Published in final edited form as:
Stroke. 2014 June ; 45(6): 1620–1625. doi:10.1161/STROKEAHA.114.005181.

Sleep duration and risk of stroke mortality among Chinese adults: the Singapore Chinese Health Study

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Abstract

Background and Purpose—Prospective relation between sleep duration and stroke risk is less studied, particularly in Asians. We examined the association between sleep duration and stroke mortality among Chinese adults.

Methods—The Singapore Chinese Health Study is a population-based cohort of 63,257 Chinese adults aged 45-74 years enrolled during 1993 through 1998. Sleep duration at baseline was assessed via in-person interview, and death information during follow-up was ascertained via record linkage with the death registry up to December 31, 2011. Cox proportional hazard models were used to calculate hazard ratios (HRs) with adjustment for other comorbidities and lifestyle risk factors of stroke mortality.

Results—During 926,752 person-years of follow-up, we documented 1,381 stroke deaths (322 from hemorrhagic and 1,059 from ischemic or non-specified strokes). Compared to individuals with 7 hours/day of sleep, the multivariate-adjusted HR (95% confidence interval) of total stroke mortality was 1.25 (1.05-1.50) for ≤5 hours/day (short duration), 1.01 (0.87-1.18) for 6 hours/day, 1.09 (0.95-1.26) for 8 hours/day, and 1.54 (1.28-1.85) for ≥9 hours/day (long duration). The increased risk of stroke death with short (1.54; 1.16-2.03) and long duration of sleep (1.95; 1.48-2.57) was seen among subjects with a history of hypertension, but not in those without hypertension. These findings were limited to risk of death from ischemic or non-specified stroke, but not observed for hemorrhagic stroke.

Conclusions—Both short and long sleep durations are associated with increased risk of stroke mortality in a Chinese population, particularly among those with a history of hypertension.

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Disclosures
The authors have no conflict of interest to declare.

Keywords

sleep; stroke; hypertension; cohort study; Chinese

INTRODUCTION

Short and long sleep durations are associated with adverse health outcomes, including diabetes,[1] coronary heart disease (CHD)[2] and total mortality.[3] However, the prospective relation between sleep duration and stroke is less studied. A meta-analysis[2] of four prospective cohorts among US[4,5] and Japanese adults[6,7] reported that both short and long sleep durations were associated with a 15% and 65% increase in risk of developing or dying of stroke, respectively. Two recent publications also reported the similar relations in European,[8] and multi-ethnic American populations.[9] In all studies, long sleep duration has been associated with an increased risk; however, the results for short sleep duration were inconsistent.[4-9]

Few studies previously have investigated ischemic and hemorrhagic strokes separately, and tested the potential risk modification by comorbid conditions, given the concern that longer sleep duration may reflect the presence of comorbidity or unhealthy status. Most previous studies were limited in the sample size of stroke outcomes for the short sleep duration category.[4,6-8] No study has been done in the Chinese population, where disease burden from stroke is increasing quickly in the past several decades.[10] We have previously shown that both short (≤5 hours/day) and long (≥9 hours/day) sleep durations were related to an increased risk of CHD mortality among Singaporean Chinese.[11] Thus, using data from the same cohort with longer duration of follow-up, we aimed to examine the prospective association between sleep duration and stroke mortality in the first such study among a Chinese population.

MATERIALS AND METHODS

Study Population

The Singapore Chinese Health Study was established between 1993 and 1998 with 63,257 Chinese (27,954 men and 35,303 women) in Singapore, aged 45-74 years.[12] The study subjects were recruited from two major dialect groups in Singapore, Hokkiens and Cantonese, who originated from Fujian and Guangdong provinces in Southern China, respectively. During the enrolment period, all study participants were residents of government housing estates, where 86% of the Singapore population resided at the time of recruitment. The Institutional Review Board of the National University of Singapore approved this study, and all enrolled subjects gave informed consent.

Ascertainment of Sleep Duration and Covariates

At recruitment, the trained interviewers conducted the face-to-face interviews using a structured questionnaire, and obtained information on height, weight, cigarette smoking, habitual physical activity, alcohol drinking and habitual dietary intake (by a validated 165-item food-frequency questionnaire). Body mass index (BMI, in kg/m^2) was calculated by

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body weight in kilogram divided by square of height in meter. Participants were asked about their history of medical conditions diagnosed by physicians, including diabetes, hypertension, CHD and stroke, and unknown status of these conditions was coded as “no” on the questionnaires. History of cancer was ascertained by self-reports and record linkage with the Singapore Cancer Registry database. Sleep duration was assessed by the following question: “On the average, during the last year, how many hours in a day did you sleep?” with the following responses: “5 hours or less”, “6 hours”, “7 hours”, “8 hours”, “9 hours”, “10 hours or more”.

Ascertainment of Stroke Mortality

Deaths were identified through record linkage with the Singapore Registry of Births and Deaths up to December 31, 2011. Underlying death causes were coded according to the International Classification of Diseases, Ninth Revision (ICD-9): codes 430-438 for all stroke deaths, 430-432 for hemorrhagic stroke, and 433-438 for ischemic or otherwise unspecified stroke. We have tried to verify unspecified stroke cases through sources of medical records in a previous pilot study: among 308 cases with available medical records, 86% were ischemic strokes and 14% were hemorrhagic strokes. This suggested that majority of the strokes classified as unspecified were actually ischemic strokes (unpublished data). As of December 31, 2011, only 47 subjects from this cohort were known to be lost to follow-up due to migration out of Singapore or for other reasons. Therefore, emigration among participants seems to be negligible in this cohort and vital statistics during follow-up was virtually complete.

Statistical Analysis

We chose a reference category of 7 hours/day because there were most subjects in this category as well as to be consistent with previous studies in the field.[2] Person-years for each participant were calculated from the date of recruitment until date of death, lost-to-follow-up or December 31, 2011, whichever occurred first. Cox proportional hazards regressions were used to calculate hazard ratios (HRs) and their 95% confidence intervals (CIs) for stroke mortality associated with different categories of sleep duration (≤5, 6, 8, ≥9 relative to 7 hours/day). We adjusted for age, year of recruitment, gender, dialect group, level of education, BMI, alcohol drinking, smoking intensity (number of cigarettes/day) and duration (number of years of smoking), level of moderate physical activity, and daily intakes of total calorie, vegetables, fruits, dietary fiber and polyunsaturated fatty acids. In a separate model, we further adjusted for history of hypertension, diabetes, CHD, stroke, and cancer, since these comorbidities could be potential mediators in the pathway between sleep duration and stroke death. Additionally, we tested the interactions between sleep duration (five categories) and these comorbidities or overweight/obesity status on the risk of stroke mortality, and performed stratified analysis by these variables. We also tested the curvilinear relation by including linear and quadratic terms of sleep duration in the regression model. Statistical computing was conducted using SAS version 9.1 (SAS Institute Inc., Cary, NC), and two sided P values <0.05 were considered statistically significant.

RESULTS

Among the 63,257 participants, 32.6% of them slept 7 hours/day, followed by 8 hours/day (27.4%) and 6 hours/day (23.3%). There was only 9.7% with ≤5 hours/day and 7.0% with ≥9 hours/day of sleep. Compared to people with 7 hours/day of sleep, individuals with short (≤5 hours/day) or long (≥9 hours/day) durations were older and more likely to have a history of hypertension, CHD, stroke, and cancer (**Table 1**). Participants with short sleep duration were less educated and those with long sleep duration were more likely to be ever smokers. There were no statistically significant differences in BMI, physical activity, and dietary habits among the different categories of sleep duration.

During a mean follow-up duration of 14.7 years, 1,381 stroke deaths (322 hemorrhagic and 1,059 ischemic or unspecified strokes) occurred among cohort participants. Compared with sleeping for 7 hours/day, both short and long durations were associated with increased risks of stroke mortality (**Table 2**), and the relations were slightly attenuated after adjustment for the comorbidities. Compared to the reference group, the multivariate-adjusted HR (95% confidence interval [CI]) of total stroke mortality was 1.25 (1.05-1.50) for ≤5 hours/day, 1.01 (0.87-1.18) for 6 hours/day, 1.09 (0.95-1.26) for 8 hours/day, and 1.54 (1.28-1.85) for ≥9 hours/day (P for quadratic effect <0.001). These associations were mainly limited to ischemic or unspecified stroke mortality, but not hemorrhagic stroke mortality (Table 2). The results were similar in men and women (**Supplemental Table I**).

We further performed stratified analysis by baseline comorbidities (**Table 3**). No significant interaction was found for any of the comorbidities, and the results were similar when stratified by baseline overweight/obesity status or history of diabetes. However, when stratified by baseline history of cardiovascular disease (CVD), the association between long sleep duration and stroke mortality was marginally stronger in those with baseline CVD (HR 2.35; 95% CI 1.54-3.60) than those without (1.43; 1.16-1.76; P for difference = 0.07). When stratified by baseline hypertension status, the U-shaped association with stroke mortality was found for short (HR 1.54; 95% CI 1.16-2.03) and long (1.95; 1.48-2.57) sleep durations among participants with a history of hypertension (P for quadratic effect <0.001), but not among those who did not report a history of hypertension (P for difference = 0.087 and 0.042 for short and long sleep duration, respectively). Compared to those without hypertension and having 6-8 hours of sleep per day, HRs (95% CIs) were 2.13 (1.68-2.70) for individuals with hypertension and having 5 or less hours of sleep per day, 2.69 (2.12-3.42) for individuals with hypertension and having 9 or more hours of sleep per day (**Supplemental Table II**).

DISCUSSION

In this large cohort of Chinese adults, we found that both short and long sleep durations were significantly associated with an increased risk of stroke mortality. The associations were observed in mortality from ischemic or unspecified stroke, but not in mortality from hemorrhagic stroke. The significant associations with short and long sleep durations were only observed among hypertensive subjects, but not among those without hypertension.

The relation between sleep duration and stroke has been investigated in several cohort studies,[4-9] and ours is the first in a Chinese population. The finding of increased stroke risk with long sleep duration is largely consistent with previous investigations in US populations,[4,5,9] Japanese[6,7] and German adults.[8] The magnitude of the association in our study (HR=1.54) is also consistent with a recent meta-analysis of four cohort studies (pooled HR=1.65),[2] and it was greater than smoking (HR=1.35) while slightly lower than hypertension (HR=1.74) and diabetes (HR=1.92) in our study population (data not shown). It has been hypothesized that long sleep may represent an epiphenomenon of comorbidity,[13] and the association could be explained by poor sleep quality or poor general health. This concurs with our finding that individuals with long sleep had higher prevalence of comorbidities, and the association was much stronger in those with prior history of CVD or hypertension compared to those without. In our study, the relation with long sleep duration was independent of those comorbidities, suggesting that other physiological mechanisms may contribute to the increased risk of stroke death. Further studies are needed to elucidate the mechanisms.

We also found that short sleep duration was related to increased stroke risk, which is consistent with a recent study in German adults,[8] where <6 hours/day sleep was related to 2-fold increased stroke risk. Earlier studies have shown a non-significant increased risk (HR 1.14; 95% CI 0.97-1.33) among postmenopausal women in US,[5] and a non-significant increased risk among men (2.00; 0.93-4.31) but not women (0.97; 0.39-2.41) in Japan.[7] However, several other studies failed to observe significant relations between short sleep and stroke risk.[4,6,9] Nevertheless, these previous studies may be limited by small sample size in the short sleep category: fewer than 60 cases in several studies,[4,6-8] and 99 cases in the Women's Health Initiative (WHI) study.[5] Short sleep duration could lead to increased risk of stroke through several biological and behavioral pathways by increasing 24-hour blood pressure and heart rate, elevating sympathetic nervous system activity, dysregulating hormonal control of appetite (reduced leptin and elevated ghrelin), increasing body weight, activating pro-inflammatory pathways, and affecting activity of the major neuroendocrine stress systems.[14-18] Individuals with insufficient sleep may also be more likely to have sleep disorders[9] or mental distress,[19] which may mediate the association with stroke risk or mortality. Previous studies have demonstrated that obstructive sleep apnoea syndrome is independently associated with an increased risk of stroke and all-cause mortality.[20,21] However, in studies that had information on depression as a comorbidity, the association was not materially changed after adjustment for depression.[5,6,8] The magnitude of the association between short sleep duration and stroke mortality was weak (HR=1.25) in our study, and the results should be interpreted cautiously and unmeasured confounders (e.g., sleep quality, sleep disorders, mental status, and occupational characteristics) may contribute to the observed relation. Further studies need to clarify whether short sleep duration is an independent risk factor for stroke mortality.

While most studies did not distinguish between ischemic and hemorrhagic strokes,[4,7-9] the JACC study examined deaths from ischemic and hemorrhagic strokes separately,[6] and the WHI study specifically evaluated the relation with ischemic stroke.[5] In the JACC study,[6] long sleep duration (≥10 hours/day) was associated with ischemic stroke in both men and women,[6] which were consistent with our findings for ischemic stroke. However, the relation with hemorrhagic stroke in the JACC study was only seen in men,[6] while no association with hemorrhagic stroke was found in our study. For short sleep duration, results from JACC study were not conclusive,[6] possibly due to small sample size and limited statistical power. Our findings for ischemic stroke concurred with findings from the WHI study, although in the latter, the association between short sleep duration and risk of ischemic stroke did not reach statistical significance.[5] We acknowledge that with 322 hemorrhagic stroke deaths, our null results could be due to low statistical power from small sample size. Future studies are still needed to confirm whether sleep duration is specifically related to ischemic stroke but not hemorrhagic stroke.

A novel finding in this study is that the increased risk with short or long duration was more prominent among participants with hypertension, and individuals with both hypertension and short/long sleep durations had substantially higher risk of stroke mortality. This finding suggests that optimal sleep duration is particularly important for hypertensive patients. Hypertension is the single most important risk factor for stroke and the mechanism linking sleep duration to stroke risk could be through the effects of blood pressure.[22] Recent studies suggest that short or long sleep durations may be related to arterial stiffening[23,24] and subclinical atherosclerosis manifested by increased carotid intima media thickness,[25] both of which are known to be induced by high blood pressure as well.[26,27] Meanwhile, arterial stiffness and increased carotid intima media thickness have been shown to be potential mechanisms for stroke development.[28,29] Thus, hypertension and sleep duration may have a synergistic effect on stroke risk through the common pathways of inducing arterial stiffening and atherosclerosis, both of which are more closely linked with ischemic rather than hemorrhagic stroke.

Strengths of this study are its large sample size, long follow-up and inclusion of many known vascular risk factors as possible covariates. There are several limitations of our study. First, as the outcome was stroke mortality, we are uncertain if the results are applicable to non-fatal stroke. There was a large proportion of unspecified strokes in our study, although our previous pilot study suggested that majority of them were ischemic strokes. This is consistent with data from the national registry that about 80% of all strokes in Singapore are ischaemic strokes.[30] Moreover, the lack of comprehensive information on sleep disorders and sleep quality limits us to further investigate whether the relation could be modified or mediated by these factors.[31] We did not collect information on working status and job characteristics (e.g., shift work) in the study, which may confound the results because they are related to both sleep duration and stroke risk.[32] Furthermore, since we measured sleep duration by self-report and only at a single time point, any subsequent change in sleep duration after recruitment could lead to non-differential misclassification and potentially underestimate the sleep-stroke association. Finally, as this is an observational study, causality should be interpreted cautiously given that residual/unmeasured confounding (e.g., depression, anxiety, and socioeconomic status) cannot be ruled out.

CONCLUSIONS

In conclusion, both short and long sleep durations are associated with an increased risk of stroke mortality in the Chinese population. This relationship was more prominent among participants with baseline hypertension compared to their normotensive counterparts. Our findings of significant association between sleep duration and ischemic stroke mortality, but not for hemorrhagic stroke mortality, also need to be confirmed in future studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We are indebted to the participants in the Singapore Chinese Health Study for their continuing outstanding support and colleagues working in the Study for their valuable help. We also thank the Ministry of Health in Singapore for assistance with the identification of mortality cases via database linkage. Finally, we acknowledge the founding and longstanding principal investigator of the Singapore Chinese Health Study, Mimi C. Yu.

Sources of Funding

The project was supported by NIH grants RO1 CA055069, R35 CA053890, RO1 CA080205, RO1 CA098497, and RO1 CA144034. The funding sources were not involved in the data collection, data analysis, manuscript writing and publication.

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Table 1

Baseline characteristics of the study population according to sleep duration in the Singapore Chinese Health Study.

Characteristics	Daily sleep duration				
	≤5 hours	6 hours	7 hours	8 hours	≥9 hours
n	6155	14733	20622	17347	4400
Age at recruitment, year	58.8 ± 8.1	56.7 ± 7.9	55.8 ± 7.7	55.9± 8.1	58.3 ± 8.5
Body mass index, kg/m^2	23.1 ± 3.3	23.2 ± 3.3	23.1 ± 3.2	23.1 ± 3.3	23.1 ± 3.5
Men (%)	2390 (38.8)	6494 (44.1)	9079 (44.0)	8022 (46.2)	1969 (44.8)
Cantonese dialect (%)	3078 (50.0)	6735 (45.7)	9474 (45.9)	7920 (45.7)	2077 (47.2)
Diabetes (%)	677 (11.0)	1273 (8.6)	1590 (7.7)	1569 (9.0)	587 (13.3)
Hypertension (%)	1750 (28.4)	3454 (23.4)	4605 (22.3)	4024 (23.2)	1221 (27.8)
Coronary heart disease (%)	374 (6.1)	580 (3.9)	724 (3.5)	657 (3.8)	263 (6.0)
Stroke (%)	135 (2.2)	170 (1.2)	224 (1.1)	269 (1.6)	149 (3.4)
Cancer (%)	243 (4.0)	421 (2.9)	556 (2.7)	536 (3.1)	180 (4.1)
Ever smoked (%)	1913 (31.1)	4455 (30.2)	5929 (28.8)	5417 (31.2)	1613 (36.7)
Weekly/daily alcohol intake (%)	685 (11.1)	1742 (11.8)	2309 (11.2)	2063 (11.9)	512 (11.6)
Weekly moderate physical activity					
<0.5 hours/week	4862 (79.0)	11459 (77.8)	16061 (77.9)	13450 (77.5)	3440 (78.2)
0.5-3.9 hours/week	797 (12.9)	2050 (13.9)	2769 (13.4)	2541 (14.7)	631 (13.3)
≥4.0 hours/week	496 (8.1)	1224 (8.3)	1792 (8.7)	1356 (7.8)	329 (7.5)
Vegetables intake, g/day	109.5 ± 64.8	112.0 ± 64.3	109.7 ± 62.8	111.3 ± 63.7	108.1 ± 62.2
Fruits intake, g/day	189.9 ± 175.1	205.1 ± 169.2	203.3 ± 162.7	206.1 ± 173.1	192.3 ± 173.6
Dietary fiber intake, g/day	12.4 ± 6.1	12.8 ± 5.8	12.6 ± 5.7	12.8 ± 5.8	12.5 ± 6.0
Polyunsaturated fatty acids, g/day	8.5 ± 4.9	8.9 ± 4.7	8.9 ± 4.8	9.0 ± 4.9	8.9 ± 5.0

Data are shown as n (%) for categorical variables and mean ± SD for continuous variables.

Table 2

Hazard ratio (95% confidence intervals) of stroke mortality according to sleep duration: Singapore Chinese Health Study (1993-2011).

	Daily sleep duration				
	≤5 hours	**6 hours**	**7 hours**	**8 hours**	**≥9 hours**
Person-years	85762	215972	308978	255697	60352
Total stroke					
Cases	179	291	380	366	165
Model 1 *	1.28 (1.07-1.53)	1.00 (0.86-1.17)	1.00	1.12 (0.97-1.29)	1.70 (1.41-2.04)
Model 2 †	1.25 (1.05-1.50)	1.01 (0.87-1.18)	1.00	1.09 (0.95-1.26)	1.54 (1.28-1.85)
Ischemic or unspecified stroke					
Cases	145	221	278	280	135
Model 1 *	1.40 (1.14-1.72)	1.03 (0.87-1.23)	1.00	1.17 (0.99-1.38)	1.88 (1.53-2.32)
Model 2 †	1.37 (1.12-1.68)	1.04 (0.87-1.24)	1.00	1.14 (0.96-1.34)	1.68 (1.36-2.06)
Hemorrhagic stroke					
Cases	34	70	102	86	30
Model 1 *	0.94 (0.64-1.40)	0.91 (0.67-1.23)	1.00	0.98 (0.74-1.31)	1.19 (0.79-1.79)
Model 2 †	0.92 (0.62-1.36)	0.91 (0.67-1.24)	1.00	0.97 (0.73-1.29)	1.14 (0.76-1.72)

* The multivariate model 1 adjusted for age at recruitment, year of recruitment (1993-1995, 1996-1998), gender, dialect (Hokkien, Cantonese), education (no formal education, primary school, secondary school or higher), body mass index (<20.0, 20.0-23.9, 24.0-27.9, and ≥28.0 kg/m^2), alcohol drinking (none, monthly, weekly, daily), years of smoking (never, <20, 20-39, and ≥40 years), dose of smoking (never, ≤12, 13-22, 23-32, ≥33 cigarettes/day), moderate activity (<0.5, 0.5-3.9, and ≥4.0 hours/week), energy intake (kcal/day), dietary intakes of vegetables, fruits, fiber, polyunsaturated fatty acids (g/day, quartiles).

† The multivariate model 2 adjusted for covariates in the model 1 plus self-reported history of physician-diagnosed hypertension, diabetes, stroke and coronary heart disease, and history of cancer reported by the nationwide cancer registry.

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Table 3

Hazard ratio (95% confidence intervals) of stroke mortality according to sleep duration: stratified by baseline comorbidities

	Daily sleep duration					*P* for interaction[†]
	≤5 hours	6 hours	7 hours	8 hours	≥9 hours	
Cardiovascular disease (including coronary heart disease and stroke)						0.12
Yes						
Cases/person-years	21/5493	44/8638	47/11672	53/10540	41/4185	
Multivariate model	1.43 (1.16-1.76)	1.25 (0.82-1.88)	1.00	1.25 (0.84-1.85)	2.35 (1.54-3.60)	
No						
Cases/person-years	158/80269	247/207335	333/297306	313/245157	124/56166	
Multivariate model	1.29 (1.07-1.57)	0.97 (0.82-1.14)	1.00	1.08 (0.92-1.25)	1.43 (1.16-1.76)	
P value for difference[‡]	0.31	0.26	-	0.50	0.070	
Hypertension						0.14
Yes						
Cases/person-years	82/23163	122/48345	133/65400	155/55902	83/15648	
Multivariate model	1.54 (1.16-2.03)	1.24 (0.97-1.59)	1.00	1.31 (1.04-1.65)	1.95 (1.48-2.57)	
No						
Cases/person-years	97/62600	169/167627	247/243577	211/199794	82/44704	
Multivariate model	1.07 (0.85-1.36)	0.88 (0.72-1.07)	1.00	0.98 (0.81-1.17)	1.27 (0.98-1.63)	
P value for difference[‡]	0.087	0.040	-	0.046	0.042	
Diabetes						0.72
Yes						
Cases/person-years	36/7797	54/15874	62/20655	81/19270	41/6484	
Multivariate model	1.28 (0.84-1.94)	1.06 (0.73-1.52)	1.00	1.33 (0.95-1.85)	1.67 (1.12-2.49)	
No						
Cases/person-years	143/77965	237/200098	318/288323	285/236427	124/53868	
Multivariate model	1.24 (1.02-1.52)	1.00 (0.84-1.18)	1.00	1.04 (0.88-1.22)	1.52 (1.23-1.87)	
P value for difference[‡]	0.89	0.73	-	0.20	0.89	
Body mass index (BMI)						0.38
BMI <25 kg/m^2						

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	Daily sleep duration					*P* for interaction[†]
	≤5 hours	6 hours	7 hours	8 hours	≥9 hours	
Cases/person-years	141/67066	239/168050	302/242930	280/199434	130/46234	
Multivariate model	1.22 (1.00-1.49)	1.04 (0.87-1.23)	1.00	1.04 (0.89-1.23)	1.59 (1.29-1.95)	
BMI ≥25 kg/m^2						
Cases/person-years	38/18697	52/47923	78/66048	86/56263	35/14118	
Multivariate model	1.39 (0.94-2.06)	0.89 (0.63-1.27)	1.00	1.28 (0.94-1.74)	1.45 (0.97-2.17)	
P value for difference[‡]	0.75	0.44	-	0.28	0.49	

*The multivariate model adjusted for age at recruitment, year of recruitment (1993-1995, 1996-1998), gender, dialect (Hokkien, Cantonese), education (no formal education, primary school, secondary school or higher), BMI (<20.0, 20.0-23.9, 24.0-27.9, and ≥28.0 kg/m^2), alcohol drinking (none, monthly, weekly, daily), years of smoking (never, <20, 20-39, and ≥40 years), dose of smoking (never, ≤12, 13-22, 23-32, ≥33 cigarettes/day), moderate activity (<0.5, 0.5-3.9, and ≥4.0 hours/week), energy intake (kcal/day), dietary intakes of vegetables, fruits, fiber, polyunsaturated fatty acids (g/day, quartiles), self-reported history of physician-diagnosed hypertension, diabetes, stroke and coronary heart disease, and history of cancer reported by the nationwide cancer registry; except for the stratified variable itself.

†P for interaction was calculated by the chi-square test for the model with and without the interaction term between sleep duration (five categories) and comoribidity (binary variable).

‡P for difference was calculated Wald test of the interaction term between specific sleep duration category (binary variable) and comoribidity (binary variable).