RESEARCH ARTICLE

Association of Sleep Disturbances With Prevalent and Incident Motoric Cognitive Risk Syndrome in Community-Residing Older Adults

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Neurology® 2024;103:e210054. doi:10.1212/WNL.0000000000210054

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Abstract

Background and Objectives

There is growing evidence that sleep disturbances are associated with cognitive impairment risk, but their association with the incidence of motoric cognitive risk syndrome (MCR)—a pre-dementia syndrome characterized by slow gait speed and cognitive complaints—is unknown. We aimed to examine the association of sleep disturbances, overall and specific subtypes, with (1) incident and (2) prevalent MCR in older adults.

Methods

Community-residing adults aged 65 years and older without dementia were recruited from population lists and included in Central Control of Mobility and Aging, a prospective cohort study, in Albert Einstein College of Medicine, Bronx, NY. We included participants with available data for MCR and Pittsburgh Sleep Quality Index (PSQI). MCR was defined as cognitive complaints reported on standardized questionnaires and slow gait speed as recorded on an electronic treadmill and was adjudicated at baseline and annual follow-up visits. Participants were divided into "good" sleepers (≤5) and "poor" sleepers (>5) based on an established PSQI cut score. Among participants without MCR at baseline, Cox proportional hazard models adjusted for (1) age, sex, and education and (2) further for comorbidity index, Geriatric Depression Scale score, and global cognitive score were used to examine the association of baseline sleep disturbances with MCR incidence. Association between poor sleep quality and prevalent MCR at baseline in the overall population was explored using multivariate logistic regression analysis.

Results

445 participants were included (56.9% women, mean age: 75.9 years [75.3; 76.5]). In MCR-free participants at baseline (n = 403), 36 developed incident MCR over a mean follow-up of 2.9 years. Poor sleepers had a higher risk of incident MCR (HR = 2.7 [1.2; 5.2]) compared with good sleepers, but this association was not significant after adjustment for depressive symptoms (adjusted hazard ratio [aHR] = 1.6 [0.7–3.4]). Among the 7 PSQI components, only sleep-related daytime dysfunction (excessive sleepiness and lower enthusiasm) showed a significant risk of MCR in fully adjusted models (aHR = 3.3 [1.5–7.4]). Prevalent MCR was not associated with poor sleep quality (OR [95% CI] = 1.1 [0.5–2.3]).

Discussion

Overall poor sleep quality was associated with incident MCR, but not with prevalent MCR. Specifically, older adults with sleep-related daytime dysfunction are at increased risk of developing MCR. Further studies are needed to validate mechanisms of this relationship.

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Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Glossary

AD = Alzheimer disease; **ADL-PI** = Activities of Daily Living—Prevention Instrument; **ADLs** = activities of daily living; **aHR** = adjusted hazard ratio; **CCMA** = Central Control of Mobility and Aging; **GDS** = Geriatric Depression Scale; **GHS** = Global Health Score; **LLFDI-D** = Late-Life Function and Disability Instrument—disability component; **MCR** = motoric cognitive risk syndrome; **OR** = odds ratio; **PSQI** = Pittsburgh Sleep Quality Index; **RBANS** = repeatable battery for the assessment of neuropsychological status.

Introduction

The rapid aging of global populations is accompanied by an attendant increase in dementia.[1] It is estimated that approximately 40% of dementia cases may be preventable.[2] Sleep disturbances are common in aging with prevalence rates reported at 37.3% in US adults aged 60–74 years and 28.0% in those aged 75 years and older.[3] Sleep disturbances and cognitive impairment frequently coexist in aging, and the association between the 2 may be bidirectional. Poor sleep quality has been shown to be associated with higher risk of dementia.[4] Sleep duration has been reported to show a U-shaped association with dementia risk; that is, both lack of and excessive sleep duration were associated with cognitive impairment and incidence of dementia.[5,6] Other sleep features have been less studied in the context of dementia, but lower sleep efficiency and excessive day sleepiness were shown to be associated with risk of dementia in 2 cohort studies.[7,8] However, the literature remains discrepant about the longitudinal relationship between sleep disturbances and future dementia risk. In a large prospective study in the Netherlands, the authors failed to show a significant risk of all-cause dementia in the general population with a poorer sleep quality.[9]

Less is known about sleep dysfunction in predementia syndromes such as motoric cognitive risk syndrome (MCR). MCR is a predementia syndrome first described in 2013 that is characterized by the presence of cognitive complaints and slow gait speed.[10] MCR diagnosis does not require cognitive tests or laboratory assays, increasing its clinical utility, especially in clinical settings with low resources worldwide. Older adults with MCR have over 2-fold higher risk of developing dementia, both Alzheimer disease (AD) and vascular dementia.[10,11] 2 recent cross-sectional studies reported higher odds of MCR in older adults with sleep disturbances.[12,13] Among 940 older adults, a significant association has been shown between prevalent MCR syndrome and the self-reported frequency of trouble falling asleep, waking early or easily, nightmares, and sleep drug use.[12] In the China Health and Retirement Longitudinal Study, community-dwelling older adults (n = 5,837) had 80% increased odds of MCR if they reported poor sleep quality.[13] More recently, in the same cohort, a moderate nap (i.e., 30–89 minutes per day) was shown to be inversely associated with lower odds of MCR.[14] These results suggest an association between sleep impairment and further cognitive decline.

However, prospective studies that have examined the risk of incidence of MCR with sleep dysfunction are lacking. There is a need to explore the effect of sleep disorders over a longer period and their putative causal relationship. Establishing the relationship between sleep dysfunction and MCR risk is important because early intervention may offer the best hope for preventing dementia.

Our main objective was to examine MCR incidence with sleep disturbances assessed by the established Pittsburgh Sleep Quality Index (PSQI) questionnaire, which examines 7 sleep components (subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, use of sleep-inducing medication, daytime dysfunction). Poor sleep quality was categorically defined using an established cut score on the total PSQI. We hypothesized that presence of poor sleep quality overall will be associated with a higher incidence of MCR. We also tested the association of each individual PSQI component with MCR incidence. To explore a putative bidirectional relationship between MCR and sleep disturbances, secondary objectives were to (1) compare MCR prevalence according to sleep quality and (2) compare onset of poor sleep quality—according to the overall PSQI score—in older adults with and without MCR.

Methods

Participants

This study included participants from the Central Control of Mobility and Aging (CCMA) cohort, whose main objective was to prospectively assess the cognitive processes and brain mechanisms that regulate mobility in aging. CCMA has been described in detail elsewhere.[15] In brief, potential participants were identified from population lists of Westchester County, NY, and screened using telephone interviews to assess eligibility and interest to participate in the study. Interested individuals were invited for an in-person visit at our center for further evaluation and enrollment. Inclusion criteria applied in CCMA were age 65 years and older and living in community. Exclusion criteria included dementia (previous physician diagnosis or diagnosed at baseline by the study investigators), inability to walk unassisted, active neurologic or psychiatric disorders that might interfere with tests, severe visual or hearing impairments, upcoming or recent medical interventions that could affect mobility, and individuals undergoing hemodialysis treatment. After obtaining signed

informed consent, in-person assessments were conducted at the Albert Einstein College of Medicine at baseline and annual follow-up visits from 2011 to 2018. For this analysis, we also excluded participants with dementia at baseline and with missing data for either MCR or PSQI.

Motoric Cognitive Risk Syndrome

The primary outcome was MCR defined using the Verghese criteria as previously applied in the CCMA cohort.[11] MCR was diagnosed if all the following criteria were met: slow gait speed, measured at normal pace on an instrumented walkway (GAITRite, CIR systems, Havertown, PA); cognitive complaints collected using standardized questionnaires; and no dementia diagnosis. Gait and cognitive complaints were assessed at each visit. Slow gait speed was defined as walking speed at normal pace that was 1 SD or below the mean for age and sex, as previously reported in this cohort.[16] Presence of cognitive complaints was ascertained by endorsing 2 or more of 21 cognitive concern items from 4 standard tests: 3 items from the Geriatric Depression Scale (GDS),[17] 1 item from the Late-Life Function and Disability Instrument—disability component (LLFDI-D),[18] 9 items from the Activities of Daily Living—Prevention Instrument (ADL-PI),[19] and 8 items in the AD8 cognitive screener[20] (eTable 1 provides individual cognitive concern items).

Sleep Quality

Poor overall sleep quality was ascertained with the widely used PSQI.[21] The PSQI has 18 items that assesses participants' self-reported sleep habits including bedtime and wake-up time and the respondent's estimate of the time taken to fall asleep and the time spent asleep. Furthermore, it also asks for the frequency or severity of specific trouble sleeping, the use of sleep-inducing medicine, daytime sleepiness, enthusiasm to get things done, and the self-rated global sleep quality in the past weeks. Participants were categorized into 2 groups based on the PSQI total score: "good" sleepers (PSQI score ≤5) and "poor" sleepers (PSQI score >5) at baseline and independently at each follow-up visit. A cut score of 5 on the PSQI had a sensitivity of 89.6% and specificity of 86.5% for distinguishing good (healthy adults with no sleep complaints) from poor (patients with sleep complaint) sleepers.[21] PSQI has strong internal consistency with Cronbach coefficients ranging from 0.7 to 0.8 in a systematic review.[22]

PSQI allows interpretation of 7 sleep components: subjective sleep quality, sleep latency (time to fall asleep), self-estimated sleep duration, sleep efficiency (ratio between total of hours asleep and total of hours in bed, expressed in percentage), sleep disturbances (frequency of 9 specific trouble sleeping concerns because of an inability to fall asleep in less than 30 minutes, waking up in the night or early morning, having to get up to use the bathroom, uncomfortable breathing, too cold or too hot feeling, bad dreams, pain, or any other reason), use of sleep-inducing medication, and daytime dysfunction (trouble staying awake during activities and less enthusiasm to get things done). Component variables were scored on a Likert scale from 0 to 3. PSQI components were then transformed as categorical binary variables according to the main clinical significance in components 1 (subjective sleep quality as fairly and very bad vs fairly and very good), 2 (sleep latency less than 30 minutes vs from 31 minutes), 3 (estimated sleep duration as more than 7 hours and between 6 and 7 hours vs less than 6 hours), 5 (no reported sleep disturbances during the past month vs at least 1), and 6 (no sleep-inducing drugs reported in the past month vs at least 1). The same procedure has been applied to categorize the following components while also considering the distribution of responses to optimize their comparability: component 4 (sleep efficiency lower than 84% vs greater than 85%) and component 7 (reported sleep-related daytime dysfunction less frequent than once a week vs at least 1/week).

Data Collection

Comprehensive clinical examination and neuropsychological assessments were performed at each visit. Grip strength, body mass index, and Short Physical Performance Battery were measured at each visit.[23] For this study, we report performance on the repeatable battery for the assessment of neuropsychological status (RBANS), an omnibus test of general mental status,[24] verbal fluency scores,[25] and Trail Making Test A and B[26] to offer an overall description of cognitive functions. Dementia was diagnosed using the DSM-IV criteria after review of all clinical and cognitive data at consensus case conference attended by a neurologist and a neuropsychologist.

Sociodemographic data (age, sex, education, numbers of years of education, ethnic group) and medical history (including previous falls) were also recorded from self-report. The Global Health Score (GHS) was measured as the sum by the self-reported presence or absence of 10 physician-diagnosed medical conditions including diabetes, chronic heart failure, arthritis, hypertension, depression, stroke, Parkinson disease, chronic obstructive pulmonary disease, angina, and myocardial infarction as previously reported.[27] Functional (LLFDI-D,[18] ADL PI[19]) and mental health standardized questionnaires were also administered. Disability was defined from standard questions and a scale for basic activities of daily living (ADLs) specifically for use in community-dwelling cohorts.[28] Depressive and anxiety symptoms were assessed using the 30-item Geriatric Depression Scale (using an established cut score of ≥10 for mild to severe depression)[17] and the Beck Anxiety Inventory,[29] respectively. The Activities-Specific Balance Confidence Scale and the Medical Outcomes Study for social support (MOS Social Support) were used to question fear of falling and social support, respectively.[30,31] Pain intensity was also assessed at each visit using dedicated and standardized questions.

Statistics

A comparison of baseline characteristics between good and poor sleepers was conducted. Chi-squared tests (or the Fisher exact test when the expected cell frequency was <5) were used for categorical variables. For quantitative variables, the Student

t test (or the Mann-Whitney *U* test for non-Gaussian distributions) was used. Categorical variables were expressed as frequency (percentage), and quantitative variables were presented as mean [95% CI]. Normality of distribution was assessed graphically and using the Shapiro-Wilk test. We also compared baseline characteristics between included and excluded participants without dementia, using the same tests as reported above. The association between prevalent poor sleep quality and MCR was examined using multivariate logistic regression analysis at baseline. The primary model was adjusted for age, sex, and education years (model 1). Because several comorbidities, including diabetes, heart disease, hypertension, stroke, depression, and poor cognitive performance, are described as risk factors of MCR,[32,33] we further adjusted for continuous GHS, GDS score, and RBANS total index score in model 2.

After excluding participants with prevalent MCR at baseline, Cox proportional hazard models were separately applied for the abnormal PSQI score (PSQI score >5), PSQI total score, and presence or absence of each individual PSQI component. The same adjustment factors were applied for model 1 and model 2. The time to event was calculated as the duration in days between the baseline visit and follow-up visit where the diagnosis of MCR syndrome was made or the final study contact. None of them developed incident dementia without previous MCR during the follow-up.

In post hoc analyses, Cox PH models were also applied to compare incident MCR according to the abnormal PSQI score at baseline after adjustment for the (1) GDS score, (2) GHS, and (3) RBANS total score separately in 3 other models to assess the individual confounding effect of these covariates. Moreover, the association of the GDS score and abnormal PSQI score with incident MCR was analyzed in the Cox proportional hazard model. Depression has a bidirectional relationship with sleep disturbances[34,35] and is also a strong risk factor of MCR,[36,37] suggesting it as a potential cofounder. Therefore, the interaction between GDS and PSQI abnormal scores was also investigated using the Cox model.

In accordance with our third objective, we excluded participants with poor sleep quality at baseline (n = 177) and applied Cox proportional hazard models to compare the onset of poor sleep quality in participants with or without MCR at baseline. Models 1 and 2 were adjusted, respectively, for age, sex, and educational years and GHS, GDS score, and RBANS total index score. The time to event was determined by calculating the number of days from the baseline visit to either the follow-up visit at which poor sleep quality was newly identified or the final study contact.

Finally, we conducted 2 sensitivity analyses. To account for reverse causation, we ran the same models after excluding participants with MCR onset during the first year of follow-up (≤365 days) because MCR may result in sleep disturbances. For this analysis, we examined the association of baseline poor sleep quality with incident MCR developing >1 year after baseline. In addition, we used an alternative definition for MCR considering ≥2 cognitive complaints in only AD8, LFDI-D, and ADL-PI (without including the GDS memory items) to avoid any potential cofounding bias due to the GDS memory item that was also used to define MCR. From participants without alternative MCR at baseline and/or incident dementia without previous MCR during follow-up, we compared incidence of alternative MCR between "poor" and "good" sleepers. The same models as reported above were applied.

Proportional hazard assumptions were evaluated visually and through interaction tests. Odds ratio (OR) and hazard ratio (HR) were reported as adjusted with [95% CI]. Statistical significance was defined as $p < 0.05$. Analyses were performed using SPSS version 29.0.2.0 (IBM SPSS Statistics). The supporting data for this study are available from the corresponding author on request from qualified investigators with appropriate ethical clearances.

Standard Protocol Approvals, Registrations, and Patient Consents

The Einstein Institutional Review Board approved the parent study protocol in compliance with the Declaration of Helsinki. Written and informed consent was obtained from all participants in the study.

Data Availability

All the authors have full access to the data used in the analyses in the study. Qualified researchers may obtain access to all deidentified data in CCMA on a substantiated request.

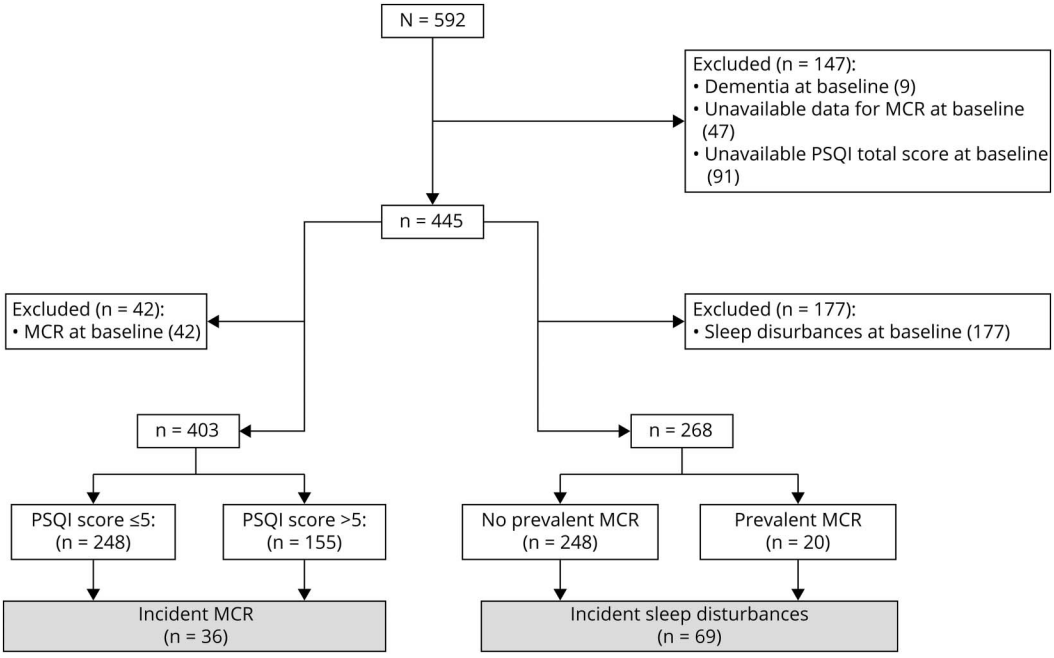
Results

From the 592 older adults initially recruited in the CCMA cohort, we included 445 individuals (mean age [95% CI]: 75.9 years [75.3–76.5] and 253 women (56.9%)) after excluding participants with dementia at baseline (n = 9) and with missing data for either MCR or PSQI (n = 138) (Figure 1). When comparing baseline characteristics between included and excluded participants without dementia, only GHS was significantly higher in included participants.

Prevalent MCR and Baseline Sleep Disturbances

Baseline characteristics in good and poor sleepers are listed in Table 1 and eTable 2. 177 (39.8%) were considered "poor" sleepers. Poor sleepers were significantly older (mean age 76.8 [75.9–77.7] years vs 75.3 [74.6–76.1] years in "good sleepers"), were more frequently disabled according to the ADL score (5.1% vs 1.5%), and had more depressive symptoms (mean GDS score 6.4 [5.7–7.0] vs 3.7 [3.3–4.1]). The prevalence of MCR was similar between groups.

Figure 1 Study Flowchart



MCR = motoric cognitive risk syndrome; PSQI = Pittsburgh Sleep Quality Index.

Poor sleep quality was not associated with a greater risk of prevalent MCR, after adjustment for age, sex, and educational years (OR [95% CI] = 1.7 [0.9–3.2]), neither after further adjustment for GHS, GDS score, and RBANS total index score (OR [95% CI] = 1.1 [0.5–2.3]).

Incidence of MCR According to the Overall PSQI Score

There were 403 participants without MCR at baseline. 36 participants (8.9%) developed incident MCR over the follow-up period: 5.6% (14) were "good sleepers" and 14.2% (22) were "poor sleepers." The mean follow-up time [95% CI] was 1069.7 days [998.5–1140.9], that is, 35.2 months. Baseline poor sleepers (PSQI total score >5) had a higher risk of incident MCR after adjustment for age, educational level, and sex in model 1 (adjusted hazard ratio [aHR] [95% CI] = 2.6 [1.3–5.0]) (Table 2) when compared with good sleepers. No statistically significant association was observed after additional adjustment for GHS, GDS score, and RBANS total scale index score in model 2 (aHR [95% CI] = 1.6 [0.7–3.4]). In post hoc analysis, there was no significant risk of incident MCR after adjustment only for the GDS score (aHR [95% CI] = 1.7 [0.9–3.6]). Poor sleepers remained associated with a higher risk of incident MCR after further adjustment, respectively, only for GHS (aHR = 2.4 [1.2–4.7]) and only for the RBANS total scale index score (aHR = 2.6 [1.3–5.1]).

The total PSQI score (continuous) also significantly predicted incident MCR in model 1, but not in model 2 (Table 2).

Figure 2 presents the survival plots without MCR in poor and good sleepers.

In a model including both baseline PSQI and GDS scores, the PSQI score was not associated with higher risk of MCR (aHR [95% CI] = 1.0 [0.9–1.1]) but the GDS score was significantly associated (aHR [95% CI] = 1.2 [1.1–1.3]). However, the interaction between these both variables was not associated with incident MCR (aHR [95% CI] = 1.0 [0.9–1.0]).

Incidence of MCR According to PSQI Components

Short sleep duration (<6h/day) and subjective bad sleep quality were associated with a higher risk of MCR in model 1, but not in model 2 (Table 2). Only frequent daytime dysfunction related to sleep disturbances significantly predicted MCR incidence in fully adjusted model 2 (aHR [95% CI] = 3.3 [1.5–7.4]).

New Poor Sleep Quality According to MCR at Baseline

Among the 268 participants considered as "good sleepers" at baseline, 20 (7.5%) had MCR. 69 (25.7%) reported new-onset poor sleep quality over follow-up (mean [95% CI] = 1082.2 [985.5–1174.9] days i.e., 35.6 months). Prevalent MCR was not associated with higher risk of incident poor sleep quality (aHR [95% CI] = 1.2 [0.5–2.7]).

Sensitivity Analyses

When participants with incident MCR during the first year (n = 3) of follow-up were excluded from those without

Table 1 Baseline Characteristics

	Overall N = 445	"Good sleepers" (PSQI score ≤5) N = 268	"Poor sleepers" (PSQI score >5) N = 177	*p* Value	Missing data
MCR prevalence (%,n)	9.4 (42)	7.5 (20)	12.4 (22)	0.08	0
Sociodemographic data					
Age (mean, 95% CI)	75.9 [75.3–76.5]	75.3 [74.6–76.1]	76.8 [75.9–77.7]	0.02	0
Female sex (%, n)	56.9 (253)	53.7 (144)	61.6 (109)	0.12	0
Ethnicity (%, n)				0.58	0
Caucasian	78.7 (350)	78.7 (211)	78.5 (139)		
Black	17.8 (79)	17.5 (47)	18.1 (32)		
Hispanic White	1.8 (8)	2.2 (6)	1.1 (2)		
Hispanic Black	0.2 (1)	0 (0)	0.6 (1)		
Asian	1.1 (5)	0.7 (2)	1.7 (3)		
Other	0.4 (2)	0.7 (2)	0 (0)		
Education years (mean, 95% CI)	14.6 [14.4–14.9]	14.7 [14.4–15.1]	14.5 [14.1–14.9]	0.45	0
Medical history					
GHS (mean, 95% CI)	1.7 [1.6–1.8]	1.6 [1.5–1.7]	1.8 [1.6–1.9]	0.08	0
Neuropsychological assessment					
RBANS total sum score (mean, 95% CI)	118.1 [116.6–119.7]	119.5 [117.5–121.6]	115.9 [113.6–118.3]	0.03	0
RBANS immediate memory index (mean, 95% CI)	97.7 [96.6–98.8]	98.7 [97.3–100.1]	96.1 [94.4–97.9]	0.02	2
RBANS visuospatial index (mean, 95% CI)	92.0 [90.7–93.2]	92.7 [91.1–94.3]	90.9 [88.9–92.9]	0.18	6
RBANS language index (mean, 95% CI)	92.8 [91.9–93.8]	93.3 [92.1–94.6]	92.1 [90.5–93.6]	0.22	1
RBANS attention index (mean, 95% CI)	99.5 [98.2–100.9]	100.4 [98.6–102.2]	98.2 [96.1–100.2]	0.11	5
RBANS delayed memory index (mean, 95% CI)	92.9 [92.0–93.9]	93.7 [92.4–95.0]	91.7 [90.3–93.2]	0.05	0
RBANS total scale index (mean, 95% CI)	91.2 [90.1–92.3]	92.3 [90.9–93.8]	89.6 [87.9–91.2]	0.02	0
Mobility, nutrition, and global health assessment					
Disability according to ADL (%,n)	2.9 (13)	1.5 (4)	5.1 (9)	0.03	0
BMI (mean, 95% CI)	29.2 [28.5–29.9]	28.7 [28.0–29.4]	30.1 [28.7–31.4]	0.06	11
Gait speed (cm/s) (mean, 95% CI)	99.1 [97.0–101.3]	101.6 [98.8–104.4]	95.5 [92.3–98.7]	0.01	0
GDS score (mean, 95% CI)	4.8 [4.4–5.1]	3.7 [3.3–4.1]	6.4 [5.7–7.0]	<0.001	0
BAI anxiety score (mean, 95% CI)	4.4 [3.9–4.9]	3.3 [2.8–3.8]	6.1 [5.2–7.1]	<0.001	1
LLFDID total score (mean, 95% CI)	69.1 [68.6–69.6]	69.8 [69.2–70.5]	68.0 [67.1–68.8]	<0.001	0

Abbreviations: BAI = Beck Anxiety Inventory; BMI = body mass index; GDS = Geriatric Depression Scale; GHS = Global Health Score; LLFDID = Late-Life Function and Disability Instrument—disability component; MCR = motoric cognitive risk syndrome; PSQI = Pittsburgh Sleep Quality Index; RBANS = repeatable battery for the assessment of neuropsychological status.

MCR at baseline (n = 403), there were 33 participants with incident MCR developing >1 year after baseline. Poor sleepers had a significantly higher risk of incident MCR developing >1 year after baseline (aHR [95% CI] = 2.1 [1.1–4.3]) in model 1, but similarly, this association did not remain significant in model 2 (aHR [95% CI] = 1.4 [0.6–2.9]).

Among 445 included participants, 34 had prevalent MCR at baseline according to alternative definition (without inclusion

Table 2 Risk of Incident MCR According to Baseline Status

	Model 1		Model 2	
	aHR	95% CI	aHR	95% CI
Poor sleep quality	2.6[a]	1.3–5.0	1.6	0.7–3.4
PSQI overall score	1.1[a]	1.0–1.2	1.0	0.9–1.1
PSQI components				
Component 1: subjective sleep quality considered as "fairly bad" or "very bad" (n = 68)	2.3[a]	1.2–4.7	1.3	0.6–2.9
Component 2: sleep latency >30 minutes (n = 81)	1.6	0.7–3.3	1.2	0.6–2.6
Component 3: sleep duration <6 h/d (n = 72)	2.3[a]	1.2–4.7	1.5	0.7–3.3
Component 4: sleep efficiency <85% (n = 168)	1.4	0.7–2.8	1.1	0.5–2.2
Component 5: sleep disturbances ≥1/mo (n = 351)	0.6	0.3–1.5	0.4	0.2–1.0
Component 6: use of medication ≥1/mo (n = 79)	1.5	0.7–3.2	1.0	0.5–2.3
Component 7: daytime dysfunction ≥1/week (n = 31)	5.0[a]	2.4–10.4	3.3[a]	1.5–7.4

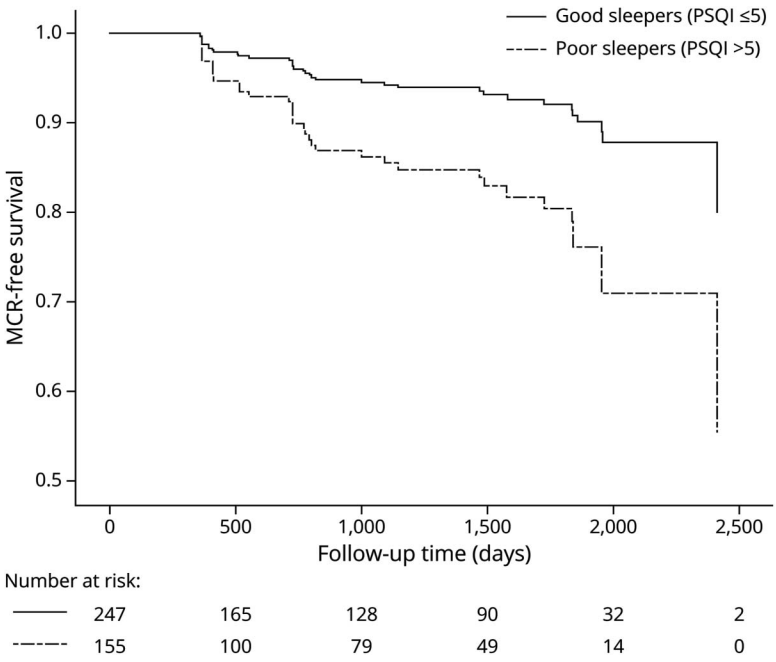
Abbreviations: aHR = adjusted hazard ratio; GDS = Geriatric Depression Scale; GHS = Global Health Score; HR = hazard ratio; PSQI = Pittsburgh Sleep Quality Index; RBANS = repeatable battery for the assessment of neuropsychological status.
Model 1 is adjusted for age, sex, and educational years.
Model 2 is adjusted for age, sex, educational years, GHS, GDS score, and RBANS total index.
[a] $p < 0.05$.

of GDS memory items). After excluding these prevalent MCR cases and 2 noncases (n = 409), 38 developed incident alternative MCR during follow-up. Risk of incident MCR was significantly higher in 157 poor sleepers (38.4%) compared with 252 good sleepers (61.6%) (aHR = 2.2 [1.2; 4.3]) in model 1, but this association did not remain significant in model 2 (aHR = 1.4 [0.7; 2.8]).

Discussion

Our findings showed that sleep dysfunction is associated with increased risk of developing incident MCR in a community-residing cohort of older adults. Specifically, individuals characterized as poor sleepers on the PSQI had a 2-fold increased incidence of MCR compared with good sleepers. Among the

Figure 2 Survival Plots



Survival plots showing cumulative risk of developing MCR based on baseline good and poor sleep status. MCR = motoric cognitive risk syndrome; PSQI = Pittsburgh Sleep Quality Index.

7 individual PSQI components, worse subjective sleep quality, short sleep duration, and frequent daytime dysfunction predicted incident MCR.

In contrast to previous cross-sectional studies,[12,13] overall poor sleep quality was not associated with a higher prevalence of MCR at baseline in our cohort. These differences may be explained by larger sample sizes in the previous 2 studies and the use of different tools or PSQI items. In addition, different tools were used to characterize sleep disturbances. In the China Health and Retirement Longitudinal Study, sleep quality was assessed based on participants' responses to the question of whether their sleep was restless.[13] The authors used PSQI in Ningbo Community Study on Aging, but only some of its components were compared with MCR prevalence.[12] Our findings regarding sleep disturbances and MCR are in line with previous studies that have reported on mild cognitive impairment (MCI) and dementia. Self-reported poor sleep quality was associated with cognitive decline or AD in a meta-analysis including 69,216 individuals aged 49 years and older (pooled RR [95% CI] = 1.49 [1.26–1.75]).[38] Risk of MCI was higher in individuals who reported trouble sleeping.[39] MCI prevalence was greater in older adults with short (<5.5 hours) or long (>8 hours) sleep duration. Of interest, this association was stronger if the sleep disorder co-occurred with slow gait speed, a key diagnostic criterion of MCR syndrome.[40] Poor sleep quality (PSQI score >5) has also been reported to increase risk of incident MCI.[41]

Depressive symptoms are a strong risk factor of both MCR and sleep disturbances.[36,42] Moreover, a significant interaction between sleep and anxiety symptoms that increased risk of incident dementia has been previously reported.[43] In the fully adjusted model in our study, the lack of association between sleep disturbances (poor sleeper or PSQI total score) and MCR incidence seemed to result from inclusion of the GDS covariate. However, the statistical interaction term between abnormal GDS and PSQI scores with incident MCR risk was not significant in our models, which may have resulted from unmeasured confounders or lack of power. Further studies in larger cohorts are needed to test this hypothesis.

Among the individual PSQI components, poor subjective sleep quality and short sleep duration were significantly associated with higher risk of incident MCR only in model 1. Only sleep-related daytime dysfunction (excessive sleepiness and lower enthusiasm) showed a 3-fold higher risk of MCR in fully adjusted models. Emerging and persistent sleepiness complaints were associated with a higher risk of incident dementia over 12 years of follow-up in approximately 7,000 community-dwelling older adults.[8] Moreover, this association was not attenuated by depressive symptoms in another observational cohort study.[44] In a recent cross-sectional study, napping between 30 and 89 minutes per day was associated with lower risk of MCR, especially in individuals who sleep less than 8 hours per night.[14] These results suggest the possibility that moderate napping could protect MCR onset risk by reducing day sleepiness, and it needs to be further examined.

In our study, participants with MCR at baseline did not develop new-onset sleep disturbances compared with participants without MCR. There was also no cross-sectional association between MCR and poor sleep quality at baseline. Hence, these results do not support a bidirectional relationship between sleep disturbances and MCR. Nonetheless, further studies are needed to test putative bidirectional association between MCR and sleep disturbances, such as cross-lag models. The literature is scarce regarding risk of incident sleep disturbances according to baseline cognitive status, but trouble sleeping is frequently reported as an early symptom of cognitive decline, including AD.[45] Women who reported regular difficulty in falling or staying asleep had a faster decline on the global cognitive score in the Nurses' Health Study cohort.[46] Poor sleep quality can lead to multiple alterations in brain structure and function and thereby increase risk of dementia.[45]

There are several possible explanations for the association between excessive day sleepiness and risk of MCR. Some authors have proposed that innate immunity activated by sleep disturbances is a key factor leading to neurodegenerative diseases, such as AD.[47] Accumulation of amyloid ß and release of tau seemed to be modified by sleep deprivation in AD mouse models.[48,49] Sleep increases glymphatic clearance, which allows clearance of neurotoxins.[50] Sleep-associated pathologies such as obstructive sleep apnea might also play a role in increasing risk of cognitive decline. Sleep apnea was associated with poorer cognitive scores over 5 years of follow-up.[51] Sleep disturbances might also be early symptoms of synucleinopathies such as Lewy body dementia.[52]

Our study has limitations. We had to exclude 23% of the participants from the parent study because of missing data, but key baseline characteristics were not significantly different between eligible and excluded participants. We used an established sleep inventory but lacked objective sleep measurements that might have provided additional insights into the relationship between sleep and MCR. Self-reported sleep complaints might be subject to recall bias, especially in participants with cognitive complaints. Our study is also limited by a relative short follow-up time, which resulted in the lower number of incident MCR cases. Finally, our sample was mainly self-identified as White (79.6%), and these findings need to be examined in more diverse populations to test generalizability.

Excessive day sleepiness is associated with greater risk of incident MCR and needs to be further examined as a potentially modifiable risk factor. Our findings also emphasize the need for an early screening of sleep disturbances as a potential preventive intervention for cognitive decline, whether depressive symptoms are present. If we failed to show an interaction between depressive symptoms and sleep disturbances significantly associated with incident MCR, the GDS

score seemed as a potential cofounding variable in analyses. This suggests the interest of dedicated observational studies and mediation analyses for a better understanding of the interplay of sleep disorders, depressive symptoms, and cognitive decline through the MCR pathway. Further clinical trials are needed to test the benefit of interventions for sleep disturbances on preventing cognitive decline, as well as cohort studies with longer follow-up periods to establish causal and bidirectional relationships between sleep disturbances and MCR. In addition, there is a need for clinicopathologic and biological studies to explain the pathologic mechanisms that link sleep disturbances to MCR and cognitive decline.

Acknowledgment

The authors acknowledge Ying Jin, Albert Einstein College of Medicine, for her advice and guidance in analyses.

Study Funding

The Central Control of Mobility in Aging was supported by National Institute on Aging grants (R01 AG044007 and R01 AG03692101A1). The content is solely the responsibility of the authors.

Disclosure

The authors report no relevant disclosures. Go to Neurology.org/N for full disclosures.

Publication History

Received by *Neurology* June 5, 2024. Accepted in final form September 10, 2024. Submitted and externally peer reviewed. The handling editor was Associate Editor Linda A. Hershey, MD, PhD, FAAN.

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