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Association of Incident Cardiovascular Disease with Periodic Limb Movements During Sleep In Older Men: Outcomes of Sleep Disorders in Older Men (MrOS) Study

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Abstract

Background—Periodic limb movements during sleep (PLMS) cause repetitive sympathetic activation and may be associated with increased cardiovascular risk. We hypothesized that PLMS frequency (PLMI) and PLMS arousal frequency (PLMAI) are predictive of incident cardiovascular disease, including coronary heart disease (CHD), peripheral arterial disease (PAD) and cerebrovascular disease (CBD) in an elderly male cohort.

Methods and Results—2,911 men in the observational MrOS sleep study cohort underwent in-home polysomnography with PLMS measurement and were followed four years for the outcomes CHD, CBD, PAD and all-cause cardiovascular disease (cCVD): CHD, CBD or PAD. Cox proportional hazards regression assessed association between PLMI, PLMAI and these outcomes. Models were minimally adjusted for age, clinic and body mass index, then fully adjusted for conventional cardiovascular risk factors. During follow-up, 500 men experienced cCVD: 345 CHD, 117 CBD and 98 PAD events. In fully adjusted models, men with PLMAI≥5 compared to the referent PLMA<1 group had 1.26-fold increased relative hazard (RH) for cCVD. Similar findings were observed for PLMI and cCVD. For PAD, men with PLMI≥30 compared to the referent PLMI<5 group had a 2-fold increased RH (1.14–3.49, p=0.025). Compared to the referent

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group, men with PLMI ≥30 had an increased risk of CHD (RH=1.31, 1.01–1.70; p=0.045) after minimal adjustment, but this association attenuated after further adjustments. After stratification, risk of incident cCVD among high PLMI and PLMAI groups was significantly elevated only for men without prevalent hypertension (p interactions <0.10).

Conclusions—These findings provide evidence that PLMS frequency is associated with incident cardiovascular disease in community dwelling elderly men.

Keywords

Epidemiology; sleep; cardiovascular diseases; hypertension

Introduction

Periodic limb movements during sleep (PLMS) are spontaneously occurring movements of the legs which occur repetitively throughout the sleeping period. PLMS occur in approximately 5% to 8% of the general population and increase in prevalence with age.[1–3] Individual limb movements last up to five seconds and consist of foot dorsiflexion and less often flexion at the knee or hip.[4] Movements occur approximately every thirty seconds and in severe cases can number well into the hundreds each night.[5] The clinical significance of these movements is unclear; however, when PLMS are associated with arousal, the result can be sleep fragmentation with potential sympathetic nervous system over-activity.[6–9] PLMS occur in a wide variety of disease states, most notably essential hypertension, stroke, congestive heart failure and the restless legs syndrome (RLS).[10–13] The presence of PLMS in both end-stage renal disease and systolic heart failure has been shown to increase mortality risk.[14,15]

Singular limb movements comprising PLMS are each accompanied by a discrete elevation in blood pressure by approximately 10 to 20 mmHg and in heart rate by about 10 beats per minute.[8,9] Studies of PLMS have also suggested that hypertension may persist in the daytime, but this association has not been demonstrated uniformly.[10,16,17] Children with PLMS also demonstrate a non-dipping nocturnal blood pressure pattern which normalizes during the day.[18] Theoretically, these repetitive sympathetic accelerations could result in increased cardiovascular risk. However, prior research has not yet established a link between PLMS and increased incidence of cardiovascular events.

Increased cardiovascular risk has been associated with the restless legs syndrome (RLS) in population studies.[19,20] RLS is a sensorimotor disorder characterized by an inexorable urge to move at night, a time when the body is at greatest need for rest. PLMS may represent an endophenotype for RLS as it occurs in the great majority of RLS cases and shares a common genetic variant with RLS.[13,21,22] Early observations suggested that persons with RLS were more likely than those without RLS to have a history of hypertension.[17] In studies using more rigorous statistical adjustment, RLS was found to be associated with prevalent cardiovascular disease including stroke and myocardial infarction, but not hypertension.[19,20]These studies, however, considered only prevalent cardiovascular disease, leaving unclear directionality and ultimately causality. An additional limitation results from the inherent subjectivity of RLS, making quantification of disease severity difficult. Measurement of PLMS provides an objective means for defining a phenotype showing specific genetic linkages to RLS.[21]

Therefore, we hypothesized that PLMS and PLMS arousal frequency are both predictive of incident cardiovascular disease, including coronary heart disease, peripheral vascular disease and stroke/transient ischemic attack in an elderly male cohort. Data from the Outcomes of

Sleep Disorders in Older Men Study (MrOS Sleep Study), a large cohort designed to examine sleep-related outcomes, were analyzed to test these hypotheses.

Methods

Participants

Between the years 2000 and 2002, the Osteoporotic Fractures in Men Study (MrOS) group conducted baseline examinations in 5,994 community-dwelling men who were 65 years of age or older and able to ambulate without assistance. Centers included Birmingham, Alabama; Minneapolis, Minnesota; Palo Alto, California; Pittsburgh, Pennsylvania; Portland, Oregon; and San Diego, California.[23,24] The MrOS Sleep Study, an ancillary study of the parent MrOS cohort, was conducted between December 2003 and March 2005 and included a comprehensive sleep assessment. Excluded were 150 men treated for sleep apnea or snoring using positive pressure therapy, dental appliance or oxygen. An additional 344 men died, 36 terminated participation, 332 met recruitment goals (prior to MrOS Sleep Study recruitment) and 1,997 refused, leaving 3,135 participants in the MrOS Sleep Study cohort. 2,911 MrOS Sleep Study participants underwent home polysomnography. 244 men in the Sleep Study cohort were missing polysomnography data either because the measure was not performed (n=179) or the collected data was unusable due to poor signal quality (n=45). Men missing polysomnography data were more likely to be of minority race, more likely to have depression and less likely to have prevalent cardiovascular disease ($p<0.05$). Protocols were approved by the Institutional Review Board at each site and participants provided signed informed consent.

Polysomnography

Sleep testing was conducted using unattended in-home polysomnography (Safiro, Compumedics, Inc., Melborne, Australia). The recording montage included: C3/A2 and C4/A1 electroencephalography, bilateral electrooculography, submental electromyography, thoracic/abdominal respiratory inductance plethysmography, naso-oral thermistry, nasal pressure transduction, oximetry, EKG and bilateral anterior tibialis piezoelectric movement sensors. Centrally-trained staff performed home visits for unit set-up and impedance value verification for each channel as previously described.[25] Data was downloaded to a central server at the Central Sleep Reading Center (Cleveland, OH) and scored by certified research polysomnologists using standard criteria.[26,27]

Apnea was defined as more than 90% decrement in thermistry amplitude for at least 10 seconds, while hypopnea was defined as at least 30% reduction in nasal pressure transduction or summed inductance bands for at least 10 seconds. This analysis included only apneas and hypopneas associated with 4% or greater desaturation. The apnea-hypopnea index (AHI) was calculated as the total number of apneas and hypopneas per hour of sleep. Arousals were scored according to AASM criteria.[27] The arousal index was calculated as the number of arousals per hour of sleep.

PLMS were scored according to standard AASM criteria in which individual movements were scored as a PLMS if duration was between 0.5 and 5 seconds and when there was a clear amplitude increase from baseline in leg channels.[28] To be considered periodic, at least four movements needed to occur in succession no less and no more than 5 and 90 seconds apart, respectively. The periodic limb movement index (PLMI) was the total number of periodic leg movements per hour of sleep. Leg movements following respiratory events were excluded unless they were part of a 4 (or more) movement cluster with at least 2 movements occurring independently of respiratory events. The periodic limb movement arousal index (PLMAI) was the total number of periodic leg movements per hour of sleep in

which EEG arousal occurred within 3 seconds of movement termination.[29] PLMI and PLMAI were examined in categories, (roughly tertiles) : PLMI as <5, 5 to <30, ≥30; PLMAI as <1, 1 to <5 and ≥5.

Incident Cardiovascular Disease Events

Participants were surveyed for potential incident cardiovascular events by postcard and/or phone contact every four months with a greater than 99% response rate. Relevant medical records and supporting documentation from any potential incident event including death certificates for fatal events were obtained by the clinical center and forwarded to the coordinating center for centralized adjudication. When no medical records were available for out-of-hospital deaths, proxy interviews with next of kin were obtained. For both nonfatal and fatal cardiovascular events, all documents were adjudicated by a board-certified cardiologist using a prespecified adjudication protocol developed using methods that had been successfully employed at the coordinating center for both prior randomized trials and epidemiological studies of cardiovascular disease. Inter-rater agreement was periodically evaluated by one or more expert adjudicator(s) in a random subset of events to ensure quality control in the outcomes adjudication process.

Confirmed cardiovascular events were grouped as follows: 1) Coronary heart disease event (CHD): acute myocardial infarction (ST or non-ST elevation), sudden coronary heart disease death, coronary artery bypass surgery, mechanical coronary revascularization, hospitalization for unstable angina, ischemic congestive heart failure, or other CHD event not described above, 2) Cerebrovascular event (CBD): stroke or transient ischemic attack, 3) Peripheral arterial disease event (PAD): acute arterial occlusion, rupture, dissection or vascular surgery for arterial disease and 4) All-cause cardiovascular disease event (cCVD): combines CHD, CBD and PAD.

Other Measurements

Participants completed questionnaires regarding demographics, medical history, physical activity, smoking and alcohol use. History of coronary heart disease was defined as prior diagnosis of myocardial infarction, angina, bypass surgery, or angioplasty by self-report. History of peripheral vascular disease was defined as prior diagnosis of intermittent claudication, aortic aneurysm repair, angioplasty or bypass procedure of lower extremity arteries, or carotid endarterectomy. Prescription and nonprescription medications were inventoried, verified by pill bottle examination, and matched to ingredient(s) using the Iowa Drug Information Service (IDIS) Drug Vocabulary (College of Pharmacy, University of Iowa, Iowa City, IA).[30] The Geriatric Depression Scale (GDS) was used with depression defined using the standard ≥ 6 cut-off.[31] Physical Activity Scale for the Elderly (PASE) measured level of physical activity.[32] Resting blood pressure, weight, height and body mass index (BMI) were also measured. Prevalent hypertension was defined by one or more of the following criteria: hypertension self-report, antihypertensive medications usage, systolic or diastolic pressure ≥ 140 or 90 mmHg, respectively. Incident hypertension was defined similarly at follow-up, approximately 3.4±0.5 years later. Cases of incident hypertension were not confirmed by an adjudicator. Of the 923 men without prevalent hypertension at baseline, 102 are missing data on incident hypertension. Of these 102, 7 had terminated before the follow-up visit, 2 refused to participate in the visit, and 61 had died before the follow-up visit. 32 attended the follow-up visit but were missing information needed to calculate incident hypertension status.

Statistical Analysis

Participant characteristics were compared for PLMI and PLMAI using chi-square tests for categorical variables, ANOVA for normally distributed continuous variables, and Kruskal-Wallis tests for continuous variables with skewed distributions.

Cox proportional hazards regression was used to assess the association between PLMI and PLMAI and risk of additional cardiovascular disease event; results are presented as hazard ratios (HR) with 95% confidence intervals (CI). Models were unadjusted, then minimally adjusted for age, clinic and BMI. Additional covariates were included in a multivariate model and were selected if they were related to PLMI or PLMAI at $p<0.10$ or were known risk factors for cCVD. Final model predictors included age, clinic site, BMI, race, depression, prevalent hypertension, diabetes, smoking, alcohol intake, physical activity, AHI, antidepressant use, and benzodiazepine use. For a predictor with three groups roughly in tertiles, there is 80% power to detect an adjusted relative hazard for these outcomes ranging from 1.20 to 1.54 when comparing the lowest and highest tertiles (CHD RH=1.27, CBD RH=1.47, PAD RH=1.54 and cCVD RH=1.20).

It is possible that PLMI or PLMAI are related to unmeasured confounders that make mortality more likely. In the case of these competing measured or unmeasured risk factors, men with the highest PLMI or PLMAI would develop fewer cCVD events because of higher mortality. To address this possibility, the Fine and Gray model was integrated into multivariate models to calculate the HR (95% CI) allowing for the competing risk of mortality.[33]

Secondary analyses were performed by adding previous diagnosis of each outcome as a covariate in the multivariate model. Interaction of PLMI and PLMAI with prevalent hypertension was explored by constructing models adjusted for clinic site, age, BMI, PLMI or PLMAI, prevalent hypertension and the interaction of prevalent hypertension and PLMI/PLMAI. Clinic site was adjusted for to account for potential differences by site in measures related to covariates. Stratifications by this parameter were performed when interaction was $p<0.10$. Interaction models were limited to cCVD outcome due to small event counts for other outcomes. Sensitivity analyses were performed by removing men who were taking dopamanergic medications (n=33) and then separately by removing men who had an AHI ≥ 5 (n=880); results were largely similar.

The association of PLMI and PLMAI with incident hypertension was examined using logistic regression, with results presented as odds ratios and 95% CIs. Men with prevalent hypertension (n=1986) were not included in these analyses. Similar minimally and multivariate adjusted models were performed as described above. All significance levels reported were two-sided. Analyses were conducted using SAS version 9.2 (SAS Institute Inc, Cary, NC).

Results

Of the 3,135 MrOS Sleep Study cohort participants, 2,911 underwent polysomnography with PLMS measurement and were included in this analysis. These participants were followed 4.4 ± 0.8 years (9 days to 5.4 years) for incident events. During this time period, 345 (11.9%) men had a coronary heart disease event (CHD), 117 (4.1%) had a cerebrovascular disease event (CBD), 98 (3.4%) had a peripheral vascular disease event (PAD), and 500 (17.3%) had at least one all-cause CVD event (cCVD).

Table 1 shows demographic characteristics, cardiovascular risk factors and disease for the overall cohort and cohort by PLMI category. 2,063 men or 70.9% of the cohort had a PLMI

> 5. High PLMI categories were associated with increasing age and arousal index, Caucasian race and depression as well as prevalent hypertension, CHD and myocardial infarction. 1,751 men or 60.2% of the cohort had a PLMAI > 1. High PLMAI categories were associated with increasing age, AHI, arousal index, Caucasian race as well as prevalent CHD and myocardial infarction (data not shown). Neither index was associated with smoking status, alcohol intake or prevalent cerebrovascular disease.

Data on incident hypertension were available for 821 out of 923 men without prevalent hypertension at the follow up visit approximately 3.4 years later. In this sample, 258 (31.4%) developed hypertension. Although higher levels of PLMI were associated with an unadjusted increase in rate of prevalent hypertension (Table 1), there was no association between PLMI and incident hypertension with adjustment. Nor was there an association between prevalent or incident hypertension and PLMAI (Table 2).

In fully adjusted models, compared to the referent PLMAI<1 group, the highest category of PLMAI was associated with a 26% increased hazard rate for incident cCVD (Table 3), with risk increasing linearly across the categories (p trend 0.04) as shown in the survival curve (Figure 1). A similar association was seen regarding PLMI category and cCVD, with men in the 5≤PLMI<30 and PLMI≥30 groups having a 25–31% increased risk compared to the reference group. In models adjusted for age, BMI and clinic site, PLMI≥30 was associated with a 31% increased hazard rate for incident CHD when compared to the PLMI<5 category, but this was no longer significant after further adjustment. Additionally, the two higher PLMI categories compared to the referent group had an approximately 2-fold increased hazard rate for incident PAD. This is shown in the survival curve in Figure 2, where both high PLMI categories confer similar increased risk of incident PAD. Incident CBD was not associated with PLM category. Results were not materially affected by further adjustment for previous diagnosis of vascular disease or exclusion of participants taking dopaminergic medications. There were 281 competing deaths for the outcome of CHD, 350 for CBD, 362 for PAD and 240 for cCVD. After accounting for the competing risk of mortality results were similar.

There was evidence for an interaction between PLMS frequency and prevalent hypertension relative to incident cCVD (Table 4). The p-values for the interaction terms for PLMS and prevalent hypertension met our pre-specified criteria for significance (o<0.10), implying the effect of PLMS on CVD depends on prevalent hypertension status. When further stratifying by prevalent hypertension, high PLMS categories were significantly associated with incident cCVD in fully adjusted models only for those without prevalent hypertension, in whom the risk of incident cCVD was 66% to 89% higher for the elevated PLM categories compared to the referent group. There was no significant association between either PLMI or PLMAI and incident cCVD in participants with prevalent hypertension.

Discussion

In this community based elderly male population, PLMS frequency, with and without arousal, was associated with increased incidence of all-cause cardiovascular disease. Compared with men in the lowest PLMI and PLMAI groups, men with PLMI≥30 and PLMAI≥5 experienced a respective 25% and 26% increased cCVD incidence. Furthermore, this association was modified by hypertension, such that among men who were non-hypertensive at baseline, elevated PLMS was associated with an approximately 2-fold increased cCVD incidence. In addition, PLMI≥30 was associated with a 2-fold increased PAD incidence rate. These relationships persisted after consideration of for multiple covariates including (but not limited to) age, BMI, AHI, blood pressure, diabetes and hypertension. Significant associations were not demonstrated between PLMS and incident

CBD or CHD; however, low event rates could have influenced these results by reducing precision and statistical power. This report extends prior cross-sectional reports, and provides evidence that PLMS are associated with both incident cCVD and PAD in elderly men. These longitudinal data from a non-clinic sample support a causal role for increased PLMS and incident vascular disease.

Several mechanisms may explain the relationship between PLMS and cCVD. Prior research has shown that PLMS in persons with RLS are accompanied by discrete increases in blood pressure and heart rate.[8,9] Chronic elevations of blood pressure in association with PLMS also have been reported in some,[10,16] but not all prior studies.[17] The relationship between RLS and hypertension is similarly unclear.[17,19,20] In our study, men with PLMI≥30 were more likely than men with PLMI<5 to have prevalent hypertension, but elevated PLMI was not associated with incident hypertension. The inability to detect association between incident hypertension and PLMS may have resulted from limited power given the high frequency of prevalent hypertension in this elderly cohort or the presence of competing risk factors for hypertension such as smoking or obesity. Additionally, PLMS and hypertension may have a stronger relationship in younger populations, as is the case in obstructive sleep apnea.[34]

In addition to discrete elevations in blood pressure with movements, PLMS has been associated with nocturnal hypertension in children.[18] Non-dipping blood pressure has been associated with increased cardiovascular morbidity.[35,36] Future studies in adult populations are needed to assess whether increased cCVD risk associated with PLMS works through a mechanism of nocturnal hypertension. In this analysis, incident cCVD was more strongly associated with increased PLMS in men without baseline hypertension. It is possible that when occurring in the presence of hypertension, repetitive sympathetic response to PLMS may have a blunted effect as the arterial system is primed to pressure variability. Furthermore, use of adrenergic blocking medication, common in the hypertensive population, may have mitigated responses to repetitive sympathetic surges at night. Our work suggests the need for further experimental research to clarify whether background differences in blood pressure level and medication use might modify responses to PLMS.

The strong association between PLMI and incident PAD suggests that PLMS may preferentially contribute to peripheral arteriopathy, which in turn may increase cardiovascular risk. PAD in this analysis included arterial occlusion, rupture or dissection and vascular surgery in any major artery. It is notable that persons with PLMS and RLS often complain of cold feet, a symptom attributed to increased vasoreactivity.[37] Additionally, peripheral vasoconstriction has been linked to PLMS in at least one small uncontrolled study.[38] PLMS could result in PAD through a mechanism of nocturnal hypertension. Repetitive elevations in blood pressure may directly damage endothelium or alter vasoreactivity through mechanical stress. Alternatively, PLMS and sympathetic hyperactivity may lead to a release of inflammatory mediators, stimulating both lipolysis and glycolysis and thus promoting endothelial damage and atherosclerosis. In fact, levels of lipoprotein-associated phospholipase A2, a marker for atherosclerosis, and C reactive protein have recently been shown to be increased in the setting of PLMS.[39] It is worth noting that PLMAI was not associated with incident PAD, perhaps because of low PAD event rate.

Although causality is difficult to discern from observational data, the evidence that PLMS preceded development of cCVD or PAD is consistent with its causal role in vascular disease. Furthermore, the results suggest that PLMS may increase risk of cardio- and peripheral vascular disease through a mechanism other than daytime hypertension. Although our analyses utilized longitudinal data, it is possible that PLMS resulted from unrecognized

cardiovascular disease or other unmeasured confounders. Whether PLMS directly increases vascular disease risk or is a marker of a generalized disorder of vasoreactivity requires further investigation.

This study has several strengths. Enrollment of these community-dwelling men was not determined on the basis of PLMS or cardiovascular disease risk and for this reason the findings can be generalized to elderly men. Incident cardiovascular disease was ascertained rigorously by a physical adjudicator unaware of the sleep study results. Finally, adjustment for multiple confounders was made including major cardiovascular risk factors. It is worth noting that the observed prevalence of PLMI > 5 (70.9%) was significantly higher than previously reported.[2] This difference could have been secondary to the older age of the subject population in this cohort but an overestimation of limb movements by piezoelectric sensors cannot be ruled out. Additionally, overscoring of PLMS cannot be ruled out as scoring allowed for the inclusion of leg movements if when occurring in a cluster, there were leg movements that occurred in-between respiratory events.

There are also limitations to consider when interpreting these findings. Although the associations of PLMI and PLMAI level and incident cCVD were statistically significant, there were other risk factors in the multivariate models with a larger effect size such as prevalent hypertension. The overall participation rate was quite high; however, since non-participants differed from participants in regards to race, depression and prevalent cardiovascular disease, it is plausible that the exclusion of these individuals may have influenced the results. As the cohort consisted of men older than 65 years who were predominantly Caucasians, the results cannot be generalized to women, persons of younger age or non-Caucasians. Information regarding RLS symptoms was not available. Although PLMS occur in approximately 80% of RLS sufferers it occurs in several other conditions and often in the elderly without RLS symptoms.[2,10–13] So whether or not these findings can be extrapolated to RLS is unclear. A single measurement of PLMS at baseline does not account for night-to-night variability and changes in PLMS over time. Furthermore, the period of follow-up was modest, limiting the number of incident events and reducing precision in estimates, particularly CBD, CHD and hypertension.

In sum, the findings of the current study provide evidence that PLMS frequency is associated with incident cardiovascular disease in community dwelling elderly men. This is an observational study which does not address causality. Future intervention studies are required to further address the potential role of PLMS treatment in the prevention of cCVD as well as to further understand the pathogenesis of vascular disease in individuals with PLMS.

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Appendix

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References

1. Scofield H, Roth T, Drake C. Periodic limb movements during sleep: population prevalence, clinical correlates, and racial differences. Sleep. 2008; 31:1221–1227. [PubMed: 18788647]
2. Ancoli-Israel S, Kripke DF, Klauber MR, Mason WJ, Fell R, Kaplan O. Periodic limb movements in sleep in community-dwelling elderly. Sleep. 1991; 14:496–500. [PubMed: 1798881]
3. Bliwise DL, Carskadon MA, Dement WC. Nightly variation of periodic leg movements in sleep in middle aged and elderly individuals. Arch Gerontol Geriatr. 1988; 7:273–279. [PubMed: 3228331]
4. Lugaresi E, Coccagna G, Mantovani M, Lebrun R. Some periodic phenomena arising during drowsiness and sleep in man. Electroencephalogr Clin Neurophysiol. 1972; 32:701–705. [PubMed: 4121520]
5. Pollmächer T, Schulz H. Periodic leg movements (PLM): their relationship to sleep stages. Sleep. 1993; 16:572–577. [PubMed: 8235243]
6. Bastuji H, García-Larrea L. Sleep/wake abnormalities in patients with periodic leg movements during sleep: factor analysis on data from 24-h ambulatory polygraphy. J Sleep Res. 1999; 8:217–223. [PubMed: 10476009]
7. Broughton R, Tolentino MA. Fragmentary pathological myoclonus in NREM sleep. Electroencephalogr Clin Neurophysiol. 1984; 57:303–309. [PubMed: 6200293]
8. Pennestri MH, Montplaisir J, Colombo R, Lavigne G, Lanfranchi PA. Nocturnal blood pressure changes in patients with restless legs syndrome. Neurology. 2007; 68:1213–1218. [PubMed: 17420405]
9. Siddiqui F, Strus J, Ming X, Lee IA, Chokroverty S, Walters AS. Rise of blood pressure with periodic limb movements in sleep and wakefulness. Clin Neurophysiol. 2007; 118:1923–1930. [PubMed: 17588809]

10. Espinar-Sierra J, Vela-Bueno A, Luque-Otero M. Periodic leg movements in sleep in essential hypertension. Psychiatry Clin Neurosci. 1997; 51:103–107. [PubMed: 9225372]
11. Coelho FM, Georgsson H, Narayansingh M, Swartz RH, Murray BJ. Higher prevalence of periodic limb movements of sleep in patients with history of stroke. J Clin Sleep Med. 2010; 6:428–430. [PubMed: 20957841]
12. Hanly PJ, Zuberi-Khokhar N. Periodic limb movements during sleep in patients with congestive heart failure. Chest. 1996; 109:1497–1502. [PubMed: 8769500]
13. Montplaisir J, Boucher S, Poirier G, Lavigne G, Lapierre O, Lesperance P. Clinical, polysomnographic, and genetic characteristics of restless legs syndrome. Mov Disord. 1997; 12:61–65. [PubMed: 8990055]
14. Benz RL, Pressman MR, Hovick ET, Peterson DD. Potential novel predictors of mortality in end-stage renal disease patients with sleep disorders. Am J Kidney Dis. 2000; 35:1052–1060. [PubMed: 10845816]
15. Yumino D, Wang H, Floras JS, Newton GE, Mak S, Ruttanaumpawan P, Parker JD, Bradley TD. Relation of periodic leg movements during sleep and mortality in patients with systolic heart failure. Am J Cardiol. 2011; 107:447–451. [PubMed: 21257013]
16. Billars L, Hicks A, Bliwise D. Hypertension risk and PLMS in restless legs syndrome. Sleep. 2007; 30:A297–A298.
17. Ohayon MM, Roth T. Prevalence of restless legs syndrome and periodic limb movement disorder in the general population. J Psychosom Res. 2002; 53:547–554. [PubMed: 12127170]
18. Wing YK, Zhang J, Ho CK, Au CT, Li AM. Periodic limb movement during sleep is associated with nocturnal hypertension in children. Sleep. 2010; 33:759–765. [PubMed: 20550016]
19. Winkelman JW, Shahar E, Sharief I, Gottlieb DJ. Polysomnographic and health-related quality of life correlates of restless legs syndrome in the Sleep Heart Health Study. Sleep. 2009; 32:772–778. [PubMed: 19544754]
20. Winkelman JW, Finn L, Young T. Prevalence and correlates of restless legs syndrome symptoms in the Wisconsin Sleep Cohort. Sleep Med. 2006; 7:545–552. [PubMed: 16740407]
21. Stefansson H, Rye DB, Hicks A, Petursson H, Ingason A, Thorgeirsson TE, Palsson S, Sigmundsson T, Sigurdsson AP, Eiriksdottir I, Soebech E, Bliwise D, Beck JM, Rosen A, Waddy S, Trotti LM, Iranzo A, Thambisetty M, Hardarson GA, Kristjansson K, Gudmundsson LJ, Thorsteinsdottir U, Kong A, Gulcher JR, Gudbjartsson D, Stefansson K. A genetic risk factor for periodic limb movements in sleep. N Engl J Med. 2007; 357:639–647. [PubMed: 17634447]
22. Winkelmann J, Schormair B, Lichtner P, Ripke S, Xiong L, Jalilzadeh S, Fulda S, Pütz B, Eckstein G, Hauk S, Trenkwalder C, Zimprich A, Stiasny-Kolster K, Oertel W, Bachmann CG, Paulus W, Peglau I, Eisensehr I, Montplaisir J, Turecki G, Rouleau G, Gieger C, Illig T, Wichmann HE, Holsboer F, Müller-Myhsok B, Meitinger T. Genome-wide association study of restless legs syndrome identifies common variants in three genomic regions. Nat Genet. 2007; 39:1000–1006. [PubMed: 17637780]
23. Orwoll E, Blank JB, Barrett-Connor E, Cauley J, Cummings S, Ensrud K, Lewis C, Cawthon PM, Marcus R, Marshall LM, McGowan J, Phipps K, Sherman S, Stefanick ML, Stone K. Design and baseline characteristics of the osteoporotic fractures in men (MrOS) study--a large observational study of the determinants of fracture in older men. Contemp Clin Trials. 2005; 26:569–585. [PubMed: 16084776]
24. Blank JB, Cawthon PM, Carrion-Petersen ML, Harper L, Johnson JP, Mitson E, Delay RR. Overview of recruitment for the osteoporotic fractures in men study (MrOS). Contemp Clin Trials. 2005; 26:557–568. [PubMed: 16085466]
25. Redline S, Sanders MH, Lind BK, Quan SF, Iber C, Gottlieb DJ, Bonekat WH, Rapoport DM, Smoth PL, Kiley JP. Methods for obtaining and analyzing unattended polysomnography data for a multicenter study. Sleep Heart Health Research Group. Sleep. 1998; 21:759–767. [PubMed: 11300121]
26. Rechtschaffen, A.; Kales, A., editors. A Manual of Standardized Terminology, Techniques, and Scoring System for Sleep Stages of Human Subjects. Washington DC: National Institutes of Health; 1968. NIH publication 204.

27. American Sleep Disorders Association. EEG arousals: scoring rules and examples: a preliminary report from the Sleep Disorders Atlas Task Force of the American Sleep Disorders Association. Sleep. 1992; 15:173–184. [PubMed: 11032543]
28. American Academy of Sleep Medicine. Recording and scoring leg movements. The Atlas Task Force. Sleep. 1993; 16:748–759. [PubMed: 8165390]
29. Claman DM, Redline S, Blackwell T, Ancoli-Israel S, Surovec S, Scott N, Cauley JA, Ensrud KE, Stone KL. Study of Osteoporotic Fractures Research Group. Prevalence and correlates of periodic limb movements in older women. J Clin Sleep Med. 2006; 2:438–445. [PubMed: 17557474]
30. Pahor M, Chrischilles EA, Guralnik JM, Brown SL, Wallace RB, Carbonin P. Drug data coding and analysis in epidemiologic studies. Eur J Epidemiol. 1994; 10:405–411. [PubMed: 7843344]
31. Sheikh J, Yesavage J. Geriatric Depression Scale: recent evidence and development of a shorter version. Clin Gerontol. 1986; 5:165–173.
32. Washburn RA, Smith KW, Jette AM, Janney CA. The Physical Activity Scale for the Elderly (PASE): Development and Evaluation. Journal of Clinical Epidemiology. 1993; 46:153–162. [PubMed: 8437031]
33. Fine JP, Gray RJ. A Proportional Hazards Model for the Subdistribution of a Competing Risk. JASA. 1999; 94:496–509.
34. Haas DC, Foster GL, Nieto FJ, Redline S, Resnick HE, Robbins JA, Young T, Pickering TG. Variable Associations Between Sleep Disordered Breathing and Hypertension: The Importance of Discriminating Between Essential Hypertension and Isolated Systolic Hypertension: the Sleep Heart Health Study. Circulation. 2005; 111:614–621. [PubMed: 15699282]
35. Muxfeldt ES, Cardoso CR, Salles GF. Prognostic value of nocturnal blood pressure reduction in resistant hypertension. Arch Intern Med. 2009; 169:874–880. [PubMed: 19433699]
36. Fagard RH, Thijs L, Staessen JA, Clement DL, De Buyzere ML, De Bacquer DA. Night-day blood pressure ratio and dipping pattern as predictors of death and cardiovascular events in hypertension. J Hum Hypertens. 2009; 23:645–653. [PubMed: 19225527]
37. Rajaram SS, Shanahan J, Ash C, Walters AS, Weisfogel G. Enhanced external counter pulsation (EECP) as a novel treatment for restless legs syndrome (RLS): a preliminary test of the vascular neurologic hypothesis for RLS. Sleep Med. 2005; 6:101–106. [PubMed: 15716213]
38. Ware JC, Blumoff R, Pittard JT. Peripheral vasoconstriction in patients with sleep related periodic leg movements. Sleep. 1988; 11:182–186. [PubMed: 2898166]
39. Bekci TT, Kayrak M, Kiyici A, Ari H, Teke T, Maden E, Akilli H. The relation between Lp-PLA2 levels with periodic limb movements. Sleep Breath. 2011 PMID:21221825 (Ahead of print).

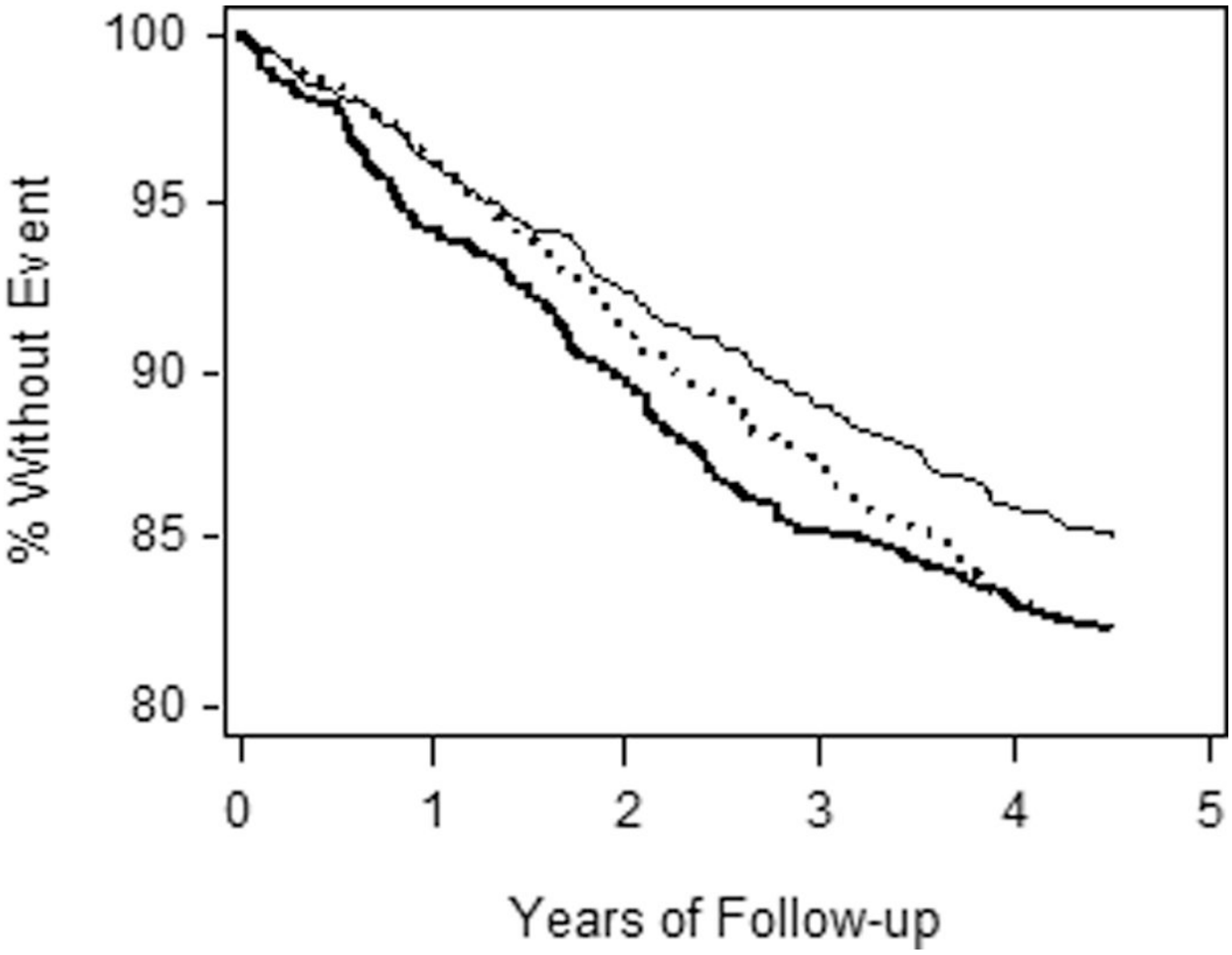

Figure 1.

Kaplan-Meier curve for incident cCVD by PLMAI category showing an increased event rate for the high PLMAI groups, PLMAI≥5 and 1≤PLMAI<5, compared to the PLMAI<1 group. PLMAI<1 ——— 1≤PLMAI<5 ------- PLMAI≥5 ———

*Figure adjusted for clinic site, age, BMI, race, depression, prevalent diabetes, prevalent hypertension, smoking, alcohol use, physical activity, use of antidepressants, use of benzodiazepines, and AHI.

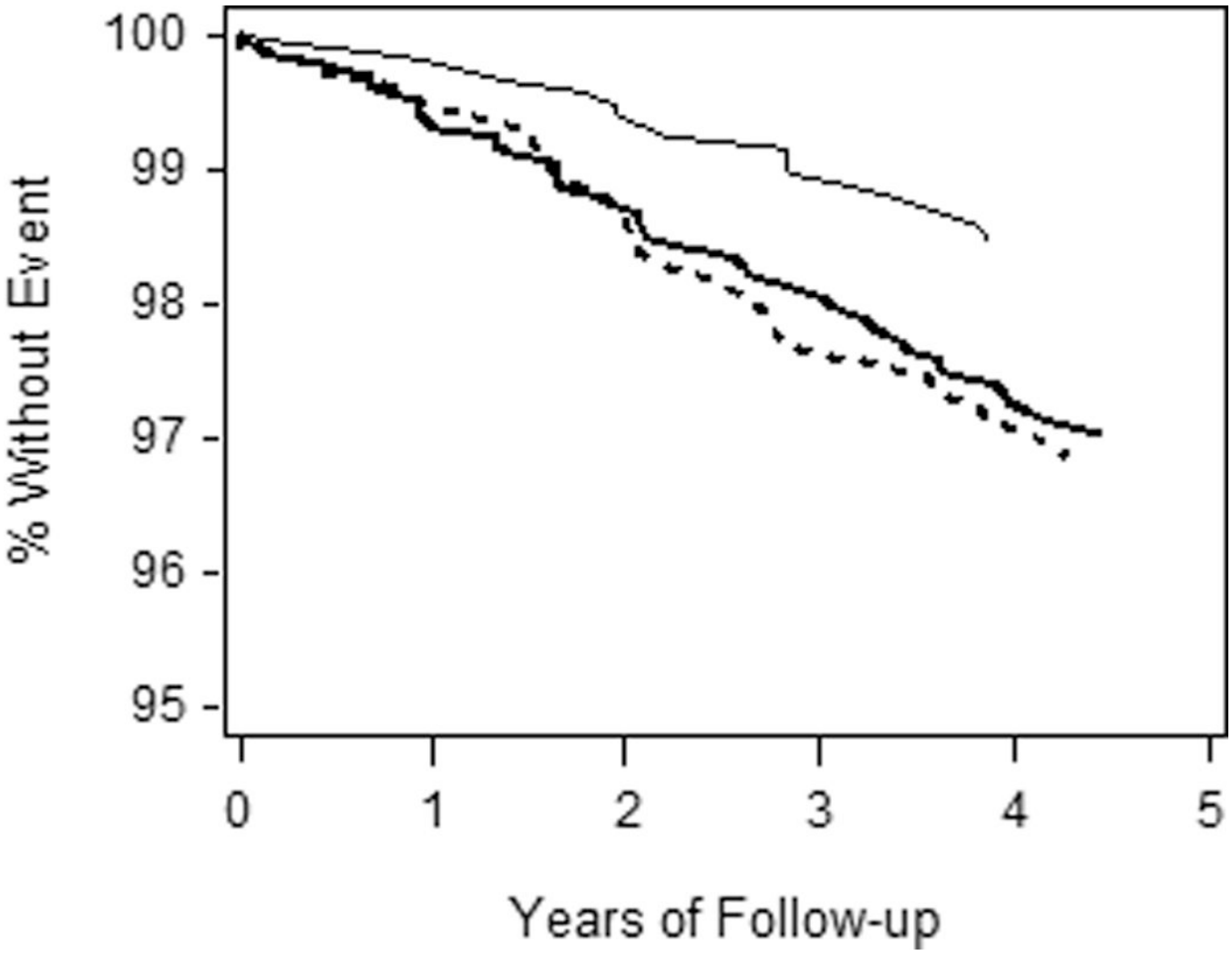

Figure 2.
Kaplan-Meier curve for incident PAD by PLMI category showing an increased event rate for the high PLMI groups, PLMI≥30 and 5≤PLMAI<30, compared to the PLMI<5 group. PLMI<5 ——— 5≤PLMI<30 ------- PLMI≥30 ———
*Figure adjusted for clinic site, age, BMI, race, depression, prevalent diabetes, prevalent hypertension, smoking, alcohol use, physical activity, use of antidepressants, use of benzodiazepines, and AHI.

Table 1

Distributions of Participant Characteristics by PLMI

Participant Characteristics	Overall Cohort (n=2911)	PLMI < 5 (n=848)	5 < PLMI < 30 (n=750)	PLMI≥30 (n=1313)	P value
Age	76.4 ± 5.5	75.6 ± 5.2	76.1 ± 5.5	77.1 ± 5.7	<.0001
Caucasian race, n (%)	2641 (90.7)	732 (86.3)	667 (88.9)	1242 (94.6)	<.0001
BMI, kg/m^2	27.2 ± 3.8	27.1 ± 3.9	27.1 ± 4.0	27.2 ± 3.7	0.80
AHI	11.7 ± 13.0	12.5 ± 13.1	11.6 ± 13.0	11.4 ± 12.9	0.06
Obstructive apnea/hr > 5, n (%)	880 (35.1)	281 (37.8)	219 (34.3)	380 (33.7)	0.17
Arousal index	23.6 ± 11.7	21.7 ± 10.4	23.3 ± 10.9	25.1 ± 12.8	<.0001
PASE score	145.7 ± 71.3	150.1 ± 74.4	141.9 ± 71.9	145.0 ± 68.9	0.06
Smoking status					
Never	1150 (39.5)	317 (37.4)	304 (40.5)	529 (40.3)	0.67
Past	1703 (58.5)	514 (60.6)	432 (57.6)	757 (57.7)	
Current	58 (2.0)	17 (2.0)	14 (1.9)	27(2.1)	
Alcohol intake (drinks/week)					
0–2	1725 (59.6)	495 (58.9)	440 (58.7)	790 (60.5)	0.78
3–13	1015 (35.1)	305 (36.3)	266 (35.5)	444 (34.0)	
≥ 14	156 (5.4)	41 (4.9)	43 (5.7)	72 (5.5)	
Use of benzodiazepine, n (%)	133 (4.6)	44 (5.2)	30 (4.0)	59 (4.5)	0.52
Use of antidepressant, n (%)	228 (7.8)	57 (6.7)	59 (7.9)	112 (8.5)	0.31
Use of dopaminergic, n (%)	33 (1.1)	8 (0.9)	11 (1.5)	14 (1.1)	0.59
Depression, n (%)	188 (6.5)	55 (6.5)	35 (4.7)	98 (7.5)	0.04
Diabetes mellitus, n (%)	387 (13.3)	104 (12.3)	91 (12.1)	192 (14.6)	0.16
Stroke or TIA (CBD), n (%)	320 (11.0)	96 (11.3)	81 (10.8)	143 (10.9)	0.93
Coronary heart dis (CHD), n (%)	869 (29.9)	218 (25.8)	213 (28.5)	438 (33.4)	0.0005
Myocardial infarct, n (%)	508 (17.5)	127 (15.0)	125 (16.7)	256 (19.5)	0.02
Peripheral vascular(PAD), n (%)	289 (10.1)	81(9.8)	72 (9.7)	136 (10.5)	0.78
Prevalent hypertension, n (%)	1986 (68.3)	553 (65.3)	508 (67.7)	925 (70.5)	0.04
Systolic BP, mmHg	126.8 ± 16.3	126.9 ± 16.2	126.4 ± 16.3	127.1 ± 16.4	0.64
Diastolic BP, mmHg	67.7 ± 9.5	68.2 ± 9.1	67.5 ± 9.5	67.5 ± 9.6	0.19
Use antihypertensive, n (%)	1713 (58.9)	471 (55.5)	435 (58.0)	807 (61.5)	0.02

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Participant Characteristics	Overall Cohort (n=2911)	PLMI < 5 (n=848)	5 < PLMI < 30 (n=750)	PLMI≥30 (n=1313)	P value
Hypertension history, n (%)	1453 (49.9)	394 (46.5)	384 (51.2)	675 (51.4)	0.06

Data shown as mean ± SD or n (%)

P-values for continuous variables from ANOVA for normally distributed variables (age, BMI, PASE score, systolic and diastolic blood pressure), Kruskal-Wallis test for skewed data (AHI, arousal index).

P-values for categorical data from chi-square test for homogeneity (race, smoking status, alcohol intake, benzodiazepine use, antidepressant use, dopaminergic use, depression, diabetes mellitus, CBD, CHD, myocardial infarction, PAD, hypertension, antihypertensive use, hypertension history).

CBD includes stroke and TIA.

CHD includes myocardial infarction, angina, coronary bypass surgery, and angioplasty.

PAD includes intermittent claudication, repair of aortic aneurysm, bypass procedure on artieries in the legs, angioplasty of lower extremity arteries, and carotid endarerectomy.

Table 2

Odds Ratios Associating Incident Hypertension to PLMI and PLMAI

		Odds Ratio (95 % CI)	
	N (%) of Event	Minimally Adjusted*	Fully Adjusted**
PLMI			
PLMI <5	80 (30.30)	1.0 (ref)	1.0 (ref)
PLMI 5 to <30	74 (33.18)	1.18 (0.80–1.74)	1.27 (0.85–1.88)
PLMI 30+	104 (31.14)	1.00 (0.70–1.42)	1.04 (0.72–1.51)
p-trend		0.9285	0.8857
PLMAI			
PLMAI <1	111 (31.44)	1.0 (ref)	1.0 (ref)
PLMAI 1 to <5	83 (31.20)	0.97 (0.68–1.37)	0.99 (0.69–1.42)
PLMAI 5+	64 (31.68)	0.93 (0.63–1.36)	0.95 (0.64–1.41)
p-trend		0.7016	0.8058

*Adjusted for clinic site, age, BMI

**Adjusted for clinic site, age, BMI, race, depression, prevalent diabetes, smoking, alcohol use, physical activity, antidepressant use, benzodiazepine use, and AHI.

Table 3

Hazard Ratios Associating Incident Cardiovascular Disease to PLMI and PLMAI

		Relative Hazard (95% Confidence Interval)		
	N (%) of Event	Unadjusted	Minimally Adjusted*	Fully Adjusted**
PLMI				
Incident CHD	345 (11.94)			
PLMI <5	84 (9.96)	1.0 (ref)	1.0 (ref)	1.0 (ref)
PLMI 5 to <30	88 (11.83)	1.20 (0.89–1.62)	1.20 (0.89–1.61)	1.19 (0.88–1.60)
PLMI 30+	173 (13.28)	1.38 (1.07–1.79)	1.31 (1.01–1.70)	1.26 (0.97–1.65)
p-trend		0.0143	0.0479	0.0936
Incident CBD	117 (4.05)			
PLMI <5	31 (3.68)	1.0 (ref)	1.0 (ref)	1.0 (ref)
PLMI 5 to <30	38 (5.11)	1.40 (0.87–2.25)	1.35 (0.84–2.18)	1.35 (0.84–2.18)
PLMI 30+	48 (3.68)	1.03 (0.65–1.61)	0.92 (0.59–1.46)	0.89 (0.56–1.40)
p-trend		0.9464	0.5818	0.4586
Incident PAD	98 (3.39)			
PLMI <5	17 (2.02)	1.0 (ref)	1.0 (ref)	1.0 (ref)
PLMI 5 to <30	30 (4.03)	2.02 (1.11–3.66)	2.05 (1.13–3.72)	2.08 (1.14–3.79)
PLMI 30+	51 (3.91)	2.01 (1.16–3.47)	2.02 (1.17–3.51)	2.00 (1.14–3.49)
p-trend		0.0206	0.0199	0.0253
Incident cCVD	500 (17.30)			
PLMI <5	120 (14.23)	1.0 (ref)	1.0 (ref)	1.0 (ref)
PLMI 5 to <30	136 (18.28)	1.32 (1.03–1.68)	1.31 (1.03–1.68)	1.31 (1.02–1.67)
PLMI 30+	244 (18.73)	1.38 (1.11–1.72)	1.30 (1.04–1.62)	1.25 (1.00–1.56)
p-trend		0.0055	0.0305	0.0731
PLMAI				
Incident CHD	345 (11.94)			
PLMAI <1	120 (10.42)	1.0 (ref)	1.0 (ref)	1.0 (ref)
PLMAI 1 to <5	117 (12.28)	1.19 (0.92–1.54)	1.16 (0.90–1.50)	1.14 (0.88–1.47)
PLMAI 5+	108 (13.76)	1.37 (1.06–1.78)	1.26 (0.97–1.64)	1.23 (0.95–1.61)
p-trend		0.0164	0.0805	0.1178
Incident CBD	117 (4.05)			
PLMAI <1	39 (3.39)	1.0 (ref)	1.0 (ref)	1.0 (ref)
PLMAI 1 to <5	43 (4.51)	1.35 (0.87–2.08)	1.31 (0.85–2.02)	1.29 (0.83–1.99)
PLMAI 5+	35 (4.46)	1.34 (0.85–2.12)	1.20 (0.76–1.91)	1.12 (0.71–1.79)
p-trend		0.1845	0.4008	0.5841
Incident PAD	98 (3.39)			
PLMAI <1	33 (2.86)	1.0 (ref)	1.0 (ref)	1.0 (ref)
PLMAI 1 to <5	31 (3.25)	1.14 (0.70–1.86)	1.12 (0.69–1.84)	1.10 (0.67–1.79)
PLMAI 5+	34 (4.33)	1.55 (0.96–2.51)	1.52 (0.93–2.46)	1.50 (0.92–2.46)
p-trend		0.0752	0.098	0.1112

		Relative Hazard (95% Confidence Interval)		
	N (%) of Event	Unadjusted	Minimally Adjusted*	Fully Adjusted**
Incident cCVD	500 (17.30)			
PLMAI <1	171 (14.84)	1.0 (ref)	1.0 (ref)	1.0 (ref)
PLMAI 1 to <5	172 (18.05)	1.24 (1.00–1.53)	1.21 (0.98–1.50)	1.19 (0.96–1.47)
PLMAI 5+	157 (20.00)	1.42 (1.14–1.76)	1.30 (1.04–1.61)	1.26 (1.01–1.57)
p-trend		0.0015	0.0186	0.0402

*Adjusted for clinic site, age, BMI

**Adjusted for clinic site, age, BMI, race, depression, prevalent diabetes,prevalent hypertension, smoking, alcohol use, physical activity, use of antidepressants, use of benzodiazepines and AHI

***CHD = coronary heart disease; CBD = cerebrovascular disease event; PAD = peripheral arterial disease event; cCVD = all-cause cardiovascular disease or CHD + CBD + PAD

Table 4

Hazard Ratios Associating Incident Cardiovascular Disease to PLMI and PLMAI by Prevalent Hypertension

	No Prevalent Hypertension (n=923)	Prevalent Hypertension (n=1986)	p-value for interaction*
PLMI			
PLMI <5	1.0 (ref)	1.0 (ref)	0.09
PLMI 5 to <30	1.83 (1.02–3.27)	1.23 (0.93–1.62)	
PLMI 30+	1.89 (1.11–3.22)	1.15 (0.90–1.47)	
p-trend	0.0249	0.3563	
PLMAI			
PLMAI <1	1.0 (ref)	1.0 (ref)	0.07
PLMAI 1 to <5	1.66 (1.01–2.73)	1.10 (0.87–1.39)	
PLMAI 5+	1.74 (1.04–2.93)	1.15 (0.90–1.48)	
p-trend	0.0317	0.2478	

Note: 2 participants lack the data necessary to determine prevalent hypertension status.

* P-values for interaction with prevalent hypertension for PLMI ≥ 30 category and when examining PLMAI as a continuous variable.

** Adjusted for clinic site, age, BMI, race, depression, prevalent diabetes, smoking, alcohol use, physical activity, use of antidepressants, use of benzodiazepines, and AHI.