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Association between late sleeping and major adverse cardiovascular events in patients with percutaneous coronary intervention

Xiao-Qing Lian[1], Kun Jiang[1], Xiang-Xuan Chen[1], Hai-Cui Dong[1], Yu-Qing Zhang[1*†] and Lian-Sheng Wang[2*†]

Abstract

Background Sleeping late has been a common phenomenon and brought harmful effects to our health. The purpose of this study was to investigate the association between sleep timing and major adverse cardiovascular events (MACEs) in patients with percutaneous coronary intervention (PCI).

Methods Sleep onset time which was acquired by the way of sleep factors questionnaire in 426 inpatients was divided into before 22:00, 22:00 to 22:59, 23:00 to 23:59 and 24:00 and after. The median follow-up time was 35 months. The endpoints included angina pectoris (AP), new myocardial infarction (MI) or unplanned repeat revascularization, hospitalization for heart failure, cardiac death, nonfatal stroke, all-cause death and the composite endpoint of all events mentioned above. Cox proportional hazards regression was applied to analyze the relationship between sleep timing and endpoint events.

Results A total of 64 composite endpoint events (CEEs) were reported, including 36 AP, 15 new MI or unplanned repeat revascularization, 6 hospitalization for heart failure, 2 nonfatal stroke and 5 all-cause death. Compared with sleeping time at 22:00–22:59, there was a higher incidence of AP in the bedtime ≥ 24:00 group (adjusted HR: 5.089; 95% CI: 1.278–20.260; $P=0.021$). In addition, bedtime ≥ 24:00 was also associated with an increased risk of CEEs in univariate Cox regression (unadjusted HR: 2.893; 95% CI: 1.452–5.767; $P=0.003$). After multivariable adjustments, bedtime ≥ 24:00 increased the risk of CEEs (adjusted HR: 3.156; 95% CI: 1.164–8.557; $P=0.024$).

Conclusion Late sleeping increased the risk of MACEs and indicated a poor prognosis. It is imperative to instruct patients with PCI to form early bedtime habits.

Keywords Late sleeping, Angina pectoris, Major adverse cardiovascular events, Composite endpoint events, Percutaneous coronary intervention

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Introduction

Cardiovascular disease (CVD) occupies a large proportion of mortality worldwide [1]. Due to the heavy burden brought by CVD, primary prevention has attracted more attention. Lifestyle changes are the main measures of prevention, including smoking cessation, weight control, low salt and fat diet, proper exercise, sufficient sleep and so on. Good sleep is beneficial to physical and mental health [2]. With the development of health consciousness, much focus is devoted to the negative effects of sleep problems.

Sleep disorders have been shown to relate to obesity, type 2 diabetes mellitus and hypertension, which are risk factors for CVD [3–5]. Short or long sleep duration was associated with increased risk of cardiovascular events and all-cause mortality [6, 7]. It has been demonstrated that poor sleep quality increases the risk of coronary artery disease (CAD) [8]. The relationship between the number of insomnia symptoms and myocardial infarction (MI) risk appeared positive in a dose-dependent fashion [9].

An increased risk for cardiac events was found among both men and women who take regular long midday naps [10]. Snoring frequency, no matter how many times per week, was positively associated with acute myocardial infarction (AMI) risk [11]. The adverse cardiovascular effects of sleep disorders may be due to high sympathetic activity, an imbalance between energy intake and expenditure, increased norepinephrine and decreased maximum endothelium-dependent venodilation [12, 13].

Sleeping late at night is a common problem especially in the young population and has recently received extensive attention for its harmful influence on health. Late sleeping has a close relationship with cardiometabolic biomarkers, which in turn results in an increased risk of CVD. It has been reported that late sleeping is associated with a higher risk of obesity [14]. Late sleeping has been found to be linked with a higher fasting glucose level in adults with diabetes [15]. Moreover, a previous study revealed that individuals with late sleeping habits had higher triglyceride and low-density lipoprotein levels [16]. A variety of cross-sectional studies have highlighted that the lifestyle of late to bed and late to rise is unwise for disrupting intrinsic circadian rhythms. It is necessary to design more convincing prospective investigations to evaluate the effects of late sleeping.

Therefore, we examined the association between late sleeping and CVD prognosis in patients with percutaneous coronary intervention (PCI) on optimal secondary prevention therapies.

Methods

Participants

All participants were selected from the previous research which enrolled 873 hospitalized patients from the First Affiliated Hospital and the Affiliated Jiangning Hospital of Nanjing Medical University (ClinicalTrials.gov identifier: NCT04636112, November 23, 2020) [17]. All patients underwent coronary angiography and completed a sleep questionnaire between April 2019 and June 2020. Patients with their first PCI were eligible for enrollment. The exclusion criteria were shift work, sleep apnea, mental disease, heart failure, end-stage renal or hepatic failure, tumor, some chronic diseases disturbing sleep and poor sleep for increased nocturia frequency. Of the 873 patients, 503 patients were enrolled according to the inclusion and exclusion criteria. During the follow-up, 46 patients were out of touch, 17 patients changed their sleep habits, 10 patients withdrew drug therapy without doctors' advice and 4 patients had a major adverse cardiovascular event (MACE) within 3 months from enrollment. Finally, the remaining 426 patients were analyzed statistically (Fig. 1), of whom 363 cases were acute coronary syndrome. All enrolled patients provided written informed consent in accordance with the ethics committee.

Data collection

Clinical data, including demographic characteristics, conventional risk factors, coronary angiography results, reperfusion therapy and the habits of smoking, drinking, diet, exercise and sleep were obtained from electronic medical record systems and face-to-face interviews. Residual Gensini score was calculated according to the percentage and segment of residual coronary artery stenosis after PCI [18]. Cardiology consultants were responsible for the decision on whether and how to perform PCI after coronary angiography.

Sleep onset time, wake-up time, sleep duration, sleep quality and daytime napping were acquired by a sleep factor questionnaire at baseline [19]. Sleep onset time was categorized as before 22:00, 22:00 to 22:59, 23:00 to 23:59 and 24:00 and after. Based on the fact that sleep onset time between 22:00 and 22:59 had the lowest incidence of CAD, we chose this timing as the reference group [20]. Wake-up time was divided into before 6:00 AM, 6:00 AM to 7:00 AM and after 7:00 AM. Sleep quality was classified into very good, fairly good, fairly poor and very poor. Sleep duration was defined as the time from sleep onset at night to wake up in the morning and was categorized as <6 h, 6–9 h and >9 h. Daytime napping referred to regular napping for at least 5 days per week [10].

Study design

We performed a prospective cohort study to assess the association of late sleeping with cardiovascular risks. The follow-up time was calculated as the period from the time of inclusion to the first occurrence of MACEs or the deadline of October 1, 2022. The patients were

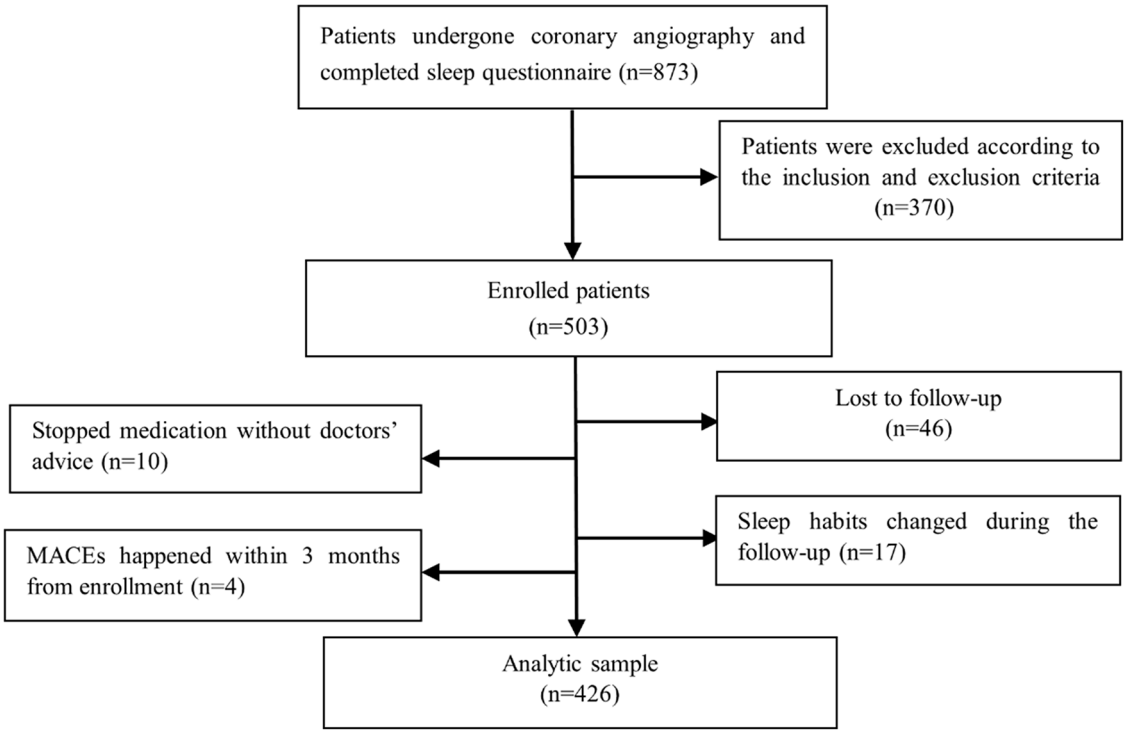

Fig. 1 Flow chart of patient selection

followed up annually and the median follow-up time was 35 months. Two investigators were responsible for collecting the patients' outcomes by a clinic visit, medical records review or telephone calls. The endpoints were MACEs, including angina pectoris (AP), new MI or unplanned repeat revascularization, hospitalization for heart failure, cardiac death, nonfatal stroke and all-cause death. The composite endpoint events (CEEs) included all MACEs mentioned above. AP was diagnosed on the basis of syndromes of coronary ischemia, electrocardiogram changes and coronary angiography. The episode of AP was acknowledged under the condition that the diagnoses from two different cardiologists were identical.

Statistical analysis

Non-normally distributed continuous data were shown as median (interquartile range) and a non-parametric test was used for testing baseline differences. Categorical variables were presented as numbers (proportions) and Chi-square test or Fish's exact test was used to examine the group differences. The cumulative endpoint event rates were evaluated by Kaplan-Meier curves. Associations between individual subgroups and the follow-up outcomes were assessed using Cox proportional hazards regression models. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated to represent the prognosis. Model 1 was univariable (unadjusted) and model 2 was adjusted for age, sex, body mass index (BMI), diabetes, hypertension, dyslipidemia, family history of CAD, smoking, drinking, diet, regular exercise and residual Gensini score. Model 3 was adjusted for all variables in model 2 plus sleep duration, sleep quality, wake-up time and daytime napping. $P<0.05$ was considered as statistically significant and all analyses were conducted using SPSS statistical software (version 25.0).

The sample size was estimated by using Cox regression model in PASS (version 2021) with a statistical power of 0.8 and a significance level of 0.05. According to previous studies, the overall event rate varied from 0.1 to 0.3, and the regression coefficient was equal to 0.5 [21, 22]. The two parameters of covariates were assumed as 0.4 and 1.5 [23]. As a result, the sample size was expected for 291 at least with a 20% drop-out rate.

Results

Baseline characteristics

There were 132 patients sleeping < 22:00, 112 patients sleeping between 22:00 to 22:59, 84 patients sleeping between 23:00 to 23:59 and 98 patients sleeping ≥ 24:00, respectively. The late bedtime group (≥ 24:00) tended to have a high proportion of men, dyslipidemia, family history of CAD, smoking ≥ 20 cigarettes/day, high-fat diet and very poor sleep quality. Patients with bedtime ≥ 24:00 were younger and more likely to have a larger BMI and a shorter sleep duration ($P<0.05$). The proportion of regular exercise and daytime napping in the late bedtime

group (≥24:00) was lower than that in the other groups (Table 1).

Clinical outcomes

A total of 64 CEEs were observed, including 36 AP, 15 new MI or unplanned repeat revascularization, 6 hospitalization for heart failure, 2 nonfatal stroke and 5 all-cause death. There was no cardiac death during follow-up in this study. The highest incidence rate was AP (8.5%), followed by new MI or unplanned repeat revascularization (3.5%), hospitalization for heart failure (1.4%), all-cause death (1.2%), and nonfatal stroke (0.5%). Significant differences were observed in the morbidity of AP and CEEs ($P<0.001$ and $P=0.014$, respectively) (Table 2).

Relationship between sleep quality, sleep duration and MACEs

As seen in Table 3, fairly poor sleep quality was significantly associated with increased risk of AP (adjusted HR: 3.462; 95% CI: 1.308–9.164; $P=0.012$) compared to very good sleep quality. Sleep quality was not found to be related with CEEs. There were significant relationships between sleep duration < 6 h and AP (adjusted HR: 3.081; 95% CI: 1.507–6.301; $P=0.002$) and CEEs (adjusted HR: 2.203; 95% CI: 1.254–3.871; $P=0.006$). No relationships between sleep > 9 h and AP and CEEs were observed after adjustment.

Association between sleep onset time and MACEs

Compared with the sleep onset time group at 22:00–22:59, there was a higher risk of AP in the bedtime ≥ 24:00 group (unadjusted HR: 5.992; 95% CI: 2.025–17.726;

Table 1 Baseline characteristics of study population according to different sleep timings

Habitual sleep onset time	< 22:00 (*n* = 132)	22:00–22:59 (*n* = 112)	23:00–23:59 (*n* = 84)	≥ 24:00 (*n* = 98)	*P*-Value
Age (years)	67 (58, 72)	62 (55, 67)	58 (53, 67)	52 (45, 58)	< 0.001
Men (n, %)	102 (77.3%)	82 (73.2%)	61 (72.6%)	88 (89.8%)	0.012
BMI (kg/m^2)	24.3 (22.4, 26.8)	25.0 (22.9, 27.0)	24.4 (22.3, 26.3)	26.0 (24.2, 28.0)	0.001
Diabetes (n, %)	27 (20.5%)	28 (25.0%)	17 (20.2%)	14 (14.3%)	0.293
Hypertension (n, %)	82 (62.1%)	64 (57.1%)	49 (58.3%)	44 (44.9%)	0.067
Dyslipidemia (n, %)	4 (3.0%)	5 (4.5%)	7 (8.3%)	10 (10.2%)	0.096
Family history of CAD (n, %)	4 (3.0%)	5 (4.5%)	3 (3.6%)	8 (8.2%)	0.347
Smoking (n, %)					
Never	49 (37.1%)	47 (42.0%)	32 (38.1%)	19 (19.4%)	< 0.001
Former	21 (15.9%)	13 (11.6%)	12 (14.3%)	6 (6.1%)	
< 20 cigarettes/day	22 (16.7%)	16 (14.3%)	10 (11.9%)	13 (13.3%)	
≥ 20 cigarettes/day	40 (30.3%)	36 (32.1%)	30 (35.7%)	60 (61.2%)	
Drinking (n, %)					
No	77 (58.3%)	62 (55.4%)	49 (58.3%)	33 (33.7%)	0.001
1 to 3 times a month	22 (16.7%)	23 (20.5%)	21 (25.0%)	25 (25.5%)	
1 to 6 times a week	13 (9.8%)	13 (11.6%)	8 (9.5%)	26 (26.5%)	
At least once a day	20 (15.2%)	14 (12.5%)	6 (7.1%)	14 (14.3%)	
Diet (n, %)					
Low-fat diet	14 (10.6%)	2 (1.8%)	6 (7.1%)	1 (1.0%)	< 0.001
Normal diet	78 (59.1%)	68 (60.7%)	51 (60.7%)	41 (41.8%)	
High-fat diet	40 (30.3%)	42 (37.5%)	27 (32.1%)	56 (57.1%)	
Regular exercise (n, %)	40 (30.3%)	38 (33.9%)	23 (27.4%)	24 (24.5%)	0.482
Residual Gensini score	12.0 (5.6, 22.0)	13.5 (4.0, 23.0)	14.0 (5.5, 24.8)	14.0 (4.0, 25.0)	0.850
Sleep duration	8.0 (7.0, 8.5)	7.0 (6.2, 7.3)	6.3 (5.6, 7.3)	6.0 (4.3, 6.6)	< 0.001
Sleep quality (n, %)					
Very poor	3 (2.3%)	1 (0.9%)	5 (6.0%)	12 (12.2%)	0.001
Fairly poor	12 (9.1%)	15 (13.4%)	12 (14.3%)	14 (14.3%)	
Fairly good	48 (36.4%)	47 (42.0%)	35 (41.7%)	45 (45.9%)	
Very good	69 (52.3%)	49 (43.8%)	32 (38.1%)	27 (27.6%)	
Wake-up time (n, %)					
Before 6:00 AM	102 (77.3%)	73 (65.2%)	29 (34.5%)	20 (20.4%)	< 0.001
6:00–7:00 AM	30 (22.7%)	35 (31.3%)	52 (61.9%)	54 (55.1%)	
After 7:00 AM	0 (0.0%)	4 (3.6%)	3 (3.6%)	24 (24.5%)	
Daytime napping (n, %)	52 (39.4%)	49 (43.8%)	37 (44.0%)	30 (30.6%)	0.186

BMI: body mass index; CAD: coronary artery disease

Table 2 Incidences of different endpoint events

Habitual sleep onset time	< 22:00 (*n* = 132)	22:00–22:59 (*n* = 112)	23:00–23:59 (*n* = 84)	≥ 24:00 (*n* = 98)	*P*-Value
Angina pectoris (n, %)	5 (3.8%)	4 (3.6%)	9 (10.7%)	18 (18.4%)	< 0.001
New myocardial infarction or unplanned repeat revascularization (n, %)	4 (3.0%)	5 (4.5%)	2 (2.4%)	4 (4.1%)	0.858
Hospitalization for heart failure (n, %)	1 (0.8%)	2 (1.8%)	0 (0.0%)	3 (3.1%)	0.333
Nonfatal stroke (n, %)	1 (0.8%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1.000
All-cause death (n, %)	4 (3.0%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	0.083
Composite endpoint events (n, %)	15 (11.4%)	12 (10.7%)	12 (14.3%)	25 (25.5%)	0.014

Table 3 Cox proportional hazard models hazard ratios for sleep quality and duration

		Angina pectoris				Composite endpoint events			
		Model 1	*P*-Value	Model 2	*P*-Value	Model 1	*P*-Value	Model 2	*P*-Value
Sleep quality	Very good	1		1		1		1	
	Fairly good	1.353 (0.599, 3.056)	0.467	1.414 (0.615, 3.252)	0.415	1.376 (0.776, 2.440)	0.275	1.472 (0.818, 2.647)	0.197
	Fairly poor	2.851 (1.155, 7.038)	0.023	3.462 (1.308, 9.164)	0.012	1.847 (0.901, 3.789)	0.094	2.129 (0.984, 4.605)	0.055
	Very poor	2.610 (0.718, 9.496)	0.145	2.156 (0.565, 8.227)	0.261	1.370 (0.407, 4.616)	0.611	1.166 (0.338, 4.021)	0.808
Sleep duration	6–9 h	1				1		1	
	< 6 h	3.796 (1.917, 7.518)	< 0.001	3.081 (1.507, 6.301)	0.002	2.345 (1.372, 4.009)	0.002	2.203 (1.254, 3.871)	0.006
	> 9 h	2.825 (0.827, 9.647)	0.097	3.378 (0.908, 12.569)	0.069	2.557 (1.079, 6.063)	0.033	2.238 (0.881, 5.687)	0.090

Model 1: unadjusted; Model 2: adjusted for age, sex, BMI, diabetes, hypertension, dyslipidemia, family history of CAD, smoking, drinking, diet, regular exercise, residual Gensini score

Table 4 Cox proportional hazard models hazard ratios for sleep onset time

		< 22:00 (*n* = 132)	*P*-Value	22:00–22:59 (*n* = 112)	23:00–23:59 (*n* = 84)	*P*-Value	≥ 24:00 (*n* = 98)	*P*-Value
Angina pectoris	Model 1	1.077 (0.289, 4.010)	0.912	1	3.086 (0.950, 10.024)	0.061	5.992 (2.025, 17.726)	0.001
	Model 2	0.989 (0.261, 3.745)	0.986	1	2.960 (0.892, 9.819)	0.076	7.036 (2.260, 21.904)	0.001
	Model 3	1.169 (0.295, 4.635)	0.824	1	2.752 (0.790, 9.587)	0.112	5.089 (1.278, 20.260)	0.021
Composite endpoint events	Model 1	1.084 (0.507, 2.316)	0.835	1	1.395 (0.627, 3.106)	0.415	2.893 (1.452, 5.767)	0.003
	Model 2	0.849 (0.388, 1.858)	0.683	1	1.425 (0.630, 3.222)	0.395	3.904 (1.854, 8.220)	< 0.001
	Model 3	0.992 (0.428, 2.298)	0.985	1	1.373 (0.574, 3.284)	0.477	3.156 (1.164, 8.557)	0.024

Model 1: unadjusted; Model 2: adjusted for age, sex, BMI, diabetes, hypertension, dyslipidemia, family history of CAD, smoking, drinking, diet, regular exercise, residual Gensini score; Model 3: adjusted for model 2, sleep duration, sleep quality, wake-up time and daytime napping

P=0.001). After adjustment in models 2 and 3, an increased risk existed in the bedtime≥24:00 group (adjusted HR: 7.036; 95% CI: 2.260-21.904; *P*=0.001 and HR: 5.089; 95% CI: 1.278–20.260; *P*=0.021). Regarding CEEs, patients with bedtime≥24:00 had a higher risk in model 1 (unadjusted HR: 2.893; 95% CI: 1.452–5.767; *P*=0.003), model 2 (adjusted HR: 3.904; 95% CI: 1.854–8.220; *P*<0.001) and model 3 (adjusted HR: 3.156; 95% CI: 1.164–8.557; *P*=0.024) (Table 4). Figure 2 demonstrates the unadjusted Kaplan-Meier curves depicting hazards for AP and CEEs among the groups. As seen in Fig. 2, AP and CEEs were higher with bedtime≥24:00 compared with other sleep timings (Fig. 2A, *P*<0.001 and Fig. 2B, *P*=0.002).

Discussion

In the present study, we investigated the association of late sleeping and MACEs using longitudinal data with a median follow-up of 35 months and observed poor prognosis in patients with bedtime≥24:00. Our study showed that sleeping≥24:00 independently increased the risk of AP and CEEs after adjusting for potential covariates.

Sleeping habits, similar to smoking and drinking, have been identified as a modified lifestyle which influences the prevalence of CVD [2]. As we all known that short sleep duration and poor sleep quality, as two important factors of sleep, have a harmful effect on cardiovascular prognosis [23, 24]. Similar to the previous studies, we also found that both poor sleep quality and short sleep duration were associated with higher risk of MACEs in our research. However, few evidence regarding the impact of late sleeping on MACEs in patients with PCI has been reported. Individuals with short or poor sleep have a great possibility to go to sleep late. Our results demonstrated that late sleeping was correlated with an increased risk of MACEs, even when sleep duration and quality were taken into consideration. A study from

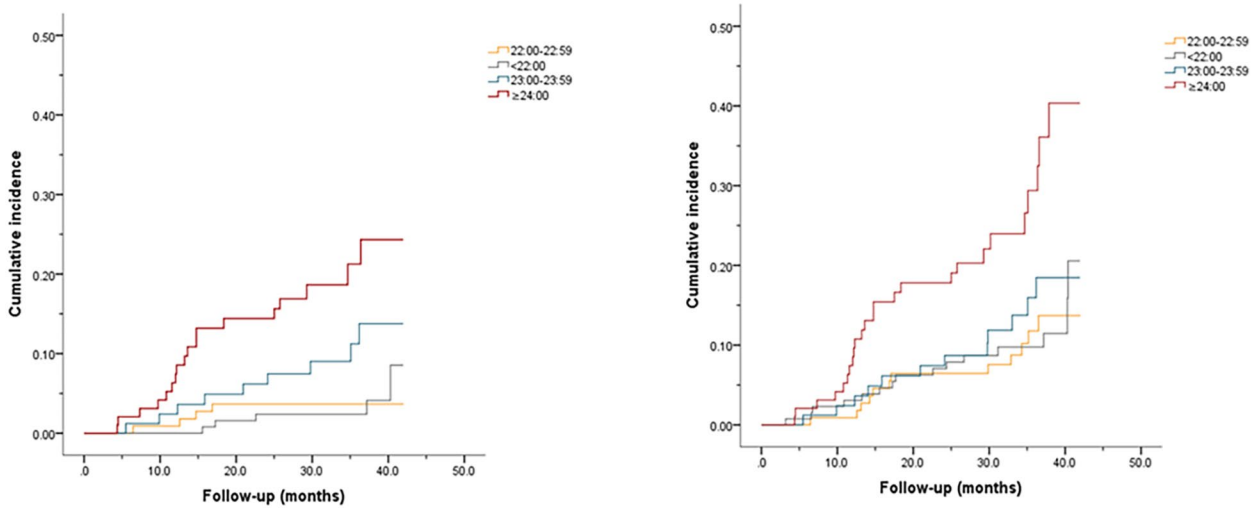

Fig. 2 Kaplan-Meier plots of cumulative risk for angina pectoris (**A**, $P < 0.001$) and composite endpoint events (**B**, $P = 0.002$) stratified by different categories of sleep onset time

Iran revealed that late bedtime was significantly associated with the presence of premature CAD, in which late bedtime was defined as bedtime after 1:00 AM [25]. The large-scale observational study also proved that later bedtimes (>23:00 and 22:01–23:00) increased the risk of AP, after adjustment for sleep duration [26].

Fan et al. revealed that individuals with weekday bedtime at 10:01–11:00 PM had the lowest occurrence of MI compared to other time periods in middle-aged and older populations [27]. Another study also reported a similar condition that earlier (<10:00 PM) and later (≥12:00 PM) sleepers had a higher risk of the composite outcome [28]. Different from the previous studies, which found a U-shaped association between bedtime and MACEs, patients in our study with bedtime<22:00 were prone to have a low incidence of MACEs despite no significant difference. The inconsistent results may be attributed to the different enrolled populations. In the two studies above, most participants were included from the community and without CVD at the time of enrollment, while the target population in our study was diagnosed as CAD. The results of multivariate Cox regression analysis in the present study indicated that patients with bedtime≥24:00 had an approximately fourfold increase in risk for AP and a twofold increase in risk for CEEs.

It is inferred that late sleeping destroys the intrinsic circadian clock, which leads to endocrine, immune and autonomic nervous system changes [29, 30]. Circadian misalignment causes an increase in postprandial glucose, a decrease of leptin and an inversion of cortisol, which contributes to insulin resistance, hyperglycemia and obesity [30–32]. In addition, circadian dysfunction could disturb sympathovagal balance, which reflects in the increased heart rate and LF/HF ratio (an indication of heart rate variability) and the reduced cardiac vagal modulation [33]. A previous study suggested that sympathetic hyperactivity itself also aroused a higher risk of coronary spasm, coronary thrombosis, and sudden death [34, 35]. In circadian disrupted mice, the increased release of proinflammatory cytokines through immune responses resulted in endothelial dysfunction in patients with CAD [29, 36]. These abnormal physiological processes closely related to cardiometabolic risks could explain our results that late sleeping increased the risk of AP and CEEs.

Undoubtedly, improving sleep could facilitate better health. Sleep extension reduced intake of fat, carbohydrates and free sugars [37]. After 6-week intervention period, participants in the sleep extension group had a significantly decrease in the systolic and diastolic beat-to-beat BP average over the 24 h recording [38]. A meta-analysis also revealed that interventions to improve sleep led to a reduced weight gain in preschool children [39]. While an abundance of data indicate that sleep disorder is associated with CVD, there is lack of large randomized clinical trials of sleep intervention on CVD prognosis. Further larger scale studies of behavior modification are required to establish the CVD effects of sleep improvement.

Limitations

Some limitations in this study should be taken into account. First, sleep information was acquired by questionnaire to evaluate the relationship between late sleeping and MACEs, so recall bias cannot be overcome. Second, despite the enrolled sample size exceeded the calculated number, a larger sample and a longer follow-up time were more persuasive. Third, we took into considerations of sleep duration, sleep quality, wake-up time and daytime napping, but sleep habits included so many

aspects that other factors such as obstructive sleep apnea syndrome were valuable to discuss. Last but not least, although AP, a self-reported symptom, was carefully identified and diagnosed by two cardiologists, we cannot completely rule out subjective factors.

Conclusion

Our findings supported the growing evidence that late sleeping was associated with CVD prognosis and bedtime ≥ 24:00 was obviously related to an increased risk of AP and CEEs in patients with PCI. Therefore, sleep timing represents a potentially novel risk factor for CVD and it is valuable to guide patients to go to bed early at night to reduce MACEs.

Abbreviations

CVD	Cardiovascular disease
CAD	Coronary artery disease
AMI	Acute myocardial infarction
PCI	Percutaneous coronary intervention
MACEs	Major adverse cardiovascular events
AP	Angina pectoris
CEEs	Composite endpoint events
HRs	Hazard ratios
CIs	Confidence intervals
BMI	Body mass index

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Author contributions

Conceptualization, Y.Q. Z; methodology, X.Q. L; validation, K. J; formal analysis, X.Q. L and H.C. D; resources, Y.Q. Z and L.S. W; data curation, X.X. C and K. J; writing—original draft preparation, X.Q. L; writing—review and editing, X.Q. L, Y.Q. Z and L.S. W; visualization, L.S. W; supervision, Y.Q. Z and L.S. W. All authors reviewed the manuscript.

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Data availability

The data analyzed in this study are available from the corresponding author.

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of the Affiliated Jiangning Hospital and the First Affiliated Hospital of Nanjing Medical University. All enrolled patients provided written informed consent in accordance with ethics committee.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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