

Sleep Rhythmicity as a Core Domain of Multidimensional Sleep Health Associated with Cognitive Impairment in Older Men

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Purpose: Sleep encompasses multiple dimensions, each potentially involving distinct parameters that collectively capture the complex features of sleep health. However, limited studies focused on the construction of objective sleep multidimensions and its associations with cognitive impairment.

Patients and Methods: The study included 2670 community-dwelling older men from the Osteoporotic Fractures in Men study. Wrist actigraphy was used to collect sleep data. Latent sleep dimensions were identified from objectively measured sleep parameters using exploratory factor analysis without prespecified structures. Longitudinal associations between sleep domains and cognitive impairment were evaluated using Cox proportional hazards models over a mean follow-up of 7.4 years. XGBoost with SHapley Additive exPlanations (SHAP) was used to rank the predictive importance of each domain.

Results: Five dimensions of sleep health framework were identified: rhythmicity, quality, duration, regularity, and timing. Disrupted rhythmicity was significantly associated with an increased risk of cognitive impairment (HR = 1.21, 95% CI: 1.07–1.37, $p = 0.002$). Longer duration (HR = 1.13, 95% CI: 1.00–1.28, $p = 0.043$), poorer regularity (HR = 1.13, 95% CI: 1.00–1.27, $p = 0.046$) and lower quality (HR = 1.13, 95% CI: 1.01–1.27, $p = 0.040$) were also linked to elevated risk in fully adjusted model. No significant association was observed between timing and cognitive impairment. SHAP analysis indicated that rhythmicity ranked high in predictive importance compared with traditional risk factors and was the most influential domain among the sleep dimensions. After stratification, disrupted rhythmicity remained significantly associated with cognitive impairment in most demographic and lifestyle subgroups.

Conclusion: Our integrative modelling approach provides novel insights into the complex relationships between distinct sleep domains and cognitive impairment, highlighting rhythmicity as a key factor for preserving cognitive health in aging men. These findings suggest that sleep-related interventions, especially for management of rhythmicity, may be a promising approach for the prevention of cognitive impairment.

Keywords: sleep, cognitive impairment, rhythmicity, aging, actigraphy

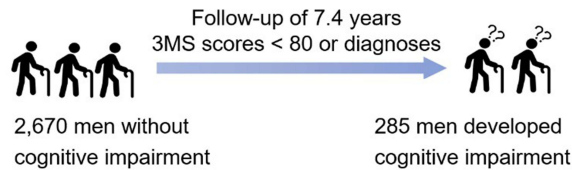
Introduction

Cognitive impairment is a major health problem affecting older people worldwide, which not only leads to a serious decline in personal quality of life, but also brings a huge burden of care and economic costs to society.¹ With the acceleration of the aging process of the population, finding modifiable factors to reduce the occurrence and development of cognitive impairment becomes a priority for public health and neuroscience research.²

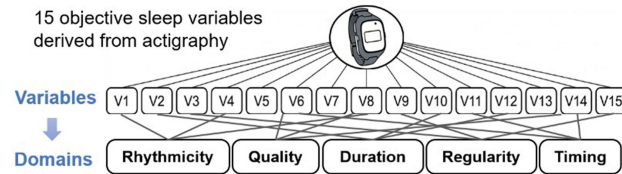
Graphical Abstract

Sleep Rhythmicity as a Core Domain of Multidimensional Sleep Health Associated with Cognitive Impairment in Older Men

1. Participants from MrOS sleep study



2. Construction of sleep health framework



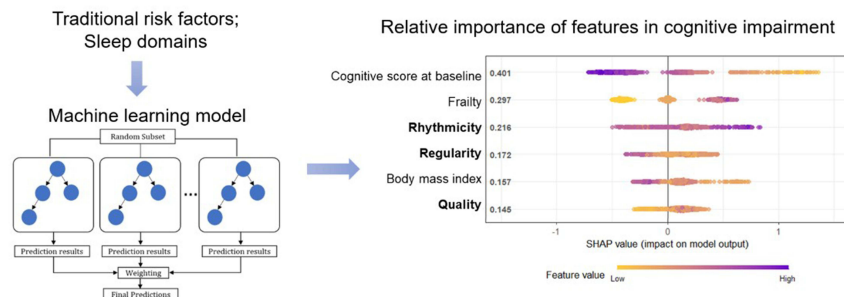
3. Cox regression

Sleep domains	HR (95% CI)
Rhythmicity	1.21 (1.07-1.37)
Regularity	1.13 (1.00-1.27)
Quality	1.13 (1.00-1.27)
Duration	1.13 (1.00-1.28)
Timing	1.00 (0.89-1.13)

0.75 1 1.25 1.5

Risk of cognitive impairment

4. Machine learning and relative importance of domains



Conclusion: Within sleep domains, rhythmicity emerging as the leading predictor of cognitive impairment in older men, followed by regularity and quality.

Sleep is a complex and multidimensional physiological process essential for brain recovery and cognitive maintenance, and its relevance to cognitive impairment is well established.^{3,4} However, previous studies focused on individual sleep parameters in isolation, such as total sleep duration, sleep efficiency, and wake after sleep onset.⁵⁻⁹ This approach of using a single metric to represent domains of sleep health is inherently limited,^{10,11} for it does not capture the integrative physiological meaning of sleep as a unified construct, nor does it elucidate the underlying relationship among individual sleep parameters or the relative contributions of different sleep domains.

To address these limitations, recent research has moved toward constructing multidimensional sleep frameworks using data-driven approaches, allowing multiple sleep characteristics to be summarized into underlying domains.^{11,12} While these approaches provide a more comprehensive representation of sleep structure, their implications for clinically relevant outcomes, particularly cognitive impairment, remain less well understood. In this study, we applied a data-driven strategy using objective actigraphy data from the Osteoporotic Fractures in Men (MrOS) Sleep Study to construct a comprehensive sleep framework. We then examined their longitudinal associations with incident cognitive impairment using Cox proportional hazards models and further quantified their relative importance based on interpretable machine-learning approaches. We aimed to identify which objectively defined sleep domains are independently associated with cognitive impairment and to determine their relative contributions to cognitive outcomes in older men.

Methods

Study Population

The MrOS Sleep Study is an ancillary study of the parent MrOS cohort, a multicenter cohort study of community-dwelling older men (website: <https://mrosonline.ucsf.edu>).¹³ Between 2003 and 2005, a total of 3135 community-dwelling men aged 65 years or



older were recruited from six US clinical centers (Birmingham, AL; Minneapolis, MN; Palo Alto, CA; Pittsburgh, PA; Portland, OR; and San Diego, CA). Cognitive assessments were subsequently administered at baseline and at four follow-up examinations (2005–2006 [mean follow-up 1.2 years], 2007–2009 [3.4 years], 2009–2012 [6.5 years], and 2014–2016 [10.8 years]). Among the 5994 men originally enrolled in the MrOS cohort, 3135 participated in the MrOS Sleep Study. Participants were excluded if they had cognitive impairment at baseline or lacked cognitive assessments ($n = 143$), had no actigraphy data ($n = 77$), had no follow-up cognitive evaluations ($n = 138$), or had missing information on sleep variables or covariates ($n = 107$). The final analytic sample consisted of individuals with complete data on sleep measures, covariates, and at least one cognitive assessment during follow-up ([Supplementary Figure 1](#)).

Sleep Variables Assessed by Actigraphy

In the MrOS Sleep Study, participants were instructed to wear an actigraphy device (Sleep-Watch-O, Ambulatory Monitoring, Inc., Ardsley, NY) on their non-dominant wrist for at least three consecutive 24-hour periods (mean $\pm$ SD: 5.13 ± 0.84 days). Activity data were recorded in 1-minute epochs. Sleep-wake states were derived from the actigraphy data using proportional integration mode with UCSD sleep-scoring algorithm.¹⁴ Actigraphy data were averaged across all valid nights for each participant to derive summary sleep parameters. Periods with excessive non-wear (defined as >2 hours during in-bed intervals or $>10\%$ of daytime intervals) were excluded to ensure data quality. Based on sleep data, we derived sleep variables and rest-activity rhythm metrics that met the following criteria:^{12,15} (1) obtained from actigraphy data related to sleep; (2) related to potential clinical and/or scientific relevance to cognitive impairment. Key sleep variables we focused on included sleep duration, sleep onset time, time in bed, midpoint of sleep, from sleep onset to wake, wake after sleep onset, sleep efficiency, and number of awakenings. Within rest-activity rhythm metrics, we included interdaily stability (IS), intradaily variability (IV), pseudo-F statistic (PsF), and acrophase,¹⁶ as they are closely related to sleep-wake patterns.^{17–20} IS quantifies the consistency of rest-activity rhythms across days, with higher values indicating greater sleep stability. IV reflects the degree of rhythm fragmentation, with higher values denoting more fragmented sleep. PsF represents the robustness or strength of the rhythmic pattern, where higher values suggest a stronger and more consolidated rhythm. Acrophase characterizes the timing of peak activity within the circadian cycle. Earlier acrophase values correspond to a tendency for earlier sleep preference, whereas later values indicate delayed sleep preference.

Cognitive Outcome

Cognitive assessments were conducted by trained staff during each clinic visit. The Modified Mini-Mental State (3MS) examination evaluated cognitive performance on a scale ranging from 0 to 100.²¹ Higher 3MS scores reflect better cognitive function, while declining scores indicate cognitive deterioration. Previous research has demonstrated that the 3MS provides high diagnostic accuracy for dementia using a cutoff score of 80.^{21,22} Cognitive impairment in this study was defined as (1) a 3MS score < 80 during follow-up visit; or (2) a self-reported physician diagnosis of dementia; or (3) use of medication for treating dementia. Participants with cognitive impairment at baseline were excluded. Follow-up duration was determined across four visits, and participants were censored at the occurrence of a cognitive event or at their last attended visit, whichever occurred first.

Covariates

Covariates were selected based on prior literature and established biological relevance to cognitive impairment. Demographic, lifestyle, and health-related factors included age at the sleep visit, race, body mass index (BMI), study site, marital status (married, widowed, separated/divorced or single), living arrangement (live alone or live with spouse, family or roommate), education level, smoking status, alcohol use, self-rated health condition, depressive symptoms assessed by the Geriatric Depression Scale, physical activity assessed by the Physical Activity Scale for the Elderly (PASE), sleep medications within the past 30 days (nonbenzodiazepines and nonbarbiturate sedative-hypnotics), caffeine intake, and tea consumption. Sleep apnea was defined as a self-reported physician diagnosis. Frailty at baseline was defined according to criteria established in previous MrOS studies:²³ (1) shrinking, defined as unintentional weight loss of $\geq 5\%$ since the baseline MrOS examination (mean $\pm$ SD years between examinations: 3.60 ± 0.49); (2) weakness, defined as grip strength in the lowest quintile within BMI quartiles or being unable to complete the grip strength test; (3) low energy, defined as a negative response to the item “Do you feel full of energy?” from the Geriatric Depression Scale; (4) slowness, defined as walking speed in the lowest height-stratified quintile or

being unable to complete the walking test; and (5) low physical activity, defined as a PASE score in the lowest quintile. Frailty status was defined as follows: robust (0 components), intermediate stage (1–2 components), and frail (≥ 3 components). In addition, self-reported medical comorbidities, including hypertension, congestive heart failure, stroke, myocardial infarction, transient ischemic attack, angina, coronary heart disease, cerebrovascular disease, diabetes, cancer, cataracts, and hearing problems, were included to account for chronic conditions that may influence both sleep characteristics and cognitive outcomes.

Statistical Analysis

Exploratory factor analysis (EFA) was conducted to identify sleep domains based on the actigraphy-derived sleep variables.²⁴ Prior to analysis, all sleep variables were standardized (mean = 0, SD = 1) to ensure comparability across measures and to improve model stability. To ensure the data sample was suitable for factor analysis, we performed Bartlett's test of sphericity ($p < 0.05$) to confirm patterned relationships among variables, and computed the Kaiser-Meyer-Olkin measure of sampling adequacy, with values above 0.6 considered acceptable. In line with previous research, we applied a “quartimax” orthogonal rotation using the *psych* package in R to simplify the factor structure and enhance interpretability, allowing the data structure to emerge without predefined domains.^{12,25}

Factors were extracted using maximum likelihood estimation. The number of factors was determined based on multiple criteria, including parallel analysis, eigenvalues, visual inspection of the scree plot, and theoretical interpretability. Parallel analysis compares observed eigenvalues with those obtained from randomly generated data, retaining factors with eigenvalues exceeding the corresponding random values. Variables were assigned to a factor if they had loadings greater than 0.6. When a variable loaded on multiple factors, it was assigned to the factor with the highest absolute loading. To maintain interpretive consistency, where higher factor scores indicate greater risk of cognitive impairment, certain sleep domain scores were reversed accordingly. Restricted cubic splines were employed to examine potential nonlinear relationships between sleep domains and the risk of cognitive impairment.²⁶

The associations between sleep domains and cognitive impairment were examined using multivariable Cox proportional hazards regression models to calculate hazard ratios (HRs) and 95% confidence intervals (CIs). For covariates that violated the proportional hazards assumption, time-dependent effects were incorporated using an extended Cox regression model, allowing the effects of these variables to vary over time.²⁷ Statistical significance was defined as $P < 0.05$. Three models were constructed: Model 1 adjusted for key demographic, lifestyle, and health-related factors, including age at the sleep visit, race, body mass index (BMI), study site, marital status (married, widowed, separated/divorced, or single), living arrangement (live alone or live with spouse, family or roommate), education level, smoking status, alcohol use, self-rated health condition, depressive symptoms and physical activity. Model 2 was further adjusted for major medical comorbidities, including hypertension, congestive heart failure, stroke, myocardial infarction, transient ischemic attack, angina, coronary heart disease, cerebrovascular disease, diabetes, cancer, cataracts, hearing problems and frailty. Based on model 2, model 3 further adjusted for sleep conditions, including sleep medications within the past 30 days (nonbenzodiazepines and nonbarbiturate sedative-hypnotics), caffeine intake, tea consumption, sleep apnea, and other sleep domains to account for their intercorrelations.

We applied the Extreme Gradient Boosting (XGBoost) algorithm with a Cox proportional hazards objective function to model the associations between sleep domains and the risk of cognitive impairment. To avoid overfitting and address potential multicollinearity, elastic net regression was first used for variable selection, incorporating the derived sleep domains, previously specified cognition-related covariates, and baseline 3MS scores. The optimal penalty parameter (λ) was determined using 10-fold cross-validation, and variables with non-zero coefficients at the optimal λ were selected. After variable selection, the dataset was randomly divided into a training set (70%) and a testing set (30%). The model development and tuning were conducted on the training set, while model performance was independently evaluated on the testing set. A five-fold cross-validation framework was implemented within the training data to prevent overfitting and ensure model robustness. Model hyperparameters were optimized using Bayesian optimization with an expected improvement acquisition function. Early stopping rounds were applied to prevent overfitting during training. A complete list of hyperparameters is given in the supplementary. Feature importance and contribution were further interpreted using SHapley Additive exPlanations (SHAP) values, which quantify the marginal impact of each feature on model predictions. Analyses were performed using the *glmnet*, *xgboost*, *rBayesianOptimization*, and *SHAPforxgboost* packages in R (version 4.5.1).^{28–31}



To minimize potential reverse causation, we conducted a sensitivity analysis excluding participants who developed the outcome within the first 2 years of follow-up in the Cox regression analysis. To more accurately define cognitive impairment, we excluded the 3MS component and restricted the outcome to self-reported dementia diagnoses only. We then examined the associations between sleep domains and the risk of dementia. Oblique rotations (oblimin and promax) were also applied in the EFA to allow for correlations between latent sleep domains and to assess the robustness of the identified factor structure. As cognitive impairment was assessed only at discrete follow-up visits, the exact onset time of the outcome was not directly observed. Therefore, we employed interval-censored Cox proportional hazards models. For each participant, the event interval was defined as the time between the last visit at which the participant was observed without evidence of cognitive impairment and the first visit at which cognitive impairment was identified. Participants who did not develop cognitive impairment during follow-up were treated as right-censored at their last available visit. These interval-censored data were analyzed using a semi-parametric proportional hazards model implemented in the *icenReg* R package.³²

Results

Baseline Characteristics

Table 1 summarizes the demographic and clinical characteristics of the study participants according to cognitive outcomes. A total of 2670 participants were included in the analysis, among whom 285 (10.7%) developed cognitive impairment during a mean (SD) follow-up of 7.4 (3.7) years. The mean (SD) age at baseline was 76.0 (5.3) years, and most participants were White (91.6%). Compared with those who remained cognitively normal, participants who developed cognitive impairment were older, had a higher BMI, were less likely to be White, had lower educational attainment, reported more depressive symptoms, and exhibited more disrupted rhythm (reflected by lower IS and higher IV).

Construction of Sleep Domains

Using EFA, we established a multidimensional sleep framework from 15 sleep-related variables (**Figure 1** and **Supplementary Table 1**). The number of domains was determined based on parallel analysis and visual inspection of the scree plot (**Supplementary Figure 2**). In accordance with previously proposed sleep health frameworks,^{11,12} five latent domains were identified, each representing distinct dimensions of sleep behavior: rhythmicity (sleep-wake pattern), timing (sleep preference for chronotype), regularity (deviation of sleep patterns across days), quality (sleep continuity and efficiency), and duration. This model accounted for 81.9% of the total variance, with strong intercorrelations observed among variables within each domain (**Supplementary Figure 3**).

Associations of Sleep Domains and Risk of Cognitive Impairment

The Cox regression was used to examine the association of sleep domains and risk of cognitive impairment (**Table 2**). After adjusting for basic health-related factors and major medical comorbidities (Model 2), disrupted rhythmicity was significantly associated with a higher risk of cognitive impairment (HR = 1.20, 95% CI = 1.06–1.36, $p = 0.003$). Longer duration (HR = 1.14, 95% CI = 1.01–1.29, $p = 0.033$), and poorer regularity (HR = 1.13, 95% CI = 1.00–1.27, $p = 0.046$) were also significantly associated with greater cognitive impairment risk. No significant association was observed for quality (HR = 1.12, 95% CI = 0.99–1.26, $p = 0.07$) and timing (HR = 1.00, 95% CI = 0.88–1.13, $p = 0.987$). After mutual adjustment for all sleep domains and other sleep conditions (Model 3), rhythmicity (HR = 1.21, 95% CI: 1.07–1.37, $p = 0.002$), regularity (HR = 1.13, 95% CI = 1.00–1.27, $p = 0.046$), and duration (HR = 1.13, 95% CI = 1.00–1.28, $p = 0.043$) remained robustly associated with cognitive impairment. Sleep quality was not significant in Models 1 and 2 but became significantly associated with cognitive impairment after full adjustment for sleep conditions (HR = 1.13, 95% CI: 1.01–1.27, $p = 0.040$). No evidence of nonlinear association was observed between sleep domains and the risk of cognitive impairment (**Supplementary Figure 4**).

Predictive Performance and Relative Importance of Sleep Domains in Cognitive Impairment

After variable selection, a total of 14 variables were included for subsequent analysis (**Supplementary Table 2**). In the best-performing XGBoost model, the concordance index (C-index) was 0.84 (95% CI: 0.80–0.89) for the training set and

Table 1 Demographic Characteristics Stratified by Cognitive Outcome

Characteristic	Overall	Non-CI	CI ^a	P value
No.	2670	2385	285	
Age at sleep visit, y, mean (SD)	76.0 (5.3)	76.0 (5.3)	77.7 (5.6)	<0.001***
BMI, kg/m ² , mean (SD) ^b	27.2 (3.8)	27.3 (3.8)	26.6 (4.0)	0.002**
Race, n (%)				0.005**
White	2445 (91.6)	2197 (92.1)	248 (87.0)	
Non-white ^c	225 (8.4)	188 (7.9)	37 (13.0)	
Education, n (%)				0.003**
Elementary school or below	118 (4.4)	100 (4.2)	18 (6.3)	
High school	1012 (37.9)	883 (37.0)	129 (45.3)	
College	809 (30.3)	728 (30.5)	81 (28.4)	
Graduate school	731 (27.4)	674(28.3)	57 (20.0)	
Smoking status, n (%)				0.044*
Never	1066 (39.9)	936 (39.2)	130 (45.6)	
Past or current	1604 (60.1)	1449 (60.8)	155 (54.4)	
Alcohol use, n (%)	1786 (66.9)	1617 (67.8)	169 (59.3)	0.005**
Hypertension, n (%)	1319 (49.4)	1181 (49.5)	138 (48.4)	0.774
Myocardial infarction, n (%)	439 (16.4)	390 (16.4)	49 (17.2)	0.781
Self-rated health, n (%)				0.159
Excellent	916 (34.3)	832 (34.9)	84 (29.5)	
Good	1420 (53.2)	1263 (53.0)	157 (55.1)	
Fair	304 (11.4)	262 (11.0)	42 (14.7)	
Poor	23 (0.9)	22 (0.9)	1 (0.4)	
Very poor	7 (0.3)	6 (0.3)	1 (0.4)	
Geriatric depression score (0–15), mean (SD)	1.7 (2.1)	1.6 (2.1)	2.1 (2.3)	<0.001***
Global PSQI score (0–21), mean (SD)	5.5 (3.2)	5.5 (3.2)	5.7 (3.4)	0.466
Sleep duration, mins, mean (SD)	384.9 (72.1)	384.5 (72.0)	388.4 (73.4)	0.396
Sleep efficiency, %, mean (SD)	82.9 (10.1)	83.0 (10.1)	82.1 (10.1)	0.190
Interdaily stability, mean (SD)	0.7 (0.1)	0.7 (0.1)	0.7 (0.1)	0.001**
Intradaily variability, mean (SD)	0.6 (0.2)	0.6 (0.2)	0.7 (0.2)	<0.001***

Notes: *P value < 0.05, ** P value < 0.01, *** P value < 0.001. ^aCognitive impairment was defined as (1) Modified Mini-Mental State (3MS) examination score < 80 during follow-up; or (2) as self-reported physician diagnosis of dementia; or (3) use of medication for treating dementia. ^bBody mass index is calculated as weight in kilograms divided by height in meters squared. ^cThis category included African American, Asian, Native Hawaiian or other Pacific Islander, American Indian or Alaskan Native, multiracial, and unknown.

Abbreviations: CI, cognitive impairment; PSQI, Pittsburgh Sleep Quality Index.

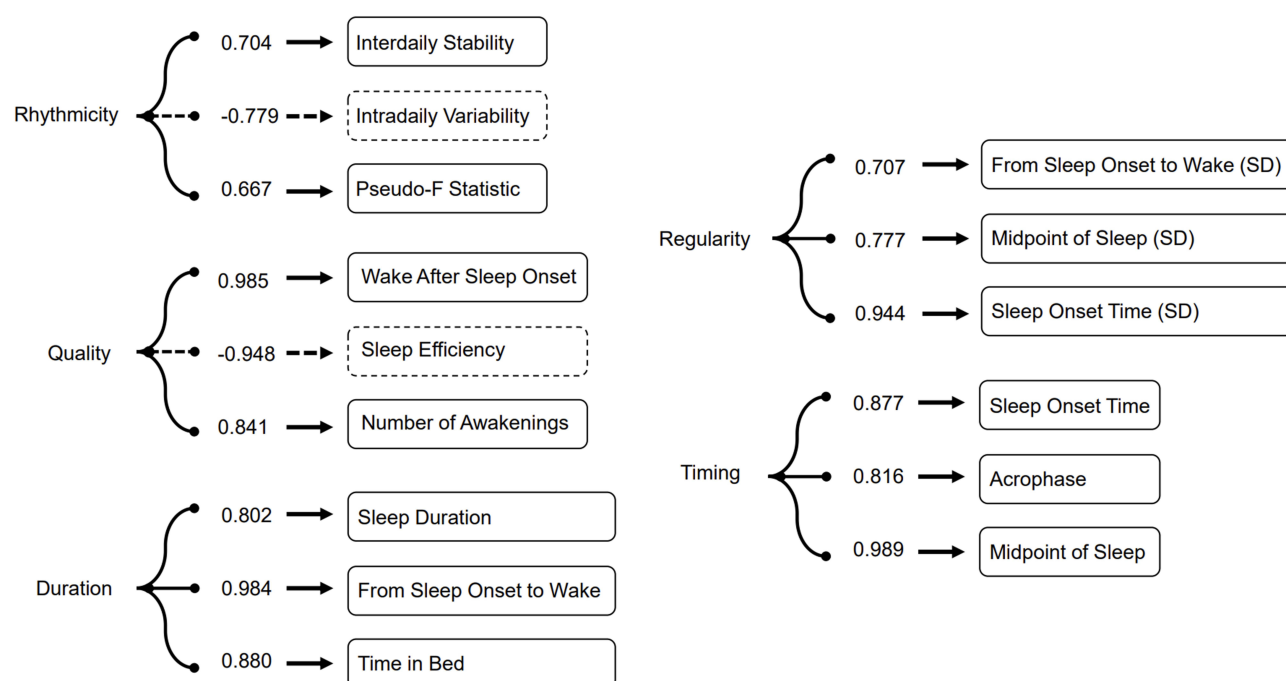


Figure 1 Exploratory factor analysis identified a five-factor model representing rhythmicity, quality, duration, regularity, and timing. Numbers indicate factor loadings for objective sleep variables; dashed line denotes negative associations between latent factors and their respective sleep variables. To maintain interpretive consistency, where higher factor scores indicate greater risk of cognitive impairment, rhythmicity was reversed in the following analysis. Abbreviation: SD, standard deviation.

0.74 (95% CI: 0.67–0.80) for the test set, indicating strong discriminative ability and good generalizability across datasets. Model hyperparameters are provided in [Supplementary Table 3](#).

SHAP analysis was used to assess the relative importance of each predictor to the model output for cognitive impairment. As shown in [Figure 2](#), baseline 3MS score was the most impactful factor (mean absolute SHAP value = 0.401), followed by frailty (0.297). Among sleep-related domains, rhythmicity ranked third overall (0.216), reflecting a consistent and substantial contribution to cognitive impairment. Regularity (0.172), quality (0.145) and duration (0.115) followed closely, each demonstrating comparable importance to conventional risk factors ([Supplementary Table 4](#)). Consistent with the Cox

Table 2 Cox Regression Analysis of Sleep Domains and Risk of Cognitive Impairment

	Model 1 ^a		Model 2 ^b		Model 3 ^c	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Rhythmicity	1.21 (1.08–1.37)	0.002**	1.20 (1.06–1.36)	0.003**	1.21 (1.07–1.37)	0.002**
Regularity	1.13 (1.01–1.27)	0.035*	1.13 (1.00–1.27)	0.046*	1.13 (1.00–1.27)	0.046*
Quality	1.12 (1.00–1.26)	0.057	1.12 (0.99–1.26)	0.070	1.13 (1.01–1.27)	0.040*
Duration	1.14 (1.01–1.29)	0.036*	1.14 (1.01–1.29)	0.033*	1.13 (1.00–1.28)	0.043*
Timing	1.02 (0.90–1.15)	0.805	1.00 (0.88–1.13)	0.987	1.00 (0.89–1.13)	0.954

Notes: *P value < 0.05, **P value < 0.01. ^aModel 1: adjusted for key demographic, lifestyle, and health-related factors, including age at the sleep visit, race, body mass index, study site, marital status, living arrangement, education level, smoking status, alcohol use, self-rated health condition, depressive symptoms and physical activity. ^bModel 2: further adjusted for major medical comorbidities, including hypertension, congestive heart failure, stroke, myocardial infarction, transient ischemic attack, angina, coronary heart disease, cerebrovascular disease, diabetes, cancer, cataracts, hearing problems and frailty. ^cModel 3: further adjusted for sleep medications within the past 30 days (nonbenzodiazepines and nonbarbiturate sedative-hypnotics), caffeine intake, and tea consumption, sleep apnea, as well as other sleep domains to account for their intercorrelations.

Abbreviation: HR, hazard ratio.

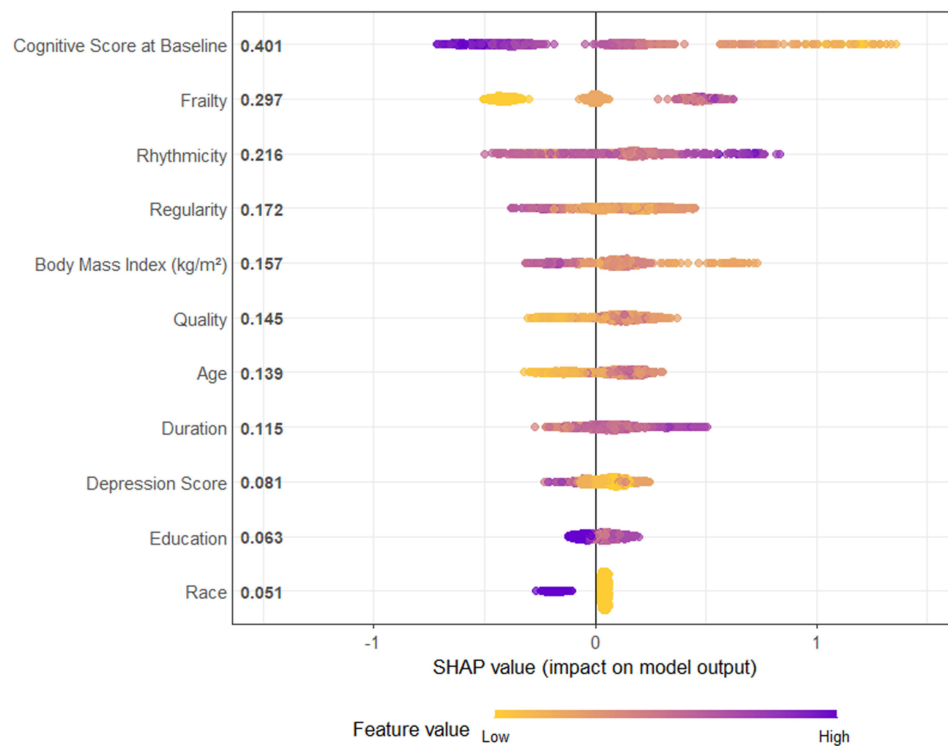


Figure 2 Shapley bee swarm plot for sleep domains and risk factors of cognitive impairment. Features are ranked on the y-axis according to their global importance, defined by the mean absolute SHAP value in descending order. Each point represents an individual observation. SHAP values indicate the contribution of each feature to the predicted risk of cognitive impairment, with positive values (to the right of the vertical line) indicating increased risk and negative values (to the left) indicating decreased risk. Color gradients from yellow to purple represent increasing raw values of each feature. For frailty, higher values indicate a greater number of frailty components. For education level, higher values indicate higher educational attainment. For race, purple represents White ethnicity and yellow represents other ethnic groups.

regression findings, the distribution of SHAP values across individuals suggested that lower rhythmicity, poorer sleep quality, longer sleep duration, and greater irregularity were associated with a higher predicted risk of cognitive impairment.

Subgroup Analysis

To evaluate the robustness of associations between sleep domains and cognitive impairment, we conducted stratified Cox regression analyses across key demographic and lifestyle subgroups, including age, BMI, education level, smoking status, and alcohol consumption with fully adjusted models (Figure 3 and [Supplementary Table 5](#)).

Disrupted rhythmicity showed the most consistent association with increased risk of cognitive impairment across subgroup analyses, including participants aged ≤ 80 years ($p = 0.034$), > 80 years ($p < 0.001$), BMI > 25 ($p = 0.025$), under-college education ($p = 0.009$), college education ($p = 0.021$), smokers ($p = 0.030$), non-drinkers ($p = 0.016$) and drinkers ($p = 0.034$). Although the association was not statistically significant in participants with BMI ≤ 25 or in non-smokers, the effect estimates remained in the same direction.

In contrast, the associations for other sleep domains were less consistent across subgroups. Quality was significantly associated with increased risk of cognitive impairment in smokers ($p = 0.035$), and drinkers ($p = 0.018$). Duration showed significant associations in the under-college subgroup ($p = 0.031$), non-drinker ($p = 0.040$) and smokers ($p = 0.042$). Regularity was positively associated with cognitive impairment risk in non-drinkers ($p = 0.003$) and those with BMI ≤ 25 ($p = 0.014$). A significant interaction between regularity and alcohol use was observed (p for interaction = 0.048). Timing did not show significant associations in any subgroup.

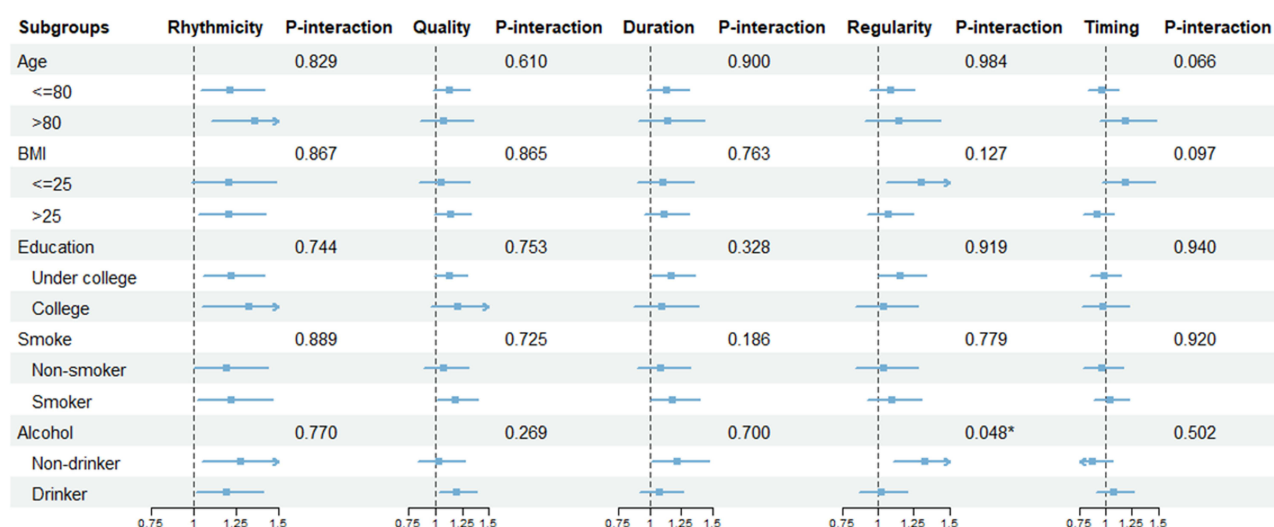


Figure 3 Subgroup analyses of associations between sleep domains and risk of cognitive impairment. Forest plots show hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations of five sleep domains (rhythmicity, quality, duration, regularity, and timing) with cognitive impairment across subgroups stratified by age, body mass index, education level, smoking status, and alcohol consumption. Smoker was defined as individuals who were past or current smokers, and non-drinker was defined as those reporting no alcohol consumption in the past 12 months. Estimates were obtained from fully adjusted Cox proportional hazards models (Model 3).

Sensitivity Analysis

After excluding participants who developed cognitive impairment within the first two years of follow-up, the overall pattern of results was similar to the primary analyses (Figure 4 and [Supplementary Table 6](#)). Rhythmicity and regularity remained associated with a higher risk of cognitive impairment across all models (Model 3: rhythmicity, HR = 1.21, 95% CI: 1.05–1.39, $p = 0.008$; regularity, HR = 1.18, 95% CI: 1.04–1.33, $p = 0.013$). Quality was not significantly associated with risk in Model 1 or Model 2, but became associated with a higher risk after further consideration for other sleep

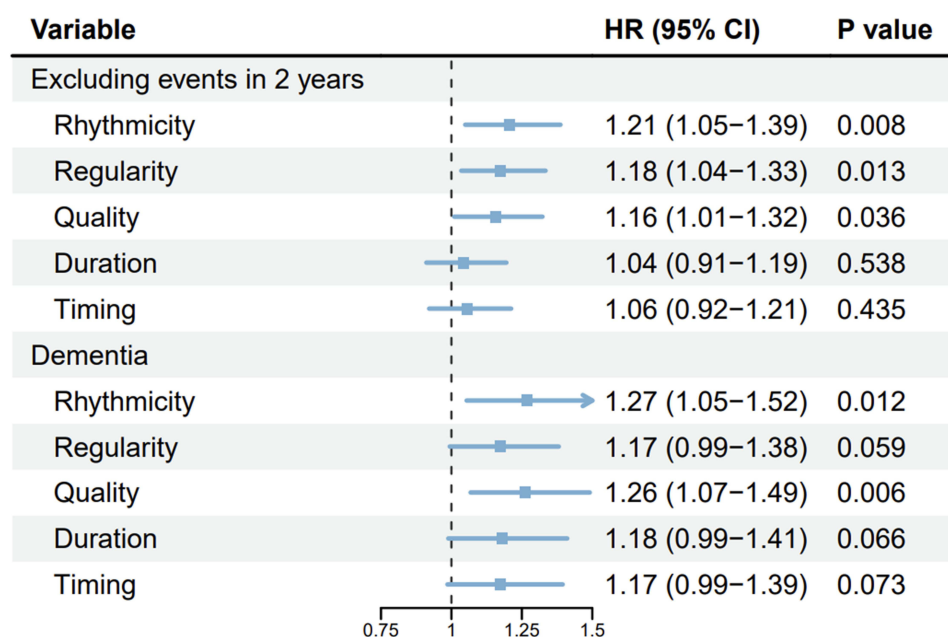


Figure 4 Sensitivity analyses of sleep domains and cognitive outcomes: cognitive impairment excluding early events and dementia diagnoses. Forest plots show hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations between sleep domains and cognitive outcomes. Analyses were conducted under two conditions: (1) excluding cognitive impairment events occurring within the first 2 years of follow-up, and (2) restricting the outcome to clinically diagnosed dementia. All estimates are derived from fully adjusted models (Model 3).

conditions (Model 3: HR = 1.16, 95% CI: 1.01–1.32, $p = 0.036$). Duration and timing were not associated with risk in all models after excluding early events.

When restricting the outcome to clinically diagnosed dementia (self-reported physician diagnosis), poorer rhythmicity and lower sleep quality were associated with increased dementia risk across all models. Although sleep duration and regularity did not reach statistical significance in the fully adjusted model, their effect estimates remained in the same direction (Figure 4 and Supplementary Table 6).

In sensitivity analyses using oblique rotations (oblimin and promax), the identified factor structure and subsequent associations were largely consistent with the primary analysis (Supplementary Tables 7 and 8). Rhythmicity remained significantly associated with cognitive impairment across all rotation methods in all models. Quality, duration, and regularity showed associations in each rotation method, although these were not consistent across models. No significant associations were observed for timing (Supplementary Tables 9 and 10). In the interval-censored models, the overall pattern of associations between sleep domains and cognitive impairment was broadly similar to the primary analysis. However, only rhythmicity demonstrated a statistically significant association with cognitive impairment in all models (Supplementary Table 11).

Discussion

Although prior studies primarily examined the relationships between individual sleep metrics and cognitive impairment, our study aimed to move beyond single sleep metric and evaluate associations of different sleep domains with cognitive outcomes in older men. Consistent with recent multidimensional sleep health frameworks,^{11,12} we constructed a five-domain structure encompassing rhythmicity, quality, duration, regularity, and timing. Our findings indicated that disrupted rhythmicity and poorer regularity were significantly associated with cognitive impairment. Longer duration and lower quality were associated with increased risk in certain conditions, whereas no association was observed for timing. Moreover, by systematically evaluating sleep domains and comparing their contributions with traditional risk factors, we provided an integrated perspective on the role of sleep in cognitive aging. Sleep domains remained among the strongest predictors even alongside established risk factors. Within sleep domains, rhythmicity emerged as most prominent predictor in the model. Taken together, these findings underscore the critical importance of multidimensional sleep health in cognitive decline, with sleep rhythmicity playing a particularly prominent role.

Rhythmicity is primarily characterized by sleep-related rest-activity rhythm patterns and captures the degree of rhythm fragmentation, day-to-day stability, and misalignment of circadian phase, reflecting disruption of the overall 24-hour sleep-wake cycle. Rhythmicity consistently emerged as the most consequential sleep domain, both in regression models and in importance rankings based on machine learning. Furthermore, in subgroup analyses, rhythmicity continued to show a protective association, suggesting that stable sleep-related rhythmicity may play a robust and generalizable role in preserving cognitive health across diverse population groups.

Disruption in rhythmicity reflects not only behavioral irregularities but also dysfunction of the endogenous central clock system, which becomes increasingly vulnerable with aging.³³ Evidence from epidemiological studies shows that more disturbed rhythms are associated with faster cognitive decline, greater risk of Alzheimer's disease, and accelerated cortical atrophy.^{34,35} In patients with established dementia, impaired rhythms further predict more rapid cognitive deterioration and disease progression.^{36,37} From a biological perspective, rhythmicity plays a central regulatory role in sleep architecture, metabolic homeostasis, and synaptic plasticity.^{38–40} Its disruption also impairs the glymphatic clearance pathway during sleep, thereby increasing β -amyloid burden and cerebrospinal fluid tau levels.^{41,42} Beyond neural mechanisms, disrupted rhythmicity is also linked to broader systemic disturbances, such as frailty, depressive symptoms, stroke, and chronic inflammation,^{43–46} each of which is independently associated with accelerated cognitive aging. Sleep rhythmicity appears to capture a multidimensional signal of physiological aging and neural vulnerability,⁴⁷ and may represent a core mechanism underlying susceptibility to cognitive decline in later life.

Beyond rhythmicity, our study also validated associations between other sleep domains and cognitive impairment, further supporting the validity of our comprehensive framework. We found that poorer sleep quality, characterized by higher sleep fragmentation and lower sleep efficiency, was associated with an increased risk of cognitive impairment. This finding aligns with extensive previous research,^{48,49} as fragmented and inefficient sleep disrupts sleep microstructure and continuity, thereby



compromising its core functions in memory consolidation and synaptic homeostasis.^{50,51} Sleep quality was not significantly associated with cognitive impairment in Models 1 and 2, but became significant only after further adjustment for other sleep-related factors (Model 3). Although the sleep domains were derived to be as independent as possible, this pattern suggests that sleep quality may not operate in isolation. Instead, its association with cognitive impairment may depend on the broader sleep context. Regarding duration, we observed that longer duration was associated with a higher risk of cognitive impairment. This finding may be related to the older average age of our study population and their generally shorter average sleep duration. In older adults, prolonged sleep duration often reflects compensatory responses to fragmented or poor-quality sleep, or diminished wake-maintenance capacity, rather than an increased physiological need for sleep. Extended sleep is also linked to broader physiological vulnerability and may further increase risk for cognitive decline in late life.⁵² When excluding early events, duration was no longer associated with cognitive impairment, suggesting that the observed association may be partly explained by reverse causation. Previous research also reported that longer sleep duration is connected to early or subclinical neurodegenerative changes in healthy adults.⁵³ The association between long sleep duration and poorer cognitive function may reflect underlying pathological processes rather than a causal risk factor. Regularity was associated with cognitive impairment in both the primary analysis and the analysis excluding early events. Previous evidence has linked sleep irregularity to smaller gray matter and hippocampal volumes, which may provide a potential pathway connecting irregular sleep patterns with cognitive impairment.⁵⁴ We also observed a significant interaction between sleep regularity and alcohol use, with the association between regularity and cognitive impairment evident only among non-drinkers. This finding suggests that the relevance of sleep regularity may differ across lifestyle subgroups and warrants further investigation. In contrast, timing was not associated with cognitive impairment in our study. This is consistent with previous reports,⁵⁵ and is further supported by subsequent variable selection procedures, which did not identify timing as a predictor. The relationship between timing and cognitive impairment may be influenced by factors such as educational attainment, underlying health conditions, sleep quality, and depressive symptoms.^{56–58}

The foremost strength of this study lies in the identification of multidimensional sleep domains, derived from multiple objective measures, without relying on predefined classifications. This approach enabled us to characterize both shared and distinct contributions of individual sleep features. In addition, by ranking the relative importance of sleep domains and risk factors associated with cognitive impairment, we provide an integrated perspective on sleep health and demonstrate that rhythmicity consistently emerged as one of the most influential determinants of cognitive impairment.

Several limitations should be acknowledged. First, the study population was restricted to older men, predominantly of White ethnicity, which may limit the generalizability of our findings. Second, our analyses focused exclusively on objective sleep measures, without incorporating additional subjective sleep domains that could yield further insights. Third, cognitive impairment was partly defined based on 3MS scores, which may be subject to educational level, measurement error and misclassification. Additionally, cognitive outcomes were assessed at different follow-up visits, and the exact time of cognitive impairment could not be precisely determined. Several covariates violated the proportional hazards assumption. We incorporated time-dependent effects, allowing for more flexible modeling of associations over follow-up. Finally, although we adjusted for a wide range of clinical confounders and dementia-related risk factors, the constraints of the available database meant that some potential confounding variables could not be accounted for.

Conclusion

In summary, this study establishes a multidimensional framework of sleep health and highlights its relevance to cognitive impairment. By integrating objective sleep measures with advanced machine-learning approaches, we demonstrated that disrupted rhythmicity was the predominant sleep domain associated with elevated risk of cognitive impairment in older men. Taken together, the results suggest that sleep-related monitoring and corresponding interventions for rhythmicity may contribute to the prevention of cognitive impairment. Future research should extend this framework to more diverse populations and further explore the mechanistic pathways and interventions of rhythmicity in preventing cognitive impairment.

Statement on the Use of Generative AI

We did not use generative AI in this study.

Data Sharing Statement

The MrOS data are available through the standard data access procedures described on the MrOS website (<https://mrosonline.ucsf.edu/>).

Ethics Approval and Consent to Participate

The MrOS Study was approved by the institutional review board at each participating clinical site and the study coordinating center, and written informed consent was obtained from all participants. Detailed information is available on the official MrOS website (<https://mrosonline.ucsf.edu/>). The current study protocol was reviewed and approved by the Ethics Committee of Peking University Sixth Hospital, Beijing, China (2025 Ethics Review No. 23). The study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

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Author Contributions

Chunlin Chen: Methodology, Writing – original draft, Visualization, Data curation, Formal analysis, Conceptualization, Software. Miaoyu Zhang: Writing – original draft, Methodology, Data curation, Software, Formal analysis. Zhilin Wang: Writing – original draft, Visualization. Shanshan Qu: Formal analysis, Validation, Writing – review & editing. Xinying Liu: Formal analysis, Validation, Writing – review & editing. Chi Zhang: Validation, Writing – review & editing. Jiahui Deng: Resources, Methodology, Writing – review & editing. Yanping Bao: Validation, Methodology, Writing – review & editing. Jie Shi: Validation, Resources, Writing – review & editing. Wenqiang Li: Validation, Supervision, Writing – review & editing. Lin Lu: Validation, Supervision, Funding acquisition, Writing – review & editing. Le Shi: Writing – review & editing, Funding acquisition, Project administration, Supervision, Methodology. All authors gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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