



Strand, L. B., Tsai Min , K., Gunnell, D., Janszky, I., Chi Pang, W., & Chang, S-S. (2016). Self-reported sleep duration and coronary heart disease mortality: A large cohort study of 400,000 Taiwanese adults. *International Journal of Cardiology*, 207, 246-251. DOI: 10.1016/j.ijcard.2016.01.044

Peer reviewed version

Link to published version (if available):  
[10.1016/j.ijcard.2016.01.044](https://doi.org/10.1016/j.ijcard.2016.01.044)

[Link to publication record in Explore Bristol Research](#)  
PDF-document

## University of Bristol - Explore Bristol Research

### General rights

This document is made available in accordance with publisher policies. Please cite only the published version using the reference above. Full terms of use are available:  
<http://www.bristol.ac.uk/pure/about/ebr-terms.html>

## Accepted Manuscript

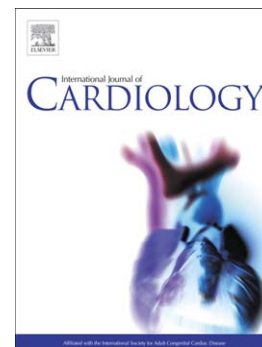
Self-reported sleep duration and coronary heart disease mortality: A large cohort study of 400,000 Taiwanese adults

Linn B. Strand, Min Kuang Tsai, David Gunnell, Imre Janszky, Chi Pang Wen, Shu-Sen Chang

PII: S0167-5273(16)30010-9  
DOI: doi: [10.1016/j.ijcard.2016.01.044](https://doi.org/10.1016/j.ijcard.2016.01.044)  
Reference: IJCA 21799

To appear in: *International Journal of Cardiology*

Received date: 19 October 2015  
Revised date: 28 November 2015  
Accepted date: 1 January 2016



Please cite this article as: Strand Linn B., Tsai Min Kuang, Gunnell David, Janszky Imre, Wen Chi Pang, Chang Shu-Sen, Self-reported sleep duration and coronary heart disease mortality: A large cohort study of 400,000 Taiwanese adults, *International Journal of Cardiology* (2016), doi: [10.1016/j.ijcard.2016.01.044](https://doi.org/10.1016/j.ijcard.2016.01.044)

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

**Title:** Self-reported sleep duration and coronary heart disease mortality: a large cohort study of 400,000 Taiwanese adults

**Author names:**

Linn B. Strand, PhD <sup>1</sup>, Min Kuang Tsai, MS <sup>2</sup>, David Gunnell, PhD <sup>3</sup>,  
Imre Janszky, MD, PhD <sup>4</sup>, Chi Pang Wen, MD, PhD <sup>5\*</sup>, Shu-Sen Chang, MD, PhD <sup>6\*</sup>

<sup>1</sup>**Affiliations:** Department of Public Health and General Practice, Norwegian University of Science and Technology, Hakon Jarls gate 11, 7495 Trondheim, Norway. **Statement of authorship:** "This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation".

<sup>2</sup>**Affiliations:** China Medical University Hospital, 91 Hsueh-Shih Road, Taichung 40402, Taiwan and Institute of Population Health Science, National Health Research Institutes, 35 Keyan Road, Zhunan Town, Miaoli County 350, Taiwan. **Statement of authorship:** "This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation".

<sup>3</sup>**Affiliations:** School of Social and Community Medicine, University of Bristol, 39 Whatley Road, Bristol BS8 2PS, United Kingdom. **Statement of authorship:** "This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation".

<sup>4</sup>**Affiliation:** Department of Public Health and General Practice, Norwegian University of Science and Technology, Hakon Jarls gate 11, 7495 Trondheim, Norway and Center for Health Care Research, St Olav Hospital, Prinsesse Kristinas gate 3, 7030 Trondheim, Norway.

**Statement of authorship:** "This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation".

<sup>5</sup> **Affiliations:** China Medical University Hospital, 91 Hsueh-Shih Road, Taichung 40402, Taiwan and Institute of Population Health Science, National Health Research Institutes, 35 Keyan Road, Zhunan Town, Miaoli County 350, Taiwan. **Statement of authorship:** "This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation".

<sup>6</sup> **Affiliation:** Institute of Health Behaviors and Community Sciences and Department of Public Health, College of Public Health, National Taiwan University, Taipei, Taiwan. **Statement of authorship:** "This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation".

**Grant support:** Linn B. Strand received a research fellowship grant from the Liaison Committee between the Central Norway Regional Health Authority and the Norwegian University of Science and Technology.

**Conflict of interest:** The authors report no relationships that could be construed as a conflict of interest.

**\*Correspondence to (two authors both acting as the corresponding authors):**

1. Chi Pang Wen

China Medical University Hospital

Postal address: 91 Hsueh-Shih Road, Taichung 40402, Taiwan

Email: cwengood@nhri.org.tw

2. Shu-Sen Chang

National Taiwan University

Postal address: No.17, Xuzhou Road, Taipei City 10055, Taiwan

Email: shusenchang@ntu.edu.tw

ACCEPTED MANUSCRIPT

**Abstract**

**Background:** Most previous studies on sleep duration and coronary heart disease (CHD) have been small and have inadequately controlled for cardiovascular risk factors and chronic diseases. Therefore, our aim was to prospectively examine the associations of sleep duration with CHD while accounting for these factors.

**Methods:** Prospective cohort study of 392 164 adults at age 20 years or older who attended a health check-up program from 1994 to 2011 in Taiwan and who have information on sleep duration, sleep medications and potential confounders. Participants answered the question: “How long do you sleep for?”—there were four response categories: (a) 0–4 h; (b) 4–6 h; (c) 6–8 h and (d) >8 h. The participants were then followed for CHD mortality from the Taiwanese cause-of-death register.

**Results:** When compared to those who slept 6-8 hours per night, the risk of dying from CHD was increased by 34% (HR 1.34, 95% Confidence Interval [CI] 0.87-2.07) and 35% (HR 1.35, 95% CI 1.11-1.65) in those who slept less than 4 hours per night and more than 8 hours per night, respectively. When stratifying by sex and age, we found some evidence for a stronger U-shaped association in females than in males and in older adults than in younger adults (p for interaction = 0.01 and 0.13, respectively).

**Conclusions:** Adequate sleep duration should be considered an important component of a healthy lifestyle. Further studies are needed to better elucidate the underlying mechanisms.

**Keywords:** Sleep duration, coronary heart disease, cardiovascular disease, epidemiology, cohort study

## Introduction

Roughly one third of the general population regularly suffers from problems with sleep.<sup>1</sup> A pooled analysis of the 2004–2007 waves of the National Health Interview Survey-Sample Adult Files (NHIS-SAF) including more than 100 000 Americans found that 28.3% of adults slept 6 or fewer hours, 8.5% slept 9 or more hours, and only 63.3% slept between 7 and 8 hours.<sup>2</sup> The prevalence of short sleep duration is increasing<sup>3</sup> and long working hours and shift-work, are likely causes.<sup>2, 4</sup>

A growing body of literature suggests that people with sleep problems are at increased risk for coronary heart disease (CHD).<sup>5-8</sup> Interestingly, sleep duration was found to have a U-shaped association with CHD in a pooled analysis of almost 500 000 subjects.<sup>9</sup> However, most previous studies on sleep duration and CHD have been small and have inadequately controlled for well-known cardiovascular risk factors and chronic diseases. Likewise, sleep medication can play an important role but most previous studies have not taken it into consideration.<sup>10, 11</sup> Therefore, we prospectively examined the association of sleep duration with death from CHD in a large cohort of almost 400 000 Taiwanese adults taking into account important potential confounders, cardiovascular risk factors, sleep medications and chronic diseases.

## Methods

### *Study population*

The study cohort consisted of 593 225 Taiwanese adults at age 20 years or older who participated in a large health check-up program from 1994 to 2011, run by MJ Health Management Institution, Taipei, Taiwan (<https://www.mjclinic.com.tw>). The participants went through a number of biochemical tests and physical examinations as previously

described.<sup>12</sup> The analysis was based on the 392 164 (66%) participants who attended check-ups between 1998 and 2011 and who have full information on sleep duration, sleep medications and potential confounding variables including sociodemographic and life style factors. The study participants gave their written consent for the use of their data from the health check-up for research. The study was approved by the National Health Research Institutes, Taiwan, and the MJ Health Management Institution.

#### *Sleep assessment*

Participants answered a question regarding sleep duration: “How long do you sleep for?”—there were four response categories: (a) 0–4 h; (b) 4–6 h; (c) 6–8 h and (d) >8 h.

#### *CHD mortality ascertainment*

From baseline, the participants were followed for CHD mortality through linkage to the Taiwanese cause-of-death register using the International Classification Diseases, Ninth Revision (ICD-9) codes 410-414 and from 2009, ICD, Tenth Revision (ICD-10) codes I20-I25).

#### *Clinical information*

Participants were measured barefoot, wearing light-weight clothes. Their weight (to the nearest 0.1 kg) and height (to the nearest mm) were measured using an auto-anthropometer, Nakamura KN-5000A (Nakamura, Tokyo, Japan) and their body mass index (BMI) was calculated (kg/m<sup>2</sup>). After 5 minutes rest, with participants seated, blood pressure was measured twice at 10-minute intervals using a computerized auto-mercury sphygmomanometer (CH-5000, Citizen, Tokyo, Japan). We used the mean of the 2 measurements in our analysis. Glucose, total cholesterol, high density lipoprotein cholesterol



(HDL-C), and triglyceride levels was measured in blood collected after overnight fasting using the Hitachi 7150 auto-analyzer (Hitachi Ltd., Tokyo, Japan).

The participants reported their education (middle school or below, high school, junior college, college or higher), marital status (single, married, divorced or separated, widowed), smoking (never, former, current), alcohol consumption (no or occasional use, former drinking, regular drinking), physical activity (inactive, low, moderate or high). They also reported whether they had a history of hypertension, diabetes or heart disease.

### *Statistical analyses*

The Kaplan–Meier method was used to evaluate the unadjusted risk for CHD death according to sleep duration. We used Cox proportional hazards models to investigate the multiaadjusted associations of sleep duration with CHD mortality. Time at entry was the date of recruitment and time of exit was 31<sup>st</sup> December 2011, or death if earlier.

First, we estimated the association of sleep duration with CHD mortality controlling for age and sex (Model 1). In the second model we controlled for age, sex, education and marital status, smoking, alcohol consumption, physical activity, history of hypertension, history of diabetes and history of heart diseases (Model 2). In the third model, we additionally controlled for potential mediators including body mass index, systolic blood pressure, fasting glucose, total cholesterol, HDL-C, triglycerides and use of hypnotics/sedatives (Model 3).

We also assessed the linear association of sleep duration with CHD by including sleep duration as a continuous variable in the models. To examine non-linear associations, we additionally included a quadratic term for this variable in separate models.

To check for effect modification by sex and age (above and below 65 years), we included interaction terms in the models and reported the p value for interaction. We also conducted analyses separately in women and men and by age group.

The proportional hazards assumption was examined by plotting Schoenfeld residuals with time and examining their correlation. To address the possibility of reverse causation, i.e. sleep duration may be affected by any CHD at baseline, we excluded CHD mortality occurring in the first two years of follow-up and repeated the analyses.

## Results

Among the 392 164 participants, there were 711 deaths from CHD during the mean follow-up time of 9.7 years. About 1.1% of the participants slept less than 4 hours every night, 19.6% slept for less than 6 hours per night, 67.6% slept between 6 and 8 hours every night and 11.7% slept more than 8 hours every night.

Characteristics of the participants according to usual sleep duration are presented in Table 1. Those who slept between 6 and 8 hours every day were least likely to present with CVD risk factors, i.e., they were younger, more educated, they were less likely to be regular drinkers, they were more physically active and they were less likely to have a history of hypertension, diabetes or heart disease. Those who usually slept 4 hours or less on the other hand, were older, less educated, more likely to be regular drinkers and had higher blood pressure than those sleeping more than 4 hours a night. They were also more likely to have a history of diabetes or heart disease.

Figure 1 shows Kaplan–Meier curves for CHD mortality according to sleep duration. The figure shows that individuals with low (0-4 hours a night) or high (>8 hours a night) sleep duration had increased risk of CHD death.

There was a U-shaped association of sleep duration with CHD mortality (p for quadratic term ranged between 0.011 and <0.001) (Table 2). In sex and age-adjusted model (Model 1), when compared to those who slept 6-8 hours per night, the risk of dying from CHD was increased by 50% (Hazard Ratio [HR] = 1.50, 95% Confidence Interval [CI] 0.97-2.30) and 53% (HR = 1.53, 95% CI 1.26-1.86) in those who slept less than 4 hours per night and more than 8 hours per night, respectively. The associations were weakened somewhat in the model adjusting for potential confounders (Model 2) - the risk of dying from CHD was increased by 34% (HR = 1.34, 95% CI 0.87-2.07) and 35% (HR = 1.35, 95% CI 1.11-1.65) in those who slept less than 4 hours per night and more than 8 hours per night, respectively. The sleep duration-CHD mortality association was similar after additionally adjusting for potential mediators (Model 3).

There was statistical evidence for sex difference in the sleep duration-CHD mortality association (p for interaction = 0.014 in Model 2) (Table 3). When stratifying by sex, we found a stronger U-shaped association in females than in males. Compared to females sleeping 6-8 hours per night, the risk of dying from CHD was increased by 82% (HR = 1.82, 95% CI 1.02-3.24) and 95% (HR = 1.95, 95% CI 1.38-2.76) in females sleeping less than 4 hours and more than 8 hours, respectively (Model 2). This non-linear relationship was not found in males.

When stratifying by age group (above and below 65 years), we found that the U-shaped relationship mainly was evident in the older adults, although statistical evidence for age

interaction was not strong ( $p$  for interaction = 0.13 in Model 2) (Table 4), possibly due to low number of CHD deaths in the younger age group ( $n=2$ ). In the older group, those who slept less than 4 hours per night had almost double the risk (HR = 1.87, 95% CI 1.18-2.97) and those who slept more than 8 hours per night had 50% increased risk (HR = 1.53, 95% CI 1.20-1.95) of dying from CHD compared to those sleeping 6-8 hours per night (Model 2). In the younger adults, these associations were not found.

A total of 640 CHD deaths occurred after the second year of follow-up, and by excluding CHD deaths occurring in the first two years the estimated associations remained essentially unchanged. In Model 2, the risk of dying from CHD was increased by 28% (HR = 1.28, 95% CI 0.80-2.03) and 31% (HR = 1.31, 95% CI 1.07-1.61) in those sleeping less than 4 hours and more than 8 hours, respectively.

## Discussion

In this very large prospective study on sleep and CHD mortality, we found a U-shaped association of sleep duration and CHD mortality. After adjustment for potential confounders and cardiovascular risk factors, the strength of the association was slightly weakened but still present. The greatest risk was found among women sleeping less than 4 hours per night and more than 8 hours per night (HR = 1.82 and 1.95, respectively). The lowest risk was found in participants sleeping between 6 and 8 hours per night. The U-shaped relationship appeared to be seen mainly in women and in older adults.

### *Findings in the context of previous research*

The largest prospective study on sleep duration and all-cause mortality to date followed more than 1.1 million individuals from the general population for mortality.<sup>13</sup> They found a non-linear association and those sleeping 7 hours per night had the lowest mortality hazard.

However, the researchers did not specifically look at CHD mortality. Our study is the largest to date on sleep duration and CHD mortality and our results are consistent with those of a systematic review and meta-analysis of 15 studies including 474,684 male and female participants, where Cappuccio et al.<sup>9</sup> found that short sleep (defined as < 5–6 hours in most of the studies) was associated with a rate ratio (RR) of 1.48 (95% CI 1.22–1.80) and long sleep (defined as >8–9 hours in most studies) was associated with a RR of 1.38 (95% CI 1.15–1.66) of dying of or developing CHD.

Several studies have suggested that women are more prone to sleep problems than men<sup>14</sup> and there is a well-known sex difference in risk of cardiovascular disease and death. Thus, a sex difference in the association of sleep duration with CHD mortality may be plausible. A German study<sup>15</sup> following almost 7000 subjects for 10 years found that men sleeping less than 5 hours per night had no increased risk of having an incident myocardial infarction (HR 1.13, 95% CI 0.66-1.92) compared to men sleeping 8 hours per night. Women sleeping less than 5 hours per night, on the other hand, had three times the risk compared to those sleeping 8 hours per night (HR 2.98, 95% CI 1.48-6.03).<sup>15</sup> Similar effect sizes have been reported in studies including only women and a study on more than 70 000 US female health professionals found that those sleeping less than 5 hours per night had 82% increased risk (HR 1.82, 95% CI 1.31-2.41) of having a coronary event.<sup>16</sup> Our findings support this as we found a U-shaped relationship only in women with those sleeping less than 4 hours having almost double the risk of dying from CHD compared to those sleeping 6-8 hours. However, these finding must be interpreted with caution. It does not necessarily suggest that short and long sleep duration is more dangerous in women. Instead, the sex difference might be explained by the lower baseline CHD risk in women.

Our finding that there was a stronger U-shaped association between sleep duration and CHD mortality in older adults ( $\geq 65$  years) as compared to younger adults ( $<65$ ) agrees with the results from a Korean study on 13 000 participants examining sleep duration and CVD mortality.<sup>17</sup> They found that the U-shaped relationship was stronger in older adults ( $\geq 60$  years) than in younger adults ( $< 60$  years). A study including almost 60 000 Chinese participants living in Singapore, found no difference in risk of CHD deaths from short or long sleep duration between younger and older adults.<sup>18</sup> They did however, set the cut-off at 60 years and it is possible that the increased risk occurs at an older age.

Most previous large-scale studies have not been able to adjust for sleep medication use,<sup>10, 11, 19</sup> a potentially important confounder of the association of sleep duration with CHD mortality. Adjusting for sleep medication use did not considerably change the estimated association in our study. Neither did we find different associations of sleep duration with CHD mortality in sleep medication users vs. non-users.

#### *Possible mechanisms*

The nature of the observed prospective association between sleep duration and CHD is largely unknown. There are several biological plausible pathways that could potentially explain the prospective association. Short sleep duration is accompanied by chronic activation of stress responses with increased activity in the hypothalamic-pituitary-adrenal axis (HPA axis)<sup>20</sup>. This stress response is accompanied by increased heart rate, decreased heart rate variability, increased blood pressure and secretion of catecholamines, all strong risk factors for CHD.<sup>21-23</sup> Thus, abnormalities in the parasympathetic nervous system may represent a biologically plausible causal link between short sleep duration and CHD. It has also been reported that sleep deprivation is associated with secretion of pro-inflammatory cytokines<sup>24</sup> and previous

studies have reported an association of short sleep duration with decreased glucose tolerance, insulin sensitivity, obesity and diabetes.<sup>25-27</sup>

In contrast, we have no reason to suspect that increased sleep duration would cause CHD. There are some possible explanations however. First, residual confounding factors could be associated with both CHD risk and an increased need for sleep. Thus, factors we don't have any information on, such as unemployment, low socioeconomic status, and undiagnosed health conditions may confound the association between long sleep and cardiovascular morbidity and mortality. In the present study, long sleepers (>8 hours a day) had a lower education level and higher likelihood of health conditions such as hypertension, diabetes, heart disease than those who slept 6-8 hours a day; we adjusted for these possible confounders and the association between long sleep duration and CHD deaths still remained. Although there could be still unadjusted residual confounding, it is also possible that long sleep duration itself could lead to CHD. However, we know of no plausible explanation for such a cause-and-effect relationship. Thus, the association of long sleep duration and CHD remains unexplained.

#### *Strengths and limitations*

The main strengths of this study are its large size (almost 400 000 participants) and the record of sleep duration. Because of the large number of participants, we were able to separately assess the associations in men and women, and in younger and older adults. Furthermore, the detailed information collected at baseline enabled us to control for a range of possible confounding factors on the observed associations.

Because some participants with short or long sleep duration at baseline could have CHD causing their sleep problems, it was important to address the possibility of reverse causation.

In a sensitivity analysis, we therefore excluded the two first years of follow-up. However, this did not change our estimates.

Similar to other prospective studies, we did not assess sleep duration in an objective manner. A recent analysis comparing sleep durations estimated from wrist actigraphy to self-reported sleep in a sample of over 600 middle-aged adults indicated moderate agreement between these measures.<sup>28</sup> Information on sleep duration was recorded at baseline only and it is likely that participant's sleep patterns changed over the follow-up period; however, our checks of the proportional hazards assumption found no evidence that the hazard ratios associated with sleep duration differed over the follow-up period.

Taiwan and some other East Asian countries such as Japan and Hong Kong have some of the lowest mortality rates from CHD in the world.<sup>29, 30</sup> Furthermore, our sample was relatively young (mean age 40.4 years), and these may have led to the relatively small number of deaths from CHD in our data. This may have reduced our power to detect any small effects of short or long sleep duration on risk of CHD death. The young age of our sample may also limit the generalizability of our findings to older people.

We had no information on the prevalence of sleep apnea syndrome or depression, both established risk factors for cardiovascular diseases.<sup>31, 32</sup> Sleep apnea patients and patients with depression often complain about difficulties falling asleep and being easily awoken<sup>33, 34</sup> and the two unmeasured variables could possibly explain the unexplained increased risk found in long sleepers. We did however; adjust for age, sex, BMI and blood pressure, all which are strong correlates of sleep apnea, depression and CHD mortality.

Observational studies inherently limit causal inference. Although we adjusted for several potential confounders in our multivariable analyses, we cannot exclude the possibility of uncontrolled confounding behind the observed associations. However, any remaining



confounder potentially able to influence our results would need to be strongly associated with both sleep duration and CHD mortality and generally be unrelated to the factors included in our models.

Finally, the sample was from a health check-up programme run by a private company and came from a slightly advantaged socioeconomic position compared to Taiwan's general population. However, the cohort showed similar characteristics such as the prevalence of smoking to that shown in a national survey<sup>35</sup> and the proportion of CHD deaths amongst all deaths was only slightly lower in the sample (5.1%) than in Taiwan's adult population (6.2%).

### *Conclusions*

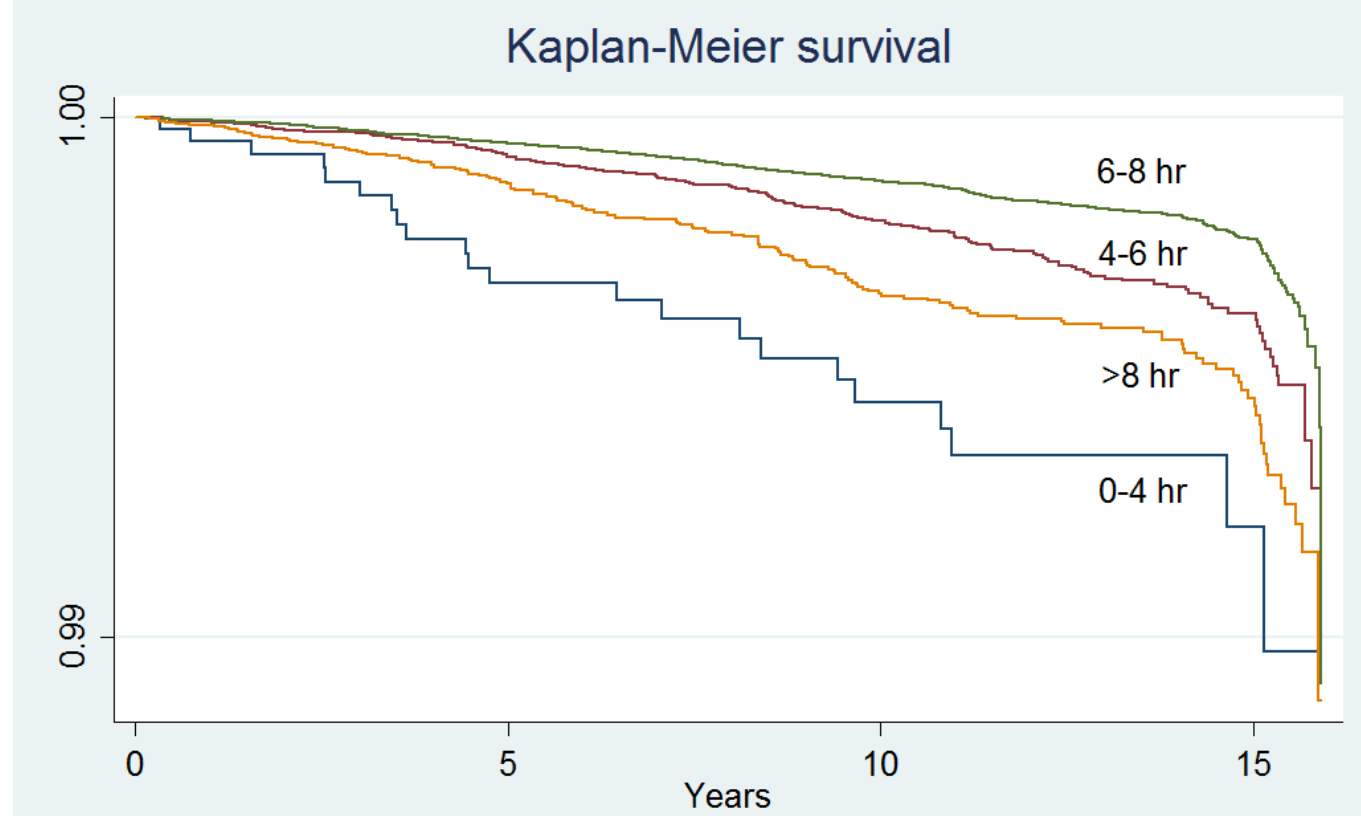
Our study suggests that both short and long sleep durations may have adverse cardiovascular consequences. Sleeping 4 or less hours per night or 8 hours or more per night was associated with an increase in risk of CHD and these associations were stronger in women and in older adults. The associations persisted even after adjustment for established CHD risk factors. Given these results adequate sleep duration should be considered an important component of a healthy lifestyle. Finally, the explanation for the increased CHD risk in patients sleeping 8 hours or longer is unclear. Further studies are needed to elucidate better the mechanisms underlying this association.

### **Acknowledgements**

Linn B. Strand received a research fellowship grant from the Liaison Committee between the Central Norway Regional Health Authority and the Norwegian University of Science and Technology.

**Figure caption**

Figure 1 Kaplan–Meier curves for coronary heart disease mortality according to sleep duration in the MJ health check-up programme, Taiwan



## Tables

Table 1 Characteristics of the participants by sleep duration in the MJ health check-up programme, Taiwan

	Total		Sleep duration (hour)							
			0-4		4-6		6-8		>8	
	n	%	n	%	n	%	n	%	n	%
Number of subjects	392,164	100.0	4,419	1.1	77,013	19.6	265,031	67.6	45,701	11.7
Male	191,656	48.9	1703	38.5	37,226	48.3	132,364	49.9	20,363	44.6
College or higher	126,702	32.3	605	13.7	22,385	29.1	90,261	34.1	13,451	29.4
Married	258,488	65.9	3,001	67.9	49,217	63.9	176,279	66.5	29,991	65.6
Current smoker	88,886	22.7	929	21.0	18,306	23.8	58,770	22.2	10,881	23.8
Regular drinker	27,034	6.9	453	10.3	5,970	7.8	16,586	6.3	4,025	8.8
Physical inactive	197,774	50.4	2,368	53.6	39,504	51.3	131,902	49.8	24,000	52.5
History of hypertension (history of hypertension + use of antihypertensive drugs)	32,945	8.4	799	18.1	8,249	10.7	19,553	7.4	4,344	9.5
History of diabetes (history of diabetes + use of diabetes drugs)	11,158	2.8	300	6.8	2,698	3.5	6,388	2.4	1,772	3.9
History of heart diseases (history of heart diseases + history of heart surgery + use of heart drugs)	14,466	3.7	411	9.3	3,744	4.9	8,364	3.2	1,947	4.3
Use of sedatives/hypnotics	6,959	1.8	409	9.3	2,029	2.6	3,642	1.4	879	1.9
	Mean	sd	Mean	sd	Mean	sd	Mean	sd	Mean	sd
Age (years)	40.4	13.5	50.2	15.3	42.9	14.5	39.4	12.8	40.7	14.6
BMI (kg/m <sup>2</sup> )	23.0	3.6	23.7	3.7	23.5	3.7	22.9	3.5	22.8	3.7
Total cholesterol (mmol/L)	5.0	0.9	5.2	1.0	5.1	1.0	5.0	0.9	5.0	1.0
HDL cholesterol (mmol/L)	1.4	0.4	1.4	0.4	1.4	0.4	1.4	0.4	1.4	0.4
Fasting glucose (mmol/L)	5.5	1.2	5.8	1.8	5.5	1.3	5.4	1.1	5.5	1.3
Triglycerides (mmol/L)	1.2	0.7	1.4	0.8	1.3	0.7	1.2	0.7	1.3	0.8
Systolic blood pressure (mmHg)	119.6	18.8	125.9	21.7	121.5	19.5	119.0	18.3	119.1	19.7

Table 2. Hazard ratios (HR) for the association of sleep duration with CHD mortality in the MJ health check-up programme, Taiwan (N = 392164)

	cases	person-years	Model 1		Model 2		Model 3	
			HR	95% CI	HR	95% CI	HR	95% CI
Sleep duration (h)								
0-4	22	40 966	1.50	0.97, 2.30	1.34	0.87, 2.07	1.36	0.88, 2.10
4-6	165	705 041	1.05	0.87, 1.26	1.03	0.85, 1.23	1.03	0.85, 1.24
6-8	382	2 600 097	1.00		1.00		1.00	
>8	142	405 585	1.53	1.26, 1.86	1.35	1.11, 1.65	1.28	1.05, 1.56
<i>p</i> for linear trend			0.040		0.13		0.29	
<i>p</i> for quadratic trend			<0.001		0.004		0.011	

Model 1: Adjusted for age and sex

Model 2: Adjusted for age, sex, education and marital status, smoking, alcohol consumption, physical activity, history of hypertension, history of diabetes and history of heart diseases

Model 3: Adjusted for age, sex, education, marital status, smoking, alcohol consumption, physical activity, history of hypertension, history of diabetes, history of heart disease, body mass index, systolic blood pressure, fasting glucose, total cholesterol, HDL cholesterol, triglycerides and use of hypnotics/sedatives

Table 3. Hazard ratios (HR) for the association of sleep duration with CHD mortality stratified by sex, in the MJ health check-up programme, Taiwan (N = 392164)

			Model 1		Model 2		Model 3	
	cases	person-years	HR	95% CI	HR	95% CI	HR	95% CI
<b>Males</b>								
Sleep duration (h)								
0-4	9	15 843	1.14	0.59, 2.22	1.00	0.51, 1.94	1.03	0.53, 2.00
4-6	108	339 173	1.07	0.86, 1.34	1.05	0.84, 1.31	1.06	0.85, 1.32
6-8	279	1 292 280						
>8	93	176 220	1.31	1.04, 1.66	1.17	0.92, 1.48	1.11	0.88, 1.41
<i>p</i> for linear trend			0.28		0.50		0.78	
<i>p</i> for quadratic trend			0.064		0.37		0.48	
<b>Females</b>								
Sleep duration (h)								
0-4	13	25 122	1.94	1.09, 3.46	1.82	1.02, 3.24	1.84	1.03, 3.29
4-6	57	365 868	1.00	0.72, 1.39	0.99	0.71, 1.37	0.99	0.72, 1.37
6-8	103	1 307 817	1.00		1.00		1.00	
>8	49	229 365	2.30	1.64, 3.24	1.95	1.38, 2.76	1.81	1.28, 2.56
<i>p</i> for linear trend			0.022		0.065		0.12	
<i>p</i> for quadratic trend			<0.001		<0.001		<0.001	
<b>p for interaction by sex and sleep duration</b>			0.012		0.014		0.025	

Model 1: Adjusted for age and sex

Model 2: Adjusted for age, sex, education and marital status, smoking, alcohol consumption, physical activity, history of hypertension, history of diabetes and history of heart diseases

Model 3: Adjusted for age, sex, education, marital status, smoking, alcohol consumption, physical activity, history of hypertension, history of diabetes, history of heart disease, body mass index, systolic blood pressure, fasting glucose, total cholesterol, HDL cholesterol, triglycerides and use of hypnotics/sedatives

Table 4 . Hazard ratios (HR) for the associations of sleep duration with CHD mortality stratified by age group (above/below 65 years), MJ health check-up programme, Taiwan (N = 392164)

	cases	person-years	Model 1		Model 2		Model 3	
			HR	95% CI	HR	95% CI	HR	95% CI
<b>Aged &lt;65 years</b>								
Sleep duration (h)								
0-4	2	33,409	0.41	0.10, 1.66	0.35	0.09, 1.41	0.36	0.09, 1.44
4-6	67	639,448	1.02	0.77, 1.35	0.99	0.75, 1.32	1.00	0.76, 1.33
6-8	182	2,465,900	1.00		1.00		1.00	
>8	43	367,432	1.32	0.94, 1.84	1.11	0.79, 1.55	1.07	0.77, 1.50
<i>p</i> for linear trend			0.13		0.28		0.38	
<i>p</i> for quadratic trend			0.75		0.56		0.50	
<b>Aged ≥ 65 years</b>								
Sleep duration (h)								
0-4	20	7,556	2.04	1.28, 3.23	1.87	1.18, 2.97	1.88	1.18, 2.99
4-6	98	65,593	1.07	0.84, 1.36	1.05	0.82, 1.34	1.05	0.82, 1.34
6-8	200	134,198	1.00		1.00		1.00	
>8	99	38,153	1.70	1.33, 2.16	1.53	1.20, 1.95	1.44	1.13, 1.84
<i>p</i> for linear trend			0.12		0.24		0.41	
<i>p</i> for quadratic trend			0.003		<0.001		0.002	
<b>p for interaction by age and sleep duration</b>			0.18		0.13		0.13	

Model 1: Adjusted for age and sex

Model 2: Adjusted for age, sex, education and marital status, smoking, alcohol consumption, physical activity, history of hypertension, history of diabetes and history of heart diseases

Model 3: Adjusted for age, sex, education, marital status, smoking, alcohol consumption, physical activity, history of hypertension, history of diabetes, history of heart disease, body mass index, systolic blood pressure, fasting glucose, total cholesterol, HDL cholesterol, triglycerides and use of hypnotics/sedatives

## References

1. Roth T. Insomnia: definition, prevalence, etiology, and consequences. *Journal of Clinical Sleep Medicine: JCSM: official publication of the American Academy of Sleep Medicine* 2007;3:S7.
2. Krueger PM, Friedman EM. Sleep Duration in the United States: A Cross-sectional Population-based Study. *Am J Epidemiol* 2009;169:1052-63.
3. Calem M, Bisla J, Begum A, et al. Increased prevalence of insomnia and changes in hypnotics use in England over 15 years: analysis of the 1993, 2000, and 2007 national psychiatric morbidity surveys. *Sleep* 2012;35:377.
4. Åkerstedt T, Knutsson A, Westerholm P, Theorell T, Alfredsson L, Kecklund G. Sleep disturbances, work stress and work hours: a cross-sectional study. *J Psychosom Res* 2002;53:741-8.
5. Sofi F, Cesari F, Casini A, Macchi C, Abbate R, Gensini GF. Insomnia and risk of cardiovascular disease: a meta-analysis. *Eur J Prev Cardiol* 2012;21:57-64.
6. Ikehara S, Iso H, Date C, et al. Association of sleep duration with mortality from cardiovascular disease and other causes for Japanese men and women: the JACC study. *Sleep* 2009;32:295.
7. Gottlieb DJ, Redline S, Nieto FJ, et al. Association of usual sleep duration with hypertension: the Sleep Heart Health Study. *Sleep* 2006;29:1009.
8. Sabanayagam C, Shankar A. Sleep duration and cardiovascular disease: results from the National Health Interview Survey. *Sleep* 2010;33:1037.
9. Cappuccio FP, Cooper D, D'Elia L, Strazullo P, Miller MA. Sleep duration predicts cardiovascular outcomes: a systematic review and meta-analysis of prospective studies. *Eur Heart J* 2011;32:1484-92.
10. Heslop P, Smith GD, Metcalfe C, Macleod J, Hart C. Sleep duration and mortality: the effect of short or long sleep duration on cardiovascular and all-cause mortality in working men and women. *Sleep Med* 2002;3:305-14.
11. Ferrie JE, Shipley MJ, Cappuccio FP, et al. A prospective study of change in sleep duration: associations with mortality in the Whitehall II cohort. *Sleep* 2007;30:1659.
12. Chang S-S, Wen CP, Tsai MK, Lawlor DA, Yang YC, Gunnell D. Adiposity, its related biologic risk factors, and suicide: a cohort study of 542,088 Taiwanese adults. *Am J Epidemiol* 2012;175:804-15.
13. Kripke DF, Garfinkel L, Wingard DL, Klauber MR, Marler MR. Mortality associated with sleep duration and insomnia. *Arch Gen Psychiat* 2002;59:131.
14. Ohayon MM. Epidemiology of insomnia: what we know and what we still need to learn. *Sleep Med Rev* 2002;6:97-111.
15. Meisinger C, Heier M, Löwel H, Schneider A, Döring A. Sleep Duration and Sleep Complaints and Risk of Myocardial Infarction in Middle-aged Men and Women from the General Population: The MONICA/KORA Augsburg Cohort Study. *Sleep* 2007;30:1121-7.
16. Ayas NT, White DP, Manson JE, et al. A prospective study of sleep duration and coronary heart disease in women. *Arch Intern Med* 2003;163:205-9.
17. Yeo Y, Ma SH, Park SK, et al. A prospective cohort study on the relationship of sleep duration with all-cause and disease-specific mortality in the Korean Multi-center Cancer Cohort study. *J Prev Med Public Health* 2013;46:271.
18. Shankar A, Koh W-P, Yuan J-M, Lee H-P, Yu MC. Sleep Duration and Coronary Heart Disease Mortality Among Chinese Adults in Singapore: A Population-based Cohort Study. *Am J Epidemiol* 2008;168:1367-73.
19. Patel SR, Ayas NT, Malhotra MR, et al. A prospective study of sleep duration and mortality risk in women. *Sleep* 2004;27:440-4.
20. Buckley TM, Schatzberg AF. On the Interactions of the Hypothalamic-Pituitary-Adrenal (HPA) Axis and Sleep: Normal HPA Axis Activity and Circadian Rhythm, Exemplary Sleep Disorders. *J Clin Endocrinol Metab* 2005;90:3106-14.

21. Irwin M, Clark C, Kennedy B, Christian Gillin J, Ziegler M. Nocturnal catecholamines and immune function in insomniacs, depressed patients, and control subjects. *Brain Behav Immun* 2003;17:365-72.
22. Farina B, Dittoni S, Colicchio S, et al. Heart rate and heart rate variability modification in chronic insomnia patients. *Behav Sleep Med* 2013:1-17.
23. Vgontzas AN, Liao D, Bixler EO, Chrousos GP, Vela-Bueno A. Insomnia with objective short sleep duration is associated with a high risk for hypertension. *Sleep* 2009;32:491.
24. Vgontzas A, Zoumakis E, Bixler E, et al. Adverse effects of modest sleep restriction on sleepiness, performance, and inflammatory cytokines. *J Clin Endocrinol Metab* 2004;89:2119.
25. Morselli L, Leproult R, Balbo M, Spiegel K. Role of sleep duration in the regulation of glucose metabolism and appetite. *Best Pract Res Clin Endocrinol Metab* 2010;24:687-702.
26. Chaput J-P, Després J-P, Bouchard C, Astrup A, Tremblay A. Sleep duration as a risk factor for the development of type 2 diabetes or impaired glucose tolerance: analyses of the Quebec Family Study. *Sleep Med* 2009;10:919-24.
27. Ayas NT, White DP, Al-Delaimy WK, et al. A prospective study of self-reported sleep duration and incident diabetes in women. *Diabetes Care* 2003;26:380-4.
28. Stevens RG. Light-at-night, circadian disruption and breast cancer: assessment of existing evidence. *Int J Epidemiol* 2009;38:963-70.
29. Cheng Y, Chen K-J, Wang C-J, Chan S-H, Chang W-C, Chen J-H. Secular trends in coronary heart disease mortality, hospitalization rates, and major cardiovascular risk factors in Taiwan, 1971–2001. *International journal of cardiology* 2005;100:47-52.
30. Finegold JA, Asaria P, Francis DP. Mortality from ischaemic heart disease by country, region, and age: Statistics from World Health Organisation and United Nations. *International Journal of Cardiology* 2013;168:934-45.
31. Gan Y, Gong Y, Tong X, et al. Depression and the risk of coronary heart disease: a meta-analysis of prospective cohort studies. *BMC Psychiatry* 2014;14.
32. Hung J, Whitford E, Hillman D, Parsons R. Association of sleep apnoea with myocardial infarction in men. *Lancet* 1990;336:261-4.
33. Benetó A, Gomez-Siurana E, Rubio-Sanchez P. Comorbidity between sleep apnea and insomnia. *Sleep Med Rev* 2009;13:287-93.
34. Ohayon MM, Roth T. Place of chronic insomnia in the course of depressive and anxiety disorders. *J Psychiatry Res* 2003;37:9-15.
35. Wen CP, Levy DT, Cheng TY, Hsu C-C, Tsai SP. Smoking behaviour in Taiwan, 2001. *Tob Control* 2005;14:i51-i5.