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ORIGINAL RESEARCH

Association of Periodic Limb Movements and Obstructive Sleep Apnea With Risk of Cardiovascular Disease and Mortality

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BACKGROUND: Obstructive sleep apnea is a well-established risk factor for cardiovascular disease (CVD). Recent studies have also linked periodic limb movements during sleep to CVD. We aimed to determine whether periodic limb movements during sleep and obstructive sleep apnea are independent or synergistic factors for CVD events or death.

METHODS AND RESULTS: We examined data from 1049 US veterans with an apnea-hypopnea index (AHI) <30 events/hour. The primary outcome was incident CVD or death. Cox proportional hazards regression assessed the relationships between the AHI, periodic limb movement index (PLMI), and the AHI×PLMI interaction with the primary outcome. We then examined whether AHI and PLMI were associated with primary outcome after adjustment for age, sex, race and ethnicity, obesity, baseline risk of mortality, and Charlson Comorbidity Index. During a median follow-up of 5.1 years, 237 of 1049 participants developed incident CVD or died. Unadjusted analyses showed an increased risk of the primary outcome with every 10-event/hour increase in PLMI (hazard ratio [HR], 1.08 [95% CI, 1.05–1.13]) and AHI (HR, 1.17 [95% CI, 1.01– 1.37]). Assessment associations of AHI and PLMI and their interaction with the primary outcome revealed no significant interaction between PLMI and AHI. In fully adjusted analyses, PLMI, but not AHI, was associated with an increased risk of primary outcome: HR of 1.05 (95% CI, 1.00–1.09) per every 10 events/hour. Results were similar after adjusting with Framingham risk score.

CONCLUSIONS: Our study revealed periodic limb movements during sleep as a risk factor for incident CVD or death among those who had AHI <30 events/hour, without synergistic association between periodic limb movements during sleep and obstructive sleep apnea.

Key Words: cardiovascular disease ■ epidemiology ■ obstructive sleep apnea ■ periodic limb movements during sleep

Disordered sleep and, in particular, obstructive sleep apnea (OSA) is a risk factor for poor cardiovascular health.[1] Population and clinic-based studies demonstrate that OSA is associated with adverse cardiovascular outcomes, including incident myocardial infarction, heart failure, arrhythmia, stroke, and death.[2–5] More recently, another sleep-related entity, periodic limb movements during sleep (PLMS), has also been linked with incident cardiovascular disease (CVD).[6,7] PLMS occur throughout sleep and can number into the hundreds every night. Associated with each limb movement of PLMS are discrete elevations in blood pressure and heart rate on the order of 20 mm Hg and 10 beats per minute, respectively, which provide a plausible biological link between PLMS and incident CVD.[8,9]

OSA and PLMS are both highly prevalent, with OSA occurring in up to one-third of US adults and

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RESEARCH PERSPECTIVE

What Is New?

- This research highlights that periodic limb movements during sleep are an independent risk factor for cardiovascular disease or death, especially in individuals with no or mild-moderate obstructive sleep apnea.

What Question Should Be Addressed Next?

- To understand the potential interaction between periodic limb movements during sleep and obstructive sleep apnea as risk factors for cardiovascular disease, longitudinal studies should be conducted that (1) assess periodic limb movements during sleep regardless of proximity to respiratory events and (2) include participants with severe obstructive sleep apnea.
- Ultimately, interventional studies targeting periodic limb movements during sleep to understand the mechanisms of cardiovascular disease, such as endothelial dysfunction, oxidative stress, and inflammation, are needed.

Nonstandard Abbreviations and Acronyms

AHI	apnea-hypopnea index
CCI	Charlson Comorbidity Index
CPAP	continuous positive airway pressure
FRS	Framingham risk score
PLMI	periodic limb movement index
PLMS	periodic limb movements during sleep

PLMS present in 8% of US middle-aged adults and 45% of US community-dwelling elderly individuals.[10–12] Furthermore, PLMS and OSA often coexist, with PLMS present in ≈48% of adults with OSA.[13] In an analysis of polysomnographic data from a large laboratory-based cohort referred for OSA evaluation, we identified several distinct polysomnographic clusters (phenotypes), including 1 characterized by a high frequency of PLMS and mild to moderate OSA.[14] This "PLMS" cluster had a 2-fold increased risk of incident CVD or death compared with a reference group, which was higher than that of other OSA clusters, characterized as "nonrapid eye movement and poor sleep" or "rapid eye movement and hypoxia."[14] Notably, risk of CVD or death was reduced among those in the PLMS cluster who regularly used continuous positive airway pressure (CPAP) therapy.[14,15]

One explanation of the above findings is that OSA and PLMS act synergistically to increase CVD or death. This is physiologically plausible, given the role that both hypoxia and autonomic dysfunction play in these sleep-related abnormalities. In OSA, cyclical arterial oxygen desaturation results from recurrent airflow cessation, whereas in PLMS, cyclical episodes of oxygen desaturation occur in the brain because of repetitive changes in cerebral hemodynamics associated with PLMS.[16] OSA and PLMS are also associated with recurrent arousal and sympathetic nervous system hyperactivation.[17] Indeed, basal autonomic regulation is shifted toward sympathetic predominance in patients with OSA with PLMS, in comparison with those with OSA alone.[15] Thus, PLMS and OSA may work synergistically to increase blood pressure and the propensity for CVD.

Therefore, in the current study, we sought to determine whether PLMS and OSA are independent or synergistic risk factors for incident CVD or death in a sleep laboratory–based cohort followed up for cardiovascular events and death. Because PLMS prevalence increases with age and occurs in up to 57% of older adults,[12,18] we also explored whether the impact of PLMS and OSA on CVD risk differs by age.

METHODS

The data that support the findings of this study are available from the senior author upon reasonable request (henry.yaggi@yale.edu).

Study Design, Participants, and Analytic Sample.

We analyzed data from the DREAM (Determining Risk of Vascular Events by Apnea Monitoring) study, a sleep laboratory–based observational cohort of veterans referred for OSA evaluation at 3 Veterans Affairs Medical Centers (West Haven, CT; Cleveland, OH; and Indianapolis, IN).[19] The DREAM study was approved by the research ethics committee at each participating center, and informed consent was waived.

Details of the DREAM study, its data acquisition, and variable definitions are described elsewhere.[14,19] Briefly, this study was designed to assess which polysomnographic metrics predict incident cardiovascular and metabolic outcomes. A total of 2041 veterans were enrolled from 2000 to 2004 and followed up through 2012 for incident CVD or death.[14] Participants gave informed consent. Time of enrollment at baseline was defined as the time of the clinical polysomnogram when a detailed characterization of polysomnography metrics and established risk factors for CVD and metabolic outcomes was assessed.

Our analytic sample included 1049 participants, with selection criteria shown in Figure 1. We elected to exclude patients with an apnea-hypopnea index (AHI) ≥30/h for 2 reasons. First, because American Academy of Sleep Medicine criteria preclude PLMS

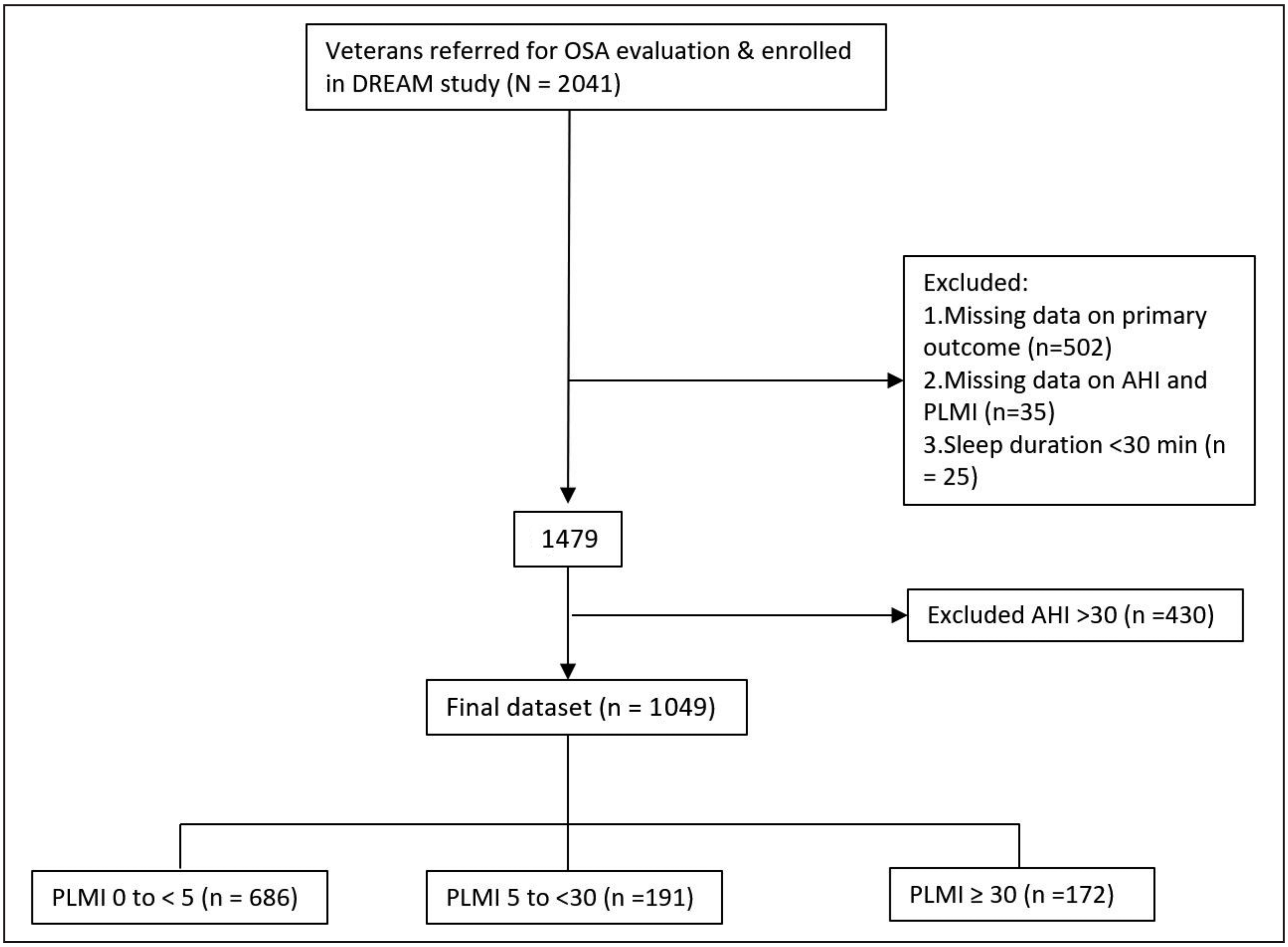

Figure 1. Selection of analytic sample.
AHI indicates apnea-hypopnea index; DREAM, Determining Risk of Vascular Events by Apnea Monitoring; OSA, obstructive sleep apnea; and PLMI, periodic limb movement index.

scoring following respiratory events; persistent cycling respiratory events in severe OSA are expected to mask PLMS burden, the key exposure in our analysis.[20] Second, we aimed to identify those at risk of adverse events not related to OSA severity alone. Severe OSA (AHI ≥30/h) has been repeatedly shown as an independent risk factor for CVD/death[21,22]; also, our preliminary data suggest that CVD risk is highest for those in the "PLMS" cluster,[14] whose members exhibited AHIs of <30/h.

Clinical Data

Demographic, anthropometric, and clinical variables, including body mass index (BMI), medical history, and medication use, were abstracted from electronic health records by trained research staff. Baseline risk of death from any cause was assessed by the Charlson Comorbidity Index (CCI),[23] with cardiovascular risk ascertained using the Framingham risk score[24] (FRS).

Polysomnography

Trained polysomnologists scored sleep stages and events at a single scoring hub (West Haven, CT) according to American Academy of Sleep Medicine criteria.[14,19] Hypopnea was defined as a 30% decrement in the nasal pressure transducer signal lasting ≥10 seconds and associated with 4% arterial oxygen desaturation.[19] PLMS were scored according to American Academy of Sleep Medicine guidelines: 8-μV increase in anterior tibialis electromyographic amplitude from baseline for 0.5 to 10.0 s, occurring in a series of ≥4 movements, no less and no more than 5 and 90 seconds apart, respectively.[25]

Exposures

AHI was defined as the sum of all apneas and hypopneas divided by total hours of sleep. The periodic limb movement index (PLMI) was computed as the total number of PLMS divided by the hours of sleep.

Outcome

Our primary outcome variable was the composite of incident CVD or death from any cause. CVD was defined as acute coronary syndrome, stroke, or transient ischemic attack, identified according to established guidelines.[26,27] The primary outcome was adjudicated using Veterans Affairs Medical Centers' centralized electronic medical record and Veterans Affairs vital status file database information, as described previously[19] (see Data S1).

Statistical Analysis

We summarized baseline characteristics and polysomnographic metrics using mean (±SD) or median (interquartile range) for continuous variables and using frequencies with proportions for categorical variables. The summary is categorized by the PLMI severity, with differences between categories for descriptive purposes assessed using χ^2, ANOVA, or Kruskal-Wallis tests, as appropriate.

We assessed the additive association between the primary outcome and both AHI and PLMI ("additive continuous model"; mutually adjusted analysis) using Cox proportional hazards time to event model. A subsequent model assessed the synergistic interaction between AHI and PLMI (AHI×PLMI term, "interaction continuous model"). Results of these primary analyses are presented as hazard ratios (HRs) with 95% CIs. Kaplan-Meier plots and log-rank tests are also used to present the results. To aid with interpretation of the potential interaction between PLMI and AHI, we assessed the association between primary outcome and PLMI for 3 categories of AHI frequency (<5/h [reference], 5 to <15/h, and 15 to <30/h) (interaction AHI categorized model). We then performed models sequentially adjusting for potential confounders: main model 1: adjusted for age, sex, race and ethnicity, and BMI; and main model 2: main model 1 plus CCI to adjust for risk of death because of comorbidities (eg, baseline CVD, diabetes, malignancy, or chronic lung disease) because death was the most frequent component of the primary outcome. Because CCI did not include hypertension, to assess whether hypertension diagnosis or antihypertensive medication prescription biased our results, we added hypertension and antihypertensive medications to main model 2 (main model 3). Finally, to assess whether baseline CVD risk rather than overall mortality was a confounding factor, we adjusted main model 2 with FRS, which includes age, sex, smoking status, cholesterol, blood pressure, and antihypertensive medications, in place of the CCI (main model 4).

Sensitivity Analyses

To evaluate whether hypoxia rather than AHI is associated with CVD or death, we replaced AHI in main model 1 with the percentage of sleep with an oxygen saturation of <90% (analysis 1; Table S1). Finally, because treatment and outcomes could differ between study sites, we adjusted the final model (main model 2) by the study site (analysis 2).

Exploratory Analyses

Because the prevalence of OSA[28,29] and PLMS increases with age, and age is associated with the primary outcome,[30] we assessed whether age is an important modifier in the exposure's association with the primary outcome. We analyzed the main model 2 in individuals older or younger than the median age at baseline (57.5 years) and as an interaction.

All tests were 2 sided with a significance level of α=0.05. Statistical analyses were conducted using SAS, version 9.4 (SAS Institute Inc, Cary, NC).

RESULTS

Overview of the Cohort

Demographic characteristics, cardiovascular risk factors, and polysomnographic metrics of the overall cohort and of the PLMI categories are presented in Table 1. Most participants were men (93.4%), with a mean±SD age of 57.3±11.7 years, a mean±SD BMI of 33.7±7.0 kg/m^2, and a median (interquartile range) AHI of 5.5 (1.6–13.4) events/hour. Participants in the highest PLMI category were significantly older, and they exhibited more hypertension, coronary artery disease, and anticholinergic and β-blocker medication use. No differences were observed between PLMS categories in smoking status, alcohol intake, prevalent myocardial infarction, or cerebrovascular disease.

Participants were followed up for a median of 5.1 years (interquartile range, 4.0–6.0 years; range, 21 days to 8.4 years). During this time, 66 (6.3%) participants experienced acute coronary syndrome,15 (1.4%) experienced stroke, 16 (1.5%) experienced transient ischemic attack, and 140 (13.4%) died.

Evaluation of Potential Synergy Between OSA and PLMS for Risk of CVD or Death

In our primary analysis, both PLMI and AHI were significantly associated with the primary outcome, with HRs of 1.08 (95% CI, 1.05–1.13) and 1.17 (95% CI, 1.01–1.37) per 10 events/hour, respectively (Table 2, additive continuous model). The AHI×PLMI interaction term was not associated with the primary outcome (P=0.80), suggesting a lack of synergy between AHI and PLMI for CVD or death. Similarly, categorized analyses demonstrated increased risk for PLMI regardless of the AHI category (Table 2, interaction AHI

Table 1. Participant Characteristics

Characteristics	All patients (N=1049)	PLMI 0 to <5 (n=686)	PLMI 5 to <30 (n=191)	PLMI ≥30 (n=172)	*P* value
Age, mean±SD, y	57.3±11.7	55.6±11.7	59.4±11.0	62.0±10.9	<0.001
Sex, male, n (%)	980 (93.4)	636 (92.7)	179 (93.7)	165 (95.9)	0.309
Race, White, n (%)	840 (80.1)	523 (76.2)	166 (86.9)	151 (87.8)	<0.001
Employed, n (%)	378 (36.0)	265 (38.6)	61 (31.9)	52 (30.2)	0.002
BMI, mean±SD, kg/m^2	33.7±7.0	33.9±7.1	32.8±6.7	33.8±7.0	0.162
ESS, mean±SD	10.8±5.8	11.2±6.0	10.8±5.7	9.4±5.2	0.052
Tobacco, current use, n (%)	360 (35.5)	229 (34.6)	69 (36.9)	62 (37.1)	0.754
Alcohol, current use, n (%)	480 (48.3)	304 (46.5)	98 (54.7)	78 (48.8)	0.145
Hypertension, n (%)	733 (69.9)	462 (67.4)	139 (72.8)	132 (76.7)	0.038
Diabetes, n (%)	327 (31.2)	201 (29.3)	59 (30.9)	67 (39.0)	0.050
Coronary artery disease, n (%)	160 (18.9)	86 (15.4)	35 (24.3)	39 (27.5)	0.001
Congestive HF, n (%)	109 (10.4)	64 (9.3)	22 (11.5)	23 (13.4)	0.255
Prior CVD, n (%)	91 (8.7)	51 (7.4)	18 (9.4)	22 (12.8)	0.076
Atrial fibrillation, n (%)	71 (6.8)	40 (5.8)	17 (8.9)	14 (8.1)	0.244
MI within past 5 y, n (%)	99 (9.4)	57 (8.3)	22 (11.5)	20 (11.6)	0.228
Renal failure, n (%)	46 (4.4)	32 (4.7)	8 (4.2)	6 (3.5)	0.788
Cancer, n (%)	89 (8.5)	53 (7.7)	19 (9.9)	17 (9.9)	0.480
Depression, n (%)	419 (39.9)	270 (39.4)	78 (40.8)	71 (41.3)	0.865
PTSD, n (%)	119 (11.3)	80 (11.7)	22 (11.5)	17 (9.9)	0.803
Dementia, n (%)	17 (1.6)	8 (1.2)	3 (1.6)	6 (3.5)	0.098
CCI, median (IQR)	1.0 (0.0–3.0)	1.0 (0.0–2.0)	1.0 (0.0–3.0)	2.0 (1.0–3.0)	<0.001
Framingham risk score, median (IQR)	23.0 (13.5–35.7)	20.7 (12.4–32.9)	25.6 (15.4–36.8)	28.9 (19.8–45.3)	<0.001
Medications, n (%)					
β-Blockers	333 (31.7)	196 (28.6)	79 (41.4)	58 (33.7)	0.003
Any antihypertensive medications	697 (67.1)	445 (65.6)	129 (68.3)	123 (71.9)	0.275
Aspirin	207 (19.7)	136 (19.8)	38 (19.9)	33 (19.2)	0.981
Coumadin	90 (8.6)	56 (8.2)	15 (7.9)	19 (11.0)	0.446
Statin	572 (54.5)	359 (52.3)	114 (59.7)	99 (57.6)	0.134
SSRI	427 (40.7)	283 (41.3)	76 (39.8)	68 (39.5)	0.883
TCA	10 (1.0)	7 (1.0)	1 (0.5)	2 (1.2)	0.784
Benzodiazepine	167 (15.9)	105 (15.3)	29 (15.2)	33 (19.2)	0.440
Anticholinergic	191 (18.2)	109 (15.9)	41 (21.5)	41 (23.8)	0.024
PLMI, median (IQR), events/h	0.0 (0.0–5.1)	0.0 (0.0–0.0)	14.6 (9.2–20.5)	53.2 (40.9–73.8)	<0.001
AHI, median (IQR), events/h	5.5 (1.6–13.4)	5.2 (1.6–13.4)	5.1 (1.8–12.2)	7.6 (1.8–15.5)	0.262
OSA severity by AHI categories, n (%)					0.101
No OSA (AHI <5/h)	499 (47.6)	333 (48.5)	95 (49.7)	71 (41.3)	
Mild OSA (5≤AHI<15/h)	320 (30.5)	200 (29.2)	65 (34.0)	55 (32.0)	
Moderate OSA (15≤AHI<30/h)	230 (21.9)	153 (22.3)	31 (16.2)	46 (26.7)	
T60–T89, median (IQR), %	1.0 (0.0–9.0)	1.0 (0.0–9.0)	1.0 (0.0–8.0)	2.0 (0.0–8.0)	0.304
Sleep efficiency, median (IQR), %	77.3 (64.0–87.5)	79.2 (65.3–88.2)	75.5 (62.5–84.4)	73.1 (60.3–84.7)	<0.001
Regular CPAP use, n (%)	299 (28.5)	190 (27.7)	58 (30.4)	51 (29.7)	0.721

Differences between categories for descriptive purposes assessed using χ^2, ANOVA, or Kruskal-Wallis tests, as appropriate. AHI indicates apnea-hypopnea index; BMI, body mass index; CCI, Charlson Comorbidity Index; CPAP, continuous positive airway pressure; CVD, cardiovascular disease; ESS, Epworth Sleepiness Scale; HF, heart failure; IQR, interquartile range; MI, myocardial infarction; OSA, obstructive sleep apnea; PLMI, periodic limb movement index; PTSD, posttraumatic stress disorder; SSRI, selective serotonin reuptake inhibitor; T60, percentage of sleep with an oxygen saturation of <60%; T89, percentage of sleep with an oxygen saturation of <89%; and TCA, tricyclic antidepressant.

Table 2. Association Between PLMI, AHI, and Their Interaction With Primary Outcome (ACS, Stroke, TIA, or Death From Any Cause)

	Description	Hazard ratio	95% CI		*P* value
Additive continuous model	PLMI (per 10/h)	1.08	1.05	1.13	<0.001
	AHI (per 10/h)	1.17	1.01	1.37	0.042
Interaction continuous model*	AHI×PLMI (per 100/h^2)	1.01	0.96	1.05	0.804
Additive AHI categorized model	PLMI (per 10/h)	1.08	1.04	1.12	<0.001
	AHI <5/h (reference)				
	AHI 5 to <15/h	1.17	0.86	1.60	0.092
	AHI 15 to <30/h	1.33	0.96	1.84	0.326
Interaction AHI categorized model†	PLMI (per 10/h) at AHI <5/h	1.07	0.98	1.14	0.102
	PLMI (per 10/h) at AHI 5 to <15/h	1.09	1.04	1.17	0.002
	PLMI (per 10/h) at AHI 15 to <30/h	1.08	1.02	1.15	0.010

ACS indicates acute coronary syndrome; AHI, apnea-hypopnea index; PLMI, periodic limb movement index; and TIA, transient ischemic attack.
*Interaction PLMI continuous model: AHI, PLMI, and PLMI×AHI; AHI and PLMI, coefficients (and hazard ratios) not shown because of uninterpretability.
†Interaction PLMI categorized model: AHI category, PLMI, and PLMI×AHI category; AHI category and PLMI coefficients (and hazard ratios) not shown because of uninterpretability.

categorized model). Categorizing PLMI into categories of <5/h (reference), 5 to <30/h, and ≥30/h demonstrated that only the PLMI ≥30/h group, but not 5 to <30/h group, was associated with the increased risk of the primary outcome (HR, 1.87 [95% CI, 1.36–2.57]) (see Figure 2 and Table S1).

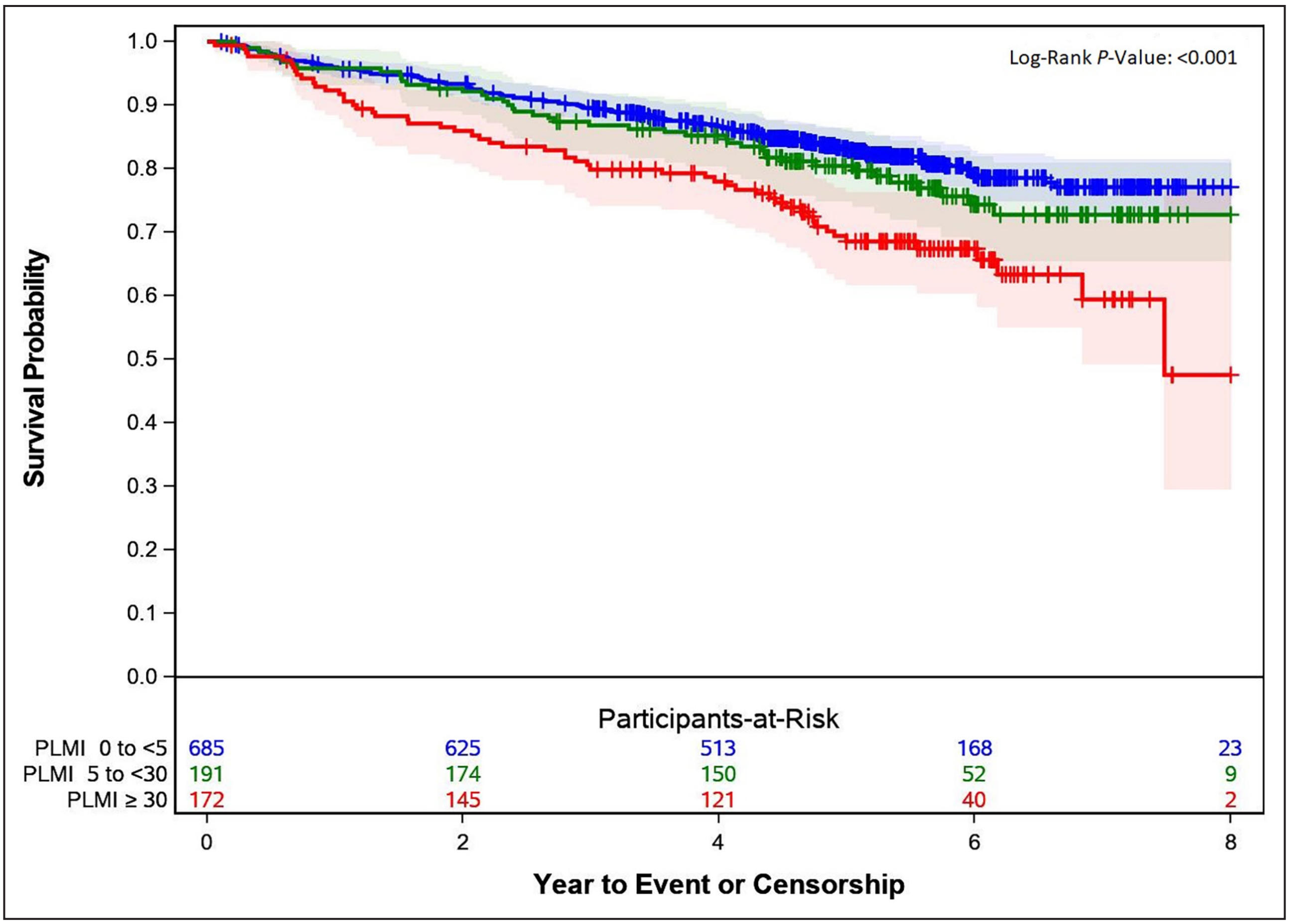

Figure 2. Kaplan-Meier curves for the association of the severity of PLMI and incidents of primary outcomes. Blue line, PLMI 0 to <5; green line, PLMI 5 to <30; and red line, PLMI ≥30. PLMI indicates periodic limb movement index.

Table 3. Cox Proportional Hazards Regression Models of the Primary Outcome (Death, ACS, Stroke, or TIA) in Participants Referred for OSA Evaluation

Model	Variable	Hazard ratio	95% CI		*P* value
Main model 1	PLMI (per 10/h)	1.06	1.01	1.11	0.010
	AHI (per 10/h)	1.10	0.93	1.30	0.278
Main model 2	PLMI (per 10/h)	1.05	1.00	1.09	0.046
	AHI (per 10/h)	1.15	0.97	1.38	0.100
Main model 3	PLMI (per 10/h)	1.04	1	1.09	0.050
	AHI (per 10/h)	1.15	0.97	1.37	0.101
Main model 4	PLMI (per 10/h)	1.06	1.02	1.11	0.009
	AHI (per 10/h)	1.22	1.03	1.44	0.024

Main model 1: PLMI, AHI, age, sex, race, and BMI; main model 2: main model 1+Charlson Comorbidity Index; main model 3: main model 2+hypertension and use of antihypertensive medication; main model 4: PLMI, AHI, race, BMI, and Framingham risk score. ACS indicates acute coronary syndrome; AHI, apnea-hypopnea index; BMI, body mass index; OSA, obstructive sleep apnea; PLMI, periodic limb movement index; and TIA, transient ischemic attack.

Association Between PLMS, OSA, and the Primary Outcome Adjusted for Confounders

After adjustment for age, sex, race and ethnicity, and BMI (main model 1, Table 3), PLMI retained its association with the outcome (HR, 1.06 [95% CI, 1.01–1.11]) but AHI did not (HR, 1.10 [95% CI, 0.93–1.30]). Adjustment for baseline risk of death using CCI (main model 2, Table 3) did not meaningfully change the results, with an HR of 1.05 (95% CI, 1.00–1.10) per 10-unit PLMI increase (*P*=0.046), nor did adjustment for hypertension status and antihypertensive medications (main model 3, Table 3). We also adjusted for baseline cardiovascular risk using the validated FRS in an assessment of whether baseline risk of CVD using FRS was a more meaningful confounder rather than the CCI (main model 4, Table 3). This revealed no change in the magnitude of the risk of PLMI (HR, 1.06 [95% CI, 1.02–1.11], per 10-unit PLMI increase; *P*=0.009]).

Sensitivity Analyses

Sensitivity analyses revealed a robust association between PLMI and the primary outcome (Table S1). Replacing the AHI with degree of hypoxemia (time below arterial oxygen saturation of 90%) (Table S2, analysis 1) did not alter the risk associated with PLMI (HR, 1.09 [95% CI, 1.05–1.13]), and there remained a lack of significant interaction effect (*P*=0.625). Adjustment of model 2 for the study site yielded persistent risk of increasing PLMI but not with AHI (Table S2, analysis 2). Finally, in a sensitivity analysis that includes participants with severe OSA (AHI ≥30/h; n=430), we observed a comparable outcome: no statistically significant interaction between OSA and PLMS (Table S3, interaction continuous model).

Exploratory Analysis

Stratifying the Main model 2 (Table 4) by median age of 57.5 years revealed that the increased risk associated with PLMI was only observed in older (HR, 1.06 [95% CI, 1.00–1.11]; *P*=0.036) but not in younger (HR, 1.01 [95% CI, 0.92–1.10]; *P*=0.915) individuals (Table 4). Unadjusted time-to-event analyses show that time to event was not different among PLMI categories in younger (<57.5 years) individuals (*P*=0.5), as shown in Figure 3, but differed markedly in individuals aged ≥57.5 years (*P*=0.005), specifically for the group with PLMI ≥30/h versus the reference group (PLMI of 0 to <5/h) (4.4 versus 4.7 years; Figure 4).

DISCUSSION

In this study, we assessed whether OSA, PLMS, or their interaction is associated with an increased risk of CVD or death among individuals undergoing evaluation for OSA. Our study revealed that individuals with AHI <30 events/hour have an increased risk of CVD or death by 5% for every 10-event/hour increase in PLMI. Notably, we did not find an interaction between AHI and PLMI for risk of the primary outcome, suggesting an absence of synergy between mild-moderate OSA and PLMS for risk of CVD or death. These findings were robust to the evaluation of different consequences of OSA (eg, hypoxia) and baseline risk of our primary outcome (eg, age, sex, race and ethnicity, or BMI; death from any cause versus cardiovascular risk; or treatment of hypertension). Finally, our findings suggest that PLMS may be a risk factor for CVD or death in older (aged ≥57.5 years) rather than younger individuals. The novel finding of our study is that measures of PLMS rather than OSA were associated with incident CVD or death in participants with no, mild, or moderate OSA.

Table 4. Cox Proportional Hazards Regression Models of the Primary Outcome (Death, ACS, Stroke, or TIA) in Patients Who Were Referred for OSA Evaluation Classified by Age

Age group	Description	Hazard ratio	95% confidence interval		*P* value
≤57.5 y old Model 2	PLMI (per 10/h)	1.01	0.92	1.1	0.915
	AHI (per 10/h)	1.26	0.95	1.67	0.114
>57.5 y old Model 2	PLMI (per 10/h)	1.06	1.00	1.11	0.036
	AHI (per 10/h)	1.13	0.91	1.40	0.232

Model 2: AHI, PLMI, Age, Race/Ethnicity, Sex, BMI, CCI. AHI indicates apnea-hypopnea index; BMI, body mass index; CCI, Charlson comorbidity index; OSA, obstructive sleep apnea; and PLMI, periodic limb movement index.

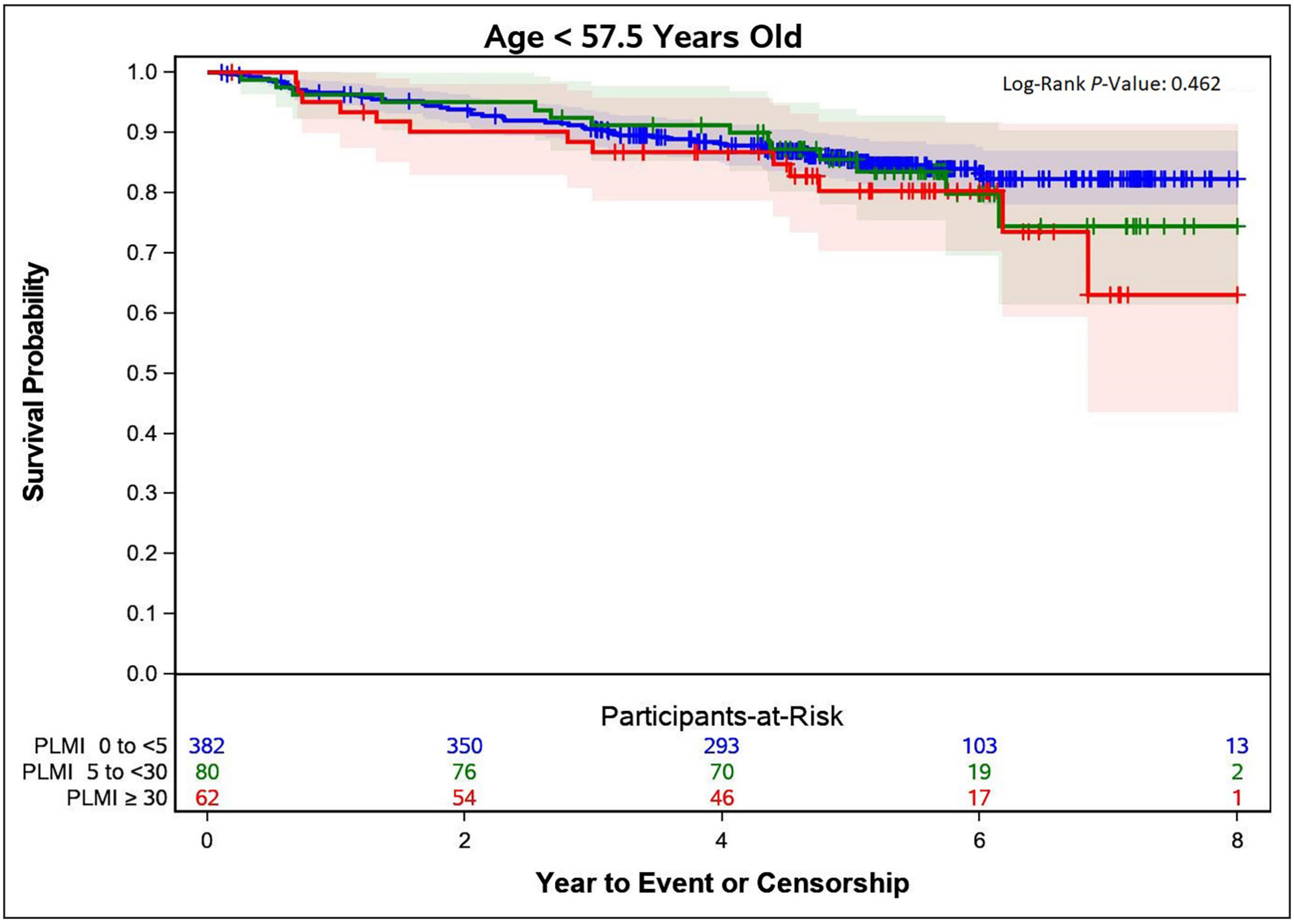

Figure 3. Kaplan-Meier curves for the association of the severity of PLMI and incidents of primary outcomes in patients aged <57.5 years.
Blue line, PLMI 0 to <5; green line, PLMI 5 to <30; and red line, PLMI ≥30. PLMI indicates periodic limb movement index.

OSA and PLMS are interrelated.[31–33] Individuals with OSA are more likely to experience PLMS than those without OSA.[33] Although the mechanisms underlying this relationship are unclear, it has been suggested that the repeated episodes of hypoxia and arousal in people with OSA may contribute to the development of PLMS.[34] On the other hand, PLMS and the associated repeated arousal may destabilize breathing and predispose to OSA, akin to what occurs in those with low arousal threshold.[35] It is also plausible that the interplay between OSA and PLMS may contribute to the risk of adverse outcomes. For instance, Murase et al[36] showed that PLMS and OSA have additive effects on systemic inflammation by increasing inflammatory markers, including plasma CRP (C-reactive protein). Basal autonomic regulation is shifted toward sympathetic predominance in patients with OSA with PLMS, compared with those with OSA alone.[15] Thus, it is plausible that OSA and PLMS act synergistically to increase the risk of CVD or death.

Our findings suggest that PLMS may be an independent predictor of incident CVD or death and that there may not be synergy between OSA and PLMS related to CVD risk. One explanation for this finding could be that the underlying pathways, such as sympathoexcitation and sleep fragmentation,[37,38] are shared by both conditions. Therefore, among individuals with a higher frequency of periodic limb movement events, especially those with PLMI ≥30/h, the dominant contributor to CVD could be the consequence of limb movements rather than apneas-hypopneas. Indeed, >72% of individuals in our cohort with highest risk (PLMI ≥30) exhibited AHIs <15; mild OSA has not been consistently associated with CVD risk.[39] It is also possible that the exclusion of individuals with severe hypoxia (when excluding those with AHI ≥30) in our analysis resulted in a lack of finding an association between OSA severity and CVD risk or death; however, this was not supported by our sensitivity analysis of including individuals with severe OSA. Notably, the magnitude of risk for AHI was meaningful (15% per 10 events/hour) but did not reach statistical significance. Lack of significance may reflect a true absence of a relationship, or that more

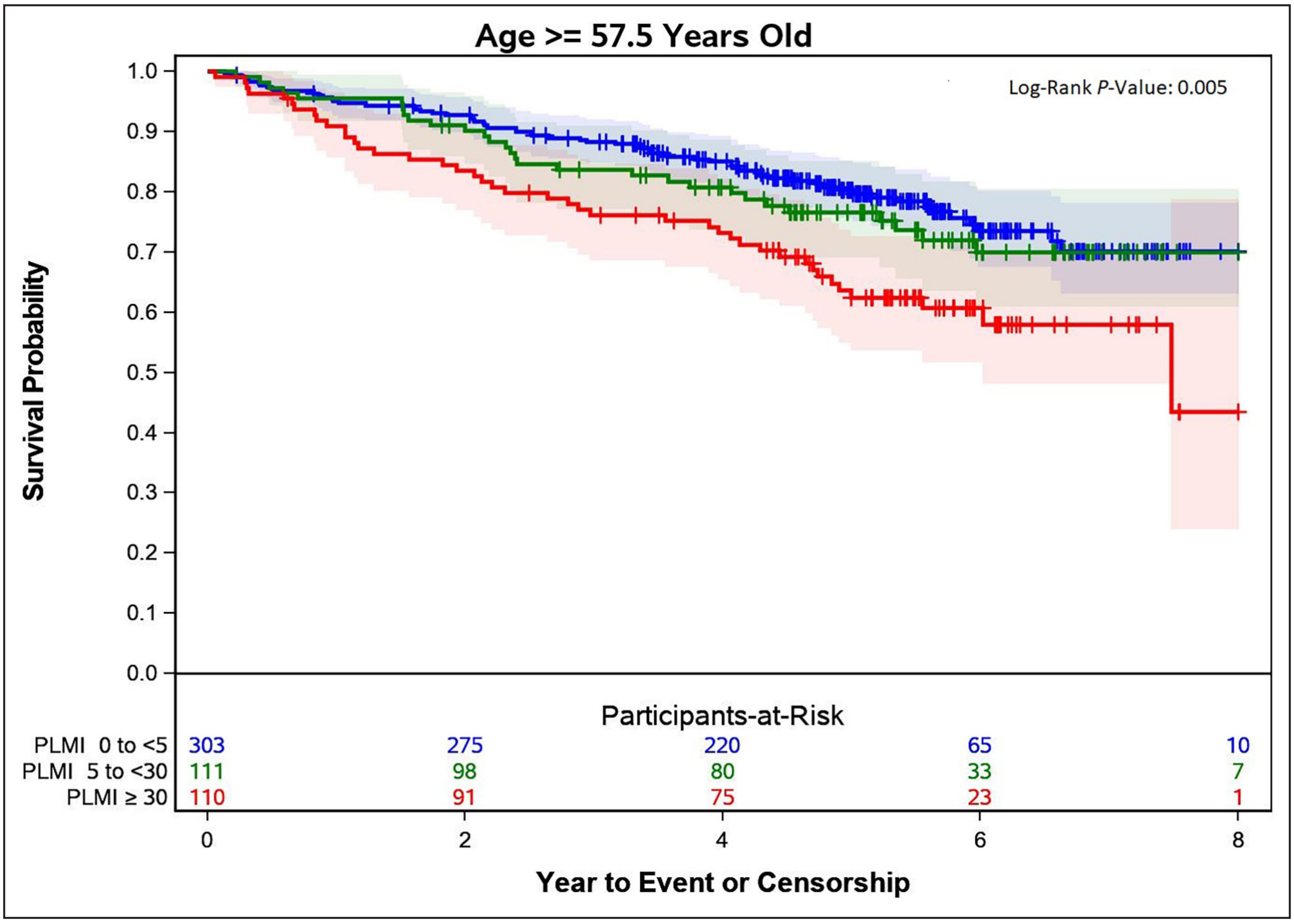

Figure 4. Kaplan-Meier curves for the association of the severity of PLMI and incidents of primary outcomes in patients aged ≥57.5 years.
Blue line, PLMI 0 to <5; green line, PLMI 5 to <30; and red line, PLMI ≥30. PLMI indicates periodic limb movement index.

precision is needed to capture CVD risk conferred by OSA. Indeed, recent work suggests that hypoxic burden rather than AHI is a strong CVD predictor.[40] Future research should include participants with severe OSA, in whom PLMS are scored regardless of respiratory events and where hypoxic burden is measured.

Our analyses showed that PLMS remained a significant independent risk factor for CVD or death, whereas mild/moderate OSA did not, after controlling for important baseline risk factors and sensitivity analyses, including accounting for degree of hypoxia, hypertension and its treatment, and validated baseline cardiovascular risk index, FRS (Tables 3 and S2). These findings further emphasize PLMS as a risk factor for CVD or death.

Several mechanisms may explain the association between PLMS and CVD. First, PLMS likely originate from neuronal generators within thoracolumbar segments of the spinal cord, which house preganglionic sympathetic nerve fibers.[41] Simultaneous activation of leg motor and sympathetic nerve fibers could cause PLMS and increased sympathetic outflow, producing leg movements, heart rate acceleration, and blood pressure elevation.[8,42] In fact, PLMS with or without arousal are associated with nocturnal blood pressure elevations, which, if chronic, may lead to daytime hypertension[43] and increased CVD risk. The repetitive increases in heart rate and blood pressure associated with individual limb movements[44] can result in recurrent mechanical tension on the vasculature and remodeling.[45] Second, the blood pressure fluctuations induced by PLMS are associated with variations in extremity and cerebral blood flow velocity.[46] This could induce sheer stress and platelet activation, ultimately leading to atherosclerosis and hypercoagulability.[45] Finally, PLMS are also associated with inflammation and endothelial dysfunction.[45,47]

Our exploratory analysis revealed that PLMS were linked to an increased risk of CVD or death in the older, but not the younger, individuals. One explanation for differential association might be that PLMS are more common among older adults, who are also more likely to die. However, we (1) assessed effect modification via an interaction analysis and (2) adjusted for age in each subgroup, which suggests that risk attributable to age alone may not account for our observations. Another possible explanation may be that older individuals are more susceptible to the adverse effects of PLMS-associated sympathoexcitation. In general, the sympathetic response to different stimuli is dampened in older individuals.[48,49] On the other hand, increased sympathetic activity in older individuals is associated with hypertension when the sympathetic surge is linked to sleep fragmentation.[50] PLMS are associated with hypertension in cross-sectional, but not longitudinal, analyses.[6,42,43] In this latter study, conducted in >2900 older men, PLMI >30 was associated with incident CVD in those without baseline hypertension, but not for those with hypertension at baseline. This finding suggests that the sympathoexcitation associated with frequent PLMS may be sufficiently large to predispose to CVD when the coronary-arterial system is not already primed by preexisting high blood pressure. Future research should aim to confirm this observation and include measurement of sympathetic biomarkers at night in older individuals with and without PLMS and with and without hypertension.

This study has several strengths. Enrollment of participants was not determined according to a predisposition for PLMS or CVD; thus, the findings can be generalized to similar populations. Data were rigorously collected and scored by highly trained and centralized polysomnographers, with high PLMS intrascorer reliability. Incident cardiovascular events and death were rigorously adjudicated by physicians unaware of the sleep study results. Finally, adjustment for multiple confounders was made, including major cardiovascular risk factors.

Our study also has limitations. First, the participants were mainly male veterans, which limits generalizability to women or civilian populations. Second, PLMS were not scored independently of respiratory events, which may have limited our ability to comprehensively assess the relationship between PLMS and OSA. We attempted to minimize the impact of this by excluding those with AHI ≥30, but this excluded assessment of interaction between PLMS and severe OSA. Future studies that score PLMS and respiratory events independently are needed. In addition, it is important to consider that the severity of OSA and frequency of PLMS can change over time. Thus, metrics of OSA and PLMS severity may have changed during the 5 years of follow-up, which may influence the relationship with our outcomes. The use of technology to longitudinally monitor both OSA[51] and PLMS[52] may provide insight into the dynamic nature of these exposures and the risk of CVD. It is plausible that CPAP use may have reduced the risk of incident CVD selectively among those with OSA. In our sensitivity analyses, CPAP use did not influence the risk of incident CVD or death, consistent with prior reports.[53,54] Notably, only 30% of participants used CPAP regularly. This highlights the need to address CPAP adherence in those with OSA and ensure longitudinal daily use monitoring to robustly account for OSA treatment. Third, because most of the events of the primary outcome were deaths, not incident CVD, our study may have lacked the power to evaluate for risk of CVD specifically, including inability to detect an interaction between AHI and PLMS. Although composite outcomes are commonly used in cardiovascular research,[55] to better understand the mechanisms of an association, future studies should be powered for CVD and risk of death independently. Last, we did not have information on restless leg syndrome, another known CVD risk factor[7]; thus, we cannot determine if the findings are attributable to PLMS alone or are confounded by restless legs syndrome.

In conclusion, our analysis demonstrates that among veterans referred for OSA evaluation who had either no or mild to moderate sleep apnea, PLMS but not OSA was the chief factor associated with the incident CVD or mortality, particularly for older individuals. We found no synergy between PLMS and OSA on CVD risk.

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Disclosures

None.

Supplemental Material

Data S1
Tables S1–S3
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