers, were 1.43 (95% CI, 1.14–1.79) for ever-smokers, 1.14 (95% CI, 0.91–1.44) for those who smoked 1–20 cigarettes/d, 1.45 (95% CI, 1.14–1.84) for those who smoked 21–30 cigarettes/d, and 1.59 (95% CI, 1.24–2.05) for those who smoked ≥31 cigarettes/d (P for trend for current smokers only=0.001).

Table 4 shows body weight change between 1994 and 2001 among men without the MS at entry in relation to

smoking status during the follow-up period. Significance in comparison with never smokers who never smoked was found in smokers who quit smoking for an increase in body weight and a slope of body weight over 7 yr. The multivariate-adjusted odds ratio for a weight gain of ≥5 kg, compared with never smokers who never smoked, was 2.45 (95% CI, 1.57–3.82) for smokers who quit smoking.

Discussion

We found a positive and dose-response relationship between the daily number of cigarettes smoked and the risk of the MS in both cross-sectional and longitudinal analyses. A slightly stronger association was observed in longitudinal analyses, and the risk of developing the MS was significant among those who smoked 21–30 cigarettes/d. Ex-smoking was also associated with a higher risk of the MS. With adjustment for potential risk factors associated with the MS, most of the association between smoking status and the risk

Table 4. Body weight change over 7 yr among Japanese male office workers without the metabolic syndrome, according to smoking status during the follow-up period

	Never smokers who never smoked (n=698)	Smokers who quit smoking (n=182)	Current smokers who never quit smoking (cigarettes/d at study end)		
			1–20 (n=427)	21–30 (n=282)	≥31 (n=220)
Body weight*					
Body weight at baseline, kg	65.7 ± 0.3	66.1 ± 0.6	65.2 ± 0.4	64.6 ± 0.5 [†]	66.7 ± 0.5
Weight gain at study end, kg	1.00 ± 0.12	2.12 ± 0.24 [†]	0.91 ± 0.16	0.84 ± 0.19	0.95 ± 0.22
Slope of body weight, kg/yr	0.15 ± 0.02	0.31 ± 0.04 [†]	0.15 ± 0.02	0.11 ± 0.03	0.13 ± 0.03
Weight gain of ≥5 kg at study end					
Proportion, %	10.9	20.9	9.8	8.9	8.6
Multivariate-adjusted odds ratio (95% CI) [‡]	1.0 (referent)	2.45 (1.57–3.82) [§]	0.91 (0.61–1.37)	0.84 (0.52–1.36)	0.87 (0.51–1.50)

Abbreviations: CI, confidence interval. *Data are means ± standard errors, being adjusted for age, family history of diabetes, alcohol intake, and regular physical activity at study entry. [†]Significance difference ($P < 0.05$) in comparison with never smokers who never smoked. [‡]Adjusted for age, family history of diabetes, alcohol intake, and regular physical activity at study entry. [§]Significance difference ($P < 0.001$) in comparison with never smokers who never smoked.

of the MS did not change. Analyses of body weight change according to smoking status during the follow-up period revealed that body weight gain was significantly higher in smokers who quit smoking than in never smokers. These results indicate that cigarette smoking is associated with an increased risk of the MS and that smoking cessation is also associated with the risk of the MS owing to subsequent body weight gain. To prevent the MS, we need not only to encourage smoking cessation but also to concomitantly help patients prevent weight gain after smoking cessation.

Although many pharmacological actions of cigarette smoking and nicotine have been demonstrated¹³, the mechanism of how cigarette smoking increases the risk of the metabolic aberrations is still not clear. A negative effect of cigarette smoking on insulin sensitivity has been documented in several studies^{2–4}. Cigarette smoking increases the circulating levels of insulin-antagonistic hormones (i.e., catecholamines, cortisol, and growth hormone)^{14–16}. An additional negative factor for the insulin-mediated glucose uptake is high circulating levels of free fatty acids, indicating increased lipolysis¹⁷. Thus, cigarette smoking may provoke the metabolic perturbations and may increase the risk of the MS.

As for mechanism of weight gain after smoking cessation, mechanisms of weight gain may include increased energy intake, decreased resting metabolic rate, decreased physical activity, and increased lipoprotein lipase activity^{18–21}. Furthermore, fat oxidation might be a critical lipostatic factor that regulates energy balance²². It has been reported that fat oxidation per kilogram lean mass was positively correlated with 24-h excretion of nicotine, including that smokers with

a high nicotine uptake use more lipids to sustain fasting resting energy expenditure than non-smokers²³. Therefore, if subjects stop smoking and do not modulate their lipid intake over time, the imbalance in lipid intake and fat oxidation may induce an increase in body fat.

Our study has several limitations. We used a modified NCEP definition with BMI instead of waist circumference. The central pattern of distribution, with its higher weighting of waist circumference, is associated with more insulin resistance than is the peripheral pattern of distribution^{24, 25}. Some data show that waist circumference predicts diabetes marginally better than BMI^{26, 27}. Nevertheless, most physicians routinely assess BMI, whereas the value of waist measurements in clinical practice has not been thoroughly examined and may require modification for different ethnic groups. A number of investigations have also shown that BMI is as effective as waist circumference for predicting the development of type 2 diabetes and other metabolic disturbances^{26–30}. Moreover, the Japan Society for the Study of Obesity has recently reported that BMI can estimate visceral fat measured by computed tomography as robustly as waist circumference and that obesity-related complications increase for a BMI ≥25 and the best combination of sensitivity and specificity for detecting subjects with multiple risk factors is a BMI of 25¹². This Society suggests that obesity is adequately specified as a BMI ≥25 in Japan where the prevalence and degree of obesity remained mild.

Second, bias in case-finding could have occurred. Specifically, smokers are more likely to visit a doctor for reasons other than the MS, so that the MS could have been found by chance. However, because all incidental cases

were found during periodic annual screening in our study, such a bias is unlikely to have occurred. Furthermore, in this study, the first incidental cases of the MS were used for the analyses. Although these may overestimate the incidence of the MS, the risk of developing the MS is not affected because of the independence of an excessive classification with smoking status.

Finally, we did not assess participants' dietary habits. Dietary lipids, fibers, or carbohydrates may influence fasting insulin levels^{31–33}, and diets with a high glycemic load and a low cereal fiber content may be associated with the risk of the MS^{34, 35}. Research is needed to clarify the causal relation between cigarette smoking and the risk of the MS.

Despite these potential limitations, our findings support the conclusion that cigarette smoking is associated with an increased risk of the MS. Because smoking cessation is related to the MS for subsequent body weight gain, health professionals should help patients avoid weight gain.

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References

- 1) Kannel WB (1981) Update on the role of cigarette smoking in coronary artery disease. *Am Heart J* **101**, 319–28.
- 2) Facchini FS, Hollenbeck CB, Jeppesen J, Chen YD, Reaven GM (1992) Insulin resistance and cigarette smoking. *Lancet* **339**, 1128–30.
- 3) Attvall S, Fowelin J, Lager I, Von Schenck H, Smith U (1993) Smoking induces insulin resistance - a potential link with the insulin resistance syndrome. *J Intern Med* **233**, 327–32.
- 4) Rönnekaa T, Rönnekaa EM, Puukka P, Pyörälä K, Laakso M (1996) Smoking is independently associated with high plasma insulin levels in nondiabetic men. *Diabetes Care* **19**, 1229–32.
- 5) Nakanishi N, Nakamura K, Matsuo Y, Suzuki K, Tatara K (2000) Cigarette smoking and risk for impaired fasting glucose and type 2 diabetes in middle-aged Japanese men. *Ann Intern Med* **133**, 183–91.
- 6) Liese AD, Mayer-Davis EJ, Haffner SM (1998) Development of the multiple metabolic syndrome: an epidemiologic perspective. *Epidemiol Rev* **20**, 157–72.
- 7) Reaven G (2002) Metabolic syndrome: pathophysiology and implications for management of cardiovascular disease. *Circulation* **106**, 286–8.
- 8) Dzien A, Dzien-Bischinger C, Hoppichler F, Lechleitner M (2004) The metabolic syndrome as a link between smoking and cardiovascular disease. *Diabetes Obes Metab* **6**, 127–32.
- 9) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (2001) 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* **285**, 2486–97.
- 10) Nakanishi N, Nishina K, Li W, Sato M, Suzuki K, Tatara K (2003) Serum γ -glutamyltransferase and development of impaired fasting glucose or type 2 diabetes in middle-aged Japanese men. *J Intern Med* **254**, 287–95.
- 11) Nakanishi N, Suzuki K, Tatara K (2003) Alcohol consumption and risk for development of impaired fasting glucose or type 2 diabetes in middle-aged Japanese men. *Diabetes Care* **26**, 48–54.
- 12) Examination Committee of Criteria for 'Obesity Disease' in Japan; Japan Society for the Study of Obesity (2002) New criteria for 'obesity disease' in Japan. *Circ J* **66**, 987–92.
- 13) Benowitz NL (1988) Pharmacologic aspects of cigarette smoking and nicotine addiction. *N Engl J Med* **319**, 1318–30.
- 14) Cryer PE, Haymond MW, Santiago JV, Shah SD (1976) Norepinephrine and epinephrine release and adrenergic mediation of smoking-associated hemodynamic and metabolic events. *N Engl J Med* **295**, 573–7.
- 15) Kirschbaum C, Wust S, Strasburger CJ (1992) 'Normal' cigarette smoking increases free cortisol in habitual smokers. *Life Sci* **50**, 435–42.
- 16) Wilkins JN, Carlson HE, Van Vunakis H, Hill MA, Gritz E, Jarvik ME (1982) Nicotine from cigarette smoking increases circulating levels of cortisol, growth hormone, and prolactin in male chronic smokers. *Psychopharmacology (Berl)* **78**, 305–8.
- 17) Bergman RN, Ader M (2000) Free fatty acids and pathogenesis of type 2 diabetes mellitus. *Trends Endocrinol Metab* **11**, 351–6.
- 18) Moffatt RJ, Owens SG (1991) Cessation from cigarette smoking: changes in body weight, body composition, resting metabolism, and energy consumption. *Metabolism* **40**, 465–70.
- 19) Stamford BA, Matter S, Fell RD, Papanek P (1986) Effects of smoking cessation on weight gain, metabolic

- rate, caloric consumption, and blood lipids. *Am J Clin Nutr* **43**, 486–94.
- 20) Ferrara CM, Kumar M, Nicklas B, McCrone S, Goldberg AP (2001) Weight gain and adipose tissue metabolism after smoking cessation in women. *Int J Obes Relat Metab Disord* **25**, 1322–6.
- 21) Perkins KA, Epstein LH, Marks BL, Stiller RL, Jacob RG (1989) The effect of nicotine on energy expenditure during light physical activity. *N Engl J Med* **320**, 898–903.
- 22) Schutz Y, Tremblay A, Weinsier RL, Nelson KM (1992) Role of fat oxidation in the long-term stabilization of body weight in obese women. *Am J Clin Nutr* **55**, 670–4.
- 23) Jensen EX, Fusch C, Jaeger P, Peheim E, Horber FF (1995) Impact of chronic cigarette smoking on body composition and fuel metabolism. *J Clin Endocrinol Metab* **80**, 2181–5.
- 24) Kissebah AH, Videlund N, Murray R, Evans DJ, Hartz AJ, Kalkhoff RK, Adams PW (1982) Relation of body fat distribution to metabolic complications of obesity. *J Clin Endocrinol Metab* **54**, 254–60.
- 25) Krotkiewski M, Bjorntorp P, Sjostrom L, Smith U (1983) Impact of obesity on metabolism in men and women. Importance of regional adipose tissue distribution. *J Clin Invest* **72**, 1150–62.
- 26) Wei M, Gaskill SP, Haffner SM, Stern MP (1997) Waist circumference as the best predictor of noninsulin dependent diabetes mellitus (NIDDM) compared to body mass index, waist/hip ratio and other anthropometric measurements in Mexican Americans. A 7-year prospective study. *Obes Res* **5**, 16–23.
- 27) Stevens J, Couper D, Pankow J, Folsom AR, Duncan BB, Nieto FJ, Jones D, Tyroler HA (2001) Sensitivity and specificity of anthropometrics for the prediction of diabetes in a biracial cohort. *Obes Res* **9**, 696–705.
- 28) Sattar N, Tan CE, Han TS, Forster L, Lean ME, Shepherd J, Packard CJ (1998) Associations of indices of adiposity with atherogenic lipoprotein subfractions. *Int J Obes Relat Metab Disord* **22**, 432–9.
- 29) Rexrode KM, Buring JE, Manson JE (2001) Abdominal and total adiposity and risk of coronary heart disease in men. *Int J Obes Relat Metab Disord* **25**, 1047–56.
- 30) Han TS, Williams K, Sattar N, Hunt KJ, Lean ME, Haffner SM (2002) Analysis of obesity and hyperinsulinemia in the development of metabolic syndrome. San Antonio Heart Study. *Obes Res* **10**, 923–31.
- 31) Anderson JW, Gustafson NS, Bryart CA, Tietzen-Clark J (1987) Dietary fiber and diabetes. *J Am Diet Assoc* **87**, 1189–97.
- 32) Mayer EJ, Newman B, Quesenberry CP Jr, Selby JV (1993) Usual dietary fat intake and insulin concentrations in healthy women twins. *Diabetes Care* **16**, 1459–69.
- 33) Miller JC (1994) Importance of glycemic index in diabetes. *Am J Clin Nutr* **59** (Suppl 3), :747S–52S.
- 34) Mennen LI, Lafay L, Feskens EJM, Novak M, Lépinay P, Balkau B (2000) Possible protective effect of bread and dairy products on the risk of the metabolic syndrome. *Nutr Res* **20**, 335–47.
- 35) McKeown NM, Meigs JB, Liu S, Saltzman E, Wilson PW, Jacques PF (2004) Carbohydrate nutrition, insulin resistance, and the prevalence of the metabolic syndrome in the Framingham Offspring Cohort. *Diabetes Care* **27**, 538–46.