

Table 3. Descriptive characteristics of subjects with metabolic syndrome at baseline (*n* = 67) and after treatment (*n* = 59)

	Diet alone			Diet plus exercise		
	Baseline (<i>n</i> = 24)	After treatment (<i>n</i> = 21)	<i>p</i>	Baseline (<i>n</i> = 43)	After treatment (<i>n</i> = 38)	<i>p</i>
No. of subjects						
With metabolic syndrome	24	6		43	2	
Without metabolic syndrome	0	15	<0.001	0	36	<0.001
Age (yrs)	52 ± 8			55 ± 6		
BMI (kg/m ²)	30.4 ± 4.9	27.1 ± 4.3	<0.001	29.2 ± 2.3	25.8 ± 2.2	<0.001
Visceral fat area (cm ²)	161 ± 52	119 ± 45	<0.001	136 ± 24	92 ± 26	<0.001
Systolic BP (mm Hg)	150 ± 15	133 ± 11	<0.001	147 ± 19	133 ± 16	<0.001
Diastolic BP (mm Hg)	91 ± 10	87 ± 9	<0.05	89 ± 10	81 ± 10	<0.01
Triglycerides (mM)	1.77 ± 0.75	1.23 ± 0.55	<0.001	2.19 ± 0.94	1.09 ± 0.29	<0.001
HDL-C (mM)	1.43 ± 0.34	1.46 ± 0.29	NS	1.43 ± 0.34	1.51 ± 0.29	<0.05
Glucose (mM)	6.82 ± 2.27	5.77 ± 2.27	<0.01	6.99 ± 2.11	5.60 ± 1.11	<0.001
$\dot{V}O_{2max}$ (mL/kg per min)	22.6 ± 3.4	24.0 ± 3.5	<0.05	22.9 ± 3.2	27.0 ± 3.8	<0.001
$\dot{V}O_{2max}$ (mL/min)	1617 ± 320	1584 ± 291	NS	1596 ± 258	1657 ± 284	NS
Visceral fat obesity (%)	100	76	<0.001	100	47	<0.001
High BP (%)	96	76	<0.001	84	74	<0.01
High triglycerides (%)	58	48	<0.05	67	13	<0.001
Low HDL-C (%)	8	5	NS	10	5	NS
High glucose (%)	67	48	<0.01	58	34	<0.01

BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; $\dot{V}O_{2max}$, maximal oxygen uptake; NS, not significant. Values are mean ± standard deviation unless otherwise specified. Qualitative data were analyzed by a χ^2 test.

knowledge, has confirmed the improvement of metabolic syndrome with increased cardiorespiratory fitness. To our knowledge, the present study is, therefore, the first to investigate the association between cardiorespiratory fitness and metabolic syndrome in overweight and obese populations.

Table 2 suggests that, even with overweight and obesity, high $\dot{V}O_{2max}$ is associated with low prevalence of metabolic syndrome. This finding is in accordance with previous

cross-sectional studies on the association of physical activity and cardiorespiratory fitness with the prevalence of metabolic syndrome (7–9). In obese patients, high cardiorespiratory fitness may prevent metabolic syndrome. Hence, clinicians should counsel their sedentary patients with obesity to become more physically active.

It is well known that an excess visceral fat accumulation is strongly associated with a high prevalence of risk factors

Table 4. Odds ratios and 95% confidence intervals for improvement of metabolic syndrome according to treatment

	Treatment		Linear trend (<i>p</i>)
	Diet alone	Diet plus exercise	
No adjustment			
1.0 (referent)		7.20 (1.47–53.1)	0.02
Adjusted for age and body weight change			
1.0 (referent)		3.68 (1.02–17.6)	0.04

for coronary heart disease, such as lipid metabolic disorders, hypertension, and type 2 diabetes. Moreover, several studies have shown that the visceral fat area above which metabolic disturbances increase is 100 or 110 cm² (25,26). Japan Society for the Study of Obesity has adopted visceral fat area of 100 cm² as the cut-off point for diagnosing high-risk obesity (16). Our data showed that average visceral fat area became <100 cm² in the group treated with diet plus exercise after weight loss, but that still remained >100 cm² in the group with diet alone. Table 3 shows that, although the prevalence of metabolic syndrome and metabolic syndrome risk factors was significantly decreased in both groups, the decreases tended to be larger in the group with diet plus exercise compared with the diet alone group. These data were accordance with previous studies on the association of visceral fat accumulation with the prevalence of risk factors for coronary heart disease.

In the present study, relative values of $\dot{V}O_{2max}$ (unit, mL/kg per min) increased significantly between baseline and after weight reduction, whereas a significant increase was not found in absolute values of $\dot{V}O_{2max}$ (unit, mL/min), even in the group treated with diet plus exercise. A study design that includes exercise of higher intensity and greater frequency and a longer intervention period, which could increase cardiorespiratory fitness, might be needed.

Aerobic exercise training may, however, be essential in treating obese patients with metabolic syndrome, even if the exercise does not increase their $\dot{V}O_{2max}$. The adjusted odds ratio for metabolic syndrome improvement in our study was 3.68 in the group with diet plus exercise training compared with diet alone, when adjusted for age and body weight change. That is to say, adding aerobic exercise training to dietary weight reduction may have a synergistic effect on the improvement of risk factors for metabolic syndrome. This is partly supported by our previous studies (27,28). In one (27), we found that the addition of exercise training contributes to the maintenance of fat-free mass and might be more effective for improving physical fitness and risk factors for coronary heart disease during weight reduction in obese women, compared with diet alone. Another study revealed that a 14-week weight-loss program with diet plus aerobic exercise training reduced visceral adipose tissue by a factor of 1.3 (diet plus exercise, 49.3 cm²; diet alone, 37.8 cm² by CT scans) compared with diet alone, after adjustment for age, menopausal status, and body weight reduction (28). These studies suggest that adding aerobic exercise training to a dietary weight-reduction program further reduces visceral adipose tissue and further improves coronary heart disease risk factors compared with diet alone, even if weight reduction is the same with either treatment.

This study has some limitations. Our findings apply primarily to overweight and obese Japanese women. Although the external validity of our data is limited, the homogeneity of our subjects reduces confounding by sociodemographic

factors, thus enhancing its internal validity. Second, subjects were not randomized to the treatments. Because our goal, in particular, was to increase subjects' adherence to the weight loss programs, the subjects' personal lifestyles and preferences were preferentially taken into account. Consequently, the numbers of subjects were imbalanced in two treatment groups. The study design without randomization may be concomitant with a type II error because of some confounding variables. This factor might partly preclude our definitive conclusion. However, at baseline, no differences were found in any variables between the groups treated with diet alone and with diet plus exercise. This suggests that assigning rather than randomizing subjects had little, if any, influence on the measurement variables.

In summary, our cross-sectional data suggest that, for overweight and obese women, a physically active lifestyle and maintenance of high cardiorespiratory fitness can be useful in primary prevention of metabolic syndrome. Our interventional study revealed that, for overweight and obese women with metabolic syndrome, adding aerobic exercise training to dietary weight reduction is a more effective (adjusted odds ratio = 3.68) treatment for improving metabolic syndrome than diet alone. However, weight-loss intervention trials of longer duration, with more frequent, higher-intensity exercise training and larger samples of obese patients with metabolic syndrome are needed to confirm the association between cardiorespiratory fitness change and metabolic syndrome improvement.

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CARDIOVASCULAR DISEASE

Is weak association between cigarette smoking and cardiovascular disease mortality observed in Japan explained by low total cholesterol?—NIPPON DATA80

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Background An international comparison has indicated that the association between smoking and cardiovascular disease (CVD) differs according to total cholesterol (TC) levels. However, little has been published about the relationship between smoking and CVD mortality among populations with various cholesterol levels.

Methods We calculated the adjusted relative hazard (RH) of smoking for CVD mortality among 8912 Japanese individuals without a history of stroke or heart disease, who were separated according to TC levels of ≥ 5.40 , 4.81–5.39, 4.26–4.80 and < 4.25 mmol/l into groups Q4, Q3, Q2 and Q1, respectively. The *P*-values for multiple interactions between TC and smoking status for CVD mortality were calculated using TC as a continuous variable, dichotomized smoking status (never vs current), and by including cross-product terms in the regression models.

Results After 19 years of follow-up, 313 men and 291 women died of CVD. The RH of CVD mortality among men who currently smoked compared with those who never smoked was increased with higher TC (RH = 2.36 in Q4) and decreased in those with lower TC (RH = 0.85 in Q1) (interaction, *P* < 0.01). The profiles for coronary heart disease (CHD) mortality and ischaemic CVD (composite endpoint of CHD and ischaemic stroke) in men and for ischaemic CVD mortality in women were identical. The interaction might be explained by a biological mechanism and by frailty of those who have never smoked with lower TC.

Conclusions Counteractive measures should be implemented against smoking targeted towards Japanese with elevated TC levels.

Keywords Cigarette smoking, total cholesterol, cardiovascular diseases, interaction, prospective studies, Japan

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Cigarette smoking is a known risk factor for both coronary heart disease (CHD) and stroke.¹ However, although the rate of cigarette smoking is high among Japanese men, mortality from ischaemic heart disease is strikingly lower than that in the USA.^{2,3} Smoking is thus considered a weaker CHD risk factor in Japan than in Western countries.^{4,5} However, cigarette smoking is closely related to CHD among Japanese immigrants living in Hawaii.⁴ Thus, the between-population difference in CHD might be explained not by ethnicity but by environmental factors. Similar to Japan, the Seven Countries Study showed

a weaker relationship between smoking and the incidence of CHD in southern Europe than in Northern Europe and Yugoslavia.⁶ People living in Asia and in southern Europe at the time of the early follow up by the Seven Countries Study had low average total cholesterol (TC) levels.⁴⁻⁶ Furthermore, some recent studies investigating the aetiology of subclinical atherosclerosis found that low-density lipoprotein cholesterol is more important for early atheroma formation, whereas smoking plays a more important role at the later stages of atherosclerosis.^{7,8}

Japanese studies reported before 2000 indicated that cigarette smoking is not a consistent risk factor for stroke.⁹⁻¹¹ However, recent analyses have revealed a close relationship between cigarette smoking and stroke in Japan.¹²⁻¹⁵ Some investigators have postulated that this change is due to a recent increase in dietary fat intake and a relative increase of the blood TC level in the general population.^{3,13} Thus, the association between smoking and cardiovascular diseases (CVD) might differ according to TC level. The aim of the present study was to determine whether TC level affects the association between smoking and CVD using a representative Japanese sample.

Methods

The subjects of this cohort study participated in the Japanese 1980 National Cardiovascular Survey, which was conducted together with a National Nutrition Survey. Nutrition is surveyed annually in Japan using standardized procedures and a questionnaire.^{13,16} All household members aged 30 years or older in 300 randomly selected census tracts throughout Japan are included. The 1980 survey included medical examinations, blood pressure (BP) measurements, blood tests and a self-administered questionnaire about lifestyle. Trained staff at local health centres in the respective districts performed the medical examinations at local health and community centres. A history of illness, including heart disease, stroke and diabetes, as well as smoking and drinking habits was obtained from the questionnaire. Height and body weight were measured, while the subjects wore light clothing and no shoes. The participants were questioned about whether they were current smokers, ex-smokers or had never smoked. Smokers were asked to describe the number of cigarettes smoked per day. Similarly, alcohol consumption was determined as never, past, current occasionally or current daily. A standard sphygmomanometer was used to measure systolic and diastolic BP. The precision and accuracy of serum TC in non-fasting blood samples were verified by the Lipid Standardization Program administered by the Center for Disease Control and Prevention, Atlanta, GA, USA.¹⁷ Diabetes was defined as non-fasting serum glucose of 11.1 mmol/l (200 mg/dl) or a self-reported history of diabetes.

A total of 10 546 individuals, aged 30 years or older, for whom baseline information regarding age, gender and blood pressure was complete in the 1980 data set constituted the study cohort (NIPPON DATA80).^{13,16} We excluded those with a history of stroke ($n=117$), CHD ($n=163$), other heart disease ($n=475$), no information about confounding factors ($n=4$), those without complete information about smoking or TC ($n=28$)

and 847 participants who were lost to follow-up. Consequently, we analysed data from 8912 participants.

As described elsewhere,^{12,15} the underlying causes of death in the Japanese National Vital Statistics were coded according to the 9th (ICD-9) and 10th (ICD-10) International Classifications of Disease for deaths through 1994 and thereafter, respectively. Details about the classification and permission to use the National Vital Statistics were obtained from the Management and Coordination Agency of the Government of Japan. The Institutional Review Board of the Shiga University of Medical Science approved the study protocol (No. 12-18, 2000).

Statistical analysis

To examine the association between cigarette smoking and CVD mortality according to TC level, participants were divided into quartiles Q4, Q3, Q2 and Q1 according to TC levels of ≥ 5.40 mmol/l (≥ 209 mg/dl), 4.81-5.39 mmol/l (186-208 mg/dl), 4.26-4.80 mmol/l (165-185 mg/dl) and Q1 (TC, <4.25 mmol/l (<164 mg/dl)). We compared the basic characteristics among the groups according to a combination of smoking and TC levels using the mean for continuous variables and ratios (%) for dichotomous variables.

Age-adjusted CVD mortality rate, relative hazards (RH) and the 95% confidence intervals (95%CI) for cigarette smoking was estimated according to TC level using the Cox proportional hazard model. Individuals who had never smoked were categorized as the reference group. We estimated the RH using age-adjusted and multivariate-adjusted models, and included the following possible confounding factors in the latter model: age, body mass index (BMI), systolic BP, use of anti-hypertensive medication, diabetes and alcohol consumption (never, past, occasional and daily). The significance of multiplicative interactions between TC (continuous) and smoking status were examined using cross-product terms in the regression model. The interaction was assessed for CVD mortality, CHD mortality, ischaemic stroke mortality and ischaemic CVD (composite endpoint of CHD and ischaemic stroke) mortality. We also separately analysed the relationship between smoking and CVD or ischaemic CVD mortality according to cholesterol level by age group (≤ 69 and >69 years, as the median age of the deceased was 69 years). SAS software (version 9.1) was used for all statistical analyses.

Results

The mean \pm SD baseline age of the participants was 50.1 ± 13.1 years and 55.5% were women. The mean TC level was 4.81 ± 0.85 mmol/l (186.2 ± 32.8 mg/dl) for men and 4.91 ± 0.88 mmol/l (190.2 ± 33.9 mg/dl) for women. Proportions of current smokers, ex-smokers and never smokers were 63.7, 18.1 and 18.2% for men and 8.8, 2.1 and 89.2% for women, respectively.

Table 1 shows the baseline characteristics of the study participants according to smoking status and TC level. Proportions of current smokers across ascending TC groups were 68.8, 65.6, 62.0 and 57.6% for men and 7.7, 8.6, 9.3 and 9.3% for women in Q1, Q2, Q3, and Q4, respectively. The mean BMI and systolic BP were higher in groups of both men and women with higher TC. Similarly, the proportion of participants

Table 1 Baseline characteristics of participants according to smoking status and total cholesterol level. NIPPON DATA80, 1980, Japan

Total cholesterol level Smoking status	Q1 (<4.25 mmol/l) ^a			Q2+Q3 (4.26–5.39 mmol/l) ^a			Q4 (≥ 5.40 mmol/l) ^a		
	Never	Ex-smoker	Current	Never	Ex-smoker	Current	Never	Ex-smoker	Current
Men									
Number of participants	173	149	709	366	361	1283	184	207	531
Age (years)	51.1	54.3	50.1	51.0	52.0	49.1	48.7	53.1	47.8
Total cholesterol (mmol/l)	3.84	3.80	3.83	4.81	4.80	4.77	5.93	6.01	5.97
Body mass index (kg/m ²)	22.4	21.7	21.4	22.9	22.7	22.3	24.0	23.3	23.5
Systolic blood pressure (mmHg)	136.3	138.9	136.2	137.5	139.1	138.2	141.1	141.7	137.7
Antihypertensive medication (%)	9	11	7	12	9	8	11	14	9
Diabetes (%)	1	5	6	7	4	7	8	10	10
Drinking status									
Never (%)	28	25	17	29	16	18	25	21	18
Past (%)	3	8	5	5	7	4	4	11	5
Occasional (%)	39	21	25	34	26	24	33	24	25
Daily (%)	29	46	53	33	49	54	38	44	52
Women									
Number of participants	1074	22	91	2152	50	217	1187	31	125
Age (years)	44.6	48.8	47.3	50.0	53.3	50.7	55.1	58.7	54.5
Total cholesterol (mmol/l)	3.87	3.89	3.81	4.81	4.91	4.83	6.03	6.16	5.98
Body mass index (kg/m ²)	22.2	21.2	21.5	22.8	22.9	22.0	23.7	24.2	23.7
Systolic blood pressure (mmHg)	128.1	134.7	127.4	132.3	136.8	131.1	139.6	146.6	141.1
Antihypertensive medication (%)	6	9	7	9	10	7	17	29	14
Diabetes (%)	2	5	2	4	12	3	6	3	7
Drinking status									
Never (%)	81	50	45	82	52	53	82	52	58
Past (%)	1	9	2	1	6	6	1	16	4
Occasional (%)	16	32	37	15	34	29	15	19	29
Daily (%)	2	9	15	2	8	12	2	13	9

^a<4.25 mmol/l, <164 mg/dl; 4.26–5.39 mmol/l, 165–208 mg/dl; ≥ 5.40 mmol/l, ≥ 209 mg/dl.

taking anti-hypertensive medication was higher in the groups with higher TC. The mean age of the women was higher in the higher TC group, but this did not apparently differ among the men. Compared with current smokers and those who had never smoked, ex-smokers tended to be older and more of them were taking anti-hypertensive medication and had diabetes. The proportions of those who had never consumed alcohol were higher among those who had never smoked.

After 19 years of follow-up, 313 men and 291 women died of CVD. Table 2 shows the risk of CVD mortality associated with cigarette smoking according to TC levels. The adjusted RH of current cigarette smoking for CVD mortality among men was the highest in Q4 (RH = 2.36; 95%CI: 1.14–4.87) and the lowest in Q1 (RH = 0.85; 95%CI: 0.49–1.49). The *P*-value for interactions between smoking status (ever vs never) and TC level (continuous) for CVD mortality were 0.01. This interaction was also unchanged, when we excluded ex-smokers (*P* for interaction <0.01). Table 2 indicates that the findings for women were inconsistent.

Because the higher CVD mortality rate in those who had never smoked with lower TC was due to frailty, we further excluded early death that occurred within 5 years. However, the observed significant interactions were unchanged (*P* for interaction, 0.02).

Disease-specific analyses revealed that the *P*-values for interactions between smoking status and total cholesterol were 0.03 for CHD deaths and 0.01 for ischaemic CVD (CHD + ischaemic stroke) in men (Table 3). Although an interaction between smoking status and TC for total CVD mortality was not apparent in women, the relationship between cholesterol and ischaemic CVD was closer in smokers than in non-smokers among women (*P* for interaction, 0.02 for ischaemic CVD).

Because the age distribution differed by TC categories in women, we analysed interactions between smoking and cholesterol for CVD or ischaemic CVD separately by age group (≤69 and >69 years). For most of the age-specific analyses except the relationship between smoking and CVD mortality according to TC level in women aged >69 years, the relationship of TC with diseases was also closer in current smokers than in those who had never smoked (data not shown).

Discussion

The present study found that the relationship between cigarette smoking and CVD mortality is affected by TC level in men. This pattern was also observed for CHD mortality and ischaemic CVD in men and for ischaemic CVD mortality in women.

Relative hazards (RH) and 95% confidence intervals (95%CI) of cardiovascular disease (CVD) mortality in relation to cigarette smoking status according to total cholesterol level (ATA80, 1980–1999, Japan)

Cholesterol level (mmol/l)	Men					
	Never smoked	Ex-smoker	Current smoker	Never smoked	Ex-smoker	Current smoker
≤164 mmol/l						
n	2839.5	2281.1	11807.8	19283.8	364.7	
mortality	20	12	51	36	2	
Crude CVD mortality rate	4.1	2.5	2.9	3.5	5.9	
Crude RH	1	0.56 (0.27–1.15)	0.70 (0.42–1.17)	1	1.60 (0.39–6.67)	2.65 (0.51–13.7)
e-adjusted RH	1	0.64 (0.31–1.34)	0.85 (0.49–1.49)	1	1.42 (0.33–6.02)	3.11 (0.62–15.7)
165–185 mmol/l						
n	2973.2	3084.5	11623.3	18863.6	316.2	
mortality	11	11	54	53	1	
Crude CVD mortality rate	1.2	2.6	4.2	3.2	5.0	
Crude RH	1	1.42 (0.61–3.31)	1.94 (1.00–3.74)	1	0.94 (0.13–6.78)	0.75 (0.08–6.43)
e-adjusted RH	1	1.32 (0.56–3.11)	1.72 (0.88–3.37)	1	0.44 (0.06–3.47)	0.52 (0.06–4.13)
186–208 mmol/l						
n	3263.6	3106.0	10416.8	19286.7	499.4	
mortality	14	17	51	62	4	
Crude CVD mortality rate	3.0	3.4	3.9	3.0	6.6	
Crude RH	1	1.03 (0.51–2.10)	1.58 (0.87–2.88)	1	1.40 (0.51–3.89)	0.90 (0.28–2.87)
e-adjusted RH	1	1.53 (0.72–3.23)	1.81 (0.98–3.33)	1	1.52 (0.51–4.56)	1.03 (0.31–3.43)
≥209 mmol/l						
n	3279.6	3488.2	9248.6	20833.7	527.2	
mortality	10	19	43	91	4	
Crude CVD mortality rate	2.0	3.2	4.7	3.2	3.7	
Crude RH	1	1.35 (0.63–2.90)	2.07 (1.04–4.16)	1	1.28 (0.47–3.49)	2.11 (0.71–6.31)
e-adjusted RH	1	1.52 (0.69–3.35)	2.36 (1.14–4.87)	1	1.16 (0.38–3.50)	2.67 (0.81–8.33)

In e-adjusted model, we adjusted for age, body mass index, systolic BP, use of anti-hypertensive medication, diabetes, and drinking category (never, past, occasional and daily).

mmol/l: < 164 mg/dl; 165–185 mmol/l: 165–185 mg/dl; 186–208 mmol/l: 186–208 mg/dl; ≥ 209 mmol/l: ≥ 209 mg/dl.

n: numbers; CVD, cardiovascular disease; Crude CVD mortality rate, Crude CVD mortality rate per 1000 person-years.

Interaction between smoking and total cholesterol for cause specific mortality. NIPPON DATA80 1980-99

	Never smoker				Current smoker				P for interaction
	N	n	Age-adjusted mortality rate	RH	N	n	Age-adjusted mortality rate	RH	
Heart diseases									
<5 mmol/l ^a)	173	4	1.3	1	709	4	0.2	0.48 (0.10-2.22)	
5-9.9 mmol/l ^a)	177	2	0.4	1	678	5	0.5	0.38 (0.06-2.27)	
10-14.9 mmol/l ^a)	189	3	1.0	1	605	14	1.2	2.07 (0.57-7.57)	
≥15 mmol/l ^a)	184	4	1.2	1	531	15	1.5	1.64 (0.52-5.19)	
	723	13		0.70 (0.32-1.54) ^c	2523	38		2.00 (1.46-2.74) ^c	
stroke									
<5 mmol/l ^a)	173	4	0.6	1	709	17	0.8	1.77 (0.51-6.17)	
5-9.9 mmol/l ^a)	177	3	0.4	1	678	22	1.7	3.50 (0.96-12.75)	
10-14.9 mmol/l ^a)	189	4	0.6	1	605	11	0.9	1.37 (0.40-4.69)	
≥15 mmol/l ^a)	184	1	0.1	1	531	12	1.4	7.99 (0.84-76.14)	
	723	12		0.55 (0.21-1.43) ^c	2523	62		1.09 (0.79-1.50) ^c	
cardiovascular diseases									
<5 mmol/l ^a)	173	8	1.9	1	709	21	1.0	1.07 (0.42-2.74)	
5-9.9 mmol/l ^a)	177	5	0.8	1	678	27	2.1	2.01 (0.72-5.63)	
10-14.9 mmol/l ^a)	189	7	1.6	1	605	25	2.1	1.70 (0.71-4.08)	
≥15 mmol/l ^a)	184	5	1.3	1	531	27	2.8	2.60 (0.94-7.18)	
	723	25		0.65 (0.36-1.19) ^c	2523	100		1.42 (1.13-1.80) ^c	
Heart diseases									
<5 mmol/l ^a)	1074	9	0.9	1	91	2	1.6	2.18 (0.34-14.11)	
5-9.9 mmol/l ^a)	1063	8	0.5	1	102	0	0.0	-	
10-14.9 mmol/l ^a)	1089	11	0.5	1	115	3	1.0	2.49 (0.62-10.00)	
≥15 mmol/l ^a)	1187	16	0.6	1	125	4	1.4	3.77 (1.21-11.74)	
	4413	44		0.88 (0.61-1.28) ^c	433	9		1.12 (0.46-2.73) ^c	
stroke									
<5 mmol/l ^a)	1074	8	0.8	1	91	1	0.9	1.50 (0.16-14.33)	
5-9.9 mmol/l ^a)	1063	14	0.8	1	102	0	0	-	
10-14.9 mmol/l ^a)	1089	13	0.6	1	115	1	0.4	0.55 (0.06-4.97)	
≥15 mmol/l ^a)	1187	22	0.8	1	125	6	2.2	4.65 (1.73-12.52)	
	4413	57		0.96 (0.70-1.34) ^c	433	8		1.98 (0.45-8.73) ^c	

Table 3 Continued

	Never smoker				Current smoker				P for interaction ^b
	N	n	Age-adjusted mortality rate	RH	N	n	Age-adjusted mortality rate	RH	
Women									
Ischaemic cardiovascular diseases									
Q1 (<4.25 mmol/l ^a)	1074	17	1.7	1	91	3	2.5	1.86 (0.45-7.62) ^d	-
Q2 (4.26-4.80 mmol/l ^a)	1063	22	1.3	1	102	0	0.0	-	-
Q3 (4.81-5.39 mmol/l ^a)	1089	24	1.2	1	115	4	1.4	1.37 (0.43-4.34)	-
Q4 (≥5.40 mmol/l ^a)	1187	38	1.3	1	125	10	3.6	4.24 (2.02-8.88)	-
Total	4413	101		0.92 (0.72-1.18) ^c	433	17		1.28 (0.65-2.50) ^c	0.02

Age-adjusted mortality rate, age-adjusted mortality rate per 1000 person-years.

In multivariate-adjusted model, we adjusted for age, body mass index, systolic BP, use of anti-hypertensive medication, diabetes and drinking category (never, past, occasional, and daily).

^a<4.25 mmol/l, <164 mg/dl; 4.26-4.80 mmol/l, 165-185 mg/dl; 4.81-5.39 mmol/l, 186-208 mg/dl; ≥5.40 mmol/l, ≥209 mg/dl.

^bP for interactions: interactions between TC (continuous) and smoking status were examined using cross-product terms in the regression model.

^cRelative hazards of cholesterol increase per 1 mmol/l (continuous) for cause specific deaths.

^dBecause of questionable model fitting, we have excluded diabetes and anti-hypertensive medication from the model.

TC, total cholesterol; N, numbers of participants; n, numbers of mortality.

The strengths of our study are that we used a representative Japanese population from a national survey, as well as a validated and standardized TC measurement.

Several possibilities could explain the interaction. From a biological viewpoint, the findings that the association of smoking with ischaemic CVD is closer among individuals with higher, than with lower TC, were consistent with those of recent studies indicating that smoking is associated more closely with advanced, than with early, subclinical atherosclerosis.^{7,8} In both the Atherosclerosis Risk in Communities (ARIC) study and in the Multiethnic Study of Atherosclerosis, Sharrett *et al.* showed that smoking was more closely associated with severe atherosclerosis (lower extremity artery disease or severe carotid artery intimal medial thickness, IMT) than with moderate IMT, and that low density lipoprotein cholesterol (LDL-C) was a more important determinant than smoking of the earliest ultrasound-detectable stage of atherosclerosis. A study of young adults similarly found that the determinants of carotid IMT were only lifetime LDL-C and (inversely) high density lipoprotein cholesterol (HDL-C), but not smoking pack-years or diabetes.¹⁸ Thus, the impact of smoking could be higher in those with high TC and lower in those with low TC. The second possibility is that higher CVD mortality among those who never smoked with lower TC explains the interaction. Although men with lower TC who had never smoked had a preferable CVD risk factor profile, they had a higher age-adjusted CVD mortality rate. We considered two explanations for this. One is that the risk of haemorrhagic stroke mortality is higher in men who had never smoked with low TC. Haemorrhagic stroke is not atheromatous, and is affected by hypertension but not by serum TC. Furthermore, some epidemiological studies suggested that lower TC is associated with higher haemorrhagic stroke risk¹⁹. Thus, haemorrhagic stroke might increase the CVD risk. However, the higher CVD mortality rates in men with lower TC who had never smoked persisted even when CHD or ischaemic CVD were the end-points. Another explanation for the higher CVD mortality rate in the subgroup of non-smokers with low TC might be personal characteristics. Most Japanese men, especially the elderly, have smoked cigarettes at some point during their lives. For example, almost 80% (77.5%) of men aged ≥20 years smoked in 1970,²⁰ and the remainder of those who had never smoked might have some degree of frailty. Although the exclusion of early death that occurred within 5 years did not alter the interaction, some residual confounding might have remained. For example, some might have had respiratory conditions before starting to smoke, such as tuberculosis or childhood asthma. Participants with poor nutrition, irrespective of symptoms, might have a higher CVD risk. Since information on history of respiratory diseases was unavailable, we could not determine the validity of this speculation. Unknown confounding factors might also exist that could explain the higher mortality in never smoked with lower TC. Further studies are required to understand the relationship between TC and CVD among Japanese who have never smoked. Regardless, both biological mechanisms and personal characteristics in men with lower TC who had never smoked might explain the interaction.

Our findings are consistent with recent changes in the relationship between smoking and CVD in Japan.^{2,13} In the two

Japanese cohorts (Tanushimaru and Ushibuka) in the Seven Countries Study, which collected baseline data between 1957 and 1964 and followed participants for 25 years, excess CHD or stroke-associated mortality⁸ did not significantly differ among smokers and non-smokers. Although most prospective studies have found a significant relationship between smoking and CHD,^{10,13,14} older studies did not find a significantly increased multiple-adjusted risk of stroke among smokers.^{9–11} However, recent studies, in which TC levels are higher, have established a significant and closer relationship between cigarette smoking and stroke, especially ischaemic stroke.^{12–15} Thus, our findings appear to be relevant and are also supported by several other epidemiological studies. The Hisayama study found that the relative risk of smoking for CHD was obviously greater among those with high, than low, TC.¹⁰ However, they did not formally test the effect-modification. A recent finding from the ARIC study also revealed a modest but significant interaction between smoking and LDL-C for CHD incidence.²¹ However, two large Korean studies (with shorter follow-ups) and a US study found that lower serum TC levels did not modify the risk relationship between smoking and CVD.^{5,22,23}

One of the limitations of this study is the use of mortality data. Lower-quality nutrition might determine early death after CVD events. Thus, the risk of TC might have been underestimated. Another limitation is the low mortality rate, especially among men who had never smoked and among women who current smoked. Our findings should be substantiated by longer studies of larger cohorts using CVD incidence data.

Mean levels of TC in Japan are rapidly increasing in Japan.² The National Nutrition Survey in Japan conducted in 2000 reported that the mean level of TC in Japan is 5.16 mmol/l (199.7 mg/dl) for men and 5.36 mmol/l (207.5 mg/dl) for women.²⁴ The prevalence of cholesterol values of ≥ 6.22 mmol/l (≥ 240 mg/dl) in the 2000 survey (12.0% for men and 17.4% for women) was double that found in an identical national survey in 1980, which was the source of our cohort data (6.1% for men and 8.5% for women).²⁴ In the same report in 2000, although the prevalence of current cigarette smoking was <50% overall (45.6% for men and 10.5% for women), it was higher among younger populations (56.8% and 55.0% in men aged 30–39 and 40–49 years, respectively; 18.5 and 13.7% in women aged 30–39 and 40–49 years).²² Thus, the impact and contribution of smoking or TC to CVD mortality, especially ischaemic CVD in Japan could increase.

In conclusion, we found that powerful effect modifications between smoking and TC for CVD mortality among Japanese men. This pattern was also observed for CHD mortality and ischaemic CVD in men and for ischaemic CVD mortality in women. Thus, the weak association of cigarette smoking with CVD mortality in Japan may be partly explained by a lower TC level. Since TC is increasing among Japanese, especially among younger men who often smoke,²⁵ greater efforts to reduce smoking are warranted in Japan and in other Asian countries.

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Appendix

List of the NIPPON DATA 80 Research Group.

NIPPON DATA80: "National Integrated Project for Prospective Observation of Non-communicable Disease And its Trends in the Aged."

Original Article

The Proportion of Individuals with Alcohol-Induced Hypertension among Total Hypertensives in a General Japanese Population: NIPPON DATA90

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Japanese men consume more alcoholic beverages than men in many other developed countries. The high consumption rate of alcoholic beverages among Japanese men may contribute to the high prevalence of hypertension in Japan. In the present study, we calculated the odds ratio for hypertension in alcohol drinkers based on recent criteria using data from a nationwide survey conducted in Japan in 1990, and estimated, among total hypertensives in a general Japanese population, the percentage of hypertensives whose condition was due to alcohol consumption. Of 3,454 male participants, 64.8% were drinkers (1 *gou/day*, 28.9%; 2 *gou/day*, 20.1%; 3 *gou/day* or more, 8.7%; ex-drinkers, 7.0%) and 49.8% were hypertensive, whereas 7.6% of 4,808 female participants were drinkers (1 *gou/day*, 5.2%; 2 *gou/day* or more, 1.3%; ex-drinkers, 1.1%) and 43.1% were hypertensive (1 *gou*=23.0 g of alcohol). In both sexes, drinkers had a higher odds ratio for hypertension than never drinkers, and there was a significant dose-response relationship between the amount of alcohol consumed and the odds ratio for hypertension. Among all hypertensives, the percentage whose hypertension was due to alcohol consumption was 34.5% (95% confidence interval, 10.9%–51.9%) for men and 2.6% (0.8%–5.8%) for women. The corresponding proportion based on daily alcohol intake was 12.7% for 1 *gou/day*, 11.1% for 2 *gou/day*, 5.8% for 3 *gou/day* or more, and 4.8% for ex-drinkers in men, and 1.8% for 1 *gou/day*, 0.7% for 2 *gou/day* or more, and –0.1% for ex-drinkers in women. In conclusion, we found that a large percentage of the hypertensives in a general Japanese male population had alcohol-induced hypertension. (*Hypertens Res* 2007; 30: 663–668)

Key Words: alcohol drinking, hypertension, Japan

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Introduction

Alcohol consumption has been associated with the development of hypertension (1–10), and Japanese men consume more alcoholic beverages than men in many other developed countries, including the United States and the United Kingdom (11–15). These facts suggest that the high consumption of alcoholic beverages among Japanese men may contribute to the high prevalence of hypertension in Japan (12, 16). Thus, it is important to clarify the proportion of hypertensives in the general Japanese population whose hypertension was induced by alcohol. Although this percentage has been determined in previous studies (17), it has not been estimated since the recent establishment of new criteria for hypertension (systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg).

In the present study, we attempted to estimate the proportion of individuals with alcohol-induced hypertension among total hypertensives in a randomly selected Japanese population using the recently established criteria for hypertension.

Methods

Study Design and Participants

NIPPON DATA (National Integrated Project for Prospective Observation of Non-communicable Disease And its Trends in the Aged) is a series of cohort studies conducted by the National Survey on Circulatory Disorders, Japan. In the present study, we analyzed baseline data from NIPPON DATA90 (data from the Fourth National Survey on Circulatory Disorders, Japan in 1990); the details of this cohort study have been reported previously (18–21).

A total of 8,384 community residents (3,504 men and 4,880 women; ≥ 30 years old) from 300 randomly selected districts participated. The overall population aged 30 and over in all districts was 10,956 and the participation rate in this survey was 76.5%. Of the 8,384 participants, 122 were excluded because of missing information in the baseline survey. The remaining 8,262 participants (3,454 men and 4,808 women) were included in the analysis. Accordingly, the participants in the present study were thought to be representative of the Japanese population.

The present study was approved by the Institutional Review Board of Shiga University of Medical Science for Ethical Issues (No.12-18, 2000).

Examination

Public health nurses asked the participants about their alcohol consumption habits and classified them into the following five groups: never drinker, current daily drinker of 1 *gou*/day, 2 *gou*/day, or 3 *gou*/day or more, or ex-drinker. The *gou* is a traditional Japanese alcohol drinking unit, and 1 *gou* is equiv-

alent to 180 mL of sake (Japanese rice wine), which contains 23.0 g of alcohol. Its alcohol content is roughly equivalent to 663 mL (1 bottle) of beer, 70 mL (two single shots) of whisky, or 110 mL (a half glass) of “shochu” (spirits made from barley, sweet potato, rice or any combination of these). In order to estimate the proportion of individuals with alcohol-induced hypertension among total hypertensives in the study population, male and female participants were classified into two categories: never drinkers and drinkers, with the latter category consisting of current drinkers and ex-drinkers. We included ex-drinkers in the drinker category because drinkers diagnosed with hypertension might have been advised to quit drinking alcohol. In addition to the above analysis, we estimated the proportion of individuals with alcohol-induced hypertension among total hypertensives by taking the quantity of alcohol consumed into consideration. In this analysis, male participants were classified into the following five categories: never drinker, 1 *gou*/day, 2 *gou*/day, 3 *gou*/day or more, and ex-drinker. Furthermore, female participants were classified into the following four categories: never drinker, 1 *gou*/day, 2 *gou*/day or more, and ex-drinker. A category of 3 *gou*/day or more was not used in women, because only 1.3% of the female participants were heavy drinkers (2 *gou*/day, $n=36$; 3 *gou*/day or more, $n=27$).

Baseline blood pressures were measured once by trained observers using a standard mercury sphygmomanometer on the right arm of seated participants after a sufficient period of rest. Information on the use of antihypertensive agents was also obtained by public health nurses. Referring to the Seventh Report of the Joint National Committee (17), hypertension was defined as a systolic blood pressure ≥ 140 mmHg, a diastolic blood pressure ≥ 90 mmHg, the use of antihypertensive agents, or any combination of these. Body mass index was calculated as weight (kg) divided by the square of height (m).

Statistical Analysis

The data were analyzed separately for men and women, because alcohol consumption habits are quite different between the sexes in Japan (7, 11, 16, 22). Initially, one way analysis of variance or a χ^2 test was used to compare risk characteristics at baseline among the different alcohol-intake categories. Next, we calculated the prevalence of hypertension in each of two alcohol drinking habit categories (never drinkers and drinkers [including ex-drinkers]). A logistic regression model was used to calculate the odds ratio for hypertension in drinkers with never drinkers serving as a reference. Age and body mass index were included in the regression models as potential confounding variables. We estimated the percentage of individuals having alcohol-induced hypertension among total hypertensives—*i.e.*, the population attributable fraction—using the following equation: [prevalence of drinkers among hypertensives \times (odds ratio – 1)]/odds ratio (23). The 95% confidence interval for the corresponding proportion was calculated using the formula pro-

Table 1. Baseline Risk Characteristics in 1990 of 8,262 Japanese Participants Based on Sex and Alcohol Drinking Habit: NIPPON DATA90

	Alcohol drinking habit				
	Never drinker	1 <i>gou</i> /day	2 <i>gou</i> /day (or more for women)	3 <i>gou</i> /day or more	Ex-drinker
Men					
Number of participants (<i>n</i> (%))	1,217 (35.2)	998 (28.9)	694 (20.1)	302 (8.7)	243 (7.0)
Age (years)* [‡]	54.3±14.7	52.9±13.5	51.1±11.8	49.4±10.9	61.3±14.1
Body mass index (kg/m ²)* [‡]	22.8±3.1	22.9±2.9	23.2±2.9	23.5±3.1	22.7±3.3
Systolic blood pressure (mmHg)* [‡]	134.8±20.0	138.4±19.9	139.0±19.0	141.0±20.1	141.8±21.1
Diastolic blood pressure (mmHg)* [‡]	81.2±10.9	84.0±11.2	85.6±11.9	86.3±12.1	84.0±12.8
Use of antihypertensive agents (%) [‡]	9.9	14.1	13.5	9.6	24.3
Women					
Number of participants (<i>n</i> (%))	4,442 (92.4)	251 (5.2)	63 (1.3)		52 (1.1)
Age (years)* [‡]	53.1±14.2	47.1±11.4	47.7±10.5		51.5±13.7
Body mass index (kg/m ²)*	22.9±3.3	22.5±3.1	22.8±3.5		22.5±3.4
Systolic blood pressure (mmHg)* [‡]	133.9±20.8	131.1±20.8	132.7±19.3		128.2±22.2
Diastolic blood pressure (mmHg)*	79.4±11.7	81.0±13.0	81.6±10.4		77.7±13.2
Use of antihypertensive agents (%) [‡]	15.9	10.8	20.6		19.2

Values indicate the mean±SD or the % of participants in that category. One *gou* contains 23.0 g of alcohol. *Mean values were compared among the categories by one way analysis of variance. [‡]Proportions were compared among the categories by a χ^2 test. [‡]The difference among the alcohol drinking habit categories was statistically significant ($p<0.05$).

posed by Greenland (24). Finally, in order to investigate the corresponding proportion of individuals with alcohol-induced hypertension by daily intake of alcohol, we analyzed the data using the above equation after classifying the male and female participants into five and four categories, respectively, based on their habits of alcohol consumption.

The statistical analysis was performed using SPSS 14.0J for Windows (SPSS Japan Inc., Tokyo, Japan). *p* values were two-sided, and values of $p<0.05$ were considered statistically significant.

Results

The mean values or proportions of risk characteristics for male and female participants grouped according to their alcohol consumption habits are summarized in Table 1. Of the 3,454 male participants (mean age, 53.3 years old), 64.8% had a current or past alcohol consumption habit and 49.8% were hypertensive, whereas only 7.6% of the 4,808 female participants (mean age, 52.7 years old) had a drinking habit and 43.1% were hypertensive. For both sexes, the mean age was higher in never drinkers and ex-drinkers than in daily drinkers. For men, the mean body mass index was lower in never drinkers and ex-drinkers than in daily drinkers of 2 *gou* day or more.

Male drinkers had a higher prevalence of hypertension compared to never drinkers (54.2% for drinkers vs. 41.7% for never drinkers), and we confirmed a significantly higher odds ratio for hypertension in drinkers after adjustment for age and body mass index (1.96; 95% confidence interval, 1.67–2.29).

Although female drinkers had a somewhat lower prevalence of hypertension (41.3% for drinkers vs. 43.3% for never drinkers), we confirmed a significantly higher odds ratio for hypertension in drinkers after adjustment for the same confounding factors (1.54; 95% confidence interval, 1.20–1.98). The proportion of individuals with alcohol-induced hypertension among total hypertensives was estimated to be 34.5% (95% confidence interval, 10.9%–51.9%) in men and 2.6% (95% confidence interval, 0.8%–5.8%) in women (the results described above are not shown in Table 1).

There was a dose-response relationship between daily alcohol intake and the odds ratio for hypertension in both sexes (Table 2). Even the odds ratio for hypertension in daily drinkers who consumed 1 *gou*/day was significantly higher in both sexes. Table 2 shows the percentage of individuals with alcohol-induced hypertension among total hypertensives in each daily-intake category. The proportion of individuals with alcohol-induced hypertension was highest in daily drinkers of 1 *gou*/day in both sexes.

Discussion

In the present study, we found a large proportion of individuals with alcohol-induced hypertension among all hypertensive participants in a representative Japanese male population. Approximately one-third of male hypertensives—but only a few percent of female hypertensives—had hypertension due to alcohol consumption. There are prominent regional differences in alcohol consumption in Japan (11, 22, 25), which may affect the proportion of individuals with alcohol-induced

Table 2. Prevalence of Hypertension, Odds Ratio for Hypertension in Alcohol Drinkers, and Proportion of Individuals with Alcohol-Induced Hypertension among Total Hypertensives in 1990 Grouped by Sex and Alcohol Drinking Habit among 8,262 Participants: NIPPON DATA90

Alcohol drinking habit	Number of participants (n (%))	Hypertension			Alcohol-induced hypertension among total hypertensives (%)
		Cases	Prevalence (%)	Adjusted odds ratio* (95% confidence interval)	
Men					
Never drinkers	1,217 (35.2)	508	41.7	1.00	
1 <i>gou</i> /day	998 (28.9)	514	51.5	1.74 (1.45–2.10)	12.7
2 <i>gou</i> /day	694 (20.1)	371	53.5	2.06 (1.67–2.53)	11.1
3 <i>gou</i> /day or more	302 (8.7)	168	55.6	2.46 (1.86–3.25)	5.8
Ex-drinkers	243 (7.0)	160	65.8	2.05 (1.49–2.81)	4.8
Women					
Never drinkers	4,442 (92.4)	1,923	43.3	1.00	
1 <i>gou</i> /day	251 (5.2)	101	40.2	1.58 (1.17–2.14)	1.8
2 <i>gou</i> /day or more	63 (1.3)	30	47.6	2.09 (1.17–3.72)	0.7
Ex-drinkers	52 (1.1)	20	38.5	0.94 (0.49–1.79)	–0.1

One *gou* contains 23.0 g of alcohol. Hypertension was defined as a systolic blood pressure ≥ 140 mmHg, a diastolic blood pressure ≥ 90 mmHg, the use of antihypertensive agents, or any combination of these. *Odds ratios were calculated by a logistic regression model adjusted for age and body mass index.

hypertension among all hypertensives (22). Therefore, only data from a nationwide random sampling survey such as ours will generate a reliable estimate of the proportion of individuals with alcohol-induced hypertension among all hypertensives in the general Japanese population.

Previously, Ueshima *et al.* (16) reported that hypertension in 32% of Japanese hypertensive men (based on previous criteria of systolic blood pressure ≥ 160 mmHg, diastolic blood pressure ≥ 95 mmHg, the use of antihypertensive agents, or any combination of these) aged 30–69 could be attributed to alcohol drinking using data from the nationwide survey in 1980. In 1990, using more recent criteria for hypertension (17) (*i.e.*, different from the above criteria), we calculated the odds ratio for the prevalence of hypertension in drinkers, and estimated the percentage of Japanese hypertensives whose condition could be attributed to alcohol. It is difficult to compare our results directly with the corresponding proportion in other countries due to the lack of available data. However, Japanese men consume more alcoholic beverages than men in many other developed countries (11–15). Klag *et al.* (12) previously reported that, in the 1970s, the prevalences of daily drinkers in a male population aged 35–59 working for an office in Japan or the United States were 48% (heavy drinkers, 6%) and 40% (heavy drinkers, 0%), respectively, and then estimated that hypertension in 29% of Japanese and 21% of American hypertensives (based on the same previous criteria) could be attributed to daily alcohol consumption (12). The prevalence of daily drinkers in Japanese male office workers is almost the same as the results from the nationwide survey in 1980 (16), although we do not have any information on the prevalence of daily drinkers in the whole male population in the United States at that time. In addition, Zhou *et al.*

(13) recently reported that in the 1990s, the mean alcohol intake per day in a male population aged 40–59 was 186.8 kcal for Japan, 70.4 kcal for the United States and 116.1 kcal for the United Kingdom (7 kcal = 1.0 g of alcohol). Judging from these observations, the proportion of individuals with alcohol-induced hypertension among all hypertensives might be much higher in the Japanese male population than in the male population in other developed countries such as the United States and the United Kingdom.

We demonstrated that even a low-to-moderate alcohol intake of 1 *gou*/day contributes to the high prevalence of hypertension in Japan. Approximately 37% of all men and 75% of all women with alcohol-induced hypertension had a low-to-moderate alcohol intake. This is because the number of low-to-moderate drinkers was much greater than the number of heavy drinkers of 2 *gou*/day or more; approximately 50% of male current drinkers and 80% of female current drinkers were in the category of low-to-moderate alcohol intake. These results suggest that moderation of alcohol intake is not enough to reduce the prevalence of hypertension in the Japanese population. From the viewpoint of preventing hypertension, quitting habitual alcohol intake or never drinking in the first place may be required rather than reducing alcohol intake. However, a J-shaped association between alcohol intake and arterial stiffness quantified by pulse wave velocity has been suggested (26), even among normotensive individuals (27). A J-shaped association between alcohol intake and coronary heart disease (28, 29) or ischemic stroke (30) has also been suggested. Therefore, the protective effect of light-to-moderate alcohol intake on atherosclerotic cardiovascular risk should also be included in the overall consideration of the influence of alcohol drinking on human health.

The present study has several limitations. First, in the interview used to assess alcohol intake habits, each participant chose the category most applicable to his or her habit among the five categories on the basis of his or her own judgement. It is possible that some participants who occasionally consume alcoholic beverages choose "never drinker," and this might have underestimated the true proportion of individuals with alcohol-induced hypertension among total hypertensives, because even such drinkers are likely to be at risk for hypertension (10). Second, we did not take the type of alcoholic beverages consumed into consideration in our analysis, because this information was not available. However, Okamura *et al.* (31) reported that the effect of alcohol consumption on blood pressure does not depend on the type of alcoholic beverages consumed. Thus, information on the type of alcoholic beverages consumed may have little effect on the results of the present study. Third, blood pressure-related social factors (*e.g.*, stress, irregular lifestyle) and dietary factors (*e.g.*, sodium intake, potassium intake) were not adjusted in the analysis, because these data were also not available. However, Choudhury *et al.* (32) reported that there was little difference in sodium and potassium intake between Japanese male drinkers and never drinkers. Finally, our results are based on data from the survey conducted in 1990. The latest nationwide survey (the Fifth National Survey on Circulatory Disorders, Japan in 2000) (33) shows that the prevalences of alcohol drinkers (including ex-drinkers) and hypertensives are 62.4% (daily drinkers, 53.6%; ex-drinkers, 8.8%) and 57.1% for men, and 10.7% (daily drinkers, 9.3%; ex-drinkers, 1.5%) and 45.3% for women, respectively. We still observed a high prevalence of alcohol drinkers and hypertensives in men in 2000. Therefore, we believe that the proportion of individuals with alcohol-induced hypertension among total hypertensives remains quite high in the general Japanese male population.

In conclusion, alcohol consumption plays an important role in the high prevalence of hypertension in the Japanese male population. Thus, in any public health approach to combating hypertension, attention should be paid to alcohol consumption. This is also applicable to other countries where the prevalence of alcohol consumption remains high or is increasing.

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Appendix

List of the NIPPON DATA90 Research Group

NIPPON DATA90: National Integrated Project for Prospective Observation of Non-communicable Disease And its Trends in the Aged.

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Effect of Combined Cardiovascular Risk Factors on Individual and Population Medical Expenditures

— A 10-Year Cohort Study of National Health Insurance in a Japanese Population —

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Background Although obesity is required for some criteria defining metabolic syndrome, clustering of other risk factors also indicates an increased risk of cardiovascular disease. Whether the relationship between cardiovascular risk factor clustering and medical expenditures differs with body mass index (BMI) requires investigation, especially in a population with a low prevalence of obesity such as that in Japan.

Methods and Results A 10-year cohort study of 4,478 Japanese National Health Insurance beneficiaries aged 40–69 years in a community between 1990 and 2001 was carried out in the present study. The clustering of cardiovascular risk factors showed a positive and graded relationship to personal medical expenditures in participants who are overweight (BMI ≥ 25.0) and normal weight (BMI < 25.0). The individual medical expenditures per month were 1.7-fold higher for participants with 2 or 3 risk factors and overweight than for those without these factors (26,782 vs 15,377 Japanese yen). Differences in the geometric means were similarly significant after adjustment for other confounding factors. However, the excess medical expenditures by risk clustering of normal weight categories within the total medical expenditures were higher than those of overweight categories because more participants were of normal weight.

Conclusions Cardiovascular risk factor clustering and being overweight can be a useful predictor of medical expenditures in a Japanese population. (*Circ J* 2007; 71: 807–813)

Key Words: Medical expenditures; Metabolic components; Overweight; Risk factors

Hypertension, dyslipidemia, diabetes and obesity are cardiovascular risk factors that are difficult to control, but which are widespread in many developed countries! These factors are often clustered^{2–6} which has resulted in a high incidence of cardiovascular disease accounted for by metabolic syndrome, recognized as visceral fat accumulation^{2–7}. The individual components of metabolic syndrome impose a major economic burden on the health-care system^{8–12}. However, few studies have examined the combined effects of multiple cardiovascular risk factors on medical expenditures^{13,14}.

Furthermore, the National Cholesterol Education Program considers each risk factor to have a similar effect on atherosclerosis¹⁵. On the contrary, the International Diabetes Federation defines waist circumference as a requirement

for a diagnosis of metabolic syndrome¹⁶. However, other studies have shown that high-risk individuals with metabolic risk factors often go undetected if obesity is a required criterion^{17,18}. Thus, whether the relationship between cardiovascular risk factor clustering and medical expenditures differs with body mass index (BMI) should be determined, especially in a population with a low prevalence of obesity such as the Japanese.

The present study examines the influence of cardiovascular risk factor clustering on medical expenditures in individuals who are overweight and of normal weight defined by BMI. Our a priori hypothesis is that clustering of cardiovascular risk factors has a positive, graded association with medical expenditures. Furthermore, we investigated whether overweight participants with risk factor clustering actually have high medical expenditures and if so, the proportion of the excess medical expenditures in the total medical expenditures consumed by these participants.

Methods

Medical Expenditures in Japan

Medical expenditures in Japan are based on a public medical insurance institution^{19,20} that comprises 2 systems. Everyone living in Japan is required to enrol in either of the 2 insurance systems, and this is called 'health-insurance for

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all'. One is for employees and their dependants and the other is for self-employed individuals, such as farmers and fishermen, retirees and their dependants. The 2 systems respectively cover 65.3% and 34.7% of the overall population. All prices are strictly controlled by a fee schedule that is set by the National Government, and calculated on the basis of 'fee-for-service'. The fee schedule is constant, regardless of insurance system. Furthermore, the same fee schedule applies to all clinics and hospitals that are approved to provide medical services under the public medical insurance system.

Study Population

Our study cohort comprised 4,535 Japanese beneficiaries of the National Health Insurance (NHI). Details of the cohort study have been reported elsewhere^{9,21,22}. Briefly, the 40–69-year-old participants lived in 7 rural towns and a village in Shiga Prefecture, West Japan, and had undergone a baseline survey between 1989 and 1991. In 1990, the study area had 82,155 residents, including 31,564 individuals aged 40–69 years, of whom 11,900 were NHI beneficiaries. Therefore, the participants in the present study represented approximately 38% of all NHI beneficiaries in this age group within this community. Monthly NHI claim files for over 10 years within the Shiga NHI Organizations were linked with the baseline survey data. Deleting the names of the participants from the linked data protected their privacy. We excluded 57 participants as a result of information missing from the baseline survey. Accordingly, 4,478 participants (1,921 men and 2,557 women) were included in the analysis. The Institutional Review Board of Shiga University of Medical Science for ethical issues approved the present study (No.16-15).

Baseline Survey and Follow-up

The baseline survey was performed by standardized methods in accordance with the Manual for Health Check-ups under the Medical Service Law for the Aged, issued by the Japan Public Health Association in 1987.²³ Public health nurses measured blood pressure with a standard mercury sphygmomanometer in individuals who had rested for at least 5 min. Hypertension was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg or taking anti-hypertensive medication. Diabetes was defined as a history of diabetes or glucosuria detected by a spot urine test with a dipstick containing a color pad. Serum high-density lipoprotein (HDL)-cholesterol and triglycerides as a marker of dyslipidemia were not measured at the baseline examination. Accordingly, dyslipidemia was defined as hypercholesterolemia with a total cholesterol level ≥ 5.69 mmol/L (220 mg/dl).

All participants were classified into the following categories on the basis of clustering of cardiovascular risk factors (hypertension, diabetes and hypercholesterolemia): none, 1, and 2–3. Because visceral fat accumulation was not measured at the baseline survey and the prevalence of obesity (BMI > 30 kg/m²) was very low (1.3%), we used a BMI of 25 kg/m² or greater as an indicator of being overweight in the present study.²⁴ Smoking and alcohol consumption habits were determined from interviews administered by the public health nurses.

Information on medical expenditures for each participant was obtained from the monthly NHI claim files, starting from April in the year following their initial health check-up until March 2001. Medical expenditures are expressed

in Japanese yen and US dollars (ie, 100 Japanese yen = \$US 0.848, at the exchange rates published on November 7th, 2006). Data regarding medical expenditures for each individual differed depending on the period of subscription to the NHI. The medical expenditures for each participant were therefore divided by the period of subscription, and are expressed as expenditures per month of follow-up. If a beneficiary withdrew from the NHI or died, follow-up was stopped at that point. Follow-up was restarted for beneficiaries who withdrew and then re-enrolled in the NHI.

Data Analysis

We evaluated medical expenditures per person per month in each of 3 categories according to the number of cardiovascular risk factors. Because the distribution of real medical expenditures was positively skewed, the data were logarithmically transformed to normalize the distribution and the results are expressed as geometric means. For participants with expenditures of 0 yen per month, logarithmic transformations were achieved by replacing 0 yen with 1 yen. Fifteen participants had total medical expenditures of 0 yen and 16 had outpatient medical expenditures of 0 yen. To compare total and outpatient medical expenditures per person in each category we performed an analysis of covariance after adjusting for age, sex, BMI, smoking (non-smoker or current smoker) and alcohol consumption (none, occasional or daily consumption) with the Bonferroni correction for multiple post-hoc comparisons. A similar analysis was also performed after stratifying by BMI at 25 kg/m². The significance of multiplicative interaction between risk factor clustering and being overweight for medical expenditures was examined by cross-product terms in the model. Because 2,604 participants had inpatient medical expenditures of 0 yen, logarithmic transformations were not performed, and we applied the Kruskal–Wallis test to compare inpatient medical expenditures among the 3 categories.

Furthermore, we compared the medical expenditures per person between overweight and normal weight participants with individual cardiovascular risk factors.

Finally, we calculated excess medical expenditures attributable to the number of metabolic risk factors. The excess medical expenditures were estimated as follows: \sum [(the arithmetic mean of total medical expenditures in each of the 5 groups except for normal weight and no risk factor group, ie, (1) normal weight with 1 risk factor, (2) normal weight with 2 or 3 risk factors, (3) overweight alone, (4) overweight with 1 other risk factor, and (5) overweight with 2 or 3 other risk factors – the arithmetic mean of total medical expenditures in normal weight and no risk factor group) \times (the number of individuals in each of the 5 categories.)]. We also examined the ratio of excess medical expenditure to the entire total medical expenditures of the population.

The statistical package SPSS 14.0J for Windows performed these analyses. All probability values were 2-tailed and the significance level was established at $p < 0.05$.

Results

The prevalence of being overweight was 21.0% (men, 18.1%; women, 23.3%) of the entire study population. Table 1 summarizes the baseline risk characteristics of the 4,478 participants grouped according to risk factor clustering. Among them, 12.9% (men, 10.7%; women, 14.5%) had 2 or 3 risk factors, and 39.5% (men, 40.8%; women,

Table 1 Baseline Risk Characteristics in 1989–1991 of 4,478 National Health Insurance Beneficiaries in Shiga, Japan, Grouped by Sex and Risk Status

Risk characteristics	Risk status category			p value
	None	1 risk factor	2 or 3 risk factors	
Men				
No. of participants (%)	931 (48.5)	782 (40.7)	208 (10.8)	
Age (years)*	52.4±8.3	55.2±8.0	55.6±8.0	<0.01
Body mass index (kg/m ²)*	22.1±2.5	22.9±2.7	24.0±2.9	<0.01
Smoking habit [†]				
Current smoker (%)	61.0	58.7	59.1	0.61
Drinking habit [‡]				
Non-drinker (%)	21.3	19.4	22.1	
Occasional drinker (%)	22.4	19.3	24.0	0.18
Daily drinker (%)	56.3	61.3	53.8	
Hypertension (%)	0.0	67.4	94.7	<0.01
Hypercholesterolemia (%)	0.0	23.0	76.9	<0.01
Diabetes (%)	0.0	9.6	35.1	<0.01
Women				
No. of participants (%)	1,204 (46.1)	984 (38.5)	369 (14.4)	
Age (years)*	52.0±8.1	56.0±7.5	58.2±6.5	<0.01
Body mass index (kg/m ²)*	22.3±2.7	23.4±3.1	24.4±2.9	<0.01
Smoking habit [†]				
Current smoker (%)	3.6	3.3	2.7	0.71
Drinking habit [‡]				
Non-drinker (%)	79.9	79.6	80.8	
Occasional drinker (%)	16.5	16.2	15.4	0.92
Daily drinker (%)	3.6	4.3	3.8	
Hypertension (%)	0.0	54.2	97.6	<0.01
Hypercholesterolemia (%)	0.0	43.6	93.8	<0.01
Diabetes (%)	0.0	2.2	12.5	<0.01

*One way analysis of variance.

[†]Chi-square test.

Values located after the mark, ±, indicate standard deviation.

Table 2 Medical Expenditures (Total, Outpatient and Inpatient) per Person Grouped by Number of Cardiovascular Risk Factors, After 10-Year Follow-up From 1990 to 2001, in National Health Insurance in Shiga, Japan

Risk status category	No. of participants	Medical costs per person per month				
		Total		Outpatient		Inpatient
		Arithmetic mean	Adjusted geometric mean	Arithmetic mean	Adjusted geometric mean	Arithmetic mean
None	2,135	16,400 yen (139 dollars)	7,361 yen (62 dollars)	8,545 yen (72 dollars)	5,420 yen (46 dollars)	7,872 yen (67 dollars)
1 risk factor	1,766	23,002 yen (195 dollars)	9,382 yen [†] (80 dollars)	12,470 yen (106 dollars)	7,034 yen [†] (60 dollars)	10,538 yen (89 dollars)
2 or 3 risk factors	577	25,090 yen (213 dollars)	10,562 yen [†] (90 dollars)	15,494 yen (131 dollars)	7,929 yen [†] (67 dollars)	9,597 yen (81 dollars)
			p<0.01*		p<0.01*	p<0.01 [‡]

100 Japanese yen = 0.848 US dollars, at the foreign exchange rate on November 7th, 2006.

*Analysis of covariance adjusted for age, sex, body mass index, smoking habit and drinking habit.

[†]Significance, vs none, for multiple post-hoc comparisons with Bonferroni correction, p<0.05.

[‡]Kruskal Wallis test.

38.6%) had 1 risk factor. In both groups with 1 or more risk factors, the prevalence of hypertension was highest followed by hypercholesterolemia. Smoking and alcohol consumption did not significantly differ between the 3 groups in both men and women. The mean BMI values were higher in participants with more risk factors.

Total person-years were 40,815 and the mean follow-up was 9.0 years. Sex-specific analyses of the medical expenditures among the 3 categories showed similar results for men and women. Therefore, we reported our findings for men and women combined. Table 2 shows that during follow-up, the total medical expenditures per person per month with 2–3 risk factors (25,090 yen or \$US 213) and

with 1 risk factor (23,002 yen or \$US 195) were higher than those in the group with no risk factors (16,400 yen or \$US 139). The geometric means of total medical expenditures after adjusting for other confounding factors showed significant differences in personal medical expenditures between the 3 categories.

Table 3 shows the medical expenditures per person in normal weight and overweight groups stratified by a BMI of 25.0 kg/m². The total medical expenditures were highest in overweight individuals with 2–3 risk factors (26,782 yen or \$US 227). On the contrary, the total medical expenditures were lowest in the normal weight group with no risk factors (15,377 yen or \$US 130). The relationship between