# Day-to-day variation in sleep duration is associated with increased all-cause mortality

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**DISCLOSURE STATEMENT**

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## ABSTRACT

**Study Objectives:** There is paucity of data on association between day-to-day variation in sleep pattern and all-cause mortality. We aim to investigate if day-to-day variation in sleep duration and onset of sleep are associated with cardiovascular and all-cause mortality.

**Methods:** Data belonging to 388 unique subjects from the Midlife in the United States (MIDUS) 2 Biomarker study (2004-09) was used in our study. Sleep onset, duration, sleep-wake cycles were collected for 7 consecutive days using the Actiwatch device. Sleep irregularity was assessed using mean and standard deviations in sleep duration and time of onset of sleep over 7 days. Cox proportional regression analysis and Fine and Gray subdistribution method were used with all-cause and cardiovascular mortality, respectively.

**Results:** Over a median of 8.6 years of follow up, 37 patients died including 10 deaths due to cardiovascular causes. There was no statistically significant increase in cardiovascular mortality with variation in sleep duration highest vs lowest tertile: HR 4.00(0.45-35.48, p 0.21). However, increased all-cause mortality was seen with the highest vs lowest tertile HR 3.99(1.33-11.94, p 0.01). Multivariable model adjusting for confounders had higher all-cause mortality with increased sleep duration variation, highest vs lowest tertile HR 4.85(1.52-15.49, $P < 0.01$).

**Conclusions:** Day to day variation in sleep duration is associated with increased all-cause mortality but not cardiovascular mortality after adjusting for mean sleep duration, inflammation, diabetes, age, BMI, renal function and blood pressure. Irregularity in the onset of sleep is not associated with all-cause mortality or cardiovascular mortality.

**Keywords:** sleep irregularity, all-cause mortality, cardiovascular disease mortality

## INTRODUCTION

Sleep is essential for health and wellbeing.[1] Sleep plays an important role in regulation of a number of physiologic responses including appetite, endothelial function, neurohumoral balance, vascular tone, blood pressure and glucose control.[2-5] The importance of sleep duration is widely recognized in various epidemiological studies.[6] Importance of sleep was endorsed by American College of Cardiology and the American Heart Association in their preventive guidelines.[7] Both more sleep and less sleep have been associated with increased cardio-metabolic risk in multiple observational studies.[6] In addition, there is a growing body of evidence showing certain disruptions in circadian rhythm are associated with increased risk of atherosclerosis and coronary artery disease.[8] Circadian rhythm disruption is associated with higher blood pressure, glucose intolerance, dyslipidemia and obesity, all of these risk factors are associated with increased cardiovascular risk.[9] Variation in day-to-day sleep may represent this chronic sleep disruption and has shown to be prevalent in the general population. A number of factors in modern society negatively influence the quality and quantity of sleep, these factors include use of artificial light, use of cell phone and other portable media devices especially immediately prior to falling asleep, in addition to increased work hours and shift work.[10] Day to day variation in sleep is not well studied and is being recognized as a potential risk factor only recently.[8] Questionnaire based studies on sleep are prone to recall bias. There are few studies using objective sleep data. We aim to access if objective actigraphy measured day to day variation in sleep is associated with increased cardiovascular mortality or all-cause mortality independently with a long duration of follow up.

## METHODS

### Study design, participants and data collection

The MIDUS2 biomarker study is a subset of Midlife in the United States, national longitudinal study of health and wellbeing. MIDUS started in 1994 with a national survey of over 7,000 Americans (aged 25 to 74). The subjects from the original MIDUS study were then followed up in 2004-2006. An African American sample was recruited in addition to the follow up subjects. This new cohort of nearly 5,900 subjects was called MIDUS 2 sample. Of these patients, 388 subjects had sleep data and were used in our study (2004-09) .(Figure 1) More details about the study design, follow up, sample selection are available at http://www.midus.wisc.edu/ and https://doi.org/10.3886/ICPSR29282.v9. Data was available as deidentified datasets for secondary analysis.[11]

### Sleep and other variables

The objective sleep data was measured using the Mini Mitter Actiwatch-64 activity monitor device. Sleep onset, duration, sleep-wake cycles were collected for seven consecutive days. Mean and standard deviations in sleep duration and time of onset of sleep over seven days were calculated to assess for sleep irregularity. Mortality data was available with a follow up until December 2016. ICD10 codes(I10-I99) were used to identify all cardiovascular mortality including those occurring in the community.
Other variables included in the analysis include age, sex, diabetes, body mass index, mean sleep duration, HDL cholesterol and non-HDL cholesterol, systolic blood pressure, diastolic blood pressure, glomerular filtration rate and C-reactive protein.

### Statistical analysis

Sleep duration and sleep onset duration data available in minutes in the dataset was divided into tertiles as it would be more clinically meaningful. Continuous variables were described as mean ± standard deviation or medians [interquartile range] and compared using the overall ANOVA test between the various tertile groups. Categorial variables were compared using chi-square test. Cox proportional hazard regression analysis was performed with all-cause mortality as the outcome. Cox Competing risk analysis for cardiovascular mortality was done with Fine and Gray subdistribution hazard.[12] Schoenfeld residuals

were used to assess the cox proportional hazard assumptions are fulfilled. Kaplan-Meier survival curves were plotted with all-cause mortality as the outcome. All statistical analysis was performed using R version 4.0.3.

## RESULTS

### Baseline characteristics

Our analysis included a total of 388 subjects. Mean age of the cohort was 54.56±11.79 years; females were 230(59.3%). BMI 30.56±7.06 kg/$m^2$. Over a median of 8.6 years of follow up, 37 patients died including 10 deaths due to cardiovascular mortality. 85 (21.9%) patients had diabetes. Further, the study cohort was divided into tertiles based on the standard deviation (SD) of the actigraphy measured sleep duration for seven consecutive days. Sleep duration SD tertiles ranges were: 11-41 minutes, 41-68 minutes and 68-258 minutes in lowest to highest tertiles respectively. Higher tertile indicates more sleep variation. Subjects in the higher tertile were younger with mean of 52.51 ±11.59 years compared to the lowest tertile 56.50±11.02 years. Notably, the group of subjects with higher sleep duration variability had a higher prevalence of diabetes 27.9 % compared to the lowest variation group 14.7%, p 0.03. The mean sleep duration was lower 353±69 minutes in the highest tertile group compared to lowest tertile 383±57 minutes, p<0.001. Standard deviations for onset in sleep were 5-57 minutes, 57-103 minutes, and 104-1107 minutes in lowest to highest tertiles respectively. Higher tertile indicates more variation in onset of sleep. Subjects in the higher tertile were younger with a mean of 52.16 ±10.88 years compared to the lowest tertile 57.26±12.10 years. Notably, the group of subjects with higher variability in sleep onset had higher prevalence of diabetes 28.7% compared to the lowest variation group 15.5%, p 0.04. The mean sleep duration was lower 339±70 minutes in the highest tertile group compared to lowest tertile 398±51 minutes, p<0.001. (Table 1)

### Sleep duration SD and mortality

Highest vs lowest tertile of SD of 7-day sleep duration was associated with increased all-cause mortality HR 3.99(1.33-11.94), p <0.01 on univariate analysis. After adjusting for age, sex, body mass index, diabetes mellitus, mean sleep duration, HDL and non-HDL cholesterol, systolic and diastolic blood pressures, renal function and C-reactive protein, day to day variation in sleep duration was independently associated with increased all-cause mortality adjusted hazard ratio (aHR) 4.85(1.52-15.49), p<0.01. Sleep variation was not associated with cardiovascular mortality highest vs lowest tertile 4.00(0.45-35.48), p 0.21(Table 2 and Figure 2).

### Sleep timing SD and mortality

Highest vs lowest tertile of SD of 7-day sleep timing was not associated with either cardiovascular mortality 0.98(0.19-4.90), p 0.98 or all-cause mortality HR 4.00(0.45-35.48), p 0.21 (**Table 2** and **Figure 2**).

## DISCUSSION

To the best of our knowledge, this is the first prospective analysis evaluating the association of sleep irregularity with all-cause mortality and cardiovascular mortality. We compared subjects with regular sleep and irregular sleep from the community. Irregularity of sleep was assessed in terms of irregularity in duration of sleep and irregularity in the timing of sleep. Our study results showed that irregular sleep is associated with greater than 3-fold increase in all-cause mortality over a median follow up of 8.6 years (Figure 3). In addition, after adjusting for various traditional cardiovascular risk factors there was increased all-cause mortality risk. While there was a trend towards increased cardiovascular mortality

with irregular sleep duration, there was no statistical significance. Irregularity in sleep timing was not associated with either increased cardiovascular mortality or all-cause mortality.

Multiple observational studies have shown that poor sleep hygiene is associated with increased cardio-metabolic risk.[13-15] Disruptions in the circadian rhythm have been shown to be associated with glucose intolerance, risk of diabetes, hyperlipidemia, hypertension, and cardiovascular disease.[16] All these risk factors are associated with increased mortality in multiple epidemiologic studies.[17] Moreover, disruption in circadian rhythm observed in shift workers, pilots, and even those with social jet leg, defined as sleeping less on weekdays and catching up on weekends are at increased cardio-metabolic risk.[18-20] Subjects with irregular sleep patterns have significant metabolic derangement at baseline. Even after adjusting for these derangements, irregularity in sleep duration is associated with increased all-cause mortality. At a behavioral level, poor sleep hygiene is associated with irregular breakfast consumption and change in number of meals which have been demonstrated to be associated with risk of obesity, diabetes and increased mortality.[21] In addition, change in neurohumoral balance, transcription of various genes including the CLOCK gene could be the potential reasons for increase in mortality seen with irregular sleep duration in our study.[22]

A recent study by Huang et al[8] has shown that sleep irregularity in both duration and timing are associated with increased cardiovascular disease risk. Our study endpoint is different, and we only evaluated for total mortality and mortality due to cardiovascular disease. In our study, there was a trend towards increased cardiovascular mortality, however this was not statistically significant. Due to the wide confidence interval, it is likely that our findings were due to low sample size. This is one of the major limitations of our study.

Irregularity in timing of sleep was not associated with neither increased cardiovascular mortality nor all-cause mortality in our cohort. This is an interesting finding and differs from the observations in the study by Huang et al[8] which showed increased CVD risk with sleep irregularity. Even though our study endpoints are different, this discrepancy in findings need to be evaluated further.

Due to the growing body of evidence of importance of duration and regularity of sleep in health and disease. This topic should become a part of preventive disease discussions in primary care clinic and preventive cardiology clinics. There are a number of limitations that need to be noted. (1) The sample size was small to modest and the study should be viewed as hypothesis generating. Pooled cohort studies need to be performed to evaluate the importance of sleep irregularity further. (2) Other sleep disorders including sleep disordered breathing were not included due to low sample size. (3) Although we used seven-day actigraphy recordings to measure day to day variation in sleep, this may not represent chronic circadian rhythm irregularity. (4) Morning-ness/evening-ness data was not available. (5) Other ways to assess sleep irregularity such as sleep irregularity index(SRI)[23] and social jet lag[24] were not evaluated in the current study.

## CONCLUSIONS

Day to day variation in sleep duration is associated with increased all-cause mortality but not cardiovascular mortality after adjusting for mean sleep duration, inflammation, diabetes, age, BMI, renal function and blood pressure. Irregularity in the onset of sleep is not associated with all-cause mortality or cardiovascular mortality.

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**Table 1:** Baseline characteristics.

| | Study Population (n = 388) | Sleep Duration SD (Tertiles)* | | | | Sleep Timing SD (Tertiles)# | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Lowest (n = 129) | Intermediate (n = 130) | Highest (n = 129) | *P* | Lowest (n = 129) | Intermediate (n = 130) | Highest (n = 129) | *P* |
| Age (years), mean (SD) | 54.56 (11.79) | 56.50 (11.02) | 54.68 (12.46) | 52.51 (11.59) | 0.024 | 57.26 (12.10) | 54.28 (11.87) | 52.16 (10.88) | 0.002 |
| Female, n (%) | 230 (59.3) | 78 (60.5) | 79 (60.8) | 73 (56.6) | 0.748 | 76 (58.9) | 84 (64.6) | 70 (54.3) | 0.236 |
| Diabetes, n (%) | 85 (21.9) | 19 (14.7) | 30 (23.1) | 36 (27.9) | 0.035 | 20 (15.5) | 28 (21.5) | 37 (28.7) | 0.038 |
| Mean sleep duration (min), mean (SD) | 371.35 (64.74) | 383.56 (57.43) | 376.76 (62.87) | 353.68 (69.97) | <0.001 | 398.67 (51.38) | 376.19 (57.04) | 339.15 (70.23) | <0.001 |
| HDL cholesterol (mg/dL), median [IQR] | 52.00 [42.00, 64.00] | 54.00 [44.00, 65.00] | 49.50 [40.00, 61.75] | 51.00 [42.00, 65.00] | 0.094 | 54.00 [45.00, 64.00] | 52.00 [40.00, 64.75] | 48.00 [42.00, 61.00] | 0.349 |
| Non-HDL cholesterol (mg/dL), mean (SD) | 129.25 (39.84) | 131.19 (37.18) | 124.96 (38.25) | 131.63 (43.75) | 0.322 | 124.64 (33.55) | 127.67 (36.20) | 135.45 (47.86) | 0.08 |
| Body mass index (kg/m$^2$), median [IQR] | 29.52 [25.60, 33.83] | 28.91 [25.12, 33.11] | 29.48 [25.86, 33.36] | 30.77 [26.11, 35.64] | 0.088 | 28.45 [25.26, 31.88] | 29.80 [25.63, 34.55] | 30.86 [26.35, 36.09] | 0.009 |
| Systolic blood pressure (mmHg), mean (SD) | 131.79 (17.04) | 133.31 (16.62) | 129.92 (18.40) | 132.15 (15.95) | 0.267 | 131.66 (16.99) | 132.00 (16.73) | 131.71 (17.52) | 0.985 |
| Diastolic blood pressure (mmHg), mean (SD) | 76.97 (10.56) | 76.39 (10.25) | 76.46 (11.18) | 78.05 (10.19) | 0.359 | 75.98 (10.19) | 76.19 (9.92) | 78.73 (11.37) | 0.066 |
| Glomerular filtration rate (ml/min), mean (SD) | 118.71 (39.23) | 117.65 (33.23) | 116.05 (38.73) | 122.46 (44.88) | 0.393 | 112.81 (36.46) | 114.69 (36.12) | 128.66 (43.10) | 0.002 |
| C-reactive protein (ug/mL), median [IQR] | 1.62 [0.76, 3.91] | 1.31 [0.65, 2.92] | 1.85 [0.79, 4.27] | 1.96 [0.89, 4.60] | 0.058 | 1.22 [0.60, 3.04] | 1.82 [0.75, 3.91] | 2.19 [0.96, 4.60] | 0.002 |

*Sleep duration SD (tertiles) in minutes: lowest tertile = 11-41 minutes; intermediate tertile = 41-68 minutes; highest tertile = 68-258 minutes.
#Sleep timing SD (tertiles) in minutes: lowest tertile = 5-57 minutes; intermediate tertile = 57-103 minutes; highest tertile = 104-1107 minutes.

**Table 2:** Cox proportion regression for all-cause mortality and fine and gray subhazard regression for cardiovascular mortality with variation in sleep duration and onset.

| | All-Cause Mortality | | Cardiovascular Mortality | |
|---|---|---|---|---|
| | **HR (95 CI)** | ***P*** | **HR (95 CI)** | ***P*** |
| **Unadjusted Models** | | | | |
| Standard deviation (min) of sleep duration* over 7 days | | | | |
| Lowest | Ref | | Ref | |
| Intermediate | 3.63 (1.19-10.99) | 0.02 | 5.11 (0.59-43.57) | 0.14 |
| Highest | 3.99 (1.33-11.94) | 0.01 | 4.00 (0.45-35.48) | 0.21 |
| Standard deviation (min) of time of sleep onset# over 7 days | | | | |
| Lowest | Ref | | Ref | |
| Intermediate | 0.84 (0.36-1.96) | 0.69 | 1.32 (0.29-5.86) | 0.72 |
| Highest | 1.1 (0.49-2.45) | 0.81 | 0.98 (0.19-4.90) | 0.98 |
| **Fully Adjusted Model** | | | | |
| Standard deviation (min) of sleep duration over 7 days | | | | |
| Lowest | Ref | | Ref | |
| Intermediate | 3.51 (1.12-10.99) | 0.03 | 4.44 (0.61-31.98) | 0.14 |
| Highest | 4.85 (1.52-15.49) | <0.01 | 4.77 (0.67-33.70) | 0.12 |
| Age (years) | 1.11 (1.07-1.17) | <0.01 | 1.12 (1.06-1.18) | <0.01 |
| Male | 1.53 (0.59-3.95) | 0.38 | 3.91 (0.56-27.27) | 0.17 |
| Non-diabetic | 1.07 (0.49-2.36) | 0.86 | 2.07 (0.39-10.83) | 0.39 |
| Mean sleep duration (min) | 0.99 (0.99-1.00) | 0.18 | 1.00 (0.99-1.01) | 0.94 |
| Body mass index ($kg/m^2$) | 0.99 (0.92-1.06) | 0.72 | 1.01 (0.86-1.19) | 0.89 |
| Non-HDL cholesterol (mg/dL) | 0.99 (0.99-1.01) | 0.88 | 0.98 (0.95-1.01) | 0.23 |
| HDL cholesterol(mg/dL) | 0.98 (0.95-1.01) | 0.19 | 0.99 (0.94-1.05) | 0.84 |
| Systolic blood pressure (mmHg) | 1.01 (0.98-1.03) | 0.64 | 0.99 (0.93-1.06) | 0.84 |
| Diastolic blood pressure (mmHg) | 0.99 (0.94-1.04) | 0.71 | 0.99 (0.87-1.12) | 0.89 |
| Glomerular filtration rate (ml/min) | 1.00 (0.99-1.01) | 0.78 | 0.99 (0.96-1.02) | 0.61 |
| C-reactive protein (ug/mL) | 1.02 (0.98-1.06) | 0.25 | 1.01 (0.93-1.12) | 0.69 |

*Sleep duration SD (tertiles) in minutes: lowest tertile = 11-41 minutes; intermediate tertile = 41-68 minutes; highest tertile = 68-258 minutes. #Sleep timing SD (tertiles) in minutes: lowest tertile = 5-57 minutes; intermediate tertile = 57-103 minutes; highest tertile = 104-1107 minutes.

**Figure 1:** Flowchart of patients included in the current study as a subset of the MIDUS 2 cohort.

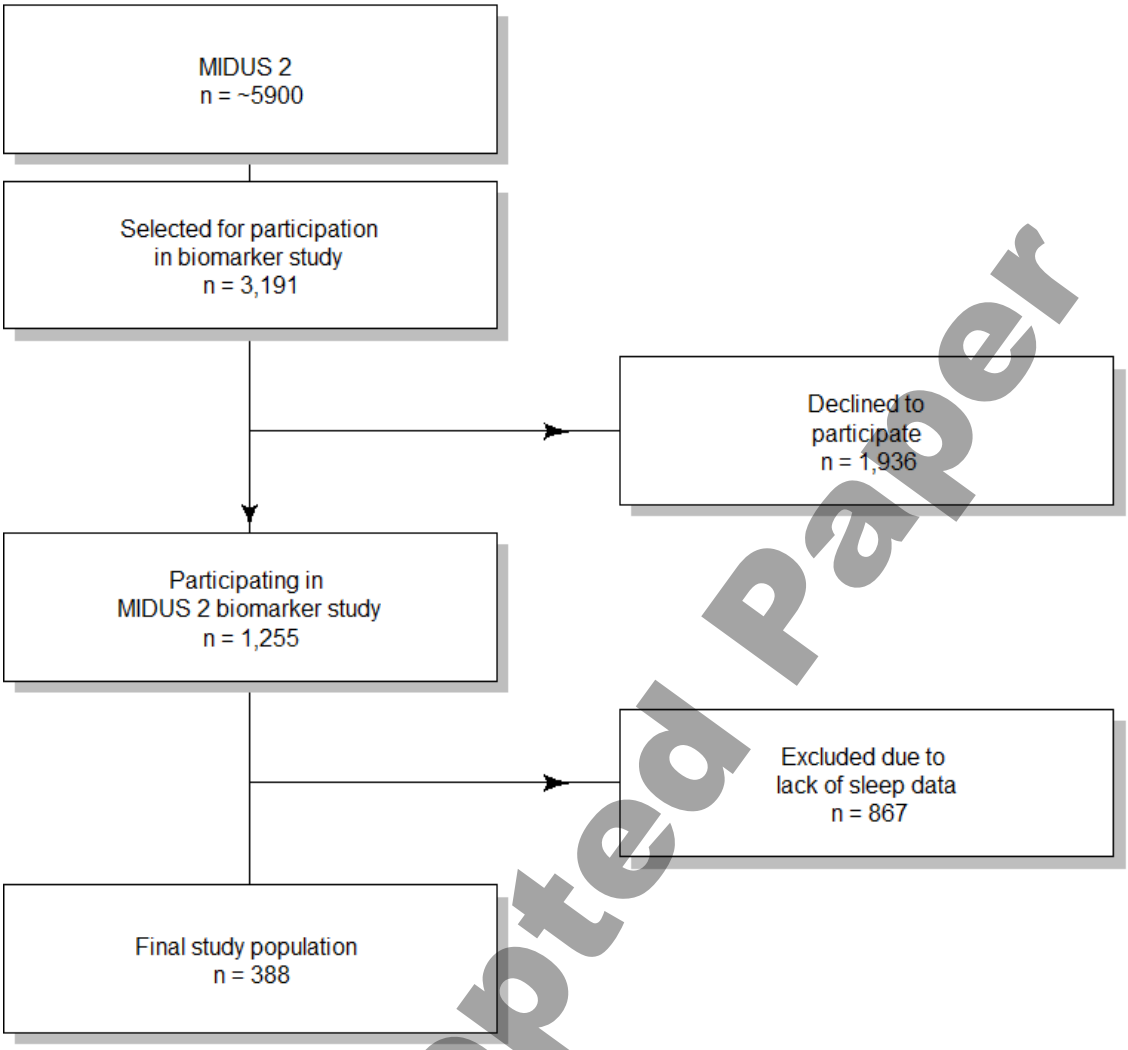
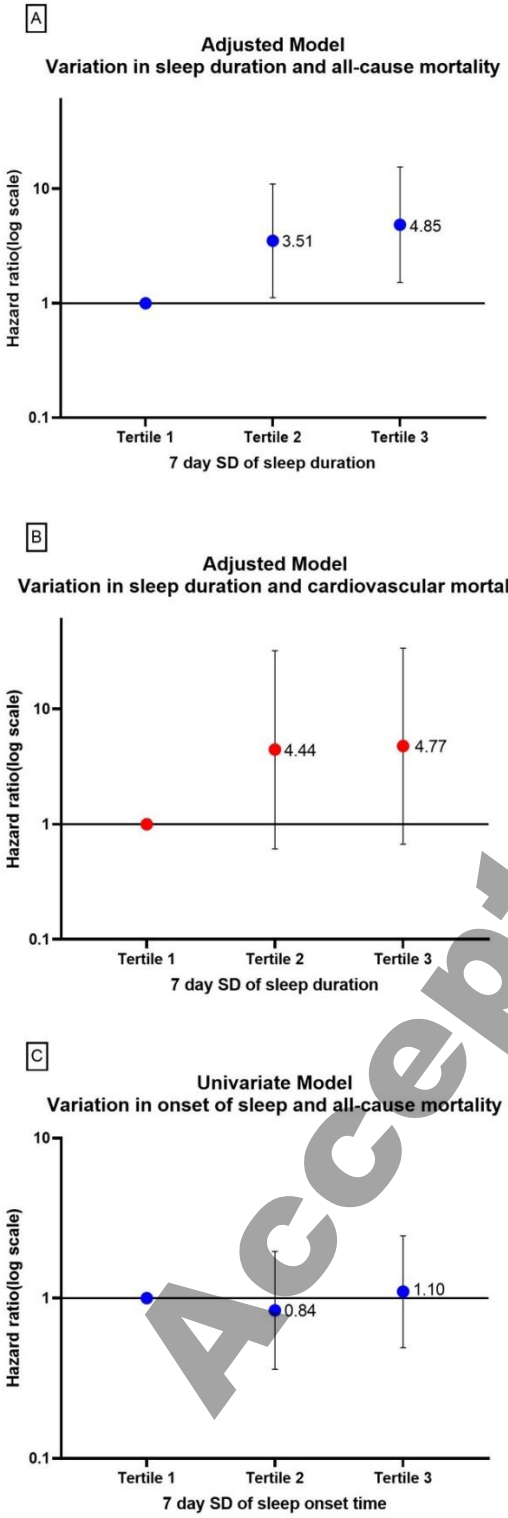
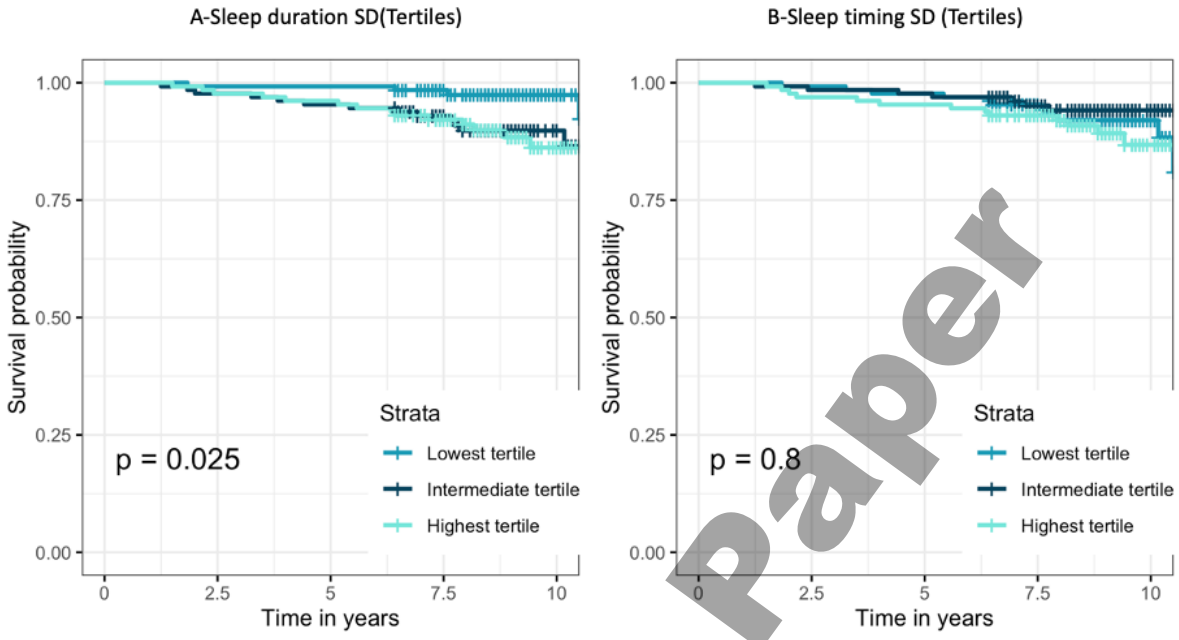


**Figure 2:** Modified forest plots.




**(A)** Adjusted model for variation in sleep duration and all-cause mortality. **(B)** Adjusted for variation in sleep duration and cardiovascular mortality. **(C)** Univariate model for variation in onset of sleep and all-cause mortality.

**Figure 3:** Kaplan-Meier plots for all-cause mortality with log-rank test *P* value inset.




**(A)** Grouped by sleep duration SD tertiles. **(B)** Grouped by sleep timing SD tertiles.