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Sleep Duration, Sleep Quality, and Mental Stress-Induced Myocardial Ischemia after Acute Myocardial Infarction

By

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Degree to be awarded: MPH

Department of Epidemiology

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Committee Chair

Sleep Duration, Sleep Quality, and Mental Stress-Induced Myocardial Ischemia after Acute Myocardial Infarction

By

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Bachelor of Medicine

Xi'an Jiaotong University, College of Medicine

2012

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An abstract of

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Abstract

Sleep Duration, Sleep Quality, and Mental Stress-Induced Myocardial Ischemia after Acute Myocardial Infarction

By Shuyang Fang

Background: Both abnormal sleep duration and poor sleep quality are associated with high cardiovascular disease mortality and adverse outcomes after myocardial infarction (MI); and an increased predisposition toward emotionally provoked myocardial ischemia may play a role. We investigated the independent and joint associations of sleep duration, and sleep quality with mental stress-induced myocardial ischemia among young MI survivors.

Methods: We studied 145 participants (64 women and 81 men) age 38 – 60 years who were hospitalized for acute MI in the previous 8 months. Patients underwent myocardial perfusion scans at rest, after mental stress, and after physical stress. Myocardial perfusion defects scores were obtained with observer-independent software. A summed difference score (SDS), the difference between stress and rest perfusion defect scores, was used to quantify the perfusion defects. The Pittsburgh Sleep Quality Index (PSQI) was used to measure sleep duration and sleep quality, which were analyzed as separate and combined scores.

Results: There was a U-shaped association between sleep duration and stress-induced myocardial ischemia (both mental and physical stress). After adjustment for relevant confounders, both short and long sleepers were found to have a higher probability of developing mental stress-induced myocardial ischemia (MSIMI) ("≤ 5 h" OR: 1.62, 95% CI: (0.41, 6.50); "6 h" OR 2.11, 95% CI: (0.54, 8.32); "≥ 8 h" OR 3.17, 95% CI: (0.81, 12.4)). Patients with poor sleep quality were also found to be associated with higher risk of MSIMI (OR: 1.31; 95% CI: 0.49 – 3.45). However, all the associations found above were not statistically significant.

Conclusion: In this pilot study we found preliminary evidence that abnormal sleep duration and poor sleep quality may be directly associated with mental stress induced myocardial ischemia in younger post MI patients, even though this association was not statistically significant.

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BACKGROUND

Over the past century, average sleep duration has decreased dramatically in the US, from approximately 9 hours to 6.8 hours per night in 2005 [1]. Accordingly, the prevalence of short sleep duration, which is generally defined as average sleep time per night less than 7 hours, has increased from 7.6% in 1975 to 9.3% in 2006, a period during which the prevalence of chronic disease, such as diabetes, obesity and coronary heart disease (CHD), increased substantially[1]. This lower average sleep duration across westernized populations correlates with increased reporting of fatigue, tiredness, and excessive daytime sleepiness[2]. It is concerning that sleep deprivation not only affects detrimental behavioral and psychological well-being, but also other aspects of physical health, as accumulating evidence suggests that sleep duration is a vital important determinant of health and mortality.

Previous studies suggested that sleep duration is associated with all-cause mortality, CHD related mortality in a U-shaped fashion [2] [3-11] [12, 13], such that the lowest risk is most often found in the group who reports sleep durations of 7 hours. In a recent meta-analysis on the association between sleep duration and mortality which included 23 studies [14], the pooled relative risk (RR) of short sleep duration for all-cause mortality and cardiovascular disease (CVD) related mortality were 1.10 [95% confidence interval (CI): 1.06, 1.15] and 1.06 (95% CI: 0.94, 1.18), respectively, even though the result for CVD mortality is not statistically significant. Similarly, among the 17 studies reporting data on long sleep duration and mortality, the pooled RRs comparing the long sleepers with medium sleepers were 1.23 (95% CI: 1.17, 1.30) for all-cause mortality, and 1.38 (95% CI: 1.13, 1.69) for cardiovascular-related mortality. Nearly uniformly, the mortality of CHD

increase with further deviation from the 7 hours range. This association persisted after adjusting for socio-demographic and established CHD risk factors.

This U-shaped association was also found between sleep duration and the incidence of CVD [12]. Amagai et al, in an analysis based on the Jichi Medical School Cohort Study, found that the hazard ratios (95% confidence intervals) for the incidence of cardiovascular diseases for individuals sleeping less than 6 hours and 9 hours or longer were 2.14 (1.11-4.13) and 1.33 (0.93-1.92) in men, and 1.46 (0.70-3.04) and 1.28 (0.88-1.87) in women, respectively, relative to those who reported sleeping 7 to 7.9 hours per day, after adjusting for age, systolic blood pressure, serum total cholesterol, body mass index, smoking and alcohol intake. Sabanayagam and Shankar [13] utilized the data from National Health Interview Survey to conduct a cross-sectional study and suggested that both short and long sleep durations to be independently associated with CVD, after adjustment of potential confounders. Compared with a sleep duration of 7 h (referent), the multivariate odds ratio (95% confidence interval) of CVD was 2.20 (1.78, 2.71), 1.33 (1.13, 1.57), 1.23 (1.06, 1.41), and 1.57 (1.31, 1.89) for sleep duration < or = 5 h, 6 h, 8 h, and > or = 9 h. This association persisted in subgroup analyses by gender, race-ethnicity, and body mass index categories. In a recent meta-analysis incorporating 15 studies by Cappuccio et al., short sleep duration was found to be related to coronary heart disease (CHD) (RR:1.48 [1.22-1.80]). For long compared to normal sleep duration, Cappuccio et al. reported an RR of 1.41 (1.19-1.68) for total CVD, 1.38 (1.15-1.66) for CHD. These results confirm the presence of a U-shape association which is consistent with the association between sleep duration and all-cause mortality. A recent large prospective cohort study conducted by Hoevenaar-Blom et al [15], demonstrated that short sleepers (≤ 6 h) had a 23% higher risk

of CHD (HR: 1.23 [1.04-1.45]) compared to normal sleepers (7 h) after adjustment for all confounders. Furthermore, short sleepers with poor sleep quality had a 79% higher risk of CHD incidence (HR: 1.79 [1.24-2.58]) compared to normal sleepers with good sleep quality.

It is believed that different mechanisms may underlie such associations at either end of the distribution of sleep duration. Specifically, previous studies found short sleep duration to be a risk factor for a variety of adverse health conditions, including obesity, impaired glucose intolerance (IGT), decreased insulin sensitivity, type 2 diabetes and hypertension [16-18] [6, 19-21]. Short sleep duration may also act through disturbances of the immune function and promote inflammation in blood vessels [22]. Another potential mechanism is that short sleep duration and disturbed sleep contribute to the increased risk of CHD by an inability of the organism to diminish sympathetic stimulation of the cardiovascular system at night and, thus, prevent rest and restoration [23]. The association between long sleep duration and CHD incidence may be explained by long sleep duration being an early symptom of disease and preceding clinical diagnosis [6].

In addition, other sleep complaints, such as poor sleep quality, sleep disturbance and insomnia symptoms, were found to potentially modify this U-shaped association. Previous studies suggested that compared to short sleepers with good sleep quality, short sleepers with poor sleep quality have higher risk of developing CHD [15] and that long sleep duration was associated with greater CHD mortality among those with poor sleep quality [11]. It was found that the association between short sleep duration and CHD risk was greatest among those with sleep disturbance [24].

Coronary artery disease (CHD), particularly Acute Coronary Syndromes (ACS), which include ST segment elevation myocardial infarction (STEMI), non-ST segment elevation myocardial infarction (NSTEMI) and unstable angina (UA), accounts for 68% of all cardiovascular disease (CVD) related deaths, which is still the most common cause of death in the US [25-27]. It is well-established that a series of disease specific factors such as the size and anatomic location of the infarction, myocardial contractility, and ventricular arrhythmias are associated with early outcome (within 30 days) of acute MI [28, 29]. Long term prognosis also correlates with well-established coronary artery disease risk factors such as diabetes, hypertension, cholesterol levels and smoking and dietary habits after acute MI [30-33]. These established CV risk factors, however, only explain half or fewer of subsequent CV events. Thus, previous risk models may not be optimal in determining individual risk for long-term adverse outcomes or in helping to identify individual patients who do not respond to therapy [34]. In addition to these biomedical factors, several psychological and social factors were found to be associated with recurrent cardiac events such as myocardial ischemia or angina and mortality after acute MI [35-37]. Depression, PTSD, anxiety, work strain, lack of social support and perceived stress were found to be associated with the outcome of acute MI [38-41].

While there is no previous literature on an association between sleep duration and MI prognosis, studies found that impaired sleep or poor sleep quality was associated with worse short and long term of prognosis of MI in terms of higher rate of MI recurrence, stroke and heart failure [42]. However, the mechanisms that may underlie this association remains uninvestigated. We hypothesize that physical and mental stress induced

myocardial ischemia could be a potential pathway between sleep duration and MI prognosis.

In order to accurately measure the effects of psychological stress on myocardial ischemia in coronary artery disease patients, researchers have devised a standardized mental stress test used in conjunction with myocardial perfusion imaging techniques to investigate the occurrence of mental stress induced myocardial ischemia (MSIMI) [43-51]. MSIMI was found to be a significant prognostic predictor after acute MI [52-55]. Development of ischemia in response to mental stress in the laboratory is independently associated with significantly higher rates of fatal and nonfatal cardiac events and predicts events over and above exercise-induced ischemia.

As discussed above, numerous previous studies consistently found a U-shaped association between sleep duration and CHD incidence and mortality. Psychological and social factors such as depression[56], perceived stress level[57], and work strain[36] were found to be associated with the severity of MSIMI, all of which are potential causal or intermediate factors for sleep duration. However, whether the U-shaped association also exists between sleep duration and the incidence and severity of MSIMI among post MI patients remains uninvestigated.

Our study will investigate whether the U-shaped relationship that was previously found between habitual sleep duration categorized as < or = 6 hours, 7 to 8 hours, and > or = 9 hours and CVD incidence/mortality, also applies to an association between habitual sleep duration and the incidence and severity of MSIMI and PSIMI.

METHODS

Participants

Participants age 18 to 59 years old at the time of screening who were hospitalized for MI in the previous 8 months were recruited through the Emory Healthcare system as part of the Myocardial Infarction and Mental Stress Study (MIMS) [56, 58] The diagnosis of MI was verified by medical record review based on standard criteria of troponin level and electrocardiogram (ECG) changes. Participants were excluded if they had unstable angina or acute MI within the past week, or a severe comorbid medical or psychiatric disorder that could influence the study results, such as malignant conditions, end stage renal disease (ESRD), current substance abuse, or schizophrenia. Other exclusion criteria included weight over 400lb, pregnancy, breast feeding, postmenopausal hormone replacement therapy (HRT), and psychotropic medications other than antidepressants and sleep medications. Participants were also excluded if they were unable to exercise on a treadmill, as assessed by having a metabolic equivalents (METs) score less than 5 on the Duke Activity Status Index (DASI).

Study design

Patients underwent three single-photon emission computed tomography (SPECT) imaging scans to quantitatively assess myocardial perfusion, one at rest, one with mental stress, and one with physical stress (standard exercise stress test or pharmacological stress test with regadenoson if unable to exercise). The two stress scans were performed on separate occasions within 1 week of each other; the order of the two tests was balanced. All testing

was done in the morning after an overnight fast, and 24 hours of withholding anti-ischemic medications. Sociodemographic and psychosocial data were collected at the first visit before cardiac testing. At the end of the study protocol, medical records were abstracted for clinical information, including catheterization data. All participants signed a written informed consent. The study protocol and informed consent were approved by the Emory University Institutional Review Board.

Mental Stress Procedure

Mental stress was induced by a standardized public speaking task [59], after 30 minutes of rest in a quiet, dim and temperature controlled room. Participants were ask to imagine a real-life stressful event, such as a close relative been mistreated in a nursing home, as asked to make up a story about this. After 2 minutes of preparation, 3 minutes of presentation was given in front of a video camera and an audience wearing white coats. Participants were also told that the speech would be evaluated by the clinical staff for content and quality. Blood pressure and heart rate were recorded at 5-minute intervals during the resting phase and at 1 minute interval during and after the mental stress task. The rate-pressure product was calculated as peak systolic pressure x peak heart rate.

Myocardial Perfusion Imaging

Participants underwent three SPECT myocardial perfusion imaging scans after injection of sestamibi radiolabeled with technetium – 99m, at rest, during mental stress and during

physical stress. Two stress tests were done in two separate days (to prevent the effects of one stress contaminating the results of the following one) up to 1 week apart on a dedicated ultrafast solid-state camera (Discovery NM 530c) without attenuation correction. Only one resting scan was performed with a sestamibi dose of 8 -15 mCi adjusting for body weight while both the stress scans were performed with 20 to 30 mCi of sestamibi at least two hours after the rest scan.

On the mental stress day, sestamibi was injected 1 minute after the onset of the public speech task. This timing is in accordance with commonly used mental stress protocols with myocardial perfusion imaging [60]. On the exercise stress day, participants underwent a standard Bruce protocol with exercise target set at 85% of maximal predicted heart rate based on sex and age. Sestamibi was injected at peak exertion. Stress images were acquired 45 to 60 minutes later. The ECG, blood pressure and heart rate were continuously monitored during the procedure. For patients who underwent the pharmacological stress test, 0.4 mg of regadenoson, an adenosine receptor agonist, was injected in 10 seconds followed by sestamibi injection.

Myocardial perfusion defects were quantified using the Emory Cardiac Toolbox, a software that provides objective quantitative assessment of perfusion. The three dimensional tracer uptake distribution in the left ventricle was oriented along the short axis and sampled onto a two-dimensional polar map. An operator independent score which to the extent and severity of perfusion defects across 17 segments of myocardium at rest and during stress, was computed by the software. Separate scores were calculated for the rest images (Summed rest score, SRS) and the stress images (summed stress score, SSS). A summed difference score (SDS), the difference between stres and rest scores, was used to

quantify the severity of ischemia with mental stress (MSIMI) or physical stress (PSIMI) [56]. A SDS score of 3 or higher was considered as evidence of MSIMI, and PSIMI was considered as positive if a SDS score ≥ 4.

Sleep Duration, Overall Sleep Quality and Other Sleep Variables

Our main predictors of interest were sleep duration and overall sleep quality, which were obtained through the Pittsburgh Sleep Quality Index (PSQI), a widely accepted and utilized questionnaire to assess subjective sleep quality and sleep related symptoms [61]. The average nighttime sleep duration during the past month was assessed by asking "How many hours of sleep on average do you usually get per night?" Short sleep duration was defined as sleeping ≤ 6 h, and it was further categorized into ≤ 5 h (extremely short sleepers) and 6 h. Normal sleep duration was defined as 7 h [62], and long sleep duration as ≥ 8 h [62]. Overall sleep quality was defined as poor if a total PSQI score was > 5, and good if total PSQI score ≤ 5 [63].

All other sleep variables were assessed through individual component scales of the PSQI, which includes 19 self-rated items divided into 7 different components of sleep evaluation. The first component, *sleep disturbance*, was assessed with 9 questions about frequency of sleep problems, such as waking up during the night or early morning, having pain or nightmares, breathing or cough problems, etc. The second component, *sleep latency*, was measured through two questions, including how many minutes it usually takes the patient to fall asleep and how often the patient was unable to fall asleep within 30 minutes. For the second question, participants used a 4-point response scale rating from 0 ("not during the

past month") to 3 ("three or more times a week"). This four-point response scale was used for all other questions on the PSQI component scales. The third component, *daytime dysfunction*, was evaluated with two items that asked participants about the frequency of difficulty performing social activities due to sleepiness, such as being unable to " keep up enthusiasm to get things done" and "having trouble staying awake while driving, eating meals, or engaging in social activities". The fourth component, *habitual sleep efficiency*, was measured using self-reported actual sleep duration per night divided by time staying in bed. The fifth component, *self-rated sleep quality*, was measured using a single question by asking patients to rate their sleep quality through a 4-point response scale from 0 ("very good") to 3 ("very bad"). The sixth component, *sleep medication use*, was assessed based on participants' report of how often they took prescription or over-the-counter medications to help them sleep. The PSQI scores have been tested to demonstrate a good test-retest reliability, with intra-class correlation coefficients ranging from 0.65 (medication use) to 0.84 (sleep latency) for the component scores [61].

Other Measurements

Demographic and lifestyle characteristics were collected using standard questionnaires before the rest SPECT scan. Clinical characteristics such as CAD severity and risk factors, medication status, and comorbid conditions were extracted through patients' electronic medical records. Blood samples were drawn for the measurements of glucose and a lipid profile after an overnight fast. Angiographic data were obtained from the coronary

angiogram performed in conjunction with the index MI. CAD severity was quantified using the Gensini scoring system [56, 58].

Depressive and anxiety symptoms, perceived stress level, social and emotional support were assessed with the Beck Depression Inventory-II (BDI-II) [56] [64], the State-Trait Anxiety Inventory (STAI) [65] [66], and the Multidimensional Scale of Perceived Social Support (MSPSS) [67], respectively. Current depressive symptoms were defined as present if the BDI-II score was > 13 (reference group, BDI-II score 0 to 13) [64].

Statistical Analysis:

Statistical analyses were conducted through Statistic Analysis System (SAS) version 9.4 (SAS Institute, Inc.). Descriptive statistics were computed by comparing sleep duration and sleep quality categories according to demographic, lifestyle, clinical and psychological characteristics, using t tests or ANOVA for continuous variables, and chi-square tests for categorical variables. Sleep duration was first categorized as ≤ 5 h (extreme short sleepers), 6 h (short sleepers), 7 h (normal sleepers, reference group), and ≥ 8 h (long sleepers). However, due to sample size, we dichotomized sleep duration into short sleepers (< 7 h) and normal sleepers (≥ 7 h) when assessing for interaction between sleep duration, overall sleep quality and PSQI component scores.

PSQI component scores ranging from 0 (best) to 3 (worst) were computed as means and standard deviations across categories of sleep duration, and one-way ANOVA test was

used to test the associations. In addition, each of these 4-point scales was further dichotomized as good (0, 1) and poor (2, 3) [68]. Proportions of dichotomized sleep variables, including long sleep latency, daytime dysfunction due to sleepiness, sleep disturbance, low sleep efficiency, high frequency of sleep medication use, self-rated poor sleep quality and overall poor sleep quality, were computed across four different categories of sleep duration, and chi-square tests were used to test the general associations.

Multivariate logistic regression models were used to evaluate the association (odds ratio (OR) and 95% confidence interval (CI)) between sleep duration, overall sleep quality, dichotomous PSQI component scores and the incidence of myocardial ischemia during mental stress (MSIMI, SDS $\geq$ 3) and physical stress (PSIMI, SDS $\geq$ 4). Multiple linear regression models were also used to assess differences in severity of myocardial ischemia quantified by stress perfusion scores across categories of sleep duration and sleep quality, adjusting for potential confounding factors. The summed difference score (SDS), which quantifies ischemia severity, was our outcome of interest for the linear regression model. Since the SDS for both mental and physical stress was highly skewed, while the summed stress scores (SSS) was approximately normally distributed, we used the SSS scores as dependent variables while adjusting for the rest score (SRS), yielding coefficients for sleep duration and sleep quality identical to those from a model where the dependent variable is the difference score (SDS), adjusted for the SRS.

For multivariate-analyses, to assess sleep duration, overall sleep quality, and individual PSQI components (and their interactions with sleep duration), in relation to myocardial

ischemia incidence or severity during mental stress and physical stress, four models were used for both the logistic model and the linear model. The first model assessed the unadjusted association. The second model adjusted for age, sex, race, current marital and employment status, current smoking and alcohol use. In the third model, we assessed potential mediating biological risk factors, by adjusting for BMI, myocardial infarction type, and previous revascularization including Percutaneous Coronary Intervention (PCI) and Coronary Artery Bypass Grafting (CABG). In the fourth model we included potential psychological mediators, by adjusting for the Beck Depression Inventory score, lifetime prevalence of major depression, the Multidimensional Scale of Perceived Social Support, and anti-depression medications.

When assessing the association between individual PSQI component and MSIMI or PSIMI incidence, the dichotomous groups (poor vs. good) were fitted into multivariate logistic model, whereas the ordinal four-pointed scales were fitted into multivariate linear model to assess the severity of MSIMI or PSIMI. Moreover, sleep duration was adjusted as a potential confounder in these models. In these models we also analyzed two-way interactions between overall sleep quality and each PSQI symptom components with dichotomous sleep duration. Furthermore, since sleep apnea may potentially modify the association between sleep duration and ischemia induced by mental or physical stress, and it was rare among individuals with normal BMI, we used obesity as a surrogate for sleep apnea and tested interactions between obesity and sleep duration.

RESULTS

Study Sample

Between 2011 and 2014, 81 male and 64 female patients younger than 60 years old with myocardial infarction (MI) within 8 months prior to enrollment were enrolled in the study. The mean age was 51.9 years. Overall, 67% of the participants were African-American, 62% had at least a high school education, and 34% had an income below the poverty level. Cardiovascular disease risk factors were prevalent in this sample. About 52% of the participants were obese (BMI $\geq$ 30 kg/m^2) and the prevalence of diabetes, hypertension and hypercholesterolemia were 28%, 73% and 67%, respectively. About half of the patients had an ST-elevation MI, 68% had previous percutaneous coronary interventions, and 21% received coronary bypass graft surgery. Psychological issues were also fairly common: 25% of the patients had history of major depressive disorder, 30% had significant depressive symptoms (BDI-II score > 13), 16% were currently taking anti-depressants, and over half of the participants had state or trait anxiety symptoms. Furthermore, about half lacked of social support according to the Multidimensional Scale of Perceived Social Support (MSPSS).

Sleep Measurements

Sleep duration and overall sleep quality (PSQI total score) were approximately normal distributed, with a mean of 6.2 h (SD: 1.7) and 8.0 (SD: 3.7), respectively. In total, 101 (70 %) of the patients had poor sleep quality (PSQI total score > 5), 85 (58%) were short sleepers (habitual sleep duration $\leq$ 6 h), and, among those, 44 (30%) had habitual sleep

duration less than 5 hours per night, whereas thirty-two (22 %) participants had habitual sleep duration ≥ 8 h (long sleepers). Both long and short sleepers were generally younger than normal sleepers, more likely to be male, black, unmarried and unemployed, with lower income and education level, higher levels of depressive and anxiety symptoms, and higher perceived stress and lower social support. However, there were no differences across sleep duration categories with respect to cardiac risk profiles, such as obesity, diabetes, hypertension and hypercholesterolemia (Table 1). Those with habitual sleep duration of ≤ 5 h per night were more likely (61%) to have had an ST-segment elevation myocardial infarction (STEMI) compared to 50% in normal sleepers; in contrast, long sleepers were more likely (53%) to have had a non-ST segment elevation myocardial infarction (NSTEMI). Both short and long sleepers were more likely (76% and 66%, respectively) underwent PCI (Percutaneous Coronary Intervention) instead of CABG (Coronary Artery Bypass Graft) as revascularization method compared to 46% in normal sleepers (Table 1).

Abnormal PSQI component scores (as dichotomous variables) were more frequent in those with abnormal sleep duration. Among those who slept less than 5 hours, 93% had poor sleep quality, 70% had low sleep efficiency and daytime sleepiness and 61% had significant sleep disturbance compared to 50%, 39%, and 43% in normal sleepers, respectively (Table 2 and Table 3). Patients with long sleep duration also tended to complain about more frequent daytime dysfunction due to sleepiness (Table 2 and Table 3).

Myocardial Perfusion

Forty-one (28.3%) participants developed myocardial perfusion defects during mental stress test (summed difference score, SDS ≥ 3) and 45 (29%) were found to have myocardial perfusion defects during physical stress (SDS ≥ 4). The median SDS with mental stress was 0.0 (interquartile range (IQR): 0, 2), and the median SDS with physical stress was 1.0 (IQR: 0, 3).

Association of Sleep duration, Overall Sleep Quality, and PSQI components with the severity and incidence of Myocardial Ischemia during Mental Stress and Physical Stress

There appeared to be a U-shaped association between sleep duration and MSIMI; however, this association was not statistically significant. After adjustment for relevant confounders, both short and long sleepers were found to have a higher probability of developing ischemia during mental stress (Table 4 and Table 5; "≤ 5 h" OR: 1.62, 95% CI: (0.41, 6.50); "6 h" OR 2.11, 95% CI: (0.54, 8.32); "≥ 8 h" OR 3.17, 95% CI: (0.81, 12.4); Model 4). This U-shaped association also was found among patients with PSIMI, however, it was not statistically significant (Table 4 and Table 5). As for overall sleep quality, it was not statistically significantly associated with either PSIMI (OR: 0.78; 95% CI: 0.29 – 2.15) or MSIMI (OR: 1.31; 95% CI: 0.49 – 3.45). (Table 4 and Table 5).

The interaction between sleep duration and overall sleep quality was not statistically significant in relation to MSIMI (Table 10; P for interaction = 0.61) or PSIMI (Table 11; P for interaction = 0.286). Interactions between all other PSQI components, obesity and sleep duration were also found not to be statistically significant (Tables 10 and 11).

As for individual PSQI components, including sleep latency, sleep disturbance, daytime sleepiness, low sleep efficiency, self-reported poor sleep quality, and frequency of sleep medication use, there was no statistically significantly association for any of them with either MSIMI or PSIMI both before (Table 6 and Table 8) and after adjusting for potential confounders (Table 7 and Table 9).

DISCUSION

In this preliminary study we found a U-shaped association between sleep duration and myocardial ischemia induced by mental and physical stress among young and middle aged survivors of acute myocardial infarction (AMI), such that the lowest odds of ischemia was found among those who reported sleep duration of 7 hours. However, theses associations were not statistically significant. Given that short sleep duration and poor sleep quality are well-established risk factors for coronary heart disease (CHD) mortality [2, 4, 14] and that MSIMI is an important prognostic indicator in post MI patients [69], these findings provide a possible explanation for the higher risk of adverse events associated with impaired sleep among post-MI patients [42, 70, 71].

While numerous previous studies examined the association between sleep duration and CHD incidence and mortality [15,72, 73], none reported on an association between sleep duration and mental stress-induced myocardial ischemia among post MI patients. However, previous studies examined associations of sleep duration and sleep quality with prognosis after AMI. Clark A, et al. [42] conducted a large prospective cohort study and found that in women, disturbed sleep was directly associated with long-term cardiovascular events, with a higher risk of subsequent AMI, stroke, and heart failure. Szymanski , et al. [74] found that sleep duration in the first few months after an AMI episode was strongly associated with post-MI mortality and that both short and long sleep duration were associated with higher mortality after MI. Previous studies also examined an association between psychological factors and MSIMI [64, 75], such as depression and perceived stress; however, none of these studies investigated the potential associations of sleep characteristics.

Potential mechanisms that might be invoked to explain the association between sleep duration and mental stress-induced myocardial ischemia include downstream physiologic effects. Short sleep duration has been found to be associated with CHD risk factors, including obesity, impaired glucose intolerance (IGT), decreased insulin sensitivity, type 2 diabetes and hypertension [16-18] [6, 19-21]. Short sleep duration may also affect immune function and promote inflammation in blood vessels [22], which may be exacerbated in response to mental stress [76]. In turn, inflammation is associated with coronary microvascular function [77], which could be a mechanism of MSIMI. Another potential mechanism is that short sleep duration and poor sleep contribute to the increased risk of MSIMI by an inability of the organism to diminish sympathetic stimulation of the cardiovascular system at night and, thus, prevent rest and restoration [23]. The association between long sleep duration and MSIMI may be explained by long sleep duration being an early symptom of disease preceding clinical diagnosis, or a marker of disease severity [6]. This was also suggested in our study by the fact that long sleepers more often had a history of diabetes mellitus, dyslipidemia, and hypertension.

Our study is the first to exam the association between sleep duration and MSIMI. A strength of our study is the use of a standardized mental stress protocol and a well-defined, relatively understudied population with an elevated abnormal sleep duration prevalence. Moreover, we used SPECT for detection of myocardial ischemia, which has established sensitivity, specificity, and reproducibility to detect MSIMI. The main limitation of our study is its small sample size, and the confidence intervals around our estimates were wide. Another limitation is that sleep hours and sleep quality were self-reported. However, it was not

feasible to obtain objective measures of sleep, such as sleep diaries, actigraphs, and polysomnography (PSG). Furthermore, the lack of information about sleep apnea among our participants was also a limitation. However, since the prevalence of sleep apnea in people with a BMI less than 30 kg/m^2 is rare, we examined the interaction of sleep duration and sleep quality with BMI groups (BMI under and over 30 kg/m^2) and found not to be statistically significant. In addition, pre-infarct sleep information was not available in our study; these data would be helpful to determine whether the MI itself affected sleep patterns, or whether sleep patterns before MI are a better predictor of MSIMI since they may not be confounded by MI severity [74]. Finally, patients with sleep apnea often complain about tiredness rather than short sleep or poor sleep quality, thus there may not be a strong correlation between sleep apnea and sleep quality or duration.

In conclusion, in this pilot study we found preliminary evidence that short and long sleep duration may be directly associated with mental stress induced myocardial ischemia in younger post MI patients, even though this association was not statistically significant. Since CHD patients who develop MSIMI are at higher risk for subsequent cardiac events and death, these results, if confirmed in a larger sample, could help explain the adverse outcomes associated with abnormal sleep duration and sleep quality among post MI patients. Our findings may point a new direction for research into the mechanisms between sleep duration and cardiovascular diseases.

REFERENCES

1. Knutson, K.L., et al., *Trends in the prevalence of short sleepers in the USA: 1975-2006.* Sleep, 2010. **33**(1): p. 37-45.
2. Cappuccio, F.P., et al., *Sleep duration predicts cardiovascular outcomes: a systematic review and meta-analysis of prospective studies.* Eur Heart J, 2011. **32**(12): p. 1484-92.
3. Grandner, M.A., et al., *Mortality associated with short sleep duration: The evidence, the possible mechanisms, and the future.* Sleep Med Rev, 2010. **14**(3): p. 191-203.
4. Cappuccio, F.P., et al., *Sleep duration and all-cause mortality: a systematic review and meta-analysis of prospective studies.* Sleep, 2010. **33**(5): p. 585-92.
5. Grandner, M.A. and N.P. Patel, *From sleep duration to mortality: implications of meta-analysis and future directions.* J Sleep Res, 2009. **18**(2): p. 145-7.
6. Ikehara, S., 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**(3): p. 295-301.
7. Kronholm, E., et al., *Self-reported sleep duration, all-cause mortality, cardiovascular mortality and morbidity in Finland.* Sleep Med, 2011. **12**(3): p. 215-21.
8. Kripke, D.F., et al., *Mortality related to actigraphic long and short sleep.* Sleep Med, 2011. **12**(1): p. 28-33.
9. Kurina, L.M., et al., *Sleep duration and all-cause mortality: a critical review of measurement and associations.* Ann Epidemiol, 2013. **23**(6): p. 361-70.
10. Magee, C.A., et al., *Investigation of the relationship between sleep duration, all-cause mortality, and preexisting disease.* Sleep Med, 2013. **14**(7): p. 591-6.
11. Suzuki, E., et al., *Sleep duration, sleep quality and cardiovascular disease mortality among the elderly: a population-based cohort study.* Prev Med, 2009. **49**(2-3): p. 135-41.

12. Amagai, Y., et al., *Sleep duration and incidence of cardiovascular events in a Japanese population: the Jichi Medical School cohort study.* J Epidemiol, 2010. **20**(2): p. 106-10.

13. Sabanayagam, C. and A. Shankar, *Sleep duration and cardiovascular disease: results from the National Health Interview Survey.* Sleep, 2010. **33**(8): p. 1037-42.

14. Gallicchio, L. and B. Kalesan, *Sleep duration and mortality: a systematic review and meta-analysis.* J Sleep Res, 2009. **18**(2): p. 148-58.

15. Hoevenaar-Blom, M.P., et al., *Sleep duration and sleep quality in relation to 12-year cardiovascular disease incidence: the MORGEN study.* Sleep, 2011. **34**(11): p. 1487-92.

16. Grandner, M.A., et al., *Sleep disturbance is associated with cardiovascular and metabolic disorders.* J Sleep Res, 2012. **21**(4): p. 427-33.

17. Akerstedt, T. and P.M. Nilsson, *Sleep as restitution: an introduction.* J Intern Med, 2003. **254**(1): p. 6-12.

18. Akerstedt, T., P.M. Nilsson, and G. Kecklund, *Sleep and Recovery.* Current Perspectives on Job-Stress Recovery, 2009. **7**: p. 205-247.

19. Mullington, J.M., et al., *Cardiovascular, inflammatory, and metabolic consequences of sleep deprivation.* Prog Cardiovasc Dis, 2009. **51**(4): p. 294-302.

20. Cappuccio, F.P., et al., *Quantity and quality of sleep and incidence of type 2 diabetes: a systematic review and meta-analysis.* Diabetes Care, 2010. **33**(2): p. 414-20.

21. Cappuccio, F.P., et al., *Gender-specific associations of short sleep duration with prevalent and incident hypertension: the Whitehall II Study.* Hypertension, 2007. **50**(4): p. 693-700.

22. Suarez, E.C., *Self-reported symptoms of sleep disturbance and inflammation, coagulation, insulin resistance and psychosocial distress: evidence for gender disparity.* Brain Behav Immun, 2008. **22**(6): p. 960-8.

23. Burgess, H.J., et al., *Sleep and circadian influences on cardiac autonomic nervous system activity.* Am J Physiol, 1997. **273**(4 Pt 2): p. H1761-8.

24. Chandola, T., et al., *The effect of short sleep duration on coronary heart disease risk is greatest among those with sleep disturbance: a prospective study from the Whitehall II cohort.* Sleep, 2010. **33**(6): p. 739-44.

25. *From the Centers for Disease Control and Prevention. Mortality from coronary heart disease and acute myocardial infarction--United States, 1998.* JAMA, 2001. **285**(10): p. 1287-8.

26. Roger, V.L., et al., *Heart disease and stroke statistics-2012 update: A report from the American heart association.* Circulation, 2012. **125**(1): p. e2-e220.

27. Brown, J.R. and G.T. O'Connor, *Coronary heart disease and prevention in the United States.* N Engl J Med, 2010. **362**(23): p. 2150-3.

28. Horton, H.L., *Risk stratification after myocardial infarction.* Ann Intern Med, 1997. **127**(11): p. 1040-1.

29. Bigger, J.T., Jr., et al., *The relationships among ventricular arrhythmias, left ventricular dysfunction, and mortality in the 2 years after myocardial infarction.* Circulation, 1984. **69**(2): p. 250-8.

30. Wilhelmsen, L., *Effects of cessation of smoking after myocardial infarction.* J Cardiovasc Risk, 1998. **5**(3): p. 173-6.

31. *Baseline serum cholesterol and treatment effect in the Scandinavian Simvastatin Survival Study (4S).* Lancet, 1995. **345**(8960): p. 1274-5.

32. Sprafka, J.M., et al., *Trends in prevalence of diabetes mellitus in patients with myocardial infarction and effect of diabetes on survival. The Minnesota Heart Survey.* Diabetes Care, 1991. **14**(7): p. 537-43.

33. Ulvenstam, G., et al., *Long-term prognosis after myocardial infarction in men with diabetes.* Diabetes, 1985. **34**(8): p. 787-92.

34. Reriani, M.K., et al., *Novel functional risk factors for the prediction of cardiovascular events in vulnerable patients following acute coronary syndrome.* Circ J, 2012. **76**(4): p. 778-83.

35. Glozier, N., et al., *Psychosocial risk factors for coronary heart disease.* Med J Aust, 2013. **199**(3): p. 179-80.

36. Rozanski, A., J.A. Blumenthal, and J. Kaplan, *Impact of psychological factors on the pathogenesis of cardiovascular disease and implications for therapy.* Circulation, 1999. **99**(16): p. 2192-217.

37. Schneiderman, N., M.A. Chesney, and D.S. Krantz, *Biobehavioral aspects of cardiovascular disease: progress and prospects.* Health Psychol, 1989. **8**(6): p. 649-76.

38. Arnold, S.V., et al., *Perceived stress in myocardial infarction: long-term mortality and health status outcomes.* J Am Coll Cardiol, 2012. **60**(18): p. 1756-63.

39. Steptoe, A. and M. Kivimaki, *Stress and cardiovascular disease.* Nat Rev Cardiol, 2012. **9**(6): p. 360-70.

40. Tully, P.J., S.M. Cosh, and B.T. Baune, *A review of the affects of worry and generalized anxiety disorder upon cardiovascular health and coronary heart disease.* Psychol Health Med, 2013. **18**(6): p. 627-44.

41. Lee, D.T., et al., *Psychological distress mediates the effects of socio-demographic and clinical characteristics on the physical health component of health-related quality of life in patients with coronary heart disease.* Eur J Prev Cardiol, 2014. **21**(1): p. 107-16.

42. Clark, A., et al., *Sleep impairment and prognosis of acute myocardial infarction: a prospective cohort study.* Sleep, 2014. **37**(5): p. 851-8.

43. Mazzuero, G., A.M. Zotti, and L. Tavazzi, *[Mental stress in the functional evaluation of recent myocardial infarct: hemodynamic aspects]*. G Ital Cardiol, 1983. **13**(9): p. 172-82.

44. Rozanski, A., et al., *Mental stress and the induction of silent myocardial ischemia in patients with coronary artery disease.* N Engl J Med, 1988. **318**(16): p. 1005-12.

45. Legault, S.E., et al., *Pathophysiology and time course of silent myocardial ischaemia during mental stress: clinical, anatomical, and physiological correlates.* Br Heart J, 1995. **73**(3): p. 242-9.

46. Blumenthal, J.A., et al., *Mental stress-induced ischemia in the laboratory and ambulatory ischemia during daily life. Association and hemodynamic features.* Circulation, 1995. **92**(8): p. 2102-8.

47. Gottdiener, J.S., et al., *Induction of silent myocardial ischemia with mental stress testing: relation to the triggers of ischemia during daily life activities and to ischemic functional severity.* J Am Coll Cardiol, 1994. **24**(7): p. 1645-51.

48. Jiang, W., et al., *Mental stress--induced myocardial ischemia and cardiac events.* JAMA, 1996. **275**(21): p. 1651-6.

49. Stone, P.H., et al., *Relationship among mental stress-induced ischemia and ischemia during daily life and during exercise: the Psychophysiologic Investigations of Myocardial Ischemia (PIMI) study.* J Am Coll Cardiol, 1999. **33**(6): p. 1476-84.

50. Jiang, W., et al., *Prevalence and clinical characteristics of mental stress-induced myocardial ischemia in patients with coronary heart disease.* J Am Coll Cardiol, 2013. **61**(7): p. 714-22.

51. Strike, P.C. and A. Steptoe, *Systematic review of mental stress-induced myocardial ischaemia.* Eur Heart J, 2003. **24**(8): p. 690-703.

52. Specchia, G., et al., *Mental stress as a provocative test in patients with various clinical syndromes of coronary heart disease.* Circulation, 1991. **83**(4 Suppl): p. II108-14.

53. Krantz, D.S., et al., *Prognostic value of mental stress testing in coronary artery disease.* Am J Cardiol, 1999. **84**(11): p. 1292-7.

54. Sheps, D.S., et al., *Mental stress-induced ischemia and all-cause mortality in patients with coronary artery disease: Results from the Psychophysiological Investigations of Myocardial Ischemia study.* Circulation, 2002. **105**(15): p. 1780-4.

55. Babyak, M.A., et al., *Prognosis after change in left ventricular ejection fraction during mental stress testing in patients with stable coronary artery disease.* Am J Cardiol, 2010. **105**(1): p. 25-8.

56. Wei, J., et al., *Depressive Symptoms Are Associated with Mental Stress-Induced Myocardial Ischemia after Acute Myocardial Infarction.* PLoS One, 2014. **9**(7): p. e102986.

57. Hemingway, H. and M. Marmot, *Evidence based cardiology: psychosocial factors in the aetiology and prognosis of coronary heart disease. Systematic review of prospective cohort studies.* BMJ, 1999. **318**(7196): p. 1460-7.

58. Vaccarino, V., et al., *Sex differences in mental stress-induced myocardial ischemia in young survivors of an acute myocardial infarction.* Psychosom Med, 2014. **76**(3): p. 171-80.

59. Goldberg, A.D., et al., *Ischemic, hemodynamic, and neurohormonal responses to mental and exercise stress. Experience from the Psychophysiological Investigations of Myocardial Ischemia Study (PIMI).* Circulation, 1996. **94**(10): p. 2402-9.

60. Hassan, M., et al., *Variability of myocardial ischemic responses to mental versus exercise or adenosine stress in patients with coronary artery disease.* J Nucl Cardiol, 2008. **15**(4): p. 518-25.

61. Buysse, D.J., et al., *The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research.* Psychiatry Res, 1989. **28**(2): p. 193-213.

62. Carroll, J.E., et al., *Sleep and multisystem biological risk: a population-based study.* PLoS One, 2015. **10**(2): p. e0118467.

63. Bruno, R.M., et al., *Poor sleep quality and resistant hypertension.* Sleep Med, 2013. **14**(11): p. 1157-63.

64. Boyle, S.H., et al., *Depressive symptoms and mental stress-induced myocardial ischemia in patients with coronary heart disease.* Psychosom Med, 2013. **75**(9): p. 822-31.

65. Moser, D.K., et al., *Relationship of persistent symptoms of anxiety to morbidity and mortality outcomes in patients with coronary heart disease.* Psychosom Med, 2011. **73**(9): p. 803-9.

66. Whittaker, K.S., et al., *Combining psychosocial data to improve prediction of cardiovascular disease risk factors and events: The National Heart, Lung, and Blood Institute--sponsored Women's Ischemia Syndrome Evaluation study.* Psychosom Med, 2012. **74**(3): p. 263-70.

67. Bekke-Hansen, S., et al., *Psycho-social factors are important for the perception of disease in patients with acute coronary disease.* Dan Med J, 2014. **61**(8): p. A4885.

68. Lajoie, P., et al., *A cross-sectional study of shift work, sleep quality and cardiometabolic risk in female hospital employees.* BMJ Open, 2015. **5**(3): p. e007327.

69. Wei, J., et al., *Meta-analysis of mental stress-induced myocardial ischemia and subsequent cardiac events in patients with coronary artery disease.* Am J Cardiol, 2014. **114**(2): p. 187-92.

70. Fernandes, N.M., et al., *Symptoms of Disturbed Sleep Predict Major Adverse Cardiac Events After Percutaneous Coronary Intervention.* Canadian Journal of Cardiology, 2014. **30**(1): p. 118-124.

71. Gislason, G.H., et al., *Increased risk of reinfarction and death in patients using sedatives after first-time myocardial infarction-a nationwide propensity score matched study.* Circulation: Cardiovascular Quality and Outcomes, 2012. **5**(3).

72. Aggarwal, S., et al., *Sleep patterns and prevalence of cardiovascular outcomes-analysis of national health and nutrition examination survey database 2007-08.* Journal of the American College of Cardiology, 2012. **59**(13): p. E1748.

73. Agarwal, S., N. Bajaj, and C. Bae, *Association between sleep duration and cardiovascular disease: Results from the national health and nutrition examination survey (NHANES 2005 - 2008).* Journal of the American College of Cardiology, 2012. **59**(13): p. E1514.

74. Szymanski, F.M., et al., *Sleep duration in the first months after ST elevation myocardial infarction: an independent predictor of all-cause mortality.* Kardiol Pol, 2014. **72**(6): p. 504-10.

75. Jiang, W., et al., *Effect of escitalopram on mental stress-induced myocardial ischemia: results of the REMIT trial.* JAMA, 2013. **309**(20): p. 2139-49.

76. Kop, W.J., et al., *Effects of acute mental stress and exercise on inflammatory markers in patients with coronary artery disease and healthy controls.* Am J Cardiol, 2008. **101**(6): p. 767-73.

77. Vaccarino, V., et al., *Inflammation is related to coronary flow reserve detected by positron emission tomography in asymptomatic male twins.* J Am Coll Cardiol, 2011. **57**(11): p. 1271-9.

TABLES

Table 1: Characteristics of participants by sleep duration and sleep quality; the Myocardial Infarction and Mental Stress (MIMS) Study, 2011-2013.

	Sleep Duration					Overall Sleep Quality		
	≤5 h	**6 h**	**7 h**	**≥ 8 h**	*P value*	**Good**	**Poor** [a]	*P value*
Number of Cases (n)	44	41	28	32		44	101	
Demographic Factors (%)								
Age (≤ 50 years)	31.8	26.8	28.6	46.9	0.288	38.6	30.7	0.350
Sex (female)	50.0	34.2	50.0	43.8	0.446	38.6	46.5	0.379
Race (black)	81.8	70.7	46.4	59.4	0.013	56.8	71.3	0.089
Marital Status (currently unmarried)	59.1	58.5	35.7	56.3	0.201	43.2	58.4	0.091
Education (less than high school)	36.4	39.0	42.9	34.4	0.913	34.1	39.6	0.529
Employment status (unemployed)	65.9	41.5	39.3	59.4	0.052	40.9	57.4	0.067
Income level (below poverty)	45.5	31.7	21.4	34.4	0.204	22.7	39.6	0.049
Lifestyle Factors (%)								
Current cigarette smoking	27.3	19.5	7.1	18.8	0.216	6.8	24.8	0.012
Alcohol use [b]	25.0	51.2	57.1	53.1	0.016	50.0	42.6	0.408
Coffee consumption [c]	45.5	53.7	64.3	65.6	0.255	61.4	53.5	0.379
Clinical Characteristics (%)								
Obesity	59.1	39.0	57.1	56.3	0.243	47.7	54.5	0.456
Diabetes	38.6	19.5	28.6	25.0	0.256	22.7	30.7	0.328
Hypertension	72.7	75.6	67.9	75.0	0.900	68.2	75.3	0.378
Hypercholesterolemia	79.6	63.4	57.1	62.5	0.180	61.4	69.3	0.350
Myocardial Infarction Type								
STEMI	61.4	51.2	50.0	46.9		50.0	54.5	
NSTEMI	38.6	48.8	50.0	53.1	0.600	50.0	45.5	0.621

Table 1 (continued)

Previous Revascularization								
CABG	15.9	17.1	32.1	21.9	0.361	20.5	20.8	0.963
PCI	77.3	75.6	46.4	65.6	0.030	59.1	72.3	0.117
Psychosocial Factors (%)								
Current Depressive Symptom [d]	40.9	31.7	21.4	21.9	0.212	2.3	42.6	0.001
Life time Prevalence of MDD	29.6	29.3	14.3	21.9	0.428	6.8	32.7	0.001
State Anxiety [e]	35.6 (12.1)	32.9 (11.3)	34.5 (12.2)	34.1 (10.2)	0.599	29.5 (9.1)	36.4 (11.7)	0.001
Trait Anxiety [f]	38.9 (10.4)	34.7 (11.2)	34.4 (10.9)	34.7 (10.5)	0.535	30.0 (8.1)	38.5 (10.8)	0.001
Social Support [g]	63.0 (18.0)	70.1 (13.8)	63.4 (19.0)	67.2 (15.7)	0.131	67.0 (17.0)	65.5 (16.6)	0.621
Current Medications (%)								
Statins	79.6	82.9	78.6	87.5	0.781	81.8	82.2	0.959
Beta blockers	88.6	90.2	85.7	87.5	0.949	84.1	90.1	0.301
ACE inhibitors	43.2	53.7	50.0	37.5	0.529	54.6	42.6	0.184
Aspirin	77.3	80.5	71.4	81.3	0.787	75.0	79.2	0.574
Anti-depressants	20.5	9.8	17.9	18.8	0.572	9.1	19.8	0.111
Sleep medications	27.3	29.3	42.9	43.8	0.915	9.1	40.6	0.001

Abbreviations: STEMI, ST segment elevation myocardial infarction; NSTEMI, Non- ST segment elevation myocardial infarction; CABG, Coronary Artery Bypass Grafting; PCI, Percutaneous Coronary Intervention; MDD, Major Depressive Disorder;

[a] Defined as Pittsburgh Sleep Quality Index total score > 5; [b] alcohol use: > 2 glasses of wine per week for man and > 1 glasses for women; [c] coffee consumption: > 1 cup per day; [d] Defined as Beck Depression Inventory (BDI-II) score > 13; [e, f] Mean (SD) of State-Trait Anxiety Inventory (STAI) score; [g] Mean (SD) of Multidimensional Scale of Perceived Social Support (MSPSS) score;

Table 2: Characteristics[1] of Pittsburgh Sleep Quality Index component scores by sleep duration; the Myocardial Infarction and Mental Stress (MIMS) Study, 2011 – 2013.

	Sleep Duration				
	≤ 5 h	**6 h**	**7 h**	**≥ 8 h**	P value[2]
Number of Cases (n)	44	41	28	32	
Sleep disturbance score	1.66 (0.64)	1.80 (0.68)	1.50 (0.64)	1.44 (0.52)	0.923
Sleep latency score	1.57 (1.13)	1.49 (1.08)	1.36 (0.95)	0.91 (0.86)	0.071
Daytime dysfunction score	0.95 (0.81)	1.05 (0.80)	0.79 (0.69)	0.91 (0.53)	0.458
Sleep efficiency score	1.64 (1.28)	1.07 (1.19)	0.68 (1.02)	0.25 (0.62)	0.019
Self-rated sleep quality score	1.66 (0.89)	1.34 (0.79)	0.93 (0.47)	0.88 (0.55)	0.239
Sleep medication use score	0.84 (1.20)	0.80 (1.17)	0.93 (1.21)	1.03 (1.28)	0.766

[1] Mean (SD); [2]one-way ANOVA test;

Table 3: Characteristics of PSQI sleep variables[1] by sleep duration; the Myocardial Infarction and Mental Stress (MIMS) Study, 2011 – 2013.

	Sleep Duration				
	≤ 5 h	**6 h**	**7 h**	**≥ 8 h**	P value
Number of Cases (n)	44	41	28	32	
Sleep disturbance (%)	61.4	70.7	42.9	43.8	0.045
Long sleep latency (%)	75.0	78.1	78.6	65.6	0.605
Daytime Dysfunction due to sleepiness (%)	70.5	73.2	64.3	81.3	0.518
Low sleep efficiency (%)	70.5	53.7	39.3	18.8	0.001
Self-rated poor sleep quality (%)	93.2	85.4	85.7	78.1	0.310
Sleep medication use (%)	38.6	36.6	42.9	43.8	0.915
Overall poor sleep quality [2] (%)	93.2	87.8	50.0	31.3	0.001

[1] defined as Pittsburgh Sleep Quality Index (PSQI) individual component score ≥ 1; [2] defined as PSQI total score > 5;

Table 4: Associations* of sleep duration, sleep quality with Mental Stress Induced Myocardial Ischemia (MSIMI) incidence and Physical Stress Induced Myocardial Ischemia (PSIMI) incidence; the MIMS-2 Study, 2011-2013;

	Sleep Duration				Overall Sleep Quality	
	≤ 5 h	**6 h**	**7 h**	**≥ 8 h**	**Good**	**Poor** [1]
MSIMI [1]						
Model 1	1.22 (0.39, 3.79)	1.70 (0.56, 5.20)	1.00	1.92 (0.60, 6.13)	1.00	1.07 (0.49, 2.37)
Model 2	1.32 (0.38, 4.54)	1.82 (0.54, 6.08)	1.00	2.41 (0.69, 8.39)	1.00	0.97 (0.42, 2.26)
Model 3	1.43 (0.38, 5.42)	1.79 (0.50, 6.40)	1.00	3.02 (0.81, 11.3)	1.00	0.94 (0.39, 2.23)
Model 4	1.62 (0.41, 6.50)	2.11 (0.54, 8.32)	1.00	3.17 (0.81, 12.4)	1.00	1.31 (0.49, 3.45)
PSIMI [2]						
Model 1	1.40 (0.48, 4.06)	1.24 (0.42, 3.69)	1.00	1.80 (0.59, 5.49)	1.00	0.82 (0.38, 1.74)
Model 2	1.19 (0.36, 3.90)	1.24 (0.37, 4.09)	1.00	2.15 (0.63, 7.32)	1.00	0.66 (0.29, 1.51)
Model 3	1.75 (0.49, 6.27)	1.67 (0.47, 5.92)	1.00	2.93 (0.80, 10.7)	1.00	0.75 (0.30, 1.89)
Model 4	2.01 (0.53, 7.61)	2.30 (0.60, 8.83)	1.00	3.17 (0.83, 12.1)	1.00	0.78 (0.29, 2.15)

*Odds ratio (OR) with 95% confidence interval (CI); [1]Defined as Pittsburgh Sleep Quality Index total score > 5; [2] incidence of MSIMI defined as a summed difference score (SDS) ≥ 3; [3] incidence of PSIMI defined as a SDS ≥ 4; Model 1 : unadjusted; Model 2: model 1 plus demographic and lifestyle factors, including age, sex, race, current marital and employment status, current smoking and alcohol use status; Model 3: model 2 plus clinical factors, including BMI, MI type, PCI and CABG; Model 4: model 3 plus sleep medication use frequency and psychological factors, including BDI-II total score, antidepressants use, life time prevalence of major depression, social support (MSPSS score);

Table 5: Associations* of sleep duration, sleep quality with Mental Stress Induced Myocardial Ischemia (MSIMI) severity[1] and Physical Stress Induced Myocardial Ischemia (PSIMI) severity[1]; the MIMS-2 Study, 2011-2013;

	Sleep Duration				Overall Sleep Quality	
	≤ 5 h	**6 h**	**7 h**	**≥ 8 h**	**Good**	**Poor** [2]
MSIMI						
Model 1	0.02 (-1.57, 1.53)	0.16 (-1.42, 1.73)	Ref.	0.81 (-0.85, 2.48)	Ref.	0.25 (-0.91, 1.41)
Model 2	0.14 (-1.81, 1.54)	0.33 (-1.31, 1.98)	Ref.	1.01 (-0.70, 2.72)	Ref.	0.11 (-1.10, 1.32)
Model 3	0.16 (-1.95, 1.62)	0.27 (-1.47, 2.00)	Ref.	1.09 (-0.68, 2.85)	Ref.	0.06 (-1.18, 1.30)
Model 4	0.27 (-1.99, 1.45)	0.13 (-1.54, 1.79)	Ref.	1.16 (-0.51, 2.84)	Ref.	0.11 (-1.16, 1.39)
PSIMI						
Model 1	0.50 (-1.42, 2.41)	0.39 (-2.33, 1.56)	Ref.	1.26 (-0.80, 3.32)	Ref.	0.10 (-1.35, 1.54)
Model 2	0.52 (-1.51. 2.55)	0.17 (-2.17, 1.83)	Ref.	1.51 (-0.57, 3.59)	Ref.	-0.11 (-1.58, 1.37)
Model 3	0.93 (-2.03, 3.90)	0.89 (-1.28, 3.06)	Ref.	0.16 (-1.94, 2.26)	Ref.	-0.05 (-1.57, 1.46)
Model 4	0.87 (-1.35, 3.09)	0.13 (-2.01, 2.27)	Ref.	1.83 (-0.33, 3.98)	Ref.	-0.01 (-1.64, 1.63)

* multivariate linear regression coefficients with 95% confidence interval (CI); [1] Defined by the summed difference score (SDS); [2]Defined as Pittsburgh Sleep Quality Index total score > 5; Model 1 : unadjusted; Model 2: model 1 plus demographic and lifestyle factors, including age, sex, race, current marital and employment status, current smoking and alcohol use status; Model 3: model 2 plus clinical factors, including BMI, MI type, PCI and CABG; Model 4: model 3 plus sleep medication use frequency, and psychological factors, including BDI-II total score, antidepressants use, life time prevalence of major depression, social support (MSPSS score);

Tables 6: Unadjusted associations* between PSQI component scores and Mental Stress Induced Myocardial Ischemia (MSIMI) severity and Physical Stress Induced Myocardial Ischemia (PSIMI) severity; the MIMS-2 Study, 2011-2013;

	MSIMI	PSIMI
Sleep disturbance	-0.38 (-1.19, 3.80)	-0.37 (-1.38, 0.65)
Sleep latency	0.17 (-0.35, 0.68)	-0.11 (-0.75, 0.53)
Daytime dysfunction due to sleepiness	-0.01 (-0.75, 0.72)	0.71 (-0.19, 1.62)
Sleep efficiency	0.07 (-0.38, 0.52)	0.34 (-0.21, 0.90)
Self-rated Sleep Quality	-0.02 (-0.70, 0.66)	0.12 (-0.73, 0.96)
Sleep medication	0.38 (-0.06, 0.82)	0.48 (-0.07, 1.02)

* linear regression coefficients with 95% confidence interval (CI), unadjusted; [1] Defined by the summed difference score (SDS);

Tables 7: Multivariate adjusted Associations* between PSQI component scores and Mental Stress Induced Myocardial Ischemia (MSIMI) severity and Physical Stress Induced Myocardial Ischemia (PSIMI) severity; the MIMS-2 Study, 2011-2013;

	MSIMI	PSIMI
Sleep disturbance score	-0.55 (-1.43, 0.34)	-0.72 (-1.89, 0.45)
Sleep latency score	0.23 (-0.32, 0.76)	-0.32 (-1.03, 0.40)
Daytime dysfunction score	-0.21 (-1.01, 0.60)	0.81 (-0.24, 1.86)
Sleep efficiency score	0.31 (-0.20, 0.51)	0.35 (-0.26, 0.96)
Self-rated Sleep Quality score	-0.31 (-1.05, 0.43)	-0.05 (-1.02, 0.92)
Sleep medication score	0.47 (-0.99, 0.93)	0.30 (-0.31, 0.91)

* linear regression coefficients with 95% confidence interval (CI), adjusted for demographic, lifestyle, clinical and psychological factors; [1] Defined by the summed difference score (SDS);

Tables 8: Unadjusted Associations* between PSQI component scores[1] and Mental Stress Induced Myocardial Ischemia (MSIMI) incidence and Physical Stress Induced Myocardial Ischemia (PSIMI) incidence; the MIMS-2 Study, 2011-2013;

	MSIMI	PSIMI
Sleep disturbance score	0.54 (0.30, 0.98)	0.69 (0.40, 1.20)
Sleep latency score	1.00 (0.71, 1.43)	0.88 (0.63, 1.24)
Daytime dysfunction score	0.97 (0.59, 1.60)	1.51 (0.93, 2.46)
Sleep efficiency score	0.90 (0.66, 1.22)	1.06 (0.79, 1.42)
Self-rated Sleep Quality score	0.87 (0.55, 1.39)	0.98 (0.62, 1.53)
Sleep medication score	1.30 (0.97, 1.74)	1.27 (0.95, 1.69)

*Odds ratio (OR) with 95% confidence interval (CI),unadjusted [1] Pittsburgh Sleep Quality Index (PSQI) individual component score ;

Tables 9: Multivariate adjusted Associations* between PSQI sleep component scores[1] and Mental Stress Induced Myocardial Ischemia (MSIMI) incidence and Physical Stress Induced Myocardial Ischemia (PSIMI) incidence; the MIMS-2 Study, 2011-2013;

	MSIMI	PSIMI
Sleep disturbance score	0.71 (0.40, 1.25)	0.70 (0.40, 1.26)
Sleep latency score	1.17 (0.77, 1.77)	0.77 (0.51, 1.18)
Daytime dysfunction score	1.10 (0.59, 2.04)	1.18 (0.66, 2.10)
Sleep efficiency score	0.93 (0.64, 1.34)	1.08 (0.76, 1.54)
Self-rated Sleep Quality score	0.88 (0.49, 1.59)	0.90 (0.51, 1.59)
Sleep medication score	1.38 (0.97, 1.97)	1.17 (0.83, 1.65)

*Odds ratio (OR) with 95% confidence interval (CI), adjusted for demographic, lifestyle, clinical and psychological factors. [1] defined as Pittsburgh Sleep Quality Index (PSQI) individual component score ;

Table 10: **Interaction between Sleep Duration, Sleep Quality, other Sleep variables[1] and Obesity [2], in relation to Mental Stress Induced Myocardial Ischemia (MSIMI), the MIMS-2 Study, 2011- 2013.**

	Sleep Duration				
	< 7 h		≥ 7 h		
	OR*	(95% CI)	OR*	(95% CI)	P for interaction
Overall Sleep Quality					0.610
Poor	1.12	(0.36 3.45)	1.12	(0.29 4.33)	
Good	0.57	(0.08 3.85)	1.00		
Sleep disturbance					0.963
Yes	1.25	(0.16 9.71)	0.01	(0.01 100)	
No	0.87	(0.34 2.26)	1.00		
Long Sleep Latency					0.608
Yes	0.71	(0.18 2.78)	0.63	(0.16 2.46)	
No	0.70	(0.14 3.53)	1.00		
Daytime Dysfunction					0.704
Yes	1.02	(0.21 4.86)	1.16	(0.25 5.24)	
No	1.26	(0.25 6.40)	1.00		
Low Sleep efficiency					0.107
Yes	1.05	(0.35 3.18)	2.46	(0.63 9.60)	
No	1.96	(0.53 7.23)	1.00		
Self-reported poor sleep quality					0.654
Yes	0.68	(0.12 3.75)	0.74	(0.14 3.94)	
No	1.55	(0.17 13.7)	1.00		
Sleep medication use					0.544
Yes	1.93	(0.54 6.85)	1.45	(0.40 5.25)	
No	0.78	(0.23 2.60)	1.00		
Obesity[2]					0.452
Yes	0.43	(0.11 1.61)	0.61	(0.17 2.19)	
No	1.10	(0.33 3.60)	1.00		

*Multivariate Odds ratio (OR) with 95% confidence interval (CI), adjusted for demographic, lifestyle, clinical and psychological factors; [1] defined as Pittsburgh Sleep Quality Index (PSQI) individual component score ≥ 1;[2] defined as BMI ≥ 30 kg/m^2

Table 11: **Interaction between Sleep Duration, Sleep Quality, other Sleep Variables[1], and Obesity [2], in relation to Physical Stress Induced Myocardial Ischemia (PSIMI), the MIMS-2 Study, 2011- 2013.**

	Sleep Duration				
	< 7 h		≥ 7 h		P for interaction
	OR*	(95% CI)	OR*	(95% CI)	
Overall Sleep Quality					0.286
Poor	1.25	(0.38 4.07)	0.30	(0.07 1.35)	
Good	1.12	(0.14 8.82)	1.00		
Sleep disturbance					0.821
Yes	0.66	(0.05 8.34)	0.55	(0.02 13.2)	
No	1.91	(0.67 5.42)	1.00		
Long Sleep Latency					0.262
Yes	0.93	(0.20 4.39)	0.65	(0.14 2.95)	
No	4.36	(0.76 25.0)	1.00		
Daytime Dysfunction					0.527
Yes	4.18	(0.75 23.3)	0.79	(0.12 5.19)	
No	2.70	(0.53 13.9)	1.00		
Low Sleep efficiency					0.416
Yes	1.69	(0.51 5.64)	1.32	(0.31 5.74)	
No	2.82	(0.72 11.1)	1.00		
Self-reported poor sleep quality					0.900
Yes	0.80	(0.15 4.26)	0.40	(0.08 2.05)	
No	1.72	(0.19 15.5)	1.00		
Sleep medication use					0.737
Yes	2.78	(0.73 10.6)	1.30	(0.33 5.07)	
No	1.57	(0.43 5.81)	1.00		
Obesity[2]					0.756
Yes	0.35	(0.09 1.35)	0.43	(0.12 1.55)	
No	1.08	(0.33 3.51)	1.00		

*Multivariate Odds ratio (OR) with 95% confidence interval (CI), adjusted for demographic, lifestyle, clinical and psychological factors; [1] defined as Pittsburgh Sleep Quality Index (PSQI) individual component score ≥ 1; [2] defined as BMI ≥ 30 kg/m^2