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Multidimensional sleep-wake changes and risk of all-cause and cardiovascular disease mortality in oldest-old women

Yue Leng

yue.leng@ucsf.edu

University of California

Sasha Milton

University of California, San Francisco

Kristine Yaffe

UCSF

Clemence Cavailles

University of Paris Cité, National Institute of Health and Medical Research (Inserm)

Meredith Wallace

University of Pittsburgh

Sonia Ancoli-Israel

University of California, San Diego

Kristine Ensrud

VA Midwest Health Care Network, Minneapolis, United States

Katie Stone

California Pacific Medical Center Research Institute

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Abstract

Sleep-wake patterns often worsen with age and are fundamental to health, yet little is known about their long-term changes in the oldest old and links to mortality risk. Among 704 community-dwelling older women (mean age 82.9 years at baseline), we objectively measured 24-hour sleep-wake parameters—including nighttime sleep, daytime napping, and circadian rest–activity rhythms—using 4-night/5-day actigraphy at baseline and again five years later. Using hierarchical clustering on principal components analysis, we identified three distinct profiles of sleep/circadian changes. Compared to those with stable patterns, women experiencing declining nighttime sleep (hazard ratio [HR] = 2.16 [95% CI: 1.26, 3.72]) or increasing 24-hour sleepiness (HR = 2.09 [1.12, 3.92]) had approximately double the risk of all-cause mortality over a median follow-up time of 2.1 years after the second sleep visit. Large increases in daytime napping duration were associated with over double the risk of all-cause (HR = 2.24 [1.25, 4.01]) and cardiovascular (CVD) mortality (HR = 2.93 [1.14, 7.51]), while decreases in nighttime sleep duration were linked to elevated CVD mortality (HR = 2.78 [1.06, 7.31]). These results, independent of comorbidities and covariates, suggest that changes in 24-hour sleep/circadian patterns among the oldest old are not simply normal aging but may serve as an important marker of increased mortality risk.

INTRODUCTION

Sleep patterns and circadian rhythms often undergo significant changes as individuals age and transition through different stages of life[1,2]. These changes, which encompass shorter sleep duration, increased fragmentation, reduced sleep efficiency, longer sleep onset latency, disrupted sleep timing, longer and more frequent daytime napping, and reduced circadian rhythmicity, have been extensively documented from middle age through the 6th or 7th decade of life[3,4]. However, little is known about changes in sleep and circadian rest-activity patterns in the oldest-old population (i.e., 8th and 9th decades of life); and there is a lack of studies that incorporate repeated measures of 24-hour sleep-wake activities over time within individuals. It also remains unknown whether age-related changes in sleep-wake patterns are a normal part of aging, or if they might pose additional health risks or serve as an indicator of increased risk for mortality.

While accumulating studies identified higher risk of all-cause or cardiovascular disease (CVD) mortality associated with short or long sleep duration, poor sleep quality, weaker rest-activity rhythms, and long daytime napping in older adults[5–11], little is known about how longitudinal changes in sleep patterns relate to mortality risk. Emerging evidence suggests that changes in sleep duration, including persistently short or long sleep, and significantly decreased or increased sleep duration over time, may be associated with an increased risk of mortality in older adults[12,13]. Notably, these studies have primarily focused on subjective measures of sleep, which often show poor correlation with objective metrics and are susceptible to measurement errors[14,15]. In addition, while sleep duration is only one metric within the 24-hour sleep-wake paradigm, there is growing recognition of the need for a multidimensional approach to evaluating sleep health, encompassing nocturnal sleep quantity and

quality, daytime napping, and circadian rest-activity rhythms (RAR)[16–18]. One recent study identified three actigraphy-based sleep health profiles (High Sleep Propensity, Adequate Sleep, and Inadequate Sleep) in older adults, and reported that older men with Inadequate Sleep had an increased risk of all-cause and CVD mortality[19]. However, it remains unclear how changes in 24-hour sleep-wake profiles are associated with mortality risk, especially in the oldest old. Given the rapid aging of the population, understanding changes in objectively measured sleep and circadian patterns among individuals living beyond their 80s is crucial. These insights—and their links to mortality risk—is critical for informing strategies to maintain sleep and circadian health in older adults and is thus of paramount importance for healthy longevity.

Using data from the large, well-characterized, multi-center cohort Study of Osteoporotic Fractures (SOF), we characterize patterns of longitudinal change in 24-hour sleep and circadian RAR over five years and investigate the association between these patterns of change and subsequent risk of all-cause and CVD mortality among community-dwelling women in their 80s and 90s. We identify three distinct patterns of sleep and circadian RAR changes and find that women with increasing 24-hour sleepiness and declining nighttime sleep have more than double the risk of mortality compared to those with stable sleep, independent of sociodemographic factors, functional impairment, global cognition, and cardiometabolic comorbidities.

RESULTS

Five-year changes in sleep and circadian RAR patterns

We studied 704 Caucasian women (mean [standard deviation, SD] with age at the baseline sleep visit (2002–2004) = 82.5 [2.9] years) who had complete actigraphy sleep data at two SOF study visits and were followed for mortality information after the second sleep visit (2006–2008) (Supplementary Fig. 1). Between the two sleep visits (median [range] inter-visit interval = 5.0 [3.4,6.3] years), there were several changes in women's sleep and circadian RAR patterns (Supplementary Table 1). On average, women showed minimal increases in total sleep time, sleep efficiency and wake after sleep onset (WASO). However, both napping duration and frequency increased considerably, while the circadian RAR parameters amplitude, mesor, and robustness showed marked decreases, indicative of worsening RAR. Acrophase moved slightly earlier, on average. Women who showed large decreases in sleep efficiency (< -9.7%), and in RAR (amplitude [< -1765.6 counts/min], mesor [< -851.8 counts/min], and robustness [pseudo-F < -622.3]) met our criteria for the "worsening" groups of those parameters (> 1 SD below the mean change). Large increases (> 1 SD above the mean change) in WASO (> + 51.0 min), napping duration (> + 117.1 min), and napping frequency (> + 6.0 naps) defined the "worsening" group for those parameters. Given the potential U-shaped relationship for sleep duration, we defined three groups for change in sleep duration: increasing (> 1 SD above the mean change, i.e., > +93.0 minutes), decreasing (< 1 SD below the mean change, i.e., <-55.1 minutes), and stable (changes within 1 SD above or below the mean, i.e., ≥ -55.1 minutes and ≤ 93.0 minutes). We also examined changes in acrophase and observed a monotonic relationship. Therefore, women whose acrophase advanced by approximately 1.1 hours were

categorized as the “earlier” group, while those with delayed or stable acrophase were combined into the “stable/later” group (Supplementary Table 1).

Associations of sleep-wake change with all-cause and cardiovascular mortality

Across a median follow-up time of 2.1 years (range: 23 days to 3.3 years) after visit nine, 90 (12.8%) women died, including 35 (5.0%) due to CVD. In comparison to the 614 women who did not die during the follow-up period (including women who were censored), women who died had a lower body mass index (BMI), had worse cognition, were more likely to report having had a myocardial infarction or using antidepressant medications, and were less likely to report good/excellent health or walking for exercise at visit nine (Supplementary Table 3).

Figure 2 and Supplementary Figs. 3–4 show the unadjusted Kaplan-Meier survival curves for the different profiles of sleep-wake change and individual sleep-wake change parameters. Compared to the SS group, women with DNS or IS had approximately double the risk of all-cause mortality. These results remained similar after adjustment for age, with a hazard ratio [HR] (95% confidence interval [CI]) of 1.90 (1.17, 3.11) and 1.92 (1.09, 3.40) for DNS and IS, respectively (Table 3). Neither DNS nor IS were associated with CVD mortality, possibly due to limited statistical power (Table 3; Fig. 2). With regards to individual sleep-wake parameters, women with large increases (i.e., worsening) in nap duration (HR [95% CI] = 2.02 [1.18,3.45]), significant decreases in amplitude (HR [95% CI] = 2.01 [1.19,3.42]), or reductions in robustness (HR [95% CI] = 1.95 [1.19,3.21]) showed a higher risk of age-adjusted all-cause mortality compared to those in the “stable/improving” group (Table 3). Meanwhile, women with substantial decreases in nighttime sleep duration or increases in nap frequency had more than double the risk of age-adjusted CVD mortality (HR [95% CI] = 2.51 [1.07, 5.91] and 2.30 [1.03, 5.15], respectively). Changes in sleep efficiency, WASO, acrophase, and mesor were not significantly associated with age-adjusted risk of all-cause or CVD mortality (Table 3).

After additional adjustment for education, BMI, diabetes, hypertension, myocardial infarction, antidepressant use, functional impairments, self-rated health and global cognition at the second sleep visit, the results remained consistent with the age-adjusted results (Fig. 3). Compared with the SS profile, the HRs [95% CI] for all-cause mortality were 2.16 [1.26, 3.72] for the DNS profile and 2.09 [1.12, 3.92] for the IS profile. In line with the age-adjusted results, large increases in napping duration were independently associated with an increased risk of all-cause and CVD mortality, while decreases in nighttime sleep duration and increases in napping frequency were linked to more than double the risk of CVD mortality. The associations between change in circadian RAR parameters and all-cause mortality were attenuated after full adjustment.

Given the potential U-shaped relationship between sleep duration and mortality[20], we stratified the analysis by baseline sleep duration to examine whether changes in nighttime sleep duration have similar implications for mortality risk among short and long sleepers. Interestingly, when the analyses were

stratified by baseline nighttime sleep duration (above or below mean), large increases in nighttime sleep duration were associated with a threefold higher risk of all-cause mortality—but only among those with long (i.e., above mean) baseline nighttime sleep (p for interaction < 0.05 for unadjusted, age-adjusted, and fully-adjusted models). Similarly, large decreases in nighttime sleep were significantly linked to higher risks of all-cause mortality (except for the fully adjusted model) and CVD mortality, again only among those with long baseline nighttime sleep (p for interaction > 0.05). Supplementary Fig. 5 shows the age-adjusted and fully adjusted HR (95% CIs) for changes in nighttime sleep duration and mortality risk, stratified by baseline nighttime sleep duration.

DISCUSSION

In this longitudinal study of women in their 80s and 90s, those experiencing either declining nighttime sleep or increasing 24-hour sleepiness as measured by actigraphy had approximately double the risk of all-cause mortality, independent of age, education, BMI, diabetes, hypertension, myocardial infarction, antidepressant use, functional impairments, self-rated health, and global cognition, compared to women with stable sleep patterns. Furthermore, large increases in daytime napping duration were associated with more than double the risk of all-cause and CVD mortality, while decreases in nighttime sleep duration were linked to an elevated risk of subsequent CVD mortality. Large increases in nighttime sleep duration were also associated with an increased risk of all-cause mortality, though this association was only observed among those with long baseline nighttime sleep. Our findings indicate that longitudinal changes in 24-hour sleep and circadian rhythm patterns among the oldest-old women are not merely a normal aspect of aging; rather, they may serve as independent markers for significant health risks and increased future mortality.

The health implications of daytime napping have been a topic of heated debate, with conflicting findings suggesting that the association may depend on several important factors, such as age, sex, nap duration, and cultural practices[21]. In a machine learning study that analyzed 47 sleep and non-sleep predictors, self-reported napping duration was among the most predictive sleep features for both all-cause and CVD mortality [22]. A growing number of studies, including several meta-analyses, have identified a significant association between long napping duration and increased risk of all-cause and CVD mortality[9,23–27], especially among older adults. Meanwhile, findings from a Mediterranean prospective cohort of middle-aged adults suggested that a short mid-day nap may have protective effects against mortality risk[28]. One recent umbrella review summarized meta-analyses and individual studies and indicated that daytime napping was significantly associated with elevated mortality risk, particularly among older adults, females, those with CVD-specific mortality, individuals napping for at least one hour per day, and studies conducted in the U.S.[29]. Notably, most (96%) of the included studies relied on self-reports to assess napping, which may yield different implications compared to objectively measured napping behaviors[30]. Furthermore, little is known about longitudinal changes in napping and their relevance to mortality risk. This is important because the health implications for individuals who

habitually nap may differ significantly from individuals who exhibit a marked increase in napping behaviors later in life.

In this study, we found that women in their 80s whose objective napping duration increased by more than 1 SD above the mean change (i.e., 117.6 minutes) over five years had more than double the subsequent risk of both all-cause and CVD mortality. This association, independent of diabetes, hypertension, and myocardial infarction, highlights the role of changes in napping as an independent marker of health. These findings corroborate a prior longitudinal study that revealed a bi-directional relationship between objective napping and cognitive aging, showing that napping duration and frequency increased substantially with aging, were exacerbated by the progression of Alzheimer's disease (AD), and were associated with an elevated risk of subsequent AD[4]. The current findings further suggest that prolonged napping in late life may not only indicate aging or declining cognitive health, but also reflect aspects of cardiovascular health and general well-being.

Interestingly, the Prospective Urban Rural Epidemiology (PURE) study, which included participants aged 35–70 years from 21 countries across seven geographic regions, found that daytime napping was associated with a higher mortality risk only in those with sufficient or longer nocturnal sleep[31]. This aligns with another study that showed similar interaction patterns between objective daytime napping and nocturnal sleep for dementia risk[32], highlighting the importance of considering daytime and nighttime sleep together. In the current study, we found that decreases in nighttime sleep duration were associated with an increased risk of CVD mortality, while changes in nighttime sleep and sleep efficiency were not associated with all-cause mortality in the overall sample. Several studies examining longitudinal changes in self-reported sleep patterns have suggested that "consistent short sleepers" or "consistent long sleepers" may be at the highest risk of mortality[12,33,34], aligning with the U-shaped relationship often reported in studies that assess sleep duration at a single time point[35,36]. It is possible that individuals in poor health are more prone to recall bias, reporting longer sleep durations, whereas actigraphy provides more accurate measurements that capture real changes over time. Notably, our findings indicate that increases in nighttime sleep duration are associated with an elevated risk of all-cause mortality—independent of comorbidities—but only among individuals with long baseline sleep durations. Further research is needed to clarify why declining nighttime sleep duration may be particularly relevant to cardiovascular health.

Using a clustering approach to analyze longitudinal changes in daytime napping, nighttime sleep, and circadian rhythmicity, we identified three distinct patterns among older women. Compared to the "Stable Sleep" pattern, the other two patterns were associated with approximately double the risk of all-cause mortality: one marked by increasing 24-hour sleepiness (characterized by large increases in daytime napping, longer and more efficient nighttime sleep, and declines in circadian RAR parameters) and another by declining nighttime sleep (modest increases in daytime napping, along with decreases in nighttime sleep duration, efficiency, and circadian RAR parameters). These findings suggest that increases in daytime napping over time—whether accompanied by worsening nighttime sleep or not—

may serve as a marker of elevated health risk. This result extends a prior study using actigraphy at a single time point, which found that a “High Sleep Propensity” profile—characterized by excessive napping combined with high sleep efficiency and aligned with our “increasing Sleepiness” profile—was protective despite napping itself being an independent risk factor, while an “Inadequate Sleep” profile (napping with low sleep maintenance, late timing, and shorter duration) was linked to a high risk for both all-cause and CVD mortality in the same cohort[19]. These conflicting findings underscore the possibility of differing health implications of 24-hour sleep-wake profiles when measured at a single point versus over multiple time points. Furthermore, the current study revealed findings that differ from our recent work in the same population, which indicated that increased risk of dementia was observed primarily among individuals with increasing 24-hour sleepiness[37]. Prior research in this sample has also suggested higher rates of mortality associated with greater cognitive decline[38]. It is possible that increasing sleepiness reflects underlying cognitive decline, which in turn elevates mortality risk, while declining nighttime sleep may be more broadly associated with deteriorating physical health in this age group.

Although the link between sleep/circadian changes and all-cause mortality persisted after accounting for selected medical conditions at the second sleep visit, the unexpectedly large shifts in sleep-wake patterns over just five years among women in their 80s may still reflect underlying health risks that serve as early warning signs of future mortality. Indeed, recent phenome-wide association studies have shown a strong connection between various sleep characteristics and a wide range of phenotypes across different body systems[39,40]. While these studies do not establish causality and residual confounding remains an explanation for findings, it is possible that there may exist biological mechanisms through which changes in sleep-wake cycles contribute to an increased mortality risk. For example, short sleep duration and sleep disturbances may trigger sustained inflammatory responses, thereby increasing the risk for subsequent conditions such as CVD, diabetes, depression, and AD[41–43]. Prolonged daytime napping has also been associated with elevated serum C-reactive protein (CRP) levels and an increased risk of metabolic, cardiovascular, and respiratory diseases[44–47], although excessive napping may be more a marker of system dysregulation than a direct cause of these adverse outcomes. It is also possible that excessive napping might impair the quantity and quality of nighttime sleep, further compounding health risks. Notably, women who exhibit both significant increases in daytime napping and enhancements in nighttime sleep duration and efficiency are still at double the risk of increased mortality, suggesting that changes in daytime napping are more likely to be the primary driver of the heightened mortality risk, independent of nighttime sleep.

This study has several strengths. It features repeated measures of actigraphy-assessed, multidimensional 24-hour sleep-wake parameters covering nighttime sleep quantity and quality, daytime napping and frequency, and circadian rest-activity rhythmicity, along with follow-up for both all-cause and CVD death in oldest-old women. We employed a novel clustering approach to derive profiles of sleep-wake changes among women in their 80s and carefully accounted for multiple comorbidities to isolate the independent effects of these changes on mortality risk. To our knowledge, this is the first study to

identify a link between changes in objectively measured 24-hour sleep and circadian rhythm patterns and subsequent mortality risk in women in late life.

However, there are also limitations. First, there is a relatively short follow-up period for mortality after the second sleep visit, although the number of endpoints remains high given the advanced age of the population. Second, the study sample consists of White older women, which may limit the generalizability of these findings to other populations. Additionally, it is possible that excessive daytime sleepiness may result from sleep apnea—a condition that has been linked with increased mortality and CVD event risk[48,49]—but we did not include polysomnography assessments, such as measures of sleep apnea, in this study. Notably, the effects of increasing sleepiness on mortality risk were independent of nighttime sleep duration and quality, which are also likely to be impacted by sleep apnea. Finally, as this is an observational study, causality cannot be inferred, and the possibility of residual confounding cannot be ruled out. While it remains inconclusive whether changes in sleep–wake patterns are merely markers or direct causes of increased mortality risk, future randomized controlled trials (RCTs) are needed to determine whether interventions targeting sleep–wake patterns can confer health benefits in the oldest-old population.

As our society rapidly ages, understanding the health implications related to poor sleep and circadian patterns among individuals in their 80s and beyond is critical to promoting healthy longevity—especially given that sleep is of paramount importance to health. This study reveals that within a mere five-year span, women in their 80s experience objectively measured changes in their 24-hour sleep and circadian patterns that are predictors of subsequent mortality. Unlike previous research that captured only a single snapshot of sleep behavior, our longitudinal approach using actigraphy uncovers dynamic changes—such as declining nighttime sleep and increasing 24-hour sleepiness—that markedly elevate the risk of both all-cause and cardiovascular death. These findings underscore that shifts in sleep patterns are not simply inevitable aspects of aging but are critical signals of underlying health risks. Our study emphasizes the need for randomized trials evaluating early detection and potential intervention strategies to improve sleep health, with the aim of enhancing longevity in the oldest-old population.

METHODS

Analytical sample

The Study of Osteoporotic Fractures (SOF), which has been previously described [50], originally enrolled community-dwelling Caucasian women aged 65 years or above. Enrollment took place at four sites across the United States—Baltimore, MD; Minneapolis, MN; Pittsburgh, PA; and Portland, OR—in 1986-88. Of 783 women who had complete actigraphic data at both SOF visits eight (i.e., baseline sleep visit, 2002-04) and nine (i.e., the second sleep visit, 2006-08), 704 women were followed after visit nine for mortality information and were included in our analysis (Supplementary Fig. 1).

Actigraphy-derived sleep-wake parameter change

Every participant in our analytical sample completed wrist actigraphy (SleepWatch-O, Ambulatory Monitoring Inc, Ardsley, New York) for measurement of nighttime sleep, napping, and circadian RAR parameters twice, five years apart (median [range] inter-visit interval = 5.0 [3.4,6.3] years). The actigraph devices produce electrical signals in response to movement and these continuous signals are summarized in one-minute segments. The SOF study used Action W-2 software that employed a scoring algorithm from the University of California, San Diego to code each time point as sleep or wake.[51] Data was gathered using proportional integration mode (PIM).[52] At both visits eight and nine, women wore the actigraphs for a minimum of three consecutive days (mean 4.1 ± 0.7 days), during which they logged their sleep times, allowing researchers to make notes and modifications.

We examined nine actigraphy-derived sleep-wake parameters from three domains: nighttime sleep (duration, efficiency, and WASO), napping (duration and frequency), and circadian RAR (amplitude, mesor, robustness, and acrophase). For nighttime sleep and napping parameters, each participant's mean daily value (across the full actigraphy recording) was used in analysis, while circadian RAR parameters were computed as single metrics across the full recording. Total sleep time (total ti.me scored as sleep during nighttime in-bed hours, in minutes), sleep efficiency (percentage of in-bed time at night scored as sleep), and WASO (total time scored as wake after first period scored as sleep during in-bed hours at night, in minutes; a measure of sleep fragmentation) comprised the nighttime sleep domain. The napping domain consisted of nap duration (total time scored as sleeping during daytime out-of-bed hours, in minutes) and nap frequency (total number of naps during daytime out-of-bed hours). A nap was defined as five minutes or more of continuous sleep not during nighttime in-bed hours, the same criteria as have been used in prior studies in SOF.[53] Four circadian RAR parameters were calculated using an extended cosine model and nonlinear least squares.[54] Amplitude, which measures the strength of the RAR in arbitrary activity units (counts/min), is defined as the difference between the highest and lowest points of activity at the peak of the fitted extended cosine curve. Mesor represents the mean level of activity of the fitted curve and is also measured in counts/min. Acrophase is the time of day (measured in portions of hours) of the peak activity of the fitted curve. Finally, we measured the robustness of the RAR by computing the goodness of fit of the extended cosine model using a pseudo-F statistic. The main predictors in our analyses were the five-year changes (visit nine minus visit eight) in each of these nine parameters.

Main outcomes

The main outcomes in this analysis were all-cause mortality and cardiovascular mortality. The methods for ascertaining mortality information in SOF have been described previously [55]. Vital status of all SOF participants was obtained every 4–6 months via postcard or telephone[56]. Death certificates were used to confirm causes of death, and a clinical epidemiologist indicated the underlying cause of death using codes from the *International Classification of Diseases 9th Revision Clinical Modification* (ICD-9-CM). The

ICD codes used to define cardiovascular deaths were as follows: 401 to less than 405, 410 to less than 415, 425, 428, 429.2, 430 to less than 439, 440 to less than 445, and 798.

Covariates and other variables

Certain participant information was obtained through self-administered questionnaires. Education level was collected at the SOF study baseline (visit one). We also used the visit nine questionnaire to obtain age, whether each participant reported walking for exercise, functional impairments (in six Instrumental Activities of Daily Living [IADLs]), self-rated health, and self-reported comorbidity information (diabetes, hypertension, stroke, and myocardial infarction) at visit nine. The visit nine questionnaire also included the Geriatric Depression Scale, which was used to assess depressive symptoms (scores of ≥ 6 were used to define depression).[57] Trained examiners also administered the Modified Mini-Mental State Examination (3MS; used to assess global cognition on a scale from 0-100).[58] BMI (measured in kilograms per meters squared) was determined based on measured height and weight. For determination of antidepressant and sleep medication use (as well as other medication use), all current medications were recorded by clinic staff (confirmed by examining pill bottles) and a computerized coding dictionary was used for classification.[60]

Statistical analyses

The five-year changes in all nine sleep and circadian RAR parameters were included in HCPC analysis (using the “FactoMineR” and “factoextra” R packages[61]), allowing identification of sleep-wake change profiles. The HCPC analysis involved unbiased hierarchical clustering performed on the principal components needed to explain 95% of the cumulative variance in the nine sleep-wake parameters. The number of clusters was chosen using the partition point with the highest relative loss of inertia. We first examined the distributions of each sleep-wake parameter and the correlations between sleep-wake parameters. We also compared visit nine characteristics (as well as sleep and circadian RAR parameter changes) across the sleep/circadian change profiles and across post-visit nine mortality status. For all comparisons, we used t-tests (two categories of the grouping variable) or ANOVA (greater than two categories of the grouping variable) for normally distributed continuous variables, Kruskal-Wallis tests for non-normally distributed continuous variables, and chi-square tests for categorical variables. All statistical tests were 2-sided and used a $p < 0.05$ threshold.

We used Cox proportional hazards models to examine the associations between sleep-wake change profiles and risk of all-cause and cardiovascular mortality following the second sleep visit. We ensured that the proportional hazards assumption was met, and time-varying covariates were unnecessary through visual inspection of Schoenfeld residuals plots and Kaplan-Meier survival curves (included in Supplementary Fig. 3–4) and using Schoenfeld tests. For the analyses that included cardiovascular mortality as the outcome, individuals who died from other causes were censored (not excluded). In addition to examining the sleep-wake change profiles, we also examined the associations of individual sleep-wake change parameters with all-cause and cardiovascular mortality. To do so, we divided each

parameter into a “worsening” group (> 1 SD worse than the mean change) and a “stable/improving” group (the remainder of the sample). For acrophase, the two groups were instead “earlier” and “stable/later”. “Worsening” total sleep time, sleep efficiency, amplitude, mesor, and robustness referred to large decreases, while “worsening” WASO, nap duration, and nap frequency referred to large increases. To account for the potential U-shaped relationship between nighttime sleep duration and mortality risk, we categorized changes in nighttime sleep duration into three groups: “increasing (an increase of > 1 SD above the mean change)”, “decreasing (a decrease of > 1 SD below the mean change)”, and “stable (changes within 1 SD above or below the mean)”. These categorical versions of the sleep-wake parameters were used in the Cox regressions, with the “stable/improving” (“stable/earlier” for acrophase, “stable” for nighttime sleep duration) group serving as the reference group. We performed unadjusted Cox regressions in addition to models that adjusted for age, education, BMI, diabetes, hypertension, myocardial infarction, antidepressant use, functional impairments, self-rated health and global cognition at visit nine (selected based on previous literature and plausibility). To explore whether baseline sleep duration moderates the relationship between changes in nighttime sleep duration and mortality risk—given that increasing sleep may be beneficial for those with short baseline sleep yet detrimental for those with long baseline sleep—we conducted secondary analyses stratified by baseline sleep duration (long/above versus short/below the mean) and tested for interaction between baseline nighttime sleep duration and its changes. Analyses were performed in RStudio version 2023.12.0 + 369 (Posit Software, PBC).

Table 1
Profiles of five-year changes in 24-hour sleep-wake activity parameters

Parameter (five-year change)	**Stable sleep (N = 307)**	**Declining Nighttime Sleep (N = 251)**	**Increasing Sleepiness (N = 146)**	**P***
Nighttime sleep duration (min)	21.8 (67.0)	-13.5 (72.4)	67.0 (87.4)	**< .001**
Sleep efficiency (%)	0.91 (8.6)	-3.7 (8.1)	8.5 (10.3)	**< .001**
Wake after sleep onset (min)	3.4 (36.9)	22.0 (39.8)	-22.1 (40.4)	**< .001**
Napping duration (min)	-8.0 (49.3)	27.3 (62.4)	108.3 (109.0)	**< .001**
Napping frequency (count)	-0.50 (2.8)	1.3 (3.3)	6.2 (7.1)	**< .001**
Acrophase (portions of hours)	-0.06 (0.96)	-0.10 (1.2)	-0.07 (1.3)	.74
Amplitude (counts/min)	-5.2 (822.0)	-972.4 (814.2)	-1520.2 (1129.1)	**< .001**
Mesor (counts/min)	3.7 (476.4)	-349.3 (393.4)	-814.8 (670.2)	**< .001**
Robustness (pseudo-F)	80.3 (356.8)	-377.2 (406.9)	-409.0 (419.2)	**< .001**
Note: Medians and interquartile ranges (IQRs) are reported. * Examined by Kruskal-Wallis tests.				

Table 2
Visit nine characteristics by profiles of sleep-wake change

	Stable sleep (N = 307)	**Declining Nighttime Sleep (N = 251)**	**Increasing Sleepiness (N = 146)**	**P**
Age (years)	87.0 (3.0)	87.0 (3.0)	88.0 (4.0)	**.03**
< 12 years education	45 (14.7)	36 (14.3)	30 (20.5)	.20
Walks for exercise	136 (44.3)	100 (39.8)	46 (31.5)	**.03**
Body mass index (kg/m^2)	25.7 (5.6)	25.7 (6.8)	25.3 (6.6)	.65
Diabetes	37 (12.1)	41 (16.3)	21 (14.4)	.35
Hypertension	200 (65.1)	166 (66.1)	96 (65.8)	.97
Stroke	28 (9.1)	29 (11.6)	22 (15.1)	.17
Myocardial infarction	55 (17.9)	37 (14.7)	29 (19.9)	.39
Depression	27 (8.8)	30 (12.0)	26 (17.8)	**.02**
3MS score (1-100)	92.0 (8.5)	91.0 (9.5)	89.0 (10.0)	**.01**
Impairment of ≥ 1 IADL	202 (65.8)	159 (63.3)	105 (71.9)	.13
Good/excellent self-rated health	253 (82.4)	193 (76.9)	110 (75.3)	**.03**
Antidepressant user	31 (10.1)	50 (19.9)	26 (17.8)	**.003**
Sleep medication user	69 (22.5)	57 (22.7)	29 (19.9)	.82

Note: For age, body mass index, and 3MS score, Kruskal-Wallis tests were used, and median and interquartile range are reported. Counts and percentages are reported for all other variables (categorical variables), for which chi-square tests (and Fisher's exact test for self-rated health) were used.

Abbreviations: 3MS, Modified Mini-Mental State Examination; IADL, Instrumental Activity of Daily Living.

Table 3
Age-adjusted associations of sleep-wake change profiles and individual parameters with all-cause and cardiovascular mortality

Parameter (five-year change) or profile		All-cause mortality (deaths/total N = 88/699)	Cardiovascular mortality (deaths/total N = 34/699)
Stable sleep		1.00 [ref]	1.00 [ref]
Declining nighttime sleep		**1.90 (1.17,3.11)**	1.68 (0.76,3.71)
Increasing sleepiness		**1.92 (1.09,3.40)**	1.84 (0.75,4.49)
Nighttime sleep duration	Increasing	1.63 (0.92,2.87)	1.43 (0.54,3.78)
	Stable	1.00 [ref]	1.00 [ref]
	Decreasing	1.63 (0.89,2.97)	**2.51 (1.07,5.91)**
Sleep efficiency	Stable/increasing	1.00 [ref]	1.00 [ref]
	Decreasing	1.48 (0.82,2.67)	2.18 (0.95,5.00)
Wake after sleep onset	Stable/decreasing	1.00 [ref]	1.00 [ref]
	Worsening	1.44 (0.80,2.61)	1.71 (0.71,4.13)
Nap duration	Stable/decreasing	1.00 [ref]	1.00 [ref]
	Increasing	**2.02 (1.18,3.45)**	2.06 (0.89,4.80)
Nap frequency	Stable/decreasing	1.00 [ref]	1.00 [ref]
	Increasing	1.78 (1.00,2.99)	**2.30 (1.03,5.15)**
Acrophase	Stable/later	1.00 [ref]	1.00 [ref]
	Earlier	0.74 (0.34,1.60)	1.42 (0.55,3.68)
Amplitude	Stable/increasing	1.00 [ref]	1.00 [ref]
	Decreasing	**1.87 (1.08,3.22)**	1.75 (0.72,4.25)
Mesor	Stable/increasing	1.00 [ref]	1.00 [ref]
	Decreasing	1.35 (0.73,2.50)	1.08 (0.38,3.10)
Robustness (pseudo-F)	Stable/increasing	1.00 [ref]	1.00 [ref]
	Decreasing	**1.71 (1.02,2.88)**	1.09 (0.42,2.84)

Note: Hazard ratios (HRs) and 95% confidence intervals (95% CIs) were calculated using Cox proportional hazards models adjusted for age at visit nine.

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Figures

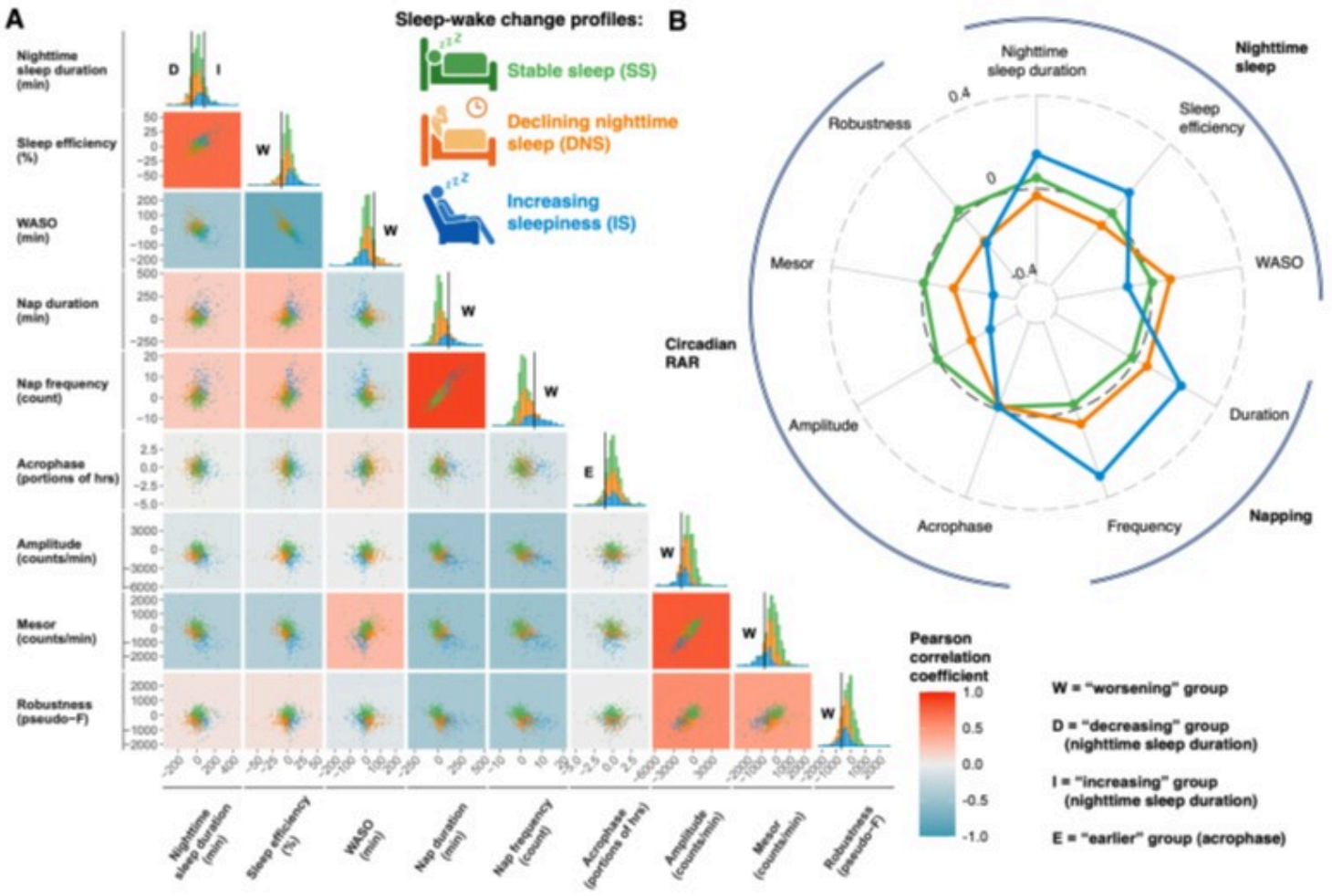

Figure 1

Profiles of the five-year changes in nighttime sleep, napping, and circadian RAR parameters. A. Correlations and distributions of sleep-wake parameter changes. Correlation strength (Pearson correlation coefficient) is represented by the color of each square. Points on the scatterplots are colored according to the sleep-wake change profiles. The diagonal shows the distribution of each sleep-wake parameter change for each of the three sleep-wake change profiles. The vertical black lines on the diagonal show the cutoffs for defining the "worsening" ("earlier" for acrophase, and "decreasing"/"increasing" for nighttime sleep duration) group for each sleep-wake parameter change (>1 standard deviation worse than the mean change), which are marked by the letter "W" ("E" for acrophase, and "D"/"I" for nighttime sleep duration). **B. Radar plot showing the normalized median changes in nighttime sleep, napping, and circadian RAR parameters for the three sleep-wake change profiles.** For all sleep-wake parameters, the line labeled "0" represents a change of zero, such that values outside of that line represent increases and values inside represent decreases. The values of the sleep-wake parameter changes are normalized such that for each parameter, the largest change in the sample is represented by 1 or -1 (depending on whether that change was an increase or decrease), and all other values are scaled relative to (divided by) that value.

Abbreviations: WASO, wake after sleep onset; RAR, rest-activity rhythms.

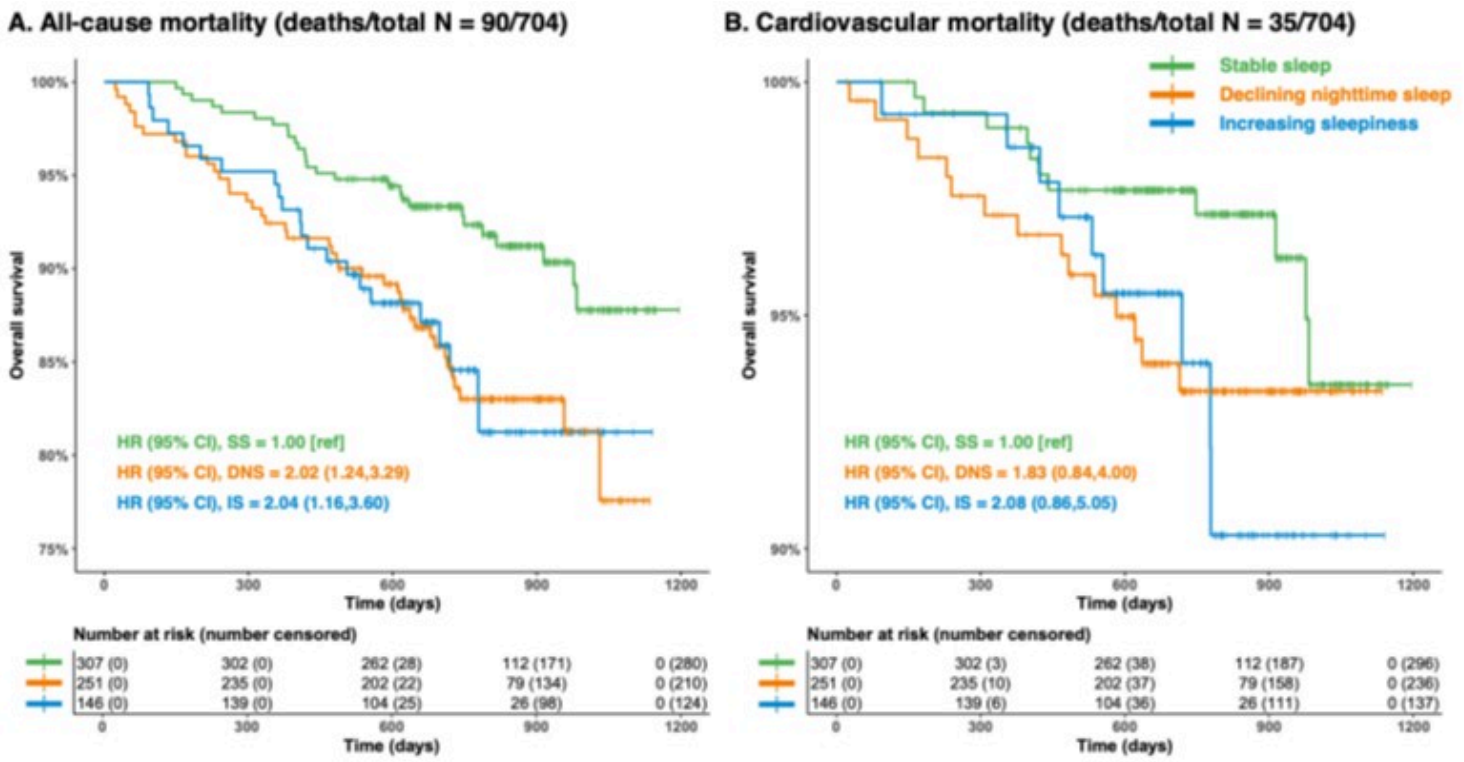

Figure 2

Unadjusted Kaplan-Meier survival curves for all-cause (A) and cardiovascular (B) mortality by the three sleep-wake change profiles. Hazard ratios (HRs) and 95% confidence intervals (95% CIs) were calculated using unadjusted Cox proportional hazards models. Time is measured in days since visit nine. Censored participants are represented by vertical markings along the survival curves.

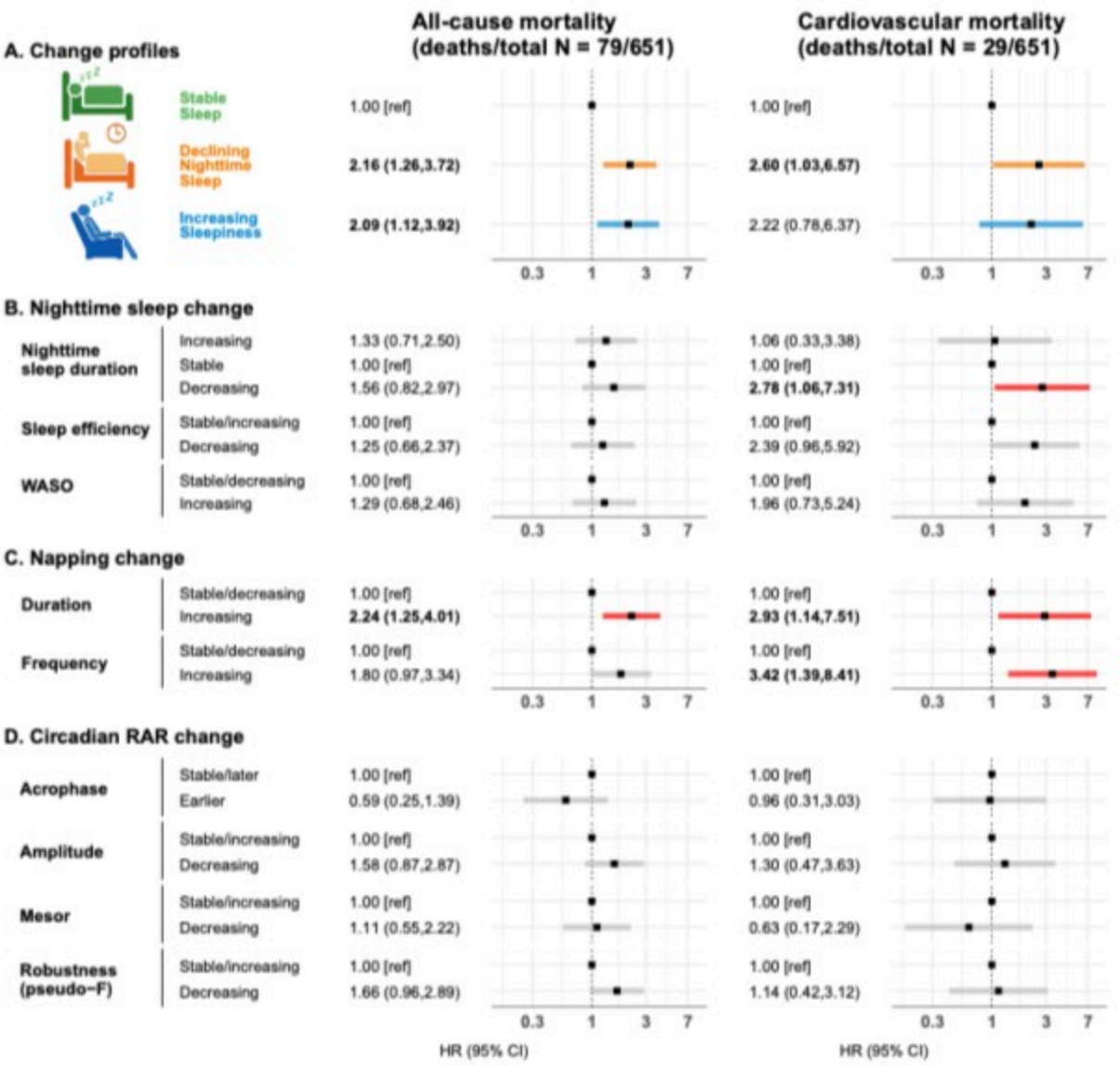

Figure 3

Multivariable-adjusted* associations of sleep-wake change profiles (A), nighttime sleep (B), napping (C) and circadian RAR (D) change parameters with all-cause and cardiovascular mortality risk. Hazard ratios (HRs) and 95% confidence intervals (95% CIs) were calculated using adjusted Cox proportional hazards models. Each individual sleep-wake change variable (other than nighttime sleep duration) was divided into two groups, a "worsening" group ("earlier" for acrophase; >1 standard deviation worse than the mean change) and a "stable/improving" group ("stable/later" for acrophase). In this figure, the groups are labeled according to whether "worsening" refers to increases or decreases for each particular parameter (e.g. the "worsening" group for sleep efficiency is labeled "decreasing", while for WASO, it is labeled "increasing"). Nighttime sleep duration was divided into a "stable" group, an "increasing group" (>1 standard deviation above the mean change), and a "decreasing" group (>1 standard deviation below the mean change).

*Adjusted for age, education, body mass index, diabetes, hypertension, myocardial infarction, antidepressant use, functional impairments, self-rated health, and global cognition at visit nine.

Abbreviations: WASO, wake after sleep onset; RAR, rest-activity rhythm.

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