Association of Sleep Duration with Mortality from Cardiovascular Disease and Other Causes for Japanese Men and Women: the JACC Study

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Study Objectives: To examine sex-specific associations between sleep duration and mortality from cardiovascular disease and other causes.
Design: Cohort study.
Setting: Community-based study.
Participants: A total of 98,634 subjects (41,489 men and 57,145 women) aged 40 to 79 years from 1988 to 1990 and were followed until 2003.
Interventions: N/A.
Measurements and Results: During a median follow-up of 14.3 years, there were 1964 deaths (men and women: 1038 and 926) from stroke, 881 (508 and 373) from coronary heart disease, 4287 (2297 and 1990) from cardiovascular disease, 5465 (3432 and 2033) from cancer, and 14,540 (8548 and 5992) from all causes. Compared with a sleep duration of 7 hours, sleep duration of 4 hours or less was associated with increased mortality from coronary heart disease for women and noncardiovascular disease/noncancer and all causes in both sexes. The respective multivariable hazard ratios were 2.32 (1.19-4.50) for coronary heart disease in women, 1.49 (1.02-2.18) and 1.47 (1.01-2.15) for noncardiovascular disease/noncancer, and 1.29 (1.02-1.64) and 1.28 (1.03-1.60) for all causes in men and women, respectively. Long sleep duration of 10 hours or longer was associated with 1.5- to 2-fold increased mortality from total and ischemic stroke, total cardiovascular disease, noncardiovascular disease/noncancer, and all causes for men and women, compared with 7 hours of sleep in both sexes. There was no association between sleep duration and cancer mortality in either sex.
Conclusions: Both short and long sleep duration were associated with increased mortality from cardiovascular disease, noncardiovascular disease/noncancer, and all causes for both sexes, yielding a U-shaped relationship with total mortality with a nadir at 7 hours of sleep.
Keywords: Sleep duration, coronary heart disease, mortality, prospective study
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PREVIOUS COHORT STUDIES HAVE DEMONSTRATED THAT SHORT OR LONG SLEEP DURATION IS ASSOCIATED WITH THE INCIDENCE OF OR MORTALITY FROM cardiovascular disease,[1-4] as well as total mortality.[1,3-6] The National Health and Nutrition Examination Survey I showed a 1.5-fold increase in the risk of stroke for persons with more than 8 hours of sleep, compared with those with 6 to 8 hours of sleep.[1] The Nurse's Health Study also reported that, compared with 8 hours of sleep, short or long sleep duration of 5 or more hours or 9 or more hours was associated with an increased incidence of coronary heart disease for women aged 40 to 65 years,[2] and, compared with 7 hours of sleep, long sleep duration of 9 or more hours was associated with mortality from cardiovascular disease, noncardiovascular disease/noncancer, and all causes, whereas short sleep duration of 5 hours or less was associated with mortality from all causes and noncardiovascular disease for women aged 40 to 65 years.[3] The Whitehall II cohort study found a U-shaped association between sleep duration and mortality from cardiovascular disease and noncardiovascular disease and between sleep duration and all causes for men and women aged 35 to 55 years.[4] An earlier report of our Japanese cohort study[5] also showed a U-shaped relationship between sleep duration and total mortality, but cause-specific analyses were not carried out. Thus, the association between short or long sleep duration and mortality from cardiovascular disease and other causes for Japanese men and women has remained unclear.

To examine the sex-specific associations of sleep duration and mortality from stroke, coronary heart disease, and other causes, as well as total mortality, we analyzed the extended follow-up data from a large-scale prospective study of approximately 98,000 Japanese men and women.

METHODS

Study Population

The Japan Collaborative Cohort Study for Evaluation of Cancer Risk sponsored by Monbusho (JACC study) was conducted from 1988 to 1990, when 110,792 subjects (46,465 men and 64,327 women) aged 40 to 79 years and living in 45 communities across Japan participated in municipal health-screening examinations and completed self-administered questionnaires, including lifestyle data and medical histories of previous cardio-

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vascular disease and cancer at baseline. The details of the study procedure have been described previously.[7] In most communities, informed consent was obtained individually and directly from members of the cohort, whereas, in several communities, informed consent was obtained at the community level after the purpose of the study and confidentiality of the data had been explained to community leaders and mayors. Of the 110,792 cohort participants, data from 6782 (2613 men and 4169 women) were excluded because of missing information on sleep duration, as were data from 5376 subjects (2363 men and 3013 women) who reported a history of cancer, stroke, or coronary heart disease. Finally, a total of 41,489 men and 57,145 women were included in the study.

Mortality Surveillance

For mortality surveillance in each of the communities, investigators conducted a systematic review of death certificates, all of which had been forwarded to the public health center in the area of residency. Mortality data were then centralized at the Ministry of Health and Welfare, and the underlying causes of death were coded for the National Vital Statistics according to the *International Classification of Diseases*, 10th revision (ICD-10). Therefore, all deaths that occurred in the cohort were ascertained by death certificates from a public health center, except for subjects who died after they had moved from their original community, in which case the subject was treated as withdrawals from observation when they moved out. Cause-specific mortality was determined separately in terms of cancer (C00-C97), total cardiovascular disease (I01-I99), coronary heart disease (I20-I25), and total stroke (I60-I69); noncardiovascular disease/noncancer was listed as the cause of death when cardiovascular disease and cancer were excluded. Stroke deaths were further subdivided into intraparenchymal hemorrhage (I61), subarachnoid hemorrhage (I60), and ischemic stroke (I63 and I693). The follow-up is believed to be complete and accurate as a result of systematic examination of death certificates and residency status. By December 31, 2003, except for 4 communities in which follow-up was terminated at the end of 1999, 14,540 subjects were treated as withdrawals from observation when they died, and 4188 subjects were treated as withdrawals from observation when they moved out of the study community. The median follow-up period for the participants was 14.3 years. This study was approved by the ethics committees of the Nagoya University School of Medicine and the University of Tsukuba.

Baseline Survey

The baseline data were collected by means of a self-administered questionnaire, which included sleep duration; demographic characteristics; and histories of hypertension, diabetes mellitus, and other chronic diseases, as well as habits related to smoking, alcohol consumption, diet, and exercise. We obtained information about the average sleep duration on weekdays during the preceding year. The average sleep duration per day was classified into 7 categories: less than 4.5 hours (≤ 4 hours); 5, 6, 7, 8, and 9 hours; and equal to or longer than 9.5 hours (≥ 10 hours). Fractions hours were rounded off (eg, 7 hours represented responses from 6.5 to 7.4 hours). Depressive symptom was assessed by using 4 psychological or behavior items[5]: (1) Do you think that your life is meaningful? (2) Do you think that you make decisions quickly? (3) Are you enjoying your life? (4) Do you feel that others rely very much on you? These 4 items were then combined into an overall index of depressive symptoms. Questions with positive/neutral or negative responses were scored as 0 or 1, respectively. Thus, the overall index of depressive symptoms had a possible range from 0 to 4 (Cronbach α coefficient of 0.52), and subjects were grouped according to whether they had no symptoms, 1 symptom, or 2 or more symptoms. The reproducibility and validity for dietary intake have been reported elsewhere.[8]

Statistical Analysis

Statistical analyses were based on sex-specific mortality rates of disease outcomes and all cause during the follow-up period from 1988-1990 to 2003 (to 1999 for 4 communities). The person-years of follow-up were calculated from the date of filling out the baseline questionnaire to death, moving out of the community, or the end of follow-up, whichever came first. Sex-specific age-adjusted mean values and prevalence of cardiovascular risk factors were calculated. The sex-specific hazard ratios with 95% confidence interval (CI) of mortality from disease outcomes and all causes were calculated with reference to the risk for 7 hours of sleep. These estimates were adjusted for age and other potential confounding factors by means of the Cox proportional hazards model. The other potential confounding factors were history of hypertension, history of diabetes, body mass index (sex-specific quintiles), smoking status (never, exsmoker, current smoker of 1-19, and current smoker of ≥ 20 cigarettes per day), alcohol consumption (nondrinker, exdrinker, current drinker of 0.1-22.9, 23.0-45.9, 46.0-68.9, and ≥ 69.0 g ethanol per day), hours of exercise (almost never and 1-2, 3-4, and ≥ 5 hours per week), hours of walking (almost never and 0.5, 0.6-0.9, and ≥ 1 hours per day), perceived mental stress (low, moderate, and high), depressive symptoms (0, 1, and ≥ 2 symptoms), education level (< 13, 13-15, 16-18, and ≥ 19 years), regular employment or not, fresh fish intake (almost never, 1 to 2 days a month, 1 to 2 days a week, 3 to 4 days a week, and almost every day). SAS (SAS, Inc., Cary, NC)(version 9.13) was used for all statistical analyses.

RESULTS

After a follow-up of 1,270,585 person-years, the deaths of 1964 (men and women: 1038 and 926) from stroke, 881 (508 and 373) from coronary heart disease, 4287 (2297 and 1990) from total cardiovascular disease, 5465 (3432 and 2033) from cancer, and 14,540 (8548 and 5992) from all causes had been documented.

Table 1 shows sex-specific age-adjusted mean values or prevalence of risk characteristics at baseline by sleep-duration category. The respective percentages of ≤ 4, 5, 6, 7, 8, 9, and ≥ 10 hours of sleep were 1%, 3%, 13%, 32%, 39%, 8%, and 4%, respectively, for men and 1%, 5%, 20%, 38%, 29%, 5%, and 2%, respectively, for women. Compared with 7 hours of sleep, short or long sleep duration tended to be associated with older age and more depressive symptoms for both men and women.

Table1—Sex-Specific, Age-Adjusted Mean Values or Prevalence of Cardiovascular Risk Factors at Baseline by Sleep Duration

	Sleep duration, h/day						
	≤ 4	5	6	7	8	9	≥ 10
Men							
No. at risk	215	1142	5513	13423	16042	3491	1663
Age, y	60.1	58.6	56.1	55.1	57.3	60.2	64.4
BMI, kg/m^2	22.3	22.7	22.9	22.6	22.6	22.4	22.5
Overweight	18.9	21.9	22.0	17.8	17.5	17.2	18.6
History of hypertension	27.0	24.8	20.4	19.4	19.9	21.5	22.9
History of diabetes	13.4	7.8	7.5	6.5	6.3	6.1	7.1
Ethanol intake, g/day	41.9	36.7	33.4	32.1	34.9	37.4	40.1
Current smoker	47.3	45.8	50.3	53.5	55.5	56.8	58.7
College or higher education	12.1	17.5	20.1	19.8	16.2	12.4	11.1
High perceived mental stress	37.9	37.7	31.4	23.6	19.3	20.3	20.8
2 or more depressive symptoms	14.5	9.2	6.1	4.5	5.2	7.3	10.0
Exercise ≥ 5 h/wk	9.5	7.5	6.8	6.7	7.2	8.8	7.8
Walking ≥ 1 h/day	42.4	45.8	46.5	49.3	51.3	53.0	51.3
Regular employment	60.7	73.1	76.7	77.8	76.6	72.9	68.8
Fresh fish intake, no./wk	6.4	6.8	6.7	6.8	7.1	7.1	7.4
Women							
No. at risk	430	2699	11668	21501	16643	2935	1269
Age, y	62.8	58.5	55.6	55.4	59.0	63.0	67.5
BMI, kg/m^2	22.8	22.8	22.9	22.8	23.0	23.1	23.2
Overweight	21.0	23.1	22.4	21.5	23.6	25.2	26.7
History of hypertension	22.9	23.6	22.1	22.2	22.8	22.0	23.9
History of diabetes	2.8	5.0	3.9	3.5	3.9	4.0	4.4
Ethanol intake, g/day	12.9	13.0	10.1	9.5	11.1	12.2	13.4
Current smoker	7.8	8.5	5.7	4.7	5.3	4.9	7.9
College or higher education	9.7	11.4	11.5	10.4	9.0	7.0	7.1
High perceived mental stress	36.8	30.7	24.6	19.2	16.7	16.6	19.4
2 or more depressive symptoms	17.1	10.1	7.4	7.0	7.8	10.6	19.1
Exercise ≥ 5 h/wk	4.3	5.2	4.4	4.3	5.1	4.4	4.3
Walking ≥ 1 h/day	50.4	49.7	51.7	51.9	52.0	53.0	44.6
Regular employment	32.5	33.7	34.8	34.1	31.6	29.4	31.1
Fresh fish intake, no./wk	6.0	6.7	6.9	7.1	7.3	7.2	7.2

Data are presented as percentage, except age, body mass index (BMI), ethanol intake, and fresh fish intake, which are presented as mean.

Men and women with short sleep duration were more likely to have high perceived mental stress, whereas those with long sleep duration were less educated.

Tables 2 show sex-specific, age-adjusted, and multivariable hazard ratios of total stroke, stroke subtypes, coronary heart disease, total cardiovascular disease, cancer, noncardiovascular disease/noncancer, and all causes by sleep duration. Increased risks of age-adjusted mortality from total and ischemic strokes and total cardiovascular disease, cancer, noncardiovascular disease/noncancer, and all causes were observed among men and women with 10 or more hours of sleep, compared with those with 7 hours of sleep. These associations, except for mortality from cancer, were slightly weaker but remained statistically significant after adjustment for cardiovascular risk factors and depressive symptoms. The respective multivariable hazard ratios (95% CI) of mortality from total and ischemic strokes, total cardiovascular disease, noncardiovascular disease/noncancer, and all causes for long sleepers were 1.66 (1.31-2.08), 1.58 (1.19-2.12), 1.56 (1.33-1.83), 1.66 (1.44-1.91), and 1.41 (1.29-1.54), respectively, for men, and 1.69 (1.29-2.20), 2.37 (1.70-3.32), 1.54 (1.28-1.86), 1.99 (1.65-2.39), and 1.56 (1.40-1.75), respectively, for women.

There was an increased risk of mortality from coronary heart disease for women with 4 or fewer hours and 5 hours of sleep, compared with those with 7 hours of sleep. The respective multivariable hazard ratios (95% CI) for those with 4 or fewer hours and 5 hours of sleep were 2.32 (1.19-4.50) and 1.64 (1.07-2.53). Short sleep of 4 or fewer hours for men tended to be associated with an increased risk of mortality from hemorrhagic stroke, although this association did not reach statistical significance (hazard ratio = 2.15, 95% CI: 0.78-5.89, P = 0.14). When stratified by alcohol-consumption status, the multivariable hazard ratios of mortality from hemorrhagic stroke for male short sleepers (≤ 4 and 5 hours of sleep) were 2.03 (1.01-4.08) for current drinkers and 1.33 (0.38-4.66) for exdrinkers or never drinkers. After further adjustment for individual quantity of alcohol consumption as a continuous variable, the multivariable hazard ratio for male short sleepers was 1.92 (95% CI: 0.96-3.86, P = 0.07). Also, short sleep duration or 4 or fewer hours was associated with increased risk of mortality from noncardiovascular disease/noncancer for both men and women; the multivariable hazard ratios were 1.49 (1.02-2.18) for men and 1.47 (1.01-2.15) for women.

Table 2—Sex-Specific Hazard Ratios and 95% Confidence Intervals for Mortality from Cardiovascular Disease and Other Causes by Sleep Duration

	Sleep duration (h/day)						
	≤ 4	5	6	7	8	9	≥ 10
Men							
Person-years	**2501**	**14176**	**69125**	**173026**	**204761**	**43152**	**18724**
Total stroke							
No.	10	28	105	244	413	126	112
Age-adjusted HR (95%CI)	1.62 (0.86-3.06)	0.95 (0.64-1.40)	0.96 (0.76-1.21)	1.00	1.15 (0.98-1.35)	1.25 (1.00-1.55)	1.90 (1.51-2.38)
Multivariable HR (95%CI)	1.56 (0.82-2.94)	0.85 (0.58-1.26)	0.95 (0.76-1.20)	1.00	1.11 (0.95-1.30)	1.14 (0.92-1.42)	1.66 (1.31-2.08)
Hemorrhagic stroke							
No.	4	11	40	82	145	31	26
Age-adjusted HR (95%CI)	2.45 (0.90-6.70)	1.29 (0.69-2.43)	1.14 (0.78-1.67)	1.00	1.30 (0.99-1.71)	1.10 (0.73-1.67)	1.73 (1.10-2.70)
Multivariable HR (95%CI)	2.15 (0.78-5.89)	1.20 (0.64-2.26)	1.13 (0.77-1.65)	1.00	1.27 (0.97-1.66)	1.01 (0.66-1.53)	1.56 (0.99-2.45)
Ischemic stroke							
No.	5	15	50	143	235	85	74
Age-adjusted HR (95%CI)	1.18 (0.48-2.87)	0.78 (0.46-1.34)	0.75 (0.55-1.04)	1.00	1.07 (0.87-1.31)	1.29 (0.98-1.69)	1.84 (1.39-2.45)
Multivariable HR (95%CI)	1.28 (0.52-3.15)	0.70 (0.41-1.20)	0.76 (0.55-1.04)	1.00	1.02 (0.83-1.26)	1.18 (0.90-1.55)	1.58 (1.19-2.12)
Coronary heart disease							
No.	1	17	53	140	206	54	37
Age-adjusted HR (95%CI)	0.31 (0.04-2.18)	1.05 (0.64-1.75)	0.86 (0.63-1.18)	1.00	1.02 (0.83-1.27)	0.99 (0.72-1.35)	1.19 (0.82-1.72)
Multivariable HR (95%CI)	0.29 (0.04-2.05)	1.02 (0.62-1.70)	0.86 (0.63-1.19)	1.00	1.02 (0.82-1.27)	0.96 (0.70-1.31)	1.12 (0.77-1.63)
Total cardiovascular disease							
No.	16	70	248	548	913	274	228
Age-adjusted HR (95%CI)	1.17 (0.71-1.92)	1.06 (0.83-1.36)	1.01 (0.87-1.18)	1.00	1.14 (1.02-1.26)	1.22 (1.05-1.41)	1.74 (1.48-2.03)
Multivariable HR (95%CI)	1.11 (0.67-1.83)	0.99 (0.77-1.27)	1.01 (0.87-1.18)	1.00	1.11 (1.00-1.24)	1.14 (0.99-1.32)	1.56 (1.33-1.83)
Cancer							
No.	26	91	413	940	1361	385	216
Age-adjusted HR (95%CI)	1.31 (0.89-1.94)	0.90 (0.72-1.12)	1.02 (0.91-1.14)	1.00	1.04 (0.96-1.13)	1.13 (1.01-1.28)	1.17 (1.00-1.35)
Multivariable HR (95%CI)	1.24 (0.84-1.83)	0.90 (0.72-1.12)	1.03 (0.92-1.16)	1.00	1.02 (0.94-1.11)	1.07 (0.95-1.21)	1.10 (0.94-1.27)
Noncardiovascular/noncancer							
No.	28	104	359	660	1040	342	286
Age-adjusted HR (95%CI)	1.76 (1.20-2.57)	1.34 (1.09-1.65)	1.23 (1.08-1.39)	1.00	1.09 (0.99-1.20)	1.30 (1.14-1.48)	1.89 (1.64-2.17)
Multivariable HR (95%CI)	1.49 (1.02-2.18)	1.20 (0.97-1.48)	1.20 (1.06-1.37)	1.00	1.06 (0.96-1.17)	1.20 (1.05-1.37)	1.66 (1.44-1.91)
All causes							
No.	70	265	1020	2148	3314	1001	730
Age-adjusted HR (95%CI)	1.42 (1.12-1.80)	1.08 (0.95-1.23)	1.08 (1.00-1.16)	1.00	1.08 (1.02-1.14)	1.21 (1.12-1.30)	1.56 (1.43-1.69)
Multivariable HR (95%CI)	1.29 (1.02-1.64)	1.02 (0.90-1.16)	1.08 (1.00-1.16)	1.00	1.06 (1.00-1.12)	1.13 (1.05-1.22)	1.41 (1.29-1.54)
Women							
Person-years	5183	34039	151458	284289	217774	37576	14801
Total stroke							
No.	12	46	125	228	339	96	80
Age-adjusted HR (95%CI)	1.15 (0.64-2.05)	1.05 (0.77-1.45)	0.95 (0.76-1.18)	1.00	1.28 (1.08-1.51)	1.35 (1.06-1.71)	1.87 (1.44-2.43)
Multivariable HR (95%CI)	1.07 (0.59-1.91)	0.99 (0.72-1.37)	0.93 (0.75-1.16)	1.00	1.24 (1.05-1.47)	1.29 (1.01-1.64)	1.69 (1.29-2.20)
Hemorrhagic stroke							
No.	3	19	54	115	142	33	13
Age-adjusted HR (95%CI)	0.74 (0.24-2.35)	1.01 (0.62-1.64)	0.84 (0.61-1.17)	1.00	1.19 (0.93-1.52)	1.16 (0.78-1.71)	0.84 (0.47-1.50)
Multivariable HR (95%CI)	0.68 (0.22-2.15)	0.93 (0.57-1.52)	0.82 (0.60-1.14)	1.00	1.17 (0.91-1.51)	1.16 (0.78-1.72)	0.78 (0.43-1.40)
Ischemic stroke							
No.	9	27	62	94	159	52	61
Age-adjusted HR (95%CI)	1.67 (0.84-3.32)	1.31 (0.86-2.02)	1.10 (0.80-1.51)	1.00	1.33 (1.03-1.72)	1.48 (1.05-2.09)	2.68 (1.92-3.73)
Multivariable HR (95%CI)	1.57 (0.79-3.13)	1.26 (0.82-1.94)	1.10 (0.79-1.51)	1.00	1.29 (1.00-1.67)	1.38 (0.98-1.95)	2.37 (1.70-3.32)
Coronary heart disease							
No.	10	28	60	83	127	45	20
Age-adjusted HR (95%CI)	2.40 (1.24-4.64)	1.68 (1.09-2.58)	1.24 (0.89-1.72)	1.00	1.27 (0.96-1.67)	1.61 (1.11-2.32)	1.16 (0.70-1.90)
Multivariable HR (95%CI)	2.32 (1.19-4.50)	1.64 (1.07-2.53)	1.23 (0.88-1.72)	1.00	1.24 (0.94-1.64)	1.52 (1.05-2.19)	1.04 (0.63-1.72)
Total cardiovascular disease							
No.	30	117	275	470	725	217	156
Age-adjusted HR (95%CI)	1.34 (0.93-1.95)	1.28 (1.04-1.56)	1.01 (0.87-1.17)	1.00	1.31 (1.16-1.47)	1.43 (1.22-1.69)	1.70 (1.41-2.04)
Multivariable HR (95%CI)	1.28 (0.88-1.86)	1.22 (1.00-1.50)	1.00 (0.86-1.16)	1.00	1.28 (1.14-1.44)	1.37 (1.17-1.62)	1.54 (1.28-1.86)
Cancer							
No.	24	113	333	672	638	156	97
Age-adjusted HR (95%CI)	1.16 (0.77-1.75)	1.10 (0.90-1.34)	0.90 (0.79-1.03)	1.00	0.97 (0.87-1.08)	1.05 (0.88-1.25)	1.28 (1.03-1.59)
Multivariable HR (95%CI)	1.14 (0.76-1.72)	1.07 (0.87-1.31)	0.90 (0.79-1.03)	1.00	0.95 (0.85-1.06)	1.01 (0.85-1.21)	1.20 (0.97-1.50)
Noncardiovascular/noncancer							
No.	29	92	314	446	676	224	161
Age-adjusted HR (95%CI)	1.56 (1.07-2.28)	1.15 (0.91-1.43)	1.35 (1.17-1.56)	1.00	1.35 (1.20-1.52)	1.72 (1.46-2.02)	2.16 (1.79-2.60)
Multivariable HR (95%CI)	1.47 (1.01-2.15)	1.07 (0.85-1.34)	1.34 (1.16-1.54)	1.00	1.33 (1.18-1.50)	1.65 (1.40-1.94)	1.99 (1.65-2.39)
All causes							
No.	83	322	949	1588	2039	597	414
Age-adjusted HR (95%CI)	1.34 (1.08-1.67)	1.17 (1.03-1.32)	1.06 (0.98-1.15)	1.00	1.18 (1.10-1.26)	1.37 (1.25-1.51)	1.70 (1.52-1.90)
Multivariable HR (95%CI)	1.28 (1.03-1.60)	1.11 (0.98-1.25)	1.05 (0.97-1.14)	1.00	1.16 (1.08-1.24)	1.32 (1.20-1.45)	1.56 (1.40-1.75)

Multivariable adjustment: age, body mass index (quintiles), history of hypertension, history of diabetes, alcohol consumption, smoking, education level, hours of exercise, hours of walking, regular employment, perceived mental stress, depressive symptoms and frequency of fresh fish intake. HR refers to hazard ratio; CI, confidence interval.

As for total cardiovascular disease for women and noncardiovascular disease and all causes for men and women, there was a U-shaped relationship between sleep duration and mortality, with a nadir at 7 hours of sleep. These associations were essentially unchanged when we excluded subjects whose events occurred within 5 years after baseline. Compared with women

who slept for 7 hours, the multivariable hazard ratios (95% CI) of mortality from total cardiovascular disease were 1.41 (0.94-2.12) for 4 hours or less, 1.24 (0.99-1.57) for 5 hours, 1.04 (0.88-1.23) for 6 hours, 1.29 (1.13-1.47) for 8 hours, 1.35 (1.12-1.62) for 9 hours, and 1.51 (1.21-1.87) for 10 hours or longer. The respective multivariable hazard ratios of mortality from noncardiovascular disease/noncancer were 1.65 (1.08-2.52), 1.32 (1.05-1.66), 1.26 (1.09-1.45), 1.08 (0.97-1.21), 1.19 (1.03-1.39) and 1.66 (1.40-1.95), respectively, for men, and 1.43 (0.94-2.18), 1.03 (0.80-1.33), 1.35 (1.16-1.58), 1.34 (1.18-1.53), 1.58 (1.32-1.90), and 1.83 (1.48-2.26), respectively, for women. Furthermore, the respective hazard ratios of mortality from all causes were 1.27 (0.96-1.68), 1.06 0.91-1.22), 1.07 (0.98-1.17), 1.04 (0.98-1.11), 1.11 (1.01-1.21) and 1.37 (1.24-1.52) for men, and 1.26 (0.98-1.62), 1.08 (0.95-1.24), 1.04 (0.95-1.14), 1.13 (1.05-1.22), 1.27 (1.14-1.42), and 1.46 (1.29-1.67) for women.

DISCUSSION

In this large-scale prospective study of Japanese men and women aged 40 to 79 years, we confirmed that, compared with 7 hours of sleep, short sleep duration of 4 hours or less was associated with a 2-fold increase in mortality from coronary heart disease for women and a 1.5-fold increase in mortality from noncardiovascular disease/noncancer and a 1.3-fold increase in total mortality for both men and women, whereas long sleep duration ($\geq$ 10 hours) was associated with a 1.5- to 2-fold increase in mortality from total stroke, ischemic stroke, total cardiovascular disease, noncardiovascular disease/noncancer and all causes for both men and women. There was a robust U-shaped relationship between sleep duration and mortality from all causes, with a nadir at 7 hours of sleep in both sexes, which extended the evidence of the earlier report,[5] based on the approximately 30% larger number of deaths.

To the best of our knowledge, ours is the first study to provide evidence of the association of short sleep duration with an increase in mortality from coronary heart disease for Asian women. Previous studies of Americans or Europeans support our findings. The Nurses' Health Study of 71,617 women aged 40 to 65 years reported that, compared with 8 hours of sleep, short sleep duration of 5 hours or less was associated with a 1.4-fold increase in risk of coronary heart disease.[2] The MONICA/KORA Augsburg Cohort Study of 3508 men and 3388 women aged 45 to 74 years showed that the risk of myocardial infarction was approximately 3 times higher for women with 5 or fewer hours of sleep, compared with 8 hours of sleep, but such an increase in risk was not observed for men.[9] We observed an increased mortality from coronary heart disease associated with short sleep only for women, and the mortality among female short sleepers did not differ significantly from that among male short sleepers. The hazard ratio (95% CI) of coronary heart disease for short sleepers in women versus those in men was 4.60 (0.58-36.2). This finding contrasts with the result that risk of mortality from cardiovascular disease, other causes, and all causes were approximately half among women than among men. The age-adjusted hazard ratios for women versus men were 0.56 (0.51-0.61) for total stroke, 0.46 (0.40-0.53) for coronary heart disease, 0.55 (0.51-0.58) for total cardiovascular disease, 0.39 (0.37-0.41) for cancer, 0.44 (0.42-0.47) for noncardiovascular disease/noncancer, and 0.45 (0.44-0.47) for all causes.

Short sleep of 4 or fewer hours was found to be associated with increased risk of mortality from hemorrhagic stroke for men, although this association was not statistically significant. However, when stratified by alcohol consumption habits, an increased risk of mortality from hemorrhagic stroke was observed among male drinkers with 4 or fewer hours and 5 hours of sleep. A cross-national study on sleep habits of approximately 35,000 men and women of 10 countries, including Japan,[10] showed that the prevalence of the use of alcohol as a sleep aid was the highest in Japan (30.3%). A recent cross-sectional survey conducted in Japan[11] also reported that the prevalence of alcohol consumption as a sleep aid at least once a week was 48% for men aged 20 years or older. It is possible that the habit of using alcohol as a sleep aid enhances the risk of mortality from hemorrhagic stroke associated with short sleep duration.

There is some evidence that may explain why short sleep duration is associated with an increase in mortality from coronary heart disease and total cardiovascular disease. Previous studies showed that short-term sleep deprivation leads to increased sympathetic nervous system activity,[12,13] elevated blood pressure,[12,14] elevated cortisol levels,[13] impaired glucose tolerance,[13] and increased inflammatory markers,[15] which may reflect and increase the risk of cardiovascular disease. Furthermore, recent epidemiologic studies have demonstrated that short sleep duration is associated with higher levels of hemoglobin A (1c),[16] total cholesterol,[17] and triglycerides,[17] higher blood pressure,[17] and increased incidence of hypertension.[18] Short sleep was also associated with increased mortality from noncardiovascular disease/noncancer for both men and women. This finding suggests other mechanisms for increasing nonspecific mortality, which need to be explored in further studies.

The association of long sleep duration with higher risks of mortality from total stroke, total cardiovascular disease, noncardiovascular disease/noncancer, and all causes observed in our study was consistent with the results of previous cohort studies.[1-3] A 10-year follow-up of the National Health and Nutrition Examination Survey I cohort comprising 7844 men and women aged 32 years and older showed a 1.5-fold increase in risk of stroke for persons with more than 8 hours of sleep, compared with those with 6 to 8 hours of sleep.[1] The Nurses' Health Study of 82,969 women aged 40 to 65 years showed that, compared with 7 hours of sleep, long sleep of 9 or more hours was associated with a 1.6-fold increase in mortality from cardiovascular disease, a 1.5-fold for noncardiovascular disease/noncancer, and a 1.4-fold for all causes.[3] Another report from the Nurses' Health Study of 71,617 women aged 40 to 65 years showed that, compared with 8 hours of sleep, long sleep of 9 or more hours was associated with 1.4-fold increased risk of coronary heart disease.[2] Although the mechanisms for the association between long sleep duration and increased mortality from cardiovascular disease and other causes were not clear, long sleep duration may be an early symptom of disease and may precede clinical diagnoses. However, the association of long sleep duration with excess mortality from total cardiovascular disease, noncardiovascular disease/noncancer, and all causes did not change substantially after exclusion of the subjects whose events occurred within 5 years from baseline.

The following limitations of our study need to be addressed. First, we could not obtain information about the quality of sleep, such as the presence or absence of sleep apnea, which is associated with increased risk of cardiovascular disease.[19] A previous cohort study of 1024 volunteers showed that short sleep duration was associated with an increased body mass index along with a reduction in leptin and elevated levels of ghrelin.[20] Since being overweight is a strong risk factor for sleep apnea, this disorder can be a confounder for the association between short sleep duration and increased risk of mortality from cardiovascular disease. However, men and women with short sleep duration enrolled in our study did not have a higher mean body mass index, and we did not have a higher percentage of overweight subjects among short sleepers than long sleepers, so that the potential confounding effect of sleep apnea may be minor. Second, data on sleep duration were obtained by self-administrated questionnaire and, thus, may include misclassification. However, self-assessed sleep duration was shown in a previous study to yield valid results in comparison with quantitative sleep assessment with actigraphy.[21] Another study has suggested, however, that depressed mood is associated with both underextimation and overestimation of habitual sleep duration.[22] We therefore conducted a statistical analysis including these psychological factors as covariates, which showed that the association between sleep duration and coronary heart disease remained substantially unchanged. Finally, we used the mortality data, rather than incidence data, as endpoints, which may lead to misclassification in the diagnosis of discuss outcomes, especially stroke, stroke subtypes, and coronary heart disease. However, the widespread use of computed tomography in local hospitals since the 1980s has probably made the diagnosis of stroke and its subtypes reported on the death certificates sufficiently accurate.[23, 24] For coronary heart disease, approximately one fourth to one third of deaths attributed to ischemic heart disease on the death certificate were misdiagnosed, according to the validation studies.[25,26] Therefore, the contamination of other cardiovascular diseases in the diagnosis of coronary heart disease would probably underestimate the excess mortality from coronary heart disease for female short sleepers, and the real association may be stronger.

The strengths of our study are its prospective design and high statistical power to detect sex-specific associations of short and long sleep duration with cause-specific mortality, as well as with total mortality.

In conclusion, short sleep duration was associated with increased mortality from coronary heart disease for women and from noncardiovascular disease/noncancer and all causes for both sexes, whereas long sleep duration was associated with increased mortality from stroke, total cardiovascular disease, noncardiovascular disease/noncancer, and all causes for both sexes, yielding a U-shaped relationship with total mortality, with a nadir at 7 hours of sleep.

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DISCLOSURE STATEMENT

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