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Periodic leg movements during sleep and cognitive functioning in the older general population

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ABSTRACT

Objective: The current evidence of a relationship between periodic leg movements during sleep (PLMS) and cognitive functioning is limited and inconsistent. This cross-sectional study assessed associations between PLMS and cognitive functioning among community-dwelling older adults.

Methods: We included community-dwelling older adults who underwent a polysomnography and a cognitive assessment. The PLMS index (PLMI) and PLMS arousal index (PLMAI) were categorized into tertiles: PLMI <5/h (reference), 5–29.9/h, ≥30/h; and PLMAI <1/h (reference), 1–4.9/h, ≥5/h. The cognitive assessment consisted of ten scores covering the main cognitive domains: global cognition, processing speed, executive function, language, episodic verbal memory, and visuospatial function. Associations between PLMI, PLMAI, and cognitive scores were assessed using regression unadjusted and adjusted models.

Results: A total of 579 individuals without dementia were included (mean age: 71.5 ± 4.4 years; men 45.4%). The number of participants in the high-PLMI categories, 5–29.9/h and ≥30/h, was 185 (32.0%) and 171 (29.5%), respectively. Participants in the high-PLMI categories showed no significant difference compared to the reference group regarding their cognitive performance according to the unadjusted and adjusted models. Similarly, we found no association between PLMAI severity and cognitive functioning.

Conclusions: This study shows no cross-sectional association between PLMS severity and cognitive functioning among community-dwelling older adults. However, given the paucity of data in this field, further studies are needed to clarify the relationship between PLMS and cognitive functioning.

1. Introduction

Periodic leg movements during sleep (PLMS) are repetitive and stereotyped muscular contractions in the legs during sleep. PLMS may be associated with clinically significant sleep disturbances or impaired daytime functioning [1]. However, increased PLMS is commonly observed in asymptomatic individuals [2]. Whether PLMS can lead to functional impairment or long-term health consequences remains a

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matter of debate.

PLMS are often time-related with arousals [3], autonomic activations (increased heart rate [4] and blood pressure [5]), and cerebral hemodynamic fluctuations [6], which may potentially affect brain health. An increase in PLMS severity is often observed in sleep and neurological diseases (such as restless legs syndrome [RLS], narcolepsy, and alpha-synucleinopathies) [7], suggesting that PLMS may also represent a marker of central nervous system dysfunction. However, little research has been conducted on the relationship between PLMS and cognitive functioning [8–10]. Two studies have been carried out in patients with Parkinson's disease [8,9]. To our knowledge, the longitudinal study by Leng et al. is the only one to have been conducted in the general population, including 2636 community-dwelling older men with an average age of 76 years [10]. Gaps remain in the literature, such as the fact that there are no data about the cross-sectional association between PLMS and cognitive functioning in the older general population.

The present cross-sectional study tested for potential associations between PLMS severity and cognitive functioning among community-dwelling older adults. We hypothesized that higher PLMS severity would be associated with poorer cognitive functioning, especially in executive function [8,10].

2. Methods

2.1. Study population

Data stemmed from CoLaus|PsyCoLaus, a prospective cohort study on community-dwelling adults [11]. The sample of the present study consisted of 579 participants who accepted both cognitive assessment (performed only in participants aged ≥65 years) and polysomnography (PSG; HypnoLaus subsample [1,2]) during the first follow-up of the study between 2009 and 2013 (Fig. S1). None of the included participants met the criteria for dementia (defined by a Clinical Dementia Rating score ≥1). The institutional Ethics Committee of the University of Lausanne approved the CoLaus|PsyCoLaus study, and all participants provided written informed consent.

2.2. Sleep assessment

Participants underwent PSG 0.8 ± 0.9 years after cognitive assessment. Sleep stages and arousals were scored according to the AASM 2007 criteria [12], and respiratory events according to the AASM 2012 criteria [13]. PLMS were scored according to the World Association of Sleep Medicine/International Restless Legs Syndrome Study Group (WASM/IRLSSG) 2006 recommendations [14] (**Supplemental methods**). We examined PLMS index (PLMI) and PLMS arousal index (PLMAI) using the following categories (roughly tertiles) [10]: PLMI <5/h (reference), 5–29.9/h, ≥30/h; and PLMAI <1/h (reference), 1–4.9/h, ≥5/h. RLS was retained if the participant reported an urge to move the legs that (i) worse during periods of rest or inactivity, (ii) was partially or totally relieved by movement, and (iii) worse in the evening or night than during the day or only occur in the evening or night. IRLSSG rating scale was administered to participants who met criteria for RLS.

2.3. Cognitive assessment

The cognitive assessment included the Mini-Mental State Examination (MMSE; global cognition), Stroop test Victoria version dot condition and word condition (processing speed), Stroop test Victoria version color-word condition (executive function), phonemic and semantic fluency (executive control and verbal ability), Free and Cued Selective Reminding Test (FCSRT) free recall and total recall (episodic verbal memory), DO-40 naming test (language), and constructional praxis task from the Consortium to Establish a Registry for Alzheimer's Disease (CERAD; visuospatial function). Cognitive scores were analyzed as continuous variables, except for the scores with a skewed distribution (MMSE, FCSRT total recall, DO-40 naming test, and CERAD constructional praxis task), which were dichotomized according to the lowest 10th percentile (**Supplemental methods** and Table S1) [15].

2.4. Clinical assessment

Education was dichotomized into ≥ high school (high school or university) vs. <high school (mandatory or apprenticeship). Body mass index (BMI) was calculated as weight/height [2]. Diabetes was defined as fasting blood glucose ≥7 mmol/L and/or antidiabetics use. Hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg and/or antihypertensive drug use. Smoking status was dichotomized into current or former smoker vs. never smoked. Excessive alcohol consumption was defined as ≥14 units/week. Depression was defined as a remitted or current major depressive disorder according to the DSM-IV criteria. Psychotropic medication was defined as using hypnotics, benzodiazepines or derivates, antidepressants, or neuroleptics. Participants were dichotomized into ApoE4 carriers vs. non-carriers (**Supplemental methods**).

2.5. Statistical analysis

Participant characteristics were compared between PLMI categories using independent T-test, Mann-Whitney test, or chi-squared test. Cross-sectional associations between PLMI and cognitive scores were tested using multivariate linear or logistic regression models. Models were unadjusted and then minimally adjusted for age, sex, and education. The fully adjusted models were additionally adjusted for other variables potentially affecting cognitive functioning: BMI, diabetes, hypertension, smoking, alcohol consumption, depression, psychotropic medication, and apnea-hypopnea index. Sensitivity analyses tested: (i) associations between PLMAI and cognitive scores, as well as associations between PLMI, PLMAI and cognitive scores (ii) after excluding 73 participants without ApoE genotype and including ApoE4 status as a confounder in the models, given its association with poorer cognitive functioning, even in older adults without dementia [16], and (iii) after further exclusion of 22 participants using antidepressants (because this medication class affects both PLMS severity and cognitive functioning). A description of how missing data were handled is provided in the **Supplemental methods**. The significance level was set at two-sided $p < 0.05$. Analyses were performed with SPSS version 26 (IBM Corp., Armonk, USA).

3. Results

3.1. Sample characteristics

The sample consisted of 579 participants aged 71.5 ± 4.4 years (range: 65–83 years), of whom 263 (45.4%) were men (Table 1). Compared with participants with PLMI <5/h, those in the high-PLMI categories were more likely to be men, less likely to be current or former smokers, had higher total sleep time, stage N2, arousal index, PLMI in the different sleep stages, and PLMAI, as well as lower rapid eye movement (REM) sleep.

3.2. Associations between PLMI and cognitive functioning

There were no significant associations between PLMI severity and cognitive scores (Table 2).

3.3. Sensitivity analyses

We found no significant association between PLMAI severity and cognitive scores (Table S2). All results were unchanged when excluding participants without ApoE genotype and including ApoE4 status in the models (Tables S3–S4) and after further exclusion of participants using

Table 1
Characteristics of the sample.

	Whole sample	PLMI <5/h	PLMI 5–29.9/h	PLMI ≥30/h	Test	*p*
Participants, n (%)	579 (100)	223 (38.5)	185 (32.0)	171 (29.5)		
Sociodemographic characteristics						
Age, years	71.5 ± 4.4	71.4 ± 4.5	71.1 ± 4.1	71.9 ± 4.5	F = 1.7	0.172
Men, n (%)	263 (45.4)	95 (42.6)	69 (37.3)	99 (57.9)[a,b]	χ^2 = 16.4	**<0.001**
Education (≥high school), n (%)	243 (42.0)	82 (36.8)	81 (43.8)	80 (46.8)	χ^2 = 4.3	0.114
Clinical characteristics						
ApoE4 carriers, n (%)[†]	115 (19.9)	46 (20.6)	34 (18.4)	35 (20.5)	χ^2 = 0.3	0.840
BMI, kg/m^2	26.9 ± 4.6	26.6 ± 4.7	27.0 ± 4.3	27.2 ± 4.8	F = 23.6	0.329
Diabetes, n (%)	105 (18.1)	36 (16.1)	35 (18.9)	34 (19.9)	χ^2 = 1.0	0.599
Hypertension, n (%)	393 (67.9)	145 (65.0)	127 (68.6)	121 (70.8)	χ^2 = 1.5	0.464
Smoking, n (%)	334 (57.7)	142 (63.7)	94 (50.8)[a]	98 (57.3)	χ^2 = 6.8	**0.032**
Alcohol (≥14 units/week), n (%)	99 (17.7)	34 (15.2)	27 (14.6)	38 (22.2)	χ^2 = 4.5	0.104
Depression, n (%)	202 (34.9)	84 (27.7)	61 (33.0)	57 (33.3)	χ^2 = 1.2	0.538
Psychotropic medication, n (%)	124 (21.4)	50 (22.4)	37 (20.0)	37 (21.6)	χ^2 = 0.4	0.836
RLS, n (%)	94 (16.2)	30 (13.5)	30 (16.2)	34 (19.9)	χ^2 = 2.9	0.230
IRLSSG rating scale ≥11, n (%)	67 (11.6)	20 (9.0)	21 (11.4)	26 (15.2)	χ^2 = 3.6	0.158
Sleep characteristics						
Total sleep time, min	386.4 ± 75.4	375.0 ± 80.1	399.1 ± 67.3[a]	387.7 ± 75.3	F = 5.2	**0.005**
Stage N1, %	14.0 ± 9.0	14.4 ± 10.9	12.9 ± 6.9	14.5 ± 8.5	F = 1.8	0.170
Stage N2, %	49.6 ± 12.1	47.8 ± 12.6	49.8 ± 11.4	51.6 ± 11.9[a]	F = 4.8	**0.009**
Stage N3, %	16.8 ± 8.7	17.6 ± 9.6	17.0 ± 7.5	15.6 ± 8.6	F = 2.7	0.065
REM sleep, %	19.6 ± 6.9	20.1 ± 7.1	20.2 ± 6.4	18.3 ± 6.9[a,b]	F = 4.5	**0.011**
Arousal index, events/h	22.7 [16.2, 31.7]	19.8 [14.3, 26.1]	22.5 [17.4, 29.3][a]	27.0 [19.9, 39.3][a,b]	H = 42.2	**<0.001**
AHI, events/h	15.7 [7.4, 28.9]	16.5 [7.8, 31.1]	14.4 [7.2, 26.6]	18.9 [7.2, 29.8]	H = 0.9	0.642
PLMI, events/h	12.3 [0.0, 36.9]	0.0 [0.0, 0.8]	15.9 [9.8, 21.3]	54.4 [41.0, 78.3]		
PLMI (stage N1), event/h	11.6 [0.0, 38.3]	0.0 [0.0, 0.0]	17.3 [7.7, 28.6][a]	53.3 [33.7, 84.3][a,b]	H = 446.0	**<0.001**
PLMI (stage N2), event/h	14.3 [0.0, 43.1]	0.0 [0.0, 0.3]	18.6 [10.7, 27.3][a]	64.1 [47.3, 91.5][a,b]	H = 508.6	**<0.001**
PLMI (stage N3), event/h	0.6 [0.0, 42.8]	0.0 [0.0, 0.0]	9.7 [0.0, 28.7][a]	74.6 [37.8, 120.0][a,b]	H = 369.0	**<0.001**
PLMI (REM sleep), event/h	0.0 [0.0, 5.6]	0.0 [0.0, 0.0]	0.0 [0.0, 4.2][a]	9.2 [1.8, 30.3][a,b]	H = 223.1	**<0.001**
PLMAI, events/h	1.3 [0.0, 5.2]	0.0 [0.0, 0.0]	2.9 [1.1, 5.0][a]	7.5 [2.7, 13.5][a,b]	H = 320.5	**<0.001**

Data are presented as mean ± standard deviation, median [interquartile range] or number of participants (%). Data were analyzed using analysis of variance (F), Kruskal-Wallis test (H), or chi-squared test (χ^2). [†]Missing data (whole sample: n = 73; PLMI <5/h: n = 27; PLMI 5–29.9/h: n = 24; PLMI ≥30/h: n = 22). [a]Significant difference compared with PLMI <5/h. [b]Significant difference compared with PLMI 5–29.9/h. Significant p-values are highlighted in bold (<0.05). Abbreviations: AHI = apnea-hypopnea index; ApoE4 = apolipoprotein E4; BMI = body mass index; IRLSSG = International Restless Legs Syndrome Study Group; PLMI = periodic leg movement index; PLMAI = periodic leg movement arousal index; REM = rapid eye movement; RLS = restless legs syndrome.

antidepressants (Tables S5–S6).

4. Discussion

To our knowledge, this is the first study assessing the cross-sectional association between PLMS and cognitive functioning in the older general population. We found no association between PLMS severity and cognitive performance, suggesting that PLMS may be unrelated to cross-sectional cognitive functioning in the older general population.

Although pathophysiological arguments suggest that PLMS may be related to consequences on brain health [3–6], limited research on the relationship between PLMS and cognitive functioning exists [8–10] and results are conflicting. In the study by Scullin et al., a higher PLMI was associated with lower executive function among 34 Parkinson's disease patients (age: 62.4 ± 8.5 years) [8]. However, the longitudinal study by Bugalho et al., which included 25 Parkinson's disease patients (age: 66.6 ± 9.4 years) failed to find an association between PLMI and changes in the Montreal Cognitive Assessment score [9]. The study by Leng et al., conducted among 2636 community-dwelling older men (age: 76.0 ± 5.0 years), examined associations between PLMI, PLMAI, and longitudinal changes in the Trail Making Test Part B and Modified Mini-Mental State examination [10]. Compared with participants in the reference group (PLMI <5/h), those with a PLMI ≥30/h showed a greater decline in the Trail Making Test Part B[10].

It is challenging to compare our study with previous works [8–10], given the differences in sample characteristics, study design, and cognitive measures. The study by Leng et al. is partly comparable to our study given that it was conducted in a sample from the general population; however, substantial differences exist and may explain the contrasting results, such as the sample characteristics (only men [10] vs. men and women), study design (longitudinal [10] vs. cross-sectional), PLMS scoring (using piezoelectric sensor [10] vs. EMG), and cognitive outcomes.

The present study has some strengths, including analyses performed on a large sample of community-dwelling older adults, scoring of PLMS based on the gold standard PSG/EMG, analysis of an extensive cognitive test battery, and adjustment of analyses for multiple confounders. Limitations were the single assessment of sleep, as studies have reported a certain night-to-night variability in the assessment of PLMS [17]. The inability to determine the time of PLMS occurrence could also be indicated as a limitation, given that disease duration may play a role on the association between sleep disorders and brain health [18]. Although there was a delay between PSG and cognitive assessment, which could also be considered a limitation of the study, we believe that this does not represent a major problem in the present analysis, given that PLMS is a chronic condition that is unlikely to disappear or show major changes within a few months [19]. Finally, other parameters, such as periodicity or time distribution of PLMS throughout the night should be explored in future studies [20].

In conclusion, this study suggests that PLMS are unrelated to cross-sectional cognitive functioning in the older general population. However, given the paucity of data in this field, further studies are needed to clarify the relationship between PLMS and brain health.

Table 2
Associations between periodic leg movement index (PLMI) severity and cognitive functioning.

	Unadjusted		Minimally adjusted		Fully adjusted	
	B (95% CI)	p	*B* (95% CI)	p	*B* (95% CI)	p
Phonemic fluency						
PLMI 5–29.9/h	0.03 (−1.59, 1.66)	0.968	−0.33 (−1.87, 1.22)	0.678	−0.40 (−1.95, 1.15)	0.609
PLMI ≥30/h	0.02 (−1.59, 1.64)	0.980	−0.04 (−1.62, 1.53)	0.959	−0.09 (−1.66, 1.49)	0.915
Semantic fluency						
PLMI 5–29.9/h	0.17 (−1.57, 1.85)	0.840	−0.19 (−1.81, 1.42)	0.814	−0.22 (−1.85, 1.40)	0.788
PLMI ≥30/h	0.14 (−1.52, 1.87)	0.870	−0.05 (−1.70, 1.59)	0.951	−0.05 (−1.69, 1.61)	0.957
FCSRT free recall						
PLMI 5–29.9/h	0.01 (−1.32, 1.33)	0.992	−0.34 (−1.56, 0.88)	0.583	−0.46 (−1.68, 0.77)	0.464
PLMI ≥30/h	−0.45 (−1.77, 0.90)	0.522	−0.19 (−1.44. 1.06)	0.764	−0.30 (−1.56, 0.95)	0.635
Stroop dot condition						
PLMI 5–29.9/h	−1.15 (−3.62, 1.33)	0.365	−0.89 (−3.36, 1.58)	0.480	−1.09 (−3.59, 1.39)	0.388
PLMI ≥30/h	2.08 (−0.45, 4.61)	0.107	1.89 (−0.65, 4.43)	0.144	1.60 (−0.95, 4.16)	0.220
Stroop word condition						
PLMI 5–29.9/h	−1.32 (−4.97, 2.32)	0.478	−0.87 (−4.49, 2.74)	0.636	−1.41 (−5.06, 2.24)	0.450
PLMI ≥30/h	2.61 (−1.10, 6.33)	0.168	2.45 (−1.25, 6.17)	0.195	1.95 (−1.78, 5.69)	0.306
Stroop color-word condition						
PLMI 5–29.9/h	−2.44 (−7.60, 2.72)	0.355	−1.79 (−6.91, 3.32)	0.491	−2.32 (−7.49, 2.84)	0.379
PLMI ≥30/h	2.21 (−3.04, 7.47)	0.410	2.15 (−3.10, 7.41)	0.422	1.67 (−3.62, 6.98)	0.535
	OR (95% CI)	***p***	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***
MMSE ≤27 points						
PLMI 5–29.9/h	0.88 (0.44, 1.77)	0.730	1.04 (0.51, 2.11)	0.923	0.95 (0.45, 1.96)	0.885
PLMI ≥30/h	1.01 (0.51, 1.99)	0.983	1.01 (0.50, 2.04)	0.980	0.90 (0.44, 1.87)	0.787
FCSRT total recall ≤42 points						
PLMI 5–29.9/h	0.63 (0.32, 1.25)	0.187	0.67 (0.33, 1.35)	0.269	0.68 (0.33, 1.39)	0.294
PLMI ≥30/h	0.61 (0.30, 1.22)	0.166	0.54 (0.26, 1.12)	0.100	0.55 (0.26, 1.16)	0.118
DO-40 naming test ≤39 points						
PLMI 5–29.9/h	1.15 (0.66, 1.98)	0.627	1.19 (0.69, 2.08)	0.525	1.14 (0.64, 2.01)	0.655
PLMI ≥30/h	0.60 (0.32, 1.13)	0.115	0.59 (0.31, 1.13)	0.113	0.57 (0.29, 1.08)	0.095
CERAD constructional praxis task ≤9 points						
PLMI 5–29.9/h	0.86 (0.47, 1.56)	0.612	0.90 (0.49, 1.66)	0.748	0.84 (0.45, 1.75)	0.592
PLMI ≥30/h	0.89 (0.48, 1.62)	0.697	0.97 (0.52, 1.80)	0.927	0.92 (0.48, 1.75)	0.798

Data are presented as unstandardized beta coefficient (*B*) or odds ratio (OR) with respective 95% confidence interval (CI) against the reference group (PLMI <5/h). Data were analyzed by linear or logistic regression models using cognitive scores as dependent variable and PLMI as independent variable. Minimally adjusted: adjusted for age (continuous), sex (men vs. women), and education (≥high school vs. <high school). Fully adjusted: additionally adjusted for body mass index (continuous), diabetes (presence vs. absence), hypertension (presence vs. absence), smoking (current or former vs. never), alcohol (≥14 vs. <14 units/week), depression (presence vs. absence), psychotropic medication (presence vs. absence), and apnea-hypopnea index (continuous). Abbreviations: CERAD = Consortium to Establish a Registry for Alzheimer's Disease; FCSRT = Free and Cued Selective Reminding Test; MMSE = Mini-Mental State Examination.

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CRediT authorship contribution statement

Nicola Andrea Marchi: Conceptualization, Methodology, Formal analysis, Writing – original draft. **Arton Peci:** Conceptualization, Methodology, Formal analysis, Writing – original draft. **José Haba-Rubio:** Conceptualization, Data curation, Writing – review & editing. **Geoffroy Solelhac:** Writing – review & editing. **Virginie Bayon:** Writing – review & editing. **Mathieu Berger:** Writing – review & editing. **Peter Vollenweider:** Data curation, Writing – review & editing. **Pedro Marques-Vidal:** Data curation, Writing – review & editing. **Armin von Gunten:** Data curation, Writing – review & editing. **Marie-Pierre Françoise Strippoli:** Data curation, Writing – review & editing. **Martin Preisig:** Data curation, Writing – review & editing. **Bogdan Draganski:** Data curation, Writing – review & editing. **Raphael Heinzer:** Conceptualization, Data curation, Writing – review & editing, Supervision.

Declaration of competing interest

No conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sleep.2023.07.011.

References

[1] Haba-Rubio J, Marti-Soler H, Tobback N, et al. Clinical significance of periodic limb movements during sleep: the HypnoLaus study. Sleep Med 2018;41:45–50. https://doi.org/10.1016/j.sleep.2017.09.014.
[2] Haba-Rubio J, Marti-Soler H, Marques-Vidal P, et al. Prevalence and determinants of periodic limb movements in the general population. Ann Neurol 2016;79(3):464–74. https://doi.org/10.1002/ana.24593.
[3] Ferri R, Rundo F, Zucconi M, et al. An evidence-based analysis of the association between periodic leg movements during sleep and arousals in restless legs syndrome. Sleep 2015;38(6):919–24. https://doi.org/10.5665/sleep.4740.
[4] Ferri R, Zucconi M, Rundo F, Spruyt K, Manconi M, Ferini-Strambi L. Heart rate and spectral EEG changes accompanying periodic and non-periodic leg movements during sleep. Clin Neurophysiol 2007;118(2):438–48. https://doi.org/10.1016/j.clinph.2006.10.007.

[5] Pennestri MH, Montplaisir J, Fradette L, Lavigne G, Colombo R, Lanfranchi PA. Blood pressure changes associated with periodic leg movements during sleep in healthy subjects. Sleep Med 2013;14(6):555–61. https://doi.org/10.1016/j.sleep.2013.02.005.
[6] Pizza F, Biallas M, Wolf M, Valko PO, Bassetti CL. Periodic leg movements during sleep and cerebral hemodynamic changes detected by NIRS. Clin Neurophysiol 2009;120(7):1329–34. https://doi.org/10.1016/j.clinph.2009.05.009.
[7] Drakatos P, Olaithe M, Verma D, et al. Periodic limb movements during sleep: a narrative review. J Thorac Dis 2021;13(11):6476–94. https://doi.org/10.21037/jtd-21-1353.
[8] Scullin MK, Fairley JA, Trotti LM, Goldstein FC, Factor SA, Bliwise DL. Sleep correlates of trait executive function and memory in Parkinson's disease. J Parkinsons Dis 2015;5(1):49–54. https://doi.org/10.3233/JPD-140475.
[9] Bugalho P, Ladeira F, Barbosa R, et al. Polysomnographic predictors of sleep, motor and cognitive dysfunction progression in Parkinson's disease: a longitudinal study. Sleep Med 2021;77:205–8. https://doi.org/10.1016/j.sleep.2020.06.020.
[10] Leng Y, Blackwell T, Stone KL, Hoang TD, Redline S, Yaffe K. Periodic limb movements in sleep are associated with greater cognitive decline in older men without dementia. Sleep 2016;39(10):1807–10. https://doi.org/10.5665/sleep.6158.
[11] Preisig M, Waeber G, Vollenweider P, et al. The PsyCoLaus study: methodology and characteristics of the sample of a population-based survey on psychiatric disorders and their association with genetic and cardiovascular risk factors. BMC Psychiatr 2009;9:9. https://doi.org/10.1186/1471-244X-9-9.
[12] Iber C, Ancoli-Israel S, Chesson A, Quan S. The AASM manual for the scoring of sleep and associated events: rules terminology and technical specifications. 2007. Published online.
[13] Berry RB, Budhiraja R, Gottlieb DJ, et al. Rules for scoring respiratory events in sleep: update of the 2007 AASM manual for the scoring of sleep and associated events. Deliberations of the sleep apnea definitions task force of the American academy of sleep medicine. J Clin Sleep Med 2012;8(5):597–619. https://doi.org/10.5664/jcsm.2172.
[14] Zucconi M, Ferri R, Allen R, et al. The official World Association of Sleep Medicine (WASM) standards for recording and scoring periodic leg movements in sleep (PLMS) and wakefulness (PLMW) developed in collaboration with a task force from the International Restless Legs Syndrome Study Group (IRLSSG). Sleep Med 2006;7(2):175–83. https://doi.org/10.1016/j.sleep.2006.01.001.
[15] Marchi NA, Berger M, Solelhac G, et al. Obstructive sleep apnea and cognitive functioning in the older general population: the moderating effect of age, sex, ApoE4, and obesity. J Sleep Res June 13, 2023:e13938. https://doi.org/10.1111/jsr.13938. Published online.
[16] Bondi MW, Salmon DP, Monsch AU, et al. Episodic memory changes are associated with the APOE-epsilon 4 allele in nondemented older adults. Neurology 1995;45(12):2203–6. https://doi.org/10.1212/wnl.45.12.2203.
[17] Sforza E, Haba-Rubio J. Night-to-night variability in periodic leg movements in patients with restless legs syndrome. Sleep Med 2005;6(3):259–67. https://doi.org/10.1016/j.sleep.2004.11.006.
[18] Ferri R, Cosentino FII, Moussouttas M, et al. Silent cerebral small vessel disease in restless legs syndrome. Sleep 2016;39(7):1371–7. https://doi.org/10.5665/sleep.5966.
[19] Gehrman P, Stepnowsky C, Cohen-Zion M, Marler M, Kripke DF, Ancoli-Israel S. Long-term follow-up of periodic limb movements in sleep in older adults. Sleep 2002;25(3):340–3. https://doi.org/10.1093/sleep/25.3.340.
[20] Ferri R. The time structure of leg movement activity during sleep: the theory behind the practice. Sleep Med 2012;13(4):433–41. https://doi.org/10.1016/j.sleep.2011.10.027.

SUPPLEMENTAL MATERIAL

Periodic leg movements during sleep and cognitive functioning in the older general population

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SUPPLEMENTAL METHODS

Cognitive assessment

- Mini-Mental State Examination (MMSE)[1]. This test assessed global cognitive functioning. It includes subtests of orientation, registration and recall of words, attention and calculation, language, and constructional praxis. The score ranges from 0 to 30.
- Free and Cued Selective Reminding Test (FCSRT)[2]. This test evaluates episodic verbal memory. Participants were asked to learn 16 words with each corresponding cue provided verbally by the tester (e.g., "fish" is the cue for the word "herring"). Initially, participants were asked to recall the words immediately after reading them. Then, three recall trials separated from each other by a distractive task (mental calculation for 20 seconds) were successively performed, from which a free recall score and a total recall score were recorded. A delayed recall of the list was also requested 20 minutes later. In our analyses, we considered two measures: free recall score and total recall score (the latter was calculated as the free recall score + number of correct cued recall). For these measures, scores ranged from 0 to 48.
- Verbal fluency tasks[3]. This test evaluates executive control and verbal ability. Participants were asked to verbally generate as many words beginning with the letter "P" as possible in a 2-minute period (phonemic verbal fluency). Then, participants were instructed to generate examples of animals in a 2-minute period (semantic verbal fluency). Proper names were scored as incorrect. The score represented the number of correct words.
- DO-40 naming test (French adaptation of the Boston naming test)[4]. This test evaluates confrontational word retrieval. Participants were asked to name 40 pictures. The score ranges from 0 to 40.
- Constructional praxis task from the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropsychological test battery[5]. This task evaluates visuospatial and visuoconstructive ability. The task involved the copying of four figures of increasing complexity (circle, diamond, overlapping rectangles, and Necker cube). The score ranges from 0 to 11.
- Stroop test Victoria version[6]. This test evaluates processing speed and attentional control (executive function). Twenty-four stimuli were presented to participants. Participants were asked to name the color of the stimuli as quickly as possible. In the "dot condition", colored dots were presented. In the "word condition", colored words were presented. In the "color-word condition", the words *blue*, *green*, *yellow*, and *red* were written in one of the three other colors (e.g., the word *green* was written in yellow ink). In our analyses, we considered the time (seconds) required to complete each task so that a higher time corresponded to a lower performance.

Sleep assessment

During a visit at the Center for Investigation and Research in Sleep (Lausanne University Hospital, Switzerland), trained technicians equipped the subjects with the polysomnographic (PSG) recorder (Titanium, Embla® Flaga, Reykjavik, Iceland) between 5 and 8 PM. Sleep recordings took place in the participants' home environment and included a total of 18 channels, in accordance with 2007 American Academy of Sleep Medicine (AASM) recommended setup specifications[7]: six electroencephalography, two electrooculography, three surface electromyography (one submental, two for right and left anterior tibialis muscles), one for electrocardiogram, nasal pressure, thoracic and abdominal belts, body position, oxygen saturation, and pulse rate. All PSG recordings were visually scored by two trained sleep technicians using Somnologica software (Version 5.1.1, by Embla® Flaga, Reykjavik, Iceland) and reviewed by a trained sleep physician. Random quality checks were performed by a second sleep physician. PLMS were scored according to the World Association of Sleep Medicine/International Restless Legs Syndrome Study Group (WASM/IRLSSG) 2006 recommendations[8]: duration of the leg movement (LM) between 0.5 and 10 seconds; minimum amplitude >8μV in voltage above resting electromyography (EMG); end of the event when the EMG decreased to <2μV above the resting level and remained below that value for 0.5 seconds; interval between 5 and 90 seconds between LM onsets; movements had to be part of a series of ≥4 consecutive movements meeting these criteria; LMs on two different legs separated by <5 seconds between movement onsets were counted as a single LM; LMs were not scored as PLMS if occurring at the end (±0.5 seconds) of a respiratory

event; and arousals and PLMS were considered associated if there were <0.5 sec between the end of one event and the onset of the other, regardless of which was first.

Genotyping

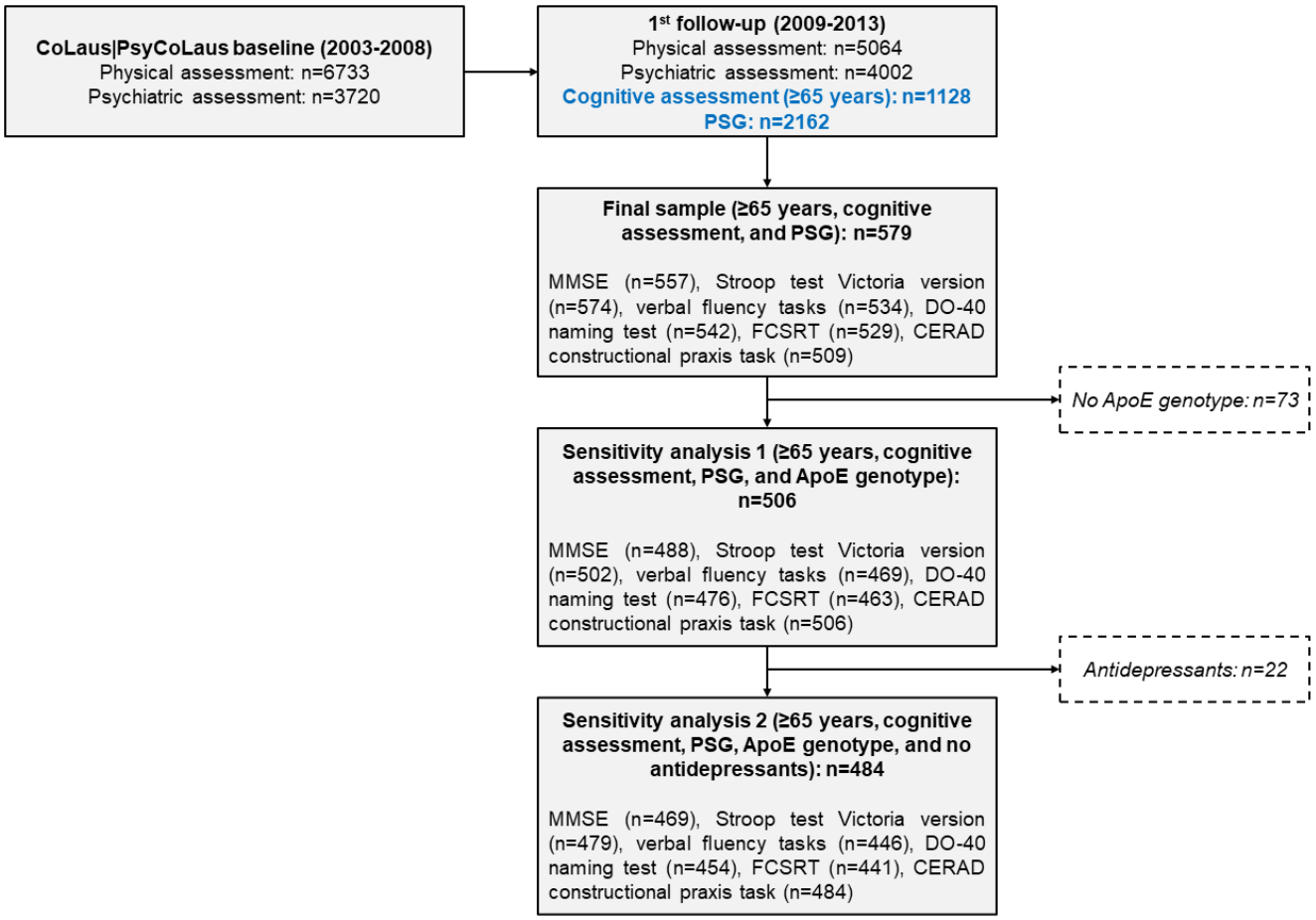
Genome-wide genotyping was performed using the Affymetrix 500K SNP array. Nuclear DNA was extracted from the whole blood of all participants. Genotypes were called using BRLMM (http://www.affymetrix.com/support/technical/whitepapers/brlmm_whitepap). Subjects were excluded from the analysis if there was inconsistency between sex and genetic data, a genotype call rate <90%, or inconsistencies of genotyping results in duplicate samples. Quality control for single nucleotide polymorphisms was performed using the following criteria: monomorphic (or with minor allele frequency <1%), call rates <90%, deviation from the Hardy-Weinberg equilibrium ($p < 1x10^{-6}$). Phased haplotypes were generated using SHAPEIT2[9,10]. Imputation was performed using minimac3[11] and the Haplotype Reference Consortium (HRC version r1.1)[12] hosted on the Michigan Imputation Server[11].

Handling of missing data

- Sleep data: no missing data.
- Cognitive data: analysis restricted to records with available data (**Figure S1**).
- Confounders:
    - Body mass index (n=4) and hypertension (n=1) missing data were replaced by data recorded at baseline of the CoLaus|PsyCoLaus study.
    - ApoE genotype (n=73): sensitivity analysis in the subsample with ApoE genotype (**Tables S3-S5**).

SUPPLEMENTAL FIGURES

Figure S1. Flowchart of the study population.



Abbreviations: ApoE = apolipoprotein E; CERAD = Consortium to Establish a Registry for Alzheimer's Disease; FCSRT = Free and Cued Selective Reminding Test; MMSE = Mini-Mental State Examination; PSG = polysomnography.

SUPPLEMENTAL TABLES

Table S1. Cognitive assessment.

Cognitive domain	Test	Task	Outcome
Global cognitive function	MMSE[1]	Complete subtests of orientation, registration and recall of words, attention and calculation, language and constructional praxis	Dichotomized: ≤27 points (=poorer performance; n=52/557, 9.3%) vs. 28-30 points
Processing speed	Stroop test Victoria version[6]	Dot condition: name the color (blue, green, yellow, red) of dots as quickly as possible	Continuous: time in seconds (higher time = poorer performance)
		Word condition: name the color of neutral words quickly as possible	Continuous: time in seconds (higher time = poorer performance)
Executive function	Stroop test Victoria version[6]	Color-word condition: name the color of words *blue*, *green*, *yellow* and *red* written in one of the three other colors as quickly as possible	Continuous: time in seconds (higher time = poorer performance)
	Verbal fluency tasks	Phonemic fluency: give as many words beginning with the letter "P" as possible in a 2-minute period	Continuous: number of words (lower number = poorer performance)
		Semantic fluency: give as many examples of "animals" as possible in a 2-minute period	Continuous: number of words (lower number = poorer performance)
Language	DO-40 naming test[4]	Name 40 pictures	Dichotomized: ≤39 words (=poorer performance; n=77/542, 14.2%) vs. 40 words
Episodic verbal memory	FCSRT[2]	Free recall: recall as many words as possible during the three recall trials	Continuous: 0 to 48 points (lower number = poorer performance)
		Total recall: free recall + correct cued recall for words that were not recalled during the free recall	Dichotomized: ≤42 words (=poorer performance; n=53/529, 10.0%) vs. 43-48 words
Visuospatial function	CERAD constructional praxis task[5]	Copy of four figures of increasing complexity (circle, diamond, overlapping rectangles, and Necker cube)	Dichotomized: ≤9 points (=poorer performance; n=70/509, 12.1%) vs. 10-11 points

Abbreviations: CERAD = Consortium to Establish a Registry for Alzheimer's Disease; FCSRT = Free and Cued Selective Reminding Test; MMSE = Mini-Mental State Examination.

Table S2. Associations between periodic leg movement arousal index (PLMAI) severity and cognitive functioning (n=579).

	Unadjusted		**Minimally adjusted**		**Fully adjusted**	
	***B* (95% CI)**	***p***	***B* (95% CI)**	***p***	***B* (95% CI)**	***p***
Phonemic fluency						
PLMAI 1-4.9/h	0.55 (-1.07, 2.18)	0.504	0.19 (-1.38, 1.75)	0.816	0.16 (-1.39, 1.72)	0.837
PLMAI ≥5/h	-0.05 (-1.67, 1.56)	0.949	-0.22 (-1.77, 1.33)	0.784	-0.39 (-1.96, 1.18)	0.629
Semantic fluency						
PLMAI 1-4.9/h	1.43 (-0.27, 3.14)	0.101	1.10 (-0.54, 2.73)	0.188	1.11 (-0.51, 2.75)	0.180
PLMAI ≥5/h	0.57 (-1.12, 2.26)	0.511	0.32 (-1.30, 1.95)	0.696	0.23 (-1.41, 1.87)	0.783
FCSRT free recall						
PLMAI 1-4.9/h	0.52 (-0.81, 1.86)	0.442	0.12 (-1.12, 1.36)	0.855	0.05 (-1.18, 1.28)	0.937
PLMAI ≥5/h	0.81 (-0.52, 2.13)	0.233	0.82 (-0.42, 2.05)	0.194	0.61 (-0.64, 1.85)	0.337
Stroop dot condition						
PLMAI 1-4.9/h	-0.98 (-3.50, 1.54)	0.447	-0.71 (-3.21, 1.80)	0.581	-0.95 (-3.45, 1.57)	0.461
PLMAI ≥5/h	0.48 (-2.04, 3.00)	0.707	0.45 (-2.05, 2.96)	0.723	0.25 (-2.30, 2.81)	0.846
Stroop word condition						
PLMAI 1-4.9/h	0.03 (-3.67, 3.73)	0.988	0.49 (-3.17, 4.15)	0.794	0.04 (-3.64, 3.72)	0.983
PLMAI ≥5/h	0.75 (-2.96, 4.45)	0.693	0.81 (-2.86, 4.48)	0.665	0.62 (-3.13, 4.37)	0.745
Stroop color-word condition						
PLMAI 1-4.9/h	0.26 (-4.96, 5.49)	0.921	0.91 (-4.27, 6.09)	0.731	0.47 (-4.74, 5.67)	0.860
PLMAI ≥5/h	-0.43 (-5.67, 4.81)	0.872	-0.24 (-5.44, 4.95)	0.926	-0.36 (-5.67, 4.95)	0.894
	OR (95% CI)	***p***	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***
MMSE ≤27 points						
PLMAI 1-4.9/h	0.69 (0.33, 1.42)	0.318	0.76 (0.36, 1.60)	0.476	0.68 (0.32, 1.46)	0.323
PLMAI ≥5/h	0.83 (0.41, 1.65)	0.591	0.87 (0.43, 1.77)	0.707	0.74 (0.36, 1.55)	0.429
FCSRT total recall ≤42 points						
PLMAI 1-4.9/h	0.84 (0.42, 1.65)	0.604	0.92 (0.45, 1.84)	0.804	0.91 (0.45, 1.85)	0.788
PLMAI ≥5/h	0.63 (0.30, 1.30)	0.211	0.62 (0.29, 1.31)	0.212	0.62 (0.29, 1.34)	0.227
DO-40 naming test ≤39 points						
PLMAI 1-4.9/h	0.69 (0.37, 1.29)	0.247	0.71 (0.38, 1.33)	0.285	0.68 (0.36, 1.29)	0.239
PLMAI ≥5/h	1.03 (0.59, 1.81)	0.905	1.06 (0.60, 1.88)	0.834	1.04 (0.57, 1.87)	0.895
CERAD constructional praxis task ≤9 points						
PLMAI 1-4.9/h	0.67 (0.35, 1.29)	0.238	0.70 (0.36, 1.35)	0.293	0.67 (0.34, 1.33)	0.252
PLMAI ≥5/h	1.06 (0.59, 1.90)	0.833	1.15 (0.64, 2.07)	0.639	1.28 (0.69, 2.39)	0.435

Data are presented as unstandardized beta coefficient (*B*) or odds ratio (OR) with respective 95% confidence interval (CI) against the reference group (PLMAI <1/h). Data were analyzed by linear or logistic regression models using cognitive scores as dependent variable and PLMAI as independent variable. Minimally adjusted: adjusted for age (continuous), sex (men vs. women), and education (≥high school vs. <high school). Fully adjusted: additionally adjusted for body mass index (continuous), diabetes (presence vs. absence), hypertension (presence vs. absence), smoking (current or former vs. never), alcohol (≥14 vs. <14 units/week), depression (presence vs. absence), psychotropic medication (presence vs. absence), and apnea-hypopnea index (continuous). Abbreviations: CERAD = Consortium to Establish a Registry for Alzheimer's Disease; FCSRT = Free and Cued Selective Reminding Test; MMSE = Mini-Mental State Examination.

Table S3. Associations between periodic leg movement index (PLMI) severity and cognitive functioning (sensitivity analysis after the exclusion of participants without ApoE genotype and adding an adjustment for ApoE4 status in the minimally adjusted model; n=506).

	Unadjusted		**Minimally adjusted**		**Fully adjusted**	
	***B* (95% CI)**	***p***	***B* (95% CI)**	***p***	***B* (95% CI)**	***p***
Phonemic fluency						
PLMI 5-29.9/h	0.17 (-1.56, 1.90)	0.848	-0.25 (-1.92, 1.41)	0.767	-0.36 (-2.02, 1.30)	0.674
PLMI ≥30/h	-0.19 (-1.93, 1.55)	0.831	-0.24 (-1.93, 1.44)	0.775	-0.38 (-2.07, 1.31)	0.661
Semantic fluency						
PLMI 5-29.9/h	0.55 (-1.26, 2.37)	0.551	0.12 (-1.61, 1.85)	0.890	-0.02 (-1.75, 1.71)	0.983
PLMI ≥30/h	0.19 (-1.62, 2.02)	0.834	0.04 (-1.71, 1.79)	0.963	-0.06 (-1.82, 1.69)	0.945
FCSRT free recall						
PLMI 5-29.9/h	0.09 (-1.32, 1.49)	0.903	-0.32 (-1.61, 0.98)	0.631	-0.34 (-1.64, 0.96)	0.606
PLMI ≥30/h	-0.55 (-1.97, 0.86)	0.440	-0.30 (-1.62, 1.01)	0.653	-0.36 (-1.68, 0.96)	0.589
Stroop dot condition						
PLMI 5-29.9/h	-1.24 (-4.03, 1.55)	0.384	-0.86 (-3.62, 1.91)	0.545	-1.05 (-3.84, 1.73)	0.458
PLMI ≥30/h	2.16 (-0.69, 5.01)	0.137	2.02 (-0.82, 4.85)	0.163	1.73 (-1.12, 4.59)	0.235
Stroop word condition						
PLMI 5-29.9/h	-1.71 (-5.85, 2.41)	0.415	-1.02 (-5.10, 3.06)	0.624	2.26 (-1.94, 6.46)	0.292
PLMI ≥30/h	2.77(-1.43, 6.98)	0.196	2.69 (-1.47, 6.87)	0.205	-1.44 (-5.54, 2.67)	0.493
Stroop color-word condition						
PLMI 5-29.9/h	-2.62 (-8.43, 3.21)	0.380	-1.60 (-7.35, 4.14)	0.584	-2.17 (-7.95, 3.62)	0.463
PLMI ≥30/h	1.83 (-4.09, 7.76)	0.544	1.87 (-4.00, 7.75)	0.532	1.44 (-4.48, 7.36)	0.633
	OR (95% CI)	***p***	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***
MMSE ≤27 points						
PLMI 5-29.9/h	0.88 (0.43, 1.80)	0.725	1.09 (0.51, 2.29)	0.818	1.12 (0.52, 2.40)	0.776
PLMI ≥30/h	0.92 (0.44, 1.89)	0.818	0.95 (0.45, 1.99)	0.893	0.87 (0.40, 1.87)	0.724
FCSRT total recall ≤42 points						
PLMI 5-29.9/h	0.48 (0.22, 1.04)	0.084	0.53 (0.24, 1.16)	0.115	0.54 (0.24, 1.21)	0.134
PLMI ≥30/h	0.60 (0.29, 1.25)	0.179	0.56 (0.26, 1.22)	0.146	0.58 (0.27, 1.27)	0.177
DO-40 naming test ≤39 points						
PLMI 5-29.9/h	1.10 (0.62, 1.96)	0.739	1.15 (0.64, 2.05)	0.645	1.15 (0.64, 2.10)	0.640
PLMI ≥30/h	0.59 (0.30, 1.15)	0.121	0.59 (0.30, 1.16)	0.125	0.58 (0.29, 1.14)	0.115
CERAD constructional praxis task ≤9 points						
PLMI 5-29.9/h	0.93 (0.50, 1.73)	0.813	0.99 (0.52, 1.87)	0.988	0.98 (0.51, 1.89)	0.950
PLMI ≥30/h	0.90 (0.47, 1.70)	0.744	0.98 (0.51, 1.88)	0.954	0.97 (0.49, 1.91)	0.923

Data are presented as unstandardized beta coefficient (*B*) or odds ratio (OR) with respective 95% confidence interval (CI) against the reference group (PLMI <5/h). Data were analyzed by linear or logistic regression models using cognitive scores as dependent variable and PLMI as independent variable. Minimally adjusted: adjusted for age (continuous), sex (men vs. women), education (≥high school vs. <high school), and ApoE4 (carriers vs. non-carriers). Fully adjusted: additionally adjusted for body mass index (continuous), diabetes (presence vs. absence), hypertension (presence vs. absence), smoking (ex- or former vs. never), alcohol (≥14 vs. <14 units/week), depression (presence vs. absence), psychotropic medication (presence vs. absence), and apnea-hypopnea index (continuous). Abbreviations: ApoE4 = apolipoprotein E4; CERAD = Consortium to Establish a Registry for Alzheimer's Disease; FCSRT = Free and Cued Selective Reminding Test; MMSE = Mini-Mental State Examination.

Table S4. Associations between periodic leg movement arousal index (PLMAI) severity and cognitive functioning (sensitivity analysis after the exclusion of participants without ApoE genotype and adding an adjustment for ApoE4 status in the minimally adjusted model; n=506).

	Unadjusted		**Minimally adjusted**		**Fully adjusted**	
	***B* (95% CI)**	***p***	***B* (95% CI)**	***p***	***B* (95% CI)**	***p***
Phonemic fluency						
PLMAI 1-4.9/h	0.45 (-1.29, 2.19)	0.614	0.07 (-1.60, 1.75)	0.932	0.06 (-1.60, 1.73)	0.941
PLMAI ≥5/h	-0.06 (-1.80, 1.68)	0.947	-0.35 (-2.02, 1.32)	0.683	-0.56 (-2.25, 1.13)	0.514
Semantic fluency						
PLMAI 1-4.9/h	1.46 (-0.36, 3.28)	0.117	1.10 (-0.64, 2.85)	0.215	1.08 (-0.66, 2.82)	0.223
PLMAI ≥5/h	0.77 (-1.05, 2.59)	0.404	0.37 (-1.37, 2.11)	0.675	0.20 (-1.56, 1.96)	0.826
FCSRT free recall						
PLMAI 1-4.9/h	0.88 (-0.54, 2.29)	0.224	0.39 (-0.91, 1.70)	0.554	0.43 (-0.86, 1.73)	0.514
PLMAI ≥5/h	0.89 (-0.52, 2.30)	0.216	0.72 (-0.59, 2.02)	0.281	0.53 (-0.78, 1.86)	0.427
Stroop dot condition						
PLMAI 1-4.9/h	-1.00 (-3.84, 1.82)	0.486	-0.61 (-3.42, 2.19)	0.668	-0.88 (-3.69, 1.93)	0.540
PLMAI ≥5/h	0.81 (-2.04, 3.66)	0.578	1.12 (-1.70, 3.95)	0.437	0.93 (-1.94, 3.81)	0.525
Stroop word condition						
PLMAI 1-4.9/h	-0.03 (-4.12, 4.16)	0.990	0.61 (-3.51, 4.73)	0.771	0.17 (-3.96, 4.31)	0.934
PLMAI ≥5/h	0.66 (-3.56, 4.88)	0.759	1.30 (-2.86, 5.47)	0.540	1.16 (-3.08, 5.41)	0.590
Stroop color-word condition						
PLMAI 1-4.9/h	0.29 (-5.59, 6.17)	0.923	1.16 (-4.64, 6.96)	0.695	0.66 (-5.51, 6.48)	0.824
PLMAI ≥5/h	-0.47 (-6.41, 5.46)	0.876	0.50 (-5.36, 6.35)	0.868	0.42 (-5.55, 6.39)	0.890
	OR (95% CI)	***p***	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***
MMSE ≤27 points						
PLMAI 1-4.9/h	0.60 (0.27, 1.33)	0.213	0.68 (0.30, 1.52)	0.348	0.64 (0.27, 1.47)	0.296
PLMAI ≥5/h	0.92 (0.45, 1.86)	0.817	1.04 (0.50, 2.14)	0.921	0.95 (0.44, 2.01)	0.888
FCSRT total recall ≤42 points						
PLMAI 1-4.9/h	0.80 (0.39, 1.65)	0.544	0.90 (0.42, 1.92)	0.792	0.90 (0.42, 1.93)	0.788
PLMAI ≥5/h	0.58 (0.26, 1.29)	0.185	0.59 (0.26, 1.35)	0.215	0.58 (0.25, 1.35)	0.204
DO-40 naming test ≤39 points						
PLMAI 1-4.9/h	0.66 (0.35, 1.25)	0.206	0.67 (0.35, 1.28)	0.224	0.66 (0.38, 1.27)	0.213
PLMAI ≥5/h	0.87 (0.48, 1.59)	0.663	0.93 (0.51, 1.71)	0.823	0.94 (0.50, 1.77)	0.855
CERAD constructional praxis task ≤9 points						
PLMAI 1-4.9/h	0.61 (0.30, 1.22)	0.163	0.63 (0.31, 1.27)	0.198	0.61 (0.30, 1.27)	0.190
PLMAI ≥5/h	1.05 (0.57, 1.93)	0.876	1.15 (0.62, 2.15)	0.648	1.31 (0.68, 2.59)	0.410

Data are presented as unstandardized beta coefficient (*B*) or odds ratio (OR) with respective 95% confidence interval (CI) against the reference group (PLMAI <1/h). Data were analyzed by linear or logistic regression models using cognitive scores as dependent variable and PLMAI as independent variable. Minimally adjusted: adjusted for age (continuous), sex (men vs. women), education (≥high school vs. <high school), and ApoE4 (carriers vs. non-carriers). Fully adjusted: additionally adjusted for body mass index (continuous), diabetes (presence vs. absence), hypertension (presence vs. absence), smoking (current or former vs. never), alcohol (≥14 vs. <14 units/week), depression (presence vs. absence), psychotropic medication (presence vs. absence), and apnea-hypopnea index (continuous). Abbreviations: ApoE4 = apolipoprotein E4; FCSRT = Free and Cued Selective Reminding Test; MMSE = Mini-Mental State Examination.

Table S5. Associations between periodic leg movement index (PLMI) severity and cognitive functioning (sensitivity analysis after the exclusion of participants without ApoE genotype and adding an adjustment for ApoE4 status in the minimally adjusted model + further exclusion of participants using antidepressants; n=484).

	Unadjusted		**Minimally adjusted**		**Fully adjusted**	
	***B* (95% CI)**	***p***	***B* (95% CI)**	***p***	***B* (95% CI)**	***p***
Phonemic fluency						
PLMI 5-29.9/h	0.13 (-1.64, 1.90)	0.888	-0.29 (-1.98, 1.41)	0.741	-0.38 (-2.07, 1.31)	0.658
PLMI ≥30/h	-0.07 (-1.87, 1.74)	0.940	-0.13 (-1.87, 1.61)	0.884	-0.28 (-2.01, 1.46)	0.756
Semantic fluency						
PLMI 5-29.9/h	0.51 (-1.35, 2.37)	0.594	0.10 (-1.68, 1.88)	0.914	-0.03 (-1.80, 1.75)	0.976
PLMI ≥30/h	0.29 (-1.60, 2.19)	0.762	0.14 (-1.68, 1.96)	0.880	0.02 (-1.80, 1.84)	0.982
FCSRT free recall						
PLMI 5-29.9/h	0.18 (-1.24, 1.60)	0.806	-0.23 (-1.53, 1.07)	0.729	-0.27 (-1.57, 1.03)	0.687
PLMI ≥30/h	-0.27 (-1.74, 1.18)	0.713	-0.09 (-1.43, 1.24)	0.892	-0.13 (-1.47, 1.20)	0.846
Stroop dot condition						
PLMI 5-29.9/h	-1.21 (-4.09, 1.67)	0.411	-0.83 (-3.69, 2.03)	0.570	-0.99 (-3.86, 1.88)	0.499
PLMI ≥30/h	2.20 (-0.78, 5.19)	0.148	2.11 (-0.86, 5.08)	0.164	1.82 (-1.15, 4.81)	0.229
Stroop word condition						
PLMI 5-29.9/h	-1.84 (-6.12, 2.43)	0.398	-1.15 (-5.37, 3.07)	0.595	-1.52 (-5.76, 2.72)	0.483
PLMI ≥30/h	2.78 (-1.65, 7.21)	0.218	2.76 (-1.61, 7.14)	0.216	2.34 (-2.05, 6.74)	0.296
Stroop color-word condition						
PLMI 5-29.9/h	-2.87 (-8.89, 3.14)	0.350	-1.87 (-7.82, 4.06)	0.536	-2.45 (-8.43, 3.52)	0.422
PLMI ≥30/h	2.19 (-4.03, 8.43)	0.490	2.27 (-3.88, 8.43)	0.470	1.79 (-4.39, 7.99)	0.569
	OR (95% CI)	***p***	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***
MMSE ≤27 points						
PLMI 5-29.9/h	0.86 (0.42, 1.76)	0.683	1.07 (0.51, 2.25)	0.862	1.09 (0.51, 2.34)	0.820
PLMI ≥30/h	0.89 (0.43, 1.86)	0.760	0.92 (0.43, 1.96)	0.830	0.86 (0.39, 1.88)	0.711
FCSRT total recall ≤42 points						
PLMI 5-29.9/h	0.48 (0.22, 1.03)	0.161	0.52 (0.23, 1.16)	0.110	0.54 (0.24, 1.21)	0.135
PLMI ≥30/h	0.58 (0.22, 1.06)	0.102	0.56 (0.26, 1.23)	0.152	0.59 (0.26, 1.32)	0.199
DO-40 naming test ≤39 points						
PLMI 5-29.9/h	1.09 (0.60, 1.95)	0.777	1.15 (0.63, 2.07)	0.654	1.12 (0.61, 2.07)	0.702
PLMI ≥30/h	0.60 (0.31, 1.19)	0.148	0.61 (0.30, 1.21)	0.157	0.59 (0.29, 1.20)	0.147
CERAD constructional praxis task ≤9 points						
PLMI 5-29.9/h	0.90 (0.46, 1.71)	0.740	0.96 (0.49, 1.85)	0.895	0.93 (0.47, 1.84)	0.835
PLMI ≥30/h	1.05 (0.54, 2.01)	0.892	1.11 (0.57, 2.17)	0.740	1.11 (0.56, 2.22)	0.735

Data are presented as unstandardized beta coefficient (*B*) or odds ratio (OR) with respective 95% confidence interval (CI) against the reference group (PLMI <5/h). Data were analyzed by linear or logistic regression models using cognitive scores as dependent variable and PLMI as independent variable. Minimally adjusted: adjusted for age (continuous), sex (men vs. women), education (≥high school vs. <high school), and ApoE4 (carriers vs. non-carriers). Fully adjusted: additionally adjusted for body mass index (continuous), diabetes (presence vs. absence), hypertension (presence vs. absence), smoking (ex- or former vs. never), alcohol (≥14 vs. <14 units/week), depression (presence vs. absence), psychotropic medication (presence vs. absence), and apnea-hypopnea index (continuous). Abbreviations: ApoE4 = apolipoprotein E4; CERAD = Consortium to Establish a Registry for Alzheimer's Disease; FCSRT = Free and Cued Selective Reminding Test; MMSE = Mini-Mental State Examination.

Table S6. Associations between periodic leg movement arousal index (PLMAI) severity and cognitive functioning (sensitivity analysis after the exclusion of participants without ApoE genotype and adding an adjustment for ApoE4 status in the minimally adjusted model + further exclusion of participants using antidepressants; n=484).

	Unadjusted		**Minimally adjusted**		**Fully adjusted**	
	***B* (95% CI)**	***p***	***B* (95% CI)**	***p***	***B* (95% CI)**	***p***
Phonemic fluency						
PLMAI 1-4.9/h	0.32 (-1.45, 2.10)	0.720	-0.01 (-1.72, 1.70)	0.991	-0.01 (-1.71, 1.69)	0.989
PLMAI ≥5/h	-0.17 (-1.98, 1.64)	0.853	-0.49 (-2.22, 1.25)	0.579	-0.70 (-2.44, 1.04)	0.430
Semantic fluency						
PLMAI 1-4.9/h	1.34 (-0.52, 3.21)	0.159	1.04 (-0.75, 2.83)	0.254	1.02 (-0.76, 2.81)	0.261
PLMAI ≥5/h	0.72 (-1.18, 2.62)	0.459	0.29 (-1.53, 2.11)	0.756	0.09 (-1.74, 1.91)	0.924
FCSRT free recall						
PLMAI 1-4.9/h	0.86 (-0.56, 2.29)	0.237	0.42 (-0.89, 1.73)	0.534	0.46 (-0.84, 1.77)	0.486
PLMAI ≥5/h	1.01 (-0.44, 2.47)	0.173	0.74 (-0.59, 2.07)	0.278	0.63 (-0.71, 1.97)	0.357
Stroop dot condition						
PLMAI 1-4.9/h	-1.00 (-3.93, 1.92)	0.500	-0.63 (-3.52, 2.27)	0.671	-0.88 (-3.77, 2.02)	0.554
PLMAI ≥5/h	0.95 (-2.05, 3.94)	0.536	1.30 (-1.66, 4.26)	0.391	1.06 (-1.93, 4.06)	0.486
Stroop word condition						
PLMAI 1-4.9/h	-0.05 (-4.38, 4.29)	0.983	0.56 (-3.71, 4.83)	0.796	0.15 (-4.13, 4.43)	0.946
PLMAI ≥5/h	0.68 (-3.76, 5.13)	0.763	1.42 (-2.96, 5.81)	0.524	1.36 (-3.07, 5.80)	0.548
Stroop color-word condition						
PLMAI 1-4.9/h	0.26 (-5.83, 6.36)	0.932	1.11 (-4.89, 7.11)	0.717	0.57 (-5.45, 6.59)	0.853
PLMAI ≥5/h	-0.40 (-6.65, 5.85)	0.901	0.68 (-5.48, 6.84)	0.829	0.59 (-5.65, 6.83)	0.854
	OR (95% CI)	***p***	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***
MMSE ≤27 points						
PLMAI 1-4.9/h	0.60 (0.27, 1.31)	0.210	0.66 (0.29, 1.48)	0.314	0.62 (0.27, 1.43)	0.267
PLMAI ≥5/h	0.87 (0.42, 1.79)	0.708	0.98 (0.47, 2.07)	0.962	0.93 (0.43, 1.99)	0.845
FCSRT total recall ≤42 points						
PLMAI 1-4.9/h	0.79 (0.38, 1.64)	0.532	0.88 (0.42, 1.89)	0.760	0.90 (0.41, 1.93)	0.782
PLMAI ≥5/h	0.54 (0.23, 1.26)	0.144	0.57 (0.24, 1.33)	0.193	0.55 (0.23, 1.32)	0.184
DO-40 naming test ≤39 points						
PLMAI 1-4.9/h	0.63 (0.32, 1.21)	0.165	0.63 (0.32, 123)	0.181	0.61 (0.31, 1.20)	0.157
PLMAI ≥5/h	0.89 (0.48, 1.65)	0.722	0.96 (0.51, 1.79)	0.900	0.98 (0.52, 1.86)	0.957
CERAD constructional praxis task ≤9 points						
PLMAI 1-4.9/h	0.59 (0.29, 1.22)	0.155	0.61 (0.29, 1.27)	0.187	0.59 (0.28, 1.25)	0.169
PLMAI ≥5/h	1.11 (0.60, 2.09)	0.730	1.21 (0.64, 2.30)	0.544	1.39 (0.71, 2.70)	0.336

Data are presented as unstandardized beta coefficient (*B*) or odds ratio (OR) with respective 95% confidence interval (CI) against the reference group (PLMAI <1/h). Data were analyzed by linear or logistic regression models using cognitive scores as dependent variable and PLMAI as independent variable. Minimally adjusted: adjusted for age (continuous), sex (men vs. women), education (≥high school vs. <high school), and ApoE4 (carriers vs. non-carriers). Fully adjusted: additionally adjusted for body mass index (continuous), diabetes (presence vs. absence), hypertension (presence vs. absence), smoking (current or former vs. never), alcohol (≥14 vs. <14 units/week), depression (presence vs. absence), psychotropic medication (presence vs. absence), and apnea-hypopnea index (continuous). Abbreviations: ApoE4 = apolipoprotein E4; FCSRT = Free and Cued Selective Reminding Test; MMSE = Mini-Mental State Examination.

SUPPLEMENTAL REFERENCES

1. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12(3):189-198. doi:10.1016/0022-3956(75)90026-6

2. Van der Linden M, Coyette F, Poitrenaud J, Adam S, Agniel A. L'épreuve de rappel libre/rappel indicé à 16 items (RL/RI-16). In: L'évaluation des troubles de la mémoire. Présentation de quatre tests de mémoire épisodique (avec leur étalonnage). In: Solal; 2004.

3. Cardebat D, Doyon B, Puel M, Goulet P, Joanette Y. [Formal and semantic lexical evocation in normal subjects. Performance and dynamics of production as a function of sex, age and educational level]. *Acta Neurol Belg*. 1990;90(4):207-217.

4. Thuillard Colombo F, Assal G. Adaptation française du test de dénomination de Boston. Versions abrégées. *Revue Européenne de Psychologie Appliquée*. Published online 1992.

5. Morris JC, Mohs RC, Rogers H, Fillenbaum G, Heyman A. Consortium to establish a registry for Alzheimer's disease (CERAD) clinical and neuropsychological assessment of Alzheimer's disease. *Psychopharmacol Bull*. 1988;24(4):641-652.

6. Bayard S, Erkes J, Moroni C, Collège des Psychologues Cliniciens spécialisés en Neuropsychologie du Languedoc Roussillon (CPCN Languedoc Roussillon). Victoria Stroop Test: normative data in a sample group of older people and the study of their clinical applications in the assessment of inhibition in Alzheimer's disease. *Arch Clin Neuropsychol*. 2011;26(7):653-661. doi:10.1093/arclin/acr053

7. Iber C, Ancoli-Israel S, Chesson A, Quan S. The AASM manual for the scoring of sleep and associated events: rules terminology and technical specifications. Published online 2007.

8. Zucconi M, Ferri R, Allen R, et al. The official World Association of Sleep Medicine (WASM) standards for recording and scoring periodic leg movements in sleep (PLMS) and wakefulness (PLMW) developed in collaboration with a task force from the International Restless Legs Syndrome Study Group (IRLSSG). *Sleep Med*. 2006;7(2):175-183. doi:10.1016/j.sleep.2006.01.001

9. Delaneau O, Marchini J, Zagury JF. A linear complexity phasing method for thousands of genomes. *Nat Methods*. 2011;9(2):179-181. doi:10.1038/nmeth.1785

10. Delaneau O, Zagury JF, Marchini J. Improved whole-chromosome phasing for disease and population genetic studies. *Nat Methods*. 2013;10(1):5-6. doi:10.1038/nmeth.2307

11. Das S, Forer L, Schönherr S, et al. Next-generation genotype imputation service and methods. *Nat Genet*. 2016;48(10):1284-1287. doi:10.1038/ng.3656

12. McCarthy S, Das S, Kretzschmar W, et al. A reference panel of 64,976 haplotypes for genotype imputation. *Nat Genet*. 2016;48(10):1279-1283. doi:10.1038/ng.3643