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Original Article

# Association of incident angina pectoris and rapid eye movement sleep in a large community-based study: the sleep heart health study

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ABSTRACT

*Background:* Sleep-disordered breathing may precipitate angina pectoris (AP) in rapid eye movement (REM) sleep. The purpose of this study was to investigate whether REM sleep is associated with the incidence of AP in different categories of apnea–hypopnea index (AHI).
*Methods:* A total of 2710 participants from Sleep Heart Health Study (59.3% women; mean age 61.7 years), who had 6–8 h of sleep; experienced an almost 11-year follow-up period. Complete polysomnography data and medical records were available for all participants. Percentage of REM sleep time (REM%) was classified into grade 1 (<20%), grade 2 (20–25%) and grade 3 (>25%). Logistic regression analysis was used to characterize the independent association between REM sleep and prevalent AP in this multi-center community-based cohort study.
*Results:* Patients with REM% of grade 3 had a higher incidence of AP than those with grade 1 and grade 2 (50.3% vs 42.4% vs 42.1%, respectively; $p = 0.003$). After adjusting for age, gender, race, AHI, marital status, education level, body mass index, sleep duration, arousal index, diabetes, hypertension and smoking status, multivariate logistic regression analysis revealed that REM% >25% was independently associated with the occurrence of AP (odds ratio = 1.500; 95% confidence interval = 1.188–1.894; $p = 0.001$).
*Conclusions:* The percentage of REM sleep time may affect the incidence of AP irrespective of AHI level. Therefore, the relationship between sleep structure and cardiovascular disease merits further exploration.



## 1. Introduction

Millions of people suffer from the discomfort of angina pectoris (AP) annually, and it is a common presenting symptom in patients with coronary artery disease (CAD) [1]. It results from myocardial ischemia and is often manifested as chest pain, pressure, squeezing, heaviness, or burning [2,3]. It has been widely recognized that age, hypertension, diabetes, smoking, abnormal lipid levels, obesity, alcohol abuse, physical inactivity, and kidney disease account for most cases of AP [4]. Furthermore, several studies have also shown that sleep duration, sleep quality, and sleep apnea are closely related to AP [5–7].

Sleep is an indispensable physiological phenomenon in humans and accounts for nearly one-third of our life. Two main types of sleep make up the sleep cycle, ie, non-rapid eye movement (NREM) and rapid eye-movement (REM) sleep [8]. REM sleep occupies approximately 20–25% of sleep time, with the remaining 75–80% being NREM sleep [9]. REM sleep is characterized by low-voltage fast brain waves occurring in combination with random movement of the eyes, low muscle tone throughout the body, and vivid dreaming [10].

Unlike in NREM sleep, heart rate becomes rapid and blood pressure increases during REM sleep. Variations of blood pressure and heart rate are also closely related to cardiovascular disease. Besides, obstructive sleep apnea (OSA) events including apnea and hypopnea were longer and more frequent during REM sleep than NREM sleep [11]. Therefore, we hypothesized that there would be a link between REM sleep and

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AP. The aim of this study was to explore whether patients with a higher percentage of REM sleep time (REM%) were more prone to AP.

## 2. Methods

### 2.1. Study design and population

The Sleep Heart Health Study (SHHS) is a multi-center cohort study of cardiovascular consequences of sleep-disordered breathing (ClinicalTrials.gov Identifier: NCT00005275). SHHS did not enroll a new cohort and was enlisted from existing cohorts of six prospective studies including the Atherosclerosis Risk in Communities Study, the Cardiovascular Health Study, the Framingham Offspring and Omni Study, the Strong Heart Study, Tucson Epidemiological Study of Obstructive Lung Disease, the cohort studies of respiratory disease in Tucson, and cohort studies of hypertension in New York. All participants underwent overnight home polysomnography. The protocol was approved by the Institutional Review Board of each participating institution. Appropriate informed consent was obtained, and procedures conformed to the Declaration of Helsinki on human research. Details of the study design have been reported previously [12]. Eligible participants were: (1) individuals that had 6–8 h of sleep; and (2) patients for whom complete polysomnography data and medical records were available. Patients who had a history of CAD, heart failure, or myocardial infarction were excluded (Fig. 1).

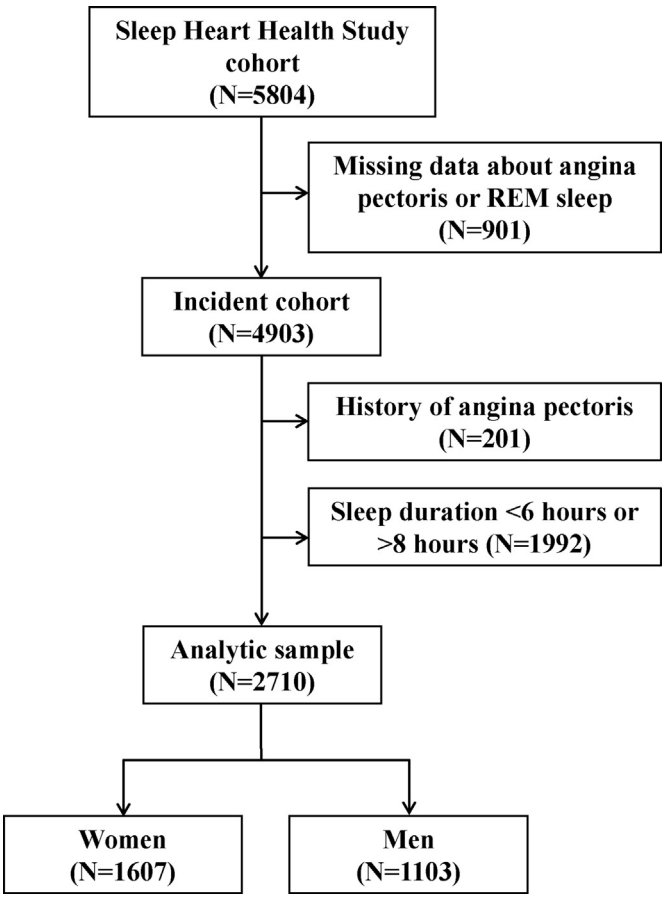


**Fig. 1.** Flow diagram of patient selection.

### 2.2. Data collection

The data was accessed based on the signed agreement with the Brigham and Women's Hospital. All participants underwent electroencephalogram-based overnight polysomnography at home, as previous described [13,14]. The REM% was classified into grade 1 (<20%), grade 2 (20%–25%), and grade 3 (>25%). The apnea–hypopnea index (AHI) were calculated as all apneas and hypopneas per hour of sleep, accompanied by at least a 4% drop in oxygen saturation. According to conventional clinical categories, AHI was classified as none (AHI < 5), mild (AHI > 5 to < 15), moderate (AHI ≥ 15 to < 30), and severe (AHI ≥ 30) [15]. Sleep duration in the subgroup analysis was categorized as 6–7 h and 7–8 h. The AP was defined as the first-episode in the average 11 years of follow-up. The age, gender, body mass index (BMI), smoking status, education level, marital status, history of diabetes and hypertension, and polysomnography data of participants were obtained from baseline examination of SHHS.

### 2.3. Statistical analysis

Descriptive statistics are presented as percentages for discrete variables and as mean ± SD for continuous variables. Bivariate comparisons between patients with and without AP were performed using the unpaired *t*-test and $\chi^2$ test, respectively. To compare continuous normally distributed variables between subgroups of REM% (grade 1, grade 2, and grade 3), analysis of variance (ANOVA) was employed. A logistic regression model was used to analyze the relationship between REM% and AP. After adjusting for age (≥60 years old vs < 60 years old), gender (men vs women), race (white vs others), AHI (≥5 events/h vs < 5 events/h), marital status (married vs others), education (>15 years vs ≤ 15 years), BMI (18–25 kg/m$^2$ vs 25–30 kg/m$^2$ vs ≥ 30 kg/m$^2$), sleep duration, arousal index, smoke status (current vs former vs no), diabetes (yes vs no) and hypertension (yes vs no), multivariable logistic regression was performed to identify independent risk factors, and to estimate the odds ratio (OR) and 95% confidence interval (CI). Furthermore, we conducted subgroup analyses using multivariate adjusted logistic regression models to identify interactions between angina and clinically relevant factors by comparing models with and without multiplicative interaction terms. *p*-Values were two-tailed and considered statistically significant at <0.05. All statistical analyses were conducted using SPSS, version 24.0 (SPSS Inc., Xi'an Jiaotong University, China).

## 3. Results

### 3.1. Participants' characteristics

Characteristics of the study population with or without AP are shown in Table 1. This study involved 2710 patients (1103 men and 1607 women, 61.7 ± 10.9 years old). Participants with AP (1192 patients, 44.0%) were more likely to be men, of Caucasian descent, and married. Patients with AP were older, experienced more sleep apnea, had higher BMI, higher REM%, higher arousal index, lower sleep time, and lower sleep time in stage 2. The characteristics of the study subjects as stratified by quartiles of REM% are presented in Table 2. Grade 1, grade 2, and grade 3 of REM% was present in 1141 (42.1%), 990 (36.5%), and 579 people (21.4%), respectively. Patients with REM% of grade 3 were younger, had lower BMI, were more likely to be current smokers, experienced less sleep apnea, and were less likely to have diabetes and hypertension. In addition, the frequency of hypopnea events was obviously higher in REM sleep than NREM sleep (45.4 ± 19.8 vs

**Table 1**
Baseline characteristics of patients.

| Characteristics | Total ($N = 2710$) | No angina ($N = 1518$) | Angina ($N = 1192$) | $p$ |
|---|---|---|---|---|
| Age, years | 61.7 ± 10.9 | 60.5 ± 12.9 | 63.4 ± 7.2 | <0.001 |
| Gender, *N* (%) | | | | 0.034 |
| Men | 1103 (40.7) | 591 (38.9) | 512 (43.0) | |
| Women | 1607 (59.3) | 927 (61.1) | 680 (57.1) | |
| BMI, kg/m$^2$ | 28.1 ± 5.0 | 27.7 ± 5.0 | 28.5 ± 4.9 | <0.001 |
| Race, *N* (%) | | | | <0.001 |
| White | 2362 (87.2) | 1204 (79.3) | 1158 (97.2) | |
| Other | 348 (12.8) | 314 (20.7) | 34 (2.9) | |
| Smoking status, *N* (%) | | | | 0.143 |
| Current smoker | 251 (9.3) | 138 (9.1) | 113 (9.5) | |
| Former smoker | 1130 (41.7) | 610 (40.2) | 520 (43.6) | |
| Never smoker | 1325 (48.9) | 767 (50.5) | 558 (46.8) | |
| Education, *N* (%) | | | | <0.001 |
| ≤5 years | 1499 (55.3) | 825 (54.4) | 674 (56.5) | |
| >15 years | 927 (34.2) | 414 (27.3) | 513 (43.0) | |
| Marital Status, *N* (%) | | | | <0.001 |
| Married | 2127 (78.5) | 1102 (72.6) | 1015 (85.2) | |
| Other | 505 (18.6) | 368 (24.2) | 137 (11.5) | |
| AHI, *N* (%) | | | | 0.002 |
| <5.0 | 1445 (53.3) | 849 (55.9) | 596 (50.0) | |
| ≥5 | 1265 (46.7) | 669 (44.1) | 596 (50.0) | |
| Diabetes mellitus, *N* (%) | 148 (5.5) | 77 (5.1) | 71 (6.0) | 0.315 |
| Hypertension, *N* (%) | 908 (33.5) | 494 (32.5) | 414 (34.7) | 0.231 |
| Sleep duration, min | 405.7 ± 29.6 | 407.7 ± 30.5 | 403.2 ± 28.3 | <0.001 |
| Time in REM sleep, min | 83.5 ± 26.3 | 82.7 ± 26.7 | 84.6 ± 25.7 | 0.065 |
| Time in stage 1 sleep, min | 19.7 ± 13.3 | 19.5 ± 13.6 | 19.9 ± 12.8 | 0.477 |
| Time in stage 2 sleep, min | 229.6 ± 51.4 | 232.4 ± 52.4 | 226.0 ± 49.9 | 0.001 |
| Time in stage 3–4 sleep, min | 73.0 ± 46.1 | 73.2 ± 46.4 | 72.7 ± 45.8 | 0.811 |
| Percentage of sleep time in REM sleep, % | 20.5 ± 6.2 | 20.2 ± 6.2 | 20.9 ± 6.1 | 0.003 |
| Percentage of sleep time in stage 1 sleep, % | 4.9 ± 3.3 | 4.8 ± 3.4 | 5.0 ± 3.2 | 0.287 |
| Percentage of sleep time in stage 2 sleep, % | 56.6 ± 12.3 | 57.0 ± 12.4 | 56.1 ± 12.1 | 0.056 |
| Percentage of sleep time in stage 3–4 sleep, % | 18.0 ± 11.2 | 17.9 ± 11.3 | 18.0 ± 11.2 | 0.896 |
| Sleep efficiency, % | 86.6 ± 5.6 | 86.8 ± 5.5 | 86.3 ± 5.6 | 0.132 |
| Arousal index, % | 17.6 ± 9.8 | 17.3 ± 10.1 | 17.9 ± 9.5 | 0.082 |

Results are presented as mean ± standard deviation or *N* (%). The *p*-values represent the difference between angina pectoris (AP) and control. AHI, apnea–hypopnea index; BMI, body mass index; REM, rapid eye movement.

**Table 2**
Subject characteristics by percentage of rapid eye movement sleep time (REM%) categories.

| Characteristics | REM% (<20%) $N = 1141$ | REM% (20–25%) $N = 990$ | REM% (>25%) $N = 579$ | $p$ |
|---|---|---|---|---|
| Age, years | 63.9 ± 11.0 | 60.7 ± 10.7 | 59.3 ± 10.2 | <0.001 |
| Gender, *N* (%) | | | | 0.126 |
| Men | 490 (42.9) | 385 (38.9) | 228 (39.4) | |
| Women | 651 (57.1) | 605 (61.1) | 351 (60.6) | |
| BMI, kg/m$^2$ | 28.4 ± 5.2 | 28.0 ± 4.9 | 27.6 ± 4.8 | 0.009 |
| Race, *N* (%) | | | | 0.194 |
| White | 1010 (88.5) | 854 (86.3) | 498 (86.0) | |
| Other | 131 (11.5) | 136 (13.7) | 81 (14.0) | |
| Smoking status, *N* (%) | | | | 0.002 |
| Current smoker | 83 (7.3) | 96 (9.7) | 72 (12.4) | |
| Former smoker | 506 (44.4) | 386 (39.0) | 238 (41.1) | |
| Never smoker | 550 (48.2) | 506 (51.1) | 269 (46.5) | |
| Education, *N* (%) | | | | 0.298 |
| ≤15 years | 648 (56.8) | 545 (55.1) | 306 (52.9) | |
| >15 years | 395 (34.6) | 319 (32.2) | 213 (36.8) | |
| Marital status, *N* (%) | | | | 0.158 |
| Married | 884 (77.5) | 782 (79.0) | 461 (79.6) | |
| Other | 232 (20.3) | 178 (18.0) | 95 (16.4) | |
| AHI, *N* (%) | | | | <0.001 |
| <5.0 | 527 (46.2) | 548 (55.4) | 370 (63.9) | |
| ≥5 | 614 (53.8) | 442 (44.7) | 209 (36.1) | |
| Diabetes mellitus, *N* (%) | 78 (6.8) | 54 (5.5) | 16 (2.8) | 0.002 |
| Hypertension, *N* (%) | 445 (39.0) | 300 (30.3) | 163 (28.2) | <0.001 |

Results are presented as mean ± standard deviation or *N* (%). *P*-values indicate the difference between the three groups. AHI, apnea–hypopnea index; BMI, body mass index; REM, rapid eye movement.

22.7 ± 16.8, $p < 0.001$). Moreover, REM sleep had higher oxygen desaturation and lower arousal index than NREM sleep. Average heart rate, $SaO_2$% and OSA was similar between the REM sleep and NREM sleep (Fig. 2).

### 3.2. Association between angina and REM%

The distribution of AP was significantly higher in those with REM% grade 3 than in those with REM% grade 1 and grade 2 (50.3%

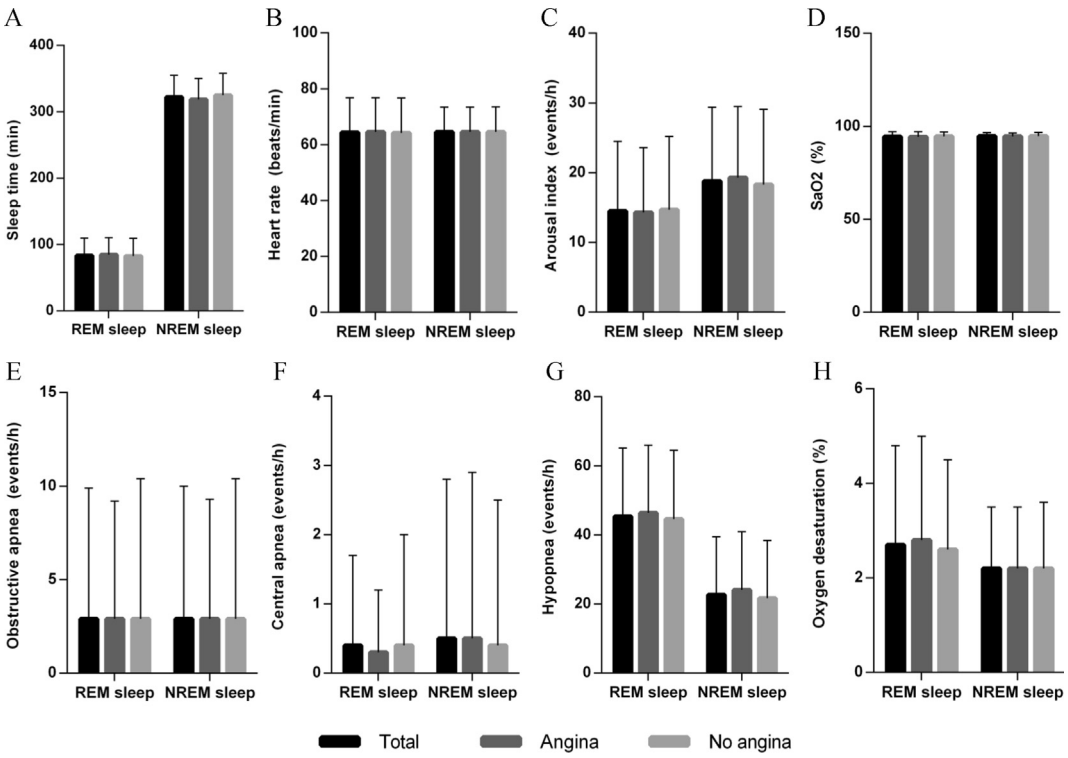


**Fig. 2.** Polysomnography data in rapid eye movement (REM) sleep and non-rapid eye movement (NREM) sleep. (A) Sleep time; (B) heart rate; (C) arousal index; (D) $SaO_2$; (E) obstructive apnea; (F) central apnea; (G) hypopnea; (H) oxygen desaturation.

vs 42.4% vs 42.1%, $p = 0.003$) (Fig. 3(a)). In a univariate model, REM% >25% was associated with an increase in AP risk (OR = 1.388; 95% CI = 1.130–1.706; $p = 0.002$). After adjusting for age, gender, race, AHI, marital status, education, BMI, sleep duration and arousal index, REM% >25% was closely related to the incidence of AP (adjusted OR = 1.500; 95% CI = 1.188–1.894; $p = 0.001$). In the final multivariate logistic regression model, REM% >25% was associated with the incidence of AP (adjusted OR = 1.510; 95% CI = 1.194–1.910; $p = 0.001$) (Table 3).

### 3.3. Subgroup analyses

Subgroup analysis was performed to further confirm the role of REM% in the incidence of AP. A statistically significant interaction stratified by sleep duration in the incident of AP was observed ($p_{interaction} = 0.021$). We found that the association between REM% and AP was stronger in participants with sleep duration of 7–8 h (adjusted OR = 2.045; 95% CI = 1.338–3.127; $p = 0.001$) than 6–7 h of sleep (adjusted OR = 1.354; 95% CI = 1.017–1.804; $p = 0.038$) (Table 4).

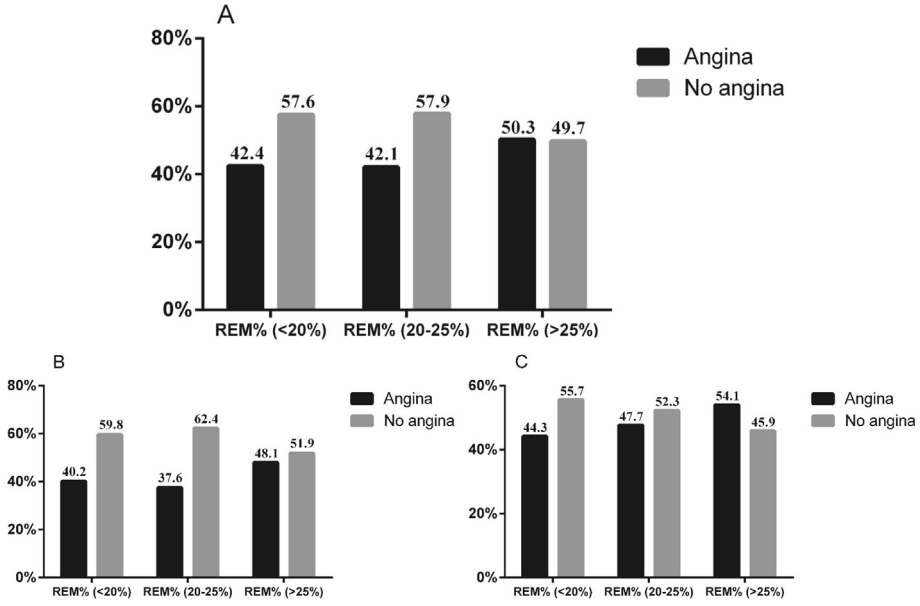


**Fig. 3.** Distribution of angina pectoris (AP) in percentage of REM sleep time (REM%) groups. (A) All participants; (B) apnea–hypopnea index (AHI) < 5; (C) AHI >5.

**Table 3**
Univariate and multivariate logistic regression analysis for angina pectoris.

| | Univariate models | *p* | Age and gender adjusted[a] | *p* | Multivariable adjusted[b] | *p* | Multivariable adjusted[c] | *p* |
|---|---|---|---|---|---|---|---|---|
| | OR (95% CI) | | OR (95% CI) | | OR (95% CI) | | OR (95% CI) | |
| All subjects | | | | | | | | |
| REM% | | | | | | | | |
| >25% | 1.388 (1.130–1.706) | 0.002 | 1.470 (1.192–1.813) | <0.001 | 1.500 (1.188–1.894) | 0.001 | 1.510 (1.194–1.910) | 0.001 |
| <20% | 1.012 (0.852–1.203) | 0.890 | 0.935 (0.784–1.115) | 0.455 | 0.903 (0.744–1.097) | 0.305 | 0.904 (0.744–1.100) | 0.314 |
| 20–25% | 1 | | 1 | | 1 | | 1 | |
| Age≥60 years | | | | | | | | |
| REM% | | | | | | | | |
| >25% | 1.463 (1.081–1.980) | 0.014 | 1.463 (1.080–1.982) | 0.014 | 1.421 (1.023–1.974) | 0.036 | 1.438 (1.032–2.004) | 0.032 |
| <20% | 0.815 (0.650–1.023) | 0.077 | 0.800 (0.637–1.005) | 0.055 | 0.778 (0.607–0.998) | 0.048 | 0.808 (0.629–1.039) | 0.097 |
| 20–25% | 1 | | 1 | | 1 | | 1 | |
| Age <60 years | | | | | | | | |
| REM% | | | | | | | | |
| >25% | 1.521 (1.132–2.045) | 0.005 | 1.521 (1.132–2.045) | 0.005 | 1.591 (1.134–2.233) | 0.007 | 1.620 (1.149–2.285) | 0.006 |
| <20% | 1.182 (0.896–1.559) | 0.238 | 1.184 (0.897–1.562) | 0.233 | 1.079 (0.786–1.483) | 0.638 | 1.050 (0.762–1.447) | 0.765 |
| 20–25% | 1 | | 1 | | 1 | | 1 | |
| Men | | | | | | | | |
| REM% | | | | | | | | |
| >25% | 1.301 (0.937–1.806) | 0.116 | 1.402 (1.000–1.966) | 0.050 | 1.385 (0.953–2.013) | 0.087 | 1.399 (0.959–2.040) | 0.081 |
| <20% | 0.988 (0.756–1.292) | 0.930 | 0.886 (0.672–1.169) | 0.393 | 0.895 (0.661–1.211) | 0.473 | 0.878 (0.647–1.191) | 0.402 |
| 20–25% | 1 | | 1 | | 1 | | 1 | |
| Women | | | | | | | | |
| REM% | | | | | | | | |
| >25% | 1.448 (1.111–1.887) | 0.006 | 1.513 (1.157–1.978) | 0.002 | 1.531 (1.134–2.069) | 0.005 | 1.536 (1.133–2.082) | 0.006 |
| <20% | 1.016 (0.811–1.273) | 0.889 | 0.966 (0.769–1.213) | 0.764 | 0.909 (0.704–1.173) | 0.463 | 0.915 (0.707–1.184) | 0.500 |
| 20–25% | 1 | | 1 | | 1 | | 1 | |

CI, confidence interval; OR, odds ratio; REM, rapid eye movement.
[a] Adjusted for gender only in the subgroup of age categories, and adjusted for age only in the subgroup of men and women.
[b] Adjusted for age, gender, race, apnea–hypopnea index (AHI), marital status, education, body mass index (BMI), sleep duration, arousal index.
[c] Adjusted for a+ diabetes, hypertension, smoke.

Considering the important impacts of age, gender, AHI on the association of REM sleep with AP, a subgroup analysis was performed to further confirm the role of daytime napping in the incidence of AP stratified by age (≥60 years old vs < 60 years old), gender (men vs women) and AHI (<5 kg/m$^2$ vs ≥ 5 kg/m$^2$). After multivariable adjusted logistic regression analysis, the association between REM% >25% and AP was stronger in age <60 years old (OR = 1.620; 95% CI = 1.149–2.285; $p$ = 0.006) and women (OR = 1.536; 95% CI = 1.133–2.082; $p$ = 0.006) (Table 3). In addition, the incidence of AP was significantly higher in participants with REM% >25% in subgroups with AHI <5 and AHI ≥5 (Fig. 3(b,c)). REM % >25% remained a risk factor for AP in individuals with AHI <5 (OR = 1.556; 95% CI = 1.146–2.114; $p$ = 0.005) and AHI ≥5 (OR = 1.473; 95% CI = 1.012–2.144; $p$ = 0.043) (Table 5). There was no significant interaction by age (≥60 years vs < 60 years), gender (women vs men) and AHI (AHI < 5 events/h vs AHI ≥ 5 events/h) in subgroup analysis ($p_{interaction}$ >0.05).

Furthermore, subgroup analyses stratified by diabetes (yes vs no), hypertension (yes vs no), smoking status (current and former vs no), race (white vs others), marital status (married vs others), education (>15 years vs ≤ 15 years), and BMI (18–25 kg/m$^2$ vs ≥ 25 kg/m$^2$) was also conducted in the investigation on the connection between daytime napping and cardiovascular events. Significant interactions were not found in these analyses (data not shown). We also investigated the association of AP with cardiovascular events stratified by AHI. There is a higher proportion of cardiovascular events in the subgroup with AHI >5 than those with AHI <5 (Fig. 4).

**Table 4**
Subgroup analysis of angina pectoris according to sleep duration.

| | | REM% (>25%) | REM% (<20%) | REM% (20–25%) |
|---|---|---|---|---|
| Sleep duration 6–7 h | | | | |
| No. of subjects, n | 1869 | 375 | 825 | 669 |
| Events, *N* (%) | 882 (47.2) | 199 (53.1) | 364 (44.1) | 319 (47.7) |
| Univariate models | | 1.241 (0.963–1.598) | 0.866 (0.706–1.063) | 1 (Ref) |
| Age and gender adjusted | | 1.304 (1.008–1.685) | 0.833 (0.677–1.025) | 1 (Ref) |
| Multivariable adjusted[a] | | 1.362 (1.024–1.810) | 0.816 (0.649–1.025) | 1 (Ref) |
| Multivariable adjusted[b] | | 1.354 (1.017–1.804) | 0.813 (0.646–1.023) | 1 (Ref) |
| Sleep duration 7–8h | | | | |
| No. of subjects, *N* | 841 | 204 | 316 | 321 |
| Events, *N* (%) | 310 (36.9) | 92 (45.1) | 120 (38.0) | 98 (30.5) |
| Univariate models | | 1.869 (1.299–2.690) | 1.393 (1.003–1.935) | 1 (Ref) |
| Age and gender adjusted | | 1.965 (1.353–2.854) | 1.183 (0.842–1.661) | 1 (Ref) |
| Multivariable adjusted[a] | | 1.953 (1.284–2.970) | 1.119 (0.767–1.632) | 1 (Ref) |
| Multivariable adjusted[b] | | 2.045 (1.338–3.127) | 1.122 (0.766–1.644) | 1(Ref) |

CI, confidence interval; OR, odds ratio; REM, rapid eye movement.
[a] Adjusted for age, gender, race, apnea–hypopnea index (AHI), marital status, education, body mass index (BMI), sleep time, arousal index.
[b] Adjusted for a+ diabetes, hypertension, smoking status.

**Table 5**
Subgroup analysis of angina pectoris according to apnea–hypopnea index.

| | | REM% (>25%) | REM% (<20%) | REM% (20–25%) |
|---|---|---|---|---|
| AHI <5, event/h | | | | |
| No. of subjects, *N* | 1445 | 370 | 527 | 548 |
| Events, *N* (%) | 596 (41.2) | 178 (48.1) | 212 (40.2) | 206 (37.6) |
| Univariate models | | 1.539 (1.178–2.011) | 1.117 (0.874–1.428) | 1 (Ref) |
| Age and gender adjusted | | 1.603 (1.221–2.103) | 1.038 (0.809–1.333) | 1 (Ref) |
| Multivariable adjusted[a] | | 1.584 (1.170–2.145) | 1.004 (0.760–1.326) | 1 (Ref) |
| Multivariable adjusted[b] | | 1.556 (1.146–2.114) | 1.003 (0.757–1.329) | 1 (Ref) |
| AHI ≥5, event/h | | | | |
| No. of subjects, *N* | 1265 | 209 | 614 | 442 |
| Events, *N* (%) | 596 (47.1) | 113 (54.1) | 272 (44.3) | 211 (47.7) |
| Univariate models | | 1.289 (0.927–1.792) | 0.871 (0.681–1.113) | 1 (Ref) |
| Age and gender adjusted | | 1.340 (0.959–1.873) | 0.826 (0.644–1.060) | 1 (Ref) |
| Multivariable adjusted[a] | | 1.446 (0.997–2.096) | 0.828 (0.630–1.089) | 1 (Ref) |
| Multivariable adjusted[b] | | 1.473 (1.012–2.144) | 0.830 (0.631–1.093) | 1 (Ref) |

CI, confidence interval; OR, odds ratio; REM, rapid eye movement.
[a] Adjusted for age, gender, race, apnea–hypopnea index (AHI), marital status, education, body mass index (BMI), sleep time, arousal index.
[b] Adjusted for a+ diabetes, hypertension, smoking status.

## 4. Discussion

Sleep consists of several different stages of NREM (stage 1, stage 2, and stage 3/4) and REM sleep [16]. Humans usually experience four or five regular sleep cycles of NREM and REM sleep throughout the night [17]. REM sleep, also known as paradoxical sleep, is physiologically different from NREM. REM sleep is marked by wake-like brain activity of low-voltage fast waves occurring in combination with low muscle tone throughout the body, and vivid dreaming [18]. The overwhelming majority of studies have focused on the role of REM sleep in memory and depression [19,20]. In the present study, our findings showed that the percentage of time spent in REM sleep may play an important role in the incidence of AP after adjusting for age, gender, race, AHI, marital status, education, BMI, sleep duration, arousal index, diabetes, hypertension, and smoke status.

AP is a vital component of CAD and is usually caused by myocardial ischemia. Patients with AP may have poor sleep quality, while sleep efficiency can also cause the occurrence of AP. However, little is known about the relationship between REM sleep and AP.

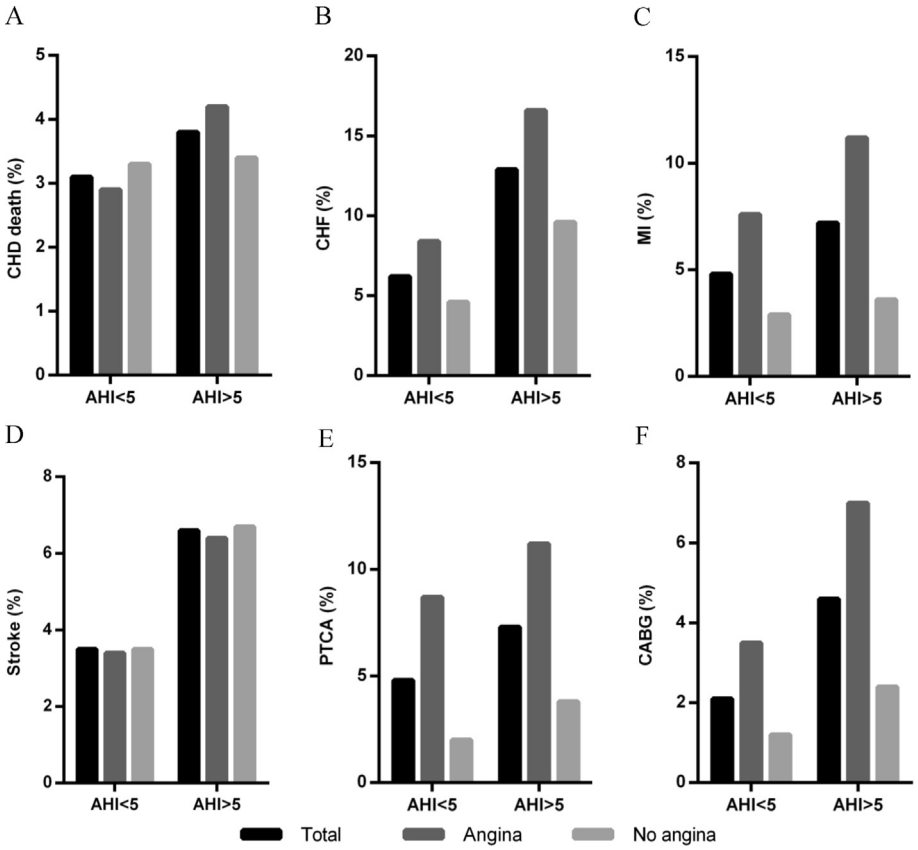


**Fig. 4.** Cardiovascular events in angina pectoris (AP) and control stratified by apnea–hypopnea index (AHI). (A) coronary heart disease (CHD) death; (B) congestive heart failure (CHF); (C) myocardial infarction (MI); (D) stroke; (E) percutaneous transluminal coronary angioplasty (PTCA); (F) coronary artery bypass grafting (CABG).

The proportion of REM sleep is normally 20–25% in adult humans and greater in infants. A previous study showed that brainstem cholinergic neurons and brainstem monoaminergic neurons were associated with the regulation of REM sleep [9]. The flip–flop switch model for REM sleep further explain many of the key properties of REM sleep and many disorders of REM sleep [21]. With increasing sleep duration, REM sleep time and REM% shift towards a higher proportion. We therefore conducted this study based on the individuals who had 6–8 h of sleep. In this study, the incidence of AP increased markedly in participants with REM% >25%. Therefore, a higher percentage of REM% is more likely to cause the occurrence of AP. Our finding showed that the frequency of hypopnea events and oxygen desaturation was higher in REM sleep than NREM sleep. Meanwhile, average heart rate, $SaO_2$% and obstructive apnea was similar in REM sleep and NREM sleep. In contrast with NREM sleep, heart rate, stroke volume, cardiac output, vascular conductance, blood pressure, baroreflex, and chemoreflex varies greatly during REM sleep [22]. Numerous studies have shown that blood pressure and heart rate variability were closely related to cardiovascular events [23]. The higher prevalence of AP in REM% >25% participance may cause by hypopnea, oxygen desaturation, the fluctuation of blood pressure and heart rate.

The occurrence of AP was usually different in gender and age groups. Therefore, we conducted subgroup analyses to further explore the role of REM in the incidence of AP. Our Results showed that the association between REM% >25% and AP were stronger in women and participants less than 60 years old. Many previous reports have focused on the connection between sleep apnea syndrome and cardiovascular disease [24,25]. However, Shah et al., showed that sleep apnea may play a cardioprotective role during acute myocardial infarction via ischemic preconditioning [26]. A large amount of evidence has demonstrated that sleep-disordered breathing was a risk factor for cardiovascular events such as myocardial infarction, stroke and heart failure [27–29]. Besides, a previous study also showed that sleep-disordered breathing may precipitate angina in REM sleep [30]. We further analyzed the relationship between REM% and AP in participants with AHI <5 and AHI ≥5. The results showed that REM% >25% had a significantly higher incidence of AP in both subgroups of AHI level. These findings indicated that higher percentage of REM may independently contribute to the incidence of AP.

### 4.1. Limitations

The current study has several potential limitations. First, the majority of the participants (87.2%) were of Caucasian descent; therefore, the results may not be generalizable to all ethnic groups. Second, the follow-up time after the first-episode of AP was missing for most patients, and thus we could not analyze this finding using a Cox proportional hazards regression model. Finally, multiple PSG over a longer period may provide more accurate information, which will be investigated in our future clinical trials.

## 5. Conclusions

Patients with REM% >25% had a higher incidence of AP. The occurrence of AP may be caused by a higher proportion of REM%. Additionally, REM% >25% remained a risk factor for AP irrespective of AHI level.

## Author contributions

B.Y. and X.M. raised the idea for the study. All authors contributed to the study design, writing and review of the report. B.Y. and X.M. performed the primary data analysis and B.Y. participated in further data analysis. X.M. handled supervision in our study. All authors approved the final version of the report.

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## Conflict of interest

We declare no conflict of interest that could be perceived as prejudicing the impartiality of the research reported herein.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2018.10.040.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sleep.2018.10.040.

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