The Association Between REM Sleep and Mortality in the MrOS and Wisconsin Sleep Cohorts

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Introduction: Sleep disorders and sleep dysregulation have been associated with several systemic and brain-based diseases, including cardiovascular disease, type 2 diabetes, dementia, and major depressive disorder. Additionally, sleep disorders and sleep characteristics (e.g. sleep duration) have been linked to higher risk of mortality. Despite the emerging evidence of a sleep-mortality association, associations of sleep architecture with mortality aren't well understood. For instance, it's plausible that rapid eye movement (REM) is associated with adverse health outcomes. After all, REM has been linked with multiple aspects of mental and physical health and REM sleep is the first stage to rebound after total sleep deprivation. We hypothesize that reduced REM sleep will be associated with increased mortality risk.

Materials and Methods: The Outcomes of Sleep Disorders in Older Men (MrOS) Sleep Study is a population-based, longitudinal study of 2,675 community-dwelling older men who underwent in-home polysomnography at study enrollment. Cox proportional hazards regression models were used to evaluate the association between percent REM and mortality rate. A core set of covariates were selected a priori based on clinical experience to include in the multivariate models. Additional covariates commonly associated with sleep architecture were evaluated using a 6-fold cross validation, forward step-wise feature selection algorithm to obtain the best candidate final regression models. A threshold effect was suspected based on Kaplan-Meier curves, so separate models were run with percent REM as a binary variable with 15% as the cut point. Several sensitivity analyses were performed to rule out alternative explanations for the findings. Data from the Wisconsin Sleep Cohort (WSC) were used to replicate the findings.

Results: The mean age in the MrOS sample was 76.3 years (SD=5.51) and the median follow up time was 12.1 years. There was a 13% higher mortality rate for every 5% reduction in REM sleep (hazard ratio [HR]=1.13, 95% CI, 1.08-1.19) after adjusting for multiple demographic, sleep and health covariates, including study site, age at sleep visit, race, education, medication use, smoking status, caffeine intake, respiratory disturbance index, and actigraphy measures. The association was also present for cardiovascular disease-related mortality (CVD) (HR=1.18, 95% CI, 1.09-1.28), cancer related mortality (HR=1.14, 95% CI, 1.03-1.26), and non-cardiovascular, non-cancer related mortality (HR=1.19, 95% CI, 1.10-1.28) (see Table 1). A possible threshold effect was seen on the Kaplan-Meier curves, particularly for cancer-related deaths (see Figure 1).

The WSC included 45.7% women and the mean age of the 1,388 individuals included was 51.5 (SD=8.5); the median follow up time was 20.8 years. The effect size for 5% reduction in REM on risk of all-cause mortality was similar in this cohort despite the younger age, inclusion of women, and longer follow-up period (HR=1.17, 95% CI, 1.03-1.34). When stratified by gender, decreased %REM was associated with all-cause mortality in women for every 5% REM 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 (see Table 1).

Table 1: Mortality Hazard Ratios from Cox Regression for the Osteoporotic Fractures in Men Study (MrOS) and Wisconsin Sleep Cohort (WSC)

Mortality Risk Ratios for the MrOS Cohort Using Percent REM as a Continuous Variable (5% Decrease)				
Outcome	Overall Number Deaths n (%)	Unadjusted HR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)
All–cause mortality (n=2,675)	1,404 (52.5%)	1.19 (1.14–1.24)	1.11 (1.04–1.15)	1.13 (1.08–1.19)
Cardiovascular mortality (n=1,761)	490 (27.8%)	1.24 (1.16–1.33)	1.13 (1.06–1.21)	1.18 (1.09–1.28)
Cancer mortality (n=1,581)	310 (19.6%)	1.16 (1.06–1.26)	1.09 (1.0–1.18)	1.14 (1.03–1.26)
Other mortality (n=1,875)	604 (32.2%)	1.26 (1.19–1.34)	1.17 (1.10–1.25)	1.19 (1.10–1.28)

Model 1: Age, Race (white versus non-white), Education, Body Mass Index (BMI), Smoking Status, Weekly Alcohol, Daily Caffeine, Antidepressants, Benzodiazepines, Sleep Medications, and Site

Model 2: Model 1 + Overall Arousal Index, Sleep Time with Saturated Oxygen Below 80%, Percent Stage N2 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

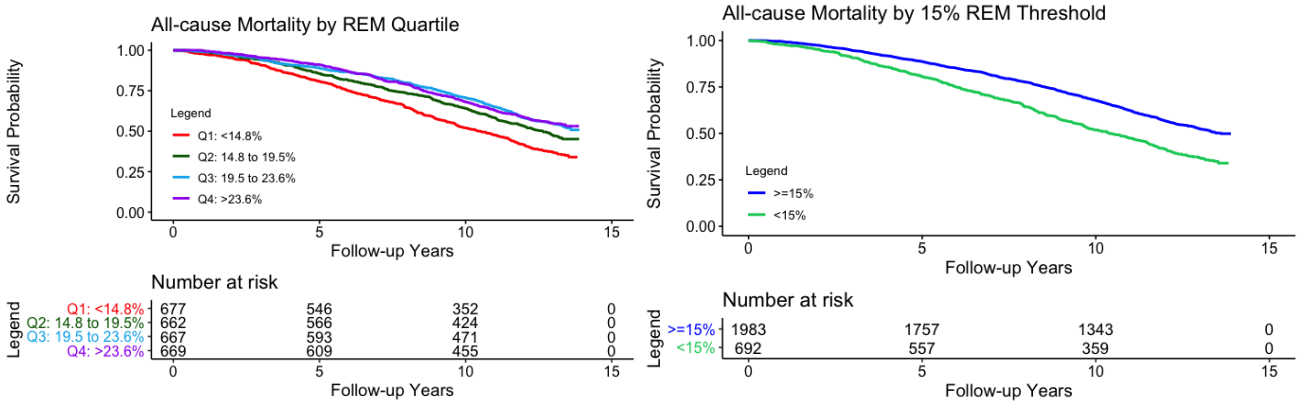
Mortality Risk Ratios for the Wisconsin Sleep Cohort Using Percent REM as a Continuous Variable (5% Decrease)				
Outcome	Overall Number Deaths n (%)	Unadjusted HR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)
All–cause mortality (n=1,386)	184 (13.3%)	1.22 (1.08–1.36)	1.14 (1.07–1.39)	1.17 (1.03–1.34)
Females (n=633)	70 (11.1%)	1.38 (1.15–1.66)	1.29 (1.06–1.57)	1.34 (1.07–1.68)
Males (n=753)	114 (15.1%)	1.11 (0.96–1.28)	1.02 (0.89–1.19)	1.09 (0.92–1.30)
Cardiovascular mortality (n=1,252)	50 (4.0%)	1.35 (1.08–1.68)	1.18 (0.95–1.48)	1.09 (0.85–1.41)
Cancer mortality (n=1,273)	71 (5.6%)	1.18 (0.94–1.47)	1.14 (0.94–1.37)	1.17 (0.91–1.40)
Other mortality (n=1,264)	63 (5.0%)	1.20 (0.99–1.42)	1.13 (0.93–1.37)	1.26 (1.01–1.58)

Abbreviations: Hazard Ratio (HR), Confidence Interval (CI)

Model 1: Age, Sex, Race (white versus non-white), Education, Body Mass Index (BMI), Smoking Status, Weekly Alcohol, Daily Caffeine, Antidepressants, and Sedatives

Model 2: Model 1 + Percent Stage N2 Sleep, Wake After Sleep Onset, Epworth Sleepiness Scale Score, Emphysema, Type 2 Diabetes, Heart Attack, and Stroke

Figure 1. Unadjusted Kaplan-Meier plots by percent REM quartile (Q1 through Q4, left column) and 15% REM threshold (right column) for all-cause mortality.



Conclusions: We found a robust association between reduced REM sleep and mortality in two independent cohorts, which persisted across different causes of death and multiple sensitivity analyses. Given the complex underlying biological functions, further studies are required to understand whether the relationship is causal. Accelerated brain aging may result in reduced REM sleep, making it a marker rather than a direct mortality risk factor. Mechanistic studies are needed and strategies to preserve REM may influence clinical therapies and reduce mortality risk, particularly for adults with <15% REM.

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