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Long sleep duration and cause-specific mortality according to physical function and self-rated health: the Ohsaki Cohort Study

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Summary
Although several studies have examined the association between sleep duration and all-cause or cause-specific mortality, it is unclear whether long sleep duration might merely reflect decreased physical strength and poorer health status. We therefore examined the association between sleep duration and all-cause and cause-specific mortality, and conducted stratified analysis based on physical function and self-rated health. This study used prospective data from the Ohsaki Cohort Study, conducted in Miyagi Prefecture, in northern Japan. This study population comprised 49 256 subjects aged 40–79 years at the baseline survey. We estimated hazard ratios (HRs) and 95% confidence intervals (CIs) of all-cause and cause-specific mortality according to the five categories of sleep duration ($\leq$6, 7, 8, 9, $\geq$10 h day^{-1}), treating 7 h as the reference group, employing Cox's proportional hazard regression analysis. We found that long sleep duration was associated with mortality. The HRs (95% CIs) of subjects who slept more than 10 h were 1.37 (1.27–1.47), 1.49 (1.30–1.71) and 1.53 (1.36–1.73) for mortality due to all causes, total cardiovascular disease and other causes of death mortality, respectively. The association between long sleep duration and stroke mortality was especially marked among subjects with limited physical function and poorer health status. However, we did not observe such a trend for mortality due to all causes, total cardiovascular disease, ischaemic heart disease, cancer or other causes of death. We conclude that, with the exception of stroke mortality, the association between long sleep duration and mortality is not modified by physical function or health status.

INTRODUCTION

Sleep duration and mortality risk have been indicated in several previous studies (Cappuccio *et al.*, 2010, 2011; Gallicchio and Kalesan, 2009). Although three meta-analyses have concluded that both long and short sleep duration were associated with an increased risk of mortality, the effect was larger among those who slept longer (long sleeper) than among short sleepers (Cappuccio *et al.*, 2010, 2011; Gallicchio and Kalesan, 2009). The meta-analysis by Cappuccio *et al.*, 2011 also reported that the hazard ratio (HR) of long sleep duration was higher than of short sleep with regard to mortality due to total cardiovascular disease (CVD) and stroke. The results of previous studies conducted in East Asia, predominantly Japan, have tended to indicate stronger HRs for both short and long sleep duration than those of studies conducted in Europe or the United States (Cappuccio *et al.*, 2010). This difference might be attributable to `differences in average sleep duration among countries, or to the longer life

expectancy in Japan (Cappuccio *et al.*, 2010; Steptoe *et al.*, 2006).

However, it remains unclear whether long sleep duration directly increases the risk, or whether it merely reflects the presence of comorbidity or unhealthy status. In a cross-sectional study, Stranges *et al.*, 2008 reported that long sleepers had lower physical activity and lower scores on the Short Form-36 physical scale. They suggested that long sleep duration was a reflection of comorbidity or poor health status. Conversely, Mesas *et al.*, 2010 conducted a stratified analysis based on health status and physical function in a prospective cohort study. They found that long sleep duration was associated with greater mortality, irrespective of health status, and considered that the association between long sleep duration and mortality would not be explained by poorer health status among long sleepers. However, their sample size was small and they did not examine causes of death, even though some studies have suggested that the association between sleep duration and mortality risk differs according to cause of death (Amagai *et al.*, 2004; Burazeri *et al.*, 2003; Ferrie *et al.*, 2007; Ikehara *et al.*, 2009; Lan *et al.*, 2007; Patel *et al.*, 2004; Qureshi *et al.*, 1997).

We therefore examined the association between sleep duration and all-cause and cause-specific mortality, and conducted stratified analysis by physical function and self-rated health.

METHODS

Study cohort

We used data obtained from the Ohsaki National Health Insurance (NHI) Cohort Study, details of which have been described elsewhere (Kuriyama *et al.*, 2006; Tsuji *et al.*, 1998). Briefly, we delivered a self-administered questionnaire, including items on sleep duration, between October and December 1994 to all NHI beneficiaries aged 40–79 years living in the catchment area of Ohsaki Public Health Center, a local government agency that provides preventive health services for residents of 14 municipalities in Miyagi Prefecture, northern Japan. Of 54 996 eligible men (26 481) and women (28 515), 52 029 (94.6%) responded (men: 24 895, women: 27 134).

To ascertain the date of, and reason for, withdrawal from the NHI, we began prospective collection of NHI withdrawal history files on 1 January 1995. We excluded 776 participants who had withdrawn from the NHI before the baseline questionnaire survey. Thus, 51 253 participants (men: 24 573, women: 26 680) ultimately formed the study cohort.

Exposure measurement

The questionnaire included items about sleep duration, as well as alcohol drinking and smoking habits, a 40-item food frequency questionnaire (FFQ), personal and family history of diseases, job status, level of education, marital status, body weight, height, time spent walking, physical function, self-rated health and perceived mental stress.

For items related to sleep duration, participants entered the mean integer number of hours of sleep they had taken per day during the last year. We categorized sleep duration into five groups: ≤ 6, 7, 8, 9 and ≥ 10 h day^{-1}. We rounded-off sleep duration to the closest whole number.

The physical function status of each subject was assessed using the self-completed questionnaires returned at the baseline survey in 1994 using the six-item physical function measure of the Medical Outcomes Study (MOS) Short-form General Health Survey (Stewart *et al.*, 1988, 1989; Tsuji *et al.*, 1999; Ware *et al.*, 1996). This measure examines the extent to which health affects a variety of physical activities, ranging from strenuous exercise to basic self-care. The validity and reliability of the MOS questionnaire have been fully established (Stewart *et al.*, 1988, 1989; Ware *et al.*, 1996). The Japanese version of the MOS scale has been reported to predict all-cause mortality, hospitalization risk and medical costs (Tsuji *et al.*, 1999). In the analysis, we classified the subjects into the following seven groups according to their self-response, which was referred to as the MOS score: level 6, able to perform vigorous activities such as lifting heavy objects, running or participating in strenuous sports; level 5, able to perform moderate activities such as moving a table, carrying groceries or bowling; level 4, able to walk uphill or climb a few flights of stairs; level 3, able to bend, lift or stoop; level 2, able to walk one block; level 1, able to perform self-care activities such as eating, dressing, bathing or using the toilet; level 0, unable to do anything unaided (Tsuji *et al.*, 1999). This classification was ordered hierarchically in terms of difficulty in performing physical tasks, and we scored the levels of each subject according to the highest physical task he/she answered as being not limited at all. For each item measured, we classified the subjects into two groups: 'limited' (levels 0–4) and 'unlimited' (levels 5 and 6).

Self-rated health was assessed through the subject's response to the question: 'How is your overall health status?'. The subjects were asked to choose one of five answers: 'bad', 'poor', 'moderate', 'good' or 'excellent', and on the basis of their responses, we classified them into two groups: 'worse' (poor or bad) and 'better' (excellent, good or moderate).

Follow-up

The end-points were mortality due to all causes, CVD [ischaemic heart disease (IHD) and stroke], cancer and other causes. We followed-up the subjects for mortality and emigration by reviewing the NHI withdrawal history files from 1 January 1995 to 31 March 2008. When a subject withdrew from the NHI system because of death, emigration or employment, the date of withdrawal and the reason were coded on the NHI withdrawal history files. Because we were unable to obtain subsequent information for subjects who

withdrew from the NHI, we discontinued their follow-up. For deaths thus identified, we investigated the causes by reviewing the death certificates filed at Ohsaki Public Health Center. Cause of death was coded by trained physicians according to the International Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) (WHO, 1992). We identified deaths due to CVD as codes I00–I99 (including IHD as codes I20–I25 and strokes as codes I60–I69), and those due to cancer as codes C00–C97.

After exclusion of subjects who had not entered responses for sleep duration (n = 1 783), and who had reported a sleep duration of <4 h or more than 12 h (n = 214), 49 256 participants (men: 23 749, women: 25 507) remained, including 8447 participants who had died due to all causes (CVD 2549; cancer 2764; other causes 3134). In order to improve the reliability of our questionnaire, we excluded participants who had reported sleep durations of <4 h or more than 14 h, because these durations were considered to be extremely long or short. Also, these subjects were less likely to have answered the question items (data not shown).

Ethical permissions

The study protocol was reviewed and approved by the ethics committee of Tohoku University School of Medicine. We considered the return of self-administered questionnaires signed by the subjects to imply their consent to participate in the study.

Statistical analysis

We counted person-years of follow-up for each of the subjects from 1 January 1995 until the date of death, the date of withdrawal from the NHI or the end of follow-up (31 March 2008), whichever occurred first. The average follow-up time was 10.8 years. The validity of the proportional hazards assumption was verified by adding a time-dependent variable to each model to confirm that the HR for each covariate did not increase or decrease over time.

We used Cox's proportional hazard regression analysis to estimate hazard ratios (HRs) and the 95% confidence intervals (CIs) of mortality according to the five categories of sleep duration ($\leq$6, 7, 8, 9 and $\geq$10 h day^{-1}), treating 7 h as the reference group. We chose 7 h as a reference group because this category had been used as a reference group in most previous studies, and we had predicted that this group would have the lowest mortality risk (Cappuccio *et al.*, 2010, 2011; Gallicchio and Kalesan, 2009). In these analyses, we considered the following parameters as covariates: age (continuous variable); sex; total caloric intake (continuous variable, calculated from the 40-item FFQ); body mass index (BMI) in kg m^{-2} (<18.5, 18.5–24.9, $\geq$25.0); marital status (married or unmarried); level of education (junior high school or less, high school or college/university or higher); job status (employed or unemployed); history of myocardial infarction; history of cancer; history of stroke; history of hypertension; history of diabetes mellitus; smoking status (never smoker, ex-smoker, current smoker one to 19 cigarettes day^{-1}, or current smoker $\geq$ 20 cigarettes day^{-1}); alcohol drinking (never drinkers, ex-drinkers, current drinkers < 27.8 g day^{-1}, current drinkers 27.8–45.59 day^{-1}, current drinkers 45.6–68.39 day^{-1} or current drinkers $\geq$ 68.4 day^{-1} ethanol); time spent walking (<1 h day^{-1}, 1 h day^{-1} or longer); perceived mental stress (low, moderate or high); self-rated health (worse or better); physical function (limited or unlimited). All the covariates we selected had been suggested to show an association with all-cause mortality or cause-specific mortality in the previous studies. We did not use a stepwise procedure. In addition, we conducted analyses stratified by physical function and self-rated health. In the stratified analyses, we excluded subjects for whom answers about health status and/or physical function were missing. Interactions between the five categories of sleep duration and physical function and self-rated health were tested for using the likelihood ratio test, which compared the models with and without cross-product interaction terms.

All statistical analyses were performed using the SAS statistical software package, version 9.2 (SAS Institute Inc., Cary, NC, USA). All the statistical tests reported were two-sided. Differences at $P < 0.05$ were accepted as statistically significant.

RESULTS

Table 1 shows the baseline characteristics, according to sleep duration, separately for both sexes. For both men and women subjects, those who slept for 10 h or more per day were more likely to be older, to have a lower daily total caloric intake, to have a history of myocardial infarction, cancer, stroke, hypertension or diabetes mellitus, to have lower perceived mental stress, to have worse self-rated health and more limited physical function and were less likely to be employed or married (P-values < 0.0001). For both men and women, subjects those who slept 6 h or less per day were younger, less likely to have a history of myocardial infarction, cancer, stroke and hypertension and less limited physical function, and were more likely to have a higher education level and perceived mental stress (P-values < 0.0001).

Table 2 shows the age- and sex-adjusted and multivariate adjusted HRs for all-cause and cause-specific mortality according to sleep duration. Among subjects who slept 10 h or more per day, there was a significantly increased risk of mortality due to all causes, total CVD, IHD, stroke and other causes, respectively. Among subjects who slept 6 h or less per day, there was a significantly increased IHD mortality, but no significant association with risk of mortality due to all causes, total CVD, stroke or other causes. In addition, all-cause, total CVD and IHD mortality risk were increased significantly among subjects who slept for 8 h

Table 1 Baseline characteristics of the subjects according to sleep duration exclude extreme sleep duration

	Sleep duration (hours per day)					
	≤6	*7*	*8*	*9*	*≥10*	P *values**
Men						
Number of subjects	2 837	6 160	9 848	2 723	2 181	
Mean age (years), SD	58.2 (11.0)	56.8 (10.5)	59.5 (10.3)	62.9 (9.4)	66.0 (8.7)	<0.0001
Mean Body Mass Index (kg m^{-2}), SD	23.6 (3.2)	23.4 (2.9)	23.3 (3.0)	23.1 (3.2)	22.9 (3.7)	<0.0001
Mean total caloric intake (kcal day^{-1}), SD	1 735.1 (647.8)	1 829.2 (629.4)	1 806.3 (640.8)	1 765.7 (641.9)	1 649.9 (651.2)	<0.0001
Having history of MI	3.7	2.6	3.2	3.2	5.5	<0.0001
Having history of cancer	3.3	2.5	2.7	3.1	4.6	<0.0001
Having hisotry of stroke	2.4	1.4	2.6	3.9	8.6	<0.0001
Having history of hypertension (%)	23.6	20.8	24.7	29.1	31.2	<0.0001
Having history of DM (%)	9.0	6.6	7.2	7.5	9.5	<0.0001
Employed (%)	58.1	62.7	58.1	51.4	41.2	<0.0001
Married (%)	86.8	89.7	89.3	90.4	86.5	<0.0001
Junior high school graduated or less	50.0	52.1	60.0	69.7	72.5	<0.0001
Never drinkers (%)	15.2	16.3	16.3	14.6	15.4	<0.0001
Never smokers	19.0	18.6	17.3	15.6	15.9	<0.0001
Time spent walking 1 h day^{-1} or longer (%)	42.2	45.4	45.2	45.0	40.2	<0.0001
High perceived mental stress (%)	20.7	15.3	11.7	11.2	11.7	<0.0001
Poor or bad self-rated health (%)	20.4	14.7	17.2	18.2	31.6	<0.0001
Limited physical function (%)	18.0	12.6	16.5	21.0	36.8	<0.0001
Women						
Number of subjects	4 840	7 486	9 199	2 259	1 723	
Mean age (years), SD	59.1 (10.5)	58.5 (10.0)	61.6 (9.3)	65.0 (8.4)	68.5 (8.6)	<0.0001
Mean Body Mass Index (kg m^{-2}), SD	23.6 (3.4)	23.7 (3.3)	23.8 (3.4)	24.0 (3.5)	23.9 (4.4)	<0.0001
Mean total caloric intake (kcal day^{-1}), SD	1 216.6 (378.6)	1 260.9 (367.5)	1 238.5 (380.5)	1 197.3 (402.2)	1 127.4 (419.9)	<0.0001
Having history of MI	2.4	1.8	2.2	3.1	4.4	<0.0001
Having history of cancer	4.0	3.1	3.8	4.1	6.2	<0.0001
Having hisotry of stroke	1.2	0.9	1.6	2.5	6.2	<0.0001
Having history of hypertension (%)	25.3	25.2	29.6	35.2	39.3	<0.0001
Having history of DM (%)	5.5	4.8	5.7	7.4	10.4	<0.0001
Employed (%)	34.4	38.2	32.1	26.4	18.3	<0.0001
Married (%)	73.1	78.6	76.9	70.6	60.3	<0.0001
Junior high school graduated orless	47.1	47.1	57.8	65.9	66.3	<0.0001
Never drinkers (%)	54.8	60.2	60.4	60.8	58.7	<0.0001
Never smokers	69.0	71.9	68.8	66.8	63.0	<0.0001
Time spent walking 1 h day^{-1} or longer (%)	37.8	39.5	38.5	38.0	31.4	<0.0001
High perceived mental stress (%)	25.3	18.7	13.5	12.2	11.1	<0.0001
Poor or bad self-rated health (%)	24.3	18.7	22.2	26.9	38.8	<0.0001
Limited physical function (%)	29.2	25.2	32.9	43.4	56.0	<0.0001

*Continuous variables were analyzed by ANOVA, and categorical variables were analyzed by chi-square test.
SD, standard deviation. MI, myocardial infarction; DM, diabetes mellitus.

and 9 h day^{-1}. Mortality risk due to stroke and other causes of death was increased significantly among subjects who slept 9 h day^{-1}.

A significant interaction between sleep duration and physical function was observed only for stroke mortality (Table 3, Fig. 1). The association between long sleep duration and risk of stroke mortality was stronger among subjects who had limited physical function than among those who had unlimited physical function. Otherwise, there were no differences in the risk of mortality due to all causes, total

Table 2 Cox proportional hazard ratios (HRs) and 95% confidence intervals (CIs) for all-cause and cause-specific mortality according to sleep duration

	Sleep duration (hours per day)				
	≤6	*7*	*8*	*9*	*≥10*
Person-years	83 530	150 684	206 537	52 157	37 066
All-cause					
No. of deaths	1 074	1 671	3 206	1 117	1 379
Age- and sex-adjusted HR (95% CI)	1.09 (1.01–1.17)	1.00 (reference)	1.10 (1.04–1.17)	1.18 (1.09–1.27)	1.63 (1.52–1.75)
Multivariable HR1 (95% CI)*	1.01 (0.93–1.09)	1.00 (reference)	1.07 (1.01–1.14)	1.14 (1.06–1.24)	1.37 (1.27–1.47)
All CVD					
No. of deaths	325	439	972	361	452
Age- and sex-adjusted HR (95% CI)	1.20 (1.04–1.39)	1.00 (reference)	1.26 (1.12–1.41)	1.39 (1.21–1.60)	1.88 (1.64–2.15)
Multivariable HR1 (95% CI)*	1.10 (0.96–1.28)	1.00 (reference)	1.21 (1.08–1.36)	1.32 (1.15–1.52)	1.49 (1.30–1.71)
IHD					
No. of deaths	81	91	224	82	83
Age- and sex-adjusted HR (95% CI)	1.49 (1.10–2.01)	1.00 (reference)	1.40 (1.10–1.79)	1.55 (1.15–2.10)	1.73 (1.28–2.35)
Multivariable HR1 (95% CI)*	1.38 (1.02–1.86)	1.00 (reference)	1.36 (1.06–1.73)	1.49 (1.10–2.02)	1.41 (1.04–1.92)
Stroke					
No. of deaths	143	203	435	166	218
Age- and sex-adjusted HR (95% CI)	1.14 (0.92–1.41)	1.00 (reference)	1.23 (1.04–1.45)	1.40 (1.14–1.73)	1.99 (1.63–2.42)
Multivariable HR1 (95% CI)*	1.05 (0.84–1.30)	1.00 (reference)	1.17 (0.99–1.39)	1.30 (1.06–1.60)	1.51 (1.24–1.85)
Cancer					
No. of deaths	366	637	1,071	335	355
Age- and sex-adjusted HR (95% CI)	1.01 (0.89–1.15)	1.00 (reference)	0.99 (0.89–1.09)	0.98 (0.85–1.12)	1.20 (1.05–1.37)
Multivariable HR1 (95% CI)*	0.97 (0.85–1.11)	1.00 (reference)	0.97 (0.88–1.07)	0.96 (0.84–1.10)	1.10 (0.96–1.25)
Other					
No. of deaths	383	595	1,163	421	572
Age- and sex-adjusted HR (95% CI)	1.08 (0.95–1.23)	1.00 (reference)	1.11 (1.01–1.23)	1.22 (1.08–1.38)	1.86 (1.66–2.09)
Multivariable HR1 (95% CI)*	0.98 (0.86–1.11)	1.00 (reference)	1.09 (0.99–1.20)	1.20 (1.06–1.36)	1.53 (1.36–1.73)

*Multivariable HR was adjusted for age (continuous variable); sex; total caloric intake (continuous variable); body mass index in kg m^{-2} (<18.5, 18.5–24.9, ≥25.0); marital status (married or unmarried); level of education (junior high school or less, high school, or college/university or higher); job status (employed or unemployed); history of myocardial infarction; history of cancer; history of stroke; history of hypertension; history of diabetes mellitus; smoking status (never smoker, ex-smoker, current smoker 1–19 cigarettes day^{-1}, or current smoker ≥ 20 cigarettes day^{-1}); alcohol drinking (never drinkers, ex-drinkers, current drinkers < 27.8 g day^{-1}, current drinkers 27.8–45.59 g day^{-1}, current drinkers 45.6–68.39, current drinkers ≥ 68.4 g day^{-1} ethanol); time spent walking (<1 h day^{-1} or 1 h day^{-1} or longer); perceived mental stress (low, moderate, or high); self-rated health (worse or better), physical function (limited or unlimited).
CVD, cardiovascular disease; IHD, ischaemic heart disease.

CVD, IHD, cancer or other causes, irrespective of whether or not subjects had limited physical function.

Table 4 shows the analysis stratified by self-rated health (worse or better). The association between long sleep duration and stroke mortality was stronger among subjects who reported worse health status than among subjects who reported better health status. In addition, the HR for short sleep duration among subjects who reported worse health status was higher than that for subjects who reported better health status. Otherwise, the risk of mortality due to all causes, total CVD, IHD, cancer and other causes showed no differences among the subjects, irrespective of health status.

DISCUSSION

In this study, we found that long sleep duration was associated with an increased risk of mortality due to all causes, total CVD, IHD, stroke and other causes, and that short sleep duration was associated with an increased risk of IHD mortality. Significant interactions were observed only

Table 3 Cox proportional hazard ratios (HRs) and 95% confidence intervals (CIs) for all-cause and cause-specific mortality stratified by physical function status

	Number of deaths	*Sleep duration (hours per day)*					P *for interaction*
		≤6	*7*	*8*	*9*	*≥10*	
All-cause							
Limited	3 362	1.08 (0.96–1.22)	1.00 (reference)	1.10 (1.00–1.21)	1.24 (1.10–1.39)	1.41 (1.26–1.57)	0.15
Unlimited	4 317	0.94 (0.85–1.05)	1.00 (reference)	1.04 (0.96–1.12)	1.04 (0.93–1.15)	1.23 (1.10–1.38)	
All-CVD							
Limited	1 278	1.06 (0.86–1.32)	1.00 (reference)	1.20 (1.01–1.42)	1.43 (1.17–1.75)	1.58 (1.31–1.91)	0.20
Unlimited	1 131	1.15 (0.93–1.41)	1.00 (reference)	1.24 (1.06–1.46)	1.24 (1.00–1.52)	1.21 (0.96–1.52)	
IHD							
Limited	263	1.31 (0.83–2.06)	1.00 (reference)	1.16 (0.79–1.69)	1.70 (1.10–2.61)	1.48 (0.97–2.26)	0.19
Unlimited	269	1.52 (0.99–2.32)	1.00 (reference)	1.63 (1.16–2.29)	1.25 (0.78–1.99)	1.38 (0.83–2.28)	
Stroke							
Limited	594	1.20 (0.87–1.65)	1.00 (reference)	1.30 (1.00–1.69)	1.57 (1.16–2.14)	1.88 (1.42–2.49)	0.04
Unlimited	501	0.93 (0.68–1.28)	1.00 (reference)	1.12 (0.89–1.41)	1.15 (0.85–1.56)	0.93 (0.65–1.34)	
Cancer							
Limited	911	1.11 (0.89–1.38)	1.00 (reference)	0.95 (0.79–1.14)	0.96 (0.76–1.22)	1.00 (0.80–1.25)	0.07
Unlimited	1 718	0.86 (0.73–1.02)	1.00 (reference)	0.95 (0.84–1.07)	0.92 (0.77–1.09)	1.15 (0.96–1.38)	
Other							
Limited	1 476	1.08 (0.89–1.31)	1.00 (reference)	1.14 (0.97–1.33)	1.29 (1.07–1.57)	1.56 (1.32–1.86)	0.41
Unlimited	1 468	0.90 (0.75–1.08)	1.00 (reference)	1.03 (0.90–1.17)	1.06 (0.88–1.27)	1.37 (1.13–1.66)	

Adjusted for age (continuous variable); sex; total caloric intake (continuous variable); body mass index in kg m^{-2}(<18.5, 18.5–24.9, ≥25.0); marital status (married or unmarried); level of education (junior high school or less, high school, or college/university or higher); job status (employed or unemployed); history of myocardial infarction; history of cancer; history of stroke; history of hypertension; history of diabetes mellitus; smoking status (never smoker, ex-smoker, current smoker 1–19 cigarettes day^{-1} or current smoker ≥ 20 cigarettes day^{-1}); alcohol drinking (never drinkers, ex-drinkers, current drinkers < 27.8 g day^{-1}, current drinkers 27.8–45.59 g day^{-1}, current drinkers 45.6–68.39, current drinkers ≥ 68.4 g day^{-1} ethanol); time spent walking (<1 h day^{-1}, or 1 h day^{-1} or longer); perceived mental stress (low, moderate, or high); self-rated health (worse or better).
CVD, cardiovascular disease; IHD, ischaemic heart disease.

for stroke mortality, the risk of which was elevated among subjects who had limited physical function or worse health status. Otherwise, the risk of mortality due to all causes, total CVD, IHD, cancer and other causes was not increased among subjects who had limited physical function or worse health status.

The present results are consistent with most previous studies, including three meta-analyses of the association between longer sleep duration and all-cause mortality, CVD mortality or CVD incidence (Cappuccio *et al.*, 2010, 2011; Gallicchio and Kalesan, 2009). In this study we have demonstrated no significant interaction between sleep duration and physical function or health status in terms of all-cause mortality, consistent with the results of Mesas *et al.*, 2010, who found that long sleepers had an increased risk of mortality irrespective of health status. We also demonstrated that stroke mortality was increased significantly among subjects who had limited physical function, but not among subjects whose physical function was not restricted. We also found that mortality due to causes other than stroke, such as total CVD, IHD, cancer and other causes, showed no significant interaction with sleep duration, physical function or health status. In the present study, interactions between long sleep duration and physical function or health status were elevated only for stroke mortality, suggesting that the mechanism responsible for the association between long sleep duration and mortality differed among causes of death. However, Mesas *et al.* did not conduct any analysis of cause-specific mortality.

Several researchers have hypothesized that long sleep duration might reflect sleep need, reflecting in turn decreased physical strength, poor health status or accompanying comorbidity (Chen *et al.*, 2008; Ikehara *et al.*, 2009; Patel, 2009; Patel *et al.*, 2004). Because long sleepers are more likely to have low physical activity and low scores on the Short Form-36 physical score scale (Stranges *et al.*, 2008), it has been hypothesized that long sleep duration might be a consequence of unrecognized chronic comorbidity. We also conducted analysis stratified by history of diseases (cancer, myocardial infarction or stroke) that would provide an objective measure of health; however, this made no appreciable difference to the result (data not shown). Therefore, with the exception of stroke mortality, our results did not support this hypothesis in terms of mortality due to all causes, total CVD, IHD, cancer and other causes.

The present study is the first large-scale epidemiological study to have examined whether or not physical function or self-rated health modifies the association between sleep duration and all-cause and cause-specific mortality. Furthermore, we recruited subjects from a large general population, allowing possible generalization of our results. We followed a large number of participants over a 14-year period; as the

Table 4 Cox proportional hazard ratios (HRs) and 95% confidence intervals (CIs) for all-cause and cause-specific mortality stratified by self-rated health

	Number of deaths	*Sleep duration (hours per day)*					P *for interaction*
		≤6	*7*	*8*	*9*	*≥10*	
All-cause							
Worse (poor or bad)	3 011	1.00 (0.88–1.14)	1.00 (reference)	1.05 (0.95–1.17)	1.18 (1.03–1.35)	1.39 (1.23–1.57)	0.61
Better (excellent to fair)	5 148	0.99 (0.90–1.09)	1.00 (reference)	1.06 (0.99–1.14)	1.07 (0.97–1.18)	1.26 (1.14–1.40)	
All-CVD							
Worse (poor or bad)	996	1.18 (0.93–1.48)	1.00 (reference)	1.23 (1.02–1.50)	1.32 (1.04–1.68)	1.59 (1.28–1.97)	0.86
Better (excellent to fair)	1 463	1.05 (0.87–1.27)	1.00 (reference)	1.21 (1.05–1.40)	1.30 (1.08–1.55)	1.33 (1.10–1.61)	
IHD							
Worse (poor or bad)	212	1.04 (0.65–1.68)	1.00 (reference)	1.10 (0.75–1.63)	1.29 (0.79–2.10)	1.11 (0.70–1.78)	0.77
Better (excellent to fair)	333	1.70 (1.14–2.53)	1.00 (reference)	1.64 (1.18–2.26)	1.57 (1.05–2.34)	1.76 (1.15–2.68)	
Stroke							
Worse (poor or bad)	452	1.45 (1.02–2.06)	1.00 (reference)	1.27 (0.94–1.73)	1.49 (1.03–2.16)	2.04 (1.48–2.82)	0.046
Better (excellent to fair)	669	0.81 (0.60–1.08)	1.00 (reference)	1.12 (0.91–1.38)	1.21 (0.93–1.56)	1.06 (0.79–1.41)	
Cancer							
Worse (poor or bad)	784	0.93 (0.73–1.18)	1.00 (reference)	0.88 (0.72–1.07)	1.02 (0.79–1.32)	1.10 (0.87–1.39)	0.60
Better (excellent to fair)	1 889	0.96 (0.82–1.12)	1.00 (reference)	0.97 (0.86–1.09)	0.88 (0.75–1.03)	1.06 (0.89–1.25)	
Other							
Worse (poor or bad)	1 231	0.94 (0.77–1.16)	1.00 (reference)	1.06 (0.90–1.26)	1.21 (0.98–1.49)	1.47 (1.22–1.77)	0.34
Better (excellent to fair)	1 796	0.99 (0.83–1.17)	1.00 (reference)	1.07 (0.94–1.21)	1.12 (0.95–1.31)	1.46 (1.23–1.72)	

Adjusted for age (continuous variable); sex; total caloric intake (continuous variable); body mass index (BMI) in kg m^{-2} (<18.5, 18.5–24.9, ≥ 25.0); marital status (married or unmarried); level of education (junior high school or less, high school, or college/university or higher); job status (employed, or unemployed); history of myocardial infarction; history of cancer; history of stroke; history of hypertension; history of diabetes mellitus; smoking status (never smoker, ex-smoker, current smoker 1–19 cigarettes day^{-1} or current smoker ≥ 20 cigarettes day^{-1}); alcohol drinking (never drinkers, ex-drinkers, current drinkers < 27.8 g day^{-1}, current drinkers 27.8–45.59 g day^{-1}, current drinkers 45.6–68.39 or current drinkers ≥ 68.4 g day^{-1} ethanol); time spent walking (<1 h day^{-1}, or 1 h day^{-1}, or longer); perceived mental stress (low, moderate or high); physical function (limited or unlimited).
CVD, cardiovascular disease; IHD, ischaemic heart disease.

response rate was 94.6%, the subjects were highly representative of the target population.

Our study also had several limitations. First, sleep duration was determined on the basis of a self-reported questionnaire, and the assessment was conducted only once. Lauderdale *et al.*, 2008 reported that the correlation between self-reported sleep duration and that measured objectively by wrist actigraphy was moderate and systematically biased. There is a possibility that some misclassification occurred in our analysis; therefore, some misclassification of sleep duration could have arisen, and this might have affected its perceived association with mortality. However, any such misclassification would have been non-differential, and thus might have led to underestimation of the impact of sleep duration. Secondly, we had no information about sleep quality, the timing of sleep, presence of sleeping disorders, the use of sleep medication or other types of medication, such as antidepressants or benzodiazepines Such factors would have an influence on sleep duration, and thereby might affect the association between long sleep duration and mortality (Suzuki *et al.*, 2009). Thus, considering the influence of such factors, our results might have been overestimated. Finally, we had no information about rotating shift work or night work, even though shift work might affect the association between sleep duration and CVD (Fujino, 2007). However, as about 15% of our study subjects were housewives, 30% were farmers and 20% were retirees, we consider that very few would have been involved in rotating or night shift work.

In conclusion, our study indicates that longer sleep duration appears to be associated with mortality due to all causes, total

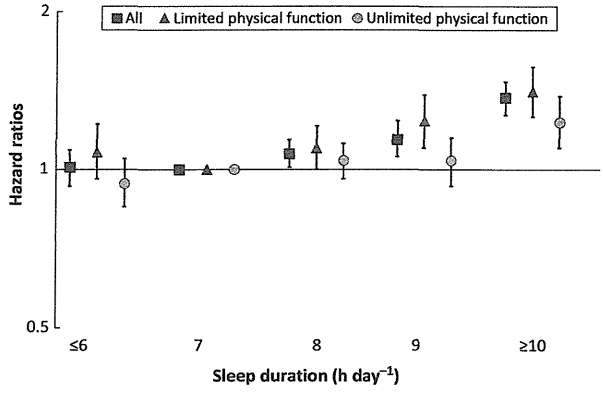

Figure 1. Sleep duration and all-cause mortality. Hazard ratio and 95% confidence intervals according to sleep duration by all subjects, subjects who had limited physical function or subjects who had unlimited physical function.

CVD, IHD and other causes, except for stroke mortality. Such an association was observed irrespective of physical function or self-rated health. The HR for stroke mortality in particular was markedly higher in subjects whose physical function was limited, or in those who had worse health status. Future studies of the association between longer sleep duration and cause-specific mortality may need to consider the effect of physical function and self-rated health.

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DISCLOSURE STATEMENT

All authors have no conflicts of interest.

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Relationship Between Serum Isoflavone Levels and Disability-Free Survival Among Community-Dwelling Elderly Individuals: Nested Case–Control Study of the Tsurugaya Project

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Background. The longer healthy life expectancy observed in Japan may be partly attributed to the Japanese diet. The researchers sought to examine whether serum isoflavone levels are associated with disability and death.

Methods. The researchers used a nested case–control study to compare serum isoflavones (daidzein, genistein, glycitein, and equol) levels between 165 participants that died or were certificated as disabled (cases) and 177 controls. Disability was defined by certification of long-term care insurance. Conditional logistic regression models were used to calculate the risk of isoflavones for the composite outcome.

Results. The proportion of cases was lower in the group with the highest levels of equol (34/91, 37%) compared with equol nonproducers (84/161, 52%). The risk of disability or death among equol producers remained reduced after adjusting for age and sex (odds ratio: 0.55, 95% confidence interval: 0.33–0.93). In a multivariate model, this *risk was also unchanged* (odds ratio: 0.51, 95% confidence interval: 0.27–0.96). There were no significant associations between daidzein, genistein, and glycitein with the composite endpoint.

Conclusions. Higher serum equol levels, but not any other isoflavones, were inversely associated with the composite endpoint of disability and death. Although it cannot be concluded that equol per se has preventive effects on disability or death, *higher equol levels appear associated with better health.*

Key Words: Isoflavone—Disability—Mortality—Nested case–control study.

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ACCORDING to the Health Report published in 2004 by the World Health Organization, both healthy life expectancy at age 0 and 60 years were the longest in Japan compared with all other countries in the world (1). Therefore, it might be important to explore the determinants of the prolonged healthy life expectancy among Japanese. For instance, this longer healthy life expectancy may be, in part, attributed to the Japanese diet, which is high in foods such as fish, green tea, and soybean. In this study, the researchers focused on the relationship between soy isoflavones and disability-free survival.

A questionnaire survey is frequently used to estimate food consumption. However, in Japan, soybean is frequently used as a raw material in seasonings, such as miso paste and soy sauce. Therefore, it might be difficult to estimate the amount of soybean consumed from food frequency questionnaires. Indeed, the researchers previously found that there was a poor correlation between the assessment of soybean consumption by dietary record and food frequency questionnaire (2). Furthermore, studies on equol, a metabolite of daidzein that is produced by intestinal bacteria in some, but not all, adults have shown that those individuals

who possessed equol-producing intestinal bacteria were more likely to benefit from soyfood consumption than those who did not (3,4). Importantly, equol production can only be assessed from blood or urine samples. Therefore, in the present study, the researchers decided to assess serum isoflavone as markers of soy intake.

Isoflavones, including genistein, daidzein, and glycitein, are found in soy and soy products (3,4). Isoflavones are known to have estrogenic effects, and consequently, may possess an ability to lower cholesterol and inhibit bone loss (3,4). Furthermore, emerging evidence suggests that isoflavones may be associated with lower risk of various cancers, including lung (5–7), prostate (8,9), and breast (10). Therefore, isoflavone levels may be associated with a lower risk of incident disability and mortality.

In the present study, the researchers used a nested case–control study design to investigate the relationship between serum isoflavone levels and risk of composite outcome of disability and death; a good indicator of healthy life expectancy.

Methods

Study Participants

As implemented in 2002 and 2003, the Tsurugaya Project was a comprehensive geriatric assessment of medical status, as well as physical and cognitive functions (11–17). The present study is based on data collected in 2002, as blood samples from that time period were available (16,17).

Of the 2,730 inhabitants aged 70 and older living in the Tsurugaya area of Sendai, Japan, 1,177 provided written informed consent to participate in the study. Because the researchers did not obtain agreement to review information regarding long-term care insurance (LTCI) in 2002, they requested agreement from the participants who underwent a comprehensive geriatric assessment in 2003. Of the 1,177 participants who underwent a comprehensive geriatric assessment in 2002, 671 underwent another comprehensive geriatric assessment in 2003, of which 657 agreed to a review of their LTCI information. The researchers excluded data from participants who were identified as having a disability on their LTCI certificate in 2003 ($n = 55$), participants who did not agree to their blood samples being analyzed or stored ($n = 6$), and participants who moved prior to being certified as disabled ($n = 6$). Of the 590 remaining participants, 208 developed a disability or died by June 30, 2009. The eligible participants were divided into eight strata according to sex and age (every 5 years; Table 1). Specifically, a select 178 cases (ie, participants that developed a disability or died) and 178 controls (ie, participants who lived without disability until June 30, 2009) were stratified. Because 14 serum samples (1 control and 13 cases) did not have sufficient serum to measure isoflavone levels (<1 mL of serum), the researchers assessed a total of 342 participants in the present study (Table 1). The Ethics Committee of the Tohoku University Graduate School of Medicine approved the study protocol.

Table 1. Age and Sex Distribution of the Eligible Participants from the Tsurugaya Project (2002–2009)

		Condition in June 2009	
Age in 2002 (y)	Sex	No Disability and Alive	Disabled or Deceased
70–74	Men	35	32
	Women	36	33
75–79	Men	27	25
	Women	50	47
80–84	Men	9	9
	Women	16	15
85–89	Men	1	1
	Women	3	3

Serum Isoflavone Measurements

Blood samples collected under non-fasting conditions were immediately cooled at 4°C, centrifuged within 4 hours at 3,000*g* at 4°C for 10 minutes, and stored at −80°C. Concentrations of serum isoflavones, namely genistein, daidzein, glycitein, and equol, were measured using triple quadrupole tandem liquid chromatography–mass spectrometry (18). These measurements were determined at a clinical testing laboratory (SRL, Tokyo, Japan). Serum albumin, total cholesterol (TC), and casual glucose levels were also measured.

Other Measurements

Information regarding smoking status, drinking status, food intake, physical activity (PA), and history of disease was surveyed via a questionnaire, and drug information was confirmed by an experienced pharmacist. The participants were instructed to fill out a brief self-administered diet history questionnaire that included 75 food items with specified serving sizes described by natural portions or standard weight and volume measures of the servings commonly consumed in the study population. The mean daily intake of nutrients was calculated by using an ad hoc computer program developed to analyze the questionnaire (14). Participants indicated the mean frequency of consumption of green tea over the previous 1 month in terms of the specified serving size by selecting one of the eight frequency categories: almost never, less than 1 cup/wk, 1 cup/wk, 2–3 cups/wk, 4–6 cups/wk, 1 cup/d, 2–3 cups/d, and greater than or equal to 4 cups/d. Subsequently, the researchers summarized this information into three groups as follows: greater than or equal to 4 cups/d, 2–3 cups/d, and less than 2 cups/d (14). In terms of meat consumption, participants indicated the mean frequency of consuming a specified serving size of (1) chicken, (2) pork or beef, (3) ham, sausage, or bacon, and (4) liver over the previous 1 month by selecting one of the frequency categories: 2 times/d, 1 time/d, 4–6 times/wk, 2–3 times/wk, 1 time/wk, less than 1 time/wk, and none. These four frequencies were summed and a total meat consumption

frequency was calculated. According to the distribution, the researchers classified participants into four groups of meat consumers: greater than or equal to 6.5 times/wk, 4.5–6.4 times/wk, 2.5–4.4 times/wk, and less than 2.5 times/wk. PA was first assessed by a self-reported single question on whether the participant had any PA in the past year. If "yes," further questions were asked about the frequency and duration of walking, brisk walking, and sports. Each PA was classified into three categories on the basis of the frequency and duration of participation: (i) "high" PA (≥3–4 times/wk for ≥30 minutes each time), (ii) "low" PA (some PA in the past year, but not enough), and (iii) "none" (no PA). In this study, the researchers used three categories according to the distribution; participants who did any level of sports or high frequency of brisk walking, participants who did low frequency of brisk walking or any level of walking, and participants who did not have PA. Symptoms of depression were assessed via the Japanese version of the 30-item geriatric depression scale (12,14). The anthropometric variables (height and body weight) were recorded according to standard protocol. Body mass index was calculated as weight in kilograms divided by height in meters squared. Functional reach, which measures how far an individual can reach forward beyond their arm's length while standing without losing balance, was measured and used as an indicator of physical function (13). The researchers used average stiffness of the right and left calcaneus as an indicator of bone mineral density. To assess stiffness, the researchers determined quantitative ultrasound parameters, such as the speed of sound (m/s), broadband ultrasound attenuation (dB/MHz), and the stiffness index (Stiffness), which was derived from speed of sound and broadband ultrasound attenuation. These parameters were measured in the right and left calcaneus using an Achilles Ultrasound Bone Densitometer (A-1000, GE-Lunar Corporation, Madison, WI) (19). Participants self-measured blood pressure at home using an automated device (HEM747IC: Omron Life Science Co. Ltd., Tokyo, Japan) (12). Participants were classified into groups based on the following categories: home hypertension, home borderline hypertension, and home normotension, according to the guidelines for home blood pressure (20). Participants prescribed antihypertensive medication were classified into the home hypertension group. The presence of diabetes was defined as a non-fasting blood glucose greater than or equal to 200 mg/dL (11.1 mmol/L) or use of antidiabetic drugs. Impaired blood glucose was classified as non-fasting blood glucose between 140–199 mg/dL (7.7–11.0 mmol/L). Participants were categorized into four TC groups: TC greater than or equal to 240 mg/dL or use of cholesterol lowering drug, TC between 200–239 mg/dL, TC between 160–199 mg/dL, and TC less than 160 mg/dL.

LTCI Certification

The researchers defined incident disability based on the LTCI certification system, which was launched as a national insurance scheme in April 2000 (21–23), and followed up those with certified incident disability until June 30, 2009.

Individuals aged 40–64 years and living in Japan, who were diagnosed with aging-related diseases (eg, Alzheimer's disease and stroke), and those aged 65 and older, who were certified as requiring care, are eligible for benefits under the LTCI certification (24). To receive LTCI services, elderly individuals or their caregivers (family or professional) must contact the municipal government to have their care requirements officially certified (22). A trained local government official visits their home to evaluate nursing care needs via a questionnaire that assesses their current physical and mental status, and use of medical services (21). Standardized scores for physical and mental functioning, as well as the estimated amount of time required for care under nine categories (ie, grooming and/or bathing, eating, using the toilet, transferring, eating, assistance with instrumental activities of daily living, behavioral problems, rehabilitation, and medical services), are then calculated using software. Based on the national average values, it is decided whether applicants should be certified to receive LTCI services, and then, the system assigns a care needs level, which is determined by a certification board comprising physicians, nurses, and other experts in health and social services, who were appointed by the local mayor. The minimum standard for LTCI was care support level 1, which requires 25 minutes of total care/d (21,25).

Care needs are assessed according to seven levels, which closely correlate with the Barthel Index (Spearman's coefficient: −0.86) and the Mini-Mental State Examination (Spearman's coefficient: −0.42) (24,26). The outcome represents a comprehensive measure of disability among elderly individuals (26).

The Sendai City Municipal Authority provided annual information regarding LTCI certification, including the care level, date of certification, relocation, and death, between June 30, 2003 and June 30, 2009. The researchers defined incident disability as the certification of an individual by the LTCI to any level of care, and the date of disability as the first date of certification. Six participants were removed from the study due to relocation during the follow-up. The researchers used a composite outcome of disability and death, which can also be considered as an indicator of disability-free survival.

Statistical Analysis

The researchers classified participants into four groups based on quartiles of isoflavone levels. However, with respect to equol, almost half of participants were nonproducers of equol (ie, equol level < 1.0 ng/mL), and consequently, the researchers used three categories, specifically, the nonproducers, lower half of equol producers (ie, equol level ≥ 1.0 ng/mL), and upper half of equol producers.

The characteristics of cases and controls were compared using the χ^2 test or t test, as appropriate. Characteristics

with respect to isoflavone levels were compared using the χ^2 test for categorical variables or ANOVA for continuous variables, as appropriate. A multiple logistic regression analysis was used to determine factors that predict equol production. This model included the following factors: smoking, alcohol drinking, blood pressure (ie, home hypertension, home borderline hypertension, and home normotension), blood glucose (diabetes, impaired blood glucose, and normal range), TC group, albumin, sex-specific quartile of functional reach, depression (geriatric depression scale ≥ 11), body mass index, sex-specific quartile of stiffness of calcaneus, history of cardiovascular disease, history of cancer, sex-specific quartile of total energy intake, green tea consumption, meat consumption, PA group, and serum daidzein concentration. The researchers also determined the factors that predict higher equol values in equol producers via a linear regression model with log-transformed equol and the above-mentioned factors.

A conditional logistic regression model on the age and sex strata was used to calculate the odds ratios (ORs) and 95% confidence intervals of isoflavones and risk of disability or death. The researchers used both crude and multiple adjusted models. In the multivariate model, the researchers adjusted for the potential confounders associated with isoflavone levels or incident disability or death mentioned above excluding serum daidzein level.

The researchers also calculated the risk of disability only (case = 142) or death only (case = 40). Furthermore, the researchers calculated the relationship of daidzein, genistein, and glycitein with composite outcome of disability and death among equol producers. The level of statistical significance was set at $p < .05$. All statistical analyses were performed using SAS software, version 9.1 (SAS Institute, Cary, NC).

Results

The baseline characteristics of control (ie, those that live without disability) and case (ie, those that developed a disability or died by the end of the follow-up period) groups are presented in Table 2. Due to age and sex matching, there were no differences observed in age and proportion of sex. TC levels, functional reach, stiffness, and PA were statistically lower among cases than controls ($p < .05$).

When the researchers compared the baseline characteristics of the participants according to each isoflavone type and their respective levels, there were no apparent age differences across all isoflavone groups. However, the proportions of women were generally lower in the higher ranges of all isoflavone levels. TC levels were also generally lower in the higher ranges of all serum isoflavone levels. The proportion of bone mineral density was significantly different in the glycitein group, but not in the daidzein, genistein, or equol groups. Although the proportion of women was lower at higher serum equol levels, the proportion of current smokers was also lower at the higher serum equol levels. When a multiple logistic regression analysis was performed to determine the predictors of equol producers, male gender was revealed as a significant predictor of higher equol production. Of all equol producers, men, nonsmokers, and participants with diabetes had higher log-transformed equol values. A higher concentration of daidzein also predicted higher log-transformed equol values ($\beta = 0.003$, $p = .002$).

The relationship between levels of different isoflavones and the composite endpoint of disability or death are presented in Table 3. There were no significant associations between daidzein, genistein, and glycitein with the composite outcome of disability or death after adjusting for age and sex. However, in the equol group, the risk of composite endpoint was lower with higher levels of equol, after control for age and sex (OR = 0.55; 95% confidence interval = 0.33–0.93). These associations remained unchanged when additional potential confounders were added to the model (OR = 0.51; 95% confidence interval = 0.27–0.96). Similarly, the relationship was unchanged when the researchers excluded participants who died without disability. Although participants with the highest isoflavone quartiles consistently showed lower risk of death (OR ≤ 0.46), this observation did not reach statistical significant due to the small number of deaths. The relationships between daidzein, genistein, and glycitein levels with the composite endpoint were also assessed among equol producers only (Table 4). The highest quartiles of the daidzein, genistein, and glycitein groups showed a nonsignificant trend for a lower risk of the composite endpoint (OR ≤ 0.86).

Discussion

The present nested case–control study is the first to show that higher levels of equol are associated with lower risk of disability or mortality. This inverse relation was also observed when the researchers compared participants with disability with controls. However, whether equol per se plays a causal role in increasing healthy life expectancy remains to be determined in future research.

There are several advantages of the present study. First, this study assessed comprehensive geriatric parameters, including physical function and depressive symptoms, which have been previously associated with incident disability or mortality. Second, the researchers used a nested case–control design, in which the measurement precedes the onset of the outcome, thus establishing the temporal relationship between the putative cause and the hypothesized effect. Third, the researchers used LTCI certification to assess disability, which is based on strictly established and uniform rules throughout Japan. This methodology enabled us to achieve higher follow-up rates, and eliminated potential selection bias in both the case and control groups. Nevertheless, this system is not perfect, as

Table 2. Comparison of Baseline Characteristics Between Control and Case Groups, the Tsurugaya Project 2002–2009.

		Condition at June 2009		
		Control	Case	
		Alive without Disability	Disability or Death	*p* Value
Numbers of participants		177	165	
Age	y, mean (*SD*)	75.9 (3.8)	76.5 (4.2)	.14
Sex	Women	59%	59%	
Smoking	Current	10%	13%	
	Past	27%	29%	
	Never	63%	55%	
Drinking	≥46 g of alcohol/d	8%	8%	.15
	23–45.9 g of alcohol/d	8%	3%	
	0–22.9 g of alcohol/d	15%	21%	
	0 g	69%	68%	
Blood pressure	Normotension	19%	16%	.76
	Borderline hypertension	12%	9%	
	Hypertension	65%	70%	
	Home BP not measured	5%	5%	
Blood glucose	Diabetes	7%	8%	.09
	Impaired blood glucose	4%	10%	
	Normoal blood glucose	89%	82%	
Cholesterol	TC ≥ 240 mg/dL or cholesterol lowering drug	34%	26%	.32
	TC 200–239 mg/dL	36%	36%	
	TC 160–199 mg/dL	24%	30%	
	TC < 160 mg/dL	6%	8%	
Albumin	g/dL, mean (*SD*)	4.4 (0.3)	4.3 (0.3)	.32
Functional reach	Could not measure	1%	1%	<.01
	Men 0–28.8 cm, women 0–25.6 cm	15%	35%	
	Men 28.9–32.1 cm, women 25.7–28.6 cm	21%	28%	
	Men 32.2–36.3 cm, women 28.7–32.2 cm	31%	18%	
	Men 36.4 cm–, women 32.3 cm–	33%	19%	
Depression	GDS ≥ 11 point	25%	35%	.0497
Body mass index	kg/m^2 (SD)	23.7 (3.0)	23.6 (3.6)	.76
Stiffness of calcaneus	Men 0%–60.4%, women 0%–49.4%	19%	30%	<.01
	Men 60.5%–71.4%, women 49.5%–56.9%	23%	25%	
	Men 71.5%–81.9%, women 58.5%–65.9%	31%	20%	
	Men 82.0%–, women 66.0%–	28%	25%	
History of CVD	Present	11%	18%	.10
History of cancer	Present	5%	10%	.06
Total energy intake	kcal/d (SD)	1616 (398)	1654 (468)	.41
Green tea consumption	≥4 cups/d	50%	45%	.43
Meat consumption	6.5 times/wk	29%	28%	.71
Physical activity	Sports or higher amount of brisk walking	27%	16%	.02
	Lower amount of brisk walking or any amount of walking	42%	56%	

Notes: CVD = cardiovascular diseases; diabetes = casual blood glucose ≥ 200 mg/dL or taking antidiabetic drugs; GDS = geriatric depression scale; home hypertensive = home systolic BP ≥ 135 mmHg and/or home diastolic BP ≥ 85 mmHg and/or user of antihypertensive medication; home borderline hypertensive = not satisfied with home hypertensive critetria and home systolic BP ≥ 125 mmHg and/or home diastolic BP ≥ 80 mmHg; home normotensive = home systolic BP < 125 mmHg and home diastolic BP < 80 mmHg without antihypertensive medication; impaired blood glucose = casual blood glucose ≥ 140 mg/dL and not taking antidiabetic drugs; *SD* = standard deviation; TC = total cholesterol.

elderly individuals or their caregivers must initiate contact with the municipal government to receive LTCI services, and thus, some elderly individuals with disability may not be certified. However, this confounder would attenuate the relationship between equol levels and the composite outcome of disability and death. Therefore, the researchers' conclusion that higher serum equol was associated with lower risk of composite endpoint of incident disability and death, should remain true. Another limitation of this study was that blood samples were collected in non-fasting conditions, potentially affecting serum isoflavone levels. Similarly, because equol production has been found to vary over time within individuals (27), the misclassification of equol status is a possibility. However, these limitations would only attenuate the relationship between equol levels and the composite outcome of disability and death.

In the present study, half of the participants were classified as equol producers, which corroborate the findings of previous reports from Asia (4,17). In the researchers' attempt to determine the predictors of equol production, they were able to only identify sex. Interestingly, among all equol producers, men, nonsmokers, and participants with diabetes had

Table 3. Serum Isoflavone Levels in the Control and Case Groups from the Tsurugaya Project (2002–2009)

		All Samples				Control vs Disabled			Control vs Death		
		Control	Case	OR1 (95% CI)	OR2 (95% CI)	Control	Case	OR2 (95% CI)	Control	Case	OR2 (95% CI)
Isoflavones	ng/mL	No Disability and Alive	Disabled or Deceased	Age and Sex Only	Multiple Adjusted	No Disability and Alive	Disabled*	Multiple Adjusted	No Disability and Alive	Deceased	Multiple Adjusted
Daidzein	–36	48	38	1	1	48	36	1	48	6	1
	36.1–76.6	43	41	1.21 (0.66–2.21)	1.42 (0.68–2.97)	43	31	1.22 (0.55–2.67)	43	15	9.31 (1.50–57.94)
	76.7–141.0	42	44	1.32 (0.73–2.41)	1.64 (0.77–3.50)	42	35	1.63 (0.73–3.66)	42	16	9.53 (1.28–71.20)
	141.1–	44	42	1.21 (0.66–2.21)	1.52 (0.73–3.19)	44	40	1.56 (0.72–3.36)	44	3	0.24 (0.02–2.95)
Genistein	–63.5	47	39	1	1	47	37	1	47	7	1
	63.6–145.2	41	44	1.30 (0.71–2.38)	1.42 (0.68–2.95)	41	35	1.21 (0.55–2.66)	41	13	4.89 (0.90–26.52)
	145.3–269.1	41	44	1.30 (0.71–2.37)	1.31 (0.63–2.71)	41	33	1.09 (0.50–2.39)	41	15	2.04 (0.43–9.71)
	269.2–	48	38	0.96 (0.52–1.75)	0.99 (0.47–2.07)	48	37	1.05 (0.49–2.28)	48	5	0.37 (0.05–2.49)
Glycitein	–1.9	43	37	1	1	43	31	1	43	10	1
	2.0–4.6	46	43	1.09 (0.60–2.01)	1.06 (0.51–2.22)	46	37	1.09 (0.49–2.43)	46	10	1.26 (0.31–5.08)
	4.7–9.8	46	41	1.04 (0.57–1.91)	1.12 (0.53–2.35)	46	36	1.27 (0.57–2.84)	46	11	0.98 (0.25–3.82)
	9.9–	42	44	1.22 (0.66–2.27)	1.31 (0.62–2.74)	42	38	1.52 (0.68–3.37)	42	9	0.46 (0.10–2.08)
Equol	–0.9	77	84	1	1	77	75	1	77	16	1
	1.0–23.5	43	47	1.00 (0.60–1.68)	1.10 (0.59–2.05)	43	38	1.01 (0.52–1.98)	43	14	1.90 (0.55–6.62)
	23.6–	57	34	0.55 (0.33–0.93)	0.51 (0.27–0.96)	57	29	0.52 (0.27–1.02)	57	10	0.45 (0.12–1.68)

Notes: 95% CI = 95% confidence interval; diabetes = casual blood glucose ≥ 200 mg/dL or taking antidiabetic drugs; OR = odds ratio; OR1 = stratified for age and sex; OR2 = further adjusted for smoking status, drinking status, blood pressure category (home hypertensive, home borderline hypertensive, home normotensive), casual blood glucose (normal glucose, impaired blood glucose, diabetes), total cholesterol (total cholesterol ≥ 240 mg/dL or user of cholesterol lowering drugs, total cholesterol between 200–239 mg/dL, total cholesterol between 160–199 mg/dL, total cholesterol < 160 mg/dL), serum albumin, sex-specific quartile of functional reach, body mass index, depressive symptom (geriatric depression scale ≥ 11 or user of antidepressants), sex-specific quartile of stiffness of calcaneus, history of cardiovascular diseases, history of cancer, and sex-specific quartile of total energy intake, green tea consumption, meat consumption, and physical activity; home hypertensive = home systolic BP ≥ 135 mmHg and/or home diastolic BP ≥ 85 mmHg and/or user of antihypertensive medication; home borderline hypertensive = does not satisfy the home hypertensive critetria, and home systolic BP ≥ 125 mmHg and/or home diastolic BP ≥ 80 mmHg; home normotensive = home systolic BP < 125 mmHg and home diastolic BP < 80 mmHg without antihypertensive medication; impaired blood glucose = casual blood glucose ≥ 140 mg/dL and not taking antidiabetic drugs.

*Participants died without incident disability was not included in this analysis.

Table 4. Comparison of Serum Isoflabove Groups Between Control and Case Group Restricted to the Equol Producer, the Tsurugaya Project, 2002–2009

		Equol Producer Only			
		Control	Case	OR1(95% CI)	OR2 (95% CI)
Isoflavones	ng/mL	Alive without Disability	Disability or Death	Age–Sex Only	Multiple Adjusted
Daidzein	–36	26	20	1	1
	36.1–76.6	24	23	1.20 (0.53–2.73)	2.67 (0.70–10.16)
	76.7–141.0	25	23	1.17 (0.51–2.67)	2.99 (0.78–11.46)
	141.1–	25	15	0.75 (0.31–1.78)	0.95 (0.26–3.47)
Genistein	–63.5	22	16	1	1
	63.6–145.2	26	29	1.47 (0.64–3.35)	2.53 (0.69–9.28)
	145.3–269.1	23	18	1.03 (0.41–2.57)	1.46 (0.33–6.51)
	269.2–	29	18	0.80 (0.34–1.93)	0.87 (0.24–3.18)
Glycitein	–1.9	21	18	1	1
	2.0–4.6	25	21	0.96 (0.41–2.25)	1.66 (0.44–6.28)
	4.7–9.8	28	23	0.95 (0.41–2.21)	1.40 (0.36–5.40)
	9.9–	26	19	0.81 (0.34–1.93)	0.75 (0.20–2.76)

Notes: 95% CI = 95% confidence interval; diabetes = casual blood glucose ≥ 200 mg/dL or taking antidiabetic drugs; OR = odds ratio; OR1 = age–sex category was used as stratified variables; OR2 = further adjusted for smoking status, drinking status, blood pressure category (home hypertensive, home borderline hypertensive, home normotensive), casual blood glucose (normal glucose, impaired blood glucose, diabetes), total cholesterol (total cholesterol ≥ 240 mg/dL or user of cholesterol lowering drugs, total cholesterol between 200–239 mg/dL, total cholesterol between 160–199 mg/dL, total cholesterol < 160 mg/dL), serum albumin, sex-specific quartile of functional reach, body mass index, depressive symptom (geriatric depression scale ≥ 11 or user of antidepressants), sex-specific quartile of stiffness of calcaneus, history of cardiovascular diseases, history of cancer, and sex-specific quartile of total energy intake, green tea consumption, meat consumption, and physical activity; home hypertensive = home systolic BP ≥ 135 mmHg and/or home diastolic BP ≥ 85 mmHg; and/or user of antihypertensive medication; home borderline hypertensive = not satisfied with home hypertensive critetria and home systolic BP ≥ 125 mmHg and/or home diastolic BP ≥ 80 mmHg; home normotensive = home systolic BP < 125 mmHg and home diastolic BP < 80 mmHg without antihypertensive medication; impaired blood glucose = casual blood glucose ≥ 140 mg/dL and not taking antidiabetic drugs.

higher equol values. However, previous studies in both Japan (28) and Europe (29) failed to find a relationship between smoking and equol levels. Additionally, a higher serum daidzein level predicted higher equol levels in equol producers. Therefore, a greater consumption of soy might increase equol level in equol producers. Thus, additional studies assessing the factors that affect equol levels are warranted.

Higher serum equol levels were found to be associated with a lower risk of disability and death. Initially, it was expected that this inverse association could be explained by superior bone mineral density (30). However, the correlation between equol levels and the bone mineral density of the calcaneus was not significant. Furthermore, adjusting for bone mineral density did not alter the risk of the composite endpoint of death and disability. Therefore, other mechanisms may play a role and should be considered. Unfortunately, the researchers' study did not have any information with respect to the causes of disability or mortality, and consequently, they were not able to clarify the factors associated with reducing risk of the composite endpoint in the higher equol group than the other groups. There are, may be, several explanations for why equol was associated with disability and death. First, as mentioned in previous studies, the benefits of soybean consumption are greater in equol producers (4). Equol is known to have a stronger affinity for the estrogen receptor than any other isoflavone. Although statistical significance was not reached, the other isoflavones were also inversely associated with disability and death. Thus, this observation supports the above hypothesis. Also, it remains possible that rather than contributing to a better health outcome per se, equol may enhance bacterial activity or improve intestinal conditions, which in turn, contribute to better health. However, the researchers were not able to confirm this scenario in their study. Thus, to clarify whether equol per se decreases the risk of disability or mortality, future intervention studies on soybean intake among equol producers are warranted.

In conclusion, it was found that higher serum equol concentrations, and no other isoflavone, are independently associated with a lower risk of the composite endpoint of disability and death. However, whether equol per se has a direct causal effect on disability or mortality remains to be elucidated. Further studies, including randomized controlled trials, which clarify the role of equol in overall health, are warranted.

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AUTHOR CONTRIBUTIONS

Study concept and design (A.H., K.O.-M., S.K., IT).

Acquisition of subjects and/or data (A.H., Y.S., Y.T., M.K,. T.T., K.O.-M., N.N., S.K., I.T.).

Analysis and interpretation of data (A.H., Y.S., Y.T., M.K., T.T., K.O.-M., N.N., S.K., I.T.).

Preparation of manuscript (A.H., A.F.).

Conflicts of Interest

There are no potential conflicts of interest that relate to the manuscript.

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自覚ストレスと循環器疾患死亡との関連

大崎国保コホート研究

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目的　これまでに，心理的ストレスは循環器系へ影響することが示唆されてきたが，自覚ストレスと循環器疾患死亡との関連についての前向きコホート研究では，結果が一致していなかった。本研究では，飲酒状況および喫煙状況について層別化し，結果について検証する。

方法　1994年，宮城県大崎保健所管内に居住する，40歳から79歳までの国民健康保険（国保）加入者全員（54,996人）へ自記式質問票を配布した。このうち，追跡開始までに国保から異動した者，がん・心筋梗塞・脳卒中の既往者，自覚ストレスに関する質問に無回答であった者を除外した，45,293人（男性21,552人，女性23,741人）を対象とした。1995年から12年間追跡したところ，循環器疾患死亡は1,751人，うち男性994人，女性757人で確認された。Cox比例ハザードモデルを用いて，自覚ストレスが少ない群を基準とした，他の群の循環器疾患死亡のリスクのハザード比と95%信頼区間（95%CI）を算出した。

結果　自覚ストレスと循環器疾患死亡との関連について，男性では，自覚ストレスが多い群では少ない群に対し，多変量補正ハザード比（95%CI, P for trend）は，1.43（1.19–1.87, $P=0.006$）であり，有意な正の関連が観察されたが，女性では関連は観察されなかった。次に，喫煙状況および飲酒状況について層別化解析を行ったところ，男性では，多変量補正ハザード比（95% CI, P for trend）は，現在喫煙者では1.76（1.28–2.41, $P=0.001$），現在飲酒者では1.56（1.16–2.09, $P=0.006$），女性でも，各々，1.61（1.20–2.16, $P=0.004$），1.42（1.08–1.87, $P=0.001$）であり，男女とも有意な正の関連が認められた。さらに，男性では現在喫煙者であり，現在飲酒者である場合，多変量補正ハザード比は，自覚ストレスの多い群では，少ない群と比較してほぼ2倍上昇し，より顕著な正の関連が認められ，有意であった（P for trend <0.001）。しかし，有意な交互作用が認められたのは，男性の喫煙習慣についてのみであった（P for interaction $=0.04$）。

結論　現在喫煙者および現在飲酒者では，男女とも有意な正の関連が認められたことから，自覚ストレスと循環器疾患死亡との関連についての男女差は，現在喫煙者および現在飲酒者の割合の男女差により説明される可能性がある。本研究の結果は，ストレス解消の手段としての喫煙習慣や飲酒習慣の見直し，あるいはストレスマネジメントや喫煙，飲酒に対する支援の強化を意味するものと考えられる。

Key words：自覚ストレス，循環器疾患，死亡率，コホート研究，喫煙，飲酒

I　緒　　言

循環器疾患は世界各国で死因の上位を占めている[1]。我が国においても，約4人に1人（27.0%）が循環器疾患で死亡しており，悪性新生物に続く，死因の第2位を占めている[2]。

循環器疾患のリスクファクターとして，喫煙，高血圧，高コレステロール血症，糖尿病など様々なものが知られている[3]。

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2000年から開始された「21世紀における国民健康づくり運動」（健康日本21）では，生活習慣および生活習慣病として大きな課題となっているものについて，9つの分野が挙げられていた。循環器疾患のリスクファクターについては，このうちの「たばこ」，「糖尿病」，「循環器病」の3つの分野として挙げられており，具体的目標が定められ，対策がとられている。この中では，ストレスについても「休養・こころの健康づくり」として挙げられている[4]。厚生労働省の「国民生活基礎調査」によれば，「性・年齢別悩み・ストレスのある者の割合」は，2000年以降，25歳以上45歳未満および45歳以上65歳未満で，男性で約5割，女性で約6割と高値を維持している[5~9]。

人体は心理的ストレスが負荷されると，その反応として，視床下部下垂体副腎系や交感神経系が活性化される。前者では，コルチゾールの上昇[10]により，内臓肥満，血管収縮作用による血圧上昇，インスリン感受性低下，血清コレステロール値の上昇および血清トリグリセリド値の上昇が起こる[11]ことが明らかになっている。また，後者では，心拍数の上昇，血管内皮・壊死による機能障害，心筋の電気的安定性の低下，血小板活性の低下，血管収縮による血圧上昇および血漿量減少が起こるため，心筋梗塞の発症や不整脈の誘発，不安定プラーク形成の促進，血栓形成に繋がる[12]ことがこれまでに報告されてきた。これらの結果，循環器疾患の発症や死亡へつながるのではないかと推測されている。

自覚ストレスと循環器疾患死亡の関連について，前向きコホート研究で自覚ストレスについて「多い，ふつう，少ない」のカテゴリーによる分布で，検討したものは，これまでに3件報告されている[13~15]が，結果は一致していない。最近のNielsenらの研究では，男女とも自覚ストレスと循環器疾患死亡との関連について有意な関連は認められなかったが，虚血性心疾患に限定して解析を行ったところ，若年の男性で正の関連が認められたと報告されている[13]。

また，平成19年の国民健康・栄養調査では，ストレス対処法として，男性では女性に比べて「飲酒」，「喫煙」を挙げた者が多かった[16]。こういった一時的なストレス解消の手段として用いられている，生活習慣について層別化し，検討した研究はこれまでに行われていなかった。

もし，飲酒状況や喫煙状況をふまえて，自覚ストレスと循環器疾患死亡との間に関連があることが解明できれば，個人や集団へ保健指導等を通じて，ストレスマネジメントへの支援を強化することで，循環器疾患死亡のリスクの減少に貢献することが期待できる可能性がある。

そこで，本研究の目的は，飲酒状況や喫煙状況で層別化し，自覚ストレスと循環器疾患死亡との関連について検証することとした。

Ⅱ　研究方法

1.　対象者

本研究は，大崎国民健康保険加入者コホート研究（大崎国保コホート研究）に基づいたものである。大崎国保コホート研究の詳細については以前に報告されているので，ここではその概略について簡単に述べる[17~22]。

1994年10月から12月に，宮城県大崎保健所管内に居住する，40歳から79歳までの国民健康保険（国保）加入者全員（54,996人）へ生活習慣に関する自記式質問票を配布し，52,029人（94.6%）から有効回答を得た。1995年1月1日，宮城県国民健康保険団体連合会から提供された，国保における喪失異動データにより，死亡と転出に関する追跡を開始した。このうち，追跡開始まで国保から異動した者776人を除外し，対象者は51,253人となった。さらに，本研究の分析では，ストレスに関する質問に回答していなかった者1,812人，がん，心筋梗塞，脳卒中の既往を持つ者（1,767人，1,384人，997人）を除外し，最終的に，45,293人（男性21,552人，女性23,741人）を解析対象者とした。

2.　調査項目

本研究で用いた調査項目は，身長，体重，ストレス状況，喫煙状況，飲酒状況，歩行時間，睡眠時間，婚姻状況，学歴，職業，高血圧の既往，糖尿病の既往である。得られた体重および身長から，体重（kg）を身長（m^2）で除し，Body mass index（BMI）を計算した。

自覚ストレスに関する質問は，「日常ストレスが多いと思われますか。」について，「1. 多い，2. ふつう，3. 少ない」を回答の選択肢とした。本研究の分析では，これらをカテゴリーとして用いた。

したがって，本研究で用いたストレスとは，ストレスとして自覚されたものを指すものとした。これを自覚ストレスと定義することとする。ただし，自覚ストレスの妥当性および信頼性についての情報はなかった。

3.　追跡調査

本研究のエンドポイントは，循環器疾患死亡，脳血管疾患死亡，心疾患死亡とした。国保における喪失異動データの閲覧により，対象者の死亡と転出を追跡した。国保から異動した対象者については，そ

の後の情報を得ることができなかったため，追跡を中止した。死因については，大崎保健所に保管された人口動態調査調査票（死亡小票）を閲覧し，確認した。死因は，訓練を受けた医師が国際疾病分類第10版（International Classification of Disease, 10th Revision）に基づきコード化した[23]。コードは，循環器疾患はI00-I99，脳血管疾患はI60-I69，心疾患はI20-I52を用いた。

12年の追跡期間中に，1,751人（男性994人，女性757人）の循環器疾患死亡を確認した。このうち，脳血管疾患死亡は男性で448人，女性で360人であり，心疾患死亡は男性で467人，女性で370人であった。

4. 統計解析

1995年1月1日から2006年12月31日までの12年間にわたって，追跡開始日から，死亡，国保からの異動，追跡終了日のいずれかが最初に生じるまで追跡した。

Cox比例ハザードモデルを用いて，ストレスが少ない群を基準とした，他の2群(多い群，ふつう群)の循環器疾患死亡リスクのハザード比と95%信頼区間を算出した。算出にあたり，年齢補正したモデルに加え，多変量補正したモデルも構築した。全ての解析は男女別に実施した。ハザード比の比例性について，カプラン・マイヤー曲線を描いて確認した。また，本研究では，喫煙状況および飲酒状況について層別化解析も実施した。同時に，非喫煙者および過去喫煙者に対する現在喫煙者，非飲酒者に対する過去飲酒者および現在飲酒者について交互作用の有無を検討した。補正項目として，年齢（40-45歳未満，45-50歳未満，50-55歳未満，55-60歳未満，60-65歳未満，65-70歳未満，70-75歳未満，75歳以上），BMI　（18.5 kg/m^{2}未満，18.5-25.0 kg/m^2，25.0 kg/m^{2}以上），喫煙状況（非喫煙，過去喫煙，現在喫煙，1-19本/日，20本/日以上），飲酒状況（非飲酒，過去飲酒，現在飲酒，アルコール摂取22.8 g未満/日，アルコール摂取22.8 g-45.6 g未満/日，アルコール摂取45.6 g以上/日），歩行時間（1時間以上/日，30分-1時間未満/日，30分未満/日），睡眠時間（6時間以下/日，7-8時間/日，9時間以上/日），婚姻状況（既婚，離別/死別，未婚），学歴(中卒，高卒，短大/大卒)，職業の有無(あり，なし)，高血圧の既往（あり，なし），糖尿病の既往（あり，なし）を考慮した。

統計解析にはSAS Version9.1（SAS Inc, Cary, NC, USA)を使用した[24]。P値は両側検定を行い，統計学的有意水準は$P<0.05$とした。

5. 倫理的配慮

本研究は，東北大学医学部・医学系研究科倫理委員会の承認を得ている。

Ⅲ 結　　果

1. 自覚ストレス別にみた対象者の基本特性

自覚ストレス別にみた対象者の基本特性を男女別に表1に示した。

男女とも自覚ストレスの多い群では，他の群に比べて，若年であり，睡眠時間が短く，就業中であり，喫煙率が高い傾向にあった。一方，男女とも，どの群においても，高血圧の既往を持つ者の割合および糖尿病の既往を持つ者の割合に差はみられなかった。

2. 自覚ストレスと循環器疾患死亡，脳血管疾患死亡，心疾患死亡リスクとの関連

表2は，自覚ストレスと循環器疾患死亡，脳血管疾患死亡，心疾患死亡の年齢補正ハザード比および多変量補正ハザード比と95%信頼区間を男女別に示したものである。

男性では，自覚ストレスの多い群は自覚ストレスの少ない群を基準とした場合，年齢補正ハザード比（95%信頼区間）は1.49（1.19-1.87）であり，循環器疾患死亡のリスクは有意に上昇した（P for trend $=0.002$)。多変量補正モデルにおいても，ハザード比（95%信頼区間）は，1.43（1.13-1.79）であり，この結果は大きく変わらなかった（P for trend $=0.006$)。よって，男性では，自覚ストレスと循環器疾患死亡に有意な正の関連が示された。また，循環器疾患死亡について，脳血管疾患死亡と心疾患死亡に分けると，自覚ストレスの多い群は自覚ストレスの少ない群を基準とした場合，心疾患死亡では，年齢補正ハザード比（95%信頼区間）は1.56（1.12-2.18）であり，有意に上昇した（P for trend $=0.01$)。脳血管疾患死亡の年齢補正ハザード比（95%信頼区間）は1.30（0.93-1.82）とリスクはわずかに上昇したが，有意ではなかった（P for trend $=0.22$)。また，多変量補正モデルにおいても，心疾患ではハザード比（95%信頼区間）1.48（1.06-2.08），脳血管疾患ではハザード比（95%信頼区間）1.24（0.88-1.75）であり，この結果は大きく変わらなかった（P for trend $=0.024$, P for trend $=0.34$)。よって，循環器疾患死亡について，脳血管疾患と心疾患死亡に分けた場合，心疾患死亡では有意な正の関連が示されたが，脳血管疾患死亡では正の関連は弱くなった。一方，女性では，循環器疾患死亡，脳血管疾患死亡，心疾患死亡のいずれも自覚ストレスとの関連は示されなかった。

表1　自覚ストレス別にみた対象者の基本特性

	男性			女性		
自覚ストレス	少ない	ふつう	多い	少ない	ふつう	多い
対象者数	4,024	14,534	2,994	3,963	15,659	4,119
平均年齢（歳）	61.4	59.2	54.6	62.7	60.9	57.2
BMI（kg/m²）	23.4	23.3	23.4	23.9	23.8	23.7
喫煙状況						
非喫煙（%）	20	19	18	89	90	86
過去喫煙（%）	26	25	24	3	2	3
喫煙20本未満/日（%）	23	23	18	6	6	7
喫煙20本以上/日（%）	31	33	41	2	2	4
飲酒状況						
非飲酒（%）	18	16	13	60	59	58
過去飲酒（%）	10	10	10	4	3	4
アルコール摂取22.8 g 未満/日（%）	22	22	22	15	13	18
アルコール摂取22.8 g 以上/日（%）	45	46	51	3	3	4
歩行時間						
1時間以上/日（%）	19	67	14	17	65	18
30分-1時間未満/日（%）	18	70	12	17	67	16
30分未満/日（%）	18	66	17	17	64	19
睡眠時間						
6時間以下/日（%）	10	11	18	16	18	28
7-8時間/日（%）	67	70	66	66	67	61
9時間以上/日（%）	23	19	16	18	15	10
婚姻状況						
既婚（%）	89	89	88	69	76	79
離婚（離別/死別）（%）	7	6	6	27	20	18
未婚（%）	4	4	6	4	3	3
学歴						
高卒（%）	30	30	38	34	33	40
短大/大卒以上（%）	8	7	10	9	7	11
勤務状況						
就業中（%）	76	81	89	41	46	54
既往歴						
高血圧（%）	23	24	22	28	28	27
糖尿病（%）	7	7	9	5	5	5

3. 喫煙状況および飲酒状況で層別化した自覚ストレスと循環器疾患死亡との関連

表3は，自覚ストレスと循環器疾患死亡の多変量補正ハザード比と95%信頼区間について，喫煙状況および飲酒状況による層別化解析の結果を男女別に示したものである。喫煙状況について，男女とも，現在喫煙者では，循環器疾患死亡のリスクは自覚ストレスの少ない群を基準とした場合，自覚ストレスの多い群，ふつう群では，有意な正の関連が示された。（男性：P for trend＝0.001，女性：P for trend＝0.004）しかし，非喫煙者および過去喫煙者では有意な正の関連は示されなかった。そこで，自覚ストレスと喫煙状況についての交互作用を確認するため，非喫煙者および過去喫煙者に対する現在喫煙者について交互作用を検討したところ，男性では統計学的に有意であったが（P for interaction＝0.04），女性では有意ではなかった。

また，飲酒状況について，現在飲酒者では，循環器疾患死亡のリスクは自覚ストレスの少ない群を基準とした場合，男女とも，自覚ストレスの多い群，ふつう群では，有意な正の関連が示された（P for trend＝0.006, P for trend＝0.001）。しかし，非飲酒者および過去喫煙者では有意な正の関連は示されなかった。そこで，自覚ストレスと飲酒状況について