Longitudinal relationships between cardiovascular events, risk factors, and time-dependent sleep duration

Daiki Kobayashi1,2, Nagato Kuriyama3, Yasuhiro Osugi4,5, Hiroko Arioka1, Osamu Takahashi1,2

1Department of Medicine, Division of General Internal Medicine, St. Luke’s International Hospital, Tokyo, Japan
2Center for Clinical Epidemiology, St. Luke’s Life Science Institute, Tokyo, Japan
3Department of Epidemiology for Community Health and Medicine, Kyoto Prefectural University of Medicine, Kyoto, Japan
4Toyota Regional Medical Center, Toyota, Japan
5Fujita Health University, Toyoake, Japan

Abstract

Background: Although many studies have evaluated the relationships between sleep duration and cardiovascular (CV) events/risk factors, longitudinal associations with time-dependent sleep duration have not been adequately assessed.

Methods: A retrospective, longitudinal study was conducted involving individuals aged 20 years or older that received annual health check-ups at St. Luke’s International Hospital from 2005 to 2010. Data collection included self-reported demographic, clinical and health habit information (including sleep duration; < 6, 6–7, 7–8, ≥ 8 h), baseline examinations, and laboratory measures for each year. We conducted mixed effects analyses to examine the associations between non-fatal CV events, risk factors, and time-dependent sleep duration longitudinally.

Results: Of the total of 31,830 participants enrolled, 70.1% of participants changed their sleep duration, and 365 participants experienced CV events during follow-up periods. Compared to those reporting 7–8 h of sleep, those reporting less than 6 h of sleep were significantly more likely to experience non-fatal CV events (odds ratio [OR] 1.78; 95% confidence interval [CI] 1.03–3.07; p = 0.04), but other groups were not (OR 1.12; 95% CI 0.70–1.77; p = 0.64 for 6–7 h and OR 1.22; 95% CI 0.68–2.23; p = 0.50 for ≥ 8 h). The shortest sleep duration was associated with a higher likelihood of obesity/overweight status (OR 1.49; 95% CI 1.32–1.69; p < 0.01).

Conclusions: Individuals reporting less than 6 h of sleep were significantly more likely to have non-fatal CV events than those reporting 7–8 h of sleep. For the risk factors, short sleep duration was associated with obesity/overweight status. (Cardiol J 2018; 25, 2: 229–235)

Key words: sleep duration, longitudinal study, cardiovascular events, cardiovascular risk factors
Introduction

Since the 1990’s, many studies have noted that people with short sleep durations have worse health outcomes [1–3]. Short sleep duration may be associated with mortality, cardiovascular (CV) events, and CV risk factors. Most of these studies indicate that getting less than 6 h of sleep per day is associated with higher incidences of these risk factors and events [2, 4, 5]. Some studies mention that longer sleep duration (more than 9 or 10 h) is also associated with higher incidences of these risk factors and events compared to adequate sleep duration (7–8 h) [6, 7]. Other studies had CV risk factors as the outcome measurements. The risk factors included hypertension [8, 9], diabetes (impaired glucose tolerance) [10–12], dyslipidemia (high cholesterol level) [13–15], metabolic syndrome [16, 17] and obesity (weight gain) [18–20]. Although the majority of prior studies suggested negative effects of short sleep duration on health outcomes, some could not demonstrate these effects [21–23]. As a result, the associations are still controversial.

Among these previous studies, most evaluated the relationships only by baseline sleep duration. For instance, one study evaluated the development of coronary heart disease with a one-time baseline sleep duration 10 years ago [3]. Very few studies have evaluated the relationships by time trends of sleep duration through longitudinal studies. In the limited number of longitudinal studies, sleep duration was repeatedly measured very few times. In addition, a previous study suggested that sleep duration variability is an independent risk factor for CV risk factors [24]. This means that most people may change their sleep habits. Therefore, longitudinal studies with time-dependent sleep duration variables are needed to evaluate the effect of sleep duration on health more precisely.

The goal of this study is to investigate the relationships between time-dependent sleep duration and CV events and risk factors using large-scale longitudinal data.

Methods

Study participants

This is a retrospective, longitudinal study with all subjects participating in an annual voluntary health check-up program at the Center for Preventive Medicine at St. Luke’s International Hospital in Tokyo, Japan from 2005 to 2010. All participants completed a questionnaire about demographic information and health habits, including sleep duration and medical history, and underwent physical examinations and laboratory tests in an annual health check-up. The same information was obtained for each year during the study period. All participants included were 20 years or older in 2005. Individuals excluded had past medical histories of CV disease, including stroke. All data were extracted from electronic medical records.

Ethical approval and informed consent

The St. Luke’s International Hospital Ethics Committee institutional review board approved this study.

Because this study was a retrospective cohort study, opt-out methodology was applied. Those that chose not to participate in the research were excluded.

Measurement

Sleep duration. Sleep duration was measured by participant response to a question about sleep duration. Participants filled the blank “Sleep duration: _ _ hours”. Participants were classified into four groups based on their answers: less than 6 h, 6 h to less than 7 h, 7 h to less than 8 h, or more than 8 h [18]. The category of 7 h to less than 8 h was considered as normal sleep duration and defined this group as the reference group in this study. Based on previous studies, a mean daily sleep time of less than 6 h was considered as a short sleep duration [25, 26].

Outcomes. Primary outcomes included non-fatal CV events and the development of CV risk factors during follow-ups. Non-fatal CV events were determined based on a self-reported questionnaire at each health check-up. The development of CV risk factors was defined as self-reported and newly diagnosed hypertension, diabetes, dyslipidemia, and overweight/obesity status or abnormal related measurements on each factor. Participants with hypertension were defined as those with a self-reported history of hypertension, a measured systolic blood pressure of 140 mm Hg or greater, or a diastolic blood pressure of 90 mm Hg or greater [27, 28]. In the same way, participants with diabetes mellitus were defined as those with a self-reported history of diabetes, a fasting blood sugar of 126 mg/dL or greater, or a hemoglobin A1c (HbA1c) of 6.5% or greater [29, 30]. Participants with dyslipidemia were defined as those with a self-reported history, a low-density lipoprotein cholesterol level of 140 mg/dL or greater, a high-density lipoprotein cholesterol
level of 40 mg/dL or less, or a triglyceride level of 150 mg/dL or greater based on the criteria of the Japan Atherosclerosis Society [31]. Overweight/obesity status was defined as a measured body mass index of 25 kg/m² or higher based on the World Health Organization criteria for Asians [32].

**Covariates.** Participants were asked about the types and amount of alcohol they consumed in a week. Calculated average daily alcohol consumption was based on the questionnaire and participants were classified into two categories, excessive alcohol consumption vs. non-excessive alcohol consumption. Excessive alcohol consumption was defined as drinking more than 28 g/day (2 drinks) for males and 14 g/day (1 drink) for females based on criteria from the Centers for Disease Control and Prevention [33].

Participants were also asked about cigarette smoking and average number of packs of cigarettes smoked daily. They were classified as current smoker, former smoker, or never a smoker.

They were also asked about exercise habits in the form of how many times they exercised per week. Participants were classified as those who exercised regularly (at least 3 times a week) or those who exercised less than 3 times per week. Participants were asked about their occupations as well. Participant occupations were divided into three categories: unemployed, non-physical job and physical job, based on the answers from the self-reported questionnaire. Marital status was divided into two categories: married and unmarried.

### Statistical methods

Cross-sectional analyses were conducted on participant characteristics at baseline in 2005. χ² tests were applied to categorical variables, and analysis of variance (ANOVA) was used for continuous variables. Then, longitudinal analyses were performed with the data from 2006 to 2010 to investigate the longitudinal association between sleep duration and CV events and risk factors. Adjusted odds ratios (OR) for binominal outcomes of future non-fatal CV events and risk factors were obtained with the model of the binominal family with the logit link function. To account for repeated observations within participants and random effects of observations, a mixed effects model was applied with an unstructured working correlation. To account for changes in sleep duration over time, sleep durations were designated differently as time-dependent variables in longitudinal analyses.

All analyses were performed in 2012 using SPSS 19.0J statistical software (IBM Japan, Tokyo, Japan) and STATA 14 (STATA Corp., College Station, TX, USA).

### Results

In 2005, 40,035 participants received annual health check-ups. Among them, 796 were excluded due to past CV events. Participant characteristics at baseline are shown in Table 1. In terms of participant demographic information, those that reported less than 6 h of sleep at baseline tended to be younger and have more physical jobs but typically smoked cigarettes frequently, had infrequent exercise habits and were unmarried. In terms of clinical factors, those reporting shorter sleep duration tended to have less comorbidities and clinical measurements (95% confidence interval [CI] 0.66–0.85).

In longitudinal analyses, 31,830 (81.1%) participants attended health check-ups at least one time during the study periods. Throughout the follow-up periods, 70.1% of individuals changed their sleep duration category from baseline. However, the proportion of each sleep duration category were stable over the study period (Fig. 1). Three hundred sixty-five (1.1%) participants developed CV events. Longitudinal analyses revealed that those reporting less than 6 h sleep duration had a significantly higher OR of 1.78 (95% CI 1.03–3.07) for non-fatal CV events compared to those reporting 7–8 h sleep duration. In terms of clinical factors, those with short sleep duration (less than 6 h) were significantly overweight/obese (OR 1.49, 95% CI 1.32–1.69) but had lower rates of development for hypertension (OR 0.75, 95% CI 0.66–0.85) and dyslipidemia (OR 0.90, 95% CI 0.81–0.98) (Table 2). Table 3 shows the longitudinal relationships between clinical measurements and time-dependent sleep duration. These results were consistent with those for clinical factors, except for HbA1c (β coefficient: 0.01, 95% CI 0.01–0.02). In terms of longer sleep duration than 8 h, participants had no significant findings for all outcomes.

### Discussion

In our longitudinal study, time-dependent short sleep duration was associated with the development of CV events and obesity/overweight status, which is consistent with the majority of previous cross-sectional and cohort studies. In contrast, time-dependent short sleep duration had favorable associations with diabetes and dyslipidemia, which is inconsistent with previous studies.
The associations between sleep duration and CV events or risk factors are still controversial, especially for specific populations such as the elderly [34] or obese people [35]. Although a conclusion was not reached, adequate sleep duration would be clinically favorable compared to extremely short or long sleep duration.

In terms of CV events, obesity/overweight status and diabetes findings in our study were consistent with the majority of previous studies, even accounting for time-dependent sleep duration. Many previous studies discuss the mechanisms for the association between short sleep duration, CV events, and obesity. These may manifest through biochemical causes [36], social-behavioral causes [37], and/or CV risk-associated diseases. One
previous study discussed the possible mechanisms for developing diabetes in association with short sleep duration [38]. According to the study, short sleep duration stimulates adipocytes and increases circulating adipokine levels. Another study suggested that short sleep duration may decrease insulin sensitivity [39]. As a result, short sleepers are susceptible to the development of diabetes. Therefore, the present findings that sleep duration less than 6 h had negative effects on health outcomes were supported.

The reasons why some findings, such as the results on hypertension and dyslipidemia, contradicted previous studies are unclear. The main difference between our study and other previous studies is that changes in sleep duration were accounted for over time within individuals. As mentioned above, approximately 70% of participants changed their sleep duration from baseline during the study period. This adaptation and other potential confounders may explain the differences in results between this study and other predominant studies. For instance, individuals with obstructive sleep apnea syndrome or insomnia described as having short sleep duration may have been treated for these disorders. As a result, hypertension, which is a major complication of these disorders, may be resolved. In addition, there are several possible factors that may be prompted by dynamic social circumstances and could be associated with

### Table 2. Longitudinal association between time-dependent sleep duration and cardiovascular events/risk factors.

<table>
<thead>
<tr>
<th>Cardiovascular event</th>
<th>Hypertension</th>
<th>Diabetes mellitus</th>
<th>Dyslipidemia</th>
<th>Overweight/obesity status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 6 h</td>
<td>1.78 (1.03–3.07)</td>
<td>0.75 (0.66–0.85)</td>
<td>1.18 (0.95–1.46)</td>
<td><strong>0.90</strong> (0.81–0.98)</td>
</tr>
<tr>
<td>6–7 h</td>
<td>1.12 (0.70–1.77)</td>
<td><strong>0.87</strong> (0.79–0.97)</td>
<td>1.11 (0.93–1.32)</td>
<td>0.95 (0.87–1.03)</td>
</tr>
<tr>
<td>7–8 h</td>
<td><strong>Reference</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>More than 8 h</td>
<td>1.22 (0.68–2.23)</td>
<td>1.06 (0.92–1.24)</td>
<td>1.10 (0.86–1.40)</td>
<td>0.96 (0.85–1.09)</td>
</tr>
</tbody>
</table>

*Adjusted odds ratios: Models were adjusted for age, gender, occupation, health habits, marital status, calorie intake and time variables. Sleep duration was treated as the time-dependent variable. The numbers in bold indicate statistical significance with a p-value less than 0.05
†Hypertension indicates those with a history of hypertension or abnormality at follow-ups
‡Diabetes mellitus indicates those with a history of diabetes mellitus or abnormality at follow-ups
§Dyslipidemia indicates those with a history of dyslipidemia or abnormality at follow-ups
**Overweight/obesity status indicates a body mass index higher than 25 kg/m² based on World Health Organization criteria for Asians at follow-ups

### Table 3. Longitudinal association between time-dependent sleep duration and cardiovascular-related factors.

<table>
<thead>
<tr>
<th>SBP</th>
<th>DBP</th>
<th>FBS</th>
<th>HbA1c</th>
<th>TC</th>
<th>LDL-C</th>
<th>HDL-C</th>
<th>TG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 6 h</td>
<td>–0.45</td>
<td>–0.29</td>
<td>0.23</td>
<td>0.01</td>
<td>–0.18</td>
<td>–0.22</td>
<td>0.66</td>
</tr>
<tr>
<td>6 h to –0.18</td>
<td>to –0.12</td>
<td>to 0.47</td>
<td>to 0.02</td>
<td>to 0.38</td>
<td>to 0.26</td>
<td>to 0.97</td>
<td>to –1.06</td>
</tr>
<tr>
<td>6–7 h</td>
<td>–0.31</td>
<td>–0.09</td>
<td>0.05</td>
<td>0.01</td>
<td>0.15</td>
<td>0.03</td>
<td><strong>0.36</strong></td>
</tr>
<tr>
<td>7–8 h to –0.09</td>
<td>to 0.05</td>
<td>to 0.25</td>
<td>to 0.01</td>
<td>to 0.60</td>
<td>to 0.41</td>
<td>to 0.52</td>
<td>to 0.29</td>
</tr>
<tr>
<td>More than 8 h Reference</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 h</td>
<td>0.21</td>
<td>0.02</td>
<td>0.03</td>
<td>0.01</td>
<td>0.30</td>
<td>0.09</td>
<td>–0.08</td>
</tr>
<tr>
<td>7–8 h to 0.57</td>
<td>to 0.23</td>
<td>to 0.33</td>
<td>to 0.01</td>
<td>to 1.01</td>
<td>to 0.69</td>
<td>to 0.17</td>
<td>to 3.37</td>
</tr>
</tbody>
</table>

*Adjusted β-coefficients: Models were adjusted for age, gender, occupation, health habits, marital status, calorie intake, treatment status outcomes and time variables. Sleep duration was treated as a time-dependent variable; The numbers in bold indicate statistical significance with a p-value less than 0.05
DBP — diastolic blood pressure; FBS — fasting blood sugar; HbA1c — hemoglobin A1c; HDL-C — high-density lipoprotein cholesterol; LDL-C — low-density lipoprotein cholesterol; SBP — systolic blood pressure; TG — triglycerides; TC — total cholesterol
the results. Social stress, sleep disturbance from night-shift working or lifestyle changes, reduced physical activity related to transportation or hormonal disorders are all examples of factors that may be related to the results. Furthermore, the fact that the category of those sleeping less than 6 h included younger participants may explain the unexpected results.

**Limitations of the study**

There are some limitations in this study. First, some of the participants were not followed-up. Although the follow-up rate was more than 80%, those that were not followed may bias the results. However, considering the retrospective nature of the study, it is believed that a greater than 80% follow-up rate is still acceptable and therefore the bias is limited. In addition, they may be more interested in their health than the general population, because this is a completely voluntary health check. This may induce selection bias. Second, our data did not contain certain confounders such as quality of sleep, history of insomnia or sleep apnea syndrome. In addition, some information was lacking which related to CV events/risk factors, such as pathology and treatment status. These confounders may have influenced the results. Self-reported sleep duration and clinical outcomes may induce recall bias. Finally, quality of sleep may also be important for precise evaluations of the discussed associations. Further studies, which are prospective, have objective measurement for sleep duration, and have information about quality of sleep are needed to evaluate the longitudinal associations.

**Conclusions**

In this study, significant associations between short sleep duration and CV events and obesity/overweight status were observed, even in consideration of sleep duration as a time-dependent variable. Relationships between sleep duration and other risk factors, including hypertension and dyslipidemia, are still controversial.

**Conflict of interest:** None declared

**References**


