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Association of Rapid Eye Movement Sleep With Mortality in Middle-aged and Older Adults

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IMPORTANCE Rapid eye movement (REM) sleep has been linked with health outcomes, but little is known about the relationship between REM sleep and mortality.

OBJECTIVE To investigate whether REM sleep is associated with greater risk of mortality in 2 independent cohorts and to explore whether another sleep stage could be driving the findings.

DESIGN, SETTING, AND PARTICIPANTS This multicenter population-based cross-sectional study used data from the Outcomes of Sleep Disorders in Older Men (MrOS) Sleep Study and Wisconsin Sleep Cohort (WSC). MrOS participants were recruited from December 2003 to March 2005, and WSC began in 1988. MrOS and WSC participants who had REM sleep and mortality data were included. Analysis began May 2018 and ended December 2019.

MAIN OUTCOMES AND MEASURES All-cause and cause-specific mortality confirmed with death certificates.

RESULTS The MrOS cohort included 2675 individuals (2675 men [100%]; mean [SD] age, 76.3 [5.5] years) and was followed up for a median (interquartile range) of 12.1 (7.8-13.2) years. The WSC cohort included 1386 individuals (753 men [54.3%]; mean [SD] age, 51.5 [8.5] years) and was followed up for a median (interquartile range) of 20.8 (17.9-22.4) years. MrOS participants had a 13% higher mortality rate for every 5% reduction in REM sleep (percentage REM sleep SD = 6.6%) after adjusting for multiple demographic, sleep, and health covariates (age-adjusted hazard ratio, 1.12; fully adjusted hazard ratio, 1.13; 95% CI, 1.08-1.19). Results were similar for cardiovascular and other causes of death. Possible threshold effects were seen on the Kaplan-Meier curves, particularly for cancer; individuals with less than 15% REM sleep had a higher mortality rate compared with individuals with 15% or more for each mortality outcome with odds ratios ranging from 1.20 to 1.35. Findings were replicated in the WSC cohort despite younger age, inclusion of women, and longer follow-up (hazard ratio, 1.13; 95% CI, 1.08-1.19). A random forest model identified REM sleep as the most important sleep stage associated with survival.

CONCLUSIONS AND RELEVANCE Decreased percentage REM sleep was associated with greater risk of all-cause, cardiovascular, and other noncancer-related mortality in 2 independent cohorts.

Editorial

Supplemental content

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Sleep issues affect approximately 50 to 70 million individuals in the US,[1] contributing to multisystemic medical consequences including cardiovascular,[2,3] metabolic,[4] psychiatric,[5,6] impaired cognition,[7,8] quality of life,[9] and all-cause mortality.[2] Numerous studies have reported on the association between sleep and mortality, most focusing on effects of self-reported sleep duration.[3,10,11] Despite emerging evidence of a sleep-mortality association, determining the aspects of sleep driving the association has been a challenge given the multidimensionality of sleep.

As a result, little is known about how the proportion of time spent in rapid eye movement (REM) sleep and non-REM sleep stages N1, N2, and N3 relate to timing or cause of death. However, decreased REM sleep has been linked with poor mental and physical health outcomes.[12-20] We postulated that less REM sleep is associated with increased mortality risk and tested this association using data from the Outcomes of Sleep Disorders in Older Men (MrOS) Sleep Study.[21] To evaluate consistency and generalizability of the findings, we replicated the analysis in the Wisconsin Sleep Cohort (WSC).[22,23]

Key Points

Question Is less rapid eye movement (REM) sleep associated with increased mortality?

Findings In this cross-sectional study of 4050 individuals from 2 independent cohorts, lower amounts of REM sleep were associated with increased risk of all-cause mortality. There was a 13% higher mortality rate over 12.1 years for every 5% reduction in REM sleep in a cohort of 2675 older men, and the finding was replicated in a cohort of 1375 middle-aged men and women followed-up for 20.8 years.

Meaning Less REM sleep is associated with increased mortality risk.

Methods

The Stanford University institutional review board ruled this project exempt because the data used were publicly available. Participants of the MrOS and WSC studies provided written informed consent.

Participants

MrOS[24] is an observational, longitudinal cohort of 5994 community-dwelling men enrolled across 6 centers throughout the US.[21,25] Individuals were 65 years or older, able to walk without assistance, and were without bilateral hip replacements.[25] The MrOS Sleep Study ancillary project included 3135 men (59.2%) recruited from December 2003 to March 2005[26]; inclusion details for the individuals analyzed are in eFigure 1A in the Supplement. All men provided written informed consent; each site received institutional review board approval.

Data from the WSC study were used for replication. The WSC started in 1988 and is an ongoing, longitudinal, population-based study of the causes, consequences, and natural history of sleep disorders. It was established from a sample of state agency employees in Wisconsin aged 30 to 60 years at enrollment.[22,23] Rationale and design were previously published.[22]

Questionnaires were mailed every 5 years, and a subsample had a sleep study every 4 years. eFigure 1B in the Supplement has a flowchart of the WSC participants analyzed. Informed consent was obtained from all participants under a University of Wisconsin-Madison Health Sciences institutional review board.

Measures

Polysomnography and Subjective Sleep Measures

In MrOS, an unattended, portable in-home baseline polysomnography was conducted at sleep visit 1 (Safiro; Compumedics).[27] The primary exposure was REM sleep, evaluated as percentage of total sleep time, and total number of minutes spent in REM sleep during a single night. Standard polysomnography characteristics were evaluated based on previously published definitions[28] (eMethods in the Supplement). Self-reported sleep data included Epworth Sleepiness Scale,[29] Pittsburgh Sleep Quality Index,[30] Functional Outcomes of Sleep Questionnaire,[31] and positive airway pressure use for more than 3 months.

In the WSC study, nocturnal in-laboratory polysomnography was collected using Grass-Telefactor Heritage digital sleep systems. Polysomnography characteristics are described in the eMethods in the Supplement. Because the current analysis included the Epworth Sleepiness Scale (which was collected beginning in 1993), the polysomnography data used were the earliest available with Epworth Sleepiness Scale data (collected via mailed survey).

Actigraphy Measures

In MrOS, home sleep-wake patterns were estimated using wrist actigraphy (SleepWatch-O; Ambulatory Monitoring) recorded in proportional integration mode.[32] Participants were asked to wear devices continuously on their nondominant wrist for 4 or more consecutive 24-hour periods and to complete sleep logs to track time in and out of bed plus when the device was removed. Sleep logs were used to edit data and set sleep intervals. Actigraphy scoring algorithms used in this study have been previously published.[33]

Actigraphy measures included mean total sleep time (minutes) while in bed, mean sleep latency (minutes), mean wake after sleep onset while in bed (minutes), mean nighttime sleep efficiency, and mean total sleep time (minutes) outside sleep interval. Data were averaged over the entire period the device was worn to best reflect usual sleep patterns. Actigraphy was not collected for the WSC study.

Mortality Outcome

In MrOS, after baseline, participants were contacted every 4 months to determine vital status. Next of kin were contacted in cases of nonresponse. Reported deaths through 2018 were confirmed by centralized review of death certificates. Of 2872 men with sleep data, 31 (1.1%) were missing information on mortality data and 166 (5.8%) ended participation during

the follow-up period and were excluded from analyses. Cause of death was categorized by *International Classification of Diseases, Ninth Revision* codes as cardiovascular (396.9-442, 966.71, and 785.51), cancer (141.9-208.0), and other (codes not in previous categories). For each analysis of cause-specific mortality, individuals who died of a different cause were censored.

In WSC, deaths through 2018 were identified by matching social security numbers with 2 death record sources: National Death Index and Wisconsin State Bureau of Health Information and Policy, Vital Records Section. Matches on social security number were verified with participants' age and sex. Cause of death was categorized using the same *International Classification of Diseases, Ninth Revision* codes as MrOS.

Other Mental and Physical Measures

In MrOS, education, race/ethnicity, body mass index (calculated as weight in kilograms divided by height in meters squared), neck and hip circumference, smoking status, weekly alcohol use, and daily caffeine intake were collected at baseline along with the 15-item Geriatric Depression Scale,[34] Modified Mini-Mental State Examination[35] (evaluated as continuous and binary variable with a score <77 indicating impairment[36]), and Physical Activity Scale for the Elderly Scale.[37]

Data on prescription and nonprescription medications were collected at baseline. Each medication was matched to its ingredient(s) using the Iowa Drug Information Service Drug Vocabulary.[38] Current use of medications known to affect sleep (antidepressants, benzodiazepines) and sleep medications (nonbenzodiazepines, nonbarbiturate sedative hypnotics) were used.

Self-reported history of physician diagnosis identified hypertension, angina, stroke, heart attack, transient ischemic attack, congestive heart failure, type 2 diabetes, chronic obstructive pulmonary disease, osteoarthritis, and rheumatoid arthritis.

In WSC, body mass index was assessed during the polysomnography visit. Data on education, race/ethnicity, smoking habits, weekly alcohol, and daily caffeine use were obtained by questionnaire. Participants reported current use of antidepressants or sedatives and physician diagnosis of hypertension, coronary artery disease, or heart attack.

Statistical Analysis

Analysis began May 2018 and ended December 2019. Missing data were considered missing at random and imputed using multivariate imputation by chained equations operationalized using the R, version 3.2.5 MICE package (R Foundation).[39] Rate of loss to follow-up was less than 10%. Based on actigraphy data, individuals with mean total sleep time more than 8 hours were categorized as long sleepers and total sleep time less than 5 hours as short sleepers.

Survival Models

Cox proportional hazards models were used to assess associations between percentage of REM sleep and all-cause, cardiovascular, cancer, and other mortality. Results are reported as hazard ratios (HRs) with 95% CIs for every 5% decrease in REM sleep (similar to SD and more clinically relevant than a 1% change). Analyses were performed using SAS, version 9.4 (SAS Institute) and R studio version 1.1.463 (R Foundation).

Cox models were built in 2 steps using a combination of clinical knowledge and empirical covariate selection. Model 1 included covariates selected based on known associations including age, race/ethnicity, education, body mass index, smoking status, alcohol, caffeine, medication use (sleep, antidepressant, or benzodiazepine), and study site. Next, more than 60 variables were evaluated using 6-fold cross-validation to select covariates to add to model 1 for final models (model 2).[40] At each fold, data from 1 site were withheld and an optimal model identified using the My.stepwise R package (R Foundation). The criterion for entry into the final model was inclusion in at least 3 of 6 optimal models. We chose not to withhold a random sample to gauge whether site was associated with variable selection. All proportional hazards assumptions were met. Potential interactions were explored using random survival forests[41,42]; potential threshold effects were evaluated using Kaplan-Meier survival curves.[43]

Sensitivity Analyses

Sensitivity analyses were conducted to rule out alternative explanations. First, analyses were run after excluding individuals censored in the first 2 years. Next, anyone with an Apnea-Hypopnea Index score greater than 30 and/or using antidepressants, benzodiazepines, or sleep medications was excluded. Another analysis excluded depressed individuals (Geriatric Depression Scale score >4 or antidepressant use). To assess residual confounding from sleep duration, we performed 2 analyses excluding individuals using different total sleep time definitions (total sleep time <5 hours or >8 hours from either polysomnography or actigraphy based on previous MrOS publication[26] and total sleep time <6 hours or >8 hours). Finally, models were run using total REM sleep minutes and dichotomized percentage of REM sleep (cut point = 15%; similar to lowest quartile threshold).

Sleep Architecture and Mortality

Conditional inference survival tree and random survival forest methods were used to explore which sleep stages may be driving significance because sleep stages were interdependent (they add up to 100%). Percentage times in each sleep stage were used as predictors of all-cause mortality in MrOS. Variable importance was calculated from random forest results using mean decreased accuracy. For more details, see the eMethods in the Supplement.

Validation

Cox models were repeated using the WSC data set after matching all possible covariates across both data sets. All-cause mortality model was stratified by sex.

Results

Characterization of Study Populations

The MrOS cohort included 2675 individuals (2675 men [100%] and 2448 white individuals [91.5%]) with a mean

Table 1. Baseline Demographic, Lifestyle, and Health Characteristics of the MrOS Cohort by REM Quartile

Characteristic	No. (%)			
	Q1: <14.8%	Q2: 14.8%-19.4%	Q3: 19.5%-23.5%	Q4: >23.6%
No.	677	662	667	669
Age, mean (SD), y				
Sleep visit	77.5 (5.7)	76.4 (5.5)	75.7 (5.5)	75.7 (5.2)
Last follow-up	86.8 (5.6)	86.7 (5.2)	86.5 (5.2)	86.4 (4.9)
Race				
White	626 (92.5)	616 (93.1)	607 (91.0)	599 (89.5)
Nonwhite[a]	51 (7.5)	46 (6.9)	60 (9.0)	70 (10.5)
Education				
<High school degree	46 (6.8)	33 (5.0)	23 (3.4)	28 (4.2)
High school degree and some college	263 (38.8)	268 (40.5)	255 (38.2)	249 (37.2)
≥College degree	368 (54.4)	361 (54.5)	389 (58.3)	392 (58.6)
Body mass index, mean (SD)[b]	27.4 (4.1)	27.2 (3.9)	27.0 (3.6)	27.2 (3.6)
Average circumference, cm				
Neck	39.5 (3.0)	39.5 (2.9)	39.4 (2.7)	39.4 (2.7)
Hip	102.9 (8.9)	103.0 (8.4)	102.7 (8.2)	103.1 (8.6)
Smoking status				
Never	272 (40.2)	247 (37.3)	283 (42.4)	254 (38.0)
Past	387 (57.2)	403 (60.9)	371 (55.6)	402 (60.1)
Current	17 (2.5)	12 (1.8)	13 (1.9)	13 (1.9)
Daily caffeine intake, mg/d	227.0 (239.9)	235.0 (232.9)	230.0 (249.9)	250.8 (262.7)
Alcohol use, drinks/wk[c]	1.7 (1.6)	2.0 (1.8)	2.0 (1.7)	1.9 (1.7)
Current medication use				
Antidepressant	83 (12.3)	40 (6.0)	44 (6.6)	34 (5.1)
Benzodiazepine	40 (5.9)	33 (5.0)	20 (3.0)	32 (4.8)
Sleep medications	84 (12.4)	88 (13.3)	70 (10.5)	79 (11.8)
Hypertension	381 (56.4)	321 (48.5)	326 (48.9)	315 (47.1)
Angina	119 (17.6)	101 (15.3)	88 (13.2)	94 (14.1)
Stroke	29 (4.3)	26 (3.9)	19 (2.8)	23 (3.4)
Heart attack	141 (20.9)	108 (16.3)	105 (15.7)	110 (16.4)
Transient ischemic attack	82 (12.1)	72 (10.9)	47 (7.1)	53 (7.9)
Congestive heart failure	56 (8.3)	33 (5.0)	32 (4.8)	40 (6.0)
Type 2 diabetes	102 (15.1)	83 (12.5)	84 (12.6)	84 (12.6)
Chronic obstructive pulmonary disease	46 (6.8)	37 (5.6)	23 (3.4)	33 (4.9)
Osteoarthritis	174 (25.7)	158 (23.9)	162 (24.3)	155 (23.2)
Rheumatoid arthritis	69 (10.2)	49 (7.4)	45 (6.7)	54 (8.1)
3TMS score (0-100), mean (SD)	92.0 (7.2)	92.9 (6.1)	93.4 (5.2)	93.1 (5.4)
Cognitive impairment based on 3TMS (score ≤77)	21 (3.1)	15 (2.3)	10 (1.5)	11 (1.6)
Physical Activity Scale for the Elderly Score (0-400), mean (SD)	134.5 (72.4)	148.7 (69.8)	148.2 (68.3)	150.5 (69.9)
Geriatric Depression Score (0-15), mean (SD)	2.1 (2.4)	1.7 (2.1)	1.5 (1.8)	1.6 (2.0)

Abbreviations: 3TMS, Teng Mini-Mental State Examination; MrOS, Outcomes of Sleep Disorders in Older Men Sleep Study; Q, quarter; REM, rapid eye movement.

[a] This category included African American, Asian, Native Hawaiian or other Pacific Islander, American Indian or Alaskan Native, multiracial, and unknown.

[b] Body mass index is calculated as weight in kilograms divided by height in meters squared.

[c] n = 2664.

(SD) age of 76.3 (5.5) years at baseline and was followed up for a median (interquartile range) of 12.1 (7.8-13.2) years. The mean (SD) age was 86.6 (5.2) years at follow-up. Percentage of REM sleep ranged from 0% to 43.9% and was normally distributed. Overall mean (SD) percentage of REM sleep was 19.2% (6.6%) (mean [SD] time in REM sleep, 69.7 [28.6] minutes) with values increasing from 14.8% in the lowest quartile to 23.6% in the highest. **Table 1** reports demographic, lifestyle, and health characteristics varying across REM sleep quartile. Those in the lowest quartile tended to be older with higher rates of antidepressant use, hypertension, heart attack, transient ischemic attack, and lower Physical Activity Scale for the Elderly scores. As expected, most sleep variables varied across quartiles (**Table 2**).

The WSC cohort included 1386 individuals (753 men [54.3%] and 1311 white individuals [94.6%]) with a mean (SD)

Table 2. Baseline Sleep Data From the Outcomes of Sleep Disorders in Older Men Sleep Study Cohort by REM Quartile

Characteristic	Mean (SD)			
	Q1: <14.8%	Q2: 14.8%-19.4%	Q3: 19.5%-23.5%	Q4: >23.6%
No.	677	662	667	669
Objective sleep measures[a]				
Stage N1				
Sleep, % time	7.8 (5.3)	7.0 (4.3)	6.3 (3.5)	6.0 (3.4)
Sleep, min	24.7 (14.7)	24.7 (13.8)	23.1 (12.5)	22.0 (12.6)
Stage N2				
Sleep, % time	69.2 (9.6)	63.8 (8.8)	61.5 (7.5)	56.7 (7.8)
Sleep, min	228.7 (63.6)	229.5 (53.3)	226.6 (46.4)	209.0 (45.7)
Stage N3				
Sleep, % time	12.3 (10.0)	11.8 (9.4)	10.7 (7.9)	9.9 (7.8)
Sleep, min	41.8 (35.5)	43.0 (34.8)	39.6 (30.1)	36.7 (28.5)
Stage REM				
Sleep, % time	10.7 (3.5)	17.4 (1.4)	21.5 (1.2)	27.4 (3.2)
Sleep, min	36.2 (15.0)	62.5 (12.4)	79.3 (13.2)	101.2 (21.2)
Time in bed, min	481.1 (84.8)	488.6 (72.3)	484.9 (69.0)	483.0 (72.3)
Total sleep time, min	330.6 (79.8)	359.0 (64.5)	368.0 (58.2)	368.1 (62.1)
Sleeper based on actigraphy				
Long (>8 h), No. (%)	41 (6.1)	50 (7.6)	38 (5.7)	61 (9.1)
Short (<5 h), No. (%)	113 (16.7)	65 (9.8)	64 (9.6)	65 (9.7)
Wake after sleep onset, min	134.5 (73.4)	115.3 (65.7)	105.3 (57.1)	102.5 (61.7)
Sleep efficiency, %	71.6 (13.5)	76.3 (11.4)	78.3 (10.2)	78.8 (10.9)
Sleep latency, min	26.6 (33.2)	24.8 (30.0)	19.4 (21.1)	21.6 (22.5)
REM latency, min	151.9 (98.4)	107.8 (70.3)	91.0 (53.8)	84.0 (58.2)
Overall arousal index	28.4 (13.9)	24.2 (11.5)	22.6 (10.5)	19.5 (8.9)
Apnea hypopnea index (3% desaturation/arousal)	25.9 (18.4)	20.5 (15.7)	19.3 (14.9)	17.1 (13.3)
Desaturation index (desaturations/h)	26.3 (19.9)	20.1 (15.3)	19.3 (14.9)	17.0 (13.1)
Periodic limb movements index	40.1 (42.0)	35.0 (37.3)	35.4 (36.4)	32.7 (34.7)
Periodic limb movements with arousals index	5.3 (6.9)	4.2 (2.8)	4.0 (5.6)	3.0 (4.1)
Sleep time with saturated oxygen below 80%, % time	0.14 (0.62)	0.08 (0.37)	1.09 (0.56)	0.05 (0.42)
No. of N2 to N1 sleep stage shifts/h	0.02 (0.07)	0.01 (0.04)	0.01 (0.04)	0.02 (0.05)
No. of N3 to N1/N2 sleep stage shifts/h	2.7 (2.0)	2.7 (1.9)	2.7 (1.7)	2.4 (1.5)
Actigraphy in bed, mean, min				
Total sleep time	375.9 (79.8)	387.1 (73.0)	385.7 (69.3)	393.1 (68.8)
Wake after sleep onset	89.7 (51.3)	77.4 (42.4)	74.3 (41.1)	70.7 (38.9)
Sleep latency	33.7 (32.8)	32.4 (36.4)	29.3 (29.4)	27.0 (26.5)
Sleep efficiency, % time	80.1 (11.9)	82.7 (10.2)	83.4 (9.5)	84.3 (8.9)
Scored sleep while outside of sleep interval	77.0 (64.0)	68.8 (61.0)	63.7 (55.7)	65.8 (56.6)
Self-reported sleep measures				
ESS score (0-18)	6.2 (3.8)	6.1 (3.8)	6.4 (3.6)	5.9 (3.5)
Excessive daytime sleepiness (ESS score >10), No. (%)	89 (13.1)	88 (13.3)	97 (14.5)	74 (11.1)
Positive airway pressure use >3 mo, No. (%)	10 (1.5)	4 (0.6)	0 (0.0)	0 (0.0)
Pittsburgh Sleep Quality Index total score	6.1 (3.6)	5.4 (3.1)	5.3 (3.0)	5.5 (3.4)
Functional Outcomes of Sleep Questionnaire total score	18.6 (1.8)	18.6 (1.6)	18.8 (1.3)	18.7 (1.5)

Abbreviations: ESS, Epworth Sleepiness Scale; REM, rapid eye movement.

[a] Non-REM sleep is broken into 3 stages (N1, N2, N3) based on frequency, amplitude, and morphology of the brain waves. These stages roughly correspond with the depth of sleep, with N1 having the lowest arousal threshold (easiest to waken) and N3 the highest (hardest to waken).

age of 51.5 (8.5) years at baseline. Participants were followed up for a median (interquartile range) of 20.8 (17.9-22.4) years (mean [SD] age at follow-up, 70.2 [7.7] years). Minutes in REM sleep (mean [SD], 67.8 [28.9] min) and percentage of REM sleep range (0%-43.0%) were similar, but overall mean percentage of REM sleep (mean [SD], 17.6% [6.5%]) was lower compared

with MrOS data, possibly owing to longer total sleep time during in-laboratory vs in-home studies.

WSC individuals were younger, had a mix of men and women, had more obesity (body mass index of 30.7 vs 27.2), consumed more alcohol (3.6 vs 1.9 drinks per week), were more likely to be current or never smokers, and had higher antidepressant and/or sedative use. Despite these differences, most measures had similar distributions across REM sleep quartiles compared with MrOS (**Table 3**).

Survival Models

In MrOS, 1404 deaths (52.5%) were reported over a median (interquartile range) follow-up of 12.1 (7.8-13.2) years. Regression analysis of percentage of REM sleep as a continuous variable showed a downward trend, reflected in the lowest quartile of percentage of REM sleep having the highest percentage of deaths for each mortality category (eTable 1 in the Supplement). A 13% higher all-cause mortality rate for every 5% reduction in REM sleep (hazard ratio [HR], 1.13; 95% CI, 1.08-1.19) was observed after adjusting for covariates (**Table 4**). The association persisted for cardiovascular disease–related mortality (HR, 1.11; 95% CI, 1.02-1.20) and other mortality (HR, 1.19; 95% CI, 1.11-1.28) but was not significant for cancer-related mortality (HR, 1.06; 95% CI, 0.96-1.17) (Table 4). Kaplan-Meier curves showed a possible threshold, particularly for cancer-related deaths (**Figure**). Individuals with less than 15% REM sleep had a higher mortality rate compared with individuals with 15% or more for all mortality definitions (HR range, 1.20-1.35) (eTable 2 in the Supplement).

Sensitivity analyses found the 1776 of 2675 individuals (66.4%) who slept 5 to 8 or 6 to 8 hours had larger effect sizes on all outcomes except cardiovascular disease–related mortality in the 6- to 8-hour group (HR, 1.00; 95% CI, 0.85-1.19). No substantial differences were found analyzing the 2591 of 2675 individuals (96.9%) who survived the first 2 years, 1684 of 2675 individuals (63.0%) without severe sleep apnea or medication use, 2291 of 2675 individuals (85.6%) without depression (eTable 3 in the Supplement), or when using absolute time in REM sleep (data not shown).

Validation in the WSC

There were fewer deaths in the WSC sample (184 [13.3%]), which was expected given younger ages. As with MrOS, those in the lowest REM sleep quartile had the highest percentages of death (eTable 1 in the Supplement). The effect size for 5% reduction in REM sleep on risk of all-cause mortality (HR, 1.17; 95% CI, 1.03-1.34) and noncardiovascular disease, noncancer-related mortality (HR, 1.26; 95% CI, 1.01-1.58) were significant despite younger age, inclusion of both men and women, longer follow-up period, reduced samples size, and event frequency. Effect sizes and direction for cardiovascular disease-related mortality (HR, 1.13; 95% CI, 0.87-1.45) and cancer-related mortality (HR, 1.13; 95% CI, 0.91-1.40) were similar to MrOS, although the smaller sample size widened CIs (Table 4).

When stratified by sex, decreased percentage of REM sleep was associated with all-cause mortality in women for every 5% REM sleep reduction (HR, 1.34; 95% CI, 1.07-1.68) but was not statistically significant in men (HR, 1.09; 95% CI, 0.92-1.30), with these estimates providing modest statistical evidence for a difference (*P* for interaction = .08).

Individuals with less than 15% REM sleep had a higher mortality rate compared with individuals with 15% or more with odds ratios ranging from 1.36 to 1.78 for all mortality definitions except cardiovascular (HR, 1.00; 95% CI, 0.52-1.90) (eTable 2 in the Supplement).

Sleep Architecture and Mortality

The first and second nodes in the conditional survival tree were percentage of REM sleep with cut points of 15.4% (similar to the lowest quartile cut point) and 10.9% (eFigure 2 in the Supplement). Percentage of N1 sleep was the fifth node with a cut point of 13.6% (eFigure 3 in the Supplement). The random survival forest model identified percentage of REM sleep as the most important sleep stage for predicting survival (mean decrease in accuracy = 0.058). Percentage of N1 sleep was a distant second at 0.001 (eFigure 3 in the Supplement). Both techniques found percentage of REM sleep overwhelmingly important compared with other stages, implying that contributions from other stages were inconsequential. This is consistent with the Cox results where the REM sleep β coefficient (0.17) was substantially higher than the N2 sleep β coefficient (0.06).

Discussion

Survival analysis of older, community-based men found an association between less REM sleep and increased mortality, which replicated in an independent data set of middle-aged men and women. Similar effect sizes (HR ranging from 1.13-1.19 per 5% REM sleep decrease) were observed in MrOS for all-cause, cardiovascular, cancer, and other mortality after adjusting for confounding demographic, sleep, and health-related covariates. These effect sizes are slightly larger than mortality risk resulting from aging 1 year (HR for age ranging from 1.11-1.16) based on MrOS data. Sensitivity analyses showed findings persisted in subgroups with sleep duration between 5 to 8 and 6 to 8 hours (except cancer), without depression, severe sleep apnea, and in those not using medications that may affect REM. In sum, decreased REM sleep was an indicator of mortality risk across a broad age range, which is consistent with the study evaluating REM sleep and mortality in the Sleep Heart Health Study.[44] When stratified by sex, there was a higher rate of all-cause mortality in women compared with men.

Despite the different outcome measures, our findings are consistent with reports linking REM sleep to other age-related diseases and conditions. Song et al[45] found that increased time in N1 sleep and less time in REM sleep were associated with worsening cognitive performance in MrOS. Smagula et al[46] evaluated the association between sleep stages and comorbid depression and anxiety in MrOS and found men with clinically significant depressive symptoms spent more time in N2 sleep and less time in REM sleep. Suh et al[47] found a short average cycle length (sequence of non-REM and REM sleep stages, both >2 minutes and not interrupted by

Table 3. Baseline Demographic, Lifestyle, and Sleep Characteristics of the Wisconsin Sleep Cohort by REM Quartile

Characteristic	Mean (SD)			
	Q1: <13.3%	Q2: 13.3%-17.5%	Q3: 17.6%-21.7%	Q4: >21.8%
No.	345	348	347	346
Age, y				
Sleep visit	53.7 (9.0)	51.6 (8.5)	50.7 (8.3)	50.0 (7.8)
Last follow-up	71.6 (8.0)	70.0 (7.7)	69.7 (7.5)	69.8 (7.4)
Sex, No. (%)				
Male	202 (58.6)	189 (54.3)	187 (53.9)	175 (50.6)
Female	143 (41.4)	159 (45.7)	160 (46.1)	171 (49.4)
Race, No. (%)				
White	323 (93.6)	328 (94.3)	330 (95.1)	330 (95.4)
Nonwhite[a]	22 (6.4)	20 (5.7)	17 (4.9)	16 (4.6)
Education, y	14.8 (2.3)	14.8 (2.3)	14.6 (2.4)	14.5 (2.3)
No.	1375			
Body mass index[b]	32.6 (8.2)	29.6 (6.0)	30.0 (5.6)	30.4 (6.6)
Mean circumference, cm				
Neck	39.1 (4.4)	37.6 (4.3)	37.7 (4.0)	37.5 (4.2)
Hip	111.6 (15.7)	106.5 (12.1)	106.8 (12.0)	107.8 (13.5)
Smoking status, No. (%)				
Never	168 (48.7)	166 (47.7)	172 (49.6)	162 (46.8)
Past	133 (38.6)	121 (34.8)	131 (37.8)	125 (36.1)
Current	44 (12.8)	61 (17.5)	44 (12.7)	59 (17.1)
Daily caffeine intake (No. of servings/d)	3.0 (2.7)	3.0 (2.5)	3.1 (2.5)	2.9 (2.6)
Alcohol use (drinks/wk)	3.0 (4.4)	3.6 (5.0)	3.8 (5.0)	4.0 (6.1)
Medication use, current, No. (%)				
Antidepressant	65 (18.8)	50 (14.4)	30 (8.6)	46 (13.3)
Sedatives	19 (5.5)	18 (5.2)	17 (4.9)	9 (2.6)
Objective sleep measures[c]				
Stage N1				
Sleep, % time	12.4 (8.3)	10.0 (6.0)	8.6 (4.7)	8.2 (4.8)
Sleep, min	42.5 (26.0)	37.0 (22.0)	33.2 (18.3)	32.0 (18.1)
Stage N2				
Sleep, % time	64.9 (10.4)	61.8 (9.0)	58.8 (9.0)	54.1 (8.8)
Sleep, min	230.0 (56.1)	232.7 (51.3)	228.4 (50.3)	215.1 (47.5)
Stage N3				
Sleep, % time	13.2 (10.5)	12.6 (9.9)	12.9 (9.5)	11.7 (8.7)
Sleep, min	46.9 (38.7)	47.0 (37.1)	49.8 (37.0)	46.2 (34.0)
Stage REM				
Sleep, % time	9.5 (3.0)	15.6 (1.3)	19.6 (1.2)	25.9 (3.7)
Sleep, min	33.8 (12.4)	58.6 (10.1)	76.2 (12.0)	102.6 (20.7)
Time in bed, min	448.7 (45.9)	451.1 (48.2)	453.5 (51.7)	455.8 (47.3)
Total sleep time, min	353.5 (60.1)	375.6 (56.8)	387.9 (57.3)	396.3 (51.8)
Wake after sleep onset, min	78.7 (44.4)	61.7 (38.3)	52.9 (33.6)	47.1 (32.8)
Sleep efficiency, %	78.8 (11.0)	83.3 (9.4)	85.6 (8.4)	87.1 (8.2)
Sleep latency, min	14.7 (16.7)	12.0 (13.5)	10.8 (12.6)	11.2 (13.8)
REM latency, min	180.0 (84.0)	124.3 (61.7)	104.6 (49.9)	91.0 (45.5)
Apnea hypopnea index (3% desaturation/arousal)	23.2 (32.2)	12.0 (18.0)	10.0 (12.0)	9.6 (11.3)
Limb movements index	33.1 (25.9)	26.6 (23.8)	23.1 (21.0)	24.2 (19.6)
Self-reported sleep measures				
ESS score of 0-18	8.7 (4.1)	8.7 (4.3)	8.9 (4.0)	8.9 (3.9)
Excessive daytime sleepiness (ESS score >10), No. (%)	103 (29.9)	102 (29.3)	130 (37.5)	117 (33.8)
Self-reported sleepiness, No. (%)	77 (22.3)	75 (21.6)	75 (21.6)	81 (23.4)

Abbreviations: ESS, Epworth Sleepiness Scale; REM, rapid eye movement.

[a] This category included black, Asian or Pacific Islander, other, and unknown.

[b] Body mass index is calculated as weight in kilograms divided by height in meters squared.

[c] Non-REM sleep is broken into 3 stages (N1, N2, N3) based on frequency, amplitude, and morphology of the brain waves. These stages roughly correspond with the depth of sleep, with N1 having the lowest arousal threshold (easiest to waken) and N3 the highest (hardest to waken).

Table 4. Mortality HRs From Cox Regression for the Osteoporotic Fractures in Men Study and Wisconsin Sleep Cohort

Outcome	Overall Deaths, No. (%)	HR (95% CI)			
		Unadjusted	Age adjusted	Model 1[a]	Model 2[b]
Mortality risk ratios for the MrOS cohort using percentage REM as a continuous variable (5% decrease) (n = 2675)					
Mortality					
All-cause	1404 (52.5)	1.19 (1.14-1.24)	1.12 (1.07-1.16)	1.11 (1.07-1.15)	1.13 (1.08-1.19)
Cardiovascular	490 (18.3)	1.24 (1.16-1.33)	1.12 (1.05-1.20)	1.11 (1.03-1.18)	1.11 (1.02-1.20)
Cancer	310 (11.5)	1.16 (1.06-1.26)	1.03 (0.95-1.13)	1.03 (0.94-1.12)	1.06 (0.96-1.17)
Other	604 (22.5)	1.26 (1.19-1.34)	1.16 (1.09-1.23)	1.16 (1.09-1.23)	1.19 (1.11-1.28)
Mortality risk ratios for the Wisconsin sleep cohort using percent REM as a continuous variable (5% decrease) (n = 1386)					
Outcome	Overall Deaths, No. (%)	HR (95% CI)			
		Unadjusted	Age/sex adjusted	Model 1[c]	Model 2[d]
Mortality					
All-cause	184 (13.3)	1.22 (1.08-1.36)	1.15 (1.03-1.29)	1.14 (1.01-1.28)	1.17 (1.03-1.34)
Male (n = 753)	114 (15.1)	1.11 (0.96-1.28)	1.02 (0.88-1.18)	1.02 (0.89-1.19)	1.09 (0.92-1.30)
Female (n = 633)	70 (11.1)	1.38 (1.15-1.66)	1.36 (1.13-1.64)	1.29 (1.06-1.57)	1.34 (1.07-1.68)
Cardiovascular	50 (3.6)	1.33 (1.07-1.66)	1.21 (0.97-1.51)	1.18 (0.94-1.47)	1.13 (0.87-1.45)
Cancer	71 (5.1)	1.16 (0.97-1.40)	1.11 (0.92-1.33)	1.14 (0.93-1.36)	1.13 (0.91-1.40)
Other	63 (4.5)	1.20 (0.98-1.46)	1.16 (0.95-1.41)	1.13 (0.93-1.37)	1.26 (1.01-1.58)

Abbreviations: HR, hazard ratio; MrOS; Outcomes of Sleep Disorders in Older Men Sleep Study; REM, rapid eye movement; WSC, Wisconsin Sleep Cohort.

[a] Model 1 included age, race (white vs nonwhite), education, body mass index, smoking status, weekly alcohol, daily caffeine, antidepressants, benzodiazepines, sleep medications, and site.

[b] Model 2 included model 1 plus overall arousal index, sleep time with saturated oxygen below 80%, percentage stage non-REM sleep stage 2 sleep, actigraphy mean scored sleep while outside of sleep interval, actigraphy wake after sleep onset, Epworth Sleepiness Scale Score, Teng Mini-Mental State Examination score, Physical Activity Scale for the Elderly score, depression, congestive heart failure, chronic obstructive pulmonary disease, type 2 diabetes, heart attack, and stroke.

[c] Model 1 included age, sex, race (white vs nonwhite), education, body mass index, smoking status, weekly alcohol, daily caffeine, antidepressants, and sedatives.

[d] Model 2 included model 1 plus percentage stage non-REM sleep stage 2 sleep, wake after sleep onset, Epworth Sleepiness Scale score, emphysema, type 2 diabetes, heart attack, and stroke.

>2 minutes of wake) were significantly associated with cognitive decline.[48] While not directly associated with mortality, these studies support the value of REM sleep and the importance of evaluating sleep stages independently from sleep duration.

In contrast, the HypnoLaus study[49] evaluated the association between different sleep stages and hypertension, diabetes, overweight/obesity, and metabolic syndrome. Although initially a higher prevalence of metabolic syndrome was observed in individuals with decreased REM sleep, after multivariate adjustment the study concluded that normal variations in sleep stages contribute little to metabolic syndrome and associated disorders.[49]

In MrOS, mean total sleep time actigraphy (in bed) was lower than expected. When combined with mean total sleep time out of bed, total daily total sleep time was similar to reports from a different, similar aged cohort.[50] A meta-analysis[10] suggested sleep duration is associated with obesity,[51] hypertension,[52] cardiovascular outcomes,[53] and all-cause mortality.[2] A 2017 meta-analysis linked sleep duration and mortality.[54] Therefore, we performed sensitivity analyses limiting the population to participants who slept 5 to 8 and 6 to 8 hours per night and found no change in effect sizes except for cancer in the 6- to 8-hour group. Further, obstructive sleep apnea has been linked to mortality, stroke, and cardiovascular disease.[55-58] We found the REM sleep and all-cause mortality association remained significant after excluding individuals with Apnea-Hypopnea Index score greater than 30 and/or using antidepressants, benzodiazepines, or sleep medications.

Dew et al[59] found an association between mortality and sleep latency more than 30 minutes and sleep efficiency less than 80%. Wallace et al[60] evaluated which sleep characteristics predicted mortality. Rhythmicity and continuity were the strongest; however, sleep stages were not evaluated.

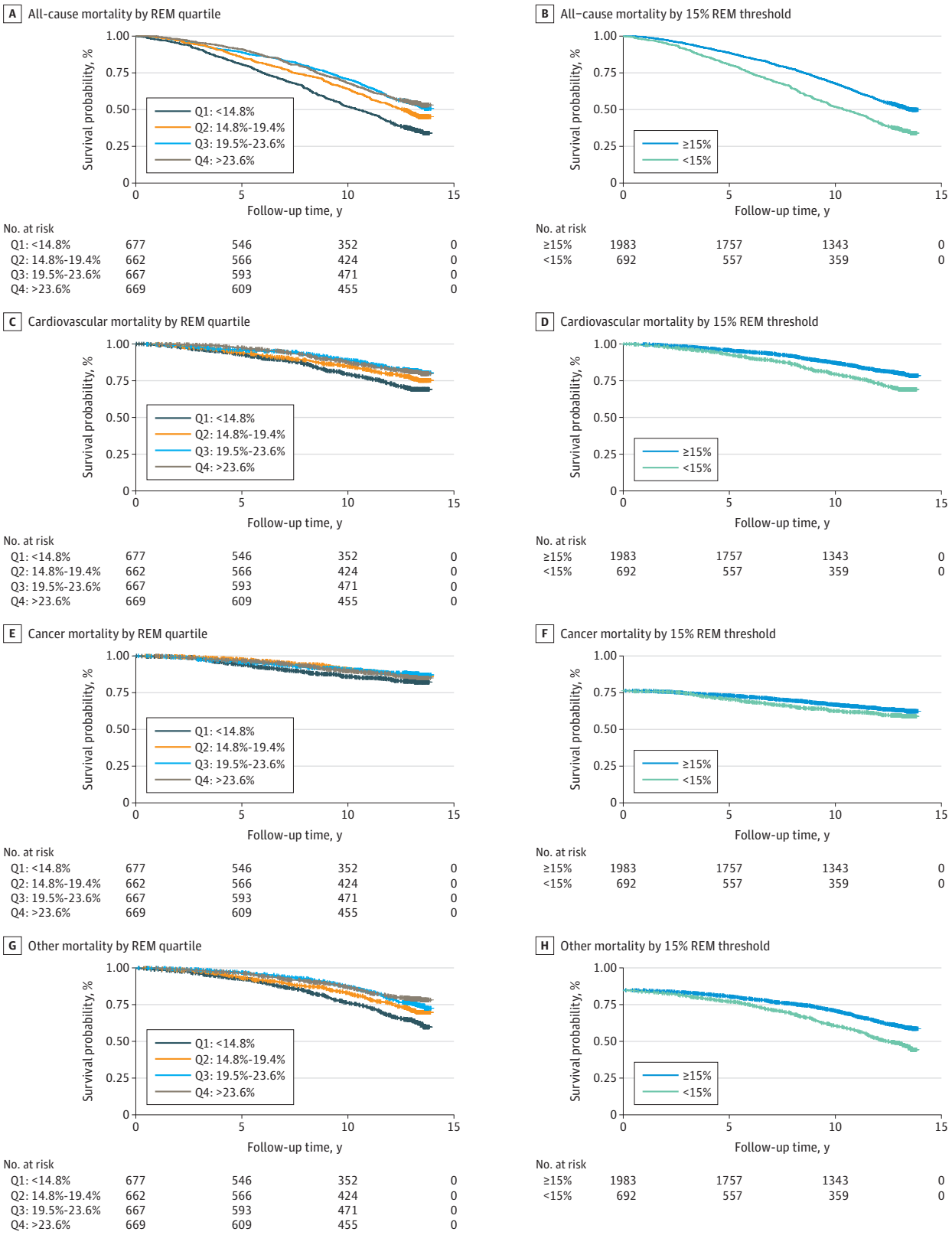
Sun et al[61] used machine learning to predict brain age from sleep electroencephalography. Results for healthy individuals correlated well with chronological age. However, individuals with significant neurologic or psychiatric disease, hypertension, or diabetes had higher brain age compared with true age. Percentage of REM sleep may be another important, easy to interpret aging biomarker. Algorithms are currently being developed to accurately measure percentage of REM sleep using consumer wearable devices, which will reduce barriers for evaluating REM sleep in the general population.

Strengths and Limitations

This study has many strengths. Parallel analyses were conducted in 2 instrumental, well-characterized, population-based sleep cohorts. Machine learning was used to strengthen the analysis, and numerous sensitivity analyses were conducted to control for potential biases.

Limitations include the possibility of unmeasured and residual confounding. To address this concern, we used clinical knowledge and empirical model building to select covariates for the final models. MrOS did not include women, and the population's mean (SD) age at baseline was 76.4 (5.5) years. However, replication in the WSC expanded the generalizability of the

Figure. Unadjusted Kaplan-Meier Plots by Percentage of REM Sleep Quartile and 15% REM Sleep Threshold in the Outcomes of Sleep Disorders in Older Men Study Cohort



Q indicates quarter; REM, rapid eye movement.

findings to include middle-aged men and women (mean [SD] age, 51.5 [8.5] years). Both MrOS and WSC comprised community-dwelling volunteers and therefore may be healthier than the general population; however, we adjusted for comorbidities and do not believe this affects the associations presented. Replication provides generalizability across a larger age group and is associated with reduction, not an elimination, of the likelihood of reverse causality. Generalizability to other races/ethnicities is limited because more than 90% of both cohorts were white. REM sleep was quantified based on 2 night of polysomnography. Although it is possible the first-night effect biased our results, it is unlikely the effect would be differential with respect to mortality. Also, another study using the MrOS polysomnography protocol found no evidence of first-night effect.[62]

Conclusions

A robust association was found between percentage of REM sleep and mortality in 2 independent cohorts, which persisted across different causes of death and multiple sensitivity analyses. Given the complex underlying biologic functions, further studies are required to understand whether the relationship is causal. Accelerated brain aging may result in less REM sleep, making it a marker rather than a direct mortality risk factor; however, mechanistic studies are needed. Strategies to preserve REM sleep may influence clinical therapies and reduce mortality risk, particularly for adults with less than 15% REM.

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Concept and design: Leary, Watson, Ancoli-Israel, Redline, Zou, Mignot, Stone.
Acquisition, analysis, or interpretation of data: Leary, Watson, Redline, Yaffe, Ravelo, Peppard, Goodman, Mignot, Stone.
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