Table 2
Incidence rate (IR) of stroke for each psychosocial job characteristic and adjusted hazard ratios (AHR; and 95% confidence intervals) for the association between psychosocial job characteristics and incident stroke according to occupational class.

	All				Occupation								Position							
					White-collar				Blue-collar				Manager				Non-manager			
	n Person-year	Case	IR	AHR	*n* Person-year	Case	IR	AHR	*n* Person-year	Case	IR	AHR	*n* Person-year	Case	IR	AHR	*n* Person-year	Case	IR	AHR
Men																				
Job characteristics																				
Low strain	499	7	132	1	223	3	128	1	276	4	135	1	282	6	203	1	217	1	42	1
	5311				2348				2963				2952				2359			
Active	955	23	220	2.1 (0.9–5.0)	480	14	271	2.1 (0.6–7.6)	475	9	170	1.5 (0.5–5.0)	583	16	249	1.4 (0.5–3.7)	372	7	174	5.4 (0.7–44.4)
	10446				5167				5279				6430				4015			
Passive	923	33	337	2.3 (1.0–5.4)	279	9	300	2.1 (0.5–8.0)	644	24	354	2.0 (0.7–6.0)	352	11	290	1.4 (0.5–4.1)	571	22	367	6.7 (0.9–50.7)
	9788				3001				6787				3789				5999			
High strain	813	28	318	2.8 (1.2–6.4)	308	6	177	1.4 (0.3–5.6)	505	22	406	3.1 (1.0–9.3)	384	13	310	2.0 (0.7–5.3)	429	15	325	8.9 (1.1–69.1)
	8808				3386				5422				4194				4614			
P value for trend				0.022				0.996				0.016				0.202				0.019
Women																				
Job characteristics																				
Low strain	676	11	148	1	318	2	57	1	358	9	228	1	193	2	97	1	483	9	167	1
	7440				3485				3955				2056				5384			
Active	947	15	143	1.2 (0.6–2.7)	488	7	132	4.2 (0.8–21.6)	459	8	154	0.9 (0.3–24)	330	5	138	2.3 (0.4–12.8)	617	10	145	0.9 (0.4–2.3)
	10498				5316				5182				3621				6877			
Passive	915	15	149	1.1 (0.5–2.5)	423	5	111	3.2 (0.6–18.7)	492	10	179	1.0 (0.4–2.4)	224	5	207	2.6 (0.5–14.2)	691	10	131	0.8 (0.3–2.0)
	10069				4496				5573				2411				7657			
High strain	825	15	166	1.3 (0.6–3.0)	267	5	176	5.6 (1.0–32.1)	558	10	162	1.0 (0.4–2.5)	202	7	322	5.3 (1.0–28.6)	623	8	117	0.7 (0.3–1.9)
	9026				2847				6179				2174				6852			
P value for trend				0.557				0.093				0.984				0.046				0.504

The hazard ratios were estimated after adjusting for age, educational attainment, smoking status, alcohol consumption, physical activity index, and study area (community).

association was found among women. There are several possible explanations for the unexpected findings among women. White-collar occupations may not necessarily represent higher socioeconomic status in Japanese women, as most white-collar women are engaged in supportive roles (Kawakami & Haratani, 1999). Service/sales occupations are typical examples, as they resemble low occupational class with instability, low pay and high job demand in many contexts (Fukuda et al., 2005; Kawakami et al., 2004). We conducted an explanatory analysis in an alternative occupational category in which service/sales workers were classed as blue-collar occupations (low occupational class). The initially observed risk of job strain among female white-collar workers was reduced and became insignificant in the explanatory analysis (hazard ratio 3.9, *P* for trend 0.331).

Second, attitudes toward work and/or perception/expression of job characteristics may also differ between genders (Virtanen et al., 2008). Evidence shows that the principal sources of stress and worry differ between Japanese men and women. For men, they are financial security and employment, whereas for women they are future care-giving and human relations (Takeda et al., 2006). In such a situation, however, women who sought to develop a career in their occupation might represent a select population of women who have climbed the ladder of success despite occupational challenges. As Japanese society has been undergoing a transition from its traditional gender roles to a more westernized pattern of active female participation in the labor force (Takeda et al., 2006), the elucidation of gender-related susceptibility to stroke following exposure to occupational stress warrants further investigation. Finally, it is possible that more women than men in our cohort were in part-time employment. This uneven distribution could account, at least in part, for the observed findings in women (Theorell, 2002). Other psychosocial factors such as social support and social roles outside work may also interact differently with occupational stress in men and women (Hall, 1992).

Study strengths and limitations

This study was based on the largest available Japanese cohort of its kind, which included both men and women. Data were obtained in a standardized fashion. Information about exposure to occupational stress was obtained from self-reports using a validated instrument rather than by assigning scores based on job description. Hence, each score more accurately represented the individual work environment (Belkić et al., 2004). We only included validated cases of incident stroke among workers who had no history of cardiovascular disease at baseline. The diagnosis of stroke was ascertained by an independent committee using accepted diagnostic criteria, thus minimizing the potential for information bias. Bias attributable to sample attrition was unlikely because the follow-up rate was high, and the relevant potential confounders were adjusted for the analyses.

In this study, occupation (white-collar and blue-collar) and position (manager and non-manager) were considered relevant indices of socioeconomic status. However, large-scale epidemiological studies often fail to account for fine occupational classifications, and our study may therefore have some measurement errors. In the explanatory analysis, the alternative classification (service/sales occupations were classed as blue-collar occupations) strengthened the risk of high strain among male blue-collar workers (hazard ratio 3.6, 95% confidence interval 1.2–10.5, *P* for trend 0.005). Furthermore, we examined the association between occupational stress and incident stroke using the combined classification based on cross-classification of both occupation and position: "white-collar + manager", "white-collar + non-manager", "blue-collar + manager", and "blue-collar + non-manager." Reflecting the main analyses, a significant association between high strain and incident stroke was found only in the combined group of blue-collar and non-manager (hazard ratio 8.9, 95% confidence interval 1.1–70.5, *P* for trend 0.014), but there was no significant association in other groups among men. In women, due to limited statistical power, the following groups were created: "either white-collar or managerial workers" and "blue-collar + non-manager". There was a significant association in the group of either white-collar or managerial workers (hazard ratio 3.9, 95% confidence interval 1.2–13.2, *P* for trend 0.028) but not in the other group of blue-collar and non-manager among women. These findings do not necessarily contradict our hypothesis that workers in less privileged occupations are more vulnerable to occupational stress, but obviously, there is room for refining the occupational classification, and if most deleterious groups are identified, preventive measures for stress reduction could be developed for the right target population.

Although our observations appear to reflect a profile of stroke incidence among community-dwelling Japanese workers (Tsutsumi et al., 2009), the shortage of statistical power is a limitation of the present study, especially in stratified analyses by gender and by occupational class. The mass screening examination program is not mandatory, and the relatively low response rate may imply that those with the worst work conditions chose to opt out of the study. Although the hazard ratios were notable, under representation of individuals with access to occupational health checks limits the ability to generalize from the findings. Further studies in more representative samples of employees are needed. Occupational classes and psychosocial job characteristics were also determined by current status. Although changes in occupation or job position are not frequent in the settings included in the study (Kayaba et al., 2005), quitting of jobs and reemployment were not analyzed. The Cronbach's alpha coefficient for job control was somewhat low, and our exposure assessment was limited to one point in time. Both of these aspects probably caused associations toward the null. Finally, there are specific limitations of the job demand-control model. High demands and low control are only two aspects of hazardous work conditions. Other potential sources of stress, such as low reward, job insecurity, or injustice, were not measured. As these different toxic components may be more sensitive in investigating class differences (i.e., job control (decision authority) that could have a ceiling effect in higher class occupations such as the self-employed), further studies are needed using other relevant occupational stress models such as effort-reward imbalance (Wege et al., 2008) and organizational justice (Elovainio et al., 2005).

Conclusion

The findings of this study suggest that the health impact of occupational stress characterized by high job demands and low control is greater among male workers in lower occupational classes. Amid significant changes in the working environment, it is imperative to accumulate observational data over a period of time to confirm the relationships between occupational class, occupational stress and stroke in Japanese women.

Conflict of interest

None.

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References

Belkić, K., Landsbergis, P. A., Schnall, P. L., & Baker, D. (2004). Is job strain a major source of cardiovascular disease risk? *Scandinavian Journal of Work & Environmental Health, 30*(4), 85–128.

Bosma, H. (2006). Socio-economic differences in health. Are control beliefs fundamental mediators? In J. Siegrist, & M. Marmot (Eds.), *Social inequalities in health. new evidence and policy implications* Oxford: Oxford University Press.

Elovainio, M., Bos, K. V. D., Linna, A., Kivimäki, M., Ala-Mursula, L., Pentti, J., et al. (2005). Combined effects of uncertainty and organizational justice on employee health: testing the uncertainty management model of fairness judgments among Finnish public sector employees. *Social Science & Medicine, 61*(12), 2501–2512.

Fukuda, Y., Nakamura, K., & Takano, T. (2005). Accumulation of health risk behaviours is associated with lower socioeconomic status and women's urban residence: a multilevel analysis in Japan. *BMC Public Health, 5*(53), 53.

Hall, E. M. (1992). Double exposure: the combined impact of the home and work environments on psychosomatic strain in Swedish women and men. *International Journal of Health Services, 22*(2), 239–260.

Hallqvist, J., Diderichsen, E., Theorell, T., Reuterwall, C., & Ahlbom, A. (1998). Is the effect of job strain on myocardial infarction risk due to interaction between high psychological demands and low decision latitude? Results from Stockholm heart epidemiology program (SHEEP). *Social Science & Medicine, 46*(11), 1405–1415.

Hemingway, H., Shipley, M., Brunner, E., Britton, A., Malik, M., & Marmot, M. (2005). Does autonomic function limk social position to coronary risk? The Whitehall II study. *Circulation, 111*(23), 3071–3077.

Hirokawa, K., Tsutsumi, A., & Kayaba, K. (2006). Impacts of educational level and employment status on mortality for Japanese women and men: the Jichi Medical School Cohort study. *European Journal of Epidemiology, 21*(9), 641–651.

Ishikawa, S., Gotoh, T., Nago, N., Kayaba, K., & , Jichi Medical School (JMS) Cohort Study Group. (2002). The Jichi Medical School (JMS) cohort study: design, baseline data and standardized mortality ratios. *Journal of Epidemiology, 12*(6), 408–417.

Kannel, W. B., & Sorlie, P. (1979). Some health benefits of physical activity: the Framingham study. *Archives of Internal Medicine, 139*(2), 857–861.

Karasek, R., & Theorell, T. (1990). *Healthy work: Stress, productivity, and the reconstruction of working life.* New York: Basic Books.

Kawakami, N., & Haratani, T. (1999). Epidemiology of job stress and health in Japan: review of current evidence and future direction. *Industrial Health, 37*, 174–186.

Kawakami, N., Haratani, T., Kobayashi, F., Ishizaki, M., Hayashi, T., Fujita, O., et al. (2004). Occupational class and exposure to job stressors among employed men and women in Japan. *Journal of Epidemiology, 14*(6), 204–211.

Kayaba, K., Tsutsumi, A., Gotoh, T., Ishikawa, S., & Miura, Y. (2005). Five-year stability of job characteristics scale scores among a Japanese working population. *Journal of Epidemiology, 15*(6), 228–234.

Kayaba, K., Yazawa, Y., Natsume, T., Yaginuma, T., Hosaka, T., Hosoda, S., et al. (1990). The relevance of psychosocial factors in acute ischemic heart disease: a case-control study of a Japanese population. *Japanese Circulation Journal, 54*, 464–471.

Kivimäki, M., Leino-Arjas, P., Luukkonen, R., Riihimäki, H., Vahtera, J., & Kirjonen, J. (2002). Work stress and risk of cardiovascular mortality: prospective cohort study of industrial employees. *British Medical Journal, 325*(7369), 857–860.

Kivimäki, M., Gimeno, D., Ferrie, J. E., Batty, G. D., Oksanen, T., Jokela, M., et al. (2009). Socioeconomic position, psychosocial work environment and cerebrovascular disease among women: the Finnish public sector study. *International Journal of Epidemiology, 38*(5), 1265–1271.

Kopp, M. S., Skrabski, A., Szekely, A., Stauder, A., & Williams, R. (2007). Chronic stress and social changes: socioeconomic determination of chronic stress. *Annals of the New York Academy of Sciences, 1113*(3), 325–338.

Kuper, H., Adami, H. O., Theorell, T., & Weiderpass, E. (2007). The socioeconomic gradient in the incidence of stroke: a prospective study in middle-aged women in Sweden. *Stroke, 38*(1), 27–33.

Lachman, M. E., & Weaver, S. L. (1998). The sense of control as a moderator of social class differences in health and well-being. *Journal of Personality and Social Psychology, 3*, 763–773.

Lester, D., Motohashi, Y., & Yang, B. (1992). The impact of the economy on suicide and homicide rates in Japan and the United States. *International Journal of Social Psychiatry, 38*(4), 314–317.

Lynch, J., Krause, N., Kaplan, G. A., Tuomilehto, J., & Salonen, J. T. (1997). Workplace conditions, socioeconomic status, and the risk of mortality and acute myocardial infarction: the Kuopio ischemic heart disease risk factor study. *American Journal of Public Health, 87*(4), 617–622.

Ministry of Internal Affairs and Communications, Statistics Bureau, Statistical Standards Department. (1998). *Standard occupational classification for Japan.* National Federation of Statistical Organizations.

Rosengren, A., Wilhelmsen, L., Welin, L., Tsipogianni, A., Teger-Nilsson, A.-C., & Wedel, H. (1990). Social influences and cardiovascular risk factors as determinants of plasma fibrinogen concentration in a general population sample of middle aged men. *British Medical Journal, 300*, 634–638.

Shishehbor, M. H., Litaker, D., Pothier, C. E., & Lauer, M. S. (2006). Association of socio-economic status with functional capacity, heart rate recovery, and all-cause mortality. *Journal of American Medical Association, 295*(7), 784–792.

Steptoe, A. (2006). Psycobiological processes linking socio-economic position with health. In J. Siegrist, & M. Marmot (Eds.), *Social inequalities in health: New evidence and policy implications.* Oxford: Oxford University Press.

Takeda, Y., Kawachi, I., Yamagata, Z., Hashimoto, S., Matsumura, Y., Oguri, S., et al. (2006). The impact of multiple role occupancy on health-related behaviours in Japan: differences by gender and age. *Public Health, 120*(10), 966–975.

Theorell, T. (2002). Job stress and fibrinogen. *European Heart Journal, 23*, 1799–1801.

Theorell, T., Tsutsumi, A., Hallqvist, J., Reuterwall, C., Hogstedt, C., Fredlund, P., et al. (1998). Decision latitude, job strain and myocardial infarction: a study of working men in Stockholm. *American Journal of Public Health, 88*(3), 382–388.

Toivanen, S. (2008). Job control and the risk of incident stroke in the working population in Sweden. *Scandinavian Journal of Work & Environmental Health, 34*(1), 40–47.

Toivanen, S., & Hemström, Ö (2008). Is the impact of job control on stroke independent of socioeconomic status? A large-scale study of the Swedish working population. *Stroke, 39*(4), 1321–1323.

Tsutsumi, A., Kayaba, K., Kario, K., & Ishikawa, S. (2009). Prospective study on occupational stress and risk of stroke. *Archives of Internal Medicine, 169*(1), 56–61.

Tsutsumi, A., Kayaba, K., Tsutsumi, K., & Igarashi, M. (2001). Association between job strain and prevalence of hypertension: a cross sectional analysis in a Japanese working population with a wide range of occupations: the Jichi Medical School cohort study. *Occupational and Environmental Medicine, 58*(6), 367–373.

Uchiyama, S., Kurasawa, T., Sekizawa, T., & Nakatsuka, H. (2005). Job strain and risk of cardiovascular events in treated hypertensive Japanese workers: hypertension Follow-Up Group Study. *Journal of Occupational Health, 47*(2), 102–111.

Ueda, K., & Matsumoto, Y. (2003). National strategy for suicide prevention in Japan. *Lancet, 361*(9360), 882.

Virtanen, M., Koskinen, S., Kivimäki, M., Honkonen, T., Vahtera, J., Ahola, K., et al. (2008). Contribution of non-work and work-related risk factors to the association between income and mental disorders in a working population: the health 2000 study. *Occupational and Environmental Medicine, 65*(3), 171–178.

Virtanen, S. V., & Notkola, V. (2002). Socioeconomic inequalities in cardiovascular mortality and the role of work: a register study of Finnish men. *International Journal of Epidemiology, 31*(3), 614–621.

Wege, N., Dragano, N., Erbel, R., Jockel, K. H., Moebus, S., Stang, A., et al. (2008). When does work stress hurt? Testing the interaction with socioeconomic position in the Heinz Nixdorf Recall Study. *Journal of Epidemiology and Community Health, 62*(4), 338–341.

Wheaton, B. (1980). The sociogenesis of psychological disorder: an attributional theory. *Journal of Health and Social Behavior, 21*, 100–124.

Yoshimasu, K., & , The Fukuoka Heart Study Group. (2001). Relation of type A behavior pattern and job-related psychosocial factors to nonfatal myocardial infarction: a case-control study of Japanese male workers and women. *Psychosomatic Medicine, 63*(5), 797–804.

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ORIGINAL ARTICLE
Cardiac Rehabilitation

Physical Activity and Risk of Fatal or Non-Fatal Cardiovascular Disease Among CVD Survivors

– The JMS Cohort Study –

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Background: Although many population-based studies have reported an association between physical activity and cardiovascular disease (CVD) among healthy populations, the association among CVD survivors has been less reported. We examined the relationship between physical activity and CVD risk among survivors.

Methods and Results: This was a prospective cohort study of 12,490 Japanese participants, including 754 individual CVD survivors. Between April 1992 and July 1995, a baseline survey was conducted in 12 communities in Japan. The mean follow-up period was 11.9 years, during which time 74 individuals had non-fatal CVD and 51 cases were fatal CVD. Among CVD survivors, analysis was performed after exclusion of participants with a history of cancer and those who died within the first 2 years of follow-up. Physical activity was analyzed in tertiles (low, moderate and heavy), and the hazard ratios (HRs) were calculated for non-fatal or fatal CVD among CVD survivors. After setting the low group as the reference, the HRs for non-fatal CVD in the moderate and heavy groups were 0.61 (95% confidence interval: 0.30–1.24) and 0.50 (0.20–1.25) (P for trend=0.059), respectively, and the HRs for fatal CVD were 0.75 (0.33–1.69) and 0.18 (0.04–0.83) (P for trend=0.026), respectively.

Conclusions: Physical activity reduced the risk of CVD, both fatal and non-fatal events, among CVD survivors. (*Circ J* 2011; **75**: 1368–1372)

Key Words: Cardiovascular diseases; Cohort studies; Motor activity; Secondary prevention; Survivors

Many population-based studies have reported that increasing physical activity reduces the risk of cardiovascular disease (CVD) in healthy populations.[1–4] Physical activity is also an important component of cardiac rehabilitation after CVD events.[5–8] Many clinical trials have been conducted to determine the effects of cardiac rehabilitation, including the physical activity components.[9–12] However, only a few population-based studies have examined the association between physical activity and CVD risk among CVD survivors. Some of these studies involved only men[13] or women,[14] small sample sizes,[15] or were inconsistent with dose–response relationships.[16,17] Determining the relationship between physical activity and CVD risk among CVD survivors in a population-based study is important evidence that will contribute to the prescribing of suitable physical activity among CVD survivors.

Additionally, most population-based studies have examined the risk of fatal CVD,[1,16,18] whereas the risk of non-fatal CVD has been rarely reported. Consideration of the detailed relationship between physical activity and CVD risk is important for understanding the effects of physical activity on CVD risk.

Therefore, the aim of the present population-based study was to determine the physical activity and CVD risk among CVD survivors in terms of fatal and non-fatal events.

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Table 1. Baseline Characteristics of the CVD Survivors

	Physical activity level			P value
	Low (n=327)	Moderate (n=251)	Heavy (n=176)	
Sex, male	48.6	43.0	38.6	0.085
Age, years	63.4 (9.4)	61.5 (9.1)	61.7 (8.0)	0.021
BMI, kg/m^2	23.7 (3.6)	23.4 (3.0)	23.0 (3.0)	0.073
SBP, mmHg	134.0 (20.8)	132.8 (20.8)	132.0 (19.8)	0.551
HDL-C, mg/dl	48.6 (13.0)	51.3 (12.6)	52.8 (12.4)	0.001
Physical activity index, –	27.1 (1.7)	31.9 (2.3)	40.3 (7.7)	<0.001
Education >15 years	69.0	75.5	67.8	0.123
Current smoking	44.3	40.2	34.7	0.115
Alcohol consumption	51.0	49.6	41.7	0.135
Current employment	42.9	56.9	72.7	<0.001
History of hypertension	40.8	30.2	29.7	0.009
History of hyperlipidemia	11.3	11.8	8.6	0.549
History of diabetes mellitus	8.7	5.0	6.3	0.237
Non-fatal CVD during follow-up	13.1	8.4	5.7	0.005
Fatal CVD during follow-up	9.2	6.8	2.3	0.013

% or mean (SD).
CVD, cardiovascular disease; BMI, body mass index; SBP, systolic blood pressure; HDL-C, high-density lipoprotein cholesterol.

Methods

Study Population

The Jichi Medical School (JMS) cohort study was instituted to clarify the factors responsible for atherosclerosis in Japan. The design and methods have been reported previously.[18–20] Baseline data were obtained during mass screening examinations between April 1992 and July 1995, and were followed up until the end of 2005. A total of 12,490 individuals, including 754 individual CVD survivors, from 12 areas participated. The overall response rate among 12 areas was 63%. Participants gave written informed consent and responded to a questionnaire at the time of enrollment. The people who moved out of their community during the observation period were followed until their date of emigration. Data on emigration of study subjects were obtained every year from their municipal governments. The mass screening examination covered height, weight, blood pressure, smoking habit, alcohol consumption and serum total cholesterol, and the questionnaire covered physical activity, medical history, employment and education. This study was approved by the Institutional Review Board of Jichi Medical School for Ethical Issues.

Baseline Measurements

Baseline measurements consisted of the mass screening examination and questionnaire.[20] At the mass screening examination, trained nurses measured height, weight and blood pressure, and collected venous blood samples. High-density lipoprotein cholesterol (HDL-C) was measured by the phosphor-tungstate precipitation method (Wako, Osaka, Japan). The questionnaire was self-administered, and only physical activity was examined by interview. Items covered in the questionnaire included smoking habit, alcohol consumption, education, employment and medical history. The medical history of CVD, which is stroke, angina, myocardial infarction (MI) and other heart disease, consisted of "never" or "ever" responses by the participants. We defined CVD survivors as those who chose "ever" and CVD non-survivors as those who chose "never." Physical activity was assessed using the Framingham Study Questionnaire as described previously,[21,22] which was administered in an interview conducted by a trained reviewer. Each subject was asked to provide the number of hours per day spent on 5 levels of physical activity (sleep, sedentary, slight, moderate, and heavy activity). Time spent in each activity was multiplied by its metabolic cost based on the oxygen consumption (1.0 for sleep, 1.1 for sedentary. 1.5 for slight, 2.5 for moderate, and 5.0 for heavy activity). These weighted hours were added up to obtain a physical activity index (PAI) score. The minimum PAI score is 24, which is equivalent to 24 h of sleep, and the maximum PAI score is 120, which is equivalent to 24 h of heavy physical activity.

CVD Diagnosis

We diagnosed both CVD incidence and death. The diagnoses of CVD incidence were carried out independently by a Diagnosis Committee. The criterion for stroke was sudden onset of a focal and nonconvulsive neurologic deficit that lasted for more than 24 h. Stroke subtypes (ie, cerebral infarction, cerebral hemorrhage and subarachnoid hemorrhage) were determined according to the criteria of the National Institute of Neurological Disorders and Stroke.[23] If an incident was suspected, forms were filled out, and duplicates of the CT and/or MRI films of the patient were obtained to confirm a diagnosis of stroke. MI was diagnosed based on the criteria of the World Health Organization Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) project a multinational collaborative project that was conducted from the mid-1980s through the mid-1990s for the monitoring of coronary events.[24]

The diagnosis of CVD death was obtained from death certificates, which were collected from the respective local public health centers with permission from the Ministry of General Affairs and the Ministry of Health, Labour and Welfare in Japan. We used the International Classification of Diseases, 10th Revision (ICD-10) for diagnostic criteria: CVD included stroke (I60–I69), MI (I01–I09, I21–I22, I27, I30–I49, I50, I51–I52), and others (within I00–I99). We did not

Table 2. Risk Between Physical Activity and Non-Fatal CVD

	Case no.	Model 1		Model 2		Model 3	
		HR (95%CI)	P for trend	HR (95%CI)	P for trend	HR (95%CI)	P for trend
Male							
Low (–29.9)	26	1.00 (Reference)	0.002	1.00 (Reference)	0.028	1.00 (Reference)	0.012
Moderate (30.0–36.8)	10	0.50 (0.22–1.16)		0.53 (0.20–1.43)		0.18 (0.05–0.66)	
Heavy (36.9–)	2	0.07 (0.01–0.53)		0.08 (0.01–0.70)		0.10 (0.01–0.94)	
Female							
Low (–28.8)	17	1.00 (Reference)	0.704	1.00 (Reference)	0.601	1.00 (Reference)	0.933
Moderate (28.9–32.2)	11	1.21 (0.55–2.68)		2.14 (0.83–5.47)		1.47 (0.52–4.16)	
Heavy (32.3–)	8	0.84 (0.34–2.07)		1.34 (0.48–3.80)		0.98 (0.32–2.96)	
Combined*							
Low (–29.9)	43	1.00 (Reference)	0.007	1.00 (Reference)	0.11	1.00 (Reference)	0.059
Moderate (28.9–36.8)	21	0.72 (0.41–1.26)		0.98 (0.54–1.78)		0.61 (0.30–1.24)	
Heavy (32.3–)	10	0.39 (0.19–0.83)		0.49 (0.21–1.14)		0.50 (0.20–1.25)	

Model 1: Adjusted for area and age.
Model 2: Adjusted for area, age, BMI, SBP, HDL-C, smoking, drinking, employment, education and history of hypertension, hyperlipidemia and diabetes.
Model 3: Excluded those who died within a 2-year follow-up.
*Additionally adjusted for sex.
CI, confidence interval; HR, hazard ratio. Other abbreviations see in Table 1.

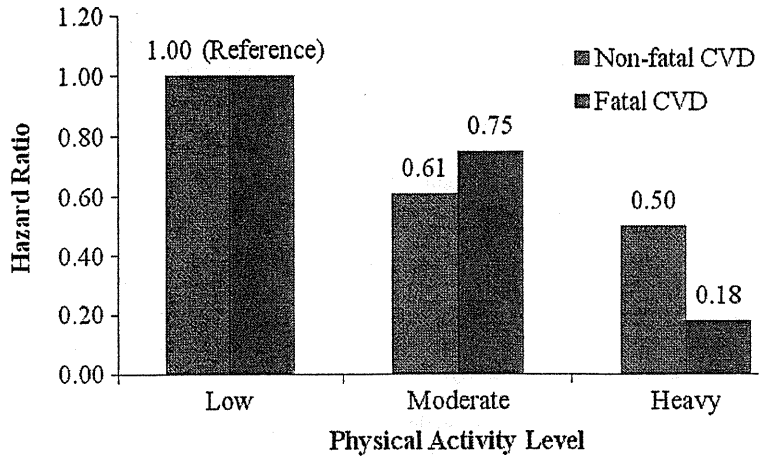

Figure. Hazard ratios for fatal and non-fatal CVD risk, using Cox's proportional hazard model adjusted for sex, area, age, body mass index, systolic blood pressure, high-density lipoprotein cholesterol, smoking, drinking, employment, education and history of hypertension, hyperlipidemia and diabetes. Excluded are those who died within a 2-year follow-up. CVD, cardiovascular disease.

include 1 case of sudden death from an unidentified cause in the category of CVD. We classified non-fatal CVD as CVD incidence and not dead from CVD within 28 days. Fatal CVD was from the ICD-10 diagnostic criteria.

Statistical Analyses

Statistical analyses were performed with SPSS version 15.0 (SPSS Japan, Inc). Subjects who had CVD history (n=754) were categorized by PAI into tertiles (low, moderate and heavy). For the comparison of baseline characteristics, we used t tests for continuous variables and the χ^2 test for categorical variables. Cox's proportional hazards model was used to calculate the hazard ratios (HRs) and 95% confidence interval (95%CI) for non-fatal or fatal CVD according to these tertiles.

The analyses were carried out after adjustment for area and age (model 1). Next, we analyzed the HRs adjusted for area, age, body mass index, systolic blood pressure, HDL-C, employment, education, smoking, drinking, and medical history of hypertension, hyperlipidemia and diabetes mellitus (model 2). Additionally, we analyzed the HRs of excluded subjects who died during the first 2 years of follow-up (model 3). Tests for linear trends were calculated by treating category scales as continuous values. To avoid reverse causality between physical activity and some diseases at baseline, we excluded subjects who were diagnosed with cancer at baseline.

Results

The follow-up rate was 99.9% and emigration was 23. Deaths totaled 143 during follow-up. During a mean follow-up of 11.9 years, non-fatal CVD events totaled 74 (9.8%): 43 (13.1%) in the low category, 21 (8.4%) in the moderate category and 10 (5.7%) in the heavy category, respectively. Fatal CVD events totaled 51 (6.8%): 30 (9.2%) in the low category, 17 (6.8%) in the moderate category and 4 (2.3%) in the heavy category, respectively. **Table 1** shows the baseline characteristics of the participants. Among tertiles, there were significant differences in age, HDL-C, current employ-

Table 3. Risk Between Physical Activity and Fatal CVD

	Case no.	Model 1		Model 2		Model 3	
		HR (95%CI)	P for trend	HR (95%CI)	P for trend	HR (95%CI)	P for trend
Male							
Low (–29.9)	17	1.00 (Reference)	0.038	1.00 (Reference)	0.070	1.00 (Reference)	0.069
Moderate (30.0–36.8)	10	0.67 (0.26–1.72)		0.73 (0.25–2.15)		0.50 (0.14–1.86)	
Heavy (36.9–)	1	0.15 (0.02–1.20)		0.16 (0.02–1.39)		0.15 (0.02–1.34)	
Female							
Low (–28.8)	13	1.00 (Reference)	0.704	1.00 (Reference)	0.139	1.00 (Reference)	0.139
Moderate (28.9–32.2)	7	0.91 (0.33–2.49)		0.79 (0.23–2.65)		0.79 (0.23–2.65)	
Heavy (32.3–)	3	0.44 (0.12–1.59)		0.19 (0.02–1.67)		0.19 (0.02–1.67)	
Combined*							
Low (–29.9)	30	1.00 (Reference)	0.012	1.00 (Reference)	0.027	1.00 (Reference)	0.026
Moderate (28.9–36.8)	17	0.77 (0.40–1.51)		0.89 (0.43–1.85)		0.75 (0.33–1.69)	
Heavy (32.3–)	4	0.28 (0.10–0.83)		0.18 (0.04–0.80)		0.18 (0.04–0.83)	

Model 1: Adjusted for area and age.
Model 2: Adjusted for area, age, BMI, SBP, HDL-C, smoking, drinking, employment, education and history of hypertension, hyperlipidemia and diabetes.
Model 3: Excluded those who died within a 2-year follow-up.
*Additionally adjusted for sex.
Abbreviations see in Tables 1,2.

ment, and history of hypertension. The mean PAI of CVD survivors was 31.8 and that of others was 33.3.

Regarding non-fatal CVD events, the HRs associated with physical activity of the low, moderate, and heavy categories were 1.00 (reference), 0.61 (0.30–1.24), and 0.50 (0.20–1.25), P=0.059 for trend, respectively. When analyzed by gender, only males among CVD survivors evidenced a significant decrease in non-fatal CVD risk (P=0.012), whereas the decrease was not significant in females (P=0.933) (**Table 2, Figure**).

As for fatal CVD events, the HRs associated with physical activity of the low, moderate, and heavy categories were 1.00 (reference), 0.75 (0.33–1.69), and 0.18 (0.04–0.83), P=0.026 for trend, respectively. Analysis by gender did not reveal a significant association (**Table 3, Figure**). We confirmed an assumption of proportionality was valid and no gender interactions were found. For the sensitivity analyses, we conducted 2 scenarios. For non-fatal CVD, all subjects who moved out were assumed to have non-fatal CVD. Next, all subjects who moved out were assumed to have survived until the end of the overall follow-up. Similar results were found. Regarding fatal CVD, all subjects who died of non-CVD or who moved out were assumed to have fatal CVD. Next, all subjects who died of non-CVD who moved out were assumed to have survived until the end of the overall follow-up. Although the association of heavy categories only became slightly weaker, similar results were found.

Discussion

This is, to our knowledge, the first population-based study in which a relationship was reported between physical activity and CVD risk, classified into non-fatal and fatal, among CVD survivors. Our results showed that physical activity was associated with a lower risk of both CVD recurrence and mortality among survivors. These inverse associations remained after being adjusted for potential confounders.

Only 4 cohort studies have reported relationships between physical activity and fatal CVD among CVD survivors.[13–16] In a small Japanese study of 80 men, higher physical activity was associated with a lower risk of cardiac death among MI survivors.[15] This study used a small sample size to determine the effects of physical activity on CVD survivors. In the Stockholm Female Coronary Risk Study with 230 participants, sedentary lifestyle increased the CVD mortality (vs. non-sedentary lifestyle was 3.15, 95%CI 1.13–8.74) among patients hospitalized for acute coronary syndrome.[14] However, this study did not determine the dose–response relationship between physical activity and CVD among survivors. Both of the above studies did not examine the dose–response relationships. In the British Regional Heart Study of 772 men, light or moderate activity was associated with a significantly lower risk of fatal CVD.[13] Vigorous activity increased the risk of fatal CVD compared with light or moderate activity. On the other hand, the HUNT Study of 2,137 men and 1,367 women with established coronary heart disease reported that the frequency, duration and intensity of physical activity significantly reduced the risk of CVD mortality.[16] Thus, the dose–response relationships were inconsistent. These 2 studies were not adjusted for physiological parameters such as cholesterol and blood pressure. The present study was adjusted for physiological indicators, and physical activity reduced the risk of CVD mortality among survivors.

Only one population-based study analyzed physical activity and risk of non-fatal CVD events among CVD survivors.[17] It focused on the change in the level of physical activity, and did not examine the dose–response relationship between physical activity and non-fatal CVD events among the survivors. Therefore, ours is the first population-based study to report a dose–response relationship between physical activity and non-fatal CVD risk among CVD survivors. Our study showed that physical activity significantly reduced the risk of non-fatal CVD, similar to the fatal CVD risk.

In our study, the mean PAI among CVD survivors was slightly less than for the others because CVD survivors were older (CVD survivors averaged 62.4 years and non-CVD survivors averaged 54.7 years). Previous studies have reported the benefits of physical activity in some aspects, for example physical activity amount, type, intensity, duration and resting period.[26–28] More study is needed to conclude the benefits of physical activity on CVD risk among CVD survivors.

The strengths of the present study were its long period of follow-up and broad coverage of patients. We precisely diag-

nosed CVD incidence using CT/MRI data, and death was established via death certificate. We also estimated the risk of non-fatal CVD, which is less reported.

However, some limitations exist. We estimated physical activity from a self-administered questionnaire. Even though this was validated in the Framingham Study, some misclassification is inevitable. Although the questionnaire is popular in Japan and worldwide, it has not been validated in a Japanese population. Also, we conducted the questionnaire with interviewers trained to obtain accurate information from all individuals. Recall bias, in which CVD survivors report less physical activity, might exist. In addition, our results for females seemed to be unclear. Previous studies reported the estimation of physical activity in females is difficult because domestic activity tends to be misclassified.[27] This may have occurred in our study for females. We may not have completely eliminated CVD survivors with severe after-effects, which could lead to a reverse causal relationship in our analysis. Although we did not obtain information on the severity of the after-effects of CVD among survivors, the one that mostly limits physical activity is stroke. We checked and found the number of stroke survivors to be 112, among the total 754 CVD survivors. Since only a portion seemed to be CVD survivors with severe after-effects, the number of our study subjects who had such complications would be small. Additionally, we made an effort to eliminate CVD survivors with severe after-effects from our analysis by excluding individuals who died within 2 years. To begin with, we considered CVD survivors who participated in the mass screening examination as having a minimal level of activities of daily living. Therefore, we think that the effect of the reverse causal relationship was small.

In conclusion, our results suggest that physical activity reduces the risk of CVD, both fatal and non-fatal events, among CVD survivors. More epidemiologic studies are needed, because there are few studies reporting the relationship between physical activity and CVD risk among survivors.

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Disclosures

None.

References

1. Kannel WB. Habitual level of physical activity and risk of coronary heart disease: The Framingham study. *Can Med Assoc J* 1967; **96:** 811–812.
2. Gillum RF, Mussolino ME, Ingram DD. Physical activity and stroke incidence in women and men: The NHANES I Epidemiologic Follow-up Study. *Am J Epidemiol* 1996; **143:** 860–869.
3. Paffenbarger RS Jr, Wing AL, Hyde RT. Physical activity as an index of heart attack risk in college alumni. *Am J Epidemiol* 1978; **108:** 161–175.
4. Sesso HD, Paffenbarger RS Jr, Lee IM. Physical activity and coronary heart disease in men: The Harvard Alumni Health Study. *Circulation* 2000; **102:** 975–980.
5. Budnick K, Campbell J, Esau L, Lyons J, Rogers N, Haennel RG. Cardiac rehabilitation for women: A systematic review. *Can J Cardiovasc Nurs* 2009; **19:** 13–25.
6. Audelin MC, Savage PD, Ades PA. Exercise-based cardiac rehabilitation for very old patients (> or =75 years): Focus on physical function. *J Cardiopulm Rehabil Prev* 2008; **28:** 163–173.
7. Tani S, Nagao K, Anazawa T, Kawamata H, Furuya S, Takahashi H. Coronary plaque regression and lifestyle modification in patients treated with pravastatin: Assessment mainly by daily aerobic exercise and an increase in the serum level of high-density lipoprotein cholesterol. *Circ J* 2010; **74:** 954–961.
8. Matsuo H, Shigematsu H. Patient-based outcomes using the Walking Impairment Questionnaire for patients with peripheral arterial occlusive disease treated with Lipo-PGE1. *Circ J* 2010; **74:** 365–370.
9. O'Connor GT, Buring JE, Yusuf S, Goldhaber SZ, Olmstead EM, Paffenbarger RS Jr, et al. An overview of randomized trials of rehabilitation with exercise after myocardial infarction. *Circulation* 1989; **80:** 234–244.
10. Piepoli MF, Corra U, Benzer W, Bjarnason-Wehrens B, Dendale P, Gaita D, et al. Secondary prevention through cardiac rehabilitation: From knowledge to implementation: A position paper from the Cardiac Rehabilitation Section of the European Association of Cardiovascular Prevention and Rehabilitation. *Eur J Cardiovasc Prev Rehabil* 2010; **17:** 1–17.
11. Hawkes AL, Atherton J, Taylor CB, Scuffham P, Eadie K, Miller NH, et al. Randomised controlled trial of a secondary prevention program for myocardial infarction patients ('ProActive Heart'): Study protocol: Secondary prevention program for myocardial infarction patients. *BMC Cardiovasc Disord* 2009; **9:** 16.
12. Tanasescu M, Leitzmann MF, Rimm EB, Willett WC, Stampfer MJ, Hu FB. Exercise type and intensity in relation to coronary heart disease in men. *JAMA* 2002; **288:** 1994–2000.
13. Wannamethee SG, Shaper AG, Walker M. Changes in physical activity, mortality, and incidence of coronary heart disease in older men. *Lancet* 1998; **351:** 1603–1608.
14. Al-Khalili F, Janszky I, Andersson A, Svane B, Schenck-Gustafsson K. Physical activity and exercise performance predict long-term prognosis in middle-aged women surviving acute coronary syndrome. *J Intern Med* 2007; **261:** 178–187.
15. Kitajima K, Sasaki J, Kono S, Arakawa K. Prognostic significance of daily physical activity after first acute myocardial infarction. *Am Heart J* 1990; **119:** 1193–1194.
16. Moholdt T, Wisløff U, Nilsen T, Slørdahl SA. Physical activity and mortality in men and women with coronary heart disease: A prospective population-based cohort study in Norway (the HUNT study). *Eur J Cardiovasc Prev Rehabil* 2008; **15:** 639–645.
17. Steffen-Batey L, Nichaman MZ, Goff DC Jr, Frankowski RF, Hanis CL, Ramsey DJ, et al. Change in level of physical activity and risk of all-cause mortality or reinfarction: The Corpus Christi Heart Project. *Circulation* 2000; **102:** 2204–2209.
18. Shibata Y, Hayasaka S, Yamada T, Goto Y, Ojima T, Ishikawa S, et al. Physical activity and cardiovascular disease in Japan: The Jichi Medical School Cohort Study. *J Epidemiol* 2010; **20:** 225–230.
19. Hayasaka S, Shibata Y, Ishikawa S, Kayaba K, Gotoh T, Noda T, et al. Physical activity and all-cause mortality in Japan: The Jichi Medical School (JMS) Cohort Study. *J Epidemiol* 2009; **19:** 24–27.
20. Ishikawa S, Gotoh T, Nago N, Kayaba K. The Jichi Medical School (JMS) Cohort Study: Design, baseline data and standardized mortality ratios. *J Epidemiol* 2002; **12:** 408–417.
21. Garcia-Palmieri MR, Costas R Jr, Cruz-Vidal M, Sorlie PD, Havlik RJ. Increased physical activity: A protective factor against heart attacks in Puerto Rico. *Am J Cardiol* 1982; **50:** 749–755.
22. Kannel WB, Sorlie P. Some health benefits of physical activity: The Framingham Study. *Arch Intern Med* 1979; **139:** 857–861.
23. Adams HP Jr, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke: Definitions for use in a multicenter clinical trial: TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke* 1993; **24:** 35–41.
24. WHO MONICA Project Principal Investigators. The World Health Organization MONICA Project 8monitoring ternds and determinats in cardiovascular disease): A major international collaboration. *J Clin Epidemiol* 1988; **41:** 105–114.
25. Tanasescu M, Leitzmann MF, Rimm EB, Willett WC, Stampfer MJ, Hu FB. Exercise type and intensity in relation to coronary heart disease in men. *JAMA* 2002; **288:** 1994–2000.
26. Murtagh EM, Boreham CA, Nevill A, Hare LG, Murphy MH. The effects of 60 minutes of brisk walking per week, accumulated in two different patterns, on cardiovascular risk. *Prev Med* 2005; **41:** 92–97.
27. Warren TY, Barry V, Hooker SP, Sui X, Church TS, Blair SN. Sedentary behaviors increase risk of cardiovascular disease mortality in men. *Med Sci Sports Exerc* 2010; **42:** 879–885.
28. Kiely DK, Wolf PA, Cupples LA, Beiser AS, Kannel WB. Physical activity and stroke risk: The Framingham Study. *Am J Epidemiol* 1994; **140:** 608–620.

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Original Article

Low Cholesterol is Associated With Mortality From Stroke, Heart Disease, and Cancer: The Jichi Medical School Cohort Study

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ABSTRACT

Background: We investigated the relationship between low cholesterol and mortality and examined whether that relationship differs with respect to cause of death.

Methods: A community-based prospective cohort study was conducted in 12 rural areas in Japan. The study subjects were 12 334 healthy adults aged 40 to 69 years who underwent a mass screening examination. Serum total cholesterol was measured by an enzymatic method. The outcome was total mortality, by sex and cause of death. Information regarding cause of death was obtained from death certificates, and the average follow-up period was 11.9 years.

Results: As compared with a moderate cholesterol level (4.14–5.17 mmol/L), the age-adjusted hazard ratio (HR) of low cholesterol (<4.14 mmol/L) for mortality was 1.49 (95% confidence interval [CI]: 1.23–1.79) in men and 1.50 (1.10–2.04) in women. High cholesterol (≥6.21 mmol/L) was not a risk factor. This association was unchanged in analyses that excluded deaths due to liver disease, which yielded age-adjusted HRs of 1.38 (95% CI, 1.13–1.67) in men and 1.49 (1.09–2.04) in women. The multivariate-adjusted HRs and 95% CIs of the lowest cholesterol group for hemorrhagic stroke, heart failure (excluding myocardial infarction), and cancer mortality significantly higher than those of the moderate cholesterol group, for each cause of death.

Conclusions: Low cholesterol was related to high mortality even after excluding deaths due to liver disease from the analysis. High cholesterol was not a risk factor for mortality.

Key words: low cholesterol; mortality; liver disease; stroke; heart disease; cohort study

INTRODUCTION

Both medical professionals and patients are well aware of the dangers of high cholesterol, but most know little about the risks of low cholesterol, despite the many studies that have examined the issue.[1–3] The first report to show a relationship between low cholesterol and cerebral hemorrhage was a Japanese cohort study,[4] and many subsequent observational studies have shown that low cholesterol is associated with cerebral hemorrhage,[5] cancer, suicide, injury, and non-coronary mortality.[6–8] However, there is no explicit evidence that these relationships are causal.

A meta-analysis of interventional trials showed that cholesterol-lowering therapy was associated with high mortality in a population with low cardiovascular risk.[9] Although this meta-analysis focused on interventions other than statins, studies of statins have also shown that statin administration is associated with increases in cancer incidence among elderly adults,[10] breast cancer incidence during the secondary prevention phase,[11] and total cancer incidence.[12]

Japanese researchers reported that the relationship between low cholesterol and mortality disappeared when deaths due to liver disease were excluded.[13]

To clarify this issue, we investigated the relationship between cholesterol and mortality with respect to cause of death (deaths due to stroke, heart disease, and cancer). In addition, the relationship between cholesterol and mortality was examined after excluding deaths due to liver disease.

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METHODS

Participants

This study was conducted as part of the Jichi Medical School (JMS) Cohort Study[13]; 12 490 men and women aged 40 to 69 years participated. The JMS Cohort Study is a prospective cohort study that began in 1992 with the aim of investigating risk factors for stroke and cardiovascular diseases. We collected baseline data from April 1992 through July 1995 in 12 rural areas of Japan and completed a follow-up in December 2005, in which 65% of the subjects from mass screening examinations participated. Of these, 96% of participants completed follow-up; incomplete data were obtained for 409 participants who were not followed until the last day of our study because they had left the study area. There were no follow-up data for 97 participants. However, data from the abovementioned 409 subjects were included in the analyses, and the day they left the area was defined as the endpoint. Informed consent for follow-up was not obtained from 95 participants and from 2 additional participants who had already left the area at the beginning of follow-up. These 97 individuals were excluded from the analyses. Furthermore, we were unable to obtain total cholesterol data for 156 participants, including 4 who did not provide informed consent. In total, we analyzed data from 12 241 participants, ie, 98% of the total number of participants. The average follow-up period was 11.9 years. We observed participants for a total of 145 312 person-years. Details regarding the JMS Cohort Study are available elsewhere.[14]

Exposure

Total cholesterol was measured by an enzymatic method (Wako, Osaka, Japan; interassay coefficient of variation: 1.5%). All samples were measured at the same laboratory (SRL, Tokyo, Japan).

Confounding factors

We obtained information on confounding factors (smoking and drinking habits, blood pressure, height, weight, and high-density lipoprotein [HDL] cholesterol) from the baseline data of the JMS Cohort Study.

Outcome

Information regarding cause of death was collected using data from death certificates and national vital statistics with the permission of the Agency of General Affairs.

We classified cause of death according to the International Classification of Diseases, 10th Revision (hemorrhagic stroke: I60, I61, I69.0, I69.1; ischemic stroke: I63, I69.3; myocardial infarction: I21, I22; heart failure: I50).

Written informed consent was obtained from all participants. The Institutional Review Board of JMS was responsible for ethical review of this research and approved the study.

Statistical analysis

Because the relationship between cholesterol and mortality is not linear, subjects were divided into 4 groups according to total cholesterol level (<4.14 mmol/L, 4.14 mmol/L to <5.17 mmol/L, 5.17 mmol/L to <6.21 mmol/L, and ≥6.21 mmol/L). The second lowest group (4.14 mmol/L to <5.17 mmol/L) was used as the reference group. However, in the analyses of ischemic stroke in men and myocardial infarction in women, the highest group was defined as ≥5.70 mmol/L because there was no ischemic stroke or myocardial infarction in subjects with a total cholesterol level ≥6.21 mmol/L. The cutoff value used for the lowest group was selected on the basis of past research,[1] and the cutoff value for the highest group was based on criteria from the mass screening examination.

A Cox proportional hazards model was used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for mortality. Both age-adjusted HRs and multivariate-adjusted HRs were calculated. The multivariate-adjusted model adjusted for age, smoking status (current/former/never), drinking status (current/former/never), systolic blood pressure, HDL cholesterol, and body mass index (BMI: <18, 18 to <22, 22 to <26, ≥26). Age, blood pressure, and HDL cholesterol were analyzed as continuous variables. All analyses were performed separately for each sex using STATA/SE for Windows (STATACORP, release 10, TX, USA). A P value of less than 0.05 was considered to indicate statistical significance.

Table 1. Baseline characteristics of participants

Variable	Men			Women		
	n	Mean	SD	*n*	Mean	SD
Age	4839	55.2	12	7495	55.3	11.3
Height (cm)	4649	162.5	6.9	7250	150.3	6.2
Body weight (kg)	4651	60.9	9.4	7252	52.4	8.0
Systolic BP (mm Hg)	4664	131.5	20.5	7297	128.3	21.0
Diastolic BP (mm Hg)	4664	79.2	12.3	7297	76.3	12.1
Total cholesterol (mmol/L)	4839	4.8	0.9	7495	5.1	0.9
HDL cholesterol (mmol/L)	4839	1.3	0.4	7495	1.4	0.3
Body mass index (kg/m^2)	4649	23.0	2.9	7250	23.2	3.2
Smoking	*n*	%		*n*	%	
Current	2280	50.5		384	5.5	
Former	1274	28.2		195	2.8	
Never	957	21.2		6362	91.7	
Drinking						
Current	3293	75.0		1692	25.0	
Former	161	3.7		103	1.5	
Never	935	21.3		4983	73.5	

Abbreviations: BP, blood pressure; HDL, high-density lipoprotein.

Table 2. Baseline characteristics of participants by cholesterol level

Men

Variable		Total cholesterol level (mmol/L) <4.14		4.14–5.16		5.17–6.20		≥6.21		P^a
		n	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)	
Age		1136	55.3 (13.2)	2142	55.6 (11.8)	1274	54.9 (11.5)	287	53.0 (10.7)	0.038
Height (cm)		1079	162.4 (7.2)	2068	162.3 (6.8)	1225	162.8 (6.9)	277	163.4 (6.4)	<.0001
Body weight (kg)		1081	58.6 (9.0)	2068	60.5 (9.1)	1225	62.8 (9.6)	277	64.3 (9.8)	<.0001
Systolic BP (mm Hg)		1095	129.0 (20.9)	2069	131.3 (20.2)	1224	133.4 (20.5)	276	134.5 (20.4)	<.0001
Diastolic BP (mm Hg)		1095	77.2 (12.1)	2069	79.1 (12.1)	1224	80.8 (12.4)	276	81.3 (12.0)	<.0001
HDL cholesterol (mmol/L)		1136	1.2 (0.3)	2142	1.3 (0.3)	1274	1.3 (0.4)	287	1.3 (0.4)	<.0001
Body mass index (kg/m^2)		1079	22.2 (2.7)	2068	22.9 (2.8)	1225	23.6 (3.0)	277	24 (2.9)	<.0001
		n	%	*n*	%	*n*	%	*n*	%	P^b
Smoking	Current	627	59.1	986	49.3	532	45.2	135	49.5	<.0001
	Former	227	21.4	579	29.0	389	33.1	79	28.9	
	Never	207	19.5	435	21.8	256	21.8	59	21.6	
Drinking	Current	760	74.4	1461	75.1	871	75.6	201	74.4	0.628
	Former	47	4.6	66	3.4	41	3.6	7	2.6	
	Never	215	21.0	418	21.5	240	20.8	62	23.0	

Women

Variable		Total cholesterol level (mmol/L) <4.14		4.14–5.16		5.17–6.20		≥6.21		P^a
		n	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)	
Age		1077	48.2 (12.7)	3050	54.4 (11.7)	2522	58.3 (9.4)	846	59.1 (7.9)	<.0001
Height (cm)		1012	152.0 (6.7)	2944	150.7 (6.2)	2463	149.4 (5.9)	831	149.3 (5.5)	<.0001
Body weight (kg)		1012	51.4 (7.7)	2944	52.2 (8.0)	2463	52.7 (8.1)	831	53.2 (7.9)	<.0001
Systolic BP[a] (mm Hg)		1030	118.8 (18.8)	2961	126.6 (20.7)	2471	131.8 (20.9)	835	135.6 (20.4)	<.0001
Diastolic BP[a] (mm Hg)		1030	71.2 (11.5)	2961	75.4 (11.8)	2471	78.2 (11.9)	835	80.4 (11.9)	<.0001
HDL cholesterol (mmol/L)		1077	1.2 (0.3)	3050	1.4 (0.3)	2522	1.4 (0.3)	846	1.4 (0.4)	<.0001
Body mass index (kg/m^2)		1012	22.3 (3.1)	2944	23 (3.1)	2463	23.6 (3.2)	831	23.8 (3.1)	<.0001
		n	%	*n*	%	*n*	%	*n*	%	P^b
Smoking	Current	79	8.1	171	6.0	100	4.3	39	4.3	<.0001
	Former	48	4.9	76	2.7	53	2.3	19	2.3	
	Never	853	87.0	2591	91.3	2184	93.5	790	93.5	
Drinking	Current	289	30.5	730	26.5	516	22.5	177	21.1	<.0001
	Former	14	1.5	34	1.2	45	2.0	10	1.2	
	Never	644	68.0	1992	72.3	1735	75.6	652	77.7	

Abbreviations: BP, blood pressure; HDL, high-density lipoprotein.
[a]One-way analysis of variance.
[b]Chi-square test.

RESULTS

All subjects were included in the age-adjusted analysis. Because of missing values, multivariate-adjusted analyses included data from only 11 869 subjects. Tables 1 and 2 show the baseline characteristics of subjects grouped by sex and cholesterol category. The background characteristics of subjects included and excluded from the multivariate-adjusted analysis did not differ.

In total, 635 men and 423 women died during the study period; 34 male deaths and 15 female deaths were due to liver diseases. Table 3a shows the number of deaths according to cause of death, including deaths due to liver disease, and incidence in each cholesterol group by sex. Liver cancer and hepatic failure were the main causes of death due to liver disease.

Table 4a shows HRs and 95% CIs for mortality by cholesterol category. Crude, age-adjusted, and multivariate-adjusted HRs are grouped by sex. Smoking status, drinking status, and BMI were entered into the models as categorical dummy variables. The multivariate-adjusted HR of the lowest cholesterol group (<4.14 mmol/L) was 1.38 (95% CI, 1.13–1.66) for men and 1.42 (1.02–2.00) for women. The HRs of men and women in the

Table 3a. Causes of death

Cause of death	Men		Women	
	n	%	*n*	%
Stroke	67	10.6	60	14.4
SAH	7	1.1	17	4.0
infarction	36	5.7	28	6.6
hemorrhage	20	3.1	13	3.0
other	4	0.6	2	0.5
Heart disease	73	11.5	60	14.2
infarction	31	4.9	27	6.0
heart failure	20	3.1	13	3.0
other	22	3.5	20	4.7
Cancer[a]	240	37.9	154	36.0
lung	69	10.9	21	5.0
stomach	26	4.1	22	5.0
colon	17	2.7	18	4.2
other	128	20.1	93	22.0
Other	255	40.1	149	34.7
pneumonia	67	10.6	25	5.9
suicide	24	3.8	17	4.0
accident	30	4.7	7	1.7
other	133	20.9	100	23.6
Total	635	100	423	100
Liver disease				
cancer	16	47.1	3	20.0
liver failure	14	41.2	11	73.3
other	4	11.7	1	6.7
Total	34	100	15	100

Abbreviation: SAH, subarachnoid hemorrhage.
[a]Including liver cancer.

Table 4a. Total cholesterol level and mortality

	Total cholesterol level (mmol/L)			
	<4.14	4.14–5.16	5.17–6.20	≥6.21
	Hazard ratio (95% CI)			
Men				
Total mortality				
Crude	1.48 (1.23–1.78)	1	0.98 (0.80–1.20)	0.85 (0.58–1.23)
Age-adjusted	1.49 (1.23–1.79)	1	1.04 (0.85–1.27)	1.12 (0.77–1.64)
Multivariate-adjusted[a]	1.38 (1.13–1.66)	1	1.09 (0.88–1.34)	1.21 (0.82–1.78)
Excluding deaths due to liver disease				
Crude	1.37 (1.13–1.66)	1	0.99 (0.81–1.22)	0.87 (0.60–1.28)
Age-adjusted	1.38 (1.13–1.67)	1	1.06 (0.86–1.29)	1.16 (0.80–1.71)
Multivariate-adjusted[a]	1.27 (1.03–1.56)	1	1.10 (0.89–1.36)	1.25 (0.85–1.85)
Women				
Total mortality				
Crude	0.92 (0.67–1.25)	1	1.07 (0.86–1.33)	1.06 (0.77–1.45)
Age-adjusted	1.50 (1.10–2.04)	1	0.92 (0.74–1.14)	0.97 (0.67–1.26)
Multivariate-adjusted[a]	1.42 (1.02–2.00)	1	0.93 (0.73–1.17)	0.93 (0.67–1.30)
Excluding deaths due to liver disease				
Crude	0.91 (0.66–1.24)	1	1.06 (0.85–1.32)	1.04 (0.76–1.44)
Age-adjusted	1.49 (1.09–2.04)	1	0.91 (0.72–1.14)	0.91 (0.66–1.26)
Multivariate-adjusted[a]	1.40 (0.99–1.98)	1	0.92 (0.72–1.17)	0.93 (0.66–1.31)

[a]Cox proportional hazards model adjusted for age, systolic blood pressure, high-density lipoprotein cholesterol, smoking, drinking, and body mass index.

Table 3b. Mortality by total cholesterol level

	Total cholesterol level (mmol/L)							
	<4.14		4.14–5.16		5.17–6.20		≥6.21	
	n	incidence[a]	*n*	incidence	*n*	incidence	*n*	incidence
Men								
Total mortality	195	15.08	258	10.27	152	10.10	30	8.77
Stroke mortality	19	1.47	29	1.15	16	1.06	3	0.88
Hemorrhagic stroke	10	0.77	10	0.40	4	0.27	2	0.58
Ischemic stroke	7	0.54	17	0.68	12	0.80	0	0.00
Heart disease mortality	21	1.62	22	0.88	15	1.00	4	1.17
Myocardial infarction	9	0.70	13	0.52	6	0.40	2	0.58
Heart failure[b]	5	0.39	6	0.24	6	0.40	2	0.58
Cancer mortality	80	6.19	91	3.62	59	3.92	10	2.92
Women								
Total mortality	53	4.25	169	4.68	151	5.01	50	4.95
Stroke mortality	6	0.48	21	0.58	24	0.80	9	0.89
Hemorrhagic stroke	5	0.40	6	0.17	13	0.43	5	0.50
Ischemic stroke	1	0.08	12	0.33	11	0.37	4	0.40
Heart disease mortality	7	0.56	26	0.72	17	0.56	5	0.50
Myocardial infarction	3	0.24	15	0.42	9	0.30	0	0.00
Heart failure[b]	4	0.32	3	0.08	2	0.07	3	0.30
Cancer mortality	19	1.52	53	1.47	56	1.86	26	2.58

[a]per 1000 person-years.
[b]excluding myocardial infarction.

Table 4b. Total cholesterol and mortality (excluding deaths within the first 5 years of follow-up)

	Total cholesterol level (mmol/L)			
	<4.14	4.14–5.16	5.17–6.20	≥6.21
	Hazard ratio (95% CI)			
Men				
Total mortality				
Crude	1.43 (1.16–1.79)	1	1.01 (0.80–1.27)	0.91 (0.60–1.40)
Age-adjusted	1.47 (1.18–1.83)	1	1.07 (0.85–1.35)	1.24 (0.81–1.89)
Multivariate-adjusted[a]	1.39 (1.10–1.74)	1	1.07 (0.84–1.37)	1.33 (0.87–2.05)
Excluding deaths due to liver disease				
Crude	1.33 (1.06–1.68)	1	1.03 (0.82–1.30)	0.94 (0.62–1.44)
Age-adjusted	1.36 (1.08–1.71)	1	1.09 (0.87–1.38)	1.28 (0.84–1.97)
Multivariate-adjusted[a]	1.27 (1.00–1.62)	1	1.11 (0.87–1.41)	1.39 (0.90–2.14)
Women				
Total mortality				
Crude	0.82 (0.57–1.20)	1	0.99 (0.77–1.29)	1.14 (0.80–1.63)
Age-adjusted	1.37 (0.94–2.00)	1	0.86 (0.66–1.11)	0.99 (0.70–1.43)
Multivariate-adjusted[a]	1.24 (0.82–1.88)	1	0.92 (0.70–1.22)	1.11 (0.76–1.61)
Excluding deaths due to liver disease				
Crude	0.80 (0.55–1.18)	1	0.99 (0.76–1.30)	1.15 (0.80–1.65)
Age-adjusted	1.34 (0.91–1.98)	1	0.86 (0.66–1.12)	0.91 (0.66–1.26)
Multivariate-adjusted[a]	1.20 (0.79–1.84)	1	0.92 (0.70–1.23)	0.93 (0.66–1.31)

[a]Cox proportional hazards model adjusted for age, systolic blood pressure, high-density lipoprotein cholesterol, smoking, drinking, and body mass index.

Table 4c. Total cholesterol and mortality (excluding participants with a history of cancer, stroke, or myocardial infarction)

	Total cholesterol levels (mmol/L)			
	<4.14	4.14–5.16	5.17–6.20	≥6.21
	Hazard ratio (95% CI)			
Men				
Total mortality				
Crude	1.49 (1.21–1.83)	1	0.96 (0.76–1.19)	0.87 (0.60–1.27)
Age-adjusted	1.48 (1.21–1.82)	1	1.02 (0.81–1.27)	1.06 (0.73–1.55)
Multivariate-adjusted[a]	1.38 (1.12–1.71)	1	1.08 (0.86–1.36)	1.25 (0.83–1.87)
Excluding deaths due to liver disease				
Crude	1.39 (1.12–1.72)	1	0.98 (0.78–1.23)	0.91 (0.62–1.33)
Age-adjusted	1.38 (1.13–1.71)	1	1.04 (0.83–1.31)	1.11 (0.76–1.62)
Multivariate-adjusted[a]	1.29 (1.03–1.60)	1	1.10 (0.88–1.39)	1.30 (0.87–1.94)
Women				
Total mortality				
Crude	0.77 (0.53–1.12)	1	1.16 (0.92–1.47)	1.09 (0.78–1.53)
Age-adjusted	1.29 (0.89–1.88)	1	0.96 (0.76–1.22)	0.90 (0.64–1.26)
Multivariate-adjusted[a]	1.28 (0.88–1.89)	1	0.99 (0.78–1.27)	0.90 (0.63–1.30)
Excluding deaths due to liver disease				
Crude	0.78 (0.53–1.14)	1	1.15 (0.90–1.47)	1.08 (0.77–1.53)
Age-adjusted	1.30 (0.89–1.91)	1	0.95 (0.75–1.22)	0.89 (0.63–1.26)
Multivariate-adjusted[a]	1.29 (0.88–1.91)	1	0.99 (0.77–1.27)	0.90 (0.62–1.30)

[a]Cox proportional hazards model adjusted for age, systolic blood pressure, high-density lipoprotein cholesterol, smoking, drinking, and body mass index.

highest cholesterol group (≥6.21 mmol/L) were not significant; the HR was less than 1 for women (HR, 0.93; 95% CI, 0.67–1.30).

Among women, there was an inverse association between total cholesterol and mortality age-adjusted analysis. The multifactor-adjusted HR in the lowest cholesterol group was 0.50 (95% CI, 0.16–1.55) in premenopausal women and 1.42 (0.98–2.06) in postmenopausal women.

Table 4a shows the same results, after excluding deaths due to liver disease. In these analyses, the age-adjusted HRs of the lowest cholesterol group were statistically significant: 1.38 (1.13–1.67) for men and 1.49 (1.09–2.04) for women. There was no difference between these results and those for all causes of mortality.

The results of analyses that excluded deaths within the first 5 years of follow-up were similar to those that included all deaths (Table 4b). In addition, the results of analysis that excluded 320 participants with a history of stroke (113), myocardial infarction (65), or cancer (142) were similar (Table 4c).

Table 5 shows HRs and 95% CIs for stroke, heart disease, and cancer mortality according to cholesterol category. The multivariate-adjusted HR of the lowest cholesterol group was higher than 1 for each cause of death and was statistically significant for cancer mortality in men.

We separately analyzed participants with and without ischemia for stroke and heart disease. Among subjects with the highest level of total cholesterol, the multivariate-adjusted HRs for ischemic stroke and myocardial infarction were not significant. The corresponding HRs for ischemic stroke in men and myocardial infarction in women were less than 1; however, the HR of the lowest group was 3.86 (95% CI, 1.18–12.68) for hemorrhagic stroke in women and 5.79 (1.07–31.27) for heart failure excluding myocardial infarction in women.

Table 5. Total cholesterol by cause of death

	Total cholesterol level (mmol/L)			
	<4.14	4.14–5.16	5.17–6.21	≥6.21
	Hazard ratio (95% CI)			
Men				
Stroke mortality				
Crude	1.23 (0.72–2.27)	1	0.92 (0.50–1.69)	0.75 (0.23–2.49)
Age-adjusted	1.28 (0.72–2.28)	1	0.98 (0.53–1.80)	1.02 (0.31–3.34)
Multivariate-adjusted[a]	1.21 (0.66–2.21)	1	0.99 (0.53–1.82)	0.98 (0.29–3.23)
Hemorrhagic stroke				
Crude	1.93 (0.81–4.62)	1	0.65 (0.21–2.01)	1.79 (0.50–6.45)
Age-adjusted	1.92 (0.80–4.61)	1	0.69 (0.22–2.19)	2.10 (0.58–7.61)
Multivariate-adjusted[a]	1.96 (0.80–4.79)	1	0.68 (0.21–2.16)	1.76 (0.38–8.09)
Ischemic stroke[b]				
Crude	0.84 (0.35–2.04)	1	1.56 (0.71–3.40)	0.48 (0.14–1.64)
Age-adjusted	0.85 (0.35–2.06)	1	1.59 (0.73–3.47)	0.58 (0.17–1.95)
Multivariate-adjusted[a]	0.79 (0.30–2.04)	1	1.55 (0.70–3.43)	0.65 (0.19–2.23)
Heart disease mortality				
Crude	1.74 (1.00–3.01)	1	1.06 (0.58–1.93)	1.36 (0.54–3.53)
Age-adjusted	1.75 (1.01–3.04)	1	1.14 (0.62–2.10)	1.93 (0.74–5.03)
Multivariate-adjusted[a]	1.36 (0.76–2.46)	1	1.04 (0.54–2.01)	2.14 (0.81–5.65)
Myocardial infarction				
Crude	1.34 (0.57–3.12)	1	0.76 (0.29–1.99)	1.38 (0.40–4.82)
Age-adjusted	1.34 (0.58–3.15)	1	0.84 (0.32–2.19)	1.84 (0.53–6.483)
Multivariate-adjusted[a]	0.99 (0.40–2.46)	1	0.86 (0.30–2.47)	2.37 (0.52–10.83)
Heart failure[c]				
Crude	1.63 (0.50–5.32)	1	1.64 (0.54–5.01)	1.94 (0.40–9.40)
Age-adjusted	1.72 (0.52–5.66)	1	1.90 (0.61–5.89)	2.77 (0.56–13.67)
Multivariate-adjusted[a]	1.32 (0.36–4.79)	1	1.59 (0.48–5.27)	3.86 (0.76–19.58)
Cancer mortality				
Crude	1.72 (1.27–2.32)	1	1.08 (0.78–1.49)	0.80 (0.42–1.53)
Age-adjusted	1.73 (1.28–2.34)	1	1.13 (0.82–1.57)	1.01 (0.53–1.95)
Multivariate-adjusted[a]	1.66 (1.22–2.27)	1	1.18 (0.85–1.66)	1.07 (0.55–2.07)
Women				
Stroke mortality				
Crude	0.83 (0.33–2.05)	1	1.37 (0.76–2.46)	1.53 (0.70–3.35)
Age-adjusted	1.41 (0.57–3.50)	1	1.19 (0.66–2.15)	1.40 (0.64–3.06)
Multivariate-adjusted[a]	1.84 (0.71–4.76)	1	1.29 (0.68–2.44)	1.52 (0.66–3.48)
Hemorrhagic stroke				
Crude	2.18 (0.70–6.81)	1	2.22 (0.92–5.37)	3.28 (1.21–8.87)
Age-adjusted	3.41 (1.07–10.85)	1	1.97 (0.80–4.85)	2.92 (1.05–8.07)
Multivariate-adjusted[a]	3.86 (1.18–12.68)	1	1.94 (0.77–4.89)	2.15 (0.68–6.77)
Ischemic stroke				
Crude	0.23 (0.03–1.81)	1	1.06 (0.48–2.39)	1.08 (0.35–3.28)
Age-adjusted	0.44 (0.06–3.39)	1	0.99 (0.44–2.23)	1.06 (0.34–3.28)
Multivariate-adjusted[a]	0.57 (0.07–4.54)	1	0.90 (0.37–2.19)	1.17 (0.36–3.85)
Heart disease mortality				
Crude	0.75 (0.33–1.73)	1	0.93 (0.53–1.65)	0.66 (0.26–1.73)
Age-adjusted	1.43 (0.62–3.40)	1	0.87 (0.50–1.55)	0.69 (0.26–1.80)
Multivariate-adjusted[a]	1.34 (0.54–3.35)	1	0.78 (0.42–1.42)	0.39 (0.11–1.30)
Myocardial infarction[b]				
Crude	0.58 (0.17–2.01)	1	0.51 (0.17–1.53)	0.53 (0.20–1.46)
Age-adjusted	1.09 (0.31–3.78)	1	0.50 (0.16–1.49)	0.49 (0.18–1.36)
Multivariate-adjusted[a]	1.07 (0.30–3.79)	1	0.38 (0.11–1.34)	0.52 (0.18–1.46)
Heart failure[c]				
Crude	3.75 (0.87–16.19)	1	0.71 (0.13–3.99)	4.22 (1.00–17.82)
Age-adjusted	6.57 (1.49–28.97)	1	0.66 (0.11–3.77)	4.00 (0.92–17.45)
Multivariate-adjusted[a]	5.79 (1.07–31.27)	1	0.72 (0.12–4.28)	2.33 (0.37–14.66)
Cancer mortality				
Crude	1.04 (0.62–1.76)	1	1.26 (0.87–1.84)	1.75 (1.09–2.80)
Age-adjusted	1.50 (0.89–2.55)	1	1.09 (0.75–1.58)	1.48 (0.92–2.36)
Multivariate-adjusted[a]	1.44 (0.83–2.49)	1	1.07 (0.72–1.59)	1.58 (0.97–2.56)

[a]Cox proportional hazards model adjusted for age, systolic blood pressure, high-density lipoprotein cholesterol, smoking, drinking, and body mass index.
[b]Cholesterol levels: <4.13, 4.14–5.16, 5.17–5.69, ≥5.70.
[c]Excluding myocardial infarction.

DISCUSSION

We noted a clear relationship between low cholesterol and increased mortality. Okamura et al[13] reported that occult liver diseases are associated with mortality; however, in the present study, the relationship between low cholesterol and increased mortality was unchanged in analyses that excluded deaths due to liver disease. Our results suggest that hemorrhagic stroke and heart failure excluding myocardial infarction, contribute to the relationship between low cholesterol and high mortality.

Studies have shown a relationship between low cholesterol and non-cardiovascular mortality; however, in addition to cancer mortality, stroke mortality and heart disease mortality were also related to low cholesterol in our analyses. The relationship between low cholesterol and hemorrhagic stroke was similar to previously reported results.[3,5] Although the relationship between high cholesterol and ischemic stroke is not constant, it may be that the risk of high cholesterol disappears due to medical interventions for ischemic stroke and that the risk of low cholesterol is thus emphasized because of a lack of such interventions for low cholesterol.

It is difficult to interpret the relationship between low cholesterol and heart disease mortality. Although a relationship between cholesterol and heart failure was reported, high cholesterol, too, was a risk factor for non-ischemic heart failure.[16] We found no report of an association between low cholesterol and heart failure. The effects of malnutrition should be considered, as should the possible presence of beriberi heart disease and alcoholism. The relationship between low cholesterol and heart disease mortality was stronger in women than in men, so a disease like hyperthyroidism, which is more common in women, may be the culprit. A meta-analysis found an increase in cardiovascular mortality associated with subclinical hyperthyroidism,[17] but further investigations are necessary to confirm this hypothesis.

Because low cholesterol is associated with high cancer mortality, low cholesterol is a key finding in cancer. Previous studies reported an increase in liver cancer[13,15]; however, in the present study, increased cancer mortality in the lowest cholesterol group was unchanged after excluding cases of liver disease from the analyses. This suggests a need for screening of cancers other than liver cancer in individuals with low cholesterol levels.

Our results differ from those of previous studies,[1,3] in that high cholesterol was not identified as a risk factor for mortality in the present study. The HR was 0.93 (0.67–1.30) for women, which indicates that the focus should be on adults with low cholesterol rather than those with high cholesterol.

Our analyses constitute a primary use of existing data. An important advantage of this study was that the follow-up rate was very high because the study was conducted in rural areas, where migration is far less than in urban areas.

Cause of death was ascertained using death certificates, so there were potential limitations in accuracy regarding cause of death. The setting was a periodical health examination to screen participants with high cholesterol. Thus, it is also necessary to consider the possibility that risk was underestimated due to medical therapy for high cholesterol.

Our results are specific to people living in rural areas of Japan and their lifestyle, and may not be applicable to urban Japanese or other ethnic groups. Because Japanese in rural areas have less coronary disease than people in Western countries, their risks from low cholesterol may be higher.

There are many factors that might contribute to the relationship between low cholesterol and high mortality. A correlation between high mortality and low cholesterol clearly exists, especially in populations with a low risk of coronary heart disease.[9] Although the dangers of a high cholesterol level are widely known, they are less important in regions—such as rural Japan—where cardiovascular disease is less common. It may therefore be necessary to highlight the risks of low cholesterol. In Japan, only LDL cholesterol and HDL cholesterol are measured at present; however, total cholesterol remains an important measure in predicting mortality.

In conclusion, we observed that low cholesterol was associated with increased risks of cancer, hemorrhagic stroke, and heart failure excluding myocardial infarction.

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REFERENCES

1. Neaton JD, Blackburn H, Jacobs D, Kuller L, Lee DJ, Sherwin R, et al. Serum cholesterol level and mortality findings for men screened in the Multiple Risk Factor Intervention Trial. Multiple Risk Factor Intervention Trial Research Group. Arch Intern Med. 1992;152:1490–500.
2. Epstein FH. Relationship between low cholesterol and disease. Evidence from epidemiological studies and preventive trials. Ann N Y Acad Sci. 1995;748:482–90.
3. Iso H, Naito Y, Kitamura A, Sato S, Kiyama M, Takayama Y, et al. Serum total cholesterol and mortality in a Japanese population. J Clin Epidemiol. 1994;47:961–9.
4. Ueshima H, Iida M, Shimamoto T, Konishi M, Tsujioka K, Tanigaki M, et al. Multivariate analysis of risk factors for stroke. Eight-year follow-up study of farming villages in Akita, Japan. Prev Med. 1980;9:722–40.
5. Iso H, Jacobs DR Jr, Wentworth D, Neaton JD, Cohen JD. Serum cholesterol levels and six-year mortality from stroke in

350,977 men screened for the multiple risk factor intervention trial. N Engl J Med. 1989;320:904–10.
6. Cummings P, Psaty BM. The association between cholesterol and death from injury. Ann Intern Med. 1994;120:848–55.
7. Lester D. Serum cholesterol levels and suicide: a meta-analysis. Suicide Life Threat Behav. 2002;32:333–46.
8. Epstein FH. Low serum cholesterol, cancer and other noncardiovascular disorders. Atherosclerosis. 1992;94:1–12.
9. Smith GD, Song F, Sheldon TA. Cholesterol lowering and mortality: the importance of considering initial level of risk. BMJ. 1993;306:1367–73.
10. Shepherd J, Blauw GJ, Murphy MB, Bollen EL, Buckley BM, Cobbe SM, et al; PROSPER study group. PROspective Study of Pravastatin in the Elderly at Risk. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. Lancet. 2002;360:1623–30.
11. Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. N Engl J Med. 1996;335:1001–9.
12. Alsheikh-Ali AA, Maddukuri PV, Han H, Karas RH. Effect of the magnitude of lipid lowering on risk of elevated liver enzymes, rhabdomyolysis, and cancer: insights from large randomized statin trials. J Am Coll Cardiol. 2007;50:409–18.
13. Okamura T, Tanaka H, Miyamatsu N, Hayakawa T, Kadowaki T, Kita Y, et al; NIPPON DATA80 Research Group. The relationship between serum total cholesterol and all-cause or cause-specific mortality in a 17.3-year study of a Japanese cohort. Atherosclerosis. 2007;190:216–23.
14. Ishikawa S, Gotoh T, Nago N, Kayaba K; Jichi Medical School (JMS) Cohort Study Group. The Jichi Medical School (JMS) Cohort Study: design, baseline data and standardized mortality ratios. J Epidemiol. 2002;12:408–17.
15. Iso H, Ikeda A, Inoue M, Sato S, Tsugane S; JPHC Study Group. Serum cholesterol levels in relation to the incidence of cancer: the JPHC study cohorts. Int J Cancer. 2009;125:2679–86.
16. Velagaleti RS, Massaro J, Vasan RS, Robins SJ, Kannel WB, Levy D. Relations of lipid concentrations to heart failure incidence: the Framingham Heart Study. Circulation. 2009;120:2345–51.
17. Ochs N, Auer R, Bauer DC, Nanchen D, Gussekloo J, Cornuz J, et al. Meta-analysis: subclinical thyroid dysfunction and the risk for coronary heart disease and mortality. Ann Intern Med. 2008;148:832–45.

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Original Article

Frequency of Citrus Fruit Intake Is Associated With the Incidence of Cardiovascular Disease: The Jichi Medical School Cohort Study

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ABSTRACT

Background: It has been reported that fruit intake protects against cardiovascular disease (CVD). However, most of the relevant studies were conducted in Western countries, and only a few investigated Japanese populations. The present cohort study assessed the effect of citrus fruit intake on the incidence of CVD and its subtypes in a Japanese population.

Methods: A baseline examination consisting of physical and blood examinations and a self-administered questionnaire was conducted during the period from April 1992 through July 1995. Dietary habits were assessed using a food frequency questionnaire that was divided into 5 categories. Citrus fruit was examined separately due to its frequent consumption by the general Japanese population. Using the Cox proportional hazards model, data from 10 623 participants (4147 men, 6476 women) who had no history of CVD or carcinoma were analyzed to assess the association between frequency of citrus fruit intake and CVD incidence.

Results: Frequent intake of citrus fruit was associated with a lower incidence of CVD: the hazard ratio for almost daily intake versus infrequent intake of citrus fruit was 0.57 (95% confidence interval: 0.33–1.01, P for trend = 0.04) in men and 0.51 (0.29–0.88, P for trend = 0.02) in women. Frequent intake of citrus fruit was also associated with lower incidences of both all stroke and cerebral infarction, but not hemorrhagic stroke or myocardial infarction.

Conclusions: Frequent intake of citrus fruit may reduce the incidence of CVD, especially cerebral infarction, in men and women.

Key words: citrus fruit; cardiovascular disease; cerebral infarction; cohort studies; Japan

INTRODUCTION

Cardiovascular disease (CVD) is a major cause of death in developed countries. In the period since World War II, the distribution of diseases in Japan has dramatically changed and has begun to resemble that of Western countries. More recently, an important research theme has been to identify methods that might reduce CVD by using preventive means such as diet.

Fruit intake has been reported to protect against CVD. Fruit contains vitamins (such as vitamin C and folate), carotenoids, flavonoids, potassium, and fiber. Reports have shown that these protect against hypertension[1,2] and atherosclerosis by inhibiting low-density lipoprotein oxidation,[3] preventing increases in homocysteine and platelet aggregation,[3,4] and improving glucose intolerance.[2] High fruit intake has also been associated with reduced CVD mortality[5–12] and incidence.[13–17] Most of these studies were conducted in Western countries, however. In Japanese cohorts, 3 prospective studies[9–11] reported a reduction in CVD mortality associated with frequent fruit intake, and 2 prospective studies[14,17] noted a reduction in CVD incidence associated with fruit intake in Japanese populations. CVD encompasses a number of conditions that affect the cardiovascular system, such as coronary heart disease, stroke, and heart failure, and the etiologies and resulting

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pathologic conditions of these CVD subtypes vary. However, little research has attempted to assess the effect of fruit intake on these subtypes.[11,14,18] The present study was carried out to examine the potential protective effects of fruit intake on the incidence of CVD and its subtypes in a Japanese population.

In Japan, citrus fruit accounted for 32.6% of annual all-fruit consumption in 2008, and it has been the most widely distributed type of fruit in Japan for more than 20 years, according to the Ministry of Agriculture, Forestry and Fisheries.[19] Because it is the most popular fruit type in Japan, we specifically evaluated citrus fruit intake and assessed its protective effects against CVD incidence.

METHODS

Study population

We evaluated data from the Jichi Medical School (JMS) Cohort Study, which previously investigated the risk factors for CVD. This study enrolled 12 490 participants (4911 men, 7579 women) from 12 communities across Japan. In Japan, a mass screening examination for CVD has been conducted since 1982 in accordance with a system established by the Health and Medical Service Law for the Aged. This system was used to collect the baseline data for the present study. A municipal government office in each community site sent a personal invitation letter by mail or provided public information. Baseline examinations were conducted from April 1992 through July 1995 and consisted of physical and blood examinations and a self-administered questionnaire. The questionnaire was designed to obtain information on anthropometric and lifestyle exposures and dietary intake. A detailed description of the standardized collection of baseline examinations was published previously by Ishikawa et al.[20] Of the 12 490 participants, 95 declined follow-up and 7 could not be contacted after baseline examination. Thus, a total of 4869 men and 7519 women were followed; the follow-up rate was 99.2%. We excluded participants with a history of CVD or carcinoma and those with missing data on fruit intake. Ultimately, data from 10 623 participants (4147 men, 6476 women) were analyzed in the present study.

Baseline examination

Physical and blood examinations

In all communities, physical examinations took place using similar protocols. All participants measured their body height without shoes. Body weight while fully clothed was recorded by subtracting 0.5 kg (in the summer) or 1 kg (in other seasons) from the recorded weight to account for clothing. Body mass index (BMI) was defined as body weight in kilograms divided by the square of body height in meters. Systolic blood pressure (SBP) was measured using the same type of fully automated sphygmomanometer, which was placed on the right arm of the participant after they had been sitting for 5 minutes. Serum cholesterol concentration was measured by taking a blood sample from the antecubital vein of seated participants. Total cholesterol (TC) and triglycerides (TG) were measured using an enzymatic method, and high-density lipoprotein (HDL) cholesterol was measured using the phosphotungstate precipitation method (Wako, Osaka, Japan; interassay coefficient of variation, 1.5%).

Anthropometric and lifestyle exposures

Further lifestyle- and health-related variables were collected using self-reported questionnaires. Physical activity index (PAI) was calculated on the basis of the criteria included in the Framingham Study.[21] The total hours of sleeping, working, and leisure time within a day were multiplied by weight, based on the oxygen consumption required for each activity. Smoking status was classified as never smoker, ex-smoker, or current smoker, and alcohol consumption was categorized as never drinker, ex-drinker, or current drinker. Education level was assessed by age at completion of the highest educational qualification. Marital status was classified as currently married or unmarried.

Dietary habits

Dietary habits were assessed using a food frequency questionnaire (FFQ) that contained 30 items, including 2 subgroups on fruit consumption, namely, citrus fruit, such as satsuma mandarins (*mikans*), and other fruits. At the beginning of the FFQ, we asked participants to describe their usual diet. They indicated how often they consumed foods daily by answering from 5 multiple choice options: 1 = infrequent, 2 = 1–2 times/month, 3 = 1–2 times/week, 4 = 3–4 times/week, and 5 = almost daily. Although there were other questions that assessed juice consumption (using the 5 categories in the FFQ), there was no mention in the FFQ of the type of juice consumed. Because of this, we excluded fruit juice consumption from our estimation of citrus fruit intake. The FFQ was based on the one used in the Japan Collaborative Cohort (JACC) Study, and the reproducibility and validity of the intake frequency were examined previously.[22] To test the reproducibility of intake frequency, the 2 FFQs were distributed at 1-year intervals. The validity of the intake frequency of the FFQ was assessed by conducting a weighted dietary record.

Follow-up

The mass screening examination system that had been conducted each year was used to follow participants. They were asked whether they had a history of CVD at the mass screening examination each year. Those with such a history were asked which hospital they had visited and when. Participants who did not attend the screening examination were contacted by mail or telephone. Public health nurses visited the homes of the participants to obtain additional information when necessary. Death certificates were collected from public health centers with the official permission of the Agency of General Affairs and the Ministry of Health, Labour and Welfare. We stopped follow-up of participants who died

before the end of the study. Death from CVD was counted in the CVD incidence data. Information concerning participants who moved out of the study area during the follow-up period was obtained annually from the relevant municipal government; these participants (n = 340) were no longer followed from the day they left the study area. The mean duration of follow-up, ie, from the time of the baseline examination until either CVD incidence, relocation to another area, or the end of the study, was 10.7 years.

Diagnostic criteria

CVD was defined as stroke, myocardial infarction, or sudden death, whichever occurred first. If a CVD event was suspected, we requested duplicate computer tomography scans or magnetic resonance images (in cases of stroke) and electrocardiograms (in cases of myocardial infarction). The diagnoses were determined independently by a diagnosis committee composed of a radiologist, a neurologist, and 2 cardiologists. A diagnosis of stroke was defined as sudden onset of a focal, nonconvulsive neurological deficit persisting longer than 24 hours. Stroke subtype was classified as cerebral infarction, hemorrhagic stroke, or undetermined, according to the criteria of the National Institute of Neurological Disorders and Stroke.[23] Myocardial infarction was diagnosed according to the criteria of the World Health Organization Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) Project.[24]

Statistical analysis

All analyses were performed separately for men and women using the Statistical Package for Social Science (SPSS) for Windows (SPSS Japan Inc., version 15.0, Tokyo, Japan). First, general characteristics were categorized by frequency of citrus fruit intake by using means (standard deviation) and proportions. Next, to clarify the associations between frequency of citrus fruit intake and potential confounders, P values were calculated using 1-way analysis of variance and the chi-square test for variables. Finally, a Cox proportional hazards model was used to calculate the hazard ratio (HR) and 95% confidence interval (CI) of the incidence of CVD in relation to the frequency of citrus fruit intake, with adjustment for age and study area (HR1), or adjustment for age, study area, BMI, SBP, TC, PAI, smoking status, alcohol consumption, education level, and marital status (HR2). Age, BMI, SBP, TC, and PAI were entered in the model as continuous variables; study area (12 areas), smoking states (current, ex-, or never smoker), alcohol consumption (current, ex-, or never drinker), education level (younger than 16 years or not at age of completion), and marital status (married or not) were entered as categorical variables.

RESULTS

During an average follow-up period of 10.7 years, we documented 488 CVD events (270 in men, 218 in women): 383 strokes (201 in men, 182 in women)—including 249 cerebral infarctions (146 in men, 103 in women) and 133 hemorrhagic strokes (55 in men, 78 in women)—and 76 myocardial infarctions (53 in men, 23 in women). These events included 301 deaths from CVD (75 in men, 64 in women): 74 from stroke (38 in men, 36 in women)—including 32 deaths from cerebral infarction (18 in men, 14 in women) and 41 deaths from hemorrhagic stroke (20 in men, 21 in women)—and 15 from myocardial infarction (10 in men, 5 in women).

The baseline characteristics of participants according to frequency of citrus fruit intake are shown in Table 1. In both men and women, frequent consumers of citrus fruit tended to be older and less likely to smoke and drink. Among men, higher citrus fruit intake was associated with less physical activity and being married. Women with a high citrus fruit intake were better educated and had a higher BMI, SBP, and serum concentrations of TC and TG. However, the distributions of BMI, SBP, and serum TC and TG concentrations were within approximately normal ranges.

As shown in Tables 2 and 3, the risks of CVD were lower in participants who frequently consumed citrus fruit, and there was a clear inverse relationship (HR for almost daily versus infrequent citrus fruit intake: 0.57, 95% CI: 0.33–1.01, P for trend = 0.04 in men; and 0.51, 0.29–0.88, P for trend = 0.02 in women). A stronger inverse relationship was found between frequency of citrus fruit intake and all-stroke risk in both men (HR for almost daily versus infrequent citrus fruit intake: 0.40, 0.20–0.81, P for trend = 0.01) and women (0.47, 0.26–0.87, P for trend = 0.02). Regarding stroke subtype, frequent intake of citrus fruit was significantly inversely associated with the risk of cerebral infarction, but not hemorrhagic stroke. There was no significant relationship between frequency of citrus fruit intake and incidence of myocardial infarction. The associations remained after multivariate adjustment.

DISCUSSION

The present results indicate that frequent consumption of citrus fruit is significantly inversely associated with CVD incidence. In particular, there were marked reductions in all-stroke and cerebral infarction risk, but not in hemorrhagic stroke risk. Frequency of citrus fruit intake was not associated with incidence of myocardial infarction.

As compared with reports that showed a reduction in the incidence of CVD[15] or cerebral infarction[13,14] based on fruit intake, the reductions found in the present study were statistically significant. Yokoyama et al[14] reported that the multivariate HR of cerebral infarction incidence was 0.51 (95% CI: 0.24–1.10, P = 0.07) among women consuming fruit 6 to 7 days per week, as compared with those consuming it 0 to 2 days per week. In the present study, the multivariate HRs of cerebral infarction incidence for almost daily intake

Table 1. Baseline relationships between frequency of citrus fruit intake and potential confounders

	Frequency of citrus fruit intake[a]					*P*	Frequency of citrus fruit intake[a]					*P*
	1 (low)	2	3	4	5 (high)		1 (low)	2	3	4	5 (high)	
	Men						Women					
No. of subjects	570	1096	1445	704	332		466	987	2092	1749	1182	
Age, y (mean ± SD)	53.2 (13.1)	52.4 (12.6)	55.0 (12.1)	57.7 (10.1)	58.7 (9.7)	<0.01	54.2 (12.9)	53.0 (12.8)	54.1 (11.9)	55.5 (10.3)	59.2 (9.0)	<0.01
Body mass index, kg/m^2 (mean ± SD)	22.8 (3.0)	23.0 (2.8)	22.9 (2.9)	23.0 (2.8)	23.0 (2.7)	0.81	22.9 (3.4)	23.0 (3.3)	23.0 (3.2)	23.0 (3.1)	23.5 (3.1)	0.001
Systolic blood pressure, mm Hg (mean ± SD)	131 (21.0)	131 (20.8)	131 (20.1)	132 (19.6)	130 (21.1)	0.27	128 (22.7)	127 (21.5)	127 (21.3)	128 (20.3)	130 (20.7)	0.02
Serum cholesterol concentration												
Total cholesterol, mg/dl (mean ± SD)	183 (35.0)	183 (34.9)	186 (34.9)	187 (32.3)	184 (34.1)	0.02	193 (36.3)	193 (35.1)	195 (33.6)	198 (35.1)	202 (34.7)	<0.01
High-density lipoprotein, mg/dl (mean ± SD)	49 (13.6)	49 (14.2)	49 (13.2)	49 (12.9)	48 (13.0)	0.50	53 (12.7)	53 (12.9)	53 (12.7)	53 (12.2)	52 (12.1)	0.69
Triglyceride, mg/dl (mean ± SD)	130 (90.2)	127 (89.5)	126 (78.3)	128 (91.0)	129 (91.5)	0.86	101 (55.4)	105 (63.6)	105 (62.3)	109 (65.5)	119 (73.8)	<0.01
Physical activity index (mean ± SD)	36.2 (10.3)	35.8 (9.5)	35.8 (9.6)	35.7 (9.0)	34.1 (8.3)	0.02	31.8 (6.3)	31.2 (5.4)	31.7 (5.6)	31.7 (5.3)	31.5 (5.1)	0.09
Current smoker, %	64.4	55.3	48.7	44.7	41.3	<0.01	10.1	10.0	5.3	3.8	3.7	<0.01
Current alcohol drinker, %	74.9	77.3	77.5	72.4	69.9	0.01	28.2	33.5	27.1	22.0	19.9	<0.01
Education level (age at completion)												
≤15 years, %	49.3	43.6	41.7	44.8	43.1	0.04	59.3	51.0	48.6	49.1	51.9	0.001
Married, %	86.9	89.7	92.2	95.1	94.5	<0.01	89.4	91.5	91.9	92.3	90.8	0.26

[a]1 = infrequent, 2 = 1–2 times/month, 3 = 1–2 times/week, 4 = 3–4 times/week, and 5 = almost daily.

Table 2. Hazard ratios and 95% confidence intervals according to frequency of citrus fruit intake adjusted for potential confounders (men)

	Frequency of citrus fruit intake					*P* for trend
	Infrequent	1–2 times/month	1–2 times/week	3–4 times/week	Almost daily	
Person-years	5785	11 847	15 333	7677	3511	
Cardiovascular disease						
No. of cases	47	60	98	44	21	
HR1[a] (95% CI[b])	1.00	0.67 (0.46–0.99)	0.73 (0.51–1.04)	0.57 (0.38–0.87)	0.58 (0.35–0.97)	0.02
HR2[c] (95% CI)	1.00	0.70 (0.47–1.05)	0.75 (0.52–1.09)	0.63 (0.41–0.97)	0.57 (0.33–1.01)	0.04
All-stroke						
No. of cases	38	44	73	33	13	
HR1 (95% CI)	1.00	0.60 (0.39–0.93)	0.66 (0.45–0.98)	0.52 (0.33–0.83)	0.43 (0.23–0.80)	0.01
HR2 (95% CI)	1.00	0.61 (0.39–0.96)	0.68 (0.45–1.03)	0.57 (0.35–0.92)	0.40 (0.20–0.81)	0.01
Cerebral infarction						
No. of cases	27	32	56	24	7	
HR1 (95% CI)	1.00	0.61 (0.37–1.02)	0.71 (0.45–1.12)	0.53 (0.31–0.92)	0.32 (0.14–0.75)	0.008
HR2 (95% CI)	1.00	0.65 (0.38–1.11)	0.73 (0.45–1.18)	0.62 (0.35–1.08)	0.28 (0.11–0.72)	0.02
Hemorrhagic stroke						
No. of cases	11	12	17	9	6	
HR1 (95% CI)	1.00	0.57 (0.25–1.29)	0.54 (0.25–1.15)	0.49 (0.20–1.19)	0.68 (0.25–1.83)	0.30
HR2 (95% CI)	1.00	0.52 (0.22–1.25)	0.57 (0.26–1.25)	0.45 (0.17–1.20)	0.71 (0.24–2.11)	0.36
Myocardial infarction						
No. of cases	10	10	16	10	7	
HR1 (95% CI)	1.00	0.57 (0.23–1.39)	0.62 (0.27–1.39)	0.68 (0.27–1.67)	1.01 (0.38–2.73)	0.91
HR2 (95% CI)	1.00	0.60 (0.25–1.49)	0.62 (0.27–1.43)	0.75 (0.30–1.86)	0.99 (0.34–2.80)	0.95

[a]Hazard ratio adjusted for age and study area.
[b]Confidence interval.
[c]Hazard ratio adjusted for age, study area, body mass index, systolic blood pressure, total cholesterol concentration, physical activity index, smoking status, alcohol consumption, education level, and marital status.

versus infrequent intake were 0.28 (95% CI: 0.11–0.72, *P* for trend = 0.02) in men and 0.39 (0.15–1.00, *P* for trend = 0.07) in women. A possible reason for this difference is the present study's focus on the effects of citrus fruit. In Japan, in addition to citrus fruit, apples, bananas, watermelons, and pears are commonly consumed. However, as compared with these other fruits, citrus fruit is richer in antioxidants such as vitamin C and β-cryptoxanthin.[25,26] These antioxidants may