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Objectively regular sleep patterns and mortality in a prospective cohort: The Multi-Ethnic Study of Atherosclerosis

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Summary

Irregular sleep and non-optimal sleep duration separately have been shown to be associated with increased disease and mortality risk. We used data from the prospective cohort Multi-Ethnic Study of Atherosclerosis sleep study (2010–2013) to investigate: do aging adults whose sleep is objectively high in regularity in timing and duration, and of sufficient duration tend to have increased survival compared with those whose sleep is lower in regularity and duration, in a diverse US sample? At baseline, sleep was measured by 7-day wrist actigraphy, concurrent with at-home polysomnography and questionnaires. Objective metrics of sleep regularity and duration from actigraphy were used for statistical clustering using sparse k-means clustering. Two sleep patterns were identified: "regular-optimal" (average duration: 7.0 ± 1.0 hr obtained regularly) and "irregular-insufficient" (duration: 5.8 ± 1.4 hr obtained with twice the irregularity). Using proportional hazard models with multivariate adjustment, we estimated all-cause mortality hazard ratios. Among 1759 participants followed for a median of 7.0 years (Q1–Q3, 6.4–7.4 years), 176 deaths were recorded. The "regular-optimal" group had a 39% lower mortality hazard than did the "irregular-insufficient" sleep group (hazard ratio [95% confidence interval]: 0.61 [0.45, 0.83]) after adjusting for socio-demographics, lifestyle, medical comorbidities and sleep disorders. In conclusion, a "regular-optimal" sleep pattern was significantly associated with a lower hazard of all-cause mortality. The regular-optimal phenotype maps behaviourally to regular bed and wake

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AUTHOR CONTRIBUTIONS

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

times, suggesting sleep benefits of adherence to recommended healthy sleep practices, with further potential benefits for longevity.

Keywords

mortality; multi-dimensional; regular sleep; sleep; variability

1 | INTRODUCTION

An established literature links non-optimal sleep duration to major health outcomes and mortality (Cappuccio et al., 2010; Kripke et al., 2011; Youngstedt & Kripke, 2004). A growing literature also emphasises that sleep irregularity may influence health outcomes by fostering unfavourable inflammatory, circadian, cardiometabolic, psychological and/or behavioural responses (Bei et al., 2016; Bei et al., 2017; Huang et al., 2020; Huang & Redline, 2019; Makarem et al., 2020; Patel et al., 2014; Phillips et al., 2017; St-Onge et al., 2020; Taylor et al., 2016; Zuraikat et al., 2020). In epidemiological studies of early adulthood, irregular sleep is associated with increased white blood cell count, reduced microvascular function, and delayed circadian rhythms (Hoopes, Berube, et al., 2021; Hoopes, D'Agata, et al., 2021; Phillips et al., 2017). In midlife and late adulthood, irregular sleep is associated with metabolic abnormalities, central obesity and risk of incident cardiovascular events (Huang et al., 2020; Huang & Redline, 2019; Lunsford-Avery et al., 2018). Irregular sleep based on participant-report has been linked to mortality (Omichi et al., 2022); however, participant-reported and objective sleep measures are only modestly correlated (Jackson et al., 2018).

Strikingly, the public health problem of irregular sleep is juxtaposed with its potential to respond to a scalable, behavioural intervention to achieve regular bed and wake times. Regular bed and wake times are a cornerstone of sleep hygiene for the general population and are emphasised in cognitive-behavioural treatments for patients with insomnia, underscoring the importance of sleep regularity for all individuals, with or without sleep disorders. Regular bed–wake schedules set the context for individuals to concurrently experience: (1) regularity of sleep timing; (2) consistency of nightly sleep duration; and (3) optimal duration. Thus, assessing multiple regularity and duration sleep metrics concurrently rather than independently may enable more faithful modelling of real-world sleep patterns.

Consequently, the research question that motivated this study was: do aging adults whose sleep is objectively high in regularity in timing and duration (consistent with regular bed and wake times), and of sufficient duration tend to have increased survival compared with those whose sleep is high in irregularity in timing and duration, and lower average duration ("regular-optimal" versus "irregular-insufficient")? We aimed to model multi-dimensional sleep data from a comprehensive sleep examination with objective sleep measures in a multi-centre cohort of US adults, the Multi-Ethnic Study of Atherosclerosis (MESA). We tested the hypothesis that an objective "regular-optimal" sleep pattern will be associated with lower mortality hazard than those who tended to sleep less regularly and optimally ("irregular-insufficient" sleep pattern). We hypothesized that regular-optimal sleep should

associate with mortality above and beyond adjustment for potential confounders, including sleep disorders.

2 | METHODS

2.1 | Multi-Ethnic Study of Atherosclerosis: Design

The MESA is a multi-site prospective community-based study aimed at investigating the progression of subclinical to clinical cardiovascular disease (CVD; Bild et al., 2002). At baseline Examination 1 (2000–2002), MESA enrolled 6814 adults of four race/ethnicities (White, Black, Hispanic, Chinese), free of evident CVD, aged 45–84 years, from areas near six academic field centres (Forsyth County, NC; Northern Manhattan and the Bronx, NY; Baltimore City and Baltimore County, MD; St Paul, MN; Northwestern, Chicago, IL; and Los Angeles, CA). MESA participants have been followed at subsequent examinations, every 2–4 years, to update their risk factor and outcome data. The MESA study, as well as the sleep examination, was approved by institutional review boards of participating institutions, and participants provided written informed consent (Bild et al., 2002).

2.2 | MESA–Sleep (2010–2013)

At Examination 5 (2010–2012), MESA invited 4077 participants to undergo a comprehensive sleep examination. Of the invited participants, 147 individuals (3.6%) were excluded because they used a positive airway pressure device, oral appliance or supplemental oxygen; 141 individuals (3.5% of invited participants) lived too far from a field site. Of the remaining 3798 invitees, 2261 consenting individuals enrolled in MESA–Sleep, and underwent sleep assessments by polysomnography, wrist actigraphy and questionnaire. The final analytic sample was 1759 participants.

The current research question focuses on data from 7-day wrist actigraphy recordings. Key actigraphy metrics such as total sleep time (duration) have been validated compared with gold-standard polysomnography (Jean-Louis et al., 2001; Lujan et al., 2021). MESA–Sleep participants were asked to wear a wrist actigraph (Actiwatch Spectrum; Philips Respironics, PA, USA) for 7 days. Resulting data were processed by the Actiware-Sleep v 5.59 software (Mini Mitter, Bend, OR, USA), and scored by trained staff at Brigham and Women's Hospital Sleep Reading Center. Scorers determined objective rest intervals by triangulating activity–rest patterns algorithmically scored by the Actiware-Sleep software with participant-actuated event markers, a sleep diary and light sensors, similar to procedures described in Ogilvie et al. (2016). Sleep apnea was assessed using the apnea–hypopnea index (AHI; hypopneas defined using 3% desaturation and 30% reduction in amplitude by polysomnography, as detailed in Chen et al., 2015). Symptoms of insomnia severity were measured by the Women's Health Insomnia Rating Scale (Levine et al., 2005). Restless legs syndrome was assessed by self-report (yes/no diagnosis).

2.3 | Exposure: Sleep patterns (cluster analysis)

We used three actigraphy sleep metrics based on the 7-day monitoring period: total sleep time (duration), night-to-night timing irregularity, and night-to-night duration irregularity. Sleep duration or total sleep time was defined as the average amount of sleep during the

main sleep period across all days. Night-to-night timing irregularity was defined as the 7-day standard deviation of the midpoint of sleep (midway between sleep onset and offset, in minutes), and 7-day night-to-night duration irregularity was defined as standard deviation of sleep duration during each main sleep period (in minutes) across the recording period. For actigraphy, valid nights were considered those with no more than an hour of "off time".

Our goal was to perform a hypothesis test, and we used an unsupervised approach, operationalizing the sleep exposure independent of the mortality outcome. We then tested whether our operationalization of regular sleep schedules was associated with time to mortality. We log transformed the standard deviation in midpoint timing and standardized all measures (mean = 0, sd = 1). We examined an elbow plot, the Gap statistic, and metrics of cluster instability to determine best "k" or number of clusters (Hennig, 2007; Tibshirani et al., 2001). The elbow plot showed an elbow at $k = 2$, which suggested diminishing returns in reduced within-cluster variance with $k > 2$. Cluster stability was assessed by normalized cluster instability (via the cstab package), and instability under bootstrapping or subsetting (via the FPC package) in which the original data are perturbed or resampled, and cluster solutions in repeatedly bootstrapped or subsetted samples are compared by pairwise similarity. These cluster stability analyses suggested that $k = 2$ resulted in clusters that were more stable than $k > 2$. We also evaluated the Gap statistic, which can be helpful in assessing the utility of clustering versus not clustering (i.e. $k = 1$ or $k > 1$), whereas most clustering diagnostics typically do not consider the possibility of $k = 1$ (no clusters). The Gap statistic is therefore able to compare $k = 1$ versus $k = 2, 3, 4$ by comparison to a reference distribution, specifically a uniform distribution overlay over the first principal component of the empirical data. This analysis likewise suggested $k = 2$ to be supported compared with $k = 1$ or $k > 2$. We further used the NbClust package, which uses 30 clustering indices; this analysis suggested a range of possible solutions, but favoured $k = 2$ by plurality vote (Charrad et al., 2014). We chose k-means clustering as our base algorithm, as it is non-parametric and entails minimal assumptions, and ran sparse k-means clustering with $k = 2$. Subsequent examination of the distributions of sleep metrics by cluster assignment suggested that "regular-optimal" and "irregular-insufficient" were appropriate labels to describe predominant tendencies in each cluster. The clusters do not have the interpretation of evidence of underlying categorical subtypes, but rather are data-driven operationalizations of features identified as aspects of irregular sleep and wake times from our conceptual model (Figure 1).

2.4 | Outcome: All-cause mortality

We considered all-cause deaths adjudicated up to 2018, at a median follow-up time of 7.0 years. Deaths were adjudicated by MESA study personnel by examination of death certificates, records of hospitalization, National Death Index searches, and obituaries as described in Bluemke et al. (2008).

2.5 | Covariates

In time-to-death analyses, we adjusted for socio-demographics, lifestyle factors, medical comorbidity and sleep disorders as potential confounders of regular sleep and mortality. Socio-demographics included: age, sex/gender, race/ethnicity, marital status, and work

schedules (day shift, non-day shift [afternoon, night, split, irregular, rotating], do not work). Lifestyle factors in primary analyses included: moderate–vigorous physical activity reported as METs per min per week (the MESA Typical Week Physical Activity Survey adapted from the Cross-Cultural Activity Participation study) and smoker status (Bild et al., 2002); sensitivity analyses included the Alternative Healthy Eating Index 2010, which reflected diet and alcohol consumption (Akbaraly et al., 2011; Leitzmann et al., 2007).

Health adjustments included depressive symptoms (Center for Epidemiologic Studies–Depression, minus restless sleep item), total number of medications (prescribed and non-prescribed taken over the last 4 weeks), body mass index (BMI) computed as measured weight in kilograms divided by height in metres squared (kg m^{-2}), and prevalent CVD–including myocardial infarction, resuscitated cardiac arrest, angina, fatal coronary heart disease, congestive heart failure, peripheral artery disease, transient ischaemic attack. These events were assessed at each exam, and adjudicated by independent experts in MESA by review of medical records or death certificates and/or confirmation by next-of-kin (Huang et al., 2020). Sensitivity analyses included adjustments for chronic lung disease, prevalent cancer, hypertension and diabetes as covariates. Hypertension was operationalized as dichotomous: meeting Joint National Committee VI (JNC 1997) criteria of high blood pressure guidelines as average systolic blood pressure (SBP) ≥ 140 mm Hg or average diastolic blood pressure (DBP) ≥ 90 mm Hg or use of antihypertensive medication. Diabetes was operationalized by 2003 American Diabetes Association fasting glucose criteria, or taking insulin or hypoglycaemics for diabetes.

Sleep apnea was characterized by the AHI (events per hr) modelled continuously; insomnia symptoms by the Women's Health Initiative Insomnia Rating Scale (Levine et al., 2005) modelled continuously, and restless legs syndrome as a categorical "yes/no" participant-report for ever having been diagnosed by a physician for this disorder. After exclusion of missingness, the sample was 1759.

2.6 | Analytic strategy

We ran Cox proportional hazard models in a complete case analysis, regressing time to death on sleep patterns at increasing levels of adjustment. Model 1 included socio-demographics; Model 2 added lifestyle factors; Model 3 added medical comorbidities; and Model 4 added metrics of common sleep disorders. We assessed model fit with and without sleep clusters. We checked proportional hazards assumptions by inspecting Kaplan–Meier curves, and assessing associations between Schoenfeld residuals and time.

An additional set of Cox models assessed whether sleep clusters added value beyond modelling individual metrics. We assessed associations between all-cause mortality and regularity and duration metrics defined using thresholds drawn from prior work showing associations of individual metrics associated with cardiometabolic diseases, with favourable sleep metrics defined as (Huang et al., 2020; Huang & Redline, 2019): midpoint standard deviation < 30 min; duration standard deviation < 60 min; and total sleep time 6–8 hr; favourable levels were coded as "1", whereas values outside of these ranges were coded "0".

In a first sensitivity analysis, in Cox proportional hazard models, we used study participant age as the time metric instead of time to death (Pencina et al., 2007). Further sensitivity analyses included propensity score matching on sleep clusters to model the sleep–mortality relationship with a lesser number of covariates, using optimal full matching as recommended for survival analyses (Austin & Stuart, 2015). We also included covariates that were not strongly associated with exposure and/or outcome in bivariate analyses or had high missingness (and consequently were not included in primary models) yet are generally important to health: income (tertiles), education, diet including alcohol (Alternative Healthy Eating Index–10), hypertension, diabetes, chronic lung disease, and prevalent cancer. Subsequent models assessed propensity-score matched samples with additional adjustment for age, sex/gender and race-ethnicity to adjust for potential residual confounding. A second set of sensitivity analyses excluded individuals who died within a year of the sleep exam to address potential reverse causality.

3 | RESULTS

Table 1 shows descriptive statistics of MESA, stratified by sleep cluster. As previously reported, compared with MESA Exam five participants without sleep data, MESA–Sleep participants with sleep data tended to smoke less (e.g. 7.1% smokers versus 8.4%), were younger, and compositionally had more racial-ethnic minorities, yet were similar in sex, BMI and diabetes (Chen et al., 2015). In MESA–Sleep, the “irregular-insufficient” sleep group averaged 5.8 ± 1.4 hr of sleep, whereas the “regular-optimal” pattern averaged 7.0 ± 1.0 hr of sleep. The “irregular-insufficient” group tended towards twice the irregularity in duration and timing regularity metrics compared with the “regular-optimal” group (“irregular-insufficient” versus “regular-optimal” duration irregularity median [inter-quartile range]: 70.7 min [55.3, 96.0] versus 31.6 min [23.1, 42.0]; timing irregularity: 100.9 min [83.0, 120.1] versus 50.4 min [37.4, 65.1]).

Sleep regularity clusters did not differ markedly with respect to AHI (regular-optimal: median 18.4 events per hr versus irregular-insufficient: 17.2 events per hr, higher is worse), insomnia symptom scores (regular-optimal: median 6 versus irregular-insufficient: median of 7, higher is worse) or restless legs syndrome history (regular-optimal 4.5% versus irregular-insufficient 5.0% prevalence).

Figure 2(a) visualizes distributions of sleep characteristics by cluster assignment. As expected, cluster analysis resulted in noticeable separation between “regular-optimal” and “irregular-insufficient” sleepers in clustering metrics (total sleep time, midpoint sd, and duration sd). Figure 2(b) indicates that sleep disorder metrics–the AHI, insomnia symptoms–were not appreciably patterned by regularity/duration clusters, which is supported by their modest or null bivariate correlations.

Figure 3 shows unadjusted Kaplan–Meier curves for sleep cluster patterns. Over time, the “regular-optimal” pattern showed a large survival advantage compared with the “irregular-insufficient” sleep pattern.

Table 2 shows adjusted Cox Proportional Hazard models regressing time to death on "regular-optimal" sleep patterns. The estimated mortality advantage for "regular-optimal" sleepers compared with "irregular-insufficient" sleepers ranged from 39% to 42% lower mortality hazard across varying levels of adjustment. Model 1 estimated that "regular-optimal" sleepers compared with "irregular-insufficient" sleepers had a hazard ratio of mortality (hazard ratio [95% confidence interval]) of 0.59 [0.43, 0.79] after socio-demographic adjustment. Further adjustment for lifestyle resulted in a hazard ratio of 0.58 [0.43, 0.79]; 0.58 [0.43, 0.80] after additional adjustment for medical comorbidity; and 0.61 [0.45, 0.83] after additional adjustment for metrics of common sleep disorders.

Table 3 compares individual regularity or duration metrics with clusters in association with mortality. Likelihood ratio tests suggested that adding sleep clusters to the regression model improved model fit over models that included individual metrics alone, suggesting added value of multiple metrics over singular metrics.

Table 4 shows regularity versus irregularity in timing and duration compared with total sleep time (< 6, 6–8, > 8 hr). Greater proportions of the 6–8 hr category were observed among the regular sleepers as compared with irregular sleepers (72.5% versus 54.4% in timing regularity, and 69.1% versus 52.4% in duration irregularity).

Results from sensitivity analyses shown in Supplemental Information did not alter conclusions drawn from primary models: the "regular-optimal" sleep group was observed to have a large survival advantage compared with the "irregular-insufficient" group adjusting or matching for additional covariates beyond those included in primary analyses or excluding deaths within the first year of the sleep exam. A further sensitivity analysis excluding individuals with < 5 days of actigraphy data (n = 10, 0.06%) and modelling the remaining sample (n = 1749, 99.4%) did not alter conclusions.

4 | DISCUSSION

In the aging MESA cohort, we found that those who–by objective measurement of sleep–wake patterns–had regular sleep schedules with adequate sleep duration ("regular-optimal") had significantly lower hazard of all-cause mortality over a median of 7.0 years of follow-up compared with the "irregular-insufficient" group. The estimated "regular-optimal" advantage in survival remained after adjustment for socio-demographics, lifestyle, medical comorbidity and metrics of common sleep disorders, and remained robust in sensitivity analyses. The "regular-optimal" and "irregular-insufficient" pattern-based classification of sleepers was more strongly associated with mortality than individual metrics of irregularity alone or duration alone. The "regular-optimal" sleep pattern is behaviourally consistent with regular bed and wake times with sleep duration tending towards recommended ranges for adults, whereas the "irregular-insufficient" sleep pattern is consistent with irregular bed and wake times and duration that may involve alternating nights of insufficient and compensatory sleep (duration variability).

Distributions of sleep regularity were largely independent of sleep disorders (Figure 2). Further, in Cox models, hazard estimates changed little after adjustment for metrics of

obstructive sleep apnea, insomnia and restless legs syndrome, suggesting that the health significance of regular sleep patterns is independent of these sleep disorders. Sleep clusters improved model fit over baseline socio-demographics (Table S3). Regularity in timing and duration and sleep duration theoretically influence health concurrently, cluster empirically, and the composite-based approach showed added value above and beyond modelling individual metrics.

A tendency of irregular sleep to co-occur with suboptimal average sleep duration suggests that an unfavourable “irregular-insufficient” sleep–wake pattern could be characterized by insufficient sleep 1 night followed by sleep compensation the next night (Chontong et al., 2016). This contracting–expanding duration pattern across the week translates to variability in duration and timing in ways distinct from variability patterns observed in social jetlag (a systematic shift in sleep timing between weekdays and weekends; Wittmann et al., 2006). A contracting–expanding duration pattern also suggests the possibility of several nights of very short sleep (e.g. < 4 hr) interspersed with nights of longer sleep. Averaging across high variability nights of duration (in our data, about twice the variability in duration between regular and irregular sleepers) may obscure this pattern. MESA participants with “irregular-insufficient” sleep averaged 71.4 min less sleep duration than those with a “regular-optimal” pattern. If individuals are observed to have lower average sleep duration, their insufficient sleep may have been obtained with high irregularity. Thus, prior research on health effects of insufficient sleep may have also implicitly captured health effects of concurrent, but unmodelled, sleep irregularity and circadian misalignment. This could help explain the robustness and ubiquity of associations of insufficient sleep with health outcomes if multiple, highly important and related sleep dimensions are concurrently unfavourable for health but only one important dimension (e.g. average sleep duration) is modelled as a proxy (Kripke et al., 2002; Kripke et al., 2011).

A growing literature has identified the critical roles of circadian rhythms in maintaining health and, conversely, adverse effects of circadian disruption on metabolism, cognition, blood pressure, cardiac function, cancer-related pathobiology, and other physiological and disease processes (Buxton et al., 2012; Scheer et al., 2009). While prior research on sleep timing has mostly focused on the deleterious effects of shiftwork, showing increased rates of diabetes, hypertension, cancer incidence, and mortality in night and rotating shiftworkers, other research suggests that mild forms of irregular sleep in the general population may contribute to adverse health outcomes (Huang et al., 2020; Huang & Redline, 2019; Phillips et al., 2017). These effects have been postulated to be due to circadian disruption resulting from day to day variability in sleep patterns, which often associate with irregularity in timing of eating, physical activity and light exposures–factors that also influence circadian rhythms (Figueiro & Pedler, 2023). However, it is plausible that sleep–wake irregularity is a general marker for a more chaotic and stressful lifestyle that increases health-related risks, and future research should characterize the social determinants of sleep timing and regularity in adults.

Our data contribute to a literature supporting targeting sleep regularity as a public health goal. Such literature and the results of this study suggest potential benefits of establishing regular bed and wake times that create the context for optimal sleep duration

obtained consistently. Behavioural interventions may target both regularity and duration in combination by promoting adherence to a regular bed and wake schedule and optimizing exposures to light and darkness (Hand et al., 2023), rather than targeting duration only or regularity only. Special consideration, however, should be given to sleep schedules whose irregularity owes more to external, socioecological factors such as work schedules, which are consequently less targetable via individual-level behavioural intervention and may require institution-level solutions.

Our data also contribute to a multi-dimensional sleep science literature that considers multiple sleep metrics simultaneously rather than one by one. Sleep scores and sleep attribute clustering are increasingly common approaches (Lee & Lawson, 2021; Lee, Mu, et al., 2022; Lee, Smith, et al., 2022; Wallace et al., 2022). Our approach extends prior research that generated multi-dimensional indices of sleep to describe global sleep differences across racial-ethnic groups (Chung et al., 2021), described potential value of a multi-dimensional sleep health framework, and that predicted mortality (Chung et al., 2023). Nevertheless, this work incorporated information from 13 sleep metrics, which generated scores that may be challenging to reproduce across settings, and included measures from polysomnography, which is not universally available. Across these studies, however, actigraphy-assessed regularity and duration emerged as consistently important metrics for their: (i) pronounced disparities; (ii) ability to be measured by wrist-worn wearables in naturalistic settings (i.e. does not require polysomnography or respondent burden of participant or patient-report); (iii) aspects that can be targeted behaviourally via regular bed and wake times; and (iv) associations with cardiovascular outcomes and, as the current study suggests, mortality. Thus, the current analysis supports the utility in using a parsimonious approach that focuses on objective measures of duration and variability in cardiovascular epidemiological settings where polysomnography is not available.

There are several study strengths. We examined a physiologically important subset of measurements of sleep variability from objective data from standardized wrist actigraphy, and generated a composite metric that described complementary aspects of regularity and duration. The study sample was a well-characterized multi-ethnic cohort with diverse participants and rigorous ascertainment of multiple potential confounders and longitudinal assessment of vital status, and results were robust to multiple sensitivity analyses.

There are several potential study limitations. The results may not reflect causality although are based on prospectively ascertained mortality patterns. Unmeasured confounders could influence the results, although we adjusted for socio-demographics, lifestyle factors, medical comorbidity and major sleep disorders. While participants of the ancillary MESA–Sleep study are comparable to MESA participants who did not participate in MESA–Sleep in health and health behaviours (Chen et al., 2015), individuals specifically on oxygen or positive airway pressure therapy were excluded; future research may focus on patient populations already on treatment who may have systematically different mortality risk. Measurement of objective sleep was comprehensive and rigorous, but at one time point; nevertheless, single time point sleep measures are consistently associated with health. Relatively low power precluded application of a prediction paradigm, stratification by biological sex, disentangling collinear metrics, and investigation of interaction effects.

Nevertheless, as the cohort matures and events accumulate, additional analyses in these data are possible. With a number of ways to capture variability in sleep, each with slightly different bases and perhaps different use cases (Fischer et al., 2021), the most appropriate regularity measure may differ based on the research question and study population.

In our data, the prevalence of individuals meeting objective sleep timing (midpoint sd < 30 min) and duration regularity (duration sd < 60 min) was low at 26% and 40.4%, respectively (Table 1). In a prior MESA study, regular sleepers meeting these criteria had substantially less CVD incidence than did less regular sleepers (Huang et al., 2020). The cut points are not definite and may be refined, but the range of irregularity beyond the first quartile and tertile/median in these metrics appears to exhibit elevated disease risk and could be described as “irregular”. Moreover, our data are consistent with a clustering of sleep duration and regularity. The prevalence of the “irregular-insufficient” cluster was approximately 42%. Although this sample prevalence should be contextualized by its data-driven origin and the demographics of the sample (large number of retirees without the social zeitgeber of work schedules), the “irregular-insufficient” group comprised a large portion of the sample and had substantially elevated mortality hazard compared with those classified as “regular-optimal” sleepers. The “regular-optimal” group obtained an average of ~7 hr of total sleep time, with an sd of ~1 hr: correspondingly, 70.5% of “regular-optimal” sleepers slept 6–8 hr with high regularity. In contrast, a majority (51.8%) of “irregular-insufficient” sleepers averaged < 6 h, with this group experiencing approximately twice the variability in sleep timing and duration compared with the “regular-optimal” group (Tables 1 and 4). Research in other cohorts has focused on objective rest–activity rhythms, finding that ~20% of aging adults in the 2011–2014 National Health and Nutrition Examination Survey were classified as having weak rhythms, whereas Latent Class analyses in the MacArthur Study of Successful Midlife Development suggest identifiable classes of irregular sleepers obtainable by self-report (Cappuccio et al., 2011; Wallace et al., 2022). It is therefore noteworthy that however it has been defined or measured, across various cohorts irregular sleep is consistently reported to be prevalent.

Both regular-optimal and irregular-insufficient clusters had normally distributed total sleep time, thus containing both “short” sleepers and “long” sleepers in the tails of their distributions. Biological sleep requirement theoretically follows a normal distribution, suggesting that healthy sleep duration does include shorter-than-recommended and longer-than-recommended natural sleepers. While some epidemiological studies have observed increased risk associated with longer sleep duration (typically defined as > 9 hr, self-reported), others have observed null associations after adjusting for a wide variety of health conditions, suggesting the possibility of residual confounding by comorbidity (Cappuccio et al., 2011; Grandner & Drummond, 2007; Magee et al., 2013). Laboratory studies have observed a ceiling/floor effect in which healthy individuals appear to stabilize sleep duration, presumably appropriate to their biological requirement (Klerman & Dijk, 2008; Wehr et al., 1993). These studies suggest that after an initial catch-up period, a healthy individual who requires 8 hr of sleep and sleeps regularly is expected to have sleep that asymptotes to 8 hr, and is unlikely and is perhaps unable to habitually obtain 10 hr. Conversely, an individual whose biological requirement is 10 hr of sleep may asymptote to 10 hr of sleep, while being unable to habitually obtain 12 hr. Further research is needed

on the relationship between health status, reported sleep, objective sleep and biological sleep requirement to better understand optimal sleep duration.

The cluster analysis was used to identify sub-groups via dimension reduction on multiple metrics which, together, captured major features that differed between regular and irregular sleep schedules (Figure 1), while acknowledging that more work is needed to capture and validate physiologically distinct sub-groups of sleepers. Although k-means clustering is simple, widely-used, easy to understand and entails minimal assumptions, a large range of options exist for researchers to reduce dimensions and summarize multi-dimensional sleep data. For example, theory could suggest that the observed multi-dimensional sleep attributes can be modelled as mixtures, perhaps as the expression of latent classes or continua, and a model-based approach that entails a greater burden of assumptions than k-means may be justified to assess such theory. Moreover, with larger datasets or different metrics, it may be informative to partition the data into more clusters than 2 to provide greater insight for sub-types. In a younger sample, for instance, one might expect social jetlag to be a more prevalent type of irregularity, whereas in a middle-aged sample one might expect irregular work schedules, such as shiftwork, to be more prevalent. The most appropriate data science paradigm and approach is likely context dependent.

While our composite approach focused more on the concurrence of sleep attributes over their independence, our holistic approach is only different (not better) than understanding independent effects. A composite approach may more faithfully model sleep schedules as experienced by the sleeper and may have aggregated statistical power; however, the corresponding limitation is that the mechanistic “inner workings” and independent effects are still not fully understood and are in need of future research. Regarding independent effects, we note that experimental circadian forced desynchrony protocols vary sleep timing while allowing sufficient sleep duration and consistent sleep duration. Although such sleep patterns do not resemble the types of irregularity that are likely prevalent in the general population, these studies emphasize the role experiments may play in elucidating mechanisms. Thus, research focusing on the complementary perspectives of independent effects, synergism and composite patterns, using both experimental approaches in controlled settings and observational data from naturalistic settings vastly enrich our understanding because it is beneficial to examine a complex multi-dimensional phenomenon such as sleep from multiple perspectives.

Finally, our study was not a clinical trial. Nevertheless, the logical endpoint of this line of research is to understand and intervene: what happens to human longevity if people with irregular sleep schedules followed expert recommendations for regular bed and wake times? This is akin to asking whether people on the Standard American Diet would benefit from switching to the Mediterranean Diet, focusing less on independent effects of specific nutrients and more on the overall pattern. As applied to sleep, with more regular sleep schedules not just one aspect of sleep would improve, but a bundle of sleep aspects would improve, with potential further benefits for longevity.

5 | CONCLUSION

Objectively-measured regular sleep patterns of optimal duration were associated with reduced mortality compared with irregular and less sufficient sleep patterns in an aging US cohort. Study findings underscore expert recommendations to maintain regular bed and wake times.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available in Multi-Ethnic Study of Atherosclerosis at https://www.mesa-nhlbi.org/

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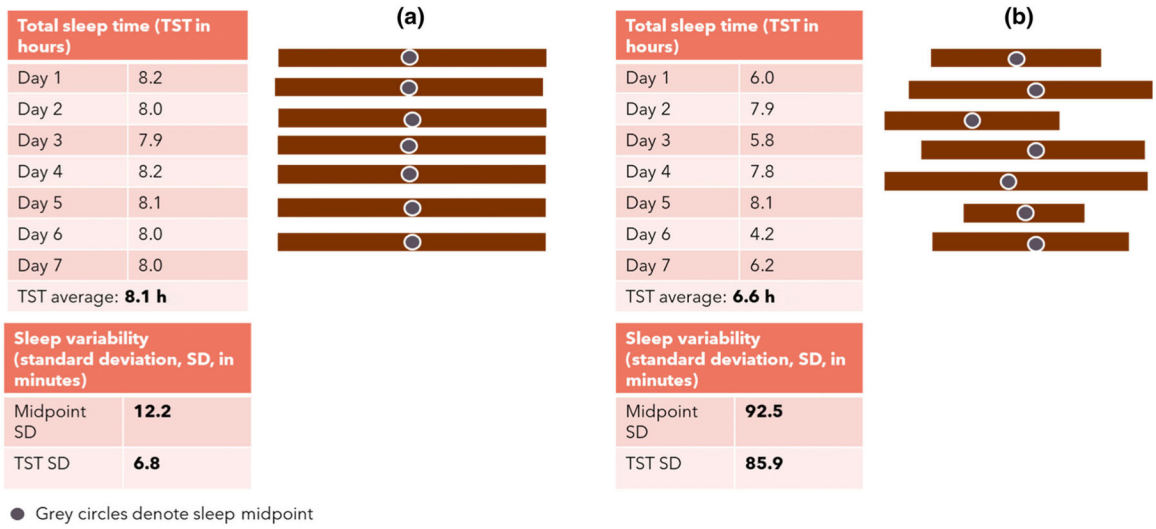

FIGURE 1.

Features of regular sleep schedules (a) versus irregular sleep schedules (b).

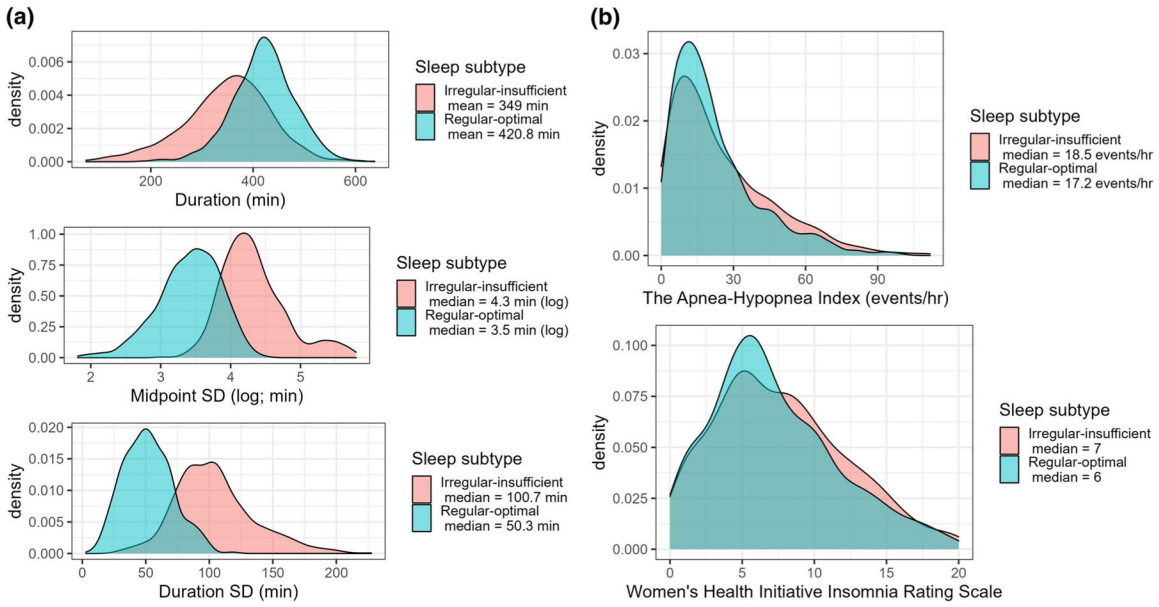

FIGURE 2.

Cluster analysis metric-level results from the Multi-Ethnic Study of Atherosclerosis (MESA; n = 1756). (a) Kernel density smoothed distributions of total sleep time (duration), midpoint SD, and duration SD, according to cluster assignment. MESA (n = 1759). (b) Distributions of the apnea–hypopnea index (AHI) and the Women's Health Initiative Insomnia Rating Scale by cluster assignment. MESA (n = 1759).

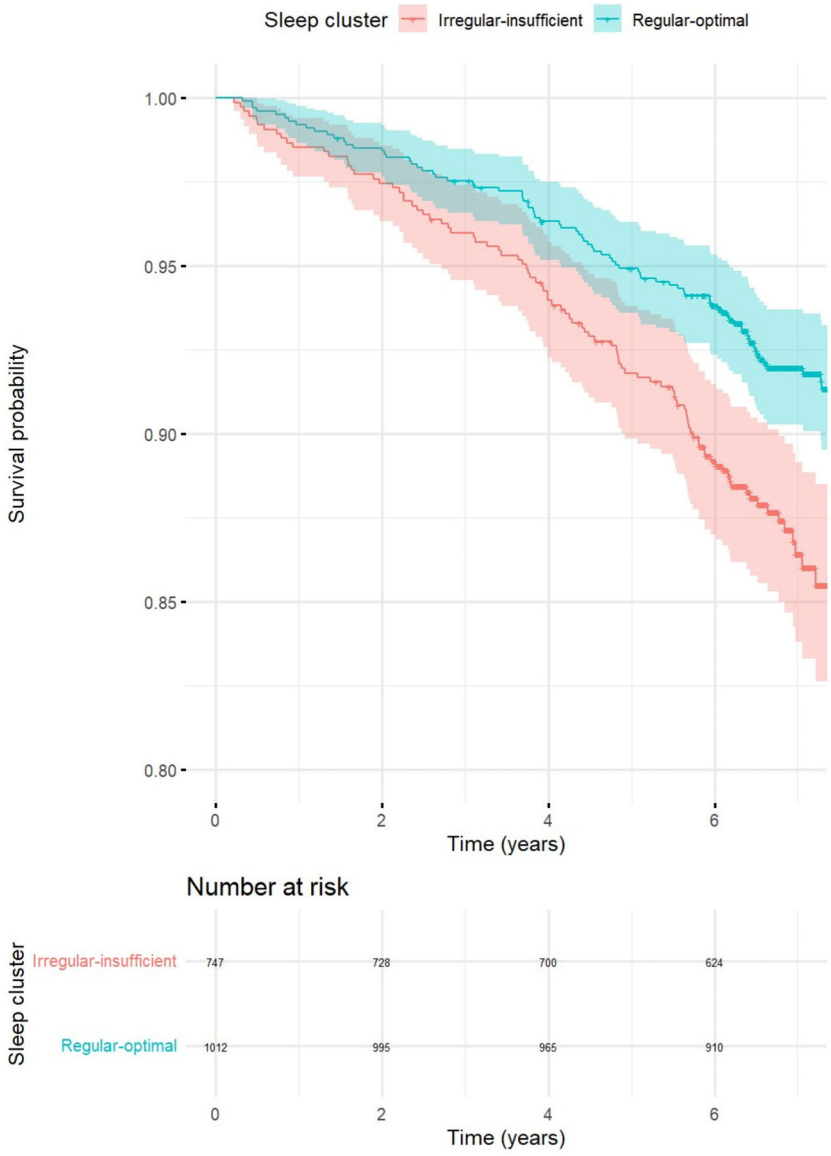

FIGURE 3.

Kaplan–Meier curves of regular schedule sleep clusters, timing regularity, duration regularity and average duration. MESA (n = 1759; Deaths = 176).

TABLE 1

Descriptive statistics for the MESA ($n = 1759$)[a]

Characteristic	Overall	Irregular-insufficient	Regular-optimal
n	1759	744	1015
Death	176 (10.0%)	94 (12.6%)	82 (8.1%)
Time to death (years)	7.01 [6.47, 7.49]	6.79 [6.34, 7.24]	7.23 [6.57, 7.64]
Midpoint sd (min; lower is better)	44.75 [29.19, 66.26]	70.68 [55.34, 95.95]	31.60 [23.11, 41.95]
Duration sd (min; lower is better)	68.27 [47.05, 96.24]	100.86 [83.01, 120.12]	50.39 [37.48, 65.11]
Duration (hr)	6.50 (1.33)	5.82 (1.40)	7.01 (1.00)
Midpoint sd < 30 min	458 (26.0%)	4 (0.5%)	454 (44.7%)
Duration sd < 60 min	711 (40.4%)	31 (4.2%)	680 (67.0%)
Duration 6–8 hr	1040 (59.1%)	326 (43.8%)	714 (70.3%)
Age (years)	68.23 (9.07)	67.70 (9.28)	68.61 (8.90)
Female	946 (53.8)	378 (50.8)	568 (56.0)
Race-ethnicity (%)			
White	646 (36.7%)	204 (27.4%)	442 (43.5%)
Chinese	200 (11.4%)	86 (11.6%)	114 (11.2%)
Black	497 (28.3%)	286 (38.4%)	211 (20.8%)
Hispanic	416 (23.6%)	168 (22.6%)	248 (24.4%)
Married	0.61 (0.49%)	0.58 (0.49%)	0.63 (0.48%)
Work schedule			
Day shift	560 (31.8%)	230 (30.9%)	330 (32.5%)
Non-day shift	221 (12.6%)	115 (15.5%)	106 (10.4%)
Do not work	978 (55.6%)	399 (53.6%)	579 (57.0%)
Moderate-vigorous physical activity	5502.04 (6436.23)	5559.04 (7334.39)	5460.26 (5692.01)
BMI (kg m^{-2})	28.67 (5.51)	29.27 (5.75)	28.23 (5.28)
Prevalent CVD	106 (6.0%)	52 (7.0%)	54 (5.3%)
CES-D scores (no sleep)	6.29 (7.12)	7.19 (7.65)	5.62 (6.63)
Total number of medications	4.00 [2.00, 7.00]	4.00 [2.00, 7.00]	4.00 [2.00, 6.00]
Restless legs (yes/no)	83 (4.7%)	37 (5.0%)	46 (4.5%)
AHI (events per hr)	23.53 (19.25)	25.13 (20.88)	22.35 (17.88)

Characteristic	Overall	Irregular-insufficient	Regular-optimal
Women's health initiative insomnia rating scale	7.42 (4.44)	7.67 (4.54)	7.23 (4.36)

[a] Values are reported as mean (sd), median [inter-quartile range], or *n* (%).

Abbreviations: AHI, apnea–hypopnea index; BMI, body mass index; CES-D, center for epidemiological studies - depression scale; CVD, cardiovascular disease.

TABLE 2

Cox proportional hazard models regressing time to death on sleep clusters

	Regular-optimal cluster
Exposure	**Hazard ratio [95% confidence interval]**
Model 1	0.59 [0.43, 0.79]
Model 2	0.58 [0.43, 0.79]
Model 3	0.58 [0.43, 0.80]
Model 4	0.61 [0.45, 0.83]

Note: Model 1 adjusts for socio-demographics: age, sex/gender, race/ethnicity, work schedules, marital status. Model 2 adjusts for lifestyle factors: smoking, moderate–vigorous physical activity. Model 3 adjusts for medical comorbidity: prevalent CVD, depressive symptoms, BMI, total medications. Model 4 adjusts for measures of major sleep disorders: AHI, insomnia symptoms, history of restless legs syndrome. MESA (n = 1759; Deaths = 176).

TABLE 3

Cox proportional hazard models[i] regressing time to death on sleep schedule clusters and individual regularity and duration metrics

	Baseline model (a)	Add sleep cluster (b)	Model fit	
Characteristic	**Hazard ratio [95% confidence interval]**	**Hazard ratio [95% confidence interval]**	**Log likelihood**	***p***
Midpoint SD < 30 min versus regular-optimal				
Midpoint SD < 30 min	0.62 [0.42, 0.90]	0.81 [0.52, 1.26]	−1208.4	
Regular-optimal		0.62 [0.43, 0.88]	−1204.8	< 0.01
Duration SD < 60 min versus regular-optimal				
Duration SD < 60 min	0.68 [0.50, 0.94]	0.95 [0.63, 1.43]	−1208.9	
Regular-optimal		0.58 [0.39, 0.86]	−1205.1	< 0.01
Total sleep time (duration) 6–8 hr versus regular-optimal				
Duration 6–8 hr	0.68 [0.50, 0.91]	0.77 [0.57, 1.06]	−1208.6	
Regular-optimal		0.61 [0.44, 0.84]	−1203.9	< 0.01

Note: Multi-Ethnic Study of Atherosclerosis (n = 1759. Deaths = 176).

[i] All models were adjusted for socio-demographic factors and lifestyle, equivalent to Model 2.

TABLE 4

Irregular versus regular timing (< 30 min midpoint sd) and duration (< 60 min duration sd) by total sleep time: < 6, 6–8 and ≥ 8 hr

	Sleep timing regularity comparison: Irregular timing versus regular timing		Sleep duration regularity comparison: Irregular duration versus regular duration	
Total sleep time	**Irregular: ≥ 30 min midpoint sd**	**Regular: < 30 min midpoint sd**	**Irregular: ≥ 60 min duration sd**	**Regular: < 60 min duration sd**
< 6 hr	36.9%	10.9%	39.4%	16.5%
6–8 hr	54.4%	72.5%	52.4%	69.1%
≥ 8 hr	8.7%	16.6%	8.2%	14.5%

Note: MESA (n = 1759).