TABLE 1. Clinical Characteristics of Study Population in 1988

Variables	Men		Women	
	MetS (−) (N=834)	MetS (+) (N=216)	MetS (−) (N=983)	MetS (+) (N=419)
Age, years	58±11	58±11	57±11	62±10†
Systolic blood pressure, mm Hg	132±20	145±18†	126±19	145±19†
Diastolic blood pressure, mm Hg	79±11	87±10†	74±10	81±11†
Antihypertensive medication, %	11.8	21.3†	9.0	29.6†
Hypertension, %	37.4	70.4†	24.0	67.5†
Proteinuria, %	7.0	11.6*	3.0	6.9†
Electrocardiogram abnormalities, %	18.7	19.7	12.5	14.6
Waist circumference, cm	80.3±7.6	88.7±6.9†	78.1±9.2	88.2±8.4*
Body mass index, kg/m^2	22.3±2.8	25.0±2.6†	22.1±2.9	24.9±3.1†
Fasting blood glucose, mmol/L	5.7±1.1	6.7±1.7†	5.5±1.0	6.3±1.7†
Diabetes, %	6.7	29.2†	3.0	17.7†
Serum total cholesterol, mmol/L	5.09±1.06	5.19±1.14	5.47±1.05	5.78±1.09†
Serum triglycerides, mmol/L	1.13 (0.43–2.95)	2.46 (0.83–7.32)†	0.90 (0.44–1.86)	1.58 (0.61–4.10)†
Serum high-density lipoprotein cholesterol, mmol/L	1.31±0.29	1.06±0.27†	1.42±0.28	1.14±0.22†
Smoking habits, %	51.6	45.8	6.2	7.9
Alcohol intake, %	59.5	69.4*	8.6	9.8
Regular exercise, %	12.2	8.8	9.2	9.3

Values are mean±SD or percentage.

Electrocardiogram abnormalities are defined as left ventricular hypertrophy (Minnesota code, 3–1) and/or ST depression (Minnesota code, 4–1, 2, 3).

Geometric mean values and 95% CIs of serum triglycerides are shown attributable to the skewed distribution.

*P<0.05, †P<0.01 vs MetS (−).

HDL indicates high-density lipoprotein.

significantly higher in subjects with MetS than in those without MetS for both sexes (men: 9.0 versus 4.8, P=0.03; women: 6.2 versus 3.4, P=0.01). The similar tendency was observed for hemorrhagic stroke only in men (5.1 versus 1.6, P=0.01).

Age- and multivariate-adjusted hazard ratios of MetS for the development of CVD were estimated for both sexes (Table 3). The age-adjusted analysis showed that MetS was a significant risk factor for CVD in men and women. These

TABLE 2. Age-Adjusted Incidence Rates of CVD, CHD, and Stroke According to MetS Status in 2452 Subjects During a 14-Year Follow Up by Sex

	Men				Women			
	Person-Years at Risk	No. of Events	Age-Adjusted Incidence Rate	P Value	Person-Years at Risk	No. of Events	Age-Adjusted Incidence Rate	P Value
Cardiovascular disease								
MetS (−)	9958	108	11.6		12 759	78	6.5	
MetS (+)	2416	50	21.8	<0.01	5078	71	12.9	<0.01
Coronary heart disease								
MetS (−)	10 213	53	5.7		13 010	17	1.5	
MetS (+)	2533	25	9.2	<0.01	5279	30	5.1	<0.01
Stroke								
MetS (−)	10 099	63	6.4		12 817	65	5.3	
MetS (+)	2477	31	14.1	<0.01	5122	50	8.8	0.06
Ischemic stroke								
MetS (−)	10 099	46	4.8		12 817	40	3.4	
MetS (+)	2477	20	9.0	0.03	5122	39	6.2	0.01
Hemorrhagic stroke								
MetS (−)	10 099	17	1.6		12 817	25	2.0	
MetS (+)	2477	11	5.1	0.01	5122	11	2.6	0.72

TABLE 3. Age- or Multivariate-Adjusted HRs for Development of CVD, CHD, or Stroke According to MetS Status in 2452 Subjects During a 14-Year Follow Up by Sex

	Men						Women					
	Age-Adjusted			Multivariate-Adjusted*			Age-Adjusted			Multivariate-Adjusted*		
	HR	(95% CI)	*P* Value	HR	(95% CI)	*P* Value	HR	(95% CI)	*P* Value	HR	(95% CI)	*P* Value
Cardiovascular disease												
MetS (−)	1.00	(reference)		1.00	(reference)		1.00	(reference)		1.00	(reference)	
MetS (+)	1.93	(1.38–2.70)	<0.01	1.86	(1.32–2.62)	<0.01	1.68	(1.22–2.33)	<0.01	1.70	(1.22–2.36)	<0.01
Coronary heart disease												
MetS (−)	1.00	(reference)		1.00	(reference)		1.00	(reference)		1.00	(reference)	
MetS (+)	1.95	(1.21–3.13)	<0.01	1.94	(1.19–3.17)	<0.01	3.11	(1.71–5.65)	<0.01	2.86	(1.56–5.24)	<0.01
Stroke												
MetS (−)	1.00	(reference)		1.00	(reference)		1.00	(reference)		1.00	(reference)	
MetS (+)	2.04	(1.33–3.14)	<0.01	1.92	(1.23–2.98)	<0.01	1.43	(0.99–2.08)	0.06	1.50	(1.03–2.19)	0.03
Ischemic stroke												
MetS (−)	1.00	(reference)		1.00	(reference)		1.00	(reference)		1.00	(reference)	
MetS (+)	1.80	(1.07–3.05)	0.03	1.68	(0.98–2.89)	0.06	1.77	(1.14–2.76)	0.01	1.78	(1.13–2.79)	0.01
Hemorrhagic stroke												
MetS (−)	1.00	(reference)		1.00	(reference)		1.00	(reference)		1.00	(reference)	
MetS (+)	2.67	(1.25–5.69)	0.01	2.54	(1.18–5.49)	0.02	0.88	(0.43–1.80)	0.72	0.99	(0.48–2.05)	0.91

*Adjusted for age, proteinuria, electrocardiogram abnormalities, serum total cholesterol, smoking habits, alcohol intake, and regular exercise.

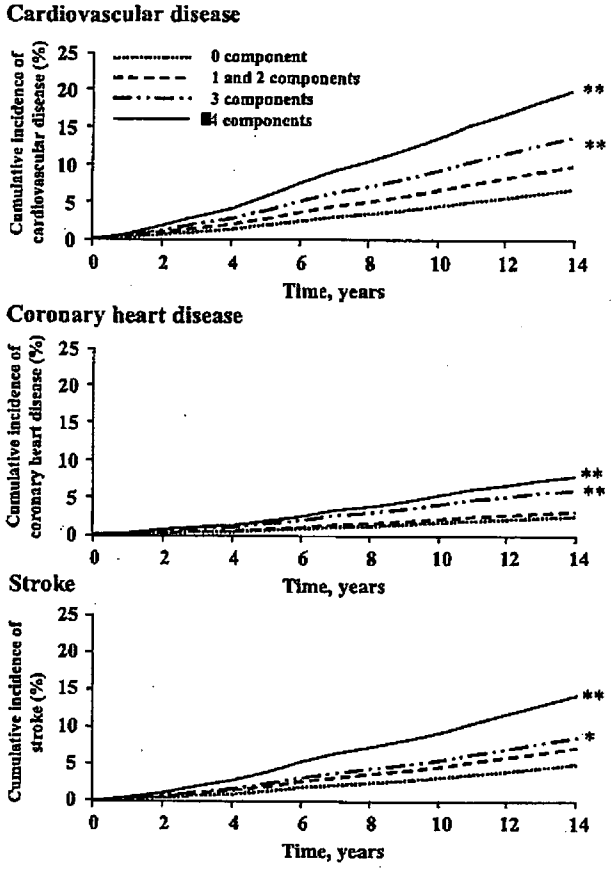
relationships remained substantially unchanged even after adjustment for the following confounding factors: age, proteinuria, electrocardiographic abnormalities, serum total cholesterol, smoking habits, alcohol intake, and regular exercise. Furthermore, MetS was found to be an independent risk factor for the development of CHD and stroke after adjustment for the confounding factors in men and women. When strokes were divided into ischemic and hemorrhagic type, multivariate-adjusted HR of MetS for ischemic stroke was marginally higher in men and significantly higher in women, whereas MetS is an independent risk factor for hemorrhagic stroke only in men.

The age- and sex-adjusted cumulative incidences of CVD, CHD, and stroke according to the number of MetS components are shown in the Figure. Because the cumulative incidence curves for one and 2 components overlapped, we combined these components. The incidences of CVD, CHD, and stroke were significantly higher among the subjects with 3 or more MetS components compared with those without any MetS component. A significant graded relationship between the number of components of MetS and the HR for developing CVD was identified from 3 MetS components and onward (Table 4). Compared with individuals with no MetS component, individuals with one, 2, 3, and 4 or more components had gradually increased HRs, respectively, for developing CVD after adjusting the confounding factors. A similar relationship was found when CVD was divided into CHD and stroke.

Because hypertension and diabetes are strong risk factors for CVD, we examined the combined as well as separate effects of MetS and hypertension or diabetes on the development of CVD. As shown in Table 5, the age- and sex-adjusted HR of CVD was significantly higher in normotensive subjects with MetS, hypertensive subjects without MetS, and hypertensive subjects with MetS compared with those without hypertension and MetS. Furthermore, there was a significant excess risk of CVD in hypertensives with MetS than in those without MetS. Similarly, the age- and sex-adjusted HR of CVD was significantly higher in nondiabetic subjects with MetS and diabetic subjects with MetS compared with those without diabetes and MetS. However, no significant difference was found in the risk of CVD in diabetic subjects without MetS. Among diabetic subjects, the risk of CVD was significantly higher in subjects with MetS than in those without MetS. These relationships remained substantially unchanged even after adjusting for the confounding factors. Furthermore, we examined the association of MetS with CVD by the multivariate analysis using hypertension and diabetes in addition to the previously mentioned risk factors as confounding factors. As a result, MetS remained a significantly independent risk factor for the development of CVD (HR, 1.38; 95% CI, 1.07 to 1.78, $P=0.01$). The risks of other risk factors were as follows: age (HR, 2.00 [per increment of 10 years]; 95% CI, 1.79 to 2.26, $P<0.01$), male sex (1.45; 1.07 to 1.97, $P=0.02$), hypertension (1.64; 1.26 to 2.12, $P<0.01$), diabetes (1.55; 1.14 to 2.13, $P<0.01$), smoking habits (1.69; 1.28 to 2.23, $P<0.01$), regular exercise (0.58; 0.39 to 0.87, $P<0.01$), proteinuria (1.64; 1.13 to 2.38, $P<0.01$), electrocardiographic abnormalities (1.29; 0.98 to 1.69, $P=0.07$), serum total cholesterol (0.99 [per increment of 1 mmol/L]; 0.89 to 1.11, $P=0.92$), and alcohol intake (0.97; 0.73 to 1.30, $P=0.84$).

Discussion

To our knowledge, our study is the first prospective cohort study of a general Japanese population with a long duration of follow up reporting the association of MetS with incident CVD using the modified NCEP definition. The sole study from Japan, which examined a similar association, was based on a diabetic population.[27] We found a clearly increased incidence of CVD during 14 years of follow up in both men



Age- and sex-adjusted cumulative incidences of CVD, CHD, and stroke according to the number of the metabolic syndrome components in 2452 subjects during a 14-year follow up. *$P<0.05$, **$P<0.01$ versus 0 component.

and women with MetS compared with those without MetS. Besides, the risk of MetS for the development of CVD remained significant even after adjustment for hypertension, diabetes, and other potentially confounding factors.

In our study, subjects with MetS had little over 70% increases in CVD risk compared with those without MetS. Similar or higher HRs (1.4- to 5.0-fold) of MetS for CVD/CHD were reported from different European and American studies.[7,13–25] Differences in the study populations, prevalence of individual components of MetS, follow-up length, and MetS definition used seem to be the main causes behind the variation in the HRs. In our study, CHD risk related to MetS is higher in women than in men, which is consistent with the studies from the Western world.[17]

Our study showed that the risk of incident combined CVD, and CHD and stroke separately, was found to increase with the number of components of MetS and increased by 3-fold or more in those with 4 or more MetS components compared with those without any component. It also revealed that the risk of CVD increased in incremental fashion with the number of components of MetS and became predictive of CVD (also CHD and stroke separately) when the number of components reached 3. This phenomenon gives credence to the requirement of ≥3 components in the NCEP definition for establishing the diagnosis of MetS. Thereby, it can be assumed that the modified NCEP definition of MetS is well predictive for CVD in the general Japanese population.

One prospective study based on a Japanese diabetic population mentioned that MetS based on the NCEP definition was predictive for CVD in men and was not in women.[27] The same authors again reported that the new International Diabetes Federation definition[34] was not predictive for CVD in either male or female patients with diabetes.[35] On the other hand, in our study, MetS based on the NCEP definition was consistently predictive of CVD not only in both men and women, but also in subjects with diabetes. We speculate that this discrepancy resulted from the difference in the cutoff point of the waist circumference between the 2 studies. The former used the waist circumference definition for abdominal obesity proposed by the Japan Society for the Study of Obesity (85 cm for men and 90 cm for women),[36] whereas in our study, we used the waist circumference definition for Asian populations (90 cm for men and 80 cm for women), which was recommend by the International Diabetes Federation to use for the Japanese population.[37] Further research is needed to refine the MetS definition, which would be applicable to various populations, including Japanese.

There was a possibility that the increased risk of MetS for CVD resulted from the influences of hypertension or diabetes, which are components of MetS and major risk factors for developing CVD. However, our stratified analysis showed that the MetS was a significant risk factor for CVD in normotensive subjects as well as in nondiabetic individuals and has a similar risk for CVD as hypertension; the risk is even higher than that of diabetes. Moreover, in the multivariate analysis, MetS was found to be a significant risk factor for CVD independent of hypertension, diabetes, and other confounding risk factors. These results imply the significant roles of MetS in the development of CVD and the need for prevention and early management of the MetS components. In addition, diabetes is not predictive of CVD in subjects without MetS in our study. This finding might suggest that good diabetic control is useful. However, because the number of our diabetic subjects without MetS is small, further studies are necessary to elucidate this issue in detail.

The strengths of our study include its longitudinal population-based study design, long duration of follow up, sufficient number of CVD events and almost perfect follow up of subjects, examining the data in men and women separately, and exclusion of patients with CVD at baseline. Moreover, it is the first study to examine prospectively CVD in relation to MetS based on a general Japanese population. One limitation of our study is that the diagnosis of MetS was based on a single measurement of its components at baseline as was the case in other epidemiological studies.[13–25,27–29] During the follow up, risk factor levels could be changed attributable to modification of lifestyle or medication, and misclassification of the MetS is possible. Thus, it would weaken the association found in this study, biasing the results toward the null hypothesis. Therefore, the true association may be stronger than that shown in our findings.

In conclusion, we have shown that the prevalence of MetS is sizeable in Japanese middle-aged men and women and it is predictive of future CVD in both sexes based on a prospective study with 14 years of follow up. Our findings suggest that early identification of MetS and appropriate behavioral and therapeutic intervention may reduce the burden of CVD in the long run.

TABLE 4. Age- or Multivariate-Adjusted HRs for Development of CVD, CHD, and Stroke According to the Number of the MetS Components in 2452 Subjects During a 14-Year Follow Up

	Population at Risk	No. of Events	Age- and Sex-Adjusted			Multivariate-Adjusted*		
			HR	(95% CI)	*P* Value	HR	(95% CI)	*P* Value
Cardiovascular disease								
No. of MetS components								
0	436	30	1.00	(reference)		1.00	(reference)	
1	756	84	1.49	(0.98–2.26)	0.06	1.45	(0.95–2.20)	0.08
2	625	72	1.47	(0.96–2.26)	0.08	1.39	(0.91–2.15)	0.15
3	394	65	2.12	(1.37–3.28)	<0.01	1.95	(1.25–3.04)	<0.01
≥4	241	56	3.19	(2.03–5.02)	<0.01	2.99	(1.89–4.73)	<0.01
Coronary heart disease								
No. of MetS components								
0	436	13	1.00	(reference)		1.00	(reference)	
1	756	35	1.41	(0.75–2.67)	0.29	1.38	(0.72–2.62)	0.33
2	625	22	1.05	(0.53–2.09)	0.89	0.95	(0.47–1.90)	0.88
3	394	32	2.55	(1.33–4.89)	<0.01	2.29	(1.18–4.47)	0.01
≥4	241	23	3.36	(1.68–6.72)	<0.01	2.96	(1.45–6.01)	<0.01
Stroke								
No. of MetS components								
0	436	20	1.00	(reference)		1.00	(reference)	
1	756	58	1.52	(0.91–2.53)	0.11	1.48	(0.89–2.47)	0.14
2	625	50	1.50	(0.89–2.53)	0.13	1.45	(0.86–2.46)	0.16
3	394	41	1.89	(1.10–3.25)	0.02	1.78	(1.03–3.09)	0.04
≥4	241	40	3.16	(1.83–5.46)	<0.01	3.05	(1.75–5.31)	<0.01

*Adjusted for age, sex, proteinuria, electrocardiogram abnormalities, serum total cholesterol, smoking habits, alcohol intake, and regular exercise.

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TABLE 5. Age- and Sex-Adjusted or Multivariate-Adjusted HRs of the MetS for Development of CVD According to the Presence or Absence of Hypertension or Diabetes in 2452 Subjects During a 14-Year Follow Up

	Population at Risk	No. of Events	Age- and Sex-Adjusted		Multivariate-Adjusted*	
			HR	(95% CI)	HR	(95% CI)
Hypertension						
HT (−)+MetS (−)	1269	89	1.00	(reference)	1.00	(reference)
HT (−)+MetS (+)	200	25	1.79	(1.14–2.79)*	1.75	(1.12–2.75)*
HT (+)+MetS (−)	548	97	1.81	(1.35–2.43)†	1.75	(1.29–2.37)†
HT (+)+MetS (+)	435	96	2.59	(1.93–3.48)†‡	2.45	(1.81–3.32)†‡
Diabetes						
DM (−)+MetS (−)	1732	171	1.00	(reference)	1.00	(reference)
DM (−)+MetS (+)	498	84	1.60	(1.23–2.09)†	1.54	(1.17–2.02)†
DM (+)+MetS (−)	85	15	1.35	(0.80–2.30)	1.38	(0.81–2.34)
DM (+)+MetS (+)	137	37	2.75	(1.93–3.93)†‡	2.60	(1.81–3.74)†‡

*Adjusted for age, sex, proteinuria, electrocardiogram abnormalities, serum total cholesterol, smoking habits, alcohol intake, and regular exercise.

*$P<0.05$, †$P<0.01$ vs reference.

‡$P<0.05$ vs HT(+)+MetS (−) or DM (+)+MetS (−).

HT indicates hypertension; DM, diabetes mellitus.

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Disclosures

None.

References

1. Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. *Diabetes*. 1988;37:1595–1607.
2. DeFronzo RA, Ferrannini E. Insulin resistance: a multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. *Diabetes Care*. 1991;14:173–194.
3. Kaplan NM. The deadly quartet. Upper-body obesity, glucose intolerance, hypertriglyceridemia, and hypertension. *Arch Intern Med*. 1989; 149:1514–1520.
4. Grundy SM, Brewer HB Jr, Cleeman JI, Smith SC Jr, Lenfant C. Definition of metabolic syndrome: report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. *Circulation*. 2004;109:433–438.
5. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA*. 2001;285:2486–2497.
6. Lorenzo C, Okoloise M, Williams K, Stern MP, Haffner SM. The metabolic syndrome as predictor of type 2 diabetes: the San Antonio Heart Study. *Diabetes Care*. 2003;26:3153–3159.
7. Lakka HM, Laaksonen DE, Lakka TA, Niskanen LK, Kumpusalo E, Tuomilehto J, Salonen JT. The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. *JAMA*. 2002;288:2709–2716.
8. Zimmet P, Alberti KG, Shaw J. Global and societal implications of the diabetes epidemic. *Nature*. 2001;414:782–787.
9. McGill HC, McMahan A, Herderick EE, Zieske AW, Malcom GT, Tracy RE, Strong JP. Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Research Group: obesity accelerates the progression of coronary atherosclerosis in young men. *Circulation*. 2002;105:2712–2718.
10. The DECODE Study Group. Is the current definition for diabetes relevant to mortality risk from all causes and cardiovascular and noncardiovascular diseases? *Diabetes Care*. 2003;26:688–696.
11. Eberly LE, Stamler J, Neaton JD. Multiple Risk Factor Intervention Trial Research Group: relation of triglyceride levels, fasting and nonfasting, to fatal and nonfatal coronary heart disease. *Arch Intern Med*. 2003;163:1077–1083.
12. Grundy SM, Balady GJ, Criqui MH, Fletcher G, Greenland P, Hiratzka LF, Houston-Miller N, Kris-Etherton P, Krumholz HM, LaRosa J, Ockene IS, Pearson TA, Reed J, Washington R, Smith SC Jr. Primary prevention of coronary heart disease: guidance from Framingham. A statement for healthcare professionals from the AHA Task Force on Risk Reduction. *Circulation*. 1998;97:1876–1887.
13. Girman CJ, Rhodes T, Mercuri M, Pyorala K, Kjekshus J, Pedersen TR, Beere PA, Gotto AM, Clearfield M, 4S Group, AFCAPS/TexCAPS Research Group. The metabolic syndrome and risk of major coronary events in the Scandinavian Simvastatin Survival Study (4S) and the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/ TexCAPS). *Am J Cardiol*. 2004;93:136–141.
14. Hu G, Qiao Q, Tuomilehto J, Balkau B, Borch-Johnsen K, Pyorala K, the DECODE Study Group. Prevalence of the metabolic syndrome and its relation to all-cause and cardiovascular mortality in non-diabetic European men and women. *Arch Intern Med*. 2004;164:1066–1076.
15. Malik S, Wong ND, Franklin SS, Kamath TV, L'Italien GJ, Pio JR, Williams GR. Impact of the metabolic syndrome on mortality from coronary heart disease, cardiovascular disease, and all causes in United States adults. *Circulation*. 2004;110:1245–1250.
16. Ford ES. The metabolic syndrome and mortality from cardiovascular disease and all-causes: findings from the National Health and Nutrition Examination Survey II Mortality Study. *Atherosclerosis*. 2004;173:309–314.
17. Hunt KJ, Resendez RG, Williams K, Haffner SM, Stern MP. National Cholesterol Education Program versus World Health Organization metabolic syndrome in relation to all-cause and cardiovascular mortality in the San Antonio Heart Study. *Circulation*. 2004;110:1251–1257.
18. Isomaa B, Almgren P, Tuomi T, Forsen B, Lahti K, Nissen M, Taskinen MR, Groop L. Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care*. 2001;24:683–689.
19. Bonora E, Kiechl S, Willeit J, Oberhollenzer F, Egger G, Bonadonna RC, Muggeo M. Carotid atherosclerosis and coronary heart disease in the metabolic syndrome: prospective data from the Bruneck study. *Diabetes Care*. 2003;26:1251–1257.
20. Bonora E, Targher G, Formentini G, Calcaterra F, Lombardi S, Marini F, Zenari L, Saggiani F, Poli M, Perbellini S, Raffaelli A, Gemma L, Santi L, Bonadonna RC, Muggeo M. The metabolic syndrome is an independent predictor of the cardiovascular disease in type 2 diabetic subjects. Prospective data from the Verona Diabetes Complications Study. *Diabet Med*. 2004;21:52–58.
21. Rutter MK, Meigs JB, Sullivan LM, D'Agostino RB Sr, Wilson PW. C-reactive protein, the metabolic syndrome, and prediction of cardiovascular events in the Framingham Offspring Study. *Circulation*. 2004;110: 380–385.
22. Sundstrom J, Riserus U, Byberg L, Zethelius B, Lithell H, Lind L. Clinical value of the metabolic syndrome for long term prediction of total and cardiovascular mortality: prospective, population based cohort study. *BMJ*. 2006;332:878–882.
23. Dekker JM, Girman C, Rhodes T, Nijpels G, Stehouwer CD, Bouter LM, Heine RJ. Metabolic syndrome and 10-year cardiovascular disease risk in the Hoorn Study. *Circulation*. 2005;112:666–673.
24. McNeill AM, Rosamond WD, Girman CJ, Golden SH, Schmidt MI, East HE, Ballantyne CM, Heiss G. The metabolic syndrome and 11-year risk of incident cardiovascular disease in the Atherosclerosis Risk in Communities Study. *Diabetes Care*. 2005;28:385–390.
25. Scuteri A, Najjar SS, Morrell CH, Lakatta EG; Cardiovascular Health Study. The metabolic syndrome in older individuals: prevalence and prediction of cardiovascular events: the Cardiovascular Health Study. *Diabetes Care*. 2005;28:882–887.
26. *Definition, Diagnosis and Classification of Diabetes Mellitus and Its Complications. Report of a WHO Consultation. Part 1: Diagnosis and Classification of Diabetes Mellitus*. Geneva: World Health Organization; 1999 (WHO/NCD/NCS99.2).
27. Sone H, Mizuno S, Fujii H, Yoshimura Y, Yamasaki Y, Ishibashi S, Katayama S, Saito Y, Ito H, Ohashi Y, Akanuma Y, Yamada N; Japan Diabetes Complications Study. Is the diagnosis of metabolic syndrome useful for predicting cardiovascular disease in Asian diabetic patients? Analysis from the Japan Diabetes Complications Study. *Diabetes Care*. 2005;28:1463–1471.
28. Chen HJ, Bai CH, Yeh WT, Chiu HC, Pan WH. Influence of metabolic syndrome and general obesity on the risk of ischemic stroke. *Stroke*. 2006;37:1060–1064.
29. Chien KL, Hsu HC, Sung FC, Su TC, Chen MF, Lee YT. Metabolic syndrome as a risk factor for coronary heart disease and stroke: an 11-year prospective cohort in Taiwan community. *Atherosclerosis*. 2006 (in press).
30. Katsuki S. Epidemiological and clinicopathological study on cerebrovascular disease in Japan. *Prog Brain Res*. 1966;21B:64–89.
31. Ohmura T, Ueda K, Kiyohara Y, Kato I, Iwamoto H, Nakayama K, Nomiyama K, Ohmori S, Yoshitake T, Shinkawa A, Hasuo Y, Fujishima M. Prevalence of type 2 (non-insulin-dependent) diabetes mellitus and impaired glucose tolerance in the Japanese general population: the Hisayama Study. *Diabetologia*. 1993;36:1198–1203.
32. Kubo M, Kiyohara Y, Kato I, Tanizaki Y, Arima H, Tanaka K, Nakamura H, Okubo K, Iida M. Trends in the incidence, mortality, and survival rate of cardiovascular disease in a Japanese community: the Hisayama study. *Stroke*. 2003;34:2349–2354.
33. World Health Organization/International Association for the Study of Obesity/International Obesity Task Force. *The Asia-Pacific Perspective: Redefining Obesity and its Treatment*. Available at: http://www.diabetes.com.au/pdf/obesity_report.pdf.
34. The International Diabetes Federation: The IDF consensus worldwide definition of metabolic syndrome, 2005. Available at: www.idf.org/webdata/docs/IDF_metasyndrome_definition.pdf. Accessed March 21, 2006.
35. Sone H, Tanaka S, Ishibashi S, Yamasaki Y, Oikawa S, Ito H, Saito Y, Ohashi Y, Akanuma Y, Yamada N; Japan Diabetes Complications Study (JDCS) Group. The new worldwide definition of metabolic syndrome is not a better diagnostic predictor of cardiovascular disease in Japanese diabetic patients than the existing definitions: additional analysis from the Japan Diabetes Complications Study. *Diabetes Care*. 2006;29:145–147.
36. Examination Committee of Criteria for 'Obesity Disease' in Japan; Japan Society for the Study of Obesity. New criteria for 'obesity disease' in Japan. *Circ J*. 2002;66:987–992.
37. Alberti KG, Zimmet P, Shaw J. Metabolic syndrome—a new world-wide definition. A consensus statement from the International Diabetes Federation. *Diabet Med*. 2006;23:469–480.

6. 放射線影響研究所成人健康調査コホート

分担研究者　児玉和紀　放射線影響研究所疫学部　主席研究員
研究協力者　笠置文善　放射線影響研究所疫学部　部長代理
研究協力者　山田美智子　放射線影響研究所臨床研究部　副部長

A．研究目的

放射線影響研究所(放影研)の成人健康調査は原爆被爆者とその対照からなるコホート調査集団について、疾病の発症や測定値等の情報を収集するため、2年毎の包括的な健康診断を1958年から現在まで継続して実施している。

肥満がインスリン抵抗性、高血圧、糖尿病、高脂血症を合併しやすいことは知られているが、欧米人に比べ肥満の程度が比較的軽度の日本人において肥満が糖尿病や心血管疾患の発症に対し、どの程度の危険度の上昇をもたらすかに関する報告は少ない。成人健康調査で身長、体重、ウエスト周囲径、ヒップ周囲径を測定した1996-98年の健診サイクルをベースラインとして、2006年4月までの糖尿病、心筋梗塞、脳卒中の新規発症を2年毎の健診で追跡し、肥満指標と糖尿病ならびに心血管疾患罹患の関係のエビデンスを得る事を目的とした。2006年度は対象者全体で解析し、いずれの肥満指標も糖尿病のリスクと正の関係を示したが、脳卒中リスクはウエスト/ヒップ比を除いて肥満指標と有意な負の関係を示した。糖尿病と脳卒中で異なる結果が得られた原因の一つとして、脂肪と筋肉では年齢に伴う変化のパターンが異なり、肥満指標の健康リスク予測における評価は年齢の影響を受けるであろう事が考えられた。2007年度は性・年齢階級別に糖尿病ならびに脳卒中発症と肥満指標の関係を検討した。

B．研究対象と方法

成人健康調査では1996-98年の健診サイクルで2999名(男性981名、女性2018名)の身長、体重、ウエスト周囲径、ヒップ周囲径を測定した。肥満指標測定時の年齢は50-95歳であった。2年毎の健診結果に基づき、糖尿病、心筋梗塞、脳卒中の新規発症を診断し、2006年4月までの追跡結果について解析した。平均追跡期間は6.8年で、その間に134名（男性50名、女性84名）の糖尿病、116名(男性36名、女性80名)の脳卒中、22名の（男性10名、女性12名）の心筋梗塞の新規発症を認めた。

2007年度は年齢による肥満指標の特徴を明らかにするため、性・年齢別(65歳未満、65－74歳、75歳以上）にウエスト周囲径ならびにＢＭＩと年齢、身体計測値、握力、収縮期血圧、ﾍﾓｸﾞﾛﾋﾞﾝA1c値、肥満指標測定前2年間の体重変化と握力変化との相関係数を求めた。性・年齢別のウエスト周囲径10ｃｍ増加に対する糖尿病と脳卒中罹患の相対リスクは喫煙、飲酒、血圧、総ｺﾚｽﾃﾛｰﾙ、HDL ｺﾚｽﾃﾛｰﾙ、ﾍﾓｸﾞﾛﾋﾞﾝA1c、がん既往、糖尿病既往を調整してCox比例ハザードモデルにより求めた。

C．研究結果

性・年齢別のウエスト周囲径ならびに BMI と年齢依存性に変化する各項目の相関係数を求めた結果、肥満指標相互(ウエスト周囲径、体重、BMI)は強い相関を示し、上腕3頭筋部の皮壁厚との相関係数は 0.4-0.5 であったが、その他の項目の間には中等度以上の相関は認められなかった。性や年齢による差も軽度であった。（表 1）

ウエスト周囲径 10ｃｍ増加に対する糖尿病ならびに脳卒中の罹患リスク（表 2）とウエスト周囲径レベル毎の相対リスク(図１)を示す。

ウエスト周囲径の増加は 75 歳未満の糖尿病罹患を有意に増加させた。性・年齢別の解析では脳卒中とウエスト周囲径の統計的に有意な関係は認められなかったが、相対リスクはいずれの性、年齢群でも 1.0 以下であった。

D．結論

年齢 50 歳以上の男女においてウエスト周囲径、ＢＭＩ等の肥満指標の増加は糖尿病発症のリスクを高めた。脳卒中発症と肥満指標に関する性、年齢別解析では統計的に有意な関係は認められなかったが、負の関係が示唆された。

表 1-1. 年齢階級別にみたウエストならびに BMI との相関係数(男性)

	ウエスト周囲径			BMI		
年齢階級	65 歳未満	65-74 歳	75 歳以上	65 歳未満	65-74 歳	75 歳以上
年齢	0.066	−0.071	−0.095	0.033	−0.078	−0.131
ウエスト周囲径	1.000	1.000	1.000	0.879	0.889	−0.112
身長	0.210	0.247	0.177	0.020	0.010	0.884
体重	0.862	0.894	0.879	0.878	0.874	0.900
BMI	0.879	0.889	0.884	1.000	1.000	1.000
握力	0.157	0.318	0.242	0.213	0.348	0.260
皮壁厚(上腕三頭筋)	0.475	0.458	0.574	0.428	0.450	0.607
総コレステロール	0.078	0.078	0.058	0.059	0.104	0.077
収縮期血圧	0.152	0.161	0.121	0.159	0.155	0.200
HbA1c	0.027	0.083	0.089	0.006	0.082	0.057
体重変化	0.259	0.144	0.197	0.245	0.151	0.183
握力変化	−0.045	0.039	0.004	−0.003	0.039	−0.018

表 1-2. 年齢階級別にみたウエストならびに BMI との相関係数(女性)

	ウエスト周囲径			BMI		
年齢階級	65 歳未満	65-74 歳	75 歳以上	65 歳未満	65-74 歳	75 歳以上
年齢	0.120	0.043	-0.131	0.078	-0.007	-0.147
身長	0.010	0.098	0.098	0.845	0.828	0.816
ウエスト周囲径	1.000	1.000	1.000	-0.143	-0.065	-0.066
体重	0.820	0.815	0.791	0.901	0.906	0.887
BMI	0.845	0.828	0.816	1.000	1.000	1.000
握力	0.045	0.080	0.137	0.066	0.110	0.166
皮壁厚(上腕三頭筋)	0.413	0.441	0.514	0.469	0.474	0.525
総コレステロール	0.114	0.049	0.082	0.077	0.078	0.112
収縮期血圧	0.313	0.226	0.143	0.351	0.257	0.155
HbA1c	0.162	0.102	0.084	0.159	0.161	0.105
体重変化	0.184	0.113	0.144	0.185	0.139	0.168
握力変化	-0.087	-0.014	-0.063	-0.077	0.036	-0.027

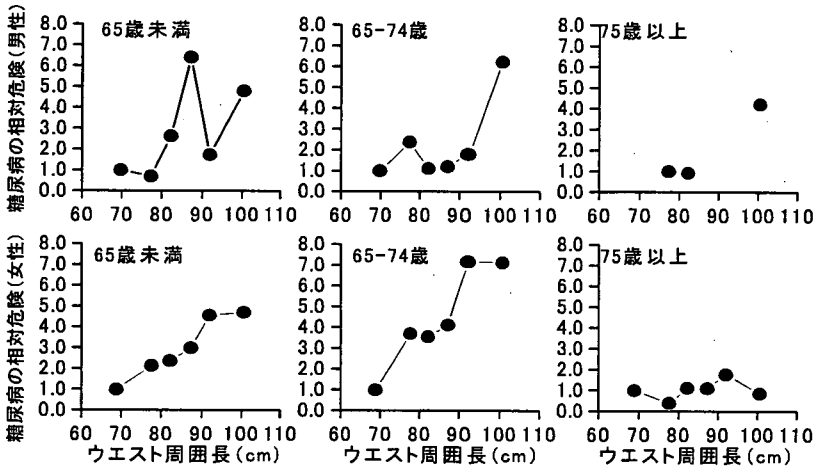
表 2. 性・年齢別にウエスト周囲径からみた罹患リスク

(ウエスト周囲径 10cm増加に対する相対リスク)

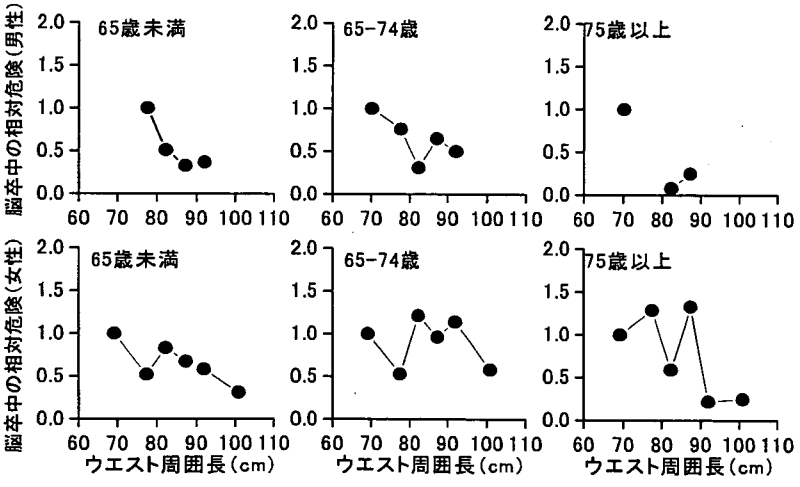
	年齢区分	罹患数/対象者数	相対リスク	95%信頼区間
糖尿病				
男性	65 歳未満	25/331	1.79	(1.04, 3.12)
	65-74 歳	22/293	1.86	(1.18, 2.86)
	75 歳以上	3/92	2.27	(0.56, 9.52)
女性	65 歳未満	22/476	1.56	(1.11, 2.11)
	65-74 歳	46/784	1.66	(1.28, 2.23)
	75 歳以上	16/377	1.14	(0.70, 1.88)
脳卒中				
男性	65 歳未満	10/397	0.66	(0.26, 1.66)
	65-74 歳	21/344	0.74	(0.42, 1.28)
	75 歳以上	5/111	0.24	(0.05, 1.02)
女性	65 歳未満	12/530	0.73	(0.35, 1.34)
	65-74 歳	48/865	0.89	(0.66, 1.18)
	75 歳以上	20/421	0.75	(0.47, 1.21)

図 1

性・年齢別にみたウエスト径による糖尿病罹患の相対リスク



性・年齢別にみたウエスト径による脳卒中罹患の相対リスク



E．2007年度の研究成果　（その他）

（公表論文）

握力は中高年の男女の死因別死亡率を予知する

Hideo Sasaki, Fumiyoshi Kasagi, Michiko Yamada, Shoichiro Fujita. Grip strength predicts cause-specific mortality in middle-aged and elderly persons. The American Journal of Medicine. 2007; 120: 337-342.

要約

握力と死亡の関係を明らかにするために、放射線影響研究所成人健康調査の中高年集団において①性・年齢別、②死因別、③追跡期間を分けた時間的推移という観点から解析を行った。

握力に関する死亡の相対リスクはCox比例ハザードモデルにより、可能性のある交絡因子を多変量解析で調整することにより推定した。

５分された握力の最高位群での参照群(５分位の第3番位)に対する死亡率の相対リスクは男性の35-54歳で0.52、55-64歳で0.72、65-74歳で0.67といずれも有意に低かった。最下位群での死亡率の相対リスクは男性の55-64歳（相対リスク：1.38）と65-74歳（相対リスク：1.38）で参照群に対し有意に高かった。女性の最下位群での死亡率の相対リスクは35-54歳（相対リスク：1.39）と65-74歳（相対リスク：1.54）で参照群に対し有意に高かった。

外因死を除く全死亡の多因子調整相対リスクは握力の5Kg増加で男性では相対リスク0.89、女性では相対リスク0.87と有意に低かった。多因子調整後の相対リスクは男性では心臓疾患、冠動脈性心疾患、肺炎による死亡で、各々0.86、0.85、0.83、女性では0.80、0.88、0.87であった。

相対リスクは追跡期間を通じて検査開始から最初の5年では0.80、20年以上の経過でも0.92と一貫していた。しかし、20年以上経過後は握力5Kg増加における相対リスクは低かった。

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CLINICAL RESEARCH STUDY

Grip Strength Predicts Cause-Specific Mortality in Middle-Aged and Elderly Persons

Hideo Sasaki, MD, PhD,[a,b] Fumiyoshi Kasagi, PhD,[c] Michiko Yamada, MD, PhD,[a] Shoichiro Fujita, PhD[d]

[a]Department of Clinical Studies, Radiation Effects Research Foundation, Hiroshima, Japan; [b]Health Management and Promotion Center, Hiroshima Atomic Bomb Casualty Council, Hiroshima, Japan; [c]Department of Epidemiology and [d]Department of Statistics, Radiation Effects Research Foundation, Hiroshima, Japan.

ABSTRACT

PURPOSE: Handgrip strength is a simple measurement used to estimate overall muscle strength but might also serve as a predictor of health-related prognosis. We investigated grip strength-mortality association in a longitudinal study.

METHODS: A total of 4912 persons (1695 men and 3217 women), 35 to 74 years old at baseline, were the subjects of this study. Members of the Adult Health Study (AHS) cohort in Hiroshima, Japan, these individuals underwent a battery of physiological tests, including handgrip-strength testing, between July 1970 and June 1972. Mortality was followed until the end of 1999. Estimates of relative risk (RR) of mortality associated with grip strength were adjusted for potentially confounding factors by Cox proportional hazard analysis.

RESULTS: Multivariate-adjusted RR of all causes of death, except for external causes, for the highest quintile of grip strength in men was 0.52 (95% confidence interval [CI], 0.33-0.80) for the age group 35-54 years, 0.72 (95% CI, 0.53-0.98) for the ages 55-64 years, and 0.67 (95% CI, 0.49-0.91) for the ages 65-74 years. These figures were significantly lower than the RR for the reference group (the third quintile). Similar trends were observed in women. Multivariate-adjusted RR of all causes of death except external causes for each 5-kg increment of grip strength was significantly low (RR: 0.89, 95% CI, 0.86-0.92 for men, RR: 0.87, 95% CI, 0.83-0.92 for women). Multivariate-adjusted RR for heart disease, stroke, and pneumonia in men was 0.85 (95% CI, 0.79-0.93), 0.90 (95% CI, 0.83-0.99), and 0.85 (95% CI, 0.75-0.98), respectively. RR for each 5-kg increment of grip strength remained 0.92 (95% CI, 0.87-0.96), even after more than 20 years of follow-up.

CONCLUSION: Grip strength is an accurate and consistent predictor of all causes of mortality in middle-aged and elderly persons.

KEYWORDS: Grip strength; Mortality; Prognosis; Cohort study

Grip-strength measurement is useful for assessing approximate overall muscle strength of middle-aged and elderly people, and longitudinal studies revealed that it also predicts health-related prognosis.[1-13] The prognostic outcomes in these studies included functional limitation, functional decline,[4,5] activities of daily living dependence,[6,13] and mortality.[1-3,8,9,11,12] The majority of the mortality studies utilized total mortality, with only one analyzing association between grip strength and cause-specific mortality.[1]

The subjects in such studies, however, were restricted to hospitalized patients[5,12] or elderly people.[1,3,6] The number of studies on association between grip strength and prognosis conducted on middle-aged, relatively healthy subjects of both sexes is limited.[2,11]

Further, most of the studies' follow-up periods were less than 10 years after baseline measurement of grip strength. Only 2 studies, one in Canada and the other in Hawaii, followed-up subjects for a longer duration, 13 and 30 years, respectively.[2,9]

Requests for reprints should be addressed to Hideo Sasaki, MD, PhD, Health Management and Promotion Center, Hiroshima A-Bomb Casualty Council, 3-8-6, Senda-machi, Naka-ku, Hiroshima 730-0052, Japan.

E-mail address: hsasaki@gentaikyo.or.jp

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The Adult Health Study (AHS) is a longitudinal cohort study conducted at the Radiation Effects Research Foundation (RERF) in Hiroshima and Nagasaki. Grip strength was measured with other physiological function tests during 1970-1972 to assess the overall physiological condition of 4912 persons in Hiroshima.[14] This population-based study is characterized as one of the largest cohort studies of middle-aged and elderly persons, with a long follow-up of more than 25 years.

The aforementioned studies of grip strength-mortality association did not clarify whether such association is universal. The present study was conducted using the large cohort to clarify grip strength-mortality association in more detail: first, by investigating association in an age and sex-specific manner, second, by studying cause-specific association, and third, by determining time trends of this association after dividing the follow-up into different time periods.

CLINICAL SIGNIFICANCE

- Grip strength is a strong and consistent predictor of all causes of mortality in middle-aged and elderly persons.
- In accordance with the present findings, regular exercise for improvement of physical and musculoskeletal fitness is eagerly recommended to improve prognosis.

METHODS

Subjects were members of the AHS cohort of RERF. The AHS was begun in 1958 by RERF's predecessor, the Atomic Bomb Casualty Commission (ABCC), as a clinical cohort study to investigate the long-term medical and biological effects of exposure to atomic-bomb radiation among the survivors and unexposed controls in Hiroshima and Nagasaki. Approximately 20,000 persons were invited to participate in biennial health examinations conducted by ABCC (and later, RERF) clinical physicians. A detailed description of the examinations, which included clinical evaluations and routine laboratory determinations, is available elsewhere.[15]

Handgrip Measurement

Current study subjects were derived from 6129 persons in the AHS cohort who underwent a battery of noninvasive age-related physiological tests between July 1970 and June 1972 in Hiroshima.[14] Handgrip strength was measured 2 times for both left and right hands with subjects in a standing position using a dynamometer in units of kilograms. Grip devices were calibrated with known weights. Subjects held the dynamometer at thigh level and were encouraged to exert the strongest possible force. The maximum grip strength among all measurements was used for the present analysis. Analysis was restricted to 4912 subjects (1695 men and 3217 women) in Hiroshima who were 35 to 74 years old at the time of examination and who had completed the grip-strength measurements, as well as provided other clinical information (Table 1).

Other Measurements

Clinical examinations included taking of medical history, general physical examinations, anthropometrical examinations including height and body weight measurements, and laboratory tests. Body mass index (BMI) was calculated as body weight (kg) divided by the square of height (m). Physical examinations included blood pressure measurement taken by sphygmomanometer at the right arm with the subject in a sitting position. General laboratory tests consisted of peripheral blood test and determination of serum cholesterol and other biochemical items. Information about smoking habits and alcohol intake was obtained from self-administrated questionnaires conducted during the period 1965-1968. Categories for smoking habits were "never," "former," and "current." For current smokers, a question was included about quantity of cigarettes smoked. Categories for alcohol intake were "never" and "former/current." Individual radiation dose estimates were based on RERF's 1986 Dosimetry System (DS86).[16]

Mortality Follow-up

Mortality was followed-up for the entire study sample from the time of grip-strength examination in 1970-1972 until the end of 1999. Deaths were routinely identified through Japan's *koseki* (obligatory household registry) system, and ascertainment is essentially complete. Causes of death were obtained from death certificates. Underlying causes of death were classified into the following categories: cancer (140-208 by International Classification of Diseases [ICD] 8th or 9th), heart disease (390-429 by ICD 8th or 9th), coronary heart disease (CHD, 410 by ICD 8th or 9th), stroke (430-438 by ICD 8th or 9th), cerebral infarction (CI, 433 and 434 by

Table 1 Clinical Characteristics of the Study Subjects

	Men	Women
Number of subjects	1689	3209
Age at examination (years)	55.5 ± 11.1	53.9 ± 10.7
Systolic blood pressure (mm Hg)	130.9 ± 23.6	125.5 ± 23.4
Diastolic blood pressure (mm Hg)	81.9 ± 26.1	78.7 ± 26.2
Total cholesterol (mg/dL)	183.7 ± 34.3	200.7 ± 37.6
Body mass index (kg/m^2)	21.7 ± 3.1	22.6 ± 3.6
Mean grip strength (kg)	46.4 ± 9.0	29.2 ± 6.3
Current smoker (%)	68.4	13.9
Cigarettes smoked (per day)	18.6	10.1
Current alcohol drinker (%)	70.0	15.7

Each continuous variable is shown as mean value ± SD.

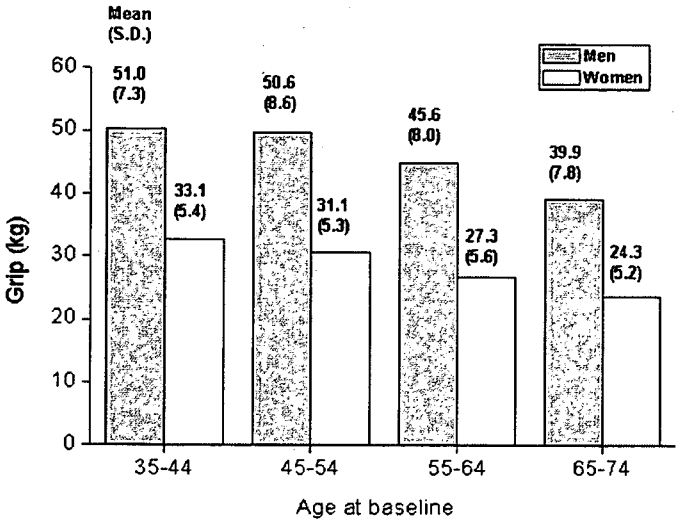

Figure 1 Average grip strength (kg) by age- and sex-specific categories.

ICD 8th or 9th), cerebral hemorrhage (CH, 431 by ICD 8th or 9th), and pneumonia (480-487 by ICD 8th or 9th). Pneumonia was chosen because it is one of the major causes of death among elderly persons in Japan.

Statistical Analysis

Relative risk (RR) of mortality associated with grip strength was adjusted multivariately for potentially confounding factors by Cox proportional hazard models, both in men and women. The factors considered in the models were age at baseline, systolic blood pressure, BMI, smoking and drinking habits, serum cholesterol level, and radiation dose. Allowance for the effect of radiation dose was necessary because the study population included atomic bomb survivors exposed to radiation. When RR of all causes of mortality except external deaths was estimated according to the sex- and age-specific quintile of grip strength, the third quintile was established as a reference. For trend test, the mean value of grip strength in each quintile was assigned to the category. In the case of cause-specific mortalities, RR was calculated for each 5-kg increment of grip strength. Analysis was carried out separately by sex. Deaths within the first 2 years after baseline were excluded from analysis.

Secular trends of multivariate-adjusted RR of all causes of death, except external causes, were calculated by dividing the follow-up period from baseline examination (within 5 years, after 5 years, after 10 years, after 15 years, and after 20 years).

RESULTS

Average age at examination was 55.5 years in men and 53.9 years in women. Average grip strength was 46.4 kg in men and 29.2 kg in women. According to average grip strength by age- and sex-specific categories, a gradual decrease was apparent in both sexes. Decrease of grip strength from 35-44 years to 65-74 years was 11.1 kg in men and 8.8 kg in women (Figure 1). Other clinical characteristics are shown in Table 1. Men tend to have higher systolic and diastolic blood pressure, and are more likely than women to smoke and to drink alcohol.

Over the 27 years of follow-up, 2483 deaths occurred besides those from external causes, which included trauma and suicide. Numbers of deaths from cancer, heart disease, stroke, and pneumonia were 784, 518, 435, and 191, respectively (Table 2).

Multivariate-adjusted RR was compared among different grip-strength categories divided into quintiles for each age and sex group, using the third quintile group as reference. In all age and sex groups, a declining trend of mortality by increment of grip strength was observed. RR of mortality for the highest quintile in men was 0.52 (95% confidence interval [CI], 0.33-0.80) for the age group 35-54 years, 0.72 (95% CI, 0.53-0.98) for ages 55-64 years, and 0.67 (95% CI, 0.49-0.91) for ages 65-74 years, which was significantly lower than that of the reference group. RR of mortality for the lowest quintile in men aged 55-64 years (RR 1.38, 95% CI, 1.01-1.89) and aged 65-74 years (RR 1.38, 95% CI, 1.01-1.88) was significantly higher than that of the reference group (Figure 2).

RR of mortality for the lowest quintile in women aged 35-54 years (RR 1.39, 95% CI, 1.02-1.90) and aged 65-74

Table 2 Number of Deaths by Cause During Follow-up Period of 30 Years

	Men	Women	Total
Number of subjects at baseline	1689	3209	4898
Mean (± SD) age at baseline (years)	55.5 ± 11.1	53.9 ± 10.7	54.4 ± 10.9
All death except external causes	1081	1402	2483
Cancer	391	393	784
Heart	185	333	518
CHD	87	122	209
Stroke	172	263	435
CI	74	105	179
CH	41	55	96
Pneumonia	82	109	191

CHD = coronary heart disease; CI = cerebral infarction; CH = cerebral hemorrhage.

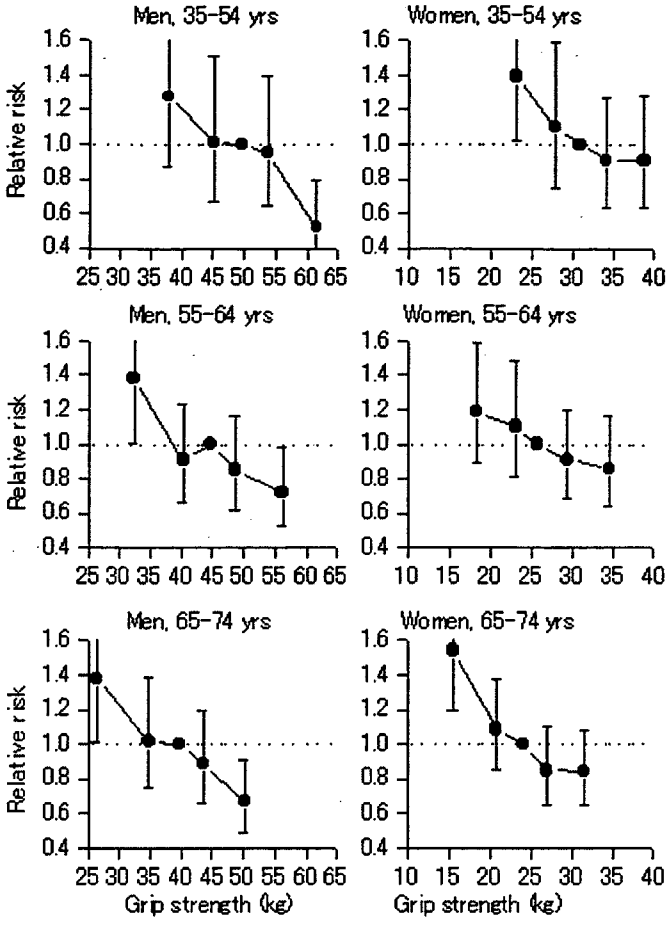

Figure 2 Multivariate-adjusted relative risk (RR) among different grip strength categories divided into quintiles in each age and sex group, using the third quintile group as reference.

years (RR 1.54, 95% CI, 1.20-1.98) was significantly higher than that of the reference group (Figure 2).

Age-adjusted RR of all causes of death, except external causes, for each 5-kg increment of grip strength in men was significantly low (RR 0.89, 95% CI, 0.86-0.92). Age-adjusted RR for heart disease, CHD, and pneumonia was 0.86 (95% CI, 0.79-0.94), 0.85 (95% CI, 0.75-0.96), and 0.83 (95% CI, 0.73-0.94), respectively. Multivariate-adjusted RR of all causes of death, except external causes, was not changed in age-adjusted values, although RR of stroke (RR 0.90, 95% CI, 0.83-0.99) and cerebral infarction (RR 0.90, 95% CI, 0.79-0.96) became statistically significant (Table 3).

Age-adjusted RR of all causes of death, except external causes, for each 5-kg increment of grip strength in women also was significantly low (RR 0.89, 95% CI, 0.84-93). Age-adjusted RR for heart disease, stroke, and cerebral infarction was 0.82 (95% CI, 0.75-0.91), 0.87 (95% CI, 0.78-0.97), and 0.81 (95% CI, 0.68-0.97), respectively. Age-adjusted RR for CHD was not significant (RR 0.90, 95% CI, 0.76-1.06). Multivariate-adjusted RR was not significantly different in age-adjusted values (Table 4). Multivariate-adjusted RR of all causes of death, except external causes, for each 5-kg increment of grip strength in women

Table 3 Relative Risk (RR) of Death for Each 5-kg Increment of Grip in Men

	Age-adjusted RR		Multivariate-adjusted RR	
All death except external causes	0.89	(0.86-0.93)	0.89	(0.86-0.92)
Cancer	0.95	(0.90-1.01)	0.94	(0.88-1.00)
Heart	0.86	(0.79-0.94)	0.85	(0.79-0.93)
CHD	0.85	(0.75-0.96)	0.83	(0.74-0.94)
Stroke	0.92	(0.84-1.00)	0.90	(0.83-0.99)
CI	0.90	(0.79-1.03)	0.90	(0.79-0.96)
CH	0.86	(0.73-1.03)	0.85	(0.72-1.01)
Pneumonia	0.83	(0.73-0.94)	0.85	(0.75-0.98)

RR was adjusted for age, systolic blood pressure, body mass index, total cholesterol, smoking habits, alcohol consumption, and radiation dose. Figures in parentheses are 95% confidence intervals (CI). CHD = coronary heart disease; CI = cerebral infarction; CH = cerebral hemorrhage.

(RR 0.87, 95% CI, 0.83-0.92) was not very different from that observed in men.

Secular trends of multivariate-adjusted RR of all causes of death, except external causes, were analyzed. RR tended to move to unity through the follow-up period, from 0.80 (95% CI, 0.74-0.87), during the initial 5 years after baseline examination, to 0.92 (95% CI, 0.87-0.96), at more than 20 years of follow-up. However, even after 20 years of follow-up, RR was significantly lower for every 5-kg increment of grip strength (Table 5).

DISCUSSION

Grip strength was a strong and consistent predictor of all causes of mortality in middle-aged and elderly persons in

Table 4 Relative Risk (RR) of Death for Each 5-kg Increment of Grip in Women

	Age-adjusted RR		Multivariate-adjusted RR	
All death except external causes	0.89	(0.84-0.93)	0.87	(0.83-0.92)
Cancer	1.00	(0.91-1.09)	0.99	(0.90-1.08)
Heart	0.82	(0.75-0.91)	0.80	(0.72-0.88)
CHD	0.90	(0.76-1.06)	0.88	(0.75-1.04)
Stroke	0.87	(0.78-0.97)	0.85	(0.76-0.95)
CI	0.81	(0.68-0.97)	0.80	(0.68-0.96)
CH	0.83	(0.66-1.05)	0.80	(0.63-1.02)
Pneumonia	0.86	(0.73-1.03)	0.87	(0.73-1.04)

RR was adjusted for age, systolic blood pressure, body mass index, total cholesterol, smoking habits, alcohol consumption, and radiation dose. Figures in parentheses are 95% confidence intervals (CI). CHD = coronary heart disease; CI = cerebral infarction; CH = cerebral hemorrhage.

Table 5 Secular Trends of Multivariate-Adjusted Relative Risk (RR) of all Death Except External Causes

Follow-up Period	RR	95% CI
≤5 years since baseline	0.80	(0.74-0.87)
>5 years	0.90	(0.87-0.93)
>10 years	0.91	(0.88-0.95)
>15 years	0.92	(0.88-0.96)
>20 years	0.92	(0.87-0.96)

RR was estimated for each 5-kg increment of grip strength. CI = confidence interval.

Japan at more than 20 years of follow-up from baseline. This association was observed in all age categories from 35 to 74 years and in both sexes. It predicted not only all causes of mortality, but also heart disease and stroke mortality.

Grip strength may be representative of overall muscular strength because it is highly correlated with other muscular strength measures, including elbow flexion, knee extension, trunk flexion, and trunk extension.[17] Maintenance of muscle strength throughout life reduces the prevalence of functional limitations that might closely relate to early death, especially in the elderly.[18-21]

Muscular strength is related to skeletal muscle mass, which also is a significant site of glucose disposal and insulin action.[22] Elevated insulin levels in persons with lower grip strength are thought to be the central feature of insulin-resistance syndrome.[23] Muscle is also the greatest reserve of protein in the body and plays an important role in immunity and other functions. People with poor muscular strength, therefore, may be more prone to injurious accidents, and their recovery from acute disease or injury may be compromised.[1] Thus, measures of muscular strength can be considered markers of the risk of metabolic disorders, which are ultimately related to risk of premature mortality, especially from cardiovascular diseases. Because muscle strength is closely related to regular physical activity, regular daily exercise to maintain muscle strength is recommended.

Most early studies analyzed data from hospitalized patients or the elderly population.[1,3,5,6,12] The present analysis concludes that the protective effects of higher grip strength were apparent both in men and women, and in a wide-range of age distribution. The results also show that such protective effects were observed even in nonhospitalized and middle-aged individuals, which demonstrates the importance of maintenance of muscle strength in the middle-age period for better health in later life.

Differences in muscle strength and body composition are known to exist between men and women, and from early adulthood on, women have, on average, 30% to 40% less muscle strength than men.[23] Several studies investigated the grip-mortality association in women, 2 of which studied elderly women aged 65 years or older, and found an inverse relationship.[1-3] Katzmarzyk and Craig failed to show that grip strength was predictive of mortality in middle-aged women, although there was a 49% increased risk of death in the lowest quartile of grip strength in men.[2] To the best of our knowledge, our study is the first to show a significant grip-mortality association in middle-aged women. However, it is noteworthy that there was a difference in relationship between grip strength and mortality between the sexes. In men, both ends of grip strength distribution are associated with mortality; in women, however, low grip strength is a risk for premature death and high grip strength is not protective. These differences may be due to the lower and narrower distribution of grip strength in women compared with the distribution in men. Age-adjusted and multivariate-adjusted RR for each 5-kg increment of grip strength for CHD was significantly low in men, but not in women. This may be due to the relatively small number of female CHD cases, because hypertensive heart disease is more prevalent than CHD in Japan, especially in women.

The impact of grip strength on mortality prognosis persisted for more than 20 years. Grip strength is shown to be a tracking phenomenon in which the measure remains consistent even if physical activity varies during the observation period.[24] Therefore, the lower RR of premature death for people with higher grip strength is stable for long observational periods.

The major limitation of the study is that many factors that might affect the observed relationship between grip strength and mortality, such as presence of diabetes, income, education, physical activity, and so on were not included in the analysis. Therefore, the present findings could be subject to residual confounding.

Half of the subjects in this study were exposed to A-bomb radiation. However, average grip strength among radiation-dose groups did not differ (data not shown), and association between grip strength and mortality was independent from radiation dose ($P > .05$). Thus, the grip-mortality association can be generalized to other human populations.

CONCLUSION

Grip strength is a strong and consistent predictor of all causes of mortality in middle-aged and elderly persons, even at more than 20 years of follow-up from baseline. In accordance with the present findings, regular exercise for improvement of physical and musculoskeletal fitness is eagerly recommended to improve prognosis.

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References

1. Rantanen T, Volpato S, Ferrucci L, et al. Handgrip strength and cause-specific and total mortality in older disabled women: exploring the mechanism. *J Am Geriatr Soc.* 2003;51:636-641.
2. Katzmarzyk PT, Craig CL. Musculoskeletal fitness and risk of mortality. *Med Sci Sports Exerc.* 2002;34:740-744.
3. Snib SA, Markides KS, Ray L, et al. Handgrip strength and mortality in older Mexican Americans. *J Am Geriatr Soc.* 2002;50:1250-1256.
4. Rantanen T, Guralnik JM, Foley D, et al. Midlife handgrip strength as a predictor of old age disability. *JAMA.* 1999;281:558-560.
5. Humphreys J, de la Maza P, Hirsch S, et al. Muscle strength as a predictor of loss of functional status in hospitalized patients. *Nutrition.* 2002;18:616-620.
6. Rantanen T, Avlund K, Suominen H, et al. Muscle strength as a predictor of onset of ADL dependence in people aged 75 years. *Aging Clin Exp Res.* 2002;14(3 suppl):10-15.
7. Davis JW, Ross PD, Preston SD, et al. Strength, physical activity, and body mass index: relationship to performance-based measures and activities of daily living among older Japanese women in Hawaii. *J Am Geriatr Soc.* 1998;46:274-279.
8. Rantanen T. Muscle strength, disability and mortality. *Scand J Med Sci Sports.* 2003;13:3-8.
9. Rantanen T, Harris T, Leveille SG, et al. Muscle strength and body mass index as long-term predictors of mortality in initially healthy men. *J Gerontol A Biol Sci Med Sci.* 2000;55:M168-M173.
10. Fujita Y, Nakamura Y, Hiraoka J, et al. Physical-strength tests and mortality among visitors to health promotion centers in Japan. *J Clin Epidemiol.* 1995;48:1349-1359.
11. Phillips P. Grip strength, mental performance and nutritional status as indicators of mortality risk among female geriatric patients. *Age Aging.* 1986;15:53-56.
12. Bohannon RW. Dynamometer measurements of handgrip strength predict multiple outcomes. *Percept Mot Skills.* 2001;93:323-328.
13. Rantanen T, Masaki K, Izmirlian G, et al. Grip strength changes over 27 yr in Japanese-American men. *J Appl Physiol.* 1998;85: 2047-2053.
14. Belsky JL, Moriyama IM, Fujita S, et al. Aging studies in atomic bomb survivors. *RERF Technical Report.* 11-78, 1978.
15. Sawada H, Kodama K, Shimizu Y, Kato H. Adult Health Study Report 6: Results of six examination cycles, 1968-80, Hiroshima and Nagasaki. *RERF Technical Report.* 3-86, 1986.
16. Roesch WC, Ed. *Reassessment of Atomic Bomb Radiation Dosimetry in Hiroshima and Nagasaki. Final Report.* Hiroshima, Japan: Radiation Effects Research Foundation, 1987.
17. Rantanen T, Era P, Kauppinen M, et al. Maximal isometric muscle strength and socio-economic status, health and physical activity in 75-year-old persons. *J Aging Phys Act.* 1994;2:206-220.
18. Metter EJ, Talbot LA, Schrager M, et al. Skeletal muscle strength as a predictor of all-cause mortality in healthy men. *J Gerontol A Biol Sci Med Sci.* 2002;57:B359-B365.
19. Morey MC, Pieper CF, Cornoni-Huntley J. Physical fitness and functional limitations in community-dwelling older adults. *Med Sci Sports Exerc.* 1998;30:715-723.
20. Huang Y, Macera CA, Blair SN, et al. Physical fitness, physical activity, and functional limitation in adults aged 40 and older. *Med Sci Sports Exerc.* 1998;30:1430-1435.
21. Brill PA, Macera CA, Davis DR, et al. Muscular strength and physical function. *Med Sci Sports Exerc.* 2000;32:412-416.
22. Lazarus R, Sparrow D, Weiss ST. Handgrip strength and insulin levels: cross-sectional and prospective associations in the Normative Aging Study. *Metabolism.* 1997;46:1266-1269.
23. Lindle RS, Metter EJ, Lynch NA, et al. Age and gender comparisons of muscle strength in 654 women and men aged 20-93 yr. *J Appl Physiol.* 1997;83:1581-1587.
24. Fortier MD, Katzmarzyk PT, Malina RM, et al. Seven-year stability of physical activity and musculoskeletal fitness in the Canadian population. *Med Sci Sports Exerc.* 2001;33:1905-1911.

7. 端野・壮瞥町研究

分担研究者　斎藤 重幸　札幌医科大学医学部第二内科　講師

A．研究目的

本邦では生活様式とくに食生活の欧米化により肥満の増加、コレステロールレベルの上昇、糖尿病の増加など代謝性の変化が、虚血性心疾患や脳梗塞などの心血管疾患への影響を大きくしていると考えられる。しかし日本人での危険因子としての高血圧の意義はいまだに無視できない。端野・壮瞥町研究は北海道二地域で地域住民検診を受診した集団対象とした疫学研究である。今年度は、①危険因子の関与、特に高血圧の意義を、心血管疾患発症を outcome に捉えた縦断研究の解析結果から示し（Hypertens. Res 2007; 30:677-682)、②腹部超音波法により評価した内臓脂肪蓄積と高血圧の関連を検討した成果から腹部肥満と高血圧の成因を論じた(Hypertens. Res 2007; 30:229-236)。またメタボリックシンドロームにおける高尿酸血症の意義を検討した(医学と薬学 2007; 57:169-171)。

B．研究方法

C．研究結果

D．考察　以上、後述。

E．結論

以上の３編の地域住民疫学研究の結果より、血圧高値は心血管疾患発症の危険因子であり、その発症は血圧レベルに相関して増加することが確認され、腹部肥満は血圧の成因に有意に関与することが解析から示された。地域一般住民の生活習慣から派生する内蔵脂肪蓄積は高血圧、高尿酸血症を含めた危険因子の集積としてメタボリックシンドロームを形成し、心血管疾患発症に関与していることが明らかであり、日本人の心血管疾患の予防のために、これらに対する管理の徹底が必要となる。

F．健康危険情報　なし

G．研究発表

1.　論文発表

1) Nakamura Y, Saitoh S, Takagi S, Ohonishi H, Chiba Y, Kato N, Akasaka H, Miura T, Tsuchihashi K, Shimamoto K. Impact of abnormal glucose tolerance, hypertension and other risk factors on coronary artery disease. Circ J 2007; 71 : 20-25.

2) 東浦勝浩，斎藤重幸，竹内　宏，高木　覚，浦　信行，島本和明．メタボリックシンドロームにおける高尿酸血症の意義．医学と薬学．2007；57：169-171.
3) Chiba Y, Saitoh S, Takagi S, Ohonishi H, Katoh N, Ohohata J, Nakagawa M, Shimamoto K. Relationship between visceral fai and cardiovascular disease risk factors: The Tanno-Sobetsu study. Hypertens. Research. 2007; 30: 229-236.
4) Eguchi M, Tsutihashi K, Saitoh S, Odawara Y, Hirano T, Nakata T, Miura T, Ura N, Kareyama M, Shimamoto K. Visceral obesity in Japanese paitients with metabolic syndrome: Reapprraisal of diagnostic criteria by CT scan. Hypertens. Research. 2007; 30: 315-324.
5) Obara F, Saitoh S, Takagi S, Shimamoto K. Influence of Hypertension on the Incidence of Cardiovascular Disease in Two Rural Communities in Japan: Tanno-Sobetsu Study. Hypertens. Research. 2007; 30: 677-682.

2. 学会発表

タイトル	演者	学会名	都市	年	分類
慢性腎臓病とメタボリックシンドロームの関連の検討：端野・壮瞥町研究	赤坂　憲、浦　信行、斎藤重幸、大西浩文、吉田英昭、三俣兼人、島本和明	第49回日本老年医学会学術集会	札幌	2007	国内学会
地域一般住民におけるメタボリックシンドロームとSF-8による健康関連QOLとの関連-端野・壮瞥町研究より-	大西浩文、斎藤重幸、赤坂　憲、三俣兼人、岡部瑞恵、森　満、島本和明	第49回日本老年医学会学術集会	札幌	2007	国内学会
高齢者での新規高血圧発症とCYP遺伝子多型の関連：端野・壮瞥町研究	赤坂　憲、斎藤重幸、勝谷友宏、杉本　研、大西浩文、浦　信行、桒木宏実、荻原俊男、島本和明	第49回日本老年医学会学術集会	札幌	2007	国内学会
メタボリックシンドロームと8年後の慢性腎臓病の関連の検討：端野・壮瞥町研究	赤坂　憲、浦　信行、斎藤重幸、大西浩文、吉田英昭、三俣兼人、島本和明	第49回日本老年医学会学術集会	札幌	2007	国内学会
地域一般住民高齢者におけるメタボリックシンドロームと尿中微量アルブミンとの関連	大西浩文、斎藤重幸、赤坂　憲、三俣兼人、岡部瑞恵、田邉谷徹也、島本和明	第49回日本老年医学会学術集会	札幌	2007	国内学会
アディポネクチンと動脈硬化の関連-加齢の影響について-	佐藤健司、吉田英昭、谷口晋也、斎藤礼衣、前田卓人、東浦勝浩、斎藤重幸、浦　信行、島本和明	第49回日本老年医学会学術集会	札幌	2007	国内学会
地域一般住民高齢者・非高齢者における腹部肥満からの高血圧発症に関する検討-端野・壮瞥町研究より-	大西浩文、斎藤重幸、赤坂　憲、三俣兼人、岡部瑞恵、島本和明	第49回日本老年医学会学術集会	札幌	2007	国内学会
地域一般住民におけるメタボリックシンドロームと主観的健康感との関連-端野・壮瞥町研究より-	大西浩文、斎藤重幸、赤坂　憲、三俣兼人、岡部瑞恵、森　満、島本和明	第49回日本老年医学会学術集会	札幌	2007	国内学会
糖尿病の動脈硬化症予防における高血圧管理の重み	斎藤重幸、島本和明	第50回日本糖尿病学会	仙台	2007	国内学会
地域一般住民におけるメタボリックシンドロームと尿中微量アルブミンとの関連-端野・壮瞥町研究-	大西浩文、斎藤重幸、加藤伸郎、赤坂　憲、三俣兼人、岡部瑞恵、森　満、島本和明	第50回日本糖尿病学会	仙台	2007	国内学会
IFGまたはIGTを有する一般住民のインスリン作用、インスリン分泌、血圧値、脂質値に関する検討	宮崎義則、斎藤重幸、赤坂　憲、三俣兼人、大西浩文、島本和明	第50回日本糖尿病学会	仙台	2007	国内学会
地域一般住民における慢性腎臓病と高血圧の心血管イベント発生リスクに関する検討-端野・壮瞥町研究より-	大西浩文、斎藤重幸、赤坂　憲、三俣兼人、千葉瑞恵、古堅　真、古川哲章、浦　信行、森　満、島本和明	第30回日本高血圧学会	沖縄	2007	国内学会
地域一般住民における血圧カテゴリと尿中微量アルブミンとの関連-端野・壮瞥町研究より-	斎藤重幸、大西浩文、赤坂　憲、三俣兼人、千葉瑞恵、古堅　真、古川哲章、島本和明	第30回日本高血圧学会	沖縄	2007	国内学会
尿中アルブミンと推定塩分摂取量の関連の検討：端野・壮瞥町研究	赤坂　憲、斎藤重幸、大西浩文、三俣兼人、浦　信行、島本和明	第30回日本高血圧学会	沖縄	2007	国内学会
減塩を実践している者とそうでない者での実際の食塩摂取量の差-INTERMAP研究（日本、中国、英国、米国）の24時間尿中Na排泄量データより-	奥田奈賀子、上島弘嗣、岡山　明、斎藤重幸、中山秀昭、坂田清美	第30回日本高血圧学会	沖縄	2007	国内学会
個人のオメガ3系脂肪酸摂取量（総計、リノレン酸、長鎖脂肪酸）と血圧との関連：INTERMAP	上島弘嗣、斎藤重幸、坂田清美、中山秀昭、奥田奈賀子、岡山　明	第30回日本高血圧学会	沖縄	2007	国内学会
A Polymorphism in Promoter Region of Cytochrome P450 4A11 Gene is Associated with a New Onset of Hypertension: the Tanno and Sobetsu Study.	Hiroshi Akasaka, Tomohiro Katsuya, Shigeyuki Saitoh, Ken Sugimoto, Hirofumi Ohnishi, Hiromi Rakugi, Nobuyuki Ura, Toshio Ogihara, Kazuaki Shimamoto	Amecian College of Cardiology	New Orleans, Louisiana, USA	2007	国際学会
慢性腎疾患とメタボリックシンドロームの関連の検討：端野・壮瞥町研究	赤坂　憲、浦　信行、斎藤重幸、大西浩文、吉田英昭、伊藤洋輔、田中尚、三俣兼人、島本和明	第50回日本腎臓学会	浜松	2007	国内学会
動脈硬化度とラミンA/C遺伝子との関連の検討：端野・壮瞥町研究	赤坂憲、斎藤重幸、大西浩文、勝谷友宏、杉本研、桒木宏実、浦信行、荻原俊男、島本和明	第39回日本動脈硬化学会	大阪	2007	国内学会
メタボリックシンドローム、リスク集積と尿中微量アルブミンとの関連-端野・壮瞥町研究-	大西浩文、斎藤重幸、加藤伸郎、赤坂　憲、三俣兼人、千葉瑞恵、森　満、島本和明	第43回日本循環器病予防学会	大津	2007	国内学会
端野・壮瞥町研究からみたメタボリックシンドロームの予後	斎藤重幸、大西浩文、赤坂　憲、島本和明	第43回日本循環器病予防学会	大津	2007	国内学会
地域一般住民における腹部肥満とメタボリックシンドローム-端野・壮瞥町研究より-	大西浩文、斎藤重幸、森　満、島本和明	第25回生理心理学会大会	札幌	2007	国内学会

H．知的財産権の出願・登録状況 なし

共同研究者：斎藤重幸、大西浩文、赤坂　憲、島本和明

Relationship between Visceral Fat and Cardiovascular Disease Risk Factors: The Tanno and Sobetsu Study

内臓脂肪測定と心血管疾患危険因子の関連

【目的】

過去に腹部CTやWCにより評価された内臓脂肪と高血圧の関連を示した報告はあるが腹部超音波法（US法）を用いた検討はない。そこで日本人一般集団でのUS法による内臓脂肪評価の有用性を評価し腹部肥満と心血管疾患危険因子、特に血圧値との関連について検討した。

【方法・結果】

研究1：　外来患者、男性45名、女性64名（平均年齢：男性55.4±19.4歳、女性67.8±10.7歳）を解析対象とし身長、体重、WC、腹部CT法によるvisceral fat area(VFA)，total fat area(TFA)、US法によるvisceral fat distance(VFD)を計測した。subcutaneous fat area(SFA)はTFAからVFAを引いて算出しVFA、SFA、VFD、BMI、WCの互いの相関を検討した。その結果、VFAとVFDの相関係数は男性r=0.660(P<0.001)、女性r=0.643(P<0.001)であった。また、VFAはBMI，WCよりもVFDとより相関が強かった。更にBMIとWCはVFAよりSFAとの相関が強い事が示された。

研究2：　地域住民検診を受診した、男性353名、女性457名（平均年齢：男性62.8±12.2歳、女性57.8±12.6歳）のVSDと血圧値の関連を検討した。その結果、BMIを補正に加えると、男性の高VFD群は低VFD群よりHBP(OR: 2.75, P<0.05)、HTG(OR: 3.35, P<0.05)で有意にオッズ比は増加した。しかしWCはHT、TGで有意な関係は得られなかった。また、女性の高VFD群は低VFD群よりHTG (OR: 6.36, P<0.05)、LHDL (OR: 2.94, P<0.05)で有意にオッズ比は増加した。しかしWCは全ての因子で有意な関連は得られなかった。

【考察ならびに結語】

重回帰分析の結果、男性ではVFDは血圧値の独立した説明変数であった。WCは男女共に血圧値と有意な関連が認めなかった。男性では、VFDは血圧値との関連を示す良い指標と考えられる。更にVFDはMSを伴う男性で血圧との関連を評価する有用な指標と考えられた。

腹囲基準を満たさなくても危険因子の蓄積するハイリスク者を見つける時にWC以外の方法で確認することが重要である。その場合にUS法は内臓脂肪の蓄積を評価する簡便で有用な方法と思われる。

Original Article

Relationship between Visceral Fat and Cardiovascular Disease Risk Factors: The Tanno and Sobetsu Study

Yu CHIBA[1], Shigeyuki SAITOH[1], Satoru TAKAGI[1], Hirofumi OHNISHI[1], Nobuo KATOH[1], Junichi OHATA[1], Motoya NAKAGAWA[1], and Kazuaki SHIMAMOTO[1]

We assessed the amount of visceral fat using ultrasonography (US) and studied its relationship to cardiovascular disease risk factors, particularly blood pressure. The subjects in the first study were 45 male and 61 female outpatients. We measured the visceral fat area (VFA) of each subject using abdominal CT and waist circumference (WC), and visceral fat distance (VFD) using US. The subjects in the second study were 353 male and 457 female inhabitants of a rural community, for whom VFD and WC were measured. We divided subjects into tertiles based on VFD and WC, and studied the relationship between each group and individual risk factors. In an analysis of outpatient subjects, the correlation coefficient between VFA and VFD was satisfactory: r=0.660 for men and r=0.643 for women. In the analysis of the rural subjects, the high VFD group had a significantly higher odds ratio than the low VFD group in high blood pressure (HBP) and hypertriglyceridemia (HTG) for men and in HBP, HTG and low high-density lipoprotein cholesterolemia (LHDL) for women. Moreover, adjusting VFD for body mass index revealed that, in comparison to WC, VFD was significantly related to risk factors. VFD was used as an independent variable in multiple regression analysis with blood pressure level as a dependent variable; no significant association between WC and blood pressure was obtained. Visceral fat assessment by US may be useful for epidemiological study and for clinics with no abdominal CT equipment for identifying high-risk individuals, such as those with metabolic syndrome. (*Hypertens Res* 2007; 30: 229–236)

***Key Words*: ultrasonography, visceral obesity, cardiovascular disease risk factors, waist circumference, hypertension**

Introduction

Obesity is often complicated by arteriosclerotic diseases such as hypertension, ischemic heart disease and cerebrovascular disease as well as by their risk factors (*1*, *2*). Since the late 1980s, these complications have been explained by the concept of a multiple risk factor syndrome such as syndrome X (*3*), the deadly quartet (*4*), and visceral fat syndrome (*5*). More recently, the term metabolic syndrome (MS) has been adopted by the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATPIII) (*6*). Visceral obesity, in which fat markedly accumulates in the peritoneal mesentery and around the greater omentum, is thought to be a fundamental pathology for MS in particular. The incidence of cardiovascular disease is high even in non-obese individuals with a body mass index (BMI) within the normal range who have an accumulation of visceral fat (*7*), and accurate assessment of both body fat distribution and visceral fat accumulation is critical for assessing the risk of arteriosclerotic disease.

Previous studies have shown that waist-to-hip ratio, waist-to-height ratio, waist circumference (WC), and visceral fat

From the [1]Second Department of Internal Medicine, Sapporo Medical University School of Medicine, Sapporo, Japan.
Address for Reprints: Hirofumi Ohnishi, M.D., Ph.D., Second Department of Internal Medicine, Sapporo Medical University School of Medicine, S-1, W-16, Chuo-ku, Sapporo 060–8543, Japan. E-mail: hohnishi@sapmed.ac.jp
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