Actigraphy and polysomnography measured sleep disturbances, inflammation, and mortality among older men

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Abstract

Objectives—To evaluate whether objectively-measured sleep characteristics are associated with mortality risk independent of inflammatory burden and comorbidity.

Methods—The MrOS Sleep Study (conducted in 2003-2005) included community-dwelling older men (n=2531; average age of 76.3 (5.5 s.d.)). Sleep measures from in-home polysomnography and wrist actigraphy and assessments of serum inflammatory markers levels (C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), tumor necrosis factor-α soluble receptor II (sTNF-RII) and interferon–γ (IFN-γ)) were obtained. Vital status was ascertained over an average follow-up of 7.4 (1.9 s.d.) years.

Results—Three of the seven main sleep measures examined were independently associated with greater inflammatory burden. Mortality risk associated with prolonged (10% total sleep

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time) blood oxygen desaturation and short (<5 hours) sleep duration was attenuated to non-significance after adjusting for inflammatory burden or medical burden/lifestyle factors. Severe blood oxygen desaturation (adjusted hazard ratio (aHR)=1.57, 95% confidence interval (CI): 1.11-2.22), sleep fragmentation (aHR=1.32, 95% CI: 1.12-1.57), and a lower percentage of sleep in rapid eye movement (REM; aHR per s.d.=0.90, 95% CI: 0.93-0.97) were independently associated with mortality.

Conclusions—Short sleep duration and prolonged blood oxygen desaturation were independently associated with inflammatory burden, which attenuated associations between these sleep characteristics and mortality. Medical and lifestyle factors also substantially attenuated most sleep-mortality associations, suggesting complex relations between sleep, inflammation, and disease. Sleep fragmentation, severe blood oxygen desaturation, and the percentage of sleep time in REM were independently related to mortality risk. Future studies with repeated measures of mediators/confounds will be necessary to achieve a mechanistic understanding of sleep-related mortality risk.

Keywords

sleep; polysomnography; actigraphy; inflammation; mortality; aging; epidemiology

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Both short and long sleep duration (1, 2), as well as other sleep factors such as sleep disordered breathing (SDB) (3, 4), have been linked to mortality risk. However, citing methodological concerns (regarding use of self-reported sleep measures and control of confounds/reverse causality), current literature reflects a lack of consensus regarding whether sleep directly influences mortality risk (5). Furthermore, if sleep does influence mortality risk, the biological pathways conferring such risk are unknown.

Sleep and diseases of aging may be related through inflammatory processes (6, 7). Inflammatory markers are strong predictors of disease and mortality (8-10). Evidence suggests certain sleep characteristics might affect inflammatory processes. Intermittent hypoxia can activate the sympathetic nervous system, proinflammatory transcription factors, and an inflammatory response (11). Short sleep duration may affect several factors conducive to a pro-inflammatory response, including increased blood pressure (12, 13), and altered metabolic/endocrine (14-16) and catecholamine signaling (17, 18). Sleep deprivation is associated with increased levels of circulating inflammatory markers such as C-reactive protein (CRP) (12, 19) and interleukin-6 (IL-6) (19, 20). Difficulty falling or staying asleep also plausibly affects human stress-responses, activating the above-mentioned cascades leading to heightened inflammation (i.e. (21)).

Observational evidence for the association between sleep and inflammation has produced mixed findings. Some studies have identified an independent association between sleep characteristics (namely, disordered breathing, duration, and quality ratings) and inflammation (22-33). Other studies have reported that associations between these sleep characteristics and inflammation are accounted for by confounders like disease and adiposity (34-39)). However, previous literature on sleep and inflammation has been limited by sample size and/or reliance upon subjective measures of sleep.

To our knowledge, the only prior investigation of whether inflammation attenuates sleep-related mortality risk relied on self-reported sleep duration (40). The current report therefore aimed to determine whether objectively measured sleep characteristics are associated with mortality risk independent of concurrent inflammation. Several factors other than sleep may also be associated with inflammation and mortality, and the relationship between sleep and inflammatory markers may be confounded by factors like adiposity and overt disease (34-39). Therefore, we assessed the relative roles of inflammatory burden and other health factors (that may be related to sleep, inflammation, and mortality (e.g. cardiovascular disease (41) and physical activity (42))) in attenuating associations between objectively measured sleep characteristics and mortality. We focused mainly on objective measures of sleep duration, fragmentation, and hypoxia, and secondarily include measures of sleep architecture (for comprehensiveness, and because some literature suggests potential interplay between sleep stage distributions and inflammation (e.g. (43))). Before our main analysis, we sought to replicate previously observed independent associations between sleep characteristics and inflammatory burden (44), and inflammatory burden with mortality (8-10).

Methods

Participants

From March 2000 to April 2002, the Osteoporotic Fractures in Men Study (MrOS) recruited 5,994 community-dwelling men 65 years of age at six clinical centers in the United States (Birmingham, Alabama; Minneapolis, Minnesota; Palo Alto, California; Monongahela Valley near Pittsburgh, Pennsylvania; Portland, Oregon; and San Diego, California) (45, 46) To be eligible to participate in the parent MrOS study, individuals had to be able to walk without assistance and be without bilateral hip replacements.

The MrOS Sleep Study was conducted between December 2003 and March 2005, and included 3,135 participants. Men were screened and excluded if they regularly used positive pressure or oral appliances during sleep for treatment of sleep apnea or used overnight nocturnal oxygen therapy (n=150). In general, men reporting nightly use of any of these devices were excluded, however seventeen men were able to forego use of their sleep devices during the night and were included in the in-home polysomnography study. Other reasons for non-participation in the Sleep Study were: death prior to sleep assessment (n=349), terminated study participation (n=39), declined sleep study (n=1997), or because MrOS Sleep Study recruitment goals had already been met prior to enrollment in the sleep study (n=324). As part of an ancillary study, inflammatory marker assays were measured from fasting serum collected at the Sleep Visit in 2562 men. A total of n=2531 men (80.7% of the Sleep Study) with complete cytokine and mortality data were included in this analysis. Ethical approval was obtained from local institutional review boards and all participants provided informed consent.

Measures

Actigraphy—The Octagonal Sleep Watch actigraphy, or SleepWatch-O, (Ambulatory Monitoring, Inc, Ardsley, NY) was used to estimate sleep/wake activity. Participants were

asked to wear actigraphs on the non-dominant wrist for a minimum of 5 consecutive 24-hour periods except when bathing or during water sports; participants were also asked to keep a sleep log which was used to edit actigraph data. The actigraph measures movement using a piezoelectric biomorph-ceramic cantilevered beam, which generates a voltage each time the actigraph is moved, generating reliable estimate of sleep-wake patterns (47). These voltages are gathered continuously and stored in one minute epochs. Data collected in digital integration mode were used for this analysis. ActionW-2 software (Ambulatory Monitoring, Inc., Ardsley, NY) was used to score the actigraphy data (for scoring algorithms details see (48, 49)). Inter-scorer reliability for scoring of this data has been previously found to be high in our group (intra-class coefficient=0.95) (48) and this measure has been shown to have good concordance with total sleep time (TST) from polysomnography (50).

Actigraphy derived parameters used in this analysis were: TST (hours per night spent sleeping in bed after "lights off"), sleep latency (amount of time until onset of sleep, defined as when participant achieved sleep for 20 continuous minutes after getting into bed) and wake after sleep onset (WASO; minutes scored awake during the interval after sleep onset). In all analyses, actigraphy measured sleep exposures were dichotomized to represent clinically distinct sleep characteristics using the following cut-offs: short sleep duration as <5 hours (vs. 5-8 hours), long sleep duration as >8 hours (vs. 5-8 hours), sleep latency 60 minutes, and WASO 90 minutes.

Polysomnography—In-home sleep studies using one night of unattended polysomnography (Safiro, Compumedics, Inc., Melbourne, Australia) were performed with recording of central electroencephalography, bilateral electrooculography, chin electromyography, electrocardiogram, nasal pressure and thermistry (for airflow measurement), chest and thoracic inductance plethysmography, finger pulse oximetry, body position, and leg movements, as described before (51). Centrally trained and certified staff members performed home visits for setup of the sleep study units. After sensors were placed and calibrated, signal quality and impedance were checked, and sensors were repositioned as needed to improve signal quality, replacing electrodes if impedances were greater than 5000 ohms, using approaches similar to those in the Sleep Health Heart Study (52). Polysomnography data quality was excellent, with a failure rate of less than 4% and more than 70% of studies graded as being of excellent or outstanding quality.

Polysomnograph derived parameters included the apnea hypopnea index (AHI), computed as the average number of apneas and hypopneas per hour of recorded sleep. Apneas were defined as a complete or almost complete cessation of airflow for more than 10 seconds. Hypopneas were defined as a >30% reduction in amplitude of either respiratory effort or airflow for more than 10 seconds associated with a 3% oxygen desaturation (53). Parameters also included were measures of nocturnal hypoxemia: the percentage of sleep time where arterial oxygen saturation was below 90% (% TST with $SaO_2<90\%$) or below 80% (% TST with $SaO_2<80\%$). In all analyses, polysomnography measured sleep exposures were dichotomized to represent clinically significant sleep characteristics with the following cut-offs: AHI 30 (to represent severe SDB), 10% TST with SaO2<90%, 1% TST with $SaO_2<80\%$. The reliability determined by rescoring studies over time indicates that inter- and intra- scorer reliability for the AHI was high (ICC>0.95). Sleep stages (rapid eye

movement (REM), stages 1, 2, and slow wave sleep (SWS)) were scored reliably (as previously reported (54) using standard criteria (55)) and were expressed as the percentage of sleep time spent in each stage per standard deviation unit.

Inflammatory markers—Serum was collected during morning clinic visits after an overnight fast. CRP was measured using the ELISA assay kit from ALPCO (CRP sensitive ELISA). This assay utilizes a sandwich Enzyme Immuno Assay, in which plate wells are coated with polyclonal antibodies to CRP. Inter-assay CVs have been reported previously (56). High levels of multiple inflammatory markers may reflect systemic inflammation which has been associated with greater mortality risk than single markers alone (9). Therefore we examined overall inflammatory burden, a computed variable equaling the number of inflammatory markers in the top quartile (0 to 5).

Comorbidity/other covariates—Covariates were chosen based on established clinical relationships to inflammation and/or mortality. Participants completed questionnaires including information on demographics, education, medical history, self-reported health status, physical activity (57), depressed mood (58), smoking, caffeine intake (59), and alcohol use. A history of the following medical conditions was gathered: any arthritis (including osteoarthritis or rheumatoid arthritis), cardiovascular disease (CVD), stroke, diabetes mellitus, chronic obstructive pulmonary disease (COPD), and hypertension. Although no information regarding cancer history was collected at the Sleep Visit, self-report of non-skin cancer was obtained from two other visits (Baseline and Visit 2) occurring approximately 3 years before and 1.5 years after the Sleep Visit; from this data, we computed a dichotomous variable indicating whether the participant reported any history of non-skin cancer. Participants were asked to bring all current medications used within the last 30 days with them to the Sleep Visit, whose ingredients were coded to active ingredients using a coding dictionary (60). Medications considered in analyses included: antidepressants, benzodiazepines, sedatives/hypnotics, NSAIDs, and corticosteriods. Cognitive function was measured using the Teng Modified Mini-Mental State Exam (3MS) (61). Body mass index (BMI) was calculated using standard methods. Resting SaO_2 level was determined just prior to sleep using the polysomnography finger pulse oximeter.

Mortality—After the Sleep Visit, participants were contacted every four months; >97% of contact are complete. Reported deaths were confirmed with death certificates and medical records when available. Cause-specific mortality (CVD, cancer, and non-CVD/non-cancer) were based on the underlying cause of death as determined by a study physician adjudicator.

Statistical analysis

Distributions of covariates, inflammation and sleep measures were summarized by mortality status. A log-transformation was applied to cytokine measures, which were initially heavily skewed, and back-transformed for ease of interpretation. Association of the sleep and inflammatory measures were assessed with linear regression in crude and multi-variable (MV; all covariates described above) adjusted models. For descriptive purposes, adjusted survival curves were plotted for mortality by level of inflammatory burden.

A series of Cox proportional models were constructed to assess the amount of sleep-mortality risk attributable to inflammatory burden, comorbidity and/or other covariates. We first modeled the association of sleep measures with mortality after adjusting for study site, age, race, and body mass index (Model 1). Intermediate models included adjustments for only the other potential covariates listed above (Model 2a) or only inflammatory burden (Model 2b). The final model (Model 3) was adjusted for all variables. Attenuation of time-to-event associations (from Cox models) does not mathematically support a causal interpretation, and therefore we also used Aalen Additive Hazards Models to assess the pattern of attenuation using a consistent scale (mortality rates in person-years). The magnitude and pattern of attenuation were the same in Cox and Aalen models, and therefore only the former are reported. Sensitivity analyses were performed for models with SDB predictors excluding those men with a history of COPD (n=132) and then excluding men with low resting SaO_2 level (92%, n=148).

Results

Baseline characteristics are shown by vital status (Table 1).

Sleep and inflammatory burden

Most participants (65.03%) had less than 2 markers in the top quartile of that markers distribution, 17.8% had 2 markers in the top quartile, 10.7% had 3 markers in the top quartile, 5.31% had 4 markers in the top quartile, and 1.8% were in the highest quartile for all markers. After adjustments for other covariates (including adiposity and chronic diseases), having 10% of TST with $SaO_2<90\%$, short sleep duration (<5 hours), and WASO 90 minutes were independently associated with inflammatory burden (Table 2). Sleep measures were also independently associated with levels of the individual markers (Supplemental Table 1; unadjusted associations available upon request). Sleep architecture measures were not independently associated with the individual inflammatory markers (stage 2 and IL-6 p=0.14, all other p's>0.30) or inflammatory burden (all p>0.29).

Inflammatory burden and mortality

In fully adjusted Cox models including sleep measures, inflammatory burden remained a significant and unique predictor of all-cause, CVD, non-CVD/non-cancer (all p trend <0.0001) but not cancer mortality.

Sleep and mortality

In Model 1, prolonged blood oxygen desaturation (10% TST $SaO_2<90\%$), having 1% TST with severe blood oxygen desaturation ($SaO_2<80\%$), short (<5 hours) sleep duration, and greater WASO (90 minutes) were associated with mortality risk (Table 3). The AHI, long (>8 hour) sleep duration, and prolonged sleep latency were not associated with mortality risk. Expressing the AHI continuously, or re-parameterizing the AHI (0-5 vs. 5-15 vs. 15-30 vs. 30) and sleep duration (5, 5-6, 6-7, 7-8, 8 hours) did not alter these findings.

Adjustments for other covariates or inflammatory burden alone substantively attenuated associations of several specific sleep factors with mortality (Table 3). Mortality risk associated with prolonged blood oxygen desaturation (10% TST SaO_2<90%) was attenuated by 54% and 39% to non-significance after adding comorbidity/other covariates or inflammatory burden alone, respectively; full adjustments resulted in a total 75% attenuation (Model 3). Having 1% TST with SaO_2<80% remained independently predictive of mortality after all adjustments (total attenuation was 2%); excluding lung cancer deaths did not alter this substantively association.

Increased mortality risk associated with short (<5 hour) sleep duration was attenuated by 40% and 29% to non-significance after adjustments in Model 2a and 2b, respectively; after all adjustments attenuation totaled 50%. Greater WASO (90 minutes) remained significantly associated with mortality risk after all adjustments (Model 3), although comorbidity/other covariates, inflammatory burden alone, and all adjustments attenuated this risk (by 32%, 6%, and 36%, respectively). Excluding deaths within 1 and 2 years of baseline did not alter the association of greater WASO with mortality (also see survival by WASO in Figure 1).

A similar pattern of results was obtained after repeating analyses excluding participants with COPD, low levels of waking SaO_2 (92%), or when adding levels of CRP and IL-6 in place of inflammatory burden.

Sleep architecture measures were not associated with all-cause mortality in any model (all crude model p's>0.20), except for the percentage of time spent in REM sleep. Greater percentage of time spent in REM sleep was associated with lower risk of all-cause mortality and non-cancer/non-CVD mortality; this association was not substantively attenuated by adjustments and retained significance in the final model (all-cause mortality HR per SD=0.90, 95% CI 0.93-0.97).

In the fully adjusted models (e.g. Model 3 including WASO), greater physical activity and higher global cognitive performance was associated with lower mortality risk (per SD on the Physical Activity Scale for the Elderly, HR 0.82, 95% CI 0.74-0.90; per SD on the 3MS, HR 0.80, 95% CI 0.75-0.86), while greater age (per year; HR 1.09, 95% CI 1.10-1.11), CVD (HR 1.32, 95% CI 1.11-1.56), diabetes (HR 1.37, 95% CI 1.09-1.73), and oral corticosteroid use (HR 1.89, 95% CI 1.22-2.94) were independently associated with increased mortality risk.

Discussion

In this large sample of community-dwelling older men, we found specific polysomnography and actigraphy assessed sleep disturbances were associated with inflammatory burden independent of BMI, lifestyle, medication, and chronic disease factors. Over 7 years of follow-up, baseline inflammatory burden independently predicted non-cancer mortality. Our main novel findings is that the mortality risk associated with prolonged nighttime blood oxygen desaturation (10% TST SaO_2<90%) and short sleep duration was substantively attenuated by adjustment for inflammatory burden alone and other medical burden/lifestyle

factors; note that the attenuation after adjusting for inflammatory burden and other health status covariates separately (Models 2a and 2b) then together (Model 3) suggests these adjustments accounted for some shared and some distinct variance in mortality risk that was attributed to these sleep characteristics (in Model 1). These findings are consistent with prior research on self-reported sleep duration, inflammation, disease, and mortality (40), and suggests these aspects of sleep may be linked to mortality through concurrent inflammation and disease.

On the other hand, the association between greater sleep fragmentation (WASO) with both CVD and non-cancer/non-CVD deaths was independent of inflammatory burden and morbidity in our study. Morbidity/other covariates somewhat attenuated the association of WASO with mortality, but inflammatory burden did not appear to have a substantial role attenuating WASO-related mortality risk. In addition, we found that the percentage of night-time sleep spent in REM stage was associated with mortality risk independent of all covariates, and this appeared to be driven by non-cancer/non-CVD deaths; future research should investigate the pathways mediating this risk.

Similarly, severe hemoglobin desaturation ($SaO_2 < 80\%$) during sleep predicted mortality, and this relationship was not substantively attenuated inflammatory burden, morbidity, or other covariates; this risk was associated with severe SDB rather than lung disease, as indicated by the fact that these relationships held after excluding men who had low levels of blood oxygen saturation during wakefulness, a history of chronic lung disease, or death from lung cancer. The overall association of severe night-time blood oxygen desaturation with all-cause mortality appeared to be driven by cancer mortality, a finding consistent with literature that suggests links between sleep apnea (which is associated with blood oxygen desaturation) and cancer (i.e. see (62)). In contrast, we found that the AHI, a commonly used measure of the rate of apneas and hypopneas (and intermittent hypoxia), was not independently associated with all-cause or cancer mortality. Instead, the AHI was associated with CVD mortality only prior to adjustment for concurrent health factors. Future studies are needed to assess whether and how distinct biological pathways link intermittent versus severe hypoxia to these different causes of death (CVD and cancer), including the potential carcinogenic role of severe hypoxia.

Strengths of our study include the objective assessments of sleep within a large sample of older adults that were not selected on the basis of sleep problems. Additional strengths include the careful examination of whether sleep-related mortality risk might be attributable to inflammatory burden or other health factors. We found that inflammatory burden alone attenuated crude relationships between prolonged blood oxygen desaturation and short sleep duration with mortality. Although this finding is consistent with a biologically plausible hypothesis (that inflammation mediates associations between these aspects of sleep and mortality), our study is limited by measuring sleep, inflammatory markers, and covariates cross-sectionally. Inflammatory processes may both precede and result from overt disease, and can influence and be influenced by sleep. Indeed, health covariates also substantially attenuated the mortality risk associated with prolonged blood oxygen desaturation and short sleep duration. Our study design does not enable an assessment of the temporal relations sleep, inflammation, disease, and mortality. Instead, our findings suggest sleep,

inflammation, and the measured health status covariates reflect somewhat overlapping pathophysiological processes relevant to longevity. Future research including repeated measures of these factors (sleep, inflammation, and health status) is needed to test whether, in fact, sleep impacts inflammatory burden to influence mortality-risk, above and beyond pre-existing disease processes.

Additional limitations should be noted. We observed a substantial role for the health status covariates studied, but we were unable to assess other physiological markers which may have driven these effects (potentially including pro-thrombotic, cortisol, or metabolic factors like blood glucose levels). Our sample consisted of only older men who were 90% Caucasian and agreed to participate in an in-depth sleep evaluation; these findings should not be generalized to other populations including younger adults, women, and some ethnic groups. Patients with severe sleep disorders may have been less likely to participate, and therefore effects of severe sleep disorders on mortality may have been missed in our study, resulting in an under-estimate of the true mortality risk associated with sleep in the population. We present all-cause, CVD, cancer, and non-CVD/non-cancer mortality associations, however our statistical power for cause-specific groups may be limited. Given the observational nature of our study, residual confounding may be present, in particular via pre-existing sub-clinical disease. Several other sleep-wake characteristics (i.e. timing, rhythmicity, perceived quality) were not included in the current study and must be investigated in future research.

Despite these limitation, to our knowledge, our study is the first to demonstrate independent associations between objectively measured sleep characteristics and a biologically proximal factor (inflammatory burden) that attenuates observed sleep-related mortality risk. Prolonged nighttime blood oxygen desaturation and short sleep duration may be markers of mortality that reflect underlying disease processes including the inflammatory response. We also found that long sleep duration was not a marker of future mortality risk, even in crudely adjusted models; this suggests, at least in older men, greater than eight hour sleep duration may not be detrimental to longevity.

However, men in our study with severe nighttime oxygen desaturation, sleep fragmentation, and less of their sleep in REM were at increased risk for mortality. Mortality risk associated with severe nighttime oxygen desaturation, sleep fragmentation, and REM sleep was independent of a range of factors (including disease and inflammation), therefore, understanding and treating these sleep disturbances successfully among older men may be especially important to preserve longevity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations

SDB	sleep disordered breathing
CRP	C-reactive protein
IL-6	interleukin-6
MrOS	Osteoporotic Fractures in Men Study
TST	total sleep time
WASO	wake after sleep onset
AHI	apnea hypopnea index
IFN-γ	interferon gamma
TNF-α	tumor necrosis factor alpha
TNF-αsRII	tumor necrosis factor alpha soluble receptor two
CVD	cardiovascular disease
COPD	chronic obstructive pulmonary disease
NSAID	non-steroidal anti-inflammatory drug
3MS	Teng Modified Mini-Mental State Exam
SaO2	blood oxygen saturation
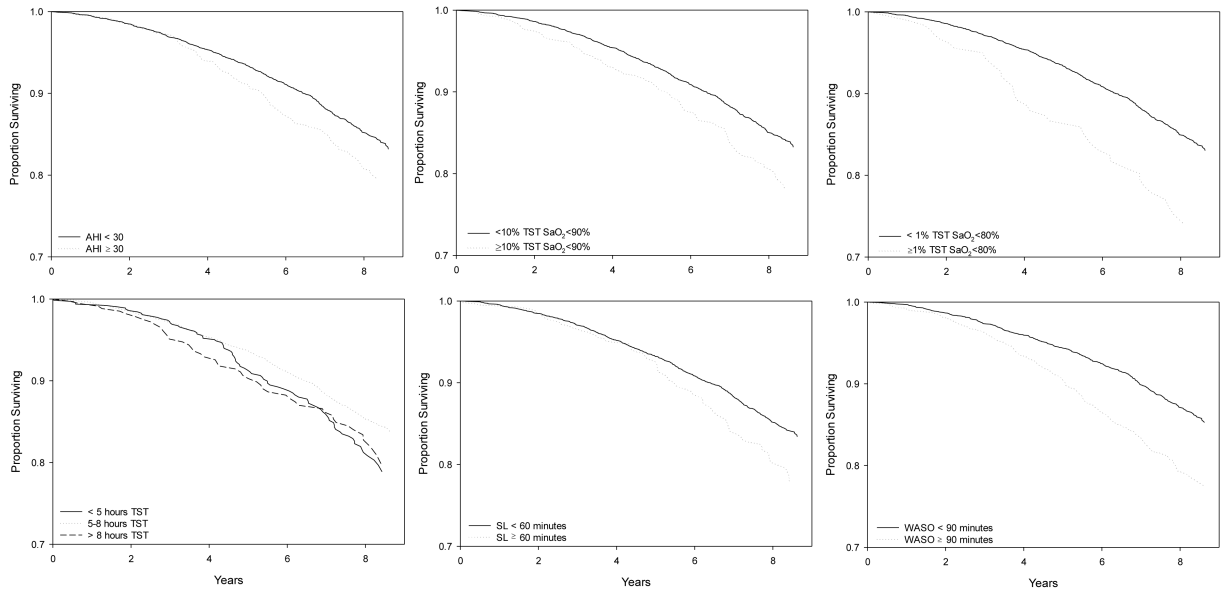
Figure 1.
MV* Adjusted Overall and Cause-Specific Survival by Sleep Characteristics. "*MV = Multivariable adjusted for age, study site, race, BMI, probable depression, cognition, smoking status, alcohol use, education, caffeine use, physical activity, chronic diseases, self-reported health and medication use; Abbreviations: CVD=Cardiovascular;"

Table 1

Sample characteristics by all-cause and cause-specific mortality (from the Sleep Visit)

		Alive	All-Cause Mortality	CVD Mortality	Cancer Mortality	Non-CVD Non-Cancer Mortality
		(n = 1903)	(n = 628)	(n = 217)	(n = 171)	(n = 240)
Age, mean (sd)		75.30 (5.01)	79.46 (5.73)	79.82 (5.81)	78.23 (5.60)	80.02 (5.66)
Caucasian		1729 (90.86)	581 (92.52)	198 (91.24)	159 (92.98)	224 (93.33)
African American		58 (3.05)	19 (3.03)	6 (2.76)	3 (1.75)	10 (4.17)
Other race		116 (6.10)	28 (4.46)	13 (5.99)	9 (5.26)	6 (2.50)
Smoking status						
	Current	37 (1.94)	12 (1.91)	2 (0.92)	8 (4.68)	2 (0.83)
	Former	1084 (56.96)	381 (60.67)	137 (63.13)	102 (59.65)	142 (59.17)
	Never	782 (41.09)	235 (37.42)	78 (35.94)	61 (35.67)	96 (40.00)
Alcohol use per week						
	<1	861 (45.39)	325 (52.00)	119 (54.84)	79 (46.20)	127 (53.59)
	1-13	937 (49.39)	265 (42.40)	88 (40.55)	84 (49.12)	93 (39.24)
	14+	99 (5.22)	35 (5.60)	10 (4.61)	8 (4.68)	17 (7.17)
Caffeine intake (mg/Day), median (IQR)		184 (36 – 368)	144 (36 – 324)	144 (36 – 320)	172 (36 – 404)	144 (0 – 324)
Self-reported health status						
	Excellent or good	1692 (88.91)	511 (81.37)	175 (80.65)	151 (88.30)	185 (77.08)
	Fair, poor, or very poor	211 (11.09)	117 (18.63)	42 (19.35)	20 (11.70)	55 (22.92)
Education						
	Less than high school	96 (5.04)	43 (6.85)	16 (7.37)	18 (10.53)	9 (3.75)
	High school diploma	282 (14.82)	134 (21.34)	52 (23.96)	26 (15.20)	56 (23.33)
	College/Graduate school	1525 (80.14)	451 (71.82)	149 (68.66)	127 (74.27)	175 (72.92)
Physical Activity (PASE) score, mean (sd)		154.23 (70.34)	122.86 (66.42)	119.89 (58.64)	133.67 (69.88)	117.86 (69.83)
Cognitive function (3MS score, 0-100), median (IQR)		95 (91 – 97)	92 (88 – 96)	92 (88 – 96)	93 (89 – 96)	91 (86 – 95)
Depression (GDS 6)		95 (5.00)	61 (9.71)	18 (8.29)	11 (6.43)	32 (13.33)
Current antidepressant use		144 (7.57)	57 (9.08)	18 (8.29)	8 (4.68)	31 (12.92)
Current benzodiazepine use		76 (3.99)	42 (6.69)	10 (4.61)	12 (7.02)	20 (8.33)

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	Alive	All-Cause Mortality	CVD Mortality	Cancer Mortality	Non-CVD Non-Cancer Mortality
	(n = 1903)	(n = 628)	(n = 217)	(n = 171)	(n = 240)
Current non-benzodiazepine anxiolytic/hypnotic use	43 (2.26)	9 (1.43)	5 (2.30)	3 (1.75)	1 (0.42)
Current NSAID use	423 (22.23)	121 (19.27)	38 (17.51)	35 (20.47)	48 (20.00)
Current corticosteroid use(oral/nasal/inhaled)	166 (8.76)	65 (10.40)	21 (9.72)	8 (4.68)	36 (15.13)
Body mass index (kilograms/meters^2), mean (sd)	27.19 (3.61)	27.02 (4.16)	27.18 (4.14)	27.42 (4.08)	26.58 (4.22)
Chronic Disease					
Cardiovascular disease[1]	605 (31.79)	305 (48.57)	115 (53.00)	69 (40.35)	121 (50.42)
Hypertension	914 (48.03)	342 (54.46)	134 (61.75)	86 (50.29)	122 (50.83)
Chronic obstructive pulmonary disease	85 (4.47)	47 (7.48)	14 (6.45)	9 (5.26)	24 (10.00)
Diabetes	201 (10.56)	94 (14.97)	36 (16.59)	21 (12.28)	37 (15.42)
Stroke	60 (3.15)	35 (5.57)	14 (6.45)	4 (2.34)	17 (7.08)
Arthritis	559 (29.39)	199 (31.69)	63 (29.03)	51 (29.82)	85 (35.42)
Any non-skin cancer history	372 (19.55)	163 (25.96)	44 (20.28)	65 (38.01)	54 (22.50)
Sleep Measures					
Severe sleep apnea (AHI≥30)	310 (16.29)	125 (19.90)	55 (25.35)	30 (17.54)	40 (16.67)
10% sleep time SaO$_2$<90%	215 (11.30)	102 (16.24)	37 (17.05)	28 (16.37)	37 (15.42)
1% with sleep time SaO$_2$<80%	65 (3.42)	41 (6.53)	15 (6.91)	17 (9.94)	9 (3.75)
Short sleep duration (<5 hours)	206 (10.83)	92 (14.67)	33 (15.21)	21 (12.35)	38 (15.83)
Long sleep duration (>8 hours)	133 (6.99)	50 (7.97)	16 (7.37)	8 (4.71)	26 (10.83)
Prolonged sleep latency (60 minutes)	182 (9.57)	84 (13.38)	30 (13.82)	22 (12.94)	32 (13.33)
Greater WASO (90 minutes)	540 (28.39)	256 (40.83)	93 (42.86)	64 (37.65)	99 (41.25)
Inflammation Markers (median (IQR))					
IL-6 (pg/ml)	1 (0.71 – 1.52)	1.40 (0.92 – 2.20)	1.55 (1.04 – 2.69)	1.19 (.77 – 1.71)	1.47 (0.90 – 2.24)
CRP (ug/ml)	1.45 (0.71 – 2.82)	1.76 (0.87 – 3.91)	2.00 (1.00 – 4.50)	1.56 (0.80 – 2.93)	1.79 (0.85 – 3.95)
TNF-α (pg/ml)	4.99 (4.12 – 6.03)	5.63 (4.53 – 6.87)	5.63 (4.70 – 6.78)	5.15 (4.10 – 6.73)	5.92 (4.78 – 7.15)
TNF-αsRII (pg/ml)	3409.60 (2792.20 – 4297.10)	4149.60 (3189.98 – 5687.65)	4229.90 (3196.90 – 5877.25)	3725.20 (2888.00 – 4976.80)	4485.15 (3389.45 – 5901.00)

	Alive	All-Cause Mortality	CVD Mortality	Cancer Mortality	Non-CVD Non-Cancer Mortality
	(n = 1903)	(n = 628)	(n = 217)	(n = 171)	(n = 240)
IFN-γ (pg/ml)	1.83 (1.04 – 3.18)	1.96 (1.16 – 3.33)	1.97 (1.30 – 3.37)	1.97 (1.08 – 3.34)	1.91 (1.12 – 3.30)
# inf markers in top quartile	1 (0 - 2)	1 (1 – 3)	2 (1 – 3)	1 (0 – 2)	2 (1 – 3)

[1] Cardiovascular disease includes myocardial infarction (MI), angina, temporary ischemic attack (TIA), claudication, or congestive heart failure (CHF)

Abbreviations: IQR=interquartile range; PASE=Physical Activity Scale for the Elderly; 3MS=Modified Mini-Mental State examination; GDS=Geriatric Depression Scale; NSAID = Nonsteroidal anti-inflammatory drug; AHI=apnea hypopnea index; SaO2=Oxygen Saturation; WASO=Wake after sleep onset; IL-6=Interleukin-6; CRP=C-Reactive Protein; TNF-α=Tumor Necrosis Factor-Alpha; TNF-αSRII=Tumor Necrosis Factor-Alpha Soluble Receptor 2; IFN-γ=Interferon Gamma

Table 2

Multivariable adjusted associations of sleep measures with inflammatory burden as the dependent variable

	β[Φ]	SE	p
AHI 30 vs. <30	0.11	0.07	0.088
10% vs. <10% TST SaO2<90%	0.24	0.08	0.002
1% vs. <1% TST SaO2<80%	-0.14	0.13	0.27
TST <5 vs. 5-8	0.20	0.08	0.013
TST >8 vs. 5-8	0.00	0.10	0.99
Sleep latency 60 vs. <60 min	0.12	0.08	0.14
WASO 90 vs. <90 min	0.13	0.05	0.024

[Φ] β coefficient (after MV adjustments) from linear regression; similar results observed using negative binomial regression

[*] MV=Multivariable models adjusted for: age, study site, race, BMI, probable depression, cognition, smoking status, alcohol use, education, caffeine use, physical activity, chronic disease (any arthritis (including osteoarthritis or rheumatoid arthritis), cardiovascular disease (CVD), stroke, diabetes mellitus, chronic obstructive pulmonary disease (COPD), and hypertension), self-reported health and medication use (antidepressants, benzodiazepines, sedatives/hypnotics, NSAIDs, and corticosteroids)

Table 3
Hazard ratio (95% CI) of mortality by sleep measures

	All cause (628 deaths)	CVD (217 deaths)	Cancer (171 deaths)	Non-cancer Non-CVD (240 deaths)
AHI 30 vs. <30				
Model 1: Crude model	1.06 (0.86-1.29)	**1.38 (1.00-1.90)**	0.89 (0.59-1.34)	0.90 (0.63-1.27)
Model 2a: Model 1 + MV	1.03 (0.84-1.27)	1.35 (0.98-1.88)	0.88 (0.58-1.33)	0.86 (0.60-1.24)
Model 2b: Model 1 + # high inflammatory markers	1.03 (0.84-1.26)	1.33 (0.97-1.84)	0.88 (0.59-1.33)	0.87 (0.61-1.24)
Model 3: Model 1 + MV* + # high inflammatory markers	1.03 (0.84-1.27)	1.34 (0.97-1.85)	0.87 (0.58-1.32)	0.87 (0.61-1.26)
10% vs. <10% TST SaO₂<90%				
Model 1: Crude model	**1.28 (1.02-1.61)**	1.24 (0.85-1.80)	1.30 (0.84-1.99)	1.32 (0.91-1.92)
Model 2a: Model 1 + MV	1.13 (0.90-1.43)	1.12 (0.77-1.64)	1.29 (0.83-2.00)	1.09 (0.74-1.60)
Model 2b: Model 1 + # high inflammatory markers	1.17 (0.93-1.46)	1.08 (0.74-1.58)	1.27 (0.83-1.96)	1.17 (0.80-1.70)
Model 3: Model 1 + MV* + # high inflammatory markers	1.07 (0.85-1.35)	1.02 (0.69-1.49)	1.27 (0.82-1.98)	1.00 (0.68-1.47)
1% vs. <1% TST SaO₂<80%				
Model 1: Crude model	**1.58 (1.15-2.20)**	1.54 (0.90-2.65)	**2.46 (1.45-4.17)**	0.99 (0.50-1.94)
Model 2a: Model 1 + MV	**1.54 (1.09-2.16)**	1.53 (0.88-2.68)	**2.30 (1.35-3.92)**	0.81 (0.37-1.78)
Model 2b: Model 1 + # high inflammatory markers	**1.54 (1.11-2.14)**	1.48 (0.86-2.55)	**2.45 (1.44-4.14)**	0.94 (0.48-1.86)
Model 3: Model 1 + MV* + # high inflammatory markers	**1.57 (1.11-2.22)**	1.62 (0.93-2.84)	**2.31 (1.36-3.94)**	0.82 (0.38-1.81)
TST <5 vs. 5-8				
Model 1: Crude model	**1.28 (1.02-1.62)**	1.25 (0.85-1.84)	0.98 (0.61-1.58)	**1.56 (1.09-2.24)**
Model 2a: Model 1 + MV	1.17 (0.92-1.48)	1.19 (0.80-1.77)	0.94 (0.58-1.53)	1.35 (0.92-1.97)
Model 2b: Model 1 + # high inflammatory markers	1.20 (0.95-1.51)	1.15 (0.78-1.69)	0.97 (0.60-1.56)	**1.45 (1.01-2.08)**
Model 3: Model 1 + MV* + # high inflammatory markers	1.12 (0.89-1.42)	1.12 (0.76-1.67)	0.93 (0.58-1.52)	1.28 (0.87-1.88)
TST >8 vs. 5-8				
Model 1: Crude model	1.02 (0.76-1.37)	0.93 (0.55-1.55)	0.59 (0.29-1.20)	1.46 (0.96-2.21)
Model 2a: Model 1 + MV	0.94 (0.69-1.27)	0.92 (0.55-1.55)	0.57 (0.27-1.17)	1.29 (0.83-2.00)
Model 2b: Model 1 + # high inflammatory markers	1.03 (0.77-1.38)	0.94 (0.56-1.57)	0.59 (0.29-1.20)	1.47 (0.97-2.22)
Model 3: Model 1 + MV* + # high inflammatory markers	0.83 (0.71-1.31)	0.95 (0.56-1.61)	0.57 (0.28-1.18)	1.32 (0.85-2.05)
Sleep latency 60 vs. <60 min				
Model 1: Crude model	1.25 (0.99-1.58)	1.24 (0.84-1.84)	1.23 (0.78-1.93)	1.28 (0.88-1.87)
Model 2a: Model 1 + MV	1.13 (0.89-1.44)	1.14 (0.76-1.71)	1.22 (0.77-1.94)	1.06 (0.71-1.58)
Model 2b: Model 1 + # high inflammatory markers	1.19 (0.94-1.50)	1.15 (0.78-1.70)	1.22 (0.77-1.92)	1.20 (0.82-1.75)
Model 3: Model 1 + MV* + # high inflammatory markers	1.12 (0.88-1.42)	1.13 (0.75-1.69)	1.25 (0.79-1.98)	1.04 (0.70-1.56)

	All cause (628 deaths)	CVD (217 deaths)	Cancer (171 deaths)	Non-cancer Non-CVD (240 deaths)
WASO 90 vs. <90 min				
Model 1: Crude model	**1.50 (1.28-1.77)**	**1.57 (1.19-2.07)**	1.30 (0.95-1.79)	**1.59 (1.23-2.07)**
Model 2a: Model 1 + MV	**1.34 (1.14-1.59)**	**1.45 (1.09-1.92)**	1.24 (0.90-1.72)	**1.36 (1.03-1.79)**
Model 2b: Model 1 + # high inflammatory markers	**1.47 (1.25-1.73)**	**1.52 (1.15-2.01)**	1.29 (0.94-1.78)	**1.56 (1.20-2.03)**
Model 3: Model 1 + MV * + # high inflammatory markers	**1.32 (1.12-1.57)**	**1.44 (1.08-1.91)**	1.24 (0.89-1.71)	**1.33 (1.01-1.76)**

Crude models is adjusted for age, study site, race, and body mass index

*
MV=Multivariable models adjusted for: age, study site, race, BMI, probable depression, cognition, alcohol use, education, smoking status, caffeine use, physical activity, chronic disease (any arthritis (including osteoarthritis or rheumatoid arthritis), cardiovascular disease, stroke, diabetes mellitus, chronic obstructive pulmonary disease (COPD), hypertension, and any non-skin cancer history), self-reported health and medication use (antidepressants, benzodiazepines, sedatives/hypnotics, NSAIDs, and corticosteroids)

Abbreviations: CVD=Cardiovascular Disease; AHI=apnea hypopnea index; TST=Total Sleep Time; SaO$_2$=Oxygen Saturation; WASO=Wake After Sleep Onset; Bold= Statistically significant.