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Sleep-Circadian Rhythms, Sleep Disparities, and Healthy Aging:

Circadian Disruption, the Lurking "Geriatric Giant"

A dissertation submitted in partial satisfaction of the requirements
for the degree Doctor of Philosophy

in

Public Health (Epidemiology)

by

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The dissertation of Alexis Garduno is approved, and it is acceptable in quality and form for publication on microfilm and electronically.

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2023

DEDICATION

To my parents, beloved husband,
and to all people in need of a good night's sleep

EPIGRAPH

"In this world, there are two times. There is mechanical time and there is body time."

"They do not keep clocks in their houses. Instead, they listen to their heartbeats. They feel the rhythms of their moods and desires."

"Then there are those who think their bodies don't exist. They live by mechanical time. They rise at seven o'clock in the morning. They eat their lunch at noon and their supper at six. They arrive at their appointments on time, precisely by the clock."

— Alan Lightman, *Einstein's Dreams*

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LIST OF ABBREVIATIONS

AD   Alzheimer's Disease

BMI   Body Mass Index

C1-5   Clusters 1 through 5

GS   Geriatric Syndrome/s

HR   Hazard Ratio

IRR   Incidence Rate Ratio

IS   Inter-daily stability

IV   Intra-daily variability

JDP   Joint Doctoral Program

L5   Activity count for least active 5 hours of the day

M10   Activity count most active 10 hours of the day

OR   Odds Ratio

RAR   Rest-activity rhythms

RUSATED   Conceptual sleep health model

SCN   Suprachiasmatic nucleus

SRI   Sleep-regulatory index

WASO   Wake after sleep onset

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PUBLICATIONS

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ABSTRACT OF THE DISSERTATION

Sleep-Circadian Rhythms, Sleep Disparities, and Healthy Aging

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Professor Andrea LaCroix, Chair

Background: Older adults exhibit fragmented circadian rhythms and undergo age-related changes in other sleep domains. Several challenges exist in conducting inclusive research for promoting healthy sleep and aging over the lifespan. Multiple sleep dimensions exist and complicate synthesis of sleep findings. Sleep health disparities also disproportionately affect the same populations that experience overall health disparities, yet diverse groups are underrepresented in sleep research.

Methods: Study 1 examined prospective associations between self-reported sleep from the Hispanic Community Health Study / Study of Latinos (n=10,640) and actigraphy-derived sleep/circadian measures from Sueño (n=1,808) with multimorbidity at follow-up. Study 2 used an ensemble of machine learning techniques to identify accelerometry-derived sleep and circadian profiles; we then examined associations between sleep-circadian profiles, fall risk, and physical functioning among 4,543 diverse older women in OPACH. Study 3 linked accelerometry data, claims, and genetic data to construct two network models to simultaneously evaluate the relationship between multiple sleep rest-activity rhythm measures with each cognitive outcome (e.g., dementia and Alzheimer's Disease).

Results: In study 1, several sleep and circadian measures were associated with comorbidity at follow-up, and we observed effect modification of these associations by place of birth and duration of residency. In study 2, we identified multiple sleep and circadian profiles using machine learning, and these profiles were associated with greater fall risk and lower physical functioning. In study 3, several circadian measures were indirectly associated with dementia and AD and shared a central hub in the network model.

Conclusion: This analysis enhances the field of life course epidemiology and sleep disparities research, having identified sleep and circadian behaviors as risk factors for disease and adverse aging outcomes. This study also highlights study designs that promote inclusive research.

1.   Introduction

1.1   Promoting Healthy Aging

There is a critical need to promote healthy aging among adults aged 65 and older. Adults aged 65+ years are expected to comprise nearly 25% percent of the population by 2060 [1]. The average lifespan is 78 years in countries with "established" healthcare and fiscal infrastructure, whereas the average lifespan is ten years shorter in other countries [2]. This age group is becoming increasingly diverse, and members from underserved backgrounds remain largely underrepresented in research studies [3]. By 2060, the adult population aged 65+ of non-Hispanic white individuals will decrease nationally to 55% from 78%; meanwhile, Black, Hispanic/Latino, and Asian older adults will increase to 12% from 9%, to 22% from 8%, and to 9% from 4% in the general population, respectively [3]. Developing and maintaining functional ability that allows for well-being at older ages (e.g., healthy aging) continues to be a primary objective of many institutions, including the recent World Health Organization's (WHO) Baseline report. It is critical to understand barriers to healthy aging.

1.2   Clarifying Health Disparities in Disease Burden and Aging

The Charlson Co-Morbidity Score (CCI) may detect accelerated aging prior to accumulation of geriatric syndromes (GSs) starting in middle-aged adults, and may also clarify disparities among diverse Latino populations. Having a higher CCI score for one's age demographic is emerging as a measure predictive of accelerated aging, as with functional and cognitive ability [4, 5]. Healthcare delivery and medical research is often focused on single diseases, yet integration of care for multiple diseases within an individual patient may improve safety and efficacy for that individual [6]. On average, older adults have a greater total number of co-morbidities: specifically, 30.4% of individuals ages 45-64 reported multi-morbidities; 64.9%

for ages 65-84, and 81.5% for those greater than 85 years old in one UK-based study [7]. CCI is a validated, simple, and commonly utilized measure to quantify the total number of chronic diseases, subsequent prognosis and risk of death associated with multimorbidity [8]. Those with one or more multi-morbidities report lower quality of life [9] and utilize inpatient care more frequently [10]. More recently, the CCI index has gained attention for predicting risk of mortality among individuals hospitalized for COVID [11].

1.3   <u>Socioeconomic and Hispanic/Latino Differences in Disease Burden</u>

There is also evidence of a health disparity in accumulation of total co-morbidities among minoritized sub-groups after accounting for age. Those of lower socioeconomic status (i) have an earlier onset of total co-morbidities and (ii) accumulate co-morbidities more rapidly with aging. The total number of chronic diseases among those living in areas with greatest economic deprivation was equivalent to the total diseases seen in those 10-15 years older living in the most affluent regions [7]. For example, Black men and women started off with a greater total number of multi-morbidities, and this burden of disease increased more steeply with aging compared to non-Hispanic white men and women [12]. Meanwhile, this same study showed that Mexican Americans had lower overall multi-morbidity burden than non-Hispanic white individuals, and the total number of comorbidities increased less steeply with aging [12]. Further work is needed in heterogenous populations to further understand the Hispanic Paradox; it is unknown the extent to which contextual factors, including place of birth, acculturation, age, and heritage may modify these trajectories of comorbidities. Social support may partially account for the Hispanic Paradox witnessed among Hispanic/Latinos who show later onset of more co-morbidities and slower accumulation. One study observed that late-life social networks were inversely associated with accelerated accumulation of co-morbidities after adjusting for job strain, education, manual

labor, and other sociodemographic factors [13]. Note, comorbidity burden in other Hispanic/Latino ethnic groups is underreported. A gap was identified recently by the 2018 workgroup, including the National Institute on Minority Health, the National Health, Lung, and Blood Institute, and the Office of Behavioral and Social Sciences research, suggesting that sleep-circadian disruption may be disproportionately affecting minoritized groups, and these sleep behaviors may contribute to disparities seen with respect to chronic disease and other health outcomes [14].

1.4   Geriatric Syndromes (GSs) and Public Health

GSs are a collection of signs and symptoms that share a similar etiology, are highly prevalent among older adults, and interfere with healthy aging by decreasing functional ability and quality of life. The term "geriatric syndrome" is not simply a collection of signs and symptoms related to a single disease state or process as implied by the term syndrome [15, 16]. GSs captures this decline in homeostatic reserve across multiple different organ systems as age increases [16]. This process reflects simultaneous aging that renders individuals with worse overall functional health [17]. The presence of one or more GSs is associated with greater disability [18], morbidity [19], and mortality [20] in older adults. GSs are prevalent among ~70-80% of adults aged 70+ years, where subsequent aging is associated with further accumulation of GSs [18, 21]. The prevalence of each individual GS differs slightly between studies, and these differences between studies are mainly driven by the varying composition of a cohort's gender and age demographic (65-69, 70-74, 75-79, vs. 80+ years old), where a greater burden of GSs is seen among women and older adults [22]. A study of nearly 20,000 community-dwelling adults observed that insomnia (37-41%) and urinary incontinence (21-37%) were the most commonly identified GSs in those in their mid-to-late sixties through their eighties [22]. Functional decline

was not common as common as other GSs in mid-to-late sixties but overtook other GSs in terms of prevalence by mid-seventies (26% up from 11%) and became most prevalent among those 80+ years old (41%) [22]. Falls (7%→17%), severe vision problems (3%→9%), severe hearing problems (19%→26%), and depressive disorders (2%→3%) double-to-quadruple in prevalence from mid-sixties to 80+ year old [21]. In the Women's Health Initiative (WHI), a study of women 65 years and older, there were some slight differences in estimated prevalence of these GSs: most noticeably a lower prevalence of reported sleep disturbances (8%) and higher prevalence of depression (8%), hearing impairment (29%), and vision impairment (21%) [23].

1.5   Identification Criteria of GSs

Identification of GSs may be based on common signs and symptoms, co-occurrence, prevalence among older adults, and shared risk factors, although formal criteria for GSs are lacking. The rationale that is commonly used to identify a chronic condition as a GS is as follows: (i) higher disease prevalence among older adults, (ii) correlations with multi-morbidity, (iii) preventable/modifiable in nature, and (iv) evidence of this potential GS sharing risk factors with other existing GSs [15]. When identifying shared risk factors of GSs, researchers have often looked to the interactive concentric model for guiding public health decision making. The interactive concentric model is focused on addressing multiple shared risk factors, in order to curb a larger proportion of absolute GS risk, as compared to a concentric approach, focused on eliminating a single risk factor [15]. This interactive concentric model fits well with the socio-ecological model, since upstream/structural factors are known to influence multiple outcomes.

1.6   Sleep, Circadian Rhythms, and GSs

Sleep disturbances is a GS and a candidate behavioral risk factor of GS co-occurrence. Yet, multiple dimensions of sleep exist (e.g. duration, regularity, satisfaction, sleep timing), as

under the RU-SATED model of sleep health [24]. It is unclear whether certain sleep profiles or

characteristics are associated with greater GS co-occurrence. Clustering of these sleep

dimensions may help elucidate which sleep profiles are more strongly associated with

accumulating more GSs. An additional challenge in studying sleep and RARs is that there are

many highly correlated sleep parameters, and separately examining each sleep parameter may

result in residual confounding by other sleep parameters. Separate behavioral profiles, comprised

of multiple sleep dimensions, may act in concert to modify disease risk. There is a growing shift

to modeling multiple dimensions of sleep and circadian behaviors simultaneously, using

dimension reduction [25] and/or clustering analyses [26] or factor analyses [27], and evaluating

associations of these sleep profiles with morbidity and mortality [28].

Some workgroups are interested in determining whether disruption in sleep rhythmicity

and other physiological rhythms are emerging GSs [29]. Circadian disruption, as evidenced by

disrupted rest-activity rhythms (RAR), manifests at older ages similar to other GSs. For example,

circadian disruption is more prevalent in older adults, multiple co-occurring symptoms stem

from more than one cause, and presence of a single GS (including circadian disruption) is

associated with a decline in an individual's overall health trajectory [15, 30]. Circadian rhythm

are endogenous rhythms governed by the central pacemaker in the hypothalamus called the

suprachiasmatic nucleus [31]. Sleep rhythmicity moderates circadian rhythms and is measured

using actigraphy to determine RARs [32]; these rest-activity patterns can be measured by activity

counts as through digital integration, which samples the actigraphy at a higher rate and sums the

total area under the curve for that individual epoch or period of sampling [32]. Activity counts

reported by an actigraphy measure duration and frequency of movement [32]; yet, rest-activity

patterns may mask diurnal fluctuations in other circadian parameters in peripheral tissues, such

as changes in melatonin levels [32]. An imposed schedule is an example of a behavior modifier that can noticeably mask circadian rhythm and disruption [32]. Individuals with a restricted schedule may have no corresponding changes in melatonin despite variations in their period of wakefulness during the day [32].

There is mixed evidence that RAR fragmentation and sleep regularity (IV and IS) are associated with progression in GSs, as evidenced by vision and/or cognitive impairment. Several studies have observed associations between RARs and individual GSs, including falls and fractures [33], cognitive impairment [34, 35], and visual impairment [36]. One study of 75-year-old men from the MrOs study observed that fragmented RARs were associated with greater cognitive decline, as evidenced by 3MS score, a brief cognitive battery of global cognitive functioning [34]. Another study among approximately 1,322 older adults from Rotterdam showed no association between RARs and dementia [37]. Challenges in generating this evidence base are (i) the availability of objectively measured RARs, (ii) long-term follow-up of older adults, and (iii) prospective measurement of GSs.

2. Sleep, Rest-Activity Rhythms, and the Charlson Comorbidity Index in the Hispanic Community Health Study/Study of Latinos and Sueño (HCHS/SOL)

2.1   Abstract

Disparities in chronic disease outcomes may arise due to differences in sleep and circadian health. We evaluated associations between self-reported sleep (from HCHS/SOL baseline, 2008-2011) and actigraphy-derived sleep/circadian measures (from Sueño, 2010-2013) with multimorbidity [modified Charlson Comorbidity Index (CCI) at HCHS/SOL Visit 2, 2011-2017]. We categorized sleep variables using standard cut-off values or tertiles, and modeled associations with CCI (count) using a zero-inflated Poisson model after accounting for the complex sampling design. Within CCI outcome models, we tested for the multiplicative interaction effect between sleep-circadian measures with age group, gender, and nativity; nativity was split into four groups based on place of birth/duration of US residence (non-US-born<10yrs., 10-20yrs., +20yrs. and US-born). After adjustment, actigraphy-assessed short (short-sleep, IRR:1.48 (95%CI:0.99-2.20)) and long sleep duration (long-sleep, IRR:1.52 (95%CI:0.95-2.43)), and sleep regularity index (T3vs.T1, IRR: 1.43 (95%CI:1.14-1.79)), in addition to self-reported insomnia symptoms (WHI insomnia score ≥9 vs. <9, IRR:1.23 (95%CI:1.13-1.34)) and excessive daytime sleepiness (ESS score ≥11 vs. <11, IRR:1.10 (0.99-1.21), were individually associated with higher overall multimorbidity 5-6 years later. Tests for interaction showed differences by nativity (two-sided, $P < 0.05$). Lower sleep satisfaction, daytime alertness, extreme sleep durations, and fragmented RARs are associated with greater chronic disease burden.

2.2   Introduction

Approximately one in three people are estimated as living with multimorbidity globally [38, 39]. The estimated prevalence of multimorbidity among the Hispanic/Latino population is 10.7%, and this group has been shown to accumulate morbidities more rapidly with aging compared to non-Hispanic white Americans, even though middle-aged Hispanic/Latino adults show a lower comorbidity burden than non-Hispanic, white adults [40, 41]. Hispanic/Latino persons in the U.S. also have a longer lifespan on average compared to white persons although a larger proportion of this lifespan is accompanied with an increased burden of disease among some Hispanic/Latino heritage groups [42].

Individuals from racial and ethnic minoritized groups more often report sleep disturbances, which may be contributing to a higher risk of cardiometabolic disease compared to other racial groups [43-46]. In 2020, the National Institutes of Health pointed to an existing gap in understanding disparities in chronic disease outcomes and subsequently called for further investigation of health and disease consequences associated with poor sleep patterns [14].

Several different sets of sleep and circadian rhythm measures are available, and so a theoretical sleep model may aid in selection of sleep measures for distinguishing healthy vs. harmful sleep patterns in the general population [24]. The RU-SATED model is a conceptual sleep health model that is a "multi-dimensional pattern of sleep-wakefulness, adapted to individual, social and environmental demands, that promotes physical and mental well-being" [24].

Existing literature predominantly investigates the relationship between sleep and morbidity with a cross-sectional design, and these cross-sectional studies have reported harmful associations between self-reported sleep disturbances or insomnia and multimorbidity [47, 48]. There are only a handful of studies that have examined the same relationship prospectively, and

these previous prospective cohort studies did not objectively measure sleep in their main sample and lacked racial or ethnic diversity [49, 50]. To begin to address these research gaps, the primary objective of this study is to evaluate associations between objectively-measured sleep and circadian rhythms (based on the RU-SATED sleep health model [24]) and the total count of chronic conditions included in the Charlson Comorbidity Index (CCI) [8, 11]. A secondary objective is to evaluate whether sleep-CCI associations differ based on place of birth and time spent residing in the U.S. We hypothesize that non-US-born Hispanic/Latino persons residing in the U.S. for more than a decade may have stronger sleep-CCI associations that more closely resemble those seen among U.S.-born Hispanic/Latino individuals when compared to non-US-born Hispanic/Latino individuals who have resided in the U.S. for less than a decade.

2.3   Methods

Hispanic Community Health Study/Study of Latinos (HCHS/SOL)

The Hispanic Community Health Study/Study of Latinos is a prospective, multi-center, community-based cohort study comprising a diverse population of Hispanic/Latino adults [51, 52]. Two-stage area probability sampling was performed to allow for unbiased inferences to Hispanic/Latinos from four urban regions, including Bronx, NY; Chicago, IL; Miami, FL; and San Diego, CA [51, 52]. Analyses accounted for sampling weights (specifically replicate weights at visit 2) and the complex sampling design. More detailed information on the study design and recruitment are described elsewhere [51, 52].

The HCHS/SOL cohort comprises adult men and women (n=16,415) who self-identify as Hispanic/Latino and were aged 18-74 years at baseline (2008-2011). HCHS/SOL participants completed questionnaires through annual follow-up over a five-year period with yearly response rates between 88.6% and 95.5% [53]. The analytic sample for the current study was restricted to

those individuals who had attended a second clinic visit in 2014-2018 (Visit 2) and had available data on the CCI outcome (n=11,623). The sample was further restricted based on complete information for confounding covariates of the associations under study (n=10,728). Slightly different analytic samples were generated based on availability of each sleep measure, resulting in samples ranging from 10,277-10,595.

Sueño HCHS/SOL Ancillary Study

From December 2010 to December 2013, the Sueño ancillary study recruited 2,252 HCHS/SOL participants who were within 30 months of their baseline visit [54]. Participants were included in the Sueño study based on any of the following inclusion criteria: 18-64 years old, did not have physician-diagnosed narcolepsy, had an apnea-hypopnea index < 50 events/hour, and were not using nocturnal positive airway pressure therapy. Additional study details are described elsewhere [55, 56]. Within the Sueño subset, we performed the same set of restrictions as for the full HCHS/SOL cohort, based on those having attended visit 2 and provided complete information on the outcome (n=2,000), then on available confounding covariates (n=1,873), and finally by the availability of each sleep measure, resulting in samples ranging from 1,467 to 1,825.

RU-SATED Sleep Health Model

Sleep and circadian health measures were selected to have coverage over each sleep health indicator from the RU-SATED model, including sleep duration, efficiency, satisfaction/quality, regularity, timing, and alertness [24]. Actigraphy-derived sleep measures were available to characterize sleep duration, efficiency, regularity, and timing in the Sueño ancillary study (n=1,876), and self-reported sleep health measures were available from the main HCHS/SOL cohort (n=10,587). Sleep questionnaires were administered at HCHS/SOL baseline

to obtain sleep health indicators; the Women's Health Initiative measure of insomnia symptoms [19, 20] was selected as a measure of satisfaction/quality and was binarized as <9 and ≥9; Epworth Sleepiness Score (ESS) [57] for daytime alertness/sleepiness and was binarized as <11 and ≥11. Participants also self-reported their habitual bedtime and waketime on weekdays and weekends, which was used to obtain the following measures: sleep duration (<5hrs./5-9hrs./>9hrs.); weekday midsleep timepoint (2:45pm-3:45am/3:45am-4:30am/4:30am-10:30am), weekday bedtime (10:00am-10:00pm/10:00pm-11:00pm/11:00pm-5:00am), and weekend waketime as average measures of sleep timing (8:00pm-7:00am/7:00am-9:00am/9:00am-3:00pm). Prior work in the Sueño cohort observed that self-reported sleep duration was moderately correlated with actigraphy-derived sleep duration, although associations between self-reported and actigraphy-derived sleep duration were influenced by gender, age, sleep efficiency, and night-to-night variability [58].

<u>Actigraphy-Derived Sleep and Circadian Health in Sueño</u>

Sueño participants were asked to continuously wear the Actiwatch Spectrum (Philips Respironics, Murrysville, PA) device on their non-dominant wrist for 7 days [55]. The sleep processing protocol is described in the Supplementary Methods, as well as in other published work [55]. Actigraphy-derived measures of sleep included the interdaily stability and sleep regularity index to represent sleep regularity [59, 60]; sleep efficiency and WASO for efficiency; and objectively measured sleep duration. Interdaily stability is a non-parametric measure of day-to-daily stability of RARs; this measure is estimated as the between-hour variance to total (between-hour plus within-hour) variance [59]. Sleep regularity index is the probability of an individual being in the same wake-sleep status (e.g., awake vs. asleep) at any two timepoints 24 hours apart averaged over the observation window [61]. Lower values of interdaily stability and

sleep regularity index represent lower day-to-day similarity or robustness [59, 60]. Both of these sleep regularity measures were operationalized as tertiles.

Sleep efficiency was defined as the proportion of time from sleep onset to sleep offset that was scored as sleep and was categorized as ≥85%, 80-85%, and <80%. Sleep duration was the total amount of time from sleep onset to offset and was categorized into short (<5 hours), normal (5-8.75 hours), and long sleepers (>8.75 hours). The definition of long sleep was slightly shortened from the definition used in HCHS/SOL to increase the size of this subgroup. WASO is the total minutes of wakefulness after defined sleep onset and categorized into ≤45 min, 45 (exclusive) – 90 min, and >90 min. Self-reported insomnia symptoms using the WHI insomnia questionnaire and ESS measures were also ascertained at the Sueño study visit and used in analyses involving the Sueño cohort; these measures were operationalized using the same cut-off values as those measured at baseline in the full HCHS/SOL cohort.

Charlson Comorbidity Index

The CCI is a weighted sum of self-reported comorbidities present at visit 2, with weighting based on the severity of the condition [8]. This study utilized a modified CCI based on available, self-report questionnaire data at visit 2, and a majority of the weightings for each disease is 1 unless stated otherwise in round brackets (#): specifically, the modified CCI includes myocardial infarction, congestive heart failure, peripheral artery disease, cerebrovascular disease, dementia or mild cognitive impairment, chronic obstructive pulmonary disease, connective tissue disease, ulcer disease or gastroesophageal reflux disease, mild liver disease, diabetes, moderate or severe renal disease (2), diabetes with end organ damage (2), any tumor, leukemia/lymphoma (2), and/or moderate or severe liver disease (3). When evaluating the

relationship between sleep and CCI, the CCI index was operationalized as a weighted count of the comorbidities with weights ascribed for severity.

<u>Descriptive Statistics</u>

We first described the overall sample using the gtsummary R package (version 1.6.1) with and without replicate weights from visit 2, and then tested for overall differences in CCI (0/1/2/3+) between sociodemographic and behavioral factors using a chi-squared test with Rao & Scott's second-order correction, and the Wilcoxon rank-sum test for complex survey samples.

<u>Count Models for Modeling Associations between Sleep and Comorbidity at Visit 2</u>

We first estimated incidence rate ratios (IRRs) between sleep and circadian rhythm measures with the CCI at visit 2 using Poisson regression models in R. To obtain the offset to calculate IRRs, we calculated the difference in time between the initial visit with measured sleep (SOL: baseline, Sueño: Sueño visit) and the follow-up visit (visit 2). Next, this time difference that represented individual study follow-up (years) was log-transformed and then added as an offset term to these Poisson regression models. IRRs allow for calculation of an increase in the weighted CCI index over a year of follow-up. These initial Poisson regression models were slightly over-dispersed (dispersion~1.2-1.3), so we shifted to using the zero-inflated Poisson (ZIP) model.

These ZIP regression models provided the IRR for no comorbidities vs. any comorbidity (in a zero-inflation model) and for between subject differences in the weighted count of comorbidities over a year of follow-up for participants who had at least one morbidity (in a count model). Analyses of the ZIP models were run in STATA (version 17), which allowed us to account for the complex survey design. The results from the ZIP regression models are reported as the main result since this method is more appropriate than Poisson regression models for zero-

inflated data. We also tested for the following statistical interactions: age-group (<45 y.o/45-64 y.o/65 y.o) x sleep, gender (male/female) x sleep, and place of birth/duration of US residence (born outside of the US <10 years US residence, born outside of the US 50 states/DC 10-20 years US residence, born outside of the US 50 states/$\geq$ 20 years in country, US-born) x sleep.

Progressive model adjustment was performed, with the base model adjusting for field center (Bronx/Chicago/Miami/San Diego), age (continuous), and gender (men/women). Then, we additionally adjusted for education (<high school, high school graduate, or >high school), household income (less than or equal to $30,000/ $30,000-50,000/more than $50,000), place of birth/duration of US residence, heritage (Mexican, Puerto Rican, Cuban, Dominican, Central American, South American, or Mixed/Other), smoking status (never/former/current), and alcohol use (never/former/current). Finally, we additionally adjusted for self-reported duration of moderate-to-vigorous physical activity (minutes/week) and body mass index (continuous in kg/m2).

2.4   Results

SOL and Sueño Population Characteristics

Accounting for the complex design and sample weights, we describe characteristics for the target population in HCHS/SOL and Sueño. The inter-quartile range of the population from SOL was 29-52 years of age and was composed of predominantly Mexican (38%), Cuban (19%), and Puerto Rican men and women (16%; Table 2.1). Most of the population had at least a high school education, with nearly 30% with a college degree; most were from households that reported earnings less than $30k/year on average. More than half of the population was born outside of the US 50 states/DC, had spent more than 10 years residing in the US after immigrating, and reported never smoking and current alcohol use. Overall, the population

reported engaging in six hours of moderate to vigorous physical activity weekly at baseline

(Table 2.1). The Sueño population differed slightly with respect to their demographic

characteristics due to differences in the enrollment criteria (e.g., younger age, different race, and

ethnicity goal proportions; Table 2.1).

Modified Charlson Multimorbidity Prevalence

The prevalence of multimorbidity using the modified CCI (e.g., 2 or more comorbidities)

was 16.7% and 13.8% within the HCHS/SOL and Sueño populations, respectively; older age

groups were more likely to report multimorbidity compared to younger age groups (Table 2.2-

2.3). In HCHS/SOL, Puerto Rican and Cuban persons had the highest number of comorbidities

compared to other heritage groups. Having two or more comorbidities at visit 2 was most

common in US-Born and Hispanic/Latino persons born outside of the US 50 states/DC and who

resided in the US for 20 years or more compared to other place of birth groups. On average, the

distribution of the CCI was similar between target populations from HCHS/SOL and Sueño (e.g.,

HCHS/SOL vs. Sueño; Table 2.2-2.3).

Sueño: Actigraphy-Derived Sleep and Multimorbidity Associations Ch

Objectively measured sleep regularity metrics (e.g., sleep regularity index and interdaily

stability) were associated with total comorbidities at visit 2. In Sueño, sleep regularity index and

lower interdaily stability tertiles were inversely associated with total comorbidities at visit 2 after

full adjustment (*P's*=0.01; Table 2.4). In the Sueño population, those in the lowest (e.g.,

unhealthiest) tertile for the sleep regularity index and interdaily stability were younger, more

often male, Puerto Rican, current drinkers, and engaged in more moderate-to-vigorous physical

activity (Table 2.5). Current smokers and U.S. born individuals were more often in the

unhealthiest tertile for the sleep regularity index or interdaily stability compared to other tertiles (Table 2.5-2.6).

Sleeping for less than 5 hours and more than 8.75 hours was positively associated with more total comorbidities at visit 2 compared to those with sleep durations between 5 and 8.75 hours (short-IRR: 1.48 (95% CI: 0.99-2.20); long-IRR: 1.52 (95% CI: 0.95-2.43); P=0.03). Other objective sleep metrics in Sueño, including sleep efficiency and WASO, were not associated with total comorbidities at follow-up (Table 2.4). In Sueño, those with insomnia symptom scores of 9 and higher had an expected count of comorbidities that was 35% higher (IRR: 1.35 (95% CI: 1.11-1.64)). Excessive daytime sleepiness was not associated with total comorbidities at visit 2.

We detected a statistical interaction between place of birth and separate objectively measured sleep measures WASO, insomnia, and excessive daytime sleepiness from Sueño (P's < 0.10; Table 2.7). The non-US-born population that had spent more time residing in the U.S. had stronger insomnia-CCI that increased across categories of years residing in the U.S (Non-US-born, 10-20 yrs. in U.S., IRR: 1.43 (95% CI: 1.06 - 1.93); Non-US-born, 20+ yrs. in U.S., IRR: 1.96 (95% CI: 1.50 - 2.57); insomnia * nativity, P = 0.07). In other words, non-US-born individuals with a greater duration of residing in the U.S. had stronger associations between insomnia and excessive daytime sleepiness with comorbidity burden (Table 2.7). A similar pattern for duration of U.S. residency was observed among non-US-born persons for excessive sleepiness (non-US-born, <10 yrs. In U.S., IRR: 1.11 (95% CI: 0.71 - 1.72); non-US-born, 20+ yrs. In U.S., IRR: 1.30 (95% CI: 0.91 - 1.86)); US-born, IRR: 1.51 (95% CI: 0.96 - 2.35); ESS * nativity, P = 0.09).

Although we observed no overall association between WASO and comorbidity burden at visit 2, we detected a statistical interaction between WASO and place of birth (WASO * nativity,

P=0.001) with respect to comorbidity burden: non-US born Hispanic/Latino people who were residing in the US between 10-20 years with WASO greater than 90 minutes had 272% higher comorbidity burden at visit 2 (IRR: 2.72 (95% CI: 1.79-4.12) as compared to those with less than 45 minutes of WASO (Table 2.7). Among all US-born and non-US born groups with greater than 10 years of U.S. residency, greater WASO was positively associated with comorbidity burden at visit 2 (Table 2.7). Although we tested statistical interactions between additional sleep-circadian measures with place of birth, age, and gender in Sueño, many of these models failed to converge due to small sample sizes.

HCHS-SOL: Self-Reported Sleep and Multimorbidity Associations

Several self-reported sleep measures, including insomnia symptoms and sleep duration, in HCHS/SOL were associated with total comorbidity burden at visit 2 (Table 2.8). In HCHS/SOL, those with insomnia symptom scores of 9 and higher had 23% higher comorbidity at visit 2 compared to the reference (IRR: 1.23 (95%CI: 1.13-1.34); *P* < 0.0001). In HCHS/SOL, short and long sleep durations were associated with more total comorbidities at visit 2, and we observed a higher effect size for short sleepers as compared to normal or long sleepers (HCHS/SOL, short IRR: 1.36 (95%CI: 1.11-1.66; long IRR: 1.11(95%CI: 1.00-1.25); *P*=0.006). Baseline characteristics of the cohort differed when stratified by tertiles of insomnia in the HCHS/SOL population. Those in the highest tertile with more reported insomnia symptoms were older, more often female, had a household income less than $30,000 per year, non-US-born with 20+ years in U.S., and reported an hour and half less of moderate to vigorous physical activity per week on average compared to those in the lowest tertile of reported insomnia symptoms (Table 2.9). The excessive daytime sleepiness and sleep timing measures (including midsleep

timepoint, weekend waketime, and weekday bedtime) based on self-report were not associated with total comorbidities.

HCHS/SOL: Place of birth-, Gender-, and Age Group Stratified Sleep-CCI Associations

In HCHS/SOL, we identified a statistical interaction between excessive daytime sleepiness and place of birth/duration of US residence (ESS * nativity, P=0.01) in relation to total comorbidities (Table 2.10). Nativity-stratified IRRs are also reported for associations between excessive daytime sleepiness and total comorbidities: non-US-born < 10 years, IRR: 1.07 (95% CI: 0.88-1.31); non-US-born 10-20 years, IRR: 1.29 (95% CI: 1.08 - 1.53); Non-US-born, 20+ yrs., IRR: 1.13 (95%CI: 1.00 - 1.28), US-born, IRR: 1.61 (95% CI: 1.31-1.97)). These nativity-stratified IRRs demonstrate that stronger associations exist between excessive daytime sleepiness and comorbidity burden at V2 among US-born Hispanic/Latino persons, as compared to non-US-born Hispanic/Latino persons. The interaction between insomnia symptoms and place of birth was not statistically significant (insomnia * nativity, P=0.11; Table 2.10), although Hispanic/Latino persons born in the US 50 states/DC showed stronger positive associations between reported insomnia symptoms and multimorbidity when compared to those who were born elsewhere (US-born, insomnia ≥9 IRR: 1.39 (95%CI: 1.11-1.75)); non-US-born, insomnia ≥9 IRRs between 1.00 and 1.14; interaction P=0.11).

Young to middle-aged adults in the HCHS/SOL population showed stronger, positive associations in self-reported insomnia with the CCI as compared to older adults aged 65+ years old (Table 2.11; age group x insomnia P=0.009). Men with more severe insomnia symptoms in the HCHS/SOL population had stronger associations with total comorbidity at visit 2 as compared to women (Table 2.11; interaction P=0.03). We also detected a statistical interaction between excessive daytime sleepiness and age group showing similar patterns as the interaction

between age group and insomnia symptoms (Table 2.11; interaction P=0.01); there was no interaction between gender and excessive daytime sleepiness in the HCHS/SOL population.

2.5   Discussion

In a diverse population of U.S. Hispanic/Latino adults, objectively measured and self-reported sleep and circadian rhythm measures were associated with a greater comorbidity burden at 5+ years of follow-up. The RU-SATED dimensions of sleep duration, satisfaction/quality (e.g., insomnia symptoms), regularity (e.g., interdaily variability and sleep regularity index), and alertness (e.g., excessive daytime sleepiness) were associated with comorbidity burden at follow-up. Study samples from HCHS/SOL and the Sueño ancillary study subsample showed comparable results for self-report-based sleep satisfaction (e.g., insomnia symptoms) and alertness (e.g., excessive daytime sleepiness). Place of birth/duration of U.S. residency modified associations for the sleep satisfaction dimension in relation to comorbidity burden. We observed stronger associations between excessive daytime sleepiness, as well as insomnia symptoms, and multimorbidity for U.S. born adults relative to non-US-born Hispanic/Latinos; within non-US-born Hispanic/Latinos, sleep-CCI associations increased by residency group category, which reflected increasing duration of U.S. residency. These results suggest that poor sleep and circadian health among non-US born Hispanic/Latino may progressively worsen comorbidity burden with greater time spent residing in U.S., even after accounting demographic and behavioral confounders. Over time, non-US-born Hispanic/Latino adults may begin to resemble US-born Hispanic/Latino adults with respect to their chronic disease outcomes partially due to the influence of poor sleep behaviors.

This current work builds off several previous studies in the HCHS/SOL and Sueño that have observed associations between sleep and circadian patterns with individual chronic

conditions that comprise the CCI. These studies have identified associations between sleep (including sleep apnea) and/or circadian rhythm with cardiovascular disease [62], diabetes and metabolic syndrome [63-65], COPD [66], rheumatoid arthritis [67], and cognitive performance [68]. One study in HCHS/SOL among those aged 45+ and with symptomatic, obstructive sleep apnea (OSA) showed approximately three times the odds of incident heart failure and stroke compared to those without OSA [69]. Moderate-to-severe sleep apnea was associated with increased risk of peripheral artery disease, with stronger associations in Hispanic/Latino persons of Mexican and Puerto Rican heritage [70].

Our study findings are consistent with prior work in other cohorts, such as SNAC-K, that examined sleep and CCI associations [49]. The SNAC-K cohort found that moderate-to-severe sleep disturbances were associated with more rapid disease accumulation after 9 years of follow-up [49]. In their study, the severity of the individuals' sleep disturbances reflected shorter sleep, greater fragmentation, and greater WASO. Both the SNAC-K and Whitehall II prospective cohort studies found that CCI was associated with shortened sleep duration (<5 hours) based on self-report [49, 50]. Another cross-sectional study among largely late middle-aged adults identified a U-shaped relationship for sleep duration and CCI: shorter (<7 hours) and sleep duration (>9 hours) was associated with greater multimorbidity [71]. In both HCHS/SOL and Sueño, we also observed that individuals with shorter and longer sleep had an elevated risk of comorbidities at follow-up.

There were several limitations of this study. First, the CCI outcome was ascertained prospectively using questionnaires, whereas other studies have ascertained this outcome using electronic medical records. The CCI outcome under study is also a modified version of the CCI, since the disease history questionnaires did not capture every disease that defined the full CCI

index. Disease history questionnaires did however capture the most prevalent diseases that comprise the CCI, including diabetes, myocardial infarction, and congestive heart failure. The impact of using this modified CCI index is that we may still be slightly underestimating the disease burden in some Hispanic/Latino adults in the target population. In addition, some of the comorbidities that comprised the modified CCI outcome measure were only measured at the follow-up visit and not baseline. Since the CCI measure would not have included the same diseases between baseline and visit 2, this study did not account for baseline comorbidity and did not address comorbidity accumulation from baseline.

Strengths of this study include objective measurement of sleep and circadian sleep measures, longitudinal follow-up, and the diversity of this group of Hispanic/Latino adults. This study also investigates long-term health consequences of poor sleep quality and patterns and considers the influence of sociocultural factors, such as place of birth and duration of U.S. residency, to further promote healthy aging. In doing so, this study addresses a research gap in understanding sleep health disparities. Given the large selection of objective sleep measures that can be derived from actigraphy data, another strength is that this study puts forth the RU-SATED sleep health model to guide selection of report-based and objective sleep measures or comprehensively evaluating associations between sleep and disease. Using the RU-SATED model, this study comprehensively evaluated several different sleep dimensions, including sleep quality, quantity, sleep regularity, and timing.

Our study expands on previous work in HCHS/SOL and Sueño by investigating a composite measure of disease burden in association with sleep, whereas prior studies in this cohort focused on individual associations between sleep and these chronic diseases. While we observed several robust associations between sleep and circadian rhythm with multimorbidity,

replication of these findings in other populations is important. Future work may also consider

investigating prospective associations between sleep-circadian patterns and multimorbidity

accumulation after longer follow-up and using repeated, objective measures of sleep.

Table 2.1. Baseline Demographic Characteristics of the HCHS/SOL study population, 2008-2011

This table was generated with unweighted and weighted estimates (weighted n, 95% CI and was based on the analytic sample.

	HCHS/SOL Participants with Sleep Information, Weighted (n=10,640)	Sueno Participants, Weighted (n=1,808)
Demographic Characteristics		
Age (mean +/- SE)	41 (29, 52)	42 (30, 51)
Female (%)	5,479 (51%)	917 (51%)
Hispanic/Latino Background		
Dominican	939 (8.8%)	229 (13%)
Central American	764 (7.2%)	106 (5.9%)
Cuban	2,038 (19%)	340 (19%)
Mexican	4,077 (38%)	674 (37%)
Puerto Rican	1,704 (16%)	373 (21%)
South American	532 (5.0%)	77 (4.2%)
Mixed/Other	585 (5.5%)	10 (0.5%)
Unknown	939 (8.8%)	
Education		
Less than High School	898 (8.4%)	95 (5.2%)
Middle School	970 (9.1%)	165 (9.1%)
High School Graduate	4,341 (41%)	770 (43%)
Vocational	1,428 (13%)	255 (14%)
College	3,002 (28%)	523 (29%)
Income		
< $30,000	7,111 (67%)	1,227 (68%)
$30,000-$50,000	2,237 (21%)	375 (21%)
> $50,000	1,292 (12%)	206 (11%)
Nativity/years in the US		
Non-US born, < 10 years in the US	2,859 (27%)	501 (28%)
Non-US born, 10-20 years in the US	2,460 (23%)	388 (21%)
Non-US born, >20 years in the US	2,912 (27%)	452 (25%)
US born	2,409 (23%)	467 (26%)
Clinical Characteristics		
BMI		
Underweight to Normal (<18.5-24.9)	2,399 (23%)	422 (23%)
Overweight (25.0-29.9)	3,952 (37%)	707 (39%)
Obese (30+)	4,290 (40%)	679 (38%)
Behavioral Characteristics		
Smoking Status		
Never	6,691 (63%)	1,111 (61%)
Former	1,843 (17%)	305 (17%)
Current	2,106 (20%)	392 (22%)
Alcohol Intake		
Never	1,931 (18%)	332 (18%)
Former	3,199 (30%)	557 (31%)
Current	5,510 (52%)	918 (51%)
Total Weekly Moderate-Vigorous Physical Activity, minutes	420 (75, 1,770)	450 (60, 1,680)

Table 2.2. Weighted Descriptive Statistics for Charlson Co-Morbidity Index at Visit 2: HCHS/SOL

This table reflected the analytic sample after accounting for the complex survey weighting.

	n	Total Charlson Comorbidities at Visit 2
	n	0	1	2	3+
Overall	10,728	6,137 (57%)	2,797 (26%)	987 (9.2%)	807 (7.5%)
Gender					
Men	4,230	2,361 (59%)	1,028 (26%)	346 (8.6%)	288 (7.2%)
Women	6,705	3,776 (56%)	1,769 (26%)	641 (9.6%)	519 (7.7%)
Age Sub-Groups					
Ages 18-44	3,829	2,911 (76%)	705 (18%)	159 (4.2%)	54 (1.4%)
Ages 45-64	6,590	2,994 (49%)	1,844 (30%)	665 (11%)	556 (9.2%)
Ages 65+	840	232 (28%)	248 (30%)	163 (19%)	197 (23%)
Heritage Group					
Dominican	866	520 (60%)	224 (26%)	65 (7.5%)	57 (6.6%)
Central America	1,660	684 (64%)	237 (22%)	89 (8.3%)	56 (5.3%)
Cuban	1,468	786 (54%)	378 (26%)	164 (11%)	140 (9.5%)
Mexican	4,504	2,700 (60%)	1,209 (27%)	345 (7.7%)	250 (5.6%)
Puerto Rican	1,682	708 (42%)	478 (28%)	253 (15%)	243 (14%)
South American	758	516 (68%)	164 (22%)	47 (6.2%)	31 (4.1%)
Mixed/Other	384	223 (58%)	107 (28%)	24 (6.2%)	30 (7.8%)
Nativity Status					
Non-US born, < 10 years in the US	2,327	1,538 (66%)	497 (21%)	176 (7.6%)	116 (5.0%)
Non-US born, 10-20 years in the US	2,453	1,521 (62%)	622 (25%)	188 (7.7%)	122 (5.0%)
Non-US born, >20 years in the US	4,261	2,027 (48%)	1,298 (30%)	475 (11%)	461 (11%)
US born	1,687	1,051 (62%)	380 (23%)	148 (8.8%)	108 (6.4%)

Table 2.3. Weighted Descriptive Statistics for Charlson Co-Morbidity Index at Visit 2: Sueno

This table reflected the analytic sample after accounting for the complex survey weighting.

	n	Total Charlson Comorbidities at Visit 2			
		0	1	2	3+
Overall	1,825	1,102 (60%)	471 (26%)	160 (8.8%)	92 (5.0%)
Gender		0	1	2	3
Men	626	385 (62%)	159 (25%)	55 (8.8%)	27 (4.3%)
Women	1,199	717 (60%)	312 (26%)	105 (8.8%)	65 (5.4%)
Age Sub-Groups		0	1	2	3
Ages 18-44	570	437 (77%)	106 (19%)	22 (3.9%)	5 (0.9%)
Ages 45-64	1,255	665 (53%)	365 (29%)	138 (11%)	87 (6.9%)
Heritage Group		0	1	2	3
Dominican	222	141 (64%)	54 (24%)	19 (8.6%)	8 (3.6%)
Central American	243	165 (68%)	51 (21%)	19 (7.8%)	8 (3.3%)
Cuban	317	191 (60%)	82 (26%)	27 (8.5%)	17 (5.4%)
Mexican	502	319 (64%)	140 (28%)	29 (5.8%)	14 (2.8%)
Puerto Rican	364	171 (47%)	105 (29%)	48 (13%)	40 (11%)
South American	164	111 (68%)	34 (21%)	16 (9.8%)	3 (1.8%)
Mixed/Other	13	4 (31%)	5 (38%)	2 (15%)	2 (15%)
Nativity Status		0	1	2	3
Non-US born, < 10 years in the US	441	300 (68%)	96 (22%)	31 (7.0%)	14 (3.2%)
Non-US born, 10-20 years in the US	444	286 (64%)	113 (25%)	34 (7.7%)	11 (2.5%)
Non-US born, >20 years in the US	658	348 (53%)	193 (29%)	69 (10%)	48 (7.3%)
US born	282	168 (60%)	69 (24%)	26 (9.2%)	19 (6.7%)

Table 2.4. Incidence Ratio Ratios between Objective and Self-Reported Sleep Measures and the Charlson Co-Morbidity Index in Sueno from Survey-Weighted, Zero-Inflated Poisson Model

	n	Model 1[a]‡		Model 2[b]‡		Model 3[c]‡	
		IRR (95% CI)	P	IRR (95% CI)	P	IRR (95% CI)	P
Sleep Regularity Index (n=1,798)			0.0006		0.004		0.01
T3: 75-100	631	Ref		Ref		Ref	
T2: 61-74	600	1.24 (0.99 - 1.56)		1.22 (0.97 - 1.53)		1.19 (0.96 - 1.49)	
T1: 0-60	567	1.60 (1.26 - 2.02)		1.47 (1.17 - 1.85)		1.43 (1.14 - 1.79)	
Interdaily Stability (n=1,467)							
T3: >0.85	492	Ref	0.001	Ref	0.008	Ref	0.01
T2: 0.75 to 0.85	509	1.29 (1.00 - 1.65)		1.24 (0.97 - 1.57)		1.23 (0.97 - 1.55)	
T1: <0.75	466	1.54 (1.23 - 1.94)		1.43 (1.14 - 1.79)		1.40 (1.12 - 1.75)	
Total Sleep Duration†, mins (n=1,469)			0.01		0.07		0.03
Ref, 5 to 8.75 hours	1,377	Ref		Ref		Ref	
Short, <5 hours	46	1.63 (1.08 - 2.47)		1.42 (0.93 - 2.16)		1.48 (0.99 - 2.20)	
Long, >8.75 hours	46	1.74 (0.92 - 3.28)		1.52 (0.91 - 2.53)		1.52 (0.95 - 2.43)	
Sleep Efficiency, % (n=1,469)			0.55		0.62		0.71
≥85	973	Ref		Ref		Ref	

Table 2.4. Incidence Ratio Ratios between Objective and Self-Reported Sleep Measures and the Charlson Co-Morbidity Index in Sueno from Survey-Weighted, Zero-Inflated Poisson Model, Continued

	n	Model 1[a]‡ IRR (95% CI)	P	Model 2[b]‡ IRR (95% CI)	P	Model 3[c]‡ IRR (95% CI)	P
80 to 85	313	0.98 (0.77 - 1.24)		0.92 (0.72 - 1.18)		0.93 (0.73 - 1.19)	
<80	183	1.16 (0.86 - 1.57)		1.07 (0.80 - 1.44)		1.05 (0.78 - 1.42)	
Wake After Sleep Onset, mins (n=1,798)			0.12		0.16		0.17
≤45 min	688	Ref		Ref		Ref	
45 to ≤90 min	935	1.16 (0.94 - 1.43)		1.17 (0.97 - 1.42)		1.18 (0.97 - 1.44)	
>90 min	175	1.35 (0.98 - 1.85)		1.25 (0.91 - 1.72)		1.22 (0.89 - 1.68)	
Insomnia (n=1,825)			0.001		0.002		0.003
<9	153	Ref		Ref		Ref	
≥9	718	1.41 (1.14 - 1.73)		1.36 (1.12 - 1.65)		1.35 (1.11 - 1.64)	
Excessive Daytime Sleepiness (n=1,824)			0.06		0.08		0.09
<11	1,479	Ref		Ref		Ref	
≥11	345	1.26 (0.99 - 1.60)		1.24 (0.97 - 1.58)		1.23 (0.97 - 1.55)	

*The logit section of the zero-inflated model modeled the probability of having non-zero and zero CCIs the same (e.g., only including an intercept term), whereas the count model included all of the confounding covariates. [a]Adjustment for field center (Bronx, Chicago, Miami, and San Diego), age (continuous), and gender (male/female).[b] Additionally adjusts for education (<high school, high school graduate, or >high school), household income (less than or equal to $30,000/ $30,000-50,000/more than 50,000), nativity (non-US-born <10 years in country, non-US-born ≥ 10 years in country, US-born), heritage (Mexican, Puerto Rican, Cuban, Dominican, Central American, South American, or Mixed/Other), smoking status (never/former/current), alcohol use (never/former/current). [c]Additionally adjusts for duration of moderate-to-vigorous physical activity (minutes) and body mass index (continuous in kg/m2).

†Sleep duration categories were broadened for the long sleepers to also include individuals with 8 hours and 45 minutes of sleep per night, since the sample size dropped dramatically among individuals who slept 8 hours and 45 minutes compared to 9 hours.

‡The reference groups for the following model are indicated for each covariate: alcohol use (ref=current drinker), body mass index (ref=Normal to Underweight), center (ref=San Diego), cigarette use (ref=never), household income (ref=<30k), nativity status (ref=Non-US Born and 10<=YRSUS <20), education (ref=high school), gender (ref=woman), marital status (ref=married), ethnicity (ref=Mexican).

Table 2.5. Baseline demographic characteristics (weighted) of the Sueno analytic sample (n=1467) stratified by tertiles for Sleep Regularity Index, 2008-2011.

This table was based on the analytic sample; the p-value were an omnibus p-value. Chi-squared test with Rao & Scott's second-order correction; Wilcoxon rank-sum test for complex survey samples.

	Sleep Regularity Index, Mean or % (SE)			
	T1 (n=466)	T2 (n=509)	T3 (n=492)	p-value
N (%); Median (IQR)				
Demographic Characteristics				
Age	46 (36, 52)	48 (40, 54)	50 (43, 56)	<0.001
Female	258 (55%)	352 (69%)	361 (73%)	<0.001
Hispanic/Latino Background				0.005
Dominican	60 (13%)	64 (13%)	60 (12%)	
Central American	47 (10%)	72 (14%)	71 (14%)	
Cuban	84 (18%)	95 (19%)	93 (19%)	
Mexican	110 (24%)	138 (27%)	138 (28%)	
Puerto Rican	129 (28%)	86 (17%)	80 (16%)	
South American	34 (7.3%)	49 (9.6%)	45 (9.1%)	
Mixed/Other	2 (0.4%)	5 (1.0%)	5 (1.0%)	
Education				0.07
Less than High School	29 (6.2%)	48 (9.4%)	57 (12%)	
Middle School	52 (11%)	45 (8.8%)	54 (11%)	
High School Graduate	182 (39%)	180 (35%)	175 (36%)	
Vocational	65 (14%)	68 (13%)	75 (15%)	
College	138 (30%)	168 (33%)	131 (27%)	
Income				0.20
< $30,000	349 (75%)	371 (73%)	340 (69%)	
$30,000-$50,000	80 (17%)	103 (20%)	104 (21%)	
> $50,000	37 (7.9%)	35 (6.9%)	48 (9.8%)	
Nativity/years in the US				<0.001
Non-US born, < 10 years in the US	109 (23%)	138 (27%)	114 (23%)	
Non-US born, 10-20 years in the US	90 (19%)	133 (26%)	134 (27%)	
Non-US born, >20 years in the US	162 (35%)	170 (33%)	202 (41%)	
US born	105 (23%)	68 (13%)	42 (8.5%)	
Clinical Characteristics				
BMI				0.20
Underweight to Normal (<18.5-24.9)	91 (20%)	92 (18%)	79 (16%)	
Overweight (25.0-29.9)	178 (38%)	188 (37%)	217 (44%)	
Obese (30+)	197 (42%)	229 (45%)	196 (40%)	
Behavioral Characteristics				
Smoking Status				<0.001
Never	262 (56%)	313 (61%)	334 (68%)	
Former	76 (16%)	111 (22%)	97 (20%)	
Current	128 (27%)	85 (17%)	61 (12%)	
Alcohol Intake				0.001
Never	85 (18%)	108 (21%)	143 (29%)	
Former	154 (33%)	166 (33%)	152 (31%)	
Current	227 (49%)	235 (46%)	197 (40%)	
Total Weekly Moderate-Vigorous Physical Activity, minutes	420 (60, 1,740)	300 (20, 1,252)	210 (0, 780)	<0.001

Table 2.6. Baseline demographic characteristics (weighted) of the Sueno analytic sample (n=1467) stratified by tertiles of Interdaily Stability, 2008-2011.

This table was based on the analytic sample; the p-value were an omnibus p-value. Chi-squared test with Rao & Scott's second-order correction; Wilcoxon rank-sum test for complex survey samples.

	Interdaily Stability Tertiles, Mean or % (SE)			
	T1 (n=466)	T2 (n=509)	T3 (n=492)	p-value
N (%); Median (IQR)				
Demographic Characteristics				
Age	46 (36, 52)	48 (40, 54)	50 (43, 56)	<0.001
Female	258 (55%)	352 (69%)	361 (73%)	<0.001
Hispanic/Latino Background				0.005
Dominican	60 (13%)	64 (13%)	60 (12%)	
Central American	47 (10%)	72 (14%)	71 (14%)	
Cuban	84 (18%)	95 (19%)	93 (19%)	
Mexican	110 (24%)	138 (27%)	138 (28%)	
Puerto Rican	129 (28%)	86 (17%)	80 (16%)	
South American	34 (7.3%)	49 (9.6%)	45 (9.1%)	
Mixed/Other	2 (0.4%)	5 (1.0%)	5 (1.0%)	
Education				0.07
Less than High School	29 (6.2%)	48 (9.4%)	57 (12%)	
Middle School	52 (11%)	45 (8.8%)	54 (11%)	
High School Graduate	182 (39%)	180 (35%)	175 (36%)	
Vocational	65 (14%)	68 (13%)	75 (15%)	
College	138 (30%)	168 (33%)	131 (27%)	
Income				0.20
< $30,000	349 (75%)	371 (73%)	340 (69%)	
$30,000-$50,000	80 (17%)	103 (20%)	104 (21%)	
> $50,000	37 (7.9%)	35 (6.9%)	48 (9.8%)	
Nativity/years in the US				<0.001
Non-US born, < 10 years in the US	109 (23%)	138 (27%)	114 (23%)	
Non-US born, 10-20 years in the US	90 (19%)	133 (26%)	134 (27%)	
Non-US born, >20 years in the US	162 (35%)	170 (33%)	202 (41%)	
US born	105 (23%)	68 (13%)	42 (8.5%)	
Clinical Characteristics				
BMI				0.20
Underweight to Normal (<18.5-24.9)	91 (20%)	92 (18%)	79 (16%)	
Overweight (25.0-29.9)	178 (38%)	188 (37%)	217 (44%)	
Obese (30+)	197 (42%)	229 (45%)	196 (40%)	
Behavioral Characteristics				
Smoking Status				<0.001
Never	262 (56%)	313 (61%)	334 (68%)	
Former	76 (16%)	111 (22%)	97 (20%)	
Current	128 (27%)	85 (17%)	61 (12%)	
Alcohol Intake				0.001
Never	85 (18%)	108 (21%)	143 (29%)	
Former	154 (33%)	166 (33%)	152 (31%)	
Current	227 (49%)	235 (46%)	197 (40%)	
Total Weekly Moderate-Vigorous Physical Activity, minutes	420 (60, 1,740)	300 (20, 1,252)	210 (0, 780)	<0.001

Table 2.7. Nativity-Stratified Associations of Objective Sleep Measures and the Charlson Co-Morbidity Index in Sueno Ancillary Study

The results presented in the table above are for the fully adjusted model. Adjustment for field center (Bronx, Chicago, Miami, and San Diego), age (continuous), and gender (male/female), education (<high school, high school graduate, or >high school), household income (less than or equal to $30,000/ $30,000-50,000/more than 50,000), nativity (non-US-born <10 years in country, non-US-born ≥ 10 years in country, US-born), heritage (Mexican, Puerto Rican, Cuban, Dominican, Central American, South American, or Mixed/Other), smoking status (never/former/current), alcohol use (never/former/current), duration of moderate-to-vigorous physical activity (minutes) and body mass index (continuous in kg/m2). Note, models did not converge after adding physical activity and BMI to the model, so models are presented without adjustment for those variables.

	Nativity			
	Non-US-born, <10 yrs. In U.S.	Non-US-born, 10-20 yrs. in U.S.	Non-US-born, 20+ yrs. in U.S.	US-Born
	IRR (95% CI)	IRR (95% CI)	IRR (95% CI)	IRR (95% CI)
Wake After Sleep Onset, mins (n=1,798)				p=0.001
>0 to ≤45 min	Ref	Ref	Ref	Ref
>45 to ≤90 min	0.81 (0.57 - 1.15)	1.20 (0.80 - 1.78)	1.32 (0.98 - 1.77)	1.56 (0.93 - 2.62)
>90 min	0.31 (0.11 - 0.89)	2.72 (1.79 - 4.12)	1.33 (0.85 - 2.06)	0.94 (0.53 - 1.67)
Insomnia (n=1,825)				P=0.07
<9	Ref	Ref	Ref	Ref
≥9	1.23 (0.77 - 1.94)	1.43 (1.06 - 1.93)	1.96 (1.50 - 2.57)	0.92 (0.63 - 1.34)
Excessive Sleepiness (n=1,824)				P=0.09
<11	Ref	Ref	Ref	Ref
≥11	1.11 (0.71 - 1.72)	1.15 (0.70 - 1.89)	1.30 (0.91 - 1.86)	1.51 (0.96 - 2.35)

Table 2.8. Incidence Ratio Ratios between Self-Reported Sleep Measures and the Charlson Co-Morbidity Index in HCHS/SOL from Survey-Weighted, Zero-Inflated Poisson Models*

	n	Model 1[a]‡ IRR (95% CI)	P	Model 2[b]‡ IRR (95% CI)	P	Model 3[c]‡ IRR (95% CI)	P
Insomnia (n=10,469)			<0.0001		<0.0001		<0.0001
<9	6,658	Ref		Ref		Ref	
≥9	3,811	1.29 (1.19 - 1.41)		1.25 (1.15 - 1.36)		1.23 (1.13 - 1.34)	
Excessive Sleepiness (n=10,595)			0.006		0.01		0.07
<11	8,426	Ref		Ref		Ref	
≥11	2,169	1.15 (1.04 - 1.28)		1.14 (1.03 - 1.26)		1.10 (0.99 - 1.21)	
Sleep Duration, hrs (n=10,277)			0.0001		0.002		0.006
Short, <5 hours	276	1.47 (1.19 - 1.82)		1.41 (1.15 - 1.73)		1.36 (1.11 - 1.66)	
Ref, 5-9 hours	7,705	Ref		Ref		Ref	
Long, >9 hours	1,306	1.18 (1.05 - 1.33)		1.12 (1.00 - 1.26)		1.11 (1.00 - 1.25)	
Midsleep Timepoint (n= 10,438)			0.049		0.08		0.07
2:45pm-3:45am	4,069	1.04 (0.95 - 1.15)		1.06 (0.96 - 1.17)		1.05 (0.95 - 1.16)	
3:45am-4:30am	3,134	Ref		Ref		Ref	
4:30am-10:30am	3,235	1.13 (1.02 - 1.24)		1.11 (1.01 - 1.22)		1.12 (1.02 - 1.23)	
Weekday Bedtime (n=10,444)			0.14		0.23		0.33
10:00am-10:00pm	3,788	Ref		Ref		Ref	
10:00pm-11:00pm	3,416	1.01 (0.90 - 1.13)		1.01 (0.91 - 1.12)		1.02 (0.91 - 1.13)	
11:00pm-5:00am	3,240	1.09 (0.99 - 1.202)		1.08 (0.98 - 1.19)		1.07 (0.97 - 1.19)	
Weekend Awake Time (n=10,381)			0.08		0.22		0.57
8:00pm-7:00am	4,310	1.08 (0.99 - 1.18)		1.06 (0.98 - 1.16)		1.04 (0.95 - 1.13)	
7:00am-9:00am	4,002	Ref		Ref		Ref	
9:00am-3:00pm	2,069	1.12 (1.01 - 1.25)		1.09 (0.98 - 1.21)		1.05 (0.94 - 1.17)	

*The logit section of the zero-inflated model modeled the probability of having non-zero and zero CCIs the same (e.g., only including an intercept term), whereas the count model included all of the confounding covariates.
[a] An Adjustment for field center (Bronx, Chicago, Miami, and San Diego), age (continuous), and gender (male/female).
[b] Additionally adjusts for education (<high school, high school graduate, or >high school), household income (less than or equal to $30,000/ $30,000-50,000/more than 50,000), nativity (non-US-born <10 years in country, non-US-born ≥ 10 years in country, US-born), heritage (Mexican, Puerto Rican, Cuban, Dominican, Central American, South American, or Mixed/Other), smoking status (never/former/current), alcohol use (never/former/current).
[c] Additionally adjusts for duration of moderate-to-vigorous physical activity (minutes) and body mass index (continuous in kg/m2).
‡The reference groups for the following model are indicated for each covariate: alcohol use (ref=current drinker), body mass index (ref=Normal to Underweight), center (ref=San Diego), cigarette use (ref=never), household income (ref=<30k), nativity status (ref=Non-US Born and 10<=YRSUS <20), education (ref=high school), gender (ref=woman), marital status (ref=married), ethnicity (ref=Mexican).

Table 2.9. Baseline demographic characteristics (weighted) of the HCHS/SOL analytic sample (n=11,748) stratified by tertiles of Insomnia, 2008-2011.

This table was based on the analytic sample; the p-value were an omnibus p-value. Chi-squared test with Rao & Scott's second-order correction; Wilcoxon rank-sum test for complex survey samples.

	Insomnia Tertiles, Mean or % (SE)			
	T1 (n=4,460)	T2 (n=3,970)	T3 (n=3,318)	p-value
N (%); Median (IQR)				
Demographic Characteristics				
Age	47 (36, 55)	49 (39, 57)	51 (43, 58)	<0.001
Female	2,284 (56%)	1,924 (62%)	2,348 (71%)	<0.001
Hispanic/Latino Background				<0.001
Dominican	254 (6.3%)	247 (8.0%)	327 (9.9%)	
Central American	451 (11%)	290 (9.4%)	306 (9.2%)	
Cuban	566 (14%)	365 (12%)	484 (15%)	
Mexican	1,906 (47%)	1,426 (46%)	1,104 (33%)	
Puerto Rican	418 (10%)	442 (14%)	773 (23%)	
South American	332 (8.2%)	205 (6.6%)	195 (5.9%)	
Mixed/Other	119 (2.9%)	122 (3.9%)	129 (3.9%)	
Education				0.009
Less than High School	496 (12%)	402 (13%)	467 (14%)	
Middle School	445 (11%)	369 (12%)	396 (12%)	
High School Graduate	1,460 (36%)	1,131 (37%)	1,241 (37%)	
Vocational	576 (14%)	436 (14%)	477 (14%)	
College	1,069 (26%)	759 (25%)	737 (22%)	
Income				<0.001
< $30,000	2,599 (64%)	2,099 (68%)	2,449 (74%)	
$30,000-$50,000	963 (24%)	650 (21%)	592 (18%)	
> $50,000	484 (12%)	348 (11%)	277 (8.3%)	
Nativity/years in the US				<0.001
Non-US born, < 10 years in the US	996 (25%)	645 (21%)	611 (18%)	
Non-US born, 10-20 years in the US	998 (25%)	703 (23%)	698 (21%)	
Non-US born, >20 years in the US	1,480 (37%)	1,234 (40%)	1,450 (44%)	
US born	572 (14%)	515 (17%)	559 (17%)	
Clinical Characteristics				
BMI				<0.001
Underweight to Normal (<18.5-24.9)	823 (20%)	569 (18%)	563 (17%)	
Overweight (25.0-29.9)	1,575 (39%)	1,200 (39%)	1,207 (36%)	
Obese (30+)	1,648 (41%)	1,328 (43%)	1,548 (47%)	
Behavioral Characteristics				
Smoking Status				<0.001
Never	2,648 (65%)	1,913 (62%)	1,905 (57%)	
Former	766 (19%)	665 (21%)	712 (21%)	
Current	632 (16%)	519 (17%)	701 (21%)	
Alcohol Intake				0.012
Never	859 (21%)	608 (20%)	630 (19%)	
Former	1,276 (32%)	1,028 (33%)	1,173 (35%)	
Current	1,911 (47%)	1,461 (47%)	1,515 (46%)	
Total Weekly Moderate-Vigorous Physical Activity, minutes	360 (60, 1,440)	300 (40, 1,440)	285 (10, 1,195)	<0.001

Table 2.10. Nativity Stratified Associations of Self-Reported Sleep Measures and the Charlson Co-Morbidity Index in HCHS/SOL Cohort, Continued

Additional information is given as to the mean of wider quartiles for select sleep timing variables with wide quartiles, as follows. The results presented in the table below are for the fully adjusted model. Adjustment for field center (Bronx, Chicago, Miami, and San Diego), age (continuous), and gender (male/female), education (<high school, high school graduate, or >high school), household income (less than or equal to $30,000/ $30,000-50,000/more than 50,000), nativity (non-US-born <10 years in country, non-US-born ≥ 10 years in country, US-born), heritage (Mexican, Puerto Rican, Cuban, Dominican, Central American, South American, or Mixed/Other), smoking status (never/former/current), and alcohol use (never/former/current).

	Nativity			
	Non-US-born, <10 yrs. In U.S. IRR (95% CI)	Non-US-born, 10-20 yrs. In U.S. IRR (95% CI)	Non-US-born, 20+ yrs. In U.S. IRR (95% CI)	US-Born IRR (95% CI)
Insomnia (n=10,469)				P=0.11
<9	Ref	Ref	Ref	Ref
≥9	1.14 (0.88 - 1.49)	1.08 (0.89 - 1.31)	1.00 (0.89 - 1.12)	1.39 (1.11 - 1.75)
Excessive Sleepiness (n=10,595)				P=0.01
<11	Ref	Ref	Ref	Ref
≥11	1.07 (0.88 - 1.31)	1.29 (1.08 - 1.53)	1.13 (1.00 - 1.28)	1.61 (1.31 - 1.97)
Sleep Duration, hrs (n=10,277)				P=0.31
Short, <5 hours	1.35 (0.73 - 2.49)	1.00 (0.67 - 1.48)	1.61 (1.15 - 2.25)	1.36 (0.95 - 1.95)
Ref, 5-9 hours	Ref	Ref	Ref	Ref
Long, >9 hours	1.02 (0.77 - 1.35)	1.25 (0.97 - 1.61)	1.10 (0.96 - 1.26)	1.10 (0.87 - 1.40)
Midsleep Timepoint (n= 10,438)				P=0.63
2:45pm-3:45am	0.99 (0.79 - 1.24)	1.25 (1.01 - 1.54)	0.97 (0.85 - 1.11)	1.21 (0.93 - 1.57)
3:45am-4:30am	Ref	Ref	Ref	Ref
4:30am-10:30am	1.11 (0.89 - 1.37)	1.13 (0.92 - 1.40)	1.07 (0.93 - 1.22)	1.23 (0.95 - 1.58)
Weekday Bedtime (n=10,444)				P=0.13
10:00am-10:00pm	Ref	Ref	Ref	Ref
10:00pm-11:00pm	1.01 (0.80 - 1.28)	1.01 (0.87 - 1.18)	1.12 (0.99 - 1.26)	0.81 (0.62 - 1.04)
11:00pm-5:00am	1.06 (0.83 - 1.34)	1.09 (0.94 - 1.26)	1.14 (1.00 - 1.31)	1.05 (0.80 - 1.36)
Weekend Awake Time (n=10,381)				P=0.16
8:00pm-7:00am	1.02 (0.85 - 1.24)	1.24 (1.04 - 1.48)	0.99 (0.88 - 1.11)	1.03 (0.80 - 1.32)
7:00am-9:00am	Ref	Ref	Ref	Ref
9:00am-3:00pm	0.92 (0.69 - 1.23)	1.01 (0.76 - 1.34)	1.05 (0.89 - 1.23)	1.20 (0.94 - 1.53)

Table 2.11. Age, or Gender Stratified Associations of Self-Reported Sleep Measures and the Charlson Co-Morbidity Index: HCHS/SOL

The results presented in the table below were for the fully adjusted model. Adjustment for field center (Bronx, Chicago, Miami, and San Diego), age (continuous), and gender (male/female), education (<high school, high school graduate, or >high school), household income (less than or equal to $30,000/ $30,000-50,000/more than 50,000), nativity (non-US-born <10 years in country, non-US-born ≥ 10 years in country, US-born), heritage (Mexican, Puerto Rican, Cuban, Dominican, Central American, South American, or Mixed/Other), smoking status (never/former/current), and alcohol use (never/former/current).

	Gender		Age Group		
	Men	Women	<45 y.o.	46-60 y.o.	60+ y.o.
	IRR (95% CI)	IRR (95% CI)	IRR (95% CI)	IRR (95% CI)	IRR (95% CI)
Insomnia (n=10,469)		p=0.03			p=0.009
<9	Ref	Ref	Ref	Ref	Ref
≥9	1.36 (1.19- 1.55)	1.14 (1.02-1.26)	1.37 (1.15 - 1.62)	1.24 (1.13 - 1.36)	1.06 (0.88 - 1.27)
Excessive Daytime Sleepiness (n=10,595)		P=0.91			P=0.01
<11	Ref	Ref	Ref	Ref	Ref
≥11	1.09 (0.94 - 1.27)	1.09 (0.96 - 1.24)	1.22 (1.00 - 1.50)	1.15 (1.03 - 1.28)	0.84 (0.67 - 1.04)

Chapter 2, in part, has been submitted for publication of the material as it may appear in the American Journal of Epidemiology. Garduno, Alexis C.; Patel, Sanjay R.; Gallo, Linda; Natarajan, Loki; Parada, Humberto; McEvoy, Linda K.; Smarr, Benjamin; LaCroix, Andrea Z. The dissertation author was the primary researcher and author of this paper.

3.   Sleep Pattern Clusters, Physical Function and Fall Risk: Geriatric Syndromes Among Older Ambulatory Women

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3.1   <u>Abstract</u>

Poor sleep is a suspected risk factor for worse physical functioning and frequent falling at older ages. There is limited research that identifies key sleep patterns among older adults that may be targeted for improving physical functioning and fall risk. Existing studies also lack objectively measured sleep, RARs, and/or prospectively collected falls data in older adults. This study simultaneously evaluated the relationship between multiple sleep and RAR dimensions with fall risk and physical functioning among 4,543 older women from the OPACH study. Uniform manifold approximation projection and K-Means clustering identified 5 sleep-RAR clusters, in order to distinguish healthy and unhealthy sleep patterns. After cross-validating these sleep clusters, we examined associations with fall risk using negative binomial models after adjusting for sociodemographic and behavioral factors. Linear regression models estimated associations between sleep clusters with the Short Physical Performance Battery (SPPB) physical functioning score, and the sub-scores, including the balance test, chair stands, and gait speed. We tested for the presence of a statistical interaction between clusters and physical functioning (sleep*SPPB) with respect to fall risk. Five sleep clusters were identified including C1 ("sleep disturbed", n=1051), C2 ("healthy", n=1043), C3 ("mild RAR, active", n=1446), C4 ("earlier sleepers, n=105), and C5 ("shorter, mildly disrupted, later sleeper", n=898). Unhealthy sleep clusters C1 and C4 were associated with a higher fall risk compared to healthy cluster C2 after

adjustment (C4, IRR: 1.76 (95%CI:1.15-2.69)). These same clusters were also associated with lower balance scores (score: 0-4) after adjustment (C1, beta: -0.11 (95% CI:-0.21 to -0.01); C4, beta: -0.30 (95%CI: -0.55 to -0.05)). Older adults with unhealthier sleep-RAR patterns are more at risk for falling, which may be partially explained by the role of sleep on balance and physical functioning.

3.2 Introduction

As they age, adults develop more fragmented sleep, along with changes in sleep architecture, earlier waketime and bedtimes, increased napping, decreased sleep efficiency, and shifts in circadian phases, relative to younger adults [72]. The RU-SATED sleep model characterizes sleep as a complex behavior that can be represented by multiple domains, including regularity, satisfaction, alertness, timing, efficiency, and duration [24]. General sleep disturbances are regarded as a common geriatric syndrome that occurs in one out of two older adults aged 65 years or older [73, 74]. By definition, GSs often co-occur with other GSs, and are related to a decline in homeostatic reserve across one or multiple functional domains (e.g., cognitive or physical) [16]. GSs are prevalent among 70-80% of adults aged 70 years or older [18, 21] and are associated with lower overall quality of life [75], greater risk of disability [18], and mortality [20]. Circadian rhythms are endogenous rhythms following a 24-hour, recurring pattern that are further modified by behavioral factors, including blue light exposure, timing of physical activity, meal consumption, and extrinsic factors [31]. Additional work is needed to clarify whether disrupted circadian rhythms are associated with aging and co-occur with other GSs.

Frequent falling is a leading cause of fatal and non-fatal injury among adults 65 years of age, and this syndrome is also the third leading cause of death from unintentional injury [76, 77].

Prior studies have observed associations between sleep quality, duration, and fragmentation with fall risk, although most of these studies relied on self-reported sleep and/or retrospectively ascertained fall history [78-80]. Other sleep dimensions have been understudied with respect to falling, including the domains of sleep regularity and timing [24]. Sleep regularity and timing are indices that are measured objectively using actigraphy and can be used to infer disruption of an individual's circadian rhythms. Physical functioning is another key health risk factor/factor that is closely tied to frequent falling, and several studies have observed associations between sleep duration and quality with physical functioning [81, 82].

A major limitation of these prior studies is reliance on self-reported sleep, or by lack of adjustment for social and behavioral confounders. Other studies are also limited, as they have focused more on the role of acute sleep deprivation and postural balance, which is a key aspect of physical functioning, yet additional work is needed to understand the role of habitual sleep and rest-activity disturbances [83]. These studies of postural balance were often conducted in controlled research settings, which may be less representative of community-based sleep behaviors, and a majority of these studies examined the role of short-term sleep deprivation [83]. For example, a small case-crossover study in a controlled setting found that older adults were more vulnerable than younger adults to the effect of sleep deprivation on postural control, which was further modified by visual impairment [84]. Another recent study in older adults with Parkinson's Disease, which is a population with documented circadian disruption, observed an association between circadian disruption, specifically reduced amplitude, and postural stability and gait initiation [85].

Two prospective cohort studies were conducted among older men and found that shorter sleep, lower sleep efficiency, and delayed peak-activity or acrophase were associated with

greater physical function decline and fall risk [78, 86]. Additional studies are needed that investigate these associations in women with respect to falling, since falling and fall-related injuries disproportionately affect women as compared to men [87-89]. Existing studies have focused on examining each sleep feature independently; yet examination of individual sleep features does not account for the synergistic or antagonistic role of other sleep patterns that co-occur within the same individual, which is a methodological gap in existing sleep research studies. Clustering of sleep measures may help identify patterns of healthy versus unhealthy sleep that are common in older women aged 70-80 years old.

Our study aims to identify healthy and unhealthy sleep-circadian clusters (e.g., profiles), using objective and subjective sleep metrics that represent each domain of the RU-SATED sleep model; next, this study examines associations between these sleep profiles with fall risk and physical function. We hypothesized that "unhealthy" sleep profiles with more fragmented sleep, shorter sleep duration, and greater total awakenings (among other sleep metrics that are directionally consistent) would be associated with greater fall risk and lower physical function. Thematically, this study may also further lay credence to the concept that some GSs, such as sleep disturbances and possibly circadian disruption, do not just co-occur but may precipitate the development of GSs that result in greater risk of injury and mortality.

3.3 Methods

Objective Physical Activity and Cardiovascular Health (OPACH) Study Sample

The OPACH Study is a prospective, ancillary study of the Women's Health Initiative (WHI) aimed at characterizing physical activity and cardiovascular health in older women. We conducted a secondary analysis in this cohort to investigate the relationships between accelerometer-measured RARs with fall risk and physical functioning. Additional information on

the OPACH study objectives, protocol and recruitment are detailed elsewhere [90]. In brief, a total of 6,489 ambulatory women consented to the study from 2012-2013 and wore an accelerometer for up to 7 days. Next, we excluded women for whom we could not obtain RAR metrics using our script (n=345). We also excluded women with greater than 50% of the epochs that did not meet data processing standards (n=450). Research technicians scored a subset of sleep duration periods as a part of another secondary analysis [91]. Manual scoring was not performed if sleep log was absent, GT3X file was missing, or there was no accelerometry at night; additionally, these technicians did not perform scoring for women who did not have measured cardiometabolic data. Due to these restrictions for manual scoring, an additional 1,151 women were excluded (Figure 3.1). Women were also excluded from this analysis if they did not return at least one falls month calendar (n=424); finally, women were excluded if they experienced an extreme number of falls (>325, n=1), leaving a final analytic sample of 4,543 participants (Figure 3.1).

To address potential concerns for selection bias, we examined baseline descriptive statistics of the overall study population (n=6,489) stratified by whether an individual was excluded from the analytic sample (included: n=4,543; excluded: n=1,946). We evaluated whether any quantitative differences in the study characteristics were statistically different among individuals included the analytic sample compared to those excluded (omnibus p-value < 0.05). Additional sensitivity analyses are discussed below.

Sleep and Rest-Activity Rhythm (RAR) Measures

ActiGraph GT3X+ triaxial accelerometers were worn continuously by participants for up to 7 consecutive days on their right hip and were only removed when swimming or bathing. ActiGraph measured activity in 15-second epochs, which were aggregated to 1-minute epochs

for the purposes of extracting sleep features. Sleep and RAR measures were chosen to represent each sleep domain from the RU-SATED model, including sleep regularity, sleep continuity/efficiency, duration, timing, alertness/sleepiness, and satisfaction/quality (see Supplementary Methods) [24]. After further data processing (see Supplementary Methods), RAR measures were calculated using non-parametric models for sleep-activity data using previously described methods [92, 93]. These RAR measures included intra-daily variability (IV), inter-daily stability (IS), average hourly activity during 5 consecutive hours with the lowest activity (L5), the start and midpoint of the L5 period, the average hourly activity during the 10 consecutive hours of the day with the highest activity (M10), and the start and midpoint of the M10 period. Intra-daily variability is a non-parametric measure that estimates the fragmentation within a single day of the rest-activity rhythm; individuals who engage in daytime napping or wake up in the middle of the night have higher IV values [92]. Inter-daily stability is a non-parametric measure of sleep regularity that measures the day-to-daily stability of RARs; this measure is estimated as the between-hour variance to total (between-hour plus within-hour) variance of sleep/wake status [54]. Individuals with higher IS values have more stable and regular rest and activity cycles between days.

We also processed total sleep duration (units=hours), sleep efficiency (units=%), sleep latency (units=hours), WASO (units=mins), and frequency of awakenings (units=count) from ActiLife version 6.11 software. Activity was sampled at 30 Hz and aggregated into 60-second Agilegraph Date Files (ADF). Individual ADF files were scored using a standard protocol by a trained technician. To identify sleep periods, technicians used participant's sleep logs and a visual review of the data for each night the participant wore the device [91]. This process is aligned with the actigraphy method guidelines from the Society of Behavioral Sleep Medicine

[94, 95]. After identifying the sleep periods, the Cole-Kripke algorithm was applied to classify epochs within the sleep period as awake or asleep [96]. Finally, we included several measures from sleep questionnaires that occurred in the same year as the Long Life Study Visit. Daytime napping and falling asleep during light activities represented the daytime alertness domain, whereas sleep quality represented the quality/satisfaction domain (see Supplementary Methods).

Fall Ascertainment

Falls were measured after ascertainment of the participant's sleep and RARs, and this primary study outcome was operationalized as the total reported number of falls over the total person-months of observation (e.g., incident fall rate). The denominator of person-months was based on the total number of calendar pages returned by the participants. Incident falls were collected using a 13-month fall calendar that women completed on a daily basis if they had fallen. A fall was defined as "lost balance and fell to the ground or a lower level or if they had to use a wall, rail, or other object to prevent themselves from falling to the ground [97]." Additional information about the collection of calendars and reliability compared to other forms of self-report are described elsewhere [98].

Physical Functioning

Physical functioning was a primary study outcome that we measured using the Short Physical Performance Battery (SPPB) for lower extremity function at the Long-Life Study home visit [99, 100]. We also hypothesized that physical functioning may be acting as a potential effect modifier and mediator between sleep and fall risk as observed in prior work between steps/day and fall risk [101]. Individuals with shorter and more disrupted sleep may have lower physical functioning, which may partially mediate associations between sleep and fall risk. At the same time, individuals with lower physical functioning may have stronger, positive

associations between sleep and fall risk. The overall SPPB score was included, as well as the scores from the three separate tests of physical functioning, including the time to complete 5 unassisted chair stands, 3 progressively difficult balance tests, and gait speed assessment over 4 meters. Each test is scored from 0 (lowest) to 4 (highest) with higher scores indicating improved physical functioning.

Machine-Learning Derived Clusters using UMAP and Unsupervised Learning

All sleep and circadian-rhythm measures were standardized prior to data reduction and clustering. A modern data reduction approach called Uniform Manifold Approximation and Projection (UMAP) was applied to preserve both local and global structure of the sleep profiles, allowing for identification of informative, reproducible clusters [102]. UMAP dimension reduction is a non-linear data reduction technique based on Riemannian geometry that identifies a lower dimensional embedding of a manifold's underlying topology [103]. After we performed UMAP data reduction, we identified distinct sleep-circadian health clusters using several alternative unsupervised machine learning methods, specifically K-means and Mixtures of Gaussian with the *sklearn* package in Python.

We plotted the number of clusters k : 0-14 on elbow plots to compare silhouette scores and SSEs for judging the cluster quality of candidate clustering models [104]. We manually tuned the hyperparameters for the data reduction UMAP procedure at the same time as the unsupervised clustering algorithms using cross-validation [105]. The number of neighbors (n_neighbors) in the embedding and minimum density (components) are hyperparameters that control the balance between local and global structure, as well as determine the distance between points (min_dist), respectively [103].

The final sleep cluster model was identified using k=5 clusters from K-Means, although we found that the silhouette scores were relatively similar between K-Means and MOG. This final cluster model also preserved a sleep island, which was a cluster with a smaller number of participants with more extreme differences in sleep indices. Next, stratified k-fold cross-validation was used to evaluate clustering and to tune the model in the presence of class imbalance in race and ethnicity between participants [106]. Stratified k-fold cross-validation was chosen to address this imbalance by maintaining the balance of the racial-ethnic group, while randomly splitting the dataset into 25 pairs of training and test sets [106]. Silhouette scores were averaged across the 25 folds of the cross-validation to perform internal validation [107]; specifically, the silhouette scores quantified the clustering quality (after ensuring balance between race and ethnicity across test and training sets) based on the closeness of classified instances and separation between different clustering groups [107]. UMAP data reduction followed by unsupervised learning yielded several, interpretable sleep profile clusters. The final set of hyperparameters for UMAP based on race and ethnicity stratified, k-fold cross-validation and cluster separation was n_neighbors = 4, min_dist=0.10, n_components=2, and metric=Euclidean.

We required that the final model have hyperparameters that resulted in an average silhouette score (e.g., across the folds) that was greater than 0.50, since manual tuning had uncovered silhouette scores within ±0.15 of this range between folds. This silhouette score threshold was used to prune the list of candidate clustering models from the list of previously described models. The final two criteria for selecting the final clustering model were to choose a model in which (i) there was the largest separation in mean and standard deviation of z-scores for most sleep indices, and (ii) these individual sleep features were directionally consistent for either

healthy or disordered sleep based on domain knowledge. In other words, the final sleep

clustering model was chosen by identifying clusters with trends in sleep features in the same

direction.

<u>Statistical Modeling</u>

We calculated descriptive statistics of population and sleep characteristics (e.g., WASO,

IS, IV) from the sample used in the complete case analysis, and these characteristics were also

stratified by sleep rhythm clusters. Using these descriptive statistics, we confirmed the face

validity of sleep clusters with unhealthier sleep patterns by checking that clusters were

directionally consistent for sleep characteristics. (e.g., greater sleep duration, lower WASO,

lower IS). As hypothesized, we confirmed that the "unhealthy" sleep clusters would have a

higher prevalence of cardiometabolic conditions, such as diabetes and cardiovascular disease

(CVD), compared to the cluster/s with healthier sleep patterns.

Multiple imputation (*mice* package) was performed with 25 rounds of imputation over

five iterations; the exposure, outcomes, and all confounding covariates were included in the

predictor matrix, in order to impute observations for missing confounding covariates. Since the

SPPB sub-scores were moderately to strongly correlated, only the overall SPPB score was

included in the predictor matrix. Prior to imputation, we examined the proportion of missingness

in the covariates that would be imputed and visually inspected for patterns of missingness.

Within the multiply imputed analytic sample, negative binomial, parametric regression

models were used to evaluate whether women with certain "unhealthy" sleep rhythm clusters (as

evidenced by shorter sleep duration, greater intra-daily variability, lower inter-daily stability,

lower sleep efficiency/greater WASO, or earlier L5 midpoint) had a higher risk of falling, as

evidenced by their fall rate over 13 months. A negative binomial regression model was used

(with the *MASS* R package, version 7.3-56), since the fall incidence is highly right-skewed that led to over-dispersed Poisson models upon inspection. To address another primary study objective, we evaluated associations between sleep-RAR clusters and physical functioning within the multiply imputed sample, since declines in physical functioning may precede frequent falling among older adults. Linear regression models were constructed between sleep rhythm clusters and the total physical functioning score (i.e., SPPB), in addition to components of the overall SPPB score including the balance test, chair stands, and gait speed.

To test for the presence of a multiplicative interaction, physical function was operationalized as a binary variable to classify lower (lower: SPPB 1-8) and higher (higher: SPPB 9-12) physical functioning, and then an interaction between this term and sleep clusters was added to the negative, binomial models for fall risk. We reported separate, stratified models for those with lower and higher physical functioning.

Progressive model adjustment was performed in models of sleep with fall risk and physical functioning to address confounding. The first model was adjusted for age (continuous in years), race and ethnicity (white/Black/Hispanic), and education (High School or GED/Some College/College Graduate+). We adjusted for race and ethnicity as a potential confounder in sleep-fall risk associations, since sleep disparities are experienced disproportionately by individuals who identify as Hispanic/Latina or Black [46, 108]. Some studies have found that Black participants have greater fall risk in later life compared to non-Hispanic white adults in later life due to greater exposure to environmental predictors of falls, including neighborhoods without sidewalks and residences in non-metropolitan areas, although other studies observed no differences between these groups [109, 110]. Next, we additionally adjusted for alcohol consumption (Non-Drinker/<1 time per week/>=1 time per week), smoking status (current

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smoker/not current smoker), total minutes spent in physical activity (continuous in minutes), CVD (yes/no), diabetes (yes/no), and cancer (yes/no). These diseases were selected for adjustment due to their known association with sleep disruption [111, 112]. The third model was progressively adjusted for body mass index (continuous in kg/m^2), sleep medications (not in the past month or less/less than once per week/1+ times per week), and depression (yes/no). We also repeated modeling between quartiles of individual sleep metrics and fall risk.

In addition, we modeled associations between quartiles of RAR measures (e.g., IV, IS, L5, M10) with fall risk and physical functioning, since these particular sleep dimensions distinguished clusters. Also, there is limited research examining the role of RAR measures on declining physical functioning. We performed sensitivity analyses to address the concern for selection bias due to missing sleep cluster data. Inverse probability censoring weighting (IPCW) was performed to upweight women in the sleep clusters with the same baseline characteristics of women who were censored from the study due to missing sleep cluster data [113, 114]. Bootstrapped 95% confidence intervals were generated for IPCW models with the multiply imputed data over n=1,000 resamples [115]. Briefly, women were sampled from the multiply imputed dataset by converting the list of multiply imputed datasets into a long version of the dataset. ICPW weighting was calculated with respect to each resample. Complete case was also performed as a sensitivity analysis, in which we re-analyzed all of the primary associations between the sleep clusters, physical functioning, and fall risk.

3.4   Results

Sleep and RAR Characteristics

On average (±SD), OPACH participants slept 8.20 (±1.26) total hours, with 95.59% (±2.71) efficiency and latency of 1.86 (±1.88) hours (Table 3.1). The average time in and out of

bed occurred at 7:29 PM (± 3.50 hrs.) and 5:32 AM (±1.69 hrs.). The average wake after onset

for participants was 21.03 (±14.40) minutes; participants awoke an average of 5.51 (±2.96) times

per night and spent on average 3.78 (±1.53) minutes awake. The average intra-daily variability

for participants was 1.12 (±0.27), whereas the average inter-daily stability for participants was

0.49 (±0.11). In terms of activity and sleep timing, the midpoint of the L5 period was between 3-

4am (3.59 ±3.35 hours), with the average L5 activity level at 9.18 (±10.45) counts. In addition,

the midpoint of the M10 period occurred at 1pm (±1.82 hrs.), with the average M10 activity level

at 115.15(±49.48) counts.

Unsupervised Machine Learning: Sleep Clusters of Sleep and RAR Parameters

We obtained a total of 5 clusters from the final clustering model that classified the sleep

patterns of 4,543 study participants, which were classified as follows: cluster 1 "sleep disturbed"

(n=1051), cluster 2 "healthy" (n=1043), cluster 3 "mild RAR disruption"(n=1446), cluster 4

"earlier sleepers" (n=105), and cluster 5 "shorter, mildly disrupted, later sleeper"(n=898; see

Figure 3.2). Cluster 2 was considered the only healthy sleep cluster, and all remaining clusters

were considered "unhealthy" sleep clusters that reflect lower overall sleep quality. Descriptive

statistics and visualizations are shown in Table 3.1 and Figure 3.2 for each sleep feature that

defines the clusters (prior to data reduction). In the top half of figure 3.2, there are three panels

that characterize sleep feature patterns for each cluster with respect to a group of indices, which

span from the RAR and sleep regularity (panel a, Figure 3.2), sleep efficiency (panel b, Figure

3.2), and then sleep timing, duration, and self-reported sleep quality (panel c, Figure 3.2). The

mean and distribution of the sleep features is shown in the lower set of panels between the

healthy cluster C2 and a select, unhealthy cluster C4. Panel d highlights that the sleep features

are directionally consistent in representing a healthy versus unhealthy sleep profile. For example,

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an unhealthy sleep profile (as demonstrated by cluster 4) has lower inter-daily stability, higher intra-daily variability, lower sleep efficiency, shorter sleep duration, greater WASO, and worse sleep quality (panel d, Figure 3.2).

Clusters 1 "sleep disturbed" and 5 "shorter, mildly disrupted, later sleeper" were also sleep clusters that exhibited more disrupted RARs for both inter-daily stability and intra-daily variability (Table 3.1). Clusters 1 and 5 have an average intra-daily variability that is half a standard deviation greater than other clusters (Table 3.1; Figure 3.2, panel a); additionally, these clusters have lower inter-daily stability, representing lower consolidation in their sleep cycle between days (Table 3.1). Cluster 4 also exhibits more fragmented RARs, as reflected by a higher intra-daily variability on par with Clusters 1 and 5 (Figure 3.2, panel a).

Inter-daily stability in clusters 2-5 decreased across each cluster by 0.20 standard deviations, whereas intra-daily variability in these clusters increased by nearly a half standard deviation between groups. Cluster 2 "Healthy" had RAR and sleep metrics that reflected healthier rest-activity-patterns; for example, cluster 2 had the lowest intra-daily variability, highest inter-daily stability, highest sleep efficiency, highest total sleep time, lowest WASO, lowest length, and frequency of awakenings, and lowest report-based, sleep quality scores (Table 3.1).

Compared to all other RU-SATED sleep features, the start and midpoint of the least active 5-hour period (e.g., L5-Start and L5-Mid) had z-scores that differed the most overall for cluster 4 compared to all other sleep clusters. Of note, the L5 period had the latest L5 midpoint numerically (11:10PM), since time was represented from 0 (12:00am) to less than 24 (11:59pm). Since the L5 period is capturing the sleep period that crosses midnight (12:00am), the C4 cluster with the "highest" L5 period corresponded to having the earliest L5 midpoint for their least

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active, sleep period compared to other clusters. Clusters C1-C3 and C5 had L5 midpoints that occurred between 1:43am to 3:50am.

Cluster 4 "earlier L5 sleep midpoint" was a sleep island, since this cluster contained the fewest number of people, and this cluster was less proximal to other clusters when visualized along the first two UMAP dimensions (Figure 3.3). Cluster 4 also had the most extreme midpoint of the L5 period with a midpoint that was 6 standard deviations higher than all other cluster groups. The total activity count for the L5 and M10 period was inversely related within clusters, where clusters 1 and 4 having the highest L5 and cluster 4 (followed by clusters 1 and 5) having the lowest M10 counts. The M10 start and midpoint decreased as cluster groups increased, except for group 5 which was more similar to group 1 or 2.

As the cluster number increased from 1-5, time spent in bed increased and total sleep time decreased (with the exception of group 4). WASO, frequency of awakenings, and length of awakenings were similar across groups, except for cluster 1 (Table 3.1, Figure 3.2, panel b). Finally, questionnaire-based sleep quality and alertness measures did not differentiate sleep cluster groups as well as other objectively measured sleep dimensions (Table 3.1, Figure 3.2, panel c).

Assessment of Heterogeneity Enrichment

There was no evidence of cluster enrichment for most potential latent factors, including age group (≥80 years old/<80 years old), race and ethnicity (white/Black/Hispanic), depression (yes/no), and diabetes (yes/no) through visual inspection (Figure 3.4). The density of the points representing individuals with cardiovascular disease were less densely clustered in cluster 2 "Healthy" (Figure 3.4). Similarly, Table 3.2 demonstrates that Cluster 2 had the lowest

prevalence of cardiovascular disease (7.2%) compared to all other clusters (C1: 13.1%, C3: 8.3%, C4: 9.9%, C5: 9.3%; overall-p = 0.001).

Comparing Fall Rates for Sleep Profiles and RAR Measures

We observed higher adjusted fall rates among women with disrupted sleep clusters 1, 3, and 4 compared to the healthy sleep cluster 2. In multiply imputed models, women in clusters 1 and 3 had a fall rate nearly 1.2 times the magnitude of the healthy sleep cluster after full adjustment (Table 3.3). Notably, the incidence risk ratio (IRR) among the "earlier sleepers" cluster 4 showed the highest risk of falling compared to the healthy sleep cluster (IRR: 1.76 (95%CI: 1.15-2.69); Table 3.3). Lower inter-daily stability quartiles (reflecting greater sleep consolidation), higher intra-daily variability, and lower M10 activity counts were individually associated with having a lower fall risk after adjustment (IS, p-value=0.002; IV, p-value=0.004; M10, p-value=0.002; Table 3.3). In addition, the complete case analysis was also consistent with the multiple imputation analysis when studying the relationships between sleep clusters with fall risk (Table 3.4).

Associations between Sleep Clusters with Physical Functioning Measures

The sleep clusters were solely associated with balance component (range: 0-4) of the physical functioning score in the analyses using multiply imputed data. Clusters 1 "disturbed sleep" and 4 "earlier sleepers" on average had an adjusted mean difference of -0.11 (95% CI: -0.21 to -0.01) and -0.30 (95% CI: -0.55 to -0.05) for balance compared to the healthy sleep cluster 2. We observed no association for sleep clusters with either the overall physical functioning score or the chair stand or gait speed sub-scores, although there was suggestion of an association for gait speed and overall physical functioning in the complete case analysis (Table 3.5).

<u>Physical Functioning - Stratified Associations between Sleep Clusters and Fall Risk</u>

There was evidence of a statistical interaction between sleep clusters and physical functioning with respect to fall risk (Sleep Clusters*SPPB, omnibus p-value=0.002; Table 3.6). Women with higher physical functioning (SPPB 9-12) with sleep patterns classified by the "sleep disturbed" cluster 1 had 1.31 times the fall risk (IRR: 1.31 (95% CI: 1.03-1.66)) compared to the healthy sleep cluster 2 (Table 3.6). Meanwhile, women with lower physical functioning (SPPB 0-8) with sleep patterns classified by the "sleep disturbed" cluster 1 had 1.11 (95% CI: 0.87-1.41) times the fall risk compared to the healthy sleep cluster. Women with lower physical functioning with sleep patterns classified by the "earlier sleepers" cluster 4 had 2.03 times the fall risk (IRR: 2.03 (95% CI: 1.16-3.58)) compared to the healthy sleep cluster 2. Women with higher physical functioning with sleep patterns classified by the "earlier sleepers" cluster 4 had 1.76 times the fall risk (IRR: 1.42 (95% CI: 0.82-2.46)) compared to the healthy sleep cluster 2.

<u>IPCW-Weighted Analyses for Missing Sleep Cluster Data</u>

The IPCW-weighted estimates were consistent with the primary statistical models for the relationship between sleep clusters and fall risk (Table 3.7). Note, the effect size of the association (seen in the primary statistical models) for sleep cluster 1 and fall risk increased after IPCW weighting (fully adjusted IRR: 1.21 (95%CI: 1.03-1.44). The relationship between sleep clusters and physical functioning scores were also consistent with prior results after IPCW weighting (Table 3.8). On the other hand, the relationships between M10 and intra-daily variability quartiles with fall risk were weakened after IPCW weighting (Table 3.7).

3.5　<u>Discussion</u>

This study provides a comprehensive examination of the relationship between sleep and RAR clusters and prospective fall risk based on daily reporting of falls. This chapter identified

several sleep and RAR profiles based on underlying sleep patterns in community-based older women; identification of these profiles allows for consideration of the influence of multiple, co-occurring sleep conditions.

Most notably, sleep cluster 4 identified earlier sleepers and was positively associated with greater fall risk and lower physical functioning, as evidenced by worse balance, compared to healthy cluster 2. Cluster 2 identified women with healthier sleep and rest-activity patterns, and this cluster exhibited the lowest IV, highest IS, highest sleep efficiency, highest total sleep time, and lowest WASO. In addition to Cluster 4, Cluster 1 was associated with greater fall risk and lower balance, and individuals identified by Cluster 1 exhibited greater WASO, higher intra-variability, and lower inter-daily rhythm stability or consolidation. Physical functioning modified associations between RARs and fall risk, where individuals with higher physical functioning showed stronger associations between sleep cluster 1 and fall risk.

The association between sleep disturbances and fragmented rest activity rhythms on fall risk is likely partially mediated through balance [116]. Older adults are generally more vulnerable to the influence of acute sleep deprivation on balance as compared to younger adults [84], which may influence this population's heightened risk of falling after experiencing sleep disturbances and fragmented RARs; others have shown that sleep may influence balance through diminishing cognitive load with aging [117]. This hypothesis is a more specific example of the conceptual model of geriatric syndromes, in which these prevalent health outcomes in older adults co-occur and are synergistic.

This study is consistent with existing prospective cohort studies in MrOS showing an association between a RAR metric that characterized the timing of the RAR, specifically acrophase, and fall risk in older adults [86]. Later timing of peak circadian activity, as

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determined by acrophase, was associated with greater risk of being a frequent faller compared to earlier acrophase timing. Measurement of the exposure and disease were similar between the OPACH and MrOS study. The MrOS study was a prospective cohort study that objectively measured RARs; this study also ascertained falls every four months after recontacting participants with postcards or over the telephone. Note, MrOS ascertained falls over a mean of 8.7 years, whereas the OPACH study measured falls in the year following actigraphy measurement. There were some methodological differences between the RARs from MrOS and this current study. Specifically, the analysis in MrOS utilizes RAR measures derived from the extended cosine model (e.g., amplitude, mesor, and acrophase), whereas this study utilizes measures derived from a non-parametric model (e.g. IV, IS, L5, L5 start and midpoint) [86]. Compared to the other rest-activity metrics derived from the extended cosine curve, acrophase is the only sleep timing metric that describes the shift in the extended cosine curve. Specifically, acrophase characterizes the time of day of peak activity and indicates a preference for earlier or later activity rhythms. The acrophase measure is most analogous to the L5 and M10 timing measures that we derived from non-parametric model. Moreover, we observed that the sleep clusters derived using unsupervised machine learning showed greater signal in predicting fall risk than quartiles of the individual rest-activity metrics. Similarly, an earlier study in MrOS also observed associations between actigraphy-based sleep disturbance metrics (e.g., <70% sleep efficiency and ≤5hrs sleep duration) and self-report-based metrics (e.g., excessive sleepiness, sleep quality) with greater odds of being a frequent faller [118].

Prior studies have observed associations between insomnia and sleep disturbances with worse performance at task-switching [112, 119], executive function and memory [120, 121]. The reduced ability to task switch following a poor night's slight may promote falling, particularly

among individuals engaged in more physically intense activities. Studies have reported that individuals who are engaged in higher physical activity, who also have higher physical functioning, are at an increased risk of falling [122-124]. Older individuals with lower physical functioning may walk less often or rest more on days with poor sleep and RARs, which may subsequently lower their risk of falling compared to individuals with higher physical functioning. An alternative explanation is that fall risk is higher in individuals with lower physical functioning, where unhealthy sleep may be influential in this relationship as compared to other risk factors for falling, including weakness and reaction time.

There are several key strengths to this chapter. This study allows for further generalizability of prior knowledge about sleep disturbances and fall risk to a diverse cohort that includes white, Black, and Hispanic/Latina older women in their late seventies and eighties. Valid, precise, and prospective measurement of the exposure and outcome was another strength of this work, since RARs were objectively measured using accelerometers at the OPACH study onset for up to 7 days. This study is well-suited to address this research question since there are limited studies with objective sleep measurements and daily surveillance of falls. Another strength is that we demonstrate that unsupervised learning can be successful at identifying behavioral clusters that are potentially meaningful when looking at declining physical function and fall risk among older adults. Examining circadian-sleep parameters independently when modeling associations between sleep and fall risk ignores that these measures co-occur and are correlated. Identifying sleep behavioral profiles, comprised of multiple sleep dimensions, allow for consideration of how sleep and rest-activity parameters act in concert to modify fall risk. Lastly, another key strength was the use of race and ethnicity stratified cross-validation to tune hyperparameters and score clustering. Use of this race and ethnicity stratified cross-validation

ensures that the model is trained over each round or fold of data using data with a balance of racial-ethnic diversity that matches the original analytic sample. This approach to cross-validation helps ensure that the model scoring is not influenced by varying racial-ethnic composition between rounds or folds of data during validation.

UMAP has several advantages compared to other data reduction techniques, including computational efficiency, flexibility to work with multiple types of variables, and fewer hyperparameters to tune compared to other data reduction techniques, such as t-SNE [102]. Although PCA is one of the most commonly used data reduction techniques, PCA is a linear, data reduction method that maximizes projected variance and identifies more global structures, when identifying principal components in the order of importance [125]. Other data reductions, such as t-SNE, identify local structure, yet the findings from t-SNE, specifically the arrangement of clusters, are less frequently re-identified when attempting to reproduce these results across samples [102].

There are a few limitations to this study. The identification of behavioral clusters is an exploratory approach to evaluate associations with sleep rhythm metrics and fall risk. The generalizability of the associations observed between sleep clusters, fall risk, and physical functioning needs further exploration. A majority of the OPACH participants had healthy sleep patterns, with the population averaging approximately 8 hours of sleep, 96% sleep efficiency, and low sleep latency. Different sleep clusters may be identified among older adults who exhibit more disrupted sleep and greater variability in their sleep as compared to the sleep patterns seen among OPACH participants. For example, short sleep is a commonly reported sleep concern among older adults, with one study estimating approximately 30% of older adults not receiving at least 7 hour of sleep per night [126]. Among adults with more disrupted sleep, we may expect

similar clusters but with greater overall difference in sleep features between groups. Additional studies are needed to confirm the reproducibility of generating these clusters among a general population with unhealthier sleep patterns, as well as among older men who were not represented in the OPACH study. Clustering sleep and RAR parameters in a population with greater variability in their sleep patterns may uncover additional sleep and RAR features that may be predictive of fall risk and declining physical function. Future researchers may also consider performing clustering with different hyperparameters or constraints (e.g., k number of clusters).

There is a growing shift to modeling multiple dimensions of sleep and circadian behaviors simultaneously, using dimension reduction [25], clustering analyses [26], or factor analyses [27], and evaluating associations of these sleep profiles with morbidity and mortality [28]. This study demonstrated that the unhealthy sleep clusters, representing disrupted RARs, lower sleep efficiency, and earlier L5 midpoint timing, are identifying poor sleepers among older adults. Older adults who are poor sleepers are more likely to have worse physical functioning and a heightened fall risk compared to healthier sleepers. Addressing sleep concerns and shifting women from unhealthy to healthy sleep clusters may further promote longevity by addressing multiple, interlinked geriatric syndromes, involving physical functioning, falls, and cognitive performance. Future work may consider reproducing this clustering in a similarly aged cohort and may also look to extend this to a broader age demographic.
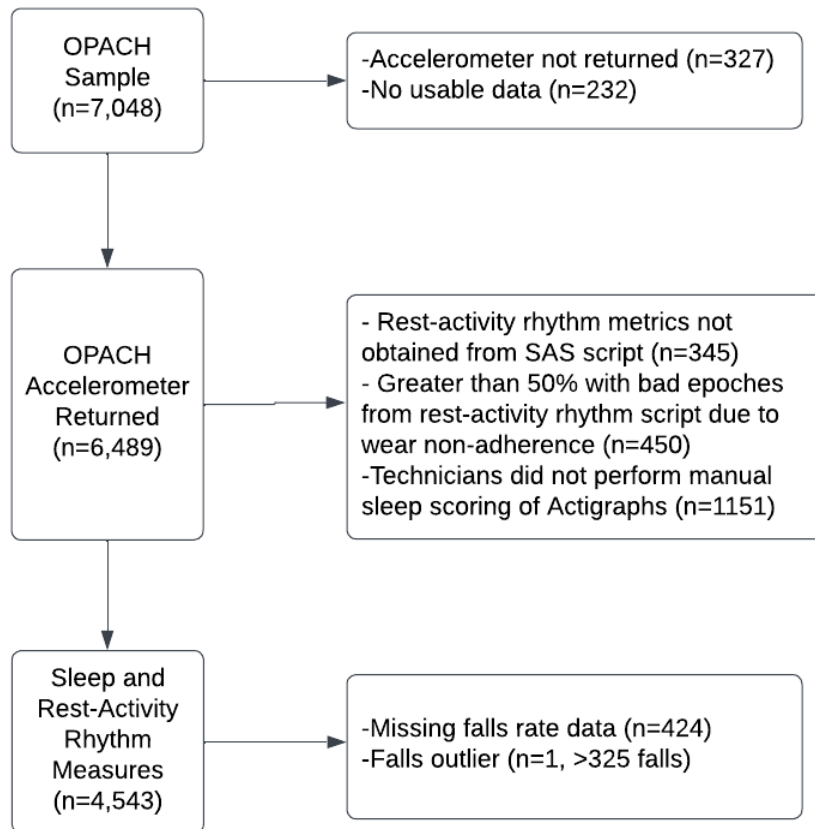
Figure 3.1. Flow chart of the patient characteristics in the Women's Health Initiative analysis (n=4,543)
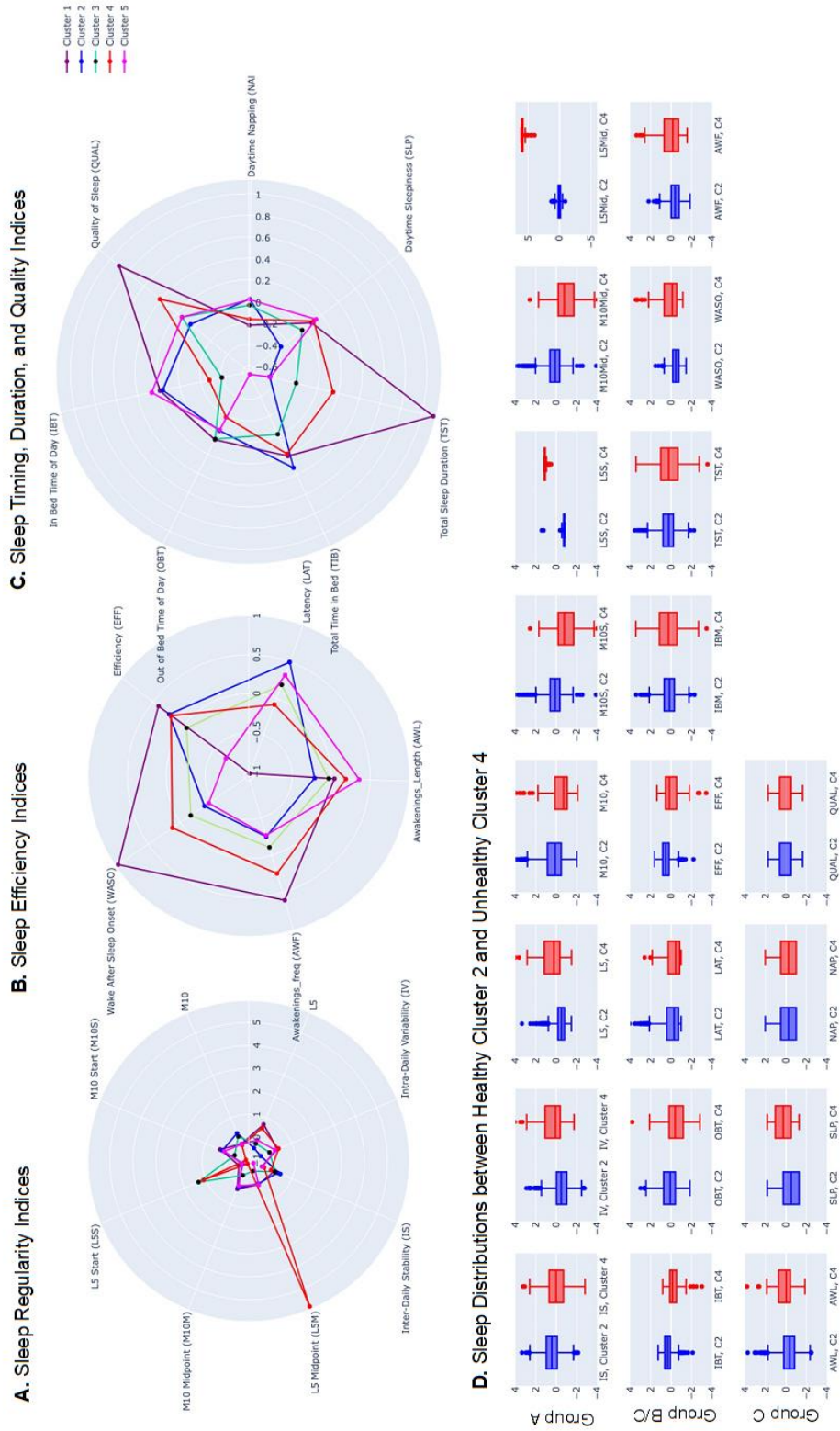
Figure 3.2. Sleep clusters characterization: radial plots of individual sleep features and select box plots for healthy and disturbed sleep clusters
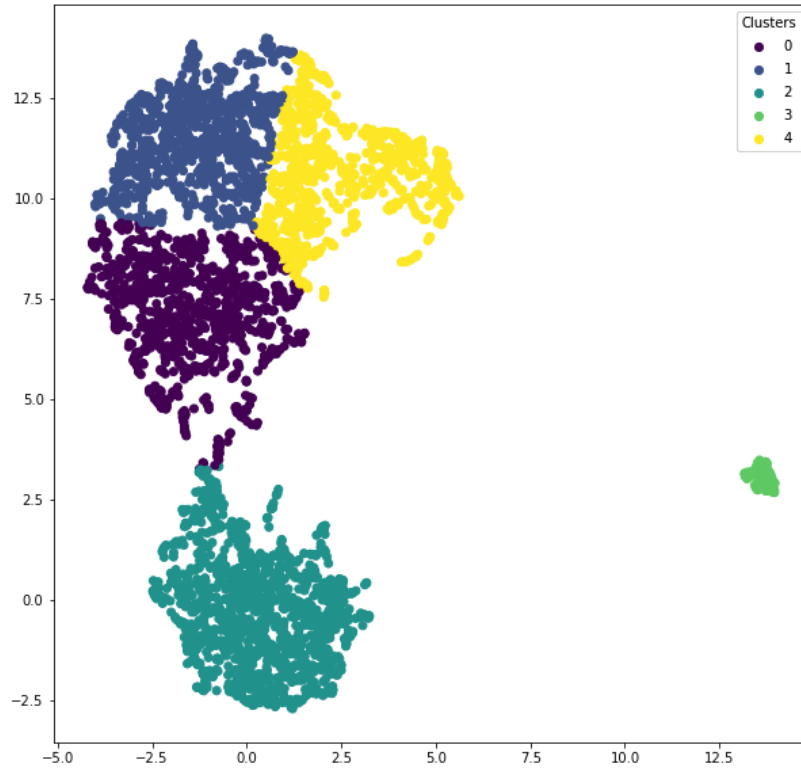
Figure 3.3. Two-dimensional visualization of k-means (k=5) clustering following the UMAP data reduction

The five clusters are shown in the figure above numbered as 0-4 with the same ordered maintained throughout the table.

For example, cluster 0 corresponds to cluster 1 in all of the other tables. The healthy reference group used in the analyses is the blue cluster.
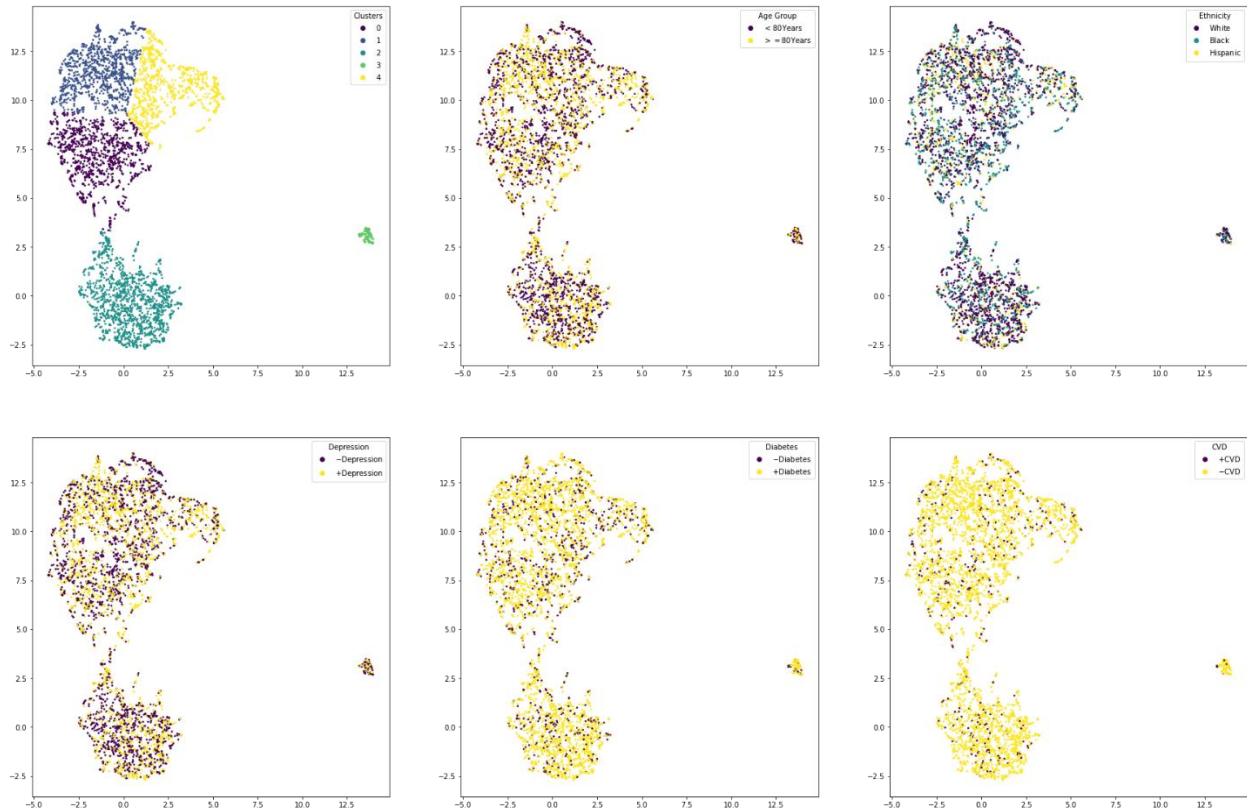
Figure 3.4. Cluster enrichment plot of clinically relevant cardiometabolic and aging phenotypes

This cluster enrichment analysis shows that there are no patterns of clinically relevant covariates that are acting as a latent variable that may be influencing clustering performance. There was suggestion that the healthy sleep cluster 2 had a lower density of CVD cases compared to the other sleep clusters. This plot influenced exploration of a sleep cluster by CVD interaction in associations between sleep and fall risk.

Table 3.1. OPACH Women Sleep Characteristics by Sleep-Circadian Clusters from K-Means

Under the cluster identifier, the names summarize the contents of the cluster. Mean and standard deviation are reported for sleep characteristics in their original units, although they were standardized prior to performing UMAP data reduction and K-means. Differences in characteristics across categories were determined using ANOVA for continuous variables.

	Total	Cluster 1 "Sleep Disturbed"	Cluster 2 "Healthy"	Sleep-Circadian Clusters* Cluster 3 "Mild Fragmentation"	Cluster 4 "Earlier L5 midpoint"	Cluster 5 "C1 with Shorter, Less Disrupted Sleep"	p-values
	n=4,543	n=1051	n=1043	n=1446	n=105	n=898	
Regularity†							
Inter-Daily Stability	0.49 (0.11)	0.44 (0.11)	0.54 (0.09)	0.51 (0.10)	0.49 (0.13)	0.44 (0.10)	<0.001
Intra-Daily Variability	1.12 (0.27)	1.21 (0.29)	0.99 (0.23)	1.11 (0.26)	1.23 (0.34)	1.18 (0.26)	<0.001
Efficiency							
In Bedtime, hrs.	19.48 (3.50)	20.03 (2.04)	20.59 (1.50)	20.11 (1.61)	18.36 (2.86)	16.65 (6.22)	<0.001
Out of Bedtime, hrs.	5.53 (1.69)	5.85 (1.56)	5.79 (1.36)	4.85 (1.53)	5.05 (2.78)	5.97 (1.90)	<0.001
Sleep latency†	1.86 (1.88)	1.96 (2.20)	1.79 (1.68)	1.94 (1.87)	1.51 (1.56)	1.75 (1.74)	0.01
Sleep efficiency, %	95.59 (2.71)	92.80 (3.17)	96.93 (1.33)	96.11 (2.00)	95.37 (2.59)	96.45 (2.00)	<0.001
Wake After Sleep Onset, mins.	21.03 (14.40)	36.99 (16.62)	14.51 (6.44)	18.11 (10.47)	23.19 (15.02)	14.59 (8.72)	<0.001
Total Night Awakenings	5.51 (2.96)	8.39 (3.24)	4.41 (1.83)	5.03 (2.44)	5.88 (3.70)	4.21 (1.97)	<0.001
Length of Awakenings, minutes	3.78 (1.53)	4.70 (1.67)	3.40 (1.34)	3.62 (1.34)	4.16 (1.78)	3.38 (1.37)	<0.001
Alertness/Sleepiness†							
Daytime Sleepiness	1.69 (1.23)	1.71 (1.19)	1.37 (1.15)	1.61 (1.20)	1.90 (1.34)	2.12 (1.25)	<0.001
Napping	1.29 (1.27)	1.44 (1.27)	0.96 (1.10)	1.29 (1.29)	1.47 (1.36)	1.51 (1.32)	<0.001
Duration							
Total Sleep Time, hrs.	8.20 (1.26)	8.46 (1.40)	8.61 (1.05)	8.19 (1.17)	8.45 (1.76)	7.41 (0.99)	<0.001
Sleep Timing							
L5 Activity Counts	9.99 (6.62)	14.63 (8.47)	7.17 (3.88)	8.60 (4.77)	13.33 (8.45)	9.72 (6.12)	<0.001
M10 Activity Counts	115.15 (49.48)	104.27 (42.95)	129.25 (54.50)	121.24 (49.25)	101.03 (62.35)	103.15 (42.68)	<0.001
L5 Start, hrs.	9.18 (10.45)	3.24 (5.98)	1.31 (1.61)	23.07 (1.76)	20.60 (1.21)	1.58 (2.28)	<0.001
M10 Start, hrs.	8.09 (1.84)	8.66 (1.94)	8.46 (1.61)	7.40 (1.56)	6.41 (2.11)	8.29 (1.91)	<0.001
L5 Midpoint, hrs.	3.59 (3.35)	3.85 (1.64)	3.72 (0.87)	1.70 (0.62)	23.10 (1.21)	3.89 (1.22)	<0.001
M10 Midpoint, hrs.	13.07 (1.82)	13.59 (1.89)	13.46 (1.61)	12.40 (1.56)	11.41 (2.11)	13.29 (1.91)	<0.001
Satisfaction/Quality							
Quality of Sleep	2.40 (0.85)	2.26 (0.83)	2.48 (0.88)	2.42 (0.85)	2.30 (0.87)	2.47 (0.83)	<0.001

†Unitless sleep features

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Table 3.2. Baseline Characteristics in OPACH (2012-2018) and Stratified by Sleep-Circadian Clusters derived from K-Means (k=5) following UMAP data reduction (n=4,543)

Under the cluster identifier, the names summarize the contents of the cluster. Mean, standard deviation, and proportions were reported across stratum of inter-daily quartile. Differences in characteristics across categories were determined using Chi square tests for proportions and ANOVA for continuous variables. Percentages shown in the total column and within each sleep cluster stratum do not add up to 100%, since the percentages include the missingness.

		Sleep-Circadian Clusters					
	Total	Cluster 1 "Sleep Disturbed"	Cluster 2 "Healthy"	Cluster 3 "Mild Frag-mentation"	Cluster 4 "Earlier L5 midpoint"	Cluster 5 "C1 with Shorter, Less Disrupted Sleep"	
	n=4,543	n=1051	n=1043	n=1446	n=105	n=898	p-values†
Age, yrs.; *mean (sd)*	78.69 (6.74)	78.70 (6.87)	77.90 (6.66)	79.28 (6.60)	80.47 (6.92)	78.43 (6.76)	<0.001
Age Groups, ≥80 Years; n (%)	2267 (49.9)	516 (49.5)	467 (44.4)	792 (54.8)	62 (59.0)	430 (47.9)	<0.001
Race-ethnicity; n (%)							<0.001
White	2288 (50.4)	456 (43.7)	520 (49.5)	830 (57.4)	63 (60.0)	419 (46.7)	
Black	1519 (33.4)	444 (42.6)	305 (29.0)	407 (28.1)	29 (27.6)	334 (37.2)	
Hispanic	736 (16.2)	143 (13.7)	226 (21.5)	209 (14.5)	13 (12.4)	145 (16.1)	
Education; n (%)							0.07
High School/GED	920 (20.3)	206 (19.8)	217 (20.6)	318 (22.0)	24 (22.9)	155 (17.3)	
Some College	1774 (39.0)	422 (40.5)	419 (39.9)	555 (38.4)	43 (41.0)	335 (37.3)	
College Graduate+	1822 (40.1)	410 (39.3)	411 (39.1)	561 (38.8)	38 (36.2)	402 (44.8)	
Self-Rated Health; n (%)							<0.001
Excel./Very Good	2269 (49.9)	419 (40.2)	593 (56.4)	765 (52.9)	49 (46.7)	443 (49.3)	
Good	1820 (40.1)	480 (46.0)	370 (35.2)	567 (39.2)	41 (39.0)	362 (40.3)	
Poor/Very Poor	439 (9.7)	139 (13.3)	85 (8.1)	111 (7.7)	15 (14.3)	89 (9.9)	
Physical Activity, total steps per day; *mean (sd)*	340.78 (98.37)	318.64 (93.05)	362.96 (100.16)	349.29 (96.98)	284.14 (96.85)	333.40 (96.23)	<0.001
Physical Function; *mean (sd)*	68.59 (26.08)	62.12 (27.73)	73.27 (24.25)	71.41 (24.85)	60.24 (27.53)	67.01 (26.15)	<0.001
Smoker Status; n (%)							0.045
Non-Smoker	4033 (88.8)	881 (84.5)	958 (91.2)	1316 (91.0)	89 (84.8)	789 (87.9)	
Current-Smoker	118 (2.6)	35 (3.4)	26 (2.5)	26 (1.8)	5 (4.8)	26 (2.9)	
Sleep Medication; n (%)							0.007
Not in the past month or less	3097 (68.2)	644 (61.7)	734 (69.8)	1013 (70.1)	69 (65.7)	637 (70.9)	
Less than once per week	358 (7.9)	79 (7.6)	78 (7.4)	124 (8.6)	9 (8.6)	68 (7.6)	
1+ times per week	690 (15.2)	193 (18.5)	166 (15.8)	200 (13.8)	14 (13.3)	117 (13.0)	
Alcohol Frequency; n (%)							<0.001
Non-Drinker	1563 (34.4)	384 (36.8)	342 (32.5)	489 (33.8)	44 (41.9)	304 (33.9)	
<1 per Week	1429 (31.5)	314 (30.1)	333 (31.7)	435 (30.1)	30 (28.6)	317 (35.3)	
≥1 per Week	1165 (25.6)	221 (21.2)	310 (29.5)	418 (28.9)	20 (19.0)	196 (21.8)	
BMI; *mean (sd)*	28.04 (5.68)	29.63 (6.22)	26.96 (5.06)	27.36 (5.39)	28.57 (5.67)	28.55 (5.75)	<0.001
Diabetes, yes; n (%)	925 (20.4)	268 (25.7)	180 (17.1)	235 (16.3)	24 (22.9)	218 (24.3)	<0.001
Cardiovascular disease, yes; n (%)	437 (9.6)	133 (12.8)	85 (8.1)	121 (8.4)	10 (9.5)	88 (9.8)	0.002
Cancer, yes; n (%)	780 (17.2)	196 (18.8)	165 (15.7)	231 (16.0)	21 (20.0)	167 (18.6)	0.14
Depression; n (%)							0.48
Yes	271 (6.0)	61 (5.8)	58 (5.5)	82 (5.7)	9 (8.6)	61 (6.8)	
No	3700 (81.4)	812 (77.9)	888 (84.5)	1187 (82.1)	79 (75.2)	734 (81.7)	

†P-value is an omnibus p-value and examines differences between non-NA categories or values.

Table 3.3. Multiply Imputed (m=25), Negative Binomial Models of Fall Rate with Sleep-Circadian Cluster Risk Factors derived from K-Means (k=5) following UMAP data reduction (n=4,543)

Abbreviations: IS – inter-daily stability; IV – intra-daily variability; L5 – activity count for least active 5 hours of the day; M10 – activity count most active 10 hours of the day . IRR: Incidence Rate Ratio. C1-5: Clusters between 1-5.   The crude model (M1) was adjusted for age, race-ethnicity, and education. Model 2 was adjusted for the following covariates including age, race-ethnicity, education, self-rated health, alcohol consumption, smoking status, total minutes spent in physical activity, cardiovascular disease, diabetes, and cancer. The fully adjusted model (M3) was adjusted for the same model covariates as model 2 and was additionally adjusted for sleep medication, depression, and body mass index.

Sleep Exposure	Categories	Model 1 IRR (95% CI)	Model 1 P-value	Model 2 IRR (95% CI)	Model 2 P-value	Model 3 IRR (95% CI)	Model 3 P-value
ML-Derived Clusters	C1 "Sleep Disturbed"	1.25 (1.05-1.47)	1.58E-04	1.19 (1.01-1.40)	0.002	1.18 (1.00-1.39)	0.002
	C2 "Healthy"	Ref		Ref		Ref	
	C3 "Mild Fragmentation"	1.18 (1.02-1.36)		1.16 (1.00-1.34)		1.16 (1.00-1.34)	
	C4 "Earlier L5 midpoint"†	1.93 (1.24-3.00)		1.78 (1.15-2.75)		1.76 (1.15-2.69)	
	C5 "C1 with Shorter, Less Disrupted Sleep"	1.09 (0.92-1.29)		1.06 (0.89-1.25)		1.05 (0.89-1.25)	
Inter-Daily Stability (IS)	Q1	1.34 (1.15-1.55)	7.03E-05	1.25 (1.07-1.47)	0.004	1.25 (1.06-1.47)	0.004
	Q2	1.17 (0.99-1.38)		1.13 (0.96-1.34)		1.13 (0.96-1.33)	
	Q3	1.20 (1.03-1.40)		1.17 (1.01-1.37)		1.16 (1.00-1.36)	
	Q4	Ref		Ref		Ref	
Intra-Daily Variability (IV)	Q1	Ref	1.39E-05	Ref	8.90E-04	Ref	7.35E-04
	Q2	1.25 (1.07-1.47)		1.23 (1.05-1.44)		1.24 (1.06-1.45)	
	Q3	1.18 (1.00-1.39)		1.16 (0.98-1.37)		1.16 (0.98-1.37)	
	Q4	1.36 (1.16-1.59)		1.27 (1.07-1.51)		1.27 (1.07-1.51)	
L5 Activity Counts‡	Q1	Ref	0.35	Ref	0.26	Ref	0.31
	Q2	1.00 (0.85-1.16)		1.00 (0.86-1.17)		1.00 (0.85-1.17)	
	Q3	0.94 (0.80-1.12)		0.96 (0.81-1.13)		0.96 (0.81-1.13)	
	Q4	1.15 (0.98-1.34)		1.17 (1.00-1.36)		1.16 (0.99-1.35)	
M10 Activity Counts‡	Q1	1.46 (1.23-1.74)	1.71E-07	1.42 (1.10-1.82)	5.30E-04	1.38 (1.07-1.78)	0.002
	Q2	1.25 (1.07-1.46)		1.22 (1.00-1.48)		1.20 (0.99-1.46)	
	Q3	1.23 (1.06-1.42)		1.23 (1.04-1.44)		1.21 (1.03-1.43)	
	Q4	Ref		Ref		Ref	

† "Earlier L5 midpoint" : An Earlier L5 midpoint corresponds to the L5 midpoint occurring later in the day according to time ordered from midnight up to 11:59pm. For this cluster, the L5 midpoint occurs within an hour of midnight, whereas the other clusters have L5 midpoints in the early morning hours after midnight.
‡The L5 activity and M10 activity counts represent total activity measured with the accelerometer that occurred during the least active 5-hour period and the most active 10-hour period.

Table 3.4. Complete Case Analysis, Linear Regression of Sleep-Circadian Cluster with Physical Functioning Markers using UMAP and K-Means (k=5; n=3,455)

Abbreviations: IS – inter-daily stability; IV – intra-daily variability; L5 – activity count for least active 5 hours of the day; M10 – activity count most active 10 hours of the day. C1-5: Clusters between 1-5. The crude model (M1) was adjusted for age, race-ethnicity, and education. Model 2 was adjusted for the following covariates including age, race-ethnicity, education, self-rated health, alcohol consumption, smoking status, total minutes spent in physical activity, cardiovascular disease, diabetes, and cancer. The fully adjusted model (M3) was adjusted for the same model covariates as model 2 and was additionally adjusted for sleep medication, depression, and body mass index.

Physical Functioning Marker	Sleep Clusters	Model 1		Model 2		Model 3	
		Beta (95% CI)	P-value	Beta (95% CI)	P-value	Beta (95% CI)	P-value
EPESE SPBB Score (0-12)	C2: "Healthy"	Ref	2.32E-08	Ref	9.08E-03	Ref	0.046
	C1: "Sleep Disturbed"	-0.63 (-0.86- -0.40)		-0.33 (-0.55- -0.10)		-0.23 (-0.46-0.01)	
	C3: "Mild Fragmentation"	0.00 (-0.21-0.21)		0.05 (-0.15-0.26)		0.10 (-0.10-0.31)	
	C4: "Earlier L5 midpoint"	-0.56 (-1.12-0.00)		-0.10 (-0.64-0.44)		0.11 (-0.45-0.68)	
	C5: "C1 with Shorter, Less Disrupted Sleep"\\	-0.26 (-0.5- -0.03)		-0.05 (-0.28-0.18)		0.05 (-0.19-0.28)	
Balance Test Score (0-4)	C2: "Healthy"	Ref	1.16E-05	Ref	8.39E-03	Ref	0.01
	C1: "Sleep Disturbed"	-0.20 (-0.30- -0.10)		-0.13 (-0.23- -0.03)		-0.11 (-0.21- -0.01)	
	C3: "Mild Fragmentation"	-0.02 (-0.11-0.08)		0.00 (-0.09-0.09)		0.02 (-0.07-0.11)	
	C4: "Earlier L5 midpoint"	-0.43 (-0.67- -0.19)		-0.32 (-0.56- -0.08)		-0.30 (-0.55- -0.05)	
	C5: "C1 with Shorter, Less Disrupted Sleep"	-0.08 (-0.19-0.02)		-0.03 (-0.13-0.07)		0.00 (-0.10-0.11)	
Chair Stand Score (0-4)	C2: "Healthy"	Ref	2.05E-05	Ref	0.18	Ref	0.47
	C1: "Sleep Disturbed"	-0.28 (-0.39- -0.16)		-0.14 (-0.25- -0.03)		-0.09 (-0.21-0.02)	
	C3: "Mild Fragmentation"	-0.06 (-0.16-0.05)		-0.04 (-0.14-0.06)		-0.02 (-0.12-0.09)	
	C4: "Earlier L5 midpoint"	-0.21 (-0.48-0.07)		-0.01 (-0.27-0.26)		0.09 (-0.19-0.37)	
	C5: "C1 with Shorter, Less Disrupted Sleep"	-0.16 (-0.28- -0.04)		-0.06 (-0.18-0.05)		-0.04 (-0.15-0.08)	
Gait Speed Score (0-4)	C2: "Healthy"	Ref	1.99E-04	Ref	0.01	Ref	0.02
	C1: "Sleep Disturbed"	-0.19 (-0.30- -0.08)		-0.09 (-0.20-0.02)		-0.04 (-0.16-0.07)	
	C3: "Mild Fragmentation"	0.05 (-0.05-0.15)		0.07 (-0.03-0.17)		0.08 (-0.02-0.18)	
	C4: "Earlier L5 midpoint"	0.05 (-0.21-0.32)		0.21 (-0.05-0.47)		0.29 (0.01-0.57)	
	C5: "C1 with Shorter, Less Disrupted Sleep"	0.00 (-0.11-0.12)		0.07 (-0.04-0.18)		0.10 (-0.02-0.21)	

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Table 3.5. Stratified Negative Binomial Models of Fall Rate with Sleep-Circadian Cluster Risk Factors using UMAP and K-Means (k=5; n=3,455)

Abbreviations: C1-5: Clusters between 1-5. The crude model (M1) was adjusted for age, race-ethnicity, and education. Model 2 was adjusted for the following covariates including age, race-ethnicity, education, self-rated health, alcohol consumption, smoking status, total minutes spent in physical activity, cardiovascular disease, diabetes, and cancer. The fully adjusted model (M3) was adjusted for the same model covariates as model 2 and was additionally adjusted for sleep medication, depression, and body mass index.

Disease Outcome	Clusters	Model 1 IRR (95% CI)	Model 1 P-value	Model 2 IRR (95% CI)	Model 2 P-value	Model 3 IRR (95% CI)	Model 3 P-value
Overall							
Fall Rate	C1	1.22 (1.04-1.42)	6.75E-04	1.16 (0.99-1.36)	5.25 E-03	1.14 (0.97-1.35)	1.69E-03
	C2	Ref		Ref		Ref	
	C3	1.16 (1.00-1.33)		1.13 (0.98-1.30)		1.15 (1.00-1.33)	
	C4	1.99 (1.41-2.86)		1.83 (1.29-2.63)		1.97 (1.38-2.84)	
	C5	1.06 (0.90-1.25)		1.03 (0.87-1.21)		1.02 (0.87-1.21)	
Cluster* SPPB			0.19		0.67		0.02
Low SPPB (SPPB 0-8)			1.77E-04		1.49 E-04		1.98E-05
Fall Rate	C2	Ref		Ref		Ref	
	C1	1.04 (95%CI: 0.82-1.31)		1.03 (95%CI: 0.81-1.31)		0.94 (95%CI: 0.73-1.20)	
	C3	1.17 (95%CI: 0.93-1.46)		1.13 (95%CI: 0.90-1.42)		1.12 (95%CI: 0.89-1.40)	
	C4	2.47 (95%CI: 1.48-4.26)		2.32 (95%CI: 1.39-3.99)		2.50 (95%CI: 1.49-4.30)	
	C5	1.01 (95%CI: 0.79-1.30)		1.03 (95%CI: 0.8-1.32)		0.99 (95%CI: 0.77-1.27)	
High SPPB (SPPB 9-12)			1.06E-02		1.02 E-02		2.49E-03
Fall Rate	C2	Ref		Ref		Ref	
	C1	1.42 (95%CI: 1.13-1.78)		1.40 (95%CI: 1.10-1.77)		1.44 (95%CI: 1.12-1.84)	
	C3	1.22 (95%CI: 1.00-1.48)		1.21 (95%CI: 1.00-1.48)		1.29 (95%CI: 1.05-1.59)	
	C4	1.65 (95%CI: 1.01-2.73)		1.68 (95%CI: 1.02-2.79)		1.75 (95%CI: 1.04-2.98)	
	C5	1.08 (95%CI: 0.86-1.36)		1.06 (95%CI: 0.84-1.33)		1.09 (95%CI: 0.85-1.38)	

Table 3.6. Multiply Imputed (m=25), Stratified Negative Binomial Models of Fall Rate with Sleep-Circadian Cluster Risk Factors using UMAP and K-Means (k=5; n=4,543)

Abbreviations: C1-5: Clusters between 1-5.   The crude model (M1) was adjusted for age, race-ethnicity, and education. Model 2 was adjusted for the following covariates including age, race-ethnicity, education, self-rated health, alcohol consumption, smoking status, total minutes spent in physical activity, cardiovascular disease, diabetes, and cancer. The fully adjusted model (M3) was adjusted for the same model covariates as model 2 and was additionally adjusted for sleep medication, depression, and body mass index.

Disease Outcome	Clusters	Model 1 IRR (95% CI)	Model 1 P-value	Model 2 IRR (95% CI)	Model 2 P-value	Model 3 IRR (95% CI)	Model 3 P-value
Overall							
Fall Rate	C1	1.25 (1.05-1.47)	1.58E-04	1.19 (1.01-1.40)	0.002	1.18 (1.00-1.39)	0.002
	C2	Ref		Ref		Ref	
	C3	1.18 (1.02-1.36)		1.16 (1.00-1.34)		1.16 (1.00-1.34)	
	C4	1.93 (1.24-3.00)		1.78 (1.15-2.75)		1.76 (1.15-2.69)	
	C5	1.09 (0.92-1.29)		1.06 (0.89-1.25)		1.05 (0.89-1.25)	
Cluster* SPPB			0.001		0.001		0.002
Low SPPB (SPPB 0-8)			0.03		0.04		0.04
Fall Rate	C2	Ref		Ref		Ref	
	C1	1.12 (0.88-1.43)		1.11 (0.87-1.41)		1.11 (0.87-1.41)	
	C3	1.20 (0.96-1.51)		1.16 (0.92-1.45)		1.16 (0.93-1.45)	
	C4	2.07 (1.16-3.70)		2.04 (1.15-3.62)		2.03 (1.16-3.58)	
	C5	1.07 (0.82-1.39)		1.07 (0.83-1.39)		1.08 (0.84-1.39)	
High SPPB (SPPB 9-12)			0.04		0.05		0.07
Fall Rate	C2	Ref		Ref		Ref	
	C1	1.33 (1.06-1.67)		1.32 (1.05-1.66)		1.31 (1.03-1.66)	
	C3	1.14 (0.94-1.39)		1.15 (0.95-1.40)		1.15 (0.95-1.41)	
	C4	1.47 (0.85-2.54)		1.46 (0.84-2.52)		1.42 (0.82-2.46)	
	C5	1.06 (0.84-1.33)		1.03 (0.82-1.31)		1.03 (0.82-1.31)	

Table 3.7. Negative Binomial Models of Fall Rate with Sleep-Circadian Cluster Risk Factors derived from K-Means (k=5) following UMAP data reduction (n=6,489) with IPCW weighting for missing accelerometry data

Abbreviations: IS – inter-daily stability; IV – intra-daily variability; L5 – activity count for least active 5 hours of the day; M10 – activity count most active 10 hours of the day. C1-5: Clusters between 1-5.   The crude model (M1) was adjusted for age, race-ethnicity, and education. Model 2 was adjusted for the following covariates including age, race-ethnicity, education, self-rated health, alcohol consumption, smoking status, total minutes spent in physical activity, cardiovascular disease, diabetes, and cancer. The fully adjusted model (M3) was adjusted for the same model covariates as model 2 and was additionally adjusted for sleep medication, depression, and body mass index.

Sleep Exposure	Categories	Model 1 IRR (95% CI)	Model 2 IRR (95% CI)	Model 3 IRR (95% CI)
ML-Derived Clusters	C1 "Sleep Disturbed"	1.32 (1.11-1.57)	1.23 (1.05-1.46)	1.21 (1.03-1.44)
	C2 "Healthy"	Ref	Ref	Ref
	C3 "Mild Fragmentation"	1.14 (0.96-1.35)	1.13 (0.96-1.33)	1.13 (0.96-1.33)
	C4 "Earlier L5 midpoint"	1.74 (1.17-2.56)	1.47 (0.99-2.16)	1.40 (0.96-2.01)
	C5 "C1 with Shorter, Less Disrupted Sleep"	0.99 (0.86-1.15)	0.96 (0.83-1.11)	0.94 (0.81-1.09)
Inter-Daily Stability	Q1	1.54 (1.27-1.83)	1.40 (1.17-1.66)	1.40 (1.17-1.65)
	Q2	1.18 (1.02-1.37)	1.13 (0.98-1.31)	1.14 (0.99-1.31)
	Q3	1.18 (1.00-1.39)	1.14 (0.97-1.33)	1.15 (0.99-1.33)
	Q4	Ref	Ref	Ref
Intra-Daily Variability	Q1	Ref	Ref	Ref
	Q2	1.01 (0.86-1.20)	0.96 (0.81-1.12)	0.97 (0.83-1.14)
	Q3	0.95 (0.80-1.13)	0.87 (0.74-1.03)	0.88 (0.75-1.04)
	Q4	1.28 (1.04-1.54)	1.07 (0.87-1.32)	1.07 (0.88-1.33)
L5 Activity Counts	Q1	0.86 (0.72-1.03)	0.87 (0.73-1.02)	0.87 (0.73-1.03)
	Q2	0.96 (0.80-1.17)	0.98 (0.82-1.17)	0.97 (0.81-1.16)
	Q3	0.94 (0.79-1.13)	0.99 (0.84-1.18)	0.97 (0.82-1.14)
	Q4	Ref	Ref	Ref
M10 Activity Counts	Q1	Ref	Ref	Ref
	Q2	1.51 (1.26-1.78)	1.29 (1.01-1.67)	1.26 (0.98-1.61)
	Q3	1.17 (0.98-1.38)	1.06 (0.85-1.28)	1.05 (0.84-1.27)
	Q4	1.02 (0.87-1.19)	0.98 (0.83-1.16)	0.97 (0.82-1.15)

Table 3.8. Linear Regression Models of Sleep-Circadian Cluster with Physical Functioning Markers using UMAP and K-Means (k=5; n=6,489) with IPCW weighting for missing accelerometry

Abbreviations: C1-5: Clusters between 1-5. The crude model (M1) was adjusted for age, race-ethnicity, and education. Model 2 was adjusted for the following covariates including age, race-ethnicity, education, self-rated health, alcohol consumption, smoking status, total minutes spent in physical activity, cardiovascular disease, diabetes, and cancer. The fully adjusted model (M3) was adjusted for the same model covariates as model 2 and was additionally adjusted for sleep medication, depression, and body mass index.

Physical Functioning Marker	Sleep Clusters	Model 1 Beta (95% CI)	Model 2 Beta (95% CI)	Model 3 Beta (95% CI)
EPESE SPBB Score (0-12)	C2: "Healthy"	Ref	Ref	Ref
	C1: "Sleep Disturbed"	-0.47 (-0.64--0.30)	-0.18 (-0.35-0.00)	-0.13 (-0.30-0.04)
	C3: "Mild Fragmentation"	-0.14 (-0.30-0.02)	-0.06 (-0.21-0.09)	-0.04 (-0.19-0.10)
	C4: "Earlier L5 midpoint"	-0.98 (-1.44--0.51)	-0.66 (-1.09--0.22)	-0.58 (-1.04--0.13)
	C5: "C1 with Shorter, Less Disrupted Sleep"	-0.16 (-0.33-0.02)	0.02 (-0.15-0.20)	0.06 (-0.12-0.23)
Balance Test Score (0-4)	C2: "Healthy"	Ref	Ref	Ref
	C1: "Sleep Disturbed"	-0.18 (-0.26--0.11)	-0.10 (-0.18--0.03)	-0.08 (-0.16--0.01)
	C3: "Mild Fragmentation"	-0.05 (-0.12-0.02)	-0.03 (-0.09-0.04)	-0.02 (-0.09-0.05)
	C4: "Earlier L5 midpoint"	-0.51 (-0.73--0.30)	-0.42 (-0.63--0.21)	-0.39 (-0.61--0.19)
	C5: "C1 with Shorter, Less Disrupted Sleep"	-0.06 (-0.14-0.02)	-0.01 (-0.08-0.07)	0.00 (-0.07-0.08)
Chair Stand Score (0-4)	C2: "Healthy"	Ref	Ref	Ref
	C1: "Sleep Disturbed"	-0.12 (-0.21--0.04)	0.00 (-0.08-0.09)	0.02 (-0.07-0.10)
	C3: "Mild Fragmentation"	-0.06 (-0.15-0.02)	-0.03 (-0.11-0.05)	-0.02 (-0.11-0.06)
	C4: "Earlier L5 midpoint"	-0.25 (-0.46--0.05)	-0.11 (-0.32-0.10)	-0.08 (-0.30-0.13)
	C5: "C1 with Shorter, Less Disrupted Sleep"	-0.07 (-0.16-0.02)	0.00 (-0.09-0.09)	0.02 (-0.07-0.10)
Gait Speed Score (0-4)	C2: "Healthy"	Ref	Ref	Ref
	C1: "Sleep Disturbed"	-0.21 (-0.29--0.13)	-0.12 (-0.20--0.04)	-0.11 (-0.19- -0.03)
	C3: "Mild Fragmentation"	-0.07 (-0.14-0.01)	-0.04 (-0.12-0.03)	-0.04 (-0.11-0.04)
	C4: "Earlier L5 midpoint"	-0.19 (-0.39-0.00)	-0.08 (-0.28-0.11)	-0.06 (-0.26-0.13)
	C5: "C1 with Shorter, Less Disrupted Sleep"	-0.05 (-0.14-0.04)	0.00 (-0.08-0.1)	0.01 (-0.07-0.10)

Chapter 3, in part, is currently being prepared for submission for publication of the material. Garduno, Alexis C.; Viswanath, Varun; Smarr, Benjamin; McEvoy, Linda K.; Xiao, Qian; Full, Kelsie; Gallo, Linda; Parada, Humberto; Crandall, Carolyn; Cauley, Jane; Tinker, Lesley F.; LaCroix, Andrea Z. The dissertation author was the primary researcher and author of this material.

4. **Bayesian Network Analysis of Rest-Activity Rhythms, Alzheimer's Disease and Dementia among Diverse Older Women in the Women's Health Initiative**

4.1   Abstract

Importance: Circadian disturbances have been observed in those diagnosed with Alzheimer's Disease (AD) and those without dementia with AD pathology. It is unknown the extent to which these results are confounded by other sleep measures.

Objective: To simultaneously evaluate the relationships between multiple sleep and circadian disturbance measures with all cause dementia in a diverse population of older women.

Design, Setting, Participants: Prospective cohort study of older women with accelerometry from baseline AD (2012-2013), linked to genetic and Centers for Medicare and Medicaid Services (CMS) claims-based (1991-2020) databases. The setting was community-dwelling participants from the Women's Health Initiative (WHI) Objective Physical Activity and Cardiovascular Health (OPACH) Study. Participants were ambulatory older women who were cognitively healthy at baseline.

Methods: Multivariable Cox proportional hazard models allowed for estimation of associations between sleep-RAR, dementia, and AD. Bayesian network models were constructed to identify direct and indirect sleep-RAR associations with AD and dementia using a bootstrapped model with 1,000 iterations. We simulated the intervention effect of sleep behavior changes, including improving inter-daily stability and lowering intra-daily RAR fragmentation, using do-calculus.

Results: Activity counts from the most active 10-hour period (M10 activity) (Q4, HR=1.91 (95%CI: 1.43-2.56), p <0.001) and the M10 period start time (Q2, HR: 0.72 (95%CI: 0.56-0.92), p=0.048) were inversely associated with incident dementia after full adjustment.

Individuals with an M10 start time prior to 8:56am were at lower risk for incident dementia. Individuals with less stable RARs (Q1) had a greater hazard of incident AD (HR, Q1: 1.15 (95% CI: 1.15 (1.02-1.29), p=0.03). M10 activity was a robust central hub (dementia: degree centrality=14, betweenness centrality=117, Kleinberg hub score=1.0) that bridged the sleep, dementia, and AD networks. The potential causal odds ratio for the total indirect association between intra-daily variability (IV) (Q1 to Q4) and AD was OR = 1.40 (95%CI:1.22-1.60), and the potential causal odds ratio for the total indirect association between IV(Q1 to Q4) and dementia was OR = 1.85 (95% CI: 1.57-2.19). Similar, indirect associations were observed between inter-daily stability (IS), AD, and dementia, although the strength of these associations was weaker.

4.2   Introduction

Dementia is a clinical syndrome defined as the acquired loss of cognitive abilities in two or more domains of sufficient severity to interfere with daily activities that is caused by brain disease or injury [127]. Alzheimer's Disease (AD) is the most common neurodegenerative form of dementia [127] and leads to worsening of memory, thought processes, and functional health [128]. In 2022, an estimated 6.5 million adults in the United States were reported as living with AD, with 75% of this population aged 75 years and older [129]. Black and Hispanic older adults have higher age-adjusted incident rates of dementia than Non-Hispanic white older adults [130], yet these race and ethnic groups are underrepresented in dementia research [131].

Older adults exhibit more fragmented sleep rhythms as they age, and they undergo a shift in their preferred waketime to a "morning lark" chronotype among other age-related changes [132]. Sleep rhythms are recurring, twenty-four-hour patterns governed by the suprachiasmatic nucleus (SCN) in the hypothalamus, and the SCN entrains other physiological clocks [133].

Sleep rhythms are further modified by light exposure, quality and timing of physical activity and meal consumption, and genetics among other factors [31]. Sleep rhythms, such as stability and synchrony, can be considered modifiable behaviors that may be associated with lower dementia risk.

Studies evaluating associations between objectively measured sleep and AD have focused largely on sleep macroarchitecture (e.g., sleep duration, efficiency) and microarchitecture, and not circadian disturbances [134-137]. Circadian disturbances have been observed among those with preclinical AD (i.e. those who have evidence of AD pathology but do not have dementia)and to further worsen with progression of mild cognitive impairment (MCI), a prodromal stage of AD [138, 139], although these studies did not consider the role of other sleep metrics. A recent study in the Women's Health Initiative observed a prospective association between weakened RARs and probable dementia; this study was conducted in predominantly white older women [93].

There is a growing shift to modeling multiple dimensions of sleep and circadian behaviors simultaneously [140, 141]. Regression-based approaches may be limited in characterizing multivariate relationships [142]. Structural learning of a network is an alternative approach that can be used to identify the network of relationships between correlated risk factors for dementia, and this approach can assist with identifying pathways for intervention and/or future study between sleep and cognition [143].

This study was aimed at disentangling associations between objectively measured sleep and rest-activity characteristics with all cause dementia and AD using Medicare Claims data. Bayesian network (BN) models allowed us to simultaneously evaluate multivariate associations between multiple sleep and circadian metrics and dementia and identify potential indirect effects.

Utilizing claims data allows for retention of a larger population of Black or Hispanic/Latina older women with accelerometry data.

4.3   Methods

Study Population:

The Objective Physical Activity and Cardiovascular Disease Health in Older Women (OPACH) Study is a prospective, ancillary study of the WHI that defined the cohort for our secondary analysis [90]. In brief, a total of 6,489 ambulatory women consented to participate in the OPACH study from 2012-2013 and wore a GT3X+ accelerometer (ActiGraph LLC, Pensacola, Florida) for up to 7 days. In this study, we excluded 345 women for whom we could not obtain RAR metrics from our accelerometry data using our script. We also excluded 450 women with greater than 50% of the epochs did not meet data processing standards. Research technicians scored a subset of sleep duration periods as a part of another secondary analysis [91]. Manual scoring is a validated approach for determining sleep intervals and reduces misclassification of wake-sleep periods. An additional 1,151 women were excluded if these technicians had not performed manual sleep scoring (Figure 4.1). Manual scoring was not performed if an accompanying sleep log was absent, the GT3X file was missing, or there was no night accelerometry wear time. Additionally, these technicians did not perform scoring for women who did not have measured cardiometabolic biomarkers.

After performing accelerometry-related exclusions, we excluded 263 individuals with no enrollment records available in the CMS dataset. Next, we required that OPACH participants be enrolled in either Medicare Part A, Part B, or A and B for at least 50% of the eligible follow-up period until the date of dementia/AD diagnosis or date of death, resulting in the exclusion of 171 women. Of note, approximately half of the OPACH population was insured under an HMO at

some point during follow-up. Periods of enrollment under an HMO are treated as missing since HMO claims and subsequent disease history are not fully captured during these enrollment periods. We adopt a more inclusive approach with enrollment to understand sleep, dementia, and AD risk in a representative, diverse population of older adults [144]. Requiring continuous enrollment would potentially exclude women with slight lapses in enrollment. Of the remaining 4,109 women, we excluded those with prevalent dementia and AD (n=206), in order to ensure that the sample was cognitively healthy at baseline. The final analytic sample after these exclusions was 3,873 women.

Sleep and Rest-Activity Measures:

Multiple sleep and RAR measures were chosen to represent each sleep domain based on the RUSATED model; the RUSATED model identifies sleep by the following domains: regularity, duration, timing, alertness/sleepiness, and satisfaction/quality [24]. Rest-activity rhythm (RAR) measures were calculated using non-parametric models for sleep-activity data using previously described methods [92, 93]. These regularity and timing measures included intra-daily variability (IV), inter-daily stability (IS), average hourly activity during five consecutive hours with the lowest activity (L5), the average hourly activity during the 10 consecutive hours of the day with the highest activity (M10), and several L5 and M10 timing markers, including L5 start, L5 midpoint, M10 start, and M10 midpoint. Higher IV corresponded to higher rhythm fragmentation during the day, as evidenced by napping or nighttime awakenings, whereas higher IS corresponded to higher rhythm stability, or less variability between RARs between days.

Sleep duration (hours) was processed from ActiLife version 6.11 software. First, the activity from the accelerometer was sampled at 30 Hz and aggregated into 60-second Agilegraph

Date Files (ADF). Individual ADF files were scored using a standard protocol by a trained technician that identified sleep periods. These technicians used participant's sleep logs and a visual review of the data for each night the participant wore the device [91]. Identification of these sleep periods aligned with the actigraphy method guidelines from the Society of Behavioral Sleep Medicine [94, 95]. Additional subjective sleep measures were collected during the LLS home-visit, or the most recent preceding WHI questionnaire assessment, including sleep quality, daytime sleepiness, and napping.

Outcome Measures:

We leveraged the Centers for Medicare and Medicaid Services Chronic Condition Data Warehouse with claims from 1991-2020 [145] to identify incident dementia and AD cases after OPACH baseline (2012-2013) through 2020. We classified women with at least one inpatient or outpatient diagnosis code with dementia or AD using the Bynum algorithm [146, 147], respectively - (see Supplement 1-2 for ICD codes included for each outcome), or as having a prescription for donepezil, rivastigmine, galantamine, or memantine [148, 149]. This Bynum algorithm definition of dementia had a sensitivity of 79%, specificity of 88%, positive predictive value of 50%, and negative predictive value of 97% among patients who were continuously enrolled for the one-year study period in Medicare Parts A and B [146]. The accuracy of this definition would be 86% assuming dementia prevalence was 20%.

Covariates:

Covariates were ascertained at the Long-Life Study (LLS) home-visit and the most recent WHI questionnaire assessment preceding accelerometry measurement. These covariates were selected based on domain knowledge of confounding or mediating factors in the association between sleep and dementia/AD for survival and network models as appropriate. Specifically,

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social behavioral factors (e.g., smoking status and alcohol use) [150, 151], and cardiometabolic conditions [91, 152] may directly or indirectly influence the relationship from sleep and RAR to cognitive outcomes, respectively.

Age was represented as continuous in years; race and ethnicity were defined as Black, Hispanic/Latina/Latino, non-Hispanic white, and education was defined as high school/GED; some college; college graduate or greater. Type 2 diabetes, cardiovascular disease, and depression were defined in all models as the presence or absence of the disease using self-reported history at baseline. The behavioral factors were defined the same across models, including smoking status (current/non-smoker) and alcohol use (non-drinker; <1 drink per week; ≥1 per week), with the exception of physical activity. In survival analyses, physical activity was modeled continuously as total physical activity in minutes.

Women were classified as having low (SPPB: 0-8) or high physical functioning (SPPB: 9-12) using the short physical performance battery (SPPB) that was measured during the LLS visit [99, 153]. In both models, social support was ascertained using the 9-item version of the Medical Outcomes Study Social Support Survey (MOS) [154]. Sleep medication use was categorized as not in the past month or less, less than once per week, and 1+ times per week. Body mass index (BMI) was categorized into the following groups: <25.0, 25.0 to 29.9, and ≥30.0 kg/m^2. Several markers used for diagnosing metabolic syndrome were included in the BN network as possible mediating factors, where each cardiometabolic marker was categorized according to this harmonized definition [155]. For example, elevated triglycerides were defined as ≥150 mg/dL; reduced HDL was defined as <50 mg/dL. Elevated fasting glucose was defined as having ≥100 mg/dL, whereas elevated blood pressure was defined as having systolic blood pressure (BP) ≥130 and/or diastolic BP ≥85 mg/dL.

<u>Statistical Analyses:</u>

Descriptive statistics characterized the sociodemographic, behavioral, and health characteristics for the overall population and stratified by quartiles of M10. We estimated associations between individual sleep and sleep rhythm metrics and incident dementia/AD using cox proportional hazard models. Models were progressively adjusted for confounding variables, including age, race-ethnicity, education, general health, alcohol use, smoking status, accelerometer-measured minutes of physical activity, cardiovascular disease, diabetes, BMI, sleep medication use, social support, and physical functioning. We tested for the presence of a statistical interaction between the rest-activity activity metrics and *APOE4* (ε4 carrier/ versus non-carrier) by including RAR* *APOE4* term in the survival models; an interaction was identified using a p-threshold of 0.05. We hypothesized that protective associations between healthy rest-activity metrics and AD or dementia would be stronger among APOE4 non-carriers compared to APOE4 carriers based on prior literature review.

<u>Bayesian Network Analysis:</u>

A BN analysis is a statistical model that represents multivariate relationships between variables. In epidemiological research, a directed acyclic graph is a specific type of graph used to formulate scientific hypotheses and can be used to identify and communicate confounding variables for adjustment. Similarly, a graph identified by a BN analysis can be constrained to prevent feedback loops, and these graphs can be undirected, partially directed, or directed. Each sleep feature, cognitive outcome, and covariate (e.g., depression, smoking status, CRP, fasting glucose) is represented as a node; edges are (direct and indirect) paths that connect each node and represent dependencies. For example, the absence of an edge between two nodes represents that these nodes are conditionally independent from other variables entered into the BN model.

A BN identifies dependencies and conditional independence between variables and can be written out as a joint probability of the conditional probabilities with the following form:

$$\Pr(X|M) = \prod \Pr(Xi|p(Xi))$$

where X comprises the set of variables (e.g., X_1 = intra-daily variability, X_2 = social support) input into the BN model M. Within this graph, nodes can represent continuous or categorical variables, and the corresponding probability distribution can be estimated by regression methods including multivariate Gaussian or non-parametric distributions for continuous, or multinomial distributions for categorical variables. There can be more than one graph that matches the dependencies represented in a BN; in other words, two or more directed graphs may have the same Markov properties and be Markov equivalent. It is also possible for Markov graphs to identify hypothetical causal networks by artificially modeling the counterfactual within each individual in the population and then estimating the potential causal relative effects.

We have chosen to undertake network analysis (using *bnlearn* R packages [156]) to characterize pathways in which sleep disturbances, insomnia, and sleep fragmentation directly influence development of dementia/AD. This network model may further identify which sleep features, such as sleep fragmentation or shortened sleep duration, are central in the dementia/AD network and bridge pathways between known risk factors, such as alcohol use, smoking status, and/or depression, with development of dementia/AD. We also hypothesized that there may be additional, indirect connections between sleep fragmentation and shortened sleep duration with dementia and/or AD through cardiometabolic factors, including body mass index, diabetes, or cardiovascular disease. First, we fit BN models to examine multivariate relationships between sleep and RAR metrics with incident dementia and AD. We fit separate BN models for each outcome, in order to examine incident dementia and AD. Within BN models, the incident

outcomes were operationalized as dementia or AD within 9 years of follow-up (yes/no).

Individuals who died prior to the end of follow-up and had not developed the outcome were

censored from network models. Based on domain knowledge, we constrained the BN network

model to prevent *age*, *race, and ethnicity, APOE4,* and *education* from having other nodes as

parents. The outcomes of *dementia* and *AD* were constrained to prevent these outcomes from

parenting any other nodes in the network.

We implemented the score-based tabu algorithm in *bnlearn* [156] to construct sleep-

dementia/AD networks using a two-step process: the first step searches the space of penalized

likelihood scores to identify all possible acyclic causal relationships between variable pairs. The

second step performs a series of conditional independence tests to rule out possible edges. We

explored use of mutual information, Pearson's Chi-Squared, Fast Mutual Information, AIC, and

BIC [156]. Bootstrap resampling was performed to learn 1,000 network structures, which were

averaged to identify the consensus network, as this consensus network has better predictive

power than choosing a single high-performing network [157].

In addition, we characterized the stability of the inferred edges by calculating arc strength

and direction strength, which is the probability of the edge or direction occurring over the total

number of networks, respectively. Using the BN models, we report associations adjusted for the

Markov Blanket (e.g., the subset of variables or parents that directly influenced these outcomes).

For each edge from the averaged BN model, the parent node is an independent variable in the

BN model that predicts the child node and is conditionally independent of other non-parents.

Based on the edges identified in the exploratory BN models, we estimated direct effects and 95%

confidence intervals for associations between sleep parameters and incident dementia and AD

after conditioning on parents identified in the BN network using multinomial and logistic

regression as appropriate. Indirect effects were estimated using the *lavaan* package for structural equation modeling (see Supplementary Methods for additional details) by constructing mediation and outcome models adjusted for parents in the BN models. We estimated 95% confidence intervals for indirect effects using bootstrapped confidence intervals over 1,000 samples.

Simulating Sleep Behavior Change in Sleep-dementia/AD Networks:

With do-calculus within the *bnlearn* package using the cpquery function, we performed a simulation in the sleep-AD and sleep-dementia networks to estimate the average treatment effect of healthy sleep behaviors (e.g., strong sleep rhythmicity in the upper quartile) on dementia and/or AD, given the observed network structure between sleep and cognitive performance. This treatment effect can be estimated by specifying a conditional, intervention distribution (e.g.,). For example, the causal odds ratio (OR) was estimated by artificially exposing each individual to the treatment (e.g., quartile 4 of intra-daily variability) and also exposing each individual to the non-treatment (e.g., quartile 1 of intra-daily variability) using the following formula:

$$Causal\ OR_{AD} = \frac{P(Y_{AD}=1\,|do(A_{Q4}=1))\,/(1-P(Y_{AD}=1\,|do(A_{Q4}=1)))}{P(Y_{AD}=1\,|do(A_{Q4}=0))\,/(1-P(Y_{AD}=1\,|do(A_{Q4}=0)))}$$

where $do(A_{Q4}=0) = do(A_{Q1}=1)$, since the reference is the lowest quartile of the IV exposure. We estimated 95% confidence intervals by performing bootstrapping with 200 samples. Based on the edges identified in the BN models, we estimated the potential causal OR for IV (treatment=Q4 vs. Q1), IS (treatment=Q1 vs. Q4), and M10 activity (treatment=Q4 vs. Q1).

4.4   Results

WHI Population Characteristics

The primary analytic sample comprised 3,873 women who were an average of 79 (±6.61) years old, of whom 32.3% self-identified as Black, 15.7% self-identified Hispanic/Latina, and

52.0% self-identified as white (Table 4.1). These women predominantly had graduated or completed some college (79.7%), were non-smokers (97.2%), and were non-drinkers or infrequent drinkers (71.5%). The mean BMI of these women was 28.01 (±5.59), with 19.8% reporting physician-diagnosed diabetes and 9.7% reporting physician-diagnosed cardiovascular disease (CVD). Depression was prevalent in 6.4% of the population, and cancer was reported in 17.2%., and 74.7% of the population reported no sleep medication use in the past month or less. In terms of overall health, a majority of participants reported to be in good to excellent health (90.6%), with moderate reported physical functioning scores averaging 68.80 (±25.87) and lower social support averaging 37.26 (±7.83; range=9-45).

RAR-Stratified Population Characteristics

IS quartiles ranged from 0.08-0.41 (Q1), 0.42-0.49 (Q2), 0.49-0.56 (Q3), and 0.56-1.00 (Q4); IV quartiles ranged from 0.36-0.92 (Q1), 0.93-1.09 (Q2), 1.10-1.29 (Q3), and 1.30-2.38 (Q4). L5 quartiles ranged from 0.10-5.75 (Q1), 5.76-8.40 (Q2), 8.41-12.36 (Q3), and 12.37-90.63 (Q4). M10 quartiles ranged from 11.35-80.34 (Q1), 80.35-108.954 (Q2), 108.95-143.53 (Q3), and 143.54-495.36 (Q4). The start of the M10 period (M10 Start) ranged from 12am-6:57am (Q1), 6:58am-7:54am (Q2), 7:55am-8:55am (Q3), and 8:56am-11:59pm (Q4). Compared to women in the lowest M10 quartile, women in the highest M10 quartile were more often <80 years old (33.0% vs. 69.9%), had more physical activity, had higher physical functioning, and reported more frequent alcohol consumption (Table 4.1). Those in the highest M10 quartile were more likely to report being in excellent or very good health and less often had diabetes, cardiovascular disease, or cancer at baseline (Table 4.1).

Time-to-Event Analysis of Dementia and AD

M10 activity counts and the M10 start time were inversely associated with incident dementia after full adjustment (Table 4.2). Individuals in the first quartile (11.35-80.34 activity count) had 1.91 times the risk of incident dementia compared to individuals in the fourth quartile (143.54-495.36 activity count) of M10 activity counts (Hazard Ratio, HR=1.91 (95% CI: 1.43-2.56)). Individuals whose M10 activity period started prior to 8:56am were at lower risk for incident dementia as compared to those whose M10 activity period started after 8:56am. For example, the HR for individuals whose M10 activity period started from 6:58am-7:54am was 0.72 (95%CI: 0.56-0.92), and the M10 activity period that started from 7:55am-8:55am had a similar yet slightly weaker association (HR: 0.78 (95% CI: 0.61-1.00)). The associations for the M10 start and midpoint were similar with respect to dementia risk.

IV was inversely associated with incident dementia after adjustment for all covariates in the fully adjusted model (except for physical activity), and this observed association was largely driven by differences between quartile 4 and 1 (HR,Q2: 0.93 (95%CI: 0.72-1.21), HR,Q3: 1.02 (95%CI: 0.79-1.31), HR,Q4: 1.30 (95%CI: 1.01-1.68; p=0.04); this association was attenuated when adjusted for physical activity (omnibus p=0.16).

IS was inversely associated with incident AD, and individuals with the least stable RARs (Q1) had a greater hazard of incident AD (HR,Q1: 1.15 (95% CI: 1.15 (1.02-1.29)) as compared to those with the most stable RARs (Q4). IV was positively associated with incident AD prior to adjustment for physical activity. There was also evidence of a linear trend between IV and AD prior to adjustment for physical activity (Table 4.2). Similarly, M10 activity count was also inversely associated with incident AD prior to adjustment for physical activity.

There were no statistical interactions between RAR metrics and APOE4 carrier status with respect to either outcome after full adjustment (p > 0.05, results not shown).

Sleep-RAR Hubs and Subnetworks for Dementia

In this section, we describe subnetworks within the sleep and dementia network model. We also identify "parent" variables that directly influence incident dementia. After 9 years of follow-up from time of accelerometry, we observed 525 incident dementia cases and 439 deaths; the 439 deaths were censored from the BN model. In the sleep and dementia network, there were several direct edges with incident dementia at 9 years follow-up in at least 50% of the 1,000 bootstrapped network models, including M10 activity, body mass index, and age group (≥80 Years; Figure 4.2). M10 activity metric was the strongest hub in the sleep-dementia network, and the robustness of this hub was evidenced by multiple centrality measures (degree centrality=14, betweenness centrality=117, Kleinberg hub score=1.0), although the closeness centrality metric was weak compared to other nodes in the network (closeness centrality=0.02). M10 activity metric was directly connected to 14 other nodes including dementia (degree), lay on many of the shortest paths between nodes (betweenness), and M10 activity was the best possible hub across the network (Kleinberg hub score). M10 activity metric was not particularly close to other nodes in the network compared to other nodes (closeness centrality). M10 activity metric had a large Markov *blanket comprising IS, IV, total sleep time, L5, L5 start, M10 midpoint, sleep latency, age, race and ethnicity, educational attainment, CVD, BMI, lipid medication, general health, physical functioning, and HDL*, indicating its specific influence on other nodes. M10 activity metric was independent of all other variables conditional on this Markov blanket.

There were several different nodes that emerged as moderate hubs after M10, which included general health (degree=11, betweenness=50, Kleinberg hub=0.72), alcohol use, (degree= 7, betweenness= 44, Kleinberg hub=0.14) IS (degree=6, betweenness=66, Kleinberg hub=0.23), and IV (degree=6, betweenness =46, Kleinberg hub=0.14). Similar to M10, IS had

overlapping Markov blankets that included other RAR metrics (*IV*, *total sleep time*, *L5*, *L5 start*, *M10 midpoint*) and sociodemographic characteristics (*age*, *race, and ethnicity*). IV and IS both had M10 and age in their Markov Blanket. There were some differences between the Markov Blankets between IS and IV. For example, IV was conditionally independent of all other variables after conditioning on *IS*, *M10*, *M10 midpoint*, *sleep latency*, and *age*. IS was conditionally independent after conditioning on *IV*, *L5*, *M10*, *M10 start time*, *M10 midpoint*, *L5 start*, *L5 midpoint*, *race and ethnicity*, and *cancer*. When examining the sleep subnetwork, there was considerable overlap in the RAR nodes appearing in each other's Markov Blankets.

Sleep and AD Network

Overall, the sleep and RAR sub-networks were similar for the sleep-dementia and sleep-AD networks, although there were some subtle differences in the sub-networks between RAR and AD (Figure 4.3). A key difference was that a direct edge connecting M10 activity and AD was not present in at least 50% of the models, although this edge existed in the sleep-dementia network (Figure 4.3). Instead, M10 was indirectly associated with AD through physical functioning. There were direct edges between age group, APOE4, and physical functioning with AD. IV and IS were indirectly associated with AD through physical functioning.

In the sleep-AD network, M10 remained a primary hub, yet the M10 hub was not as dominant in this network, and was more closely tied with age group, ethnicity, and general health in the sleep-AD network (Figure 4.3). In contrast to the sleep-dementia network, a path between ethnicity and education opened up with the AD outcome through general health, which is the parent of physical functioning in the sleep-AD network. Another path between M10 activity and AD opened through the general health node.

L5 start time had the most unique Markov Blanket compared to all other sleep timing metrics, including *IS, L5, M10, L5 midpoint, age, race, and ethnicity, APOE4 carrier status,* and *education*. The Markov Blanket for other sleep timing blankets were relatively small and primarily included RAR metrics and occasionally *age* as well as *race and ethnicity*. Another key difference is that the L5 start is the only sleep metric that is parented by APOE4, and this direct edge is only present in the AD network.

BN-Derived Associations between Sleep-RAR, Dementia and AD

We report associations that were adjusted based on the structure identified by the BN network in this section (Table 4.3). Higher quartiles of M10 were strongly associated with incident dementia ($M10_{Q4}$ OR: 0.35 (95%CI: 0.27-0.46)) and AD ($M10_{Q4}$OR = 0.36 (95%CI: 0.27-0.49)) after adjustment for the Markov Blanket (Table 4.3). Note, an edge was observed between M10 and the outcome in 89% of models for dementia and in 26% of models for AD, which indicates lower confidence in the M10 edge in the AD model (Table 4.3). Based on the Markov property, we observe that IV and IS were indirectly associated with incident dementia and AD through M10 (P[M10|IS+ IV]). The odds of incident dementia mediated by M10 were 1.07 times higher (OR=1.07 (95%CI: 1.05-1.09) among individuals in the highest quartile of IV compared to individuals in the lowest quartile of IV). There was also suggestion of a linear trend for intra-daily variability and AD (IV_{Q2} OR : 1.01 (95%CI: 1.01-1.02), IV_{Q3} OR: 1.02 (95%CI: 1.02-1.03), IV_{Q4} OR: 1.04 (95%CI: 1.02-1.05); Table 4.3). There was a weak indirect effect between IS, dementia, and AD.

Simulated RAR Intervention on AD or Dementia

There was a protective treatment effect observed at higher M10 quartiles for both incident dementia and AD after 9 years of follow-up in the simulated experiment. The potential

causal OR for the association between M10 and AD was 0.59 (95%CI: 0.51-0.68), whereas the potential causal OR for the association between M10 and dementia was 0.32 (95%CI: 0.25-0.42) (Table 4.4). A harmful treatment effect was observed for both intra-daily variability and inter-daily stability in relation to incident AD and dementia (Table 4.4). On average, older women who moved to the highest intra-daily variability quartile would have 1.40 times the odds of developing AD compared to if they remained in the lowest intra-daily variability quartile (OR=1.40 (95%CI: 1.22-1.60); Table 4.4). The potential causal ORS for inter-daily stability and AD and dementia were 1.07 (95%CI: 0.95-1.20) and 1.29 (95%CI: 1.14-1.48) (Table 4.4), respectively.

4.5   Discussion

We have identified several interconnected sleep and RAR measures that were associated with incident dementia and AD among a population of diverse older women. The BN model identified M10 as a mediator between IV and IS with dementia and AD. Artificially intervening on M10 showed a protective treatment effect for both incident dementia and AD, and artificially intervening on the IS and IV showed a harmful treatment effect for incident dementia and AD. In time-to-event analyses, IS and IV were associated with incident AD only. Associations observed from time-to-event analyses for M10 were directionally consistent with the BN models.

As demonstrated in this current work, BN networks can address existing challenges in sleep research: BN models allowed for disentangling the influence of highly correlated sleep measures. BN models also characterized the key list of parents (e.g., exposures) that directly influenced the child (e.g., outcome) nodes. For example, BN models identified that incident dementia and AD were conditionally independent of all other modeled comorbidities, depression, and alcohol use, given M10, BMI, age, APOE4, and race-ethnicity.

Our findings are consistent with other prospective cohort studies examining associations between objectively measured RARs and dementia [35, 93]. A prior study was conducted among predominantly white older women who had completed both the OPACH and WHI Memory Study (WHIMS) with available accelerometry and telephone-administered cognitive assessments [93]. This OPACH study similarly observed that lower M10 was associated with higher risk for incident MCI and probable dementia [93]. This study expanded on this prior work through incorporation of the CMS claims data to further explore the generalizability of these findings to a more diverse population of Black and Hispanic/Latina older women.

The midpoint of M10 was also associated with MCI and probable dementia, in contrast to this present study that observed no association with any sleep timing parameters. Some studies have observed an association between L5 timing and dementia. For example, an earlier "lights out" time, which may be most comparable to our L5 timing measures, was associated with higher dementia risk in the Rotterdam Study, although no association was observed between IS or IV with dementia [37]. Another study among older community-dwelling women in the Study of Osteoporotic Fractures demonstrated that earlier L5 timing was associated with higher dementia risk based on a test for trend [35].

Findings from the time-to-event analyses are consistent with existing literature with respect to the handful of prospective cohort studies with objectively measured RAR metrics and clinician-diagnosed AD, which have more often shown direct effects between IV and the closely related measure of napping duration or frequency with AD risk [158, 159]. We may not have observed an association with napping since the napping measure evaluated was based on self-report, in contrast to objectively estimating daytime naps. In two Rush Memory and Aging project studies, longer and more frequent napping [159], higher IV, and lower inter-daily

variability were associated with higher AD risk [158]; the non-parametric sleep rhythm measures (e.g., IV and IS) were associated with incident conversion from MCI to AD [158].

In addition, this study identified the M10 activity component of the RAR model as predictive of lower dementia and a potential mediator in the influence of sleep on dementia and AD risk. However, the literature is mixed with respect to whether physical activity is associated with dementia, with several studies, including a systematic literature review, concluding that studies of physical activity and dementia with less than 10 years of follow-up are more likely to observe an association as compared to studies with follow-up longer than 10 years [160, 161]. These studies that observed no association between physical activity and dementia commonly utilized self-reported physical activity. Nevertheless, several studies with long-term follow-up have demonstrated associations between physical activity with incident dementia [162-164]. Another study examining questionnaire-based physical activity at midlife observed strong protective associations for dementia and AD, with a stronger protective effect of physical activity observed among APOE e4 carriers [163]. Lastly, this study in OPACH also observed associations between moderate intensity stepping and lower mild cognitive impairment and dementia risk [164].

There were several key strengths. For example, sleep and RAR metrics were measured objectively for one week, and these co-exposures preceded the outcome temporally. Another strength in exposure-disease ascertainment was that dementia and AD were tracked in the claims data for nearly one decade following the sleep measurement. Construction of a network model also allowed for the examination of related sleep parameters simultaneously; simultaneous identification allowed us to determine which rest activity metric was most influential in the behavioral network. Modeling of indirect relationships revealed that disrupted sleep may be

acting on dementia and AD risk through physical activity. Lastly, this study was designed to maximize diversity of the study population of older women and subsequently generalizability; identification of dementia and AD from the CMS claims data allowed us to retain the diversity of the original OPACH sample (32.2% Black and 15.7% Hispanic/Latina).

This study was not without limitations. While BN models are capable of detecting potential causal relationships, identification of these direct relationships assumes that there are no unmeasured factors that may influence the structural BN model. In addition, the current BN model does not allow for the presence of feedback loops between factors and assumes an acyclic BN structure; additional work may explore the application of dynamic BN models to account for the cyclic relationships. In this work, we chose not to utilize the dynamic BN model for estimating time-varying risk models, since many of the participant characteristics were measured at the same timepoint, specifically baseline, with the exception of the dementia and AD outcomes [165].

Moreover, we included a term for race and ethnicity in our model to begin exploring identification of health disparities in dementia and AD incidence. We advise cautious interpretation of the race and ethnicity term in the BN model, since race and ethnicity are social constructs that maybe potentially useful for health surveillance and detecting health disparities, but race and ethnicity definitions are imperfect measures, and this BN model does not account for other important characteristics that affect health and quality of care, including language preference, place of birth, and other social determinants of health [166]. The conditional probability distribution for dementia and AD showed that AD was directly influenced by M10 along with race and ethnicity and was independent of other measured sociodemographic and behavioral factors. Nevertheless, the purpose of these models is for evaluating potential

associations and differences in health outcomes between groups and are not developed for the purpose of prediction.

The present study showed that M10 was strongly associated with incident dementia and AD risk among a diverse population of older women. These results suggest women with more irregular sleep patterns are more likely to develop incident AD as compared to women with more regular sleep patterns due to the indirect influence of sleep on M10 activity. Future studies may further explore sleep-AD network modeling with additional physical activity metrics; M10 activity could be replaced with other physical activity metrics (e.g., steps per day, MVPA, etc.) to further characterize indirect pathways from sleep through steps per day or MVPA on dementia and AD. Another future direction is to explore potential associations between APOE4 carrier status and sleep timing measures, in order to understand whether APOE4 may be potentially influencing sleep timing. Development of additional measures of circadian disturbance may also be worth exploring in public health research.
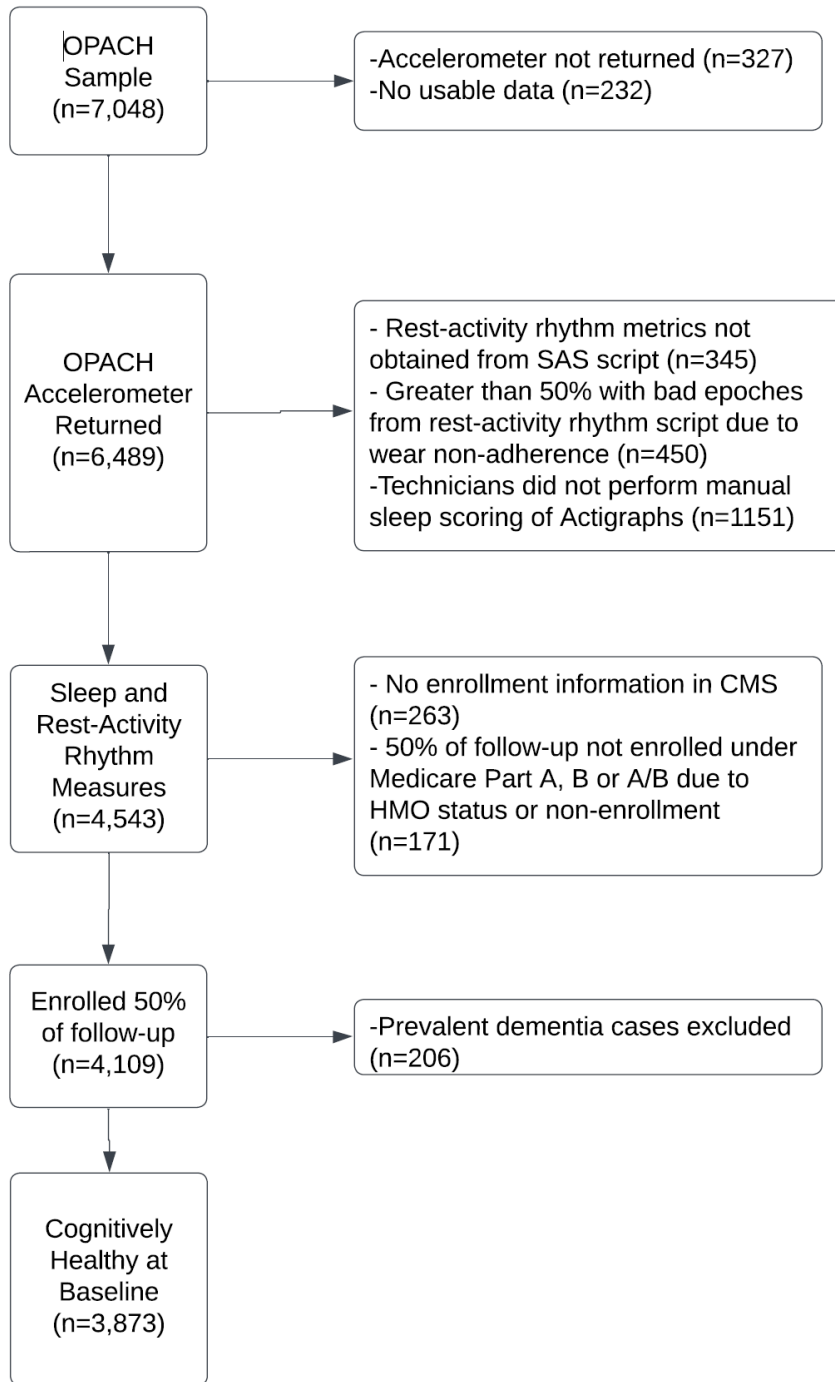
Figure 4.1. Flow diagram: Women's Health Initiative
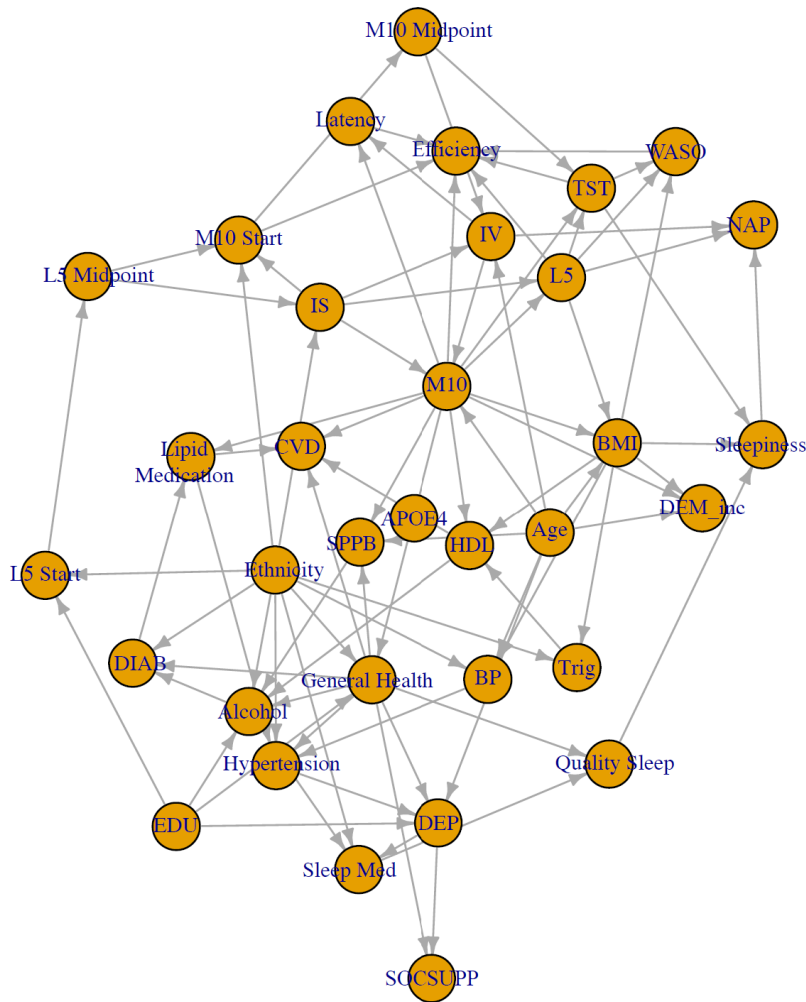
Figure 4.2. Sleep-RAR and Dementia Bayesian Network

Arrows are visualized if they occur in 50% of the bootstrapped network model run over 1,000 iterations. Note, the smoking node and cancer did not have edges that went into the network; this node still exists in the network, yet no other nodes connected to smoking in more than 49% of the network models for the bootstrapped network model.

Abbreviations: AD = incident Alzheimer's Disease at 9 years; APOE4 = APOE4 carrier status (yes/no); IS = inter-daily stability quartiles; IV = intra-daily variability quartiles; L5= L5 activity count quartiles; L5 Start = start time of L5 period quartiles; L5 Midpoint = midpoint time of L5 period; M10= M10 activity count quartiles; M10 Start = start time of M10 period quartiles; M10 Midpoint = midpoint time of M10 period; TST = total sleep time; WASO = wake after sleep onset; Efficiency = sleep efficiency; Latency = Sleep Latency; Quality Sleep = quality sleep; Sleepiness = daytime sleepiness; Nap = daytime napping; DEP = depression; Education = educational attainment; General Health = general health categories; Alcohol Use = alcohol use; Sleep Med = sleep medication; BP = blood pressure medication; Lipid Med = lipid medication; DIAB = diabetes; Hypertension = hypertension medication; Ethnicity= race and ethnicity; Trig = triglycerides; HDL = HDL; BMI = BMI category; SPPB = physical functioning; Age (continuous); SOCSUPP = social support

Figure 4.3. Sleep-RAR and AD Bayesian Network

Arrows are visualized if they occur in 50% of the bootstrapped network model run over 1,000 iterations.

Abbreviations: AD = incident Alzheimer's Disease at 9 years; APOE4 = APOE4 carrier status (yes/no); IS = inter-daily stability quartiles; IV = intra-daily variability quartiles; L5= L5 activity count quartiles; L5 Start = start time of L5 period quartiles; L5 Midpoint = midpoint time of L5 period; M10= M10 activity count quartiles; M10 Start = start time of M10 period quartiles; M10 Midpoint = midpoint time of M10 period; TST = total sleep time; WASO = wake after sleep onset; Efficiency = sleep efficiency; Latency = Sleep Latency; Quality Sleep = quality sleep; Sleepiness = daytime sleepiness; Nap = daytime napping; DEP = depression; Education = educational attainment; General Health = general health categories; Alcohol Use = alcohol use; Sleep Med = sleep medication; BP = blood pressure medication; Lipid Med = lipid medication; DIAB = diabetes; Hypertension = hypertension medication; Ethnicity= race and ethnicity; Trig = triglycerides; HDL = HDL; BMI = BMI category; SPPB = physical functioning; Age (continuous); SOCSUPP = social support

Table 4.1. Baseline Characteristics in OPACH and Stratified by M10 Quartiles (n=3,873)

Mean, standard deviation, and proportions were reported across stratum of M10 quartile. Differences in characteristics across categories were determined using Chi square tests for proportions and ANOVA for continuous variables.

		M10 Quartiles				
	Total	Quartile 1 (n=967)	Quartile 2 (n=967)	Quartile 3 (n=967)	Quartile 4 (n=967)	p-values
Age, yrs.; *mean (sd)*	78.83 (6.61)	81.99 (6.06)	79.39 (6.49)	78.12 (6.30)	75.83 (6.07)	<0.001
Age Groups, ≥80 Years; n (%)	1963 (50.7)	676 (69.9)	513 (53.1)	453 (46.8)	319 (33.0)	<0.001
Race-ethnicity; n (%)						<0.001
white	2013 (52.0)	583 (60.3)	500 (51.7)	489 (50.6)	439 (45.4)	
Black	1252 (32.3)	300 (31.0)	348 (36.0)	317 (32.8)	285 (29.5)	
Hispanic/Latina	608 (15.7)	84 (8.7)	119 (12.3)	161 (16.6)	243 (25.1)	
Education; n (%)						0.10
High School/GED	782 (20.3)	182 (18.9)	201 (20.9)	194 (20.3)	203 (21.0)	
Some College	1530 (39.7)	420 (43.6)	383 (39.9)	370 (38.6)	355 (36.7)	
College Graduate+	1540 (40.0)	361 (37.5)	376 (39.2)	394 (41.1)	408 (42.2)	
Self-Rated Health; n (%)						<0.001
Excel./Very Good	1973 (51.1)	325 (33.7)	469 (48.6)	540 (56.0)	637 (66.0)	
Good	1527 (39.5)	464 (48.1)	423 (43.8)	356 (36.9)	282 (29.2)	
Poor/Very Poor	364 (9.4)	175 (18.2)	73 (7.6)	69 (7.2)	46 (4.8)	
Physical Activity, total steps per day; *mean (sd)*	341.02 (97.75)	236.33 (59.73)	314.68 (52.63)	369.66 (60.30)	443.34 (73.01)	<0.001
Physical Function; n (%)						<0.001
Low (0-8 SPBB)	68.80 (25.87)	49.81 (26.50)	67.52 (24.09)	74.23 (21.66)	83.67 (17.66)	
Social Support; *mean (sd)*	37.26 (7.83)	36.67 (7.78)	37.12 (7.96)	37.39 (7.80)	37.84 (7.73)	0.02
Smoker Status, Smoker; n (%)	100 (2.8)	35 (4.0)	28 (3.2)	24 (2.7)	13 (1.4)	0.01
Sleep Medication; n (%)						0.02
Not in the past month or less	2644 (74.7)	621 (72.2)	674 (76.2)	666 (74.3)	680 (76.1)	
Less than once per week	304 (8.6)	67 (7.8)	69 (7.8)	77 (8.6)	90 (10.1)	
1+ times per week	591 (16.7)	172 (20.0)	141 (16.0)	153 (17.1)	124 (13.9)	
Alcohol Frequency; n (%)						<0.001
Non-Drinker	1311 (36.9)	391 (45.0)	344 (38.9)	309 (34.5)	265 (29.4)	
<1 per Week	1230 (34.6)	309 (35.6)	316 (35.7)	302 (33.7)	300 (33.3)	
≥1 per Week	1014 (28.5)	168 (19.4)	224 (25.3)	285 (31.8)	337 (37.4)	
BMI; *mean (sd)*	28.01 (5.59)	29.61 (5.98)	28.67 (5.55)	27.67 (5.31)	26.14 (4.89)	<0.001
Diabetes, yes; n (%)	766 (19.8)	260 (26.9)	228 (23.6)	162 (16.8)	116 (12.0)	<0.001
Cardiovascular disease, yes; n (%)	374 (9.7)	157 (16.2)	106 (11.0)	71 (7.3)	40 (4.1)	<0.001
Cancer, yes; n (%)	666 (17.2)	202 (20.9)	188 (19.4)	138 (14.3)	136 (14.1)	<0.001
Depression, no ; n (%)	3181 (93.6)	772 (92.1)	781 (93.0)	804 (94.5)	820 (94.6)	0.11
APOE4 non-carrier; n (%)	2359 (78.7)	155 (21.8)	156 (20.8)	159 (20.7)	168 (22.0)	0.90

Table 4.2. Hazard Model of Objectively Measured Sleep and Sleep Rhythm Metrics with All Cause Dementia and Alzheimer's Disease

The fully adjusted model was adjusted for the following covariates including age, race-ethnicity, education, self-rated health, physical function, alcohol consumption, smoking status, total minutes spent in physical activity, cardiovascular disease, diabetes, body mass index, sleep medications, physical functioning, and social support

| Sleep/Sleep | Category | Dementia (n=2947, events=525) | | | | AD (n=2947, events=333) | | | |
| | | Adjusted | | Adjusted + PA | | Adjusted | | Adjusted + PA | |
		HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Inter-Daily Stability	Q4	Ref	0.13	Ref	0.29	Ref	0.002	Ref	0.03
	Q1	1.28 (0.99-1.65)		1.19 (0.92-1.56)		1.21 (1.08-1.35)		1.15 (1.02-1.29)	
	Q2	1.31 (1.02-1.68)		1.26 (0.98-1.62)		1.20 (1.08-1.34)		1.17 (1.05-1.31)	
	Q3	1.23 (0.96-1.57)		1.20 (0.94-1.54)		1.13 (1.01-1.26)		1.11 (1.00-1.24)	
Intra-Daily Variability	Q1	Ref	0.04	Ref	0.16	Ref	0.001	Ref	0.05
	Q2	0.93 (0.72-1.21)		0.91 (0.70-1.18)		1.00 (0.90-1.11)		0.97 (0.87-1.09)	
	Q3	1.02 (0.79-1.31)		0.97 (0.74-1.26)		1.05 (0.94-1.17)		1.00 (0.89-1.12)	
	Q4	1.30 (1.01-1.68)		1.20 (0.91-1.59)		1.22 (1.09-1.37)		1.14 (1.00-1.29)	
L5 Activity Count	Q1	Ref	0.66	Ref	0.50	Ref	0.80	Ref	0.73
	Q2	0.99 (0.77-1.27)		1.00 (0.78-1.28)		0.96 (0.87-1.07)		0.97 (0.87-1.08)	
	Q3	1.06 (0.83-1.35)		1.08 (0.85-1.38)		0.96 (0.86-1.07)		0.98 (0.88-1.09)	
	Q4	1.14 (0.89-1.46)		1.18 (0.92-1.51)		1.00 (0.90-1.12)		1.03 (0.92-1.16)	
L5 Start	Q1	Ref	0.36	Ref	0.39	Ref	0.11	Ref	0.14
	Q2	0.92 (0.72-1.18)		0.92 (0.72-1.18)		1.08 (0.97-1.20)		1.08 (0.97-1.21)	
	Q3	1.14 (0.90-1.45)		1.12 (0.88-1.43)		1.15 (1.03-1.28)		1.13 (1.02-1.27)	
	Q4	1.09 (0.86-1.38)		1.09 (0.86-1.39)		1.08 (0.97-1.20)		1.09 (0.98-1.21)	
L5 Midpoint	Q1	Ref	0.97	Ref	0.94	Ref	0.25	Ref	0.34
	Q2	1.02 (0.81-1.29)		1.02 (0.81-1.29)		0.94 (0.84-1.05)		0.94 (0.84-1.05)	
	Q3	0.97 (0.76-1.23)		0.96 (0.76-1.22)		0.96 (0.86-1.07)		0.96 (0.86-1.06)	
	Q4	0.97 (0.76-1.25)		0.96 (0.74-1.23)		1.04 (0.93-1.17)		1.03 (0.92-1.15)	
M10 Activity Count	Q4	Ref	<0.001	NA		Ref	0.001	NA	
	Q1	1.91 (1.43-2.56)				1.24 (1.10-1.41)			
	Q2	1.46 (1.11-1.92)				1.10 (0.98-1.23)			
	Q3	1.22 (0.93-1.60)				1.00 (0.89-1.11)			
M10 Start	Q4	Ref	0.0495	Ref	0.048	Ref	0.58	Ref	0.54
	Q1	0.81 (0.64-1.03)		0.81 (0.64-1.03)		0.93 (0.83-1.04)		0.93 (0.83-1.04)	
	Q2	0.72 (0.57-0.92)		0.72 (0.56-0.92)		0.94 (0.84-1.05)		0.94 (0.84-1.05)	
	Q3	0.77 (0.60-0.98)		0.77 (0.60-0.98)		0.95 (0.85-1.06)		0.94 (0.84-1.05)	
M10 Midpoint	Q4	Ref	0.05	Ref	0.05	Ref	0.58	Ref	0.56
	Q1	0.82 (0.64-1.04)		0.82 (0.65-1.04)		0.93 (0.83-1.04)		0.93 (0.83-1.04)	
	Q2	0.72 (0.56-0.92)		0.72 (0.56-0.91)		0.94 (0.84-1.05)		0.94 (0.84-1.04)	
	Q3	0.78 (0.61-1.00)		0.78 (0.61-1.00)		0.95 (0.85-1.06)		0.95 (0.85-1.06)	

Table 4.3. Network associations and stability of rest-activity parameters, dementia, and Alzheimer's Disease

The RAR metrics are parents or predictors of the outcome based on the derived sleep-dementia and sleep-AD networks. Analyses adjusted for confounding variables identified in the BN model by identifying shared parents between the exposure and the outcome. Adjustment performed for confounding variables based on the BN model since associations are conditionally independent of all other variables depicted in the BN model. The indirect effects reported for IV and IS are the indirect effects of these sleep parameters acting through the M10 activity parameter on the outcome.

Outcome (Child)	Effect	Predictors (Parents)	Strength‡	Direction‡	Odds Ratio (95% CI) Sleep-Dementia Network
Incident Dementia	Direct	M10_Q2	0.89	1	0.61 (0.48-0.77)
		M10_Q3			0.50 (0.39-0.63)
		M10_Q4			0.35 (0.27-0.46)
	Indirect through M10	IV_Q2	0.89 (0.89*1)	0.99 (1*0.99)	1.02 (1.01-1.03)
		IV_Q3			1.04 (1.03-1.05)
		IV_Q4			1.07 (1.05-1.09)
	Indirect through M10	IS_Q2	0.88 (0.89*0.99)	1 (1*1)	1.06 (1.04-1.07)
		IS_Q3			1.03 (1.02-1.04)
		IS_Q4			1.02 (1.01-1.03)
Incident Alzheimer's Disease	Direct	M10_Q2	0.26	1	0.70 (0.53-0.91)
		M10_Q3			0.55 (0.42-0.72)
		M10_Q4			0.36 (0.27-0.49)
	Indirect through M10	IV_Q2	0.26 (0.26*1)	0.98 (1*0.98)	1.01 (1.01-1.02)
		IV_Q3			1.02 (1.02-1.03)
		IV_Q4			1.04 (1.02-1.05)
	Indirect through M10	IS_Q2	0.26 (0.26*0.99)	1 (1*1)	1.03 (1.02-1.05)
		IS_Q3			1.02 (1.01-1.03)
		IS_Q4			1.01 (1.01-1.02)

‡Strength and direction are estimated for indirect effects by multiplying the strength and direction across each edge, which is indicated in the brackets. For example, 0.58 for the indirect effect for IV through M10 had a strength of 0.58 for the arrow from M10 to AD and a strength of 1 for the arrow from IV to M10 in the AD BN model.

Table 4.4. Simulated Sleep-Dementia/AD Network Propagation: Predicting Changes in the Odds Ratio of Dementia and AD Due to Sleep Rhythm Intervention

Simulated Intervention	Change in Target Behavior (s) (Reference to Treatment)	Outcome	Potential Causal Odds Ratio for the Outcome (95% Confidence Intervals)
M10	Q1 to Q4	AD	0.59 (0.51-0.68)
IV	Q1 to Q4	AD	1.40 (1.22-1.60)
IS	Q4 to Q1	AD	1.07 (0.95-1.20)
M10	Q1 to Q4	DEM	0.32 (0.25-0.42)
IV	Q1 to Q4	DEM	1.85 (1.57-2.19)
IS	Q4 to Q1	DEM	1.29 (1.14-1.48)

Chapter 4, in part is currently being prepared for submission for publication of the material. Garduno, Alexis C.; Natarajan, Loki; McEvoy, Linda K.; Smarr, Benjamin; Parada, Humberto; Gallo, Linda; Xiao, Qian; Full, Kelsie; Baker, Laura D.; Eaton, Charles B.; Henderson, Victor W.; Liu, Longjian; Hery, Chloe; LaCroix, Andrea Z. The dissertation author was the primary researcher and author of this material.

5.   Discussion

5.1   <u>Summary of Key Findings</u>

Findings from this dissertation all contribute to the body of work around sleep disparities, GSs, and life course epidemiology. Chapter 2 was conducted to further understand sleep disparities on total morbidity among diverse Hispanic/Latino men and women, and this chapter may inform development of RAR interventions. Chapter 3 demonstrates that circadian disturbances may be a shared risk factor for two critical GSs, specifically physical function and fall risk. Chapter 4 examined associations between sleep and circadian disturbances with dementia and AD in CMS claims. Building on Chapter 3, physical functioning was included in these network models and allowed for identification of potentially etiologic pathways through which sleep and circadian disturbances were associated, directly or indirectly, with dementia and AD. All of these chapters highlight different approaches for simultaneously studying sleep and RAR measures and for developing RAR focused intervention studies to improve aging.

There were several risk factors that emerged as the primary sleep and circadian characteristics across Chapters 2-4, including IS/SRI, IV, M10, and L5 start time. Lower IS/SRI was associated with a greater total multimorbidity and higher fall risk. IS and IV were indirectly associated with incident dementia through M10 activity and BMI, whereas IS and IV were indirectly associated with AD through physical functioning (Chap. 4). Chapters 2-4 support the hypothesis that circadian disruption, in addition to general sleep disturbances (e.g., shortened sleep), meet the informal criteria for inclusion as a GS. The informal criteria for GSs are (i) collection of signs and symptoms, that often co-occur together (as evidenced by associations between circadian disturbances, falls and dementia in Chapters 2-4), (ii) occur more frequently in older adults, and (iii) are related to gradual decline in homeostatic reserve across one or multiple

cognitive and functional domains [16]. In general, formal criteria for GS are currently lacking and are needed for identifying emerging syndromes, especially those observed with new digital health tools and sequencing technologies [15].

Higher IV was associated with greater total multimorbidity, higher fall risk, and was indirectly associated with incident dementia. In contrast to IS, we did not observe a direct association with dementia in time-to-event models after adjusting for total amount of time spent in physical activity. Additionally, the BN analyses suggested that M10 was a mediator of associations between IV, dementia, and AD risk. This raises an important conceptual (or causal pathway) issue about whether to consider physical activity as a mediator or confounder in associations between sleep, dementia, and AD. This mediating pathway is plausible, since individuals who engage in physical activity may expend more energy and this activity may improve mood or anxiety that may increase sleep latency; individuals who engage in physical activity may more easily sleep through the night and so require less daytime napping. In Chapter 4, we observed that M10 was highly correlated with physical activity (r=0.80).

M10 activity was a strong risk factor for fall risk, which is an outcome with significant public health burden. Older women identified by the "healthy sleep cluster" had M10 values that were approximately 1.20 times greater than the M10 values for other clusters, with the exception of the mild RAR cluster that had higher physical activity, higher intra-daily "unhealthier" variability, and higher "healthier" IS (C3). The earlier sleeper cluster was most strongly associated with fall risk, and this early sleep cluster also had lower M10 values. We did not evaluate M10 activity in Chapter 2 since we were primarily interested in the sleep regularity under the RU-SATED model. The RU-SATED model does not include all of the RAR metrics, and M10 and IV were not considered a measure of sleep regularity (unlike IS). Some may view

IV as more closely related to the alertness (e.g., daytime alertness) domain from the RU-SATED model, since IV is highly sensitive to napping [167].

The findings for sleep timings are mixed in Chapters 2-4. In Chapter 2, there were no associations observed between any sleep timing measures and multimorbidity. In Chapter 4, L5 start time appears to be a collider for AD risk, since both the APOE4 and age nodes point to L5 start time. In Chapter 3, individuals who were earlier sleepers also had earlier M10 start times, suggesting a harmful association between M10 start time and fall risk among individuals with disrupted sleep. In Chapter 4, earlier M10 start times were associated with a lower risk of dementia. Chapter 3 and 4 taken together suggest that M10 start time may be protective among individuals with high sleep efficiency and minimal sleep disturbances, and conversely, M10 start time may be harmful among individuals with irregular sleep patterns and disturbed sleep.

5.2   Contribution to Research and Implications

The original work of this dissertation advances the literature demonstrating that sleep is a multidimensional construct, and the multidimensional RU-SATED sleep model is a helpful framework for epidemiologists to use when selecting sleep measures to evaluate. Through this dissertation, we develop a more holistic understanding of sleep health. Similar to others, we have employed unsupervised learning approaches to identify sleep profiles that showed different profiles of each RU-SATED dimension, including regularity, satisfaction, alertness, timing, efficiency, and duration [27, 168]. Identification of sleep profiles is largely data-driven and differs from a confirmatory factor analysis that seeks to confirm a hypothetical structure of the RU-SATED model as done more recently with objective sleep measures [27, 169].

In Chapter 2, we identified sleep regularity as a critical sleep domain and risk factor for predicting multimorbidity accumulation. These findings are consistent with two recent studies by

Wallace et al. [27] conducted in MrOs and SOF and Chung et al. in the Multi-Ethnic Study of Atherosclerosis (MESA) [168] that simultaneously examined associations between machine learned sleep profiles using a RUSATED-informed clustering approach with respect to all-cause and cardiovascular mortality. Few studies have examined sleep with respect to multimorbidity; it is important to note that historically the Charlson Comorbidity Index is used to predict all-cause mortality.

There are conflicting results on napping and many of these studies utilize self-reported napping. The Wallace clusters suggest that a greater propensity for sleep, largely driven by napping, was a protective cluster relative to mortality. The results from Chapter 3 and Chapter 4 are in conflict with this finding. In Chapters 3 and 4, we observed that higher IV quartiles were individually associated with a higher rate of falling, dementia, and AD although the results were less robust for AD after adjusting for physical activity. The results from Chapter 3 and 4 with respect to falling, physical function, and dementia are consistent with a recent meta-analysis that demonstrated a J-shaped association between napping and all-cause mortality [170]. Another study conducted in more than 7,000 participants from NHANES, who were nationally representative of the study population, observed that IV was associated with a greater risk for all-cause mortality that survived adjustment for behavioral factors [171].

Rest-activity fragmentation and sleep irregularity, as evidenced by higher IV and lower IS, are key risk factors for identifying older adults at risk for worse aging. In Chapter 4, IV and IS were indirectly associated with dementia and AD. These results are consistent with results observed among individuals with pre-clinical AD and among individuals with MCI who progressed to AD [138, 139]. First, a cross-sectional study observed that that two biomarkers for the presence of preclinical amyloid plaque pathology (including PiB imaging and cerebrospinal

fluid phosphorylated-tau to amyloid ratio) were associated with greater IV among cognitively normal individuals [138]. Another study conducted in the Rush Memory and Aging Project observed that increased IV was associated with incident AD (HR=1.22 (95%CI: 1.04-1.42), although this result lost significance after adjustment for physical activity and APOE4 carrier status [139]. Lastly, this study identified that changes in IV and IS accelerate after diagnosis of mild cognitive impairment and further accelerate with diagnosis of AD [139]. Despite SCN being identified as a key clock that entrains biological clocks, there is limited research suggesting which dementia subtypes are more sensitive to RAR and sleep disturbances. The mediating role of physical activity in the BN models may suggest that the cardiovascular hypothesis of AD is biologically plausible [172].

5.3   Limitations

This dissertation work was not without limitations. The primary theme of this dissertation work is focused on the role of sleep and circadian disruption on aging. Throughout Chapters 2-4, an important inclusion criterion that influenced identification of the study population was the age of adults. In Chapter 2, a limitation was that the diverse population of Hispanic/Latino men and women were predominantly middle-aged. Those who are middle-aged are considered to be younger than when one would expect multimorbidity to develop. While we observed some individuals developing multimorbidity earlier in life, associations between sleep and circadian disturbances and multimorbidity accumulation may strengthen or accelerate at older ages when multimorbidity development is more common. Longer follow-up of HCHS/SOL and Sueno is required to better evaluate this particular relationship among this same population when they reach 60 or 70 years of age or older.

Another limitation is that objective measures of sleep and circadian disturbance measured in the Women's Health Initiative (Chapters 3-4) were derived from hip-worn accelerometers as compared to wrist-worn accelerometers. Additional studies are needed to better understand differences in estimation of sleep and RAR measurements between wrist-worn and hip-worn placements. One study of the ActiGraph GT3X+ in younger children suggested that hip-worn accelerometers obtained estimates of sleep timing that were closer to the gold standard estimated from polysomnography [173]. Hip-worn accelerometers detected sleep onset 6 minutes later than PSG as compared to wrist-worn accelerometers that estimated a sleep onset that was 21 minutes later than PSG (p <0.05). Hip-worn accelerometers appeared to overestimate sleep duration by approximately 20 minutes, whereas wrist-worn accelerometers underestimated sleep duration. This validation paper in children could not make a recommendation on the placement of Actigraph GT3X+ for measuring sleep. Wrist-worn placement outperformed hip-worn replacement with respect to the sleep efficiency domains, hip-worn accelerometers underestimated WASO, and slightly overestimated sleep efficiency. We may have failed to observe associations between WASO and sleep efficiency in Chapters 3 and 4 due to the use of hip-worn accelerometers. It is worth noting that this validation showed slight underestimation of WASO, and overestimation of sleep efficiency compared to PSG among wrist-worn accelerometers too. In Chapter 2, we may not have been able to detect associations with respect to sleep efficiency due to the need for PSG measurement of this particular sleep domain. Another study conducted in 17 older adults (aged 50-75 years) who completed a night of PSG with one hip-worn and two wrist-worn accelerometers (dominant and non-dominant) hand suggested that hip-worn accelerometers under-estimated sleep duration by 37 minutes, underestimated sleep efficiency by 10%, and over-estimated wake after sleep onset [174]. This study was limited as it

was intended as a feasibility pilot and did not calculate concordance by comparing epoch levels. This finding differs from the earlier study that was conducted in a larger sample of children.

An ongoing challenge in the sleep research field is the study and evaluation of multiple sleep measures simultaneously. To address this ongoing challenge, new machine learning techniques, including clustering and BN analysis, may be helpful in addressing this challenge. Yet, reproducibility may be challenging when applying these methods to another cohort of a different demographic. A limitation of the results in Chapter 3 is that use of an unsupervised machine learning approach, with or without data reduction, may disagree on definitions of the sleep and circadian rhythm profiles. Some differences may arise in defining these sleep groups based on the sample's sleep health, demographic characteristics, device placement, and use of derived sleep and RAR measures. There are diagnostic characteristics that allow one to pre-define the expected number of groups to identify, but choices around the algorithm, number of groups, and tuning of the hyperparameters may produce different sleep profiles. Similarly in network models, operationalization of certain variables may influence the structure of the network learned. For example, in Chapter 4, modeling age as continuous as compared to binary with a cut point at 80 years of age altered the structure of the learned network.

5.4   Recommendations for Future Research

There are multiple areas for further exploration that build off of Chapters 2-4. Additional studies are needed to understand the relationship between sleep and circadian disturbances with GSs and multimorbidity among diverse older adults. Additional studies may seek to follow heterogeneous populations of Hispanic/Latino men and women, such as participants from Sueno and HCHS/SOL studies. Another Sueno visit may allow for evaluation of changes in RAR with aging. This longer follow-up allowed for further characterizations of the same associations

examined in Chapters 2-4 and allow for further generalizability of these study findings to non-US-born and US-born Hispanic/Latino participants. While we found evidence of sleep disparities as residency duration increased among non-US-born Hispanic/Latino individuals, it may also be important to incorporate qualitative and mixed methods analysis to further understand social, cultural, structural, and environmental differences that may be driving shift in patterns between sleep and multimorbidity. Minoritized populations are generally underrepresented in studies on sleep-circadian health and aging, so additional studies are needed in other non-US born populations.

Additional research may look to reproduce the sleep clusters and BN models in cohorts other than the Women's Health Initiative. Reproduction of these sleep clusters, as well as the BN analysis, may be heavily influenced by the age group of participants. It may be advisable for future research to explore strategies for clustering age groups and potentially gender-stratified sleep clusters. Additional studies may employ propensity mapping or covariate balancing techniques to aggregate sleep and circadian sample characteristics in a population that is representative of a broad range of participants.

Future studies may also consider the use of dynamic BN modeling if there are multiple measurements of sleep-circadian metrics over time. In Chapter 4, the dynamic BN was not appropriate due to the non-repeated nature of the accelerometry data after the initial 7-day consecutive measurement period. Another area of further development would be to explore generation of a broader BN model with inclusion of all GSs beyond physical functioning, cognitive health, and sleep-circadian parameters, and evaluation of gender differences between BN geriatric network models.

5.5   Concluding Remarks

The research furthered the evidence base surrounding sleep, circadian disruption (as evidenced by RAR), and GS development. This dissertation demonstrated: 1) associations between separate dimensions of sleep and circadian health with multimorbidity, 2) that multiple sleep and circadian parameters define healthy and unhealthy sleep profiles and sleep profiles are associated with frequent falling and physical functioning, and 3) sleep and circadian health measures are directly and indirectly associated with dementia and possibly AD. This work supports multiple contributions of circadian disruption to varied GSs when taken together with existing literature.

APPENDIX A: Supplementary Materials to Chapter 2

Supplementary Methods

Actigraphy-Derived Sleep and Circadian Health in Sueño

These devices collected activity and light data in 30-second epochs, and then sleep periods were scored at the central reading center at Brigham and Women's Hospital. These sleep periods were scored based on sleep diaries and sleep habits, using event markers for in and out of bedtimes, and a sudden drop in signal intensity for activity and light readings. At the epoch-level, sleep-wake status was classified based on the Actiware 5.59 scoring algorithm with 5 immobile minutes to define sleep onset, 0 minutes to define sleep offset, and an activity count of 40 to classify the epoch as awake versus asleep.

Rationale for Sleep-Circadian Measure Operationalization

Sleep and circadian rhythm measures were operationalized in each count model based on the standard definition used by clinicians and researchers, which was previously described. In the absence of a standard definition, these sleep measures were operationalized as tertiles. We chose to operationalize these sleep measures as tertiles, since tertiles (i) allows for examination of sleep health on the continuum that is present in the general population (as opposed to focused solely on dichotomization of healthy versus disordered sleep), (ii) is a unified approach when limited evidence exists about threshold effects of each sleep measure in association with comorbidity burden, and (iii) may also help inform choice of alternative modeling strategies for identifying possible non-linear or dose-response effects in sleep-CCI associations. As previously stated, the study outcome CCI was operationalized as a weighted count based on severity of the disease.

Descriptive Statistics of CCI Group Differences

The CCI was also categorized into groups (0/1/2/3+) solely for descriptive analyses that estimated prevalence of comorbidity burden at visit 2. We were specifically interested in summarizing group differences in CCI across age groups (18-44/45-64/65+ years old in HCHS/SOL and 18-44/45-64 in Sueño), heritage, and nativity groups. Nativity group is defined as the place of birth/duration of US residence at baseline (non-US-born, <10 years in the US/ non-US-born, 10-20 years in the US/>20 years in the US/US-born). Henceforth, non-US-born will refer to participants born outside of the US 50 states/DC, and participants born outside within the U.S. territories are categorized as non-US-born. We estimated prevalence of the comorbidity burden at visit 2 between certain sociodemographic groups to facilitate comparisons between this sample with other studies. Lastly, we examined weighted, sample characteristics stratified by tertiles of sleep measures and performed the same tests for overall differences.

Table A.1. Incidence Ratio Ratios between Alternative Inter-Daily Stability Sleep Measures and the Charlson Co-Morbidity Index in Sueno from Survey-Weighted, Zero-Inflated Poisson Model

	n	Model 1‡ IRR (95% CI)	Model 1‡ P	Model 2‡ IRR (95% CI)	Model 2‡ P	Model 3‡ IRR (95% CI)	Model 3‡ P
Interdaily Stability (Primary) (n=1,467)							
T3: >0.85	492	Ref	0.001	Ref	0.008	Ref	0.01
T2: 0.75 to 0.85	509	1.29 (1.00 - 1.65)		1.24 (0.97 - 1.57)		1.23 (0.97 - 1.55)	
T1: <0.75	466	1.54 (1.23 - 1.94)		1.43 (1.14 - 1.79)		1.40 (1.12 - 1.75)	
Inter-Daily Stability (Secondary) (n=1,470)			0.10		0.29		0.29
T3: >0.61	497	Ref		Ref		Ref	
T2: 0.51-0.61	488	1.29 (1.01 - 1.66)		1.20 (0.94 - 1.54)		1.21 (0.94 - 1.54)	
T1: <0.51	485	1.03 (0.79 - 1.35)		1.05 (0.80 - 1.37)		1.07 (0.82 - 1.40)	

*The logit section of the zero-inflated model modeled the probability of having non-zero and zero CCIs the same (e.g., only including an intercept term), whereas the count model included all of the confounding covariates. [a] Adjustment for field center (Bronx, Chicago, Miami, and San Diego), age (continuous), and gender (male/female). [b] Additionally adjusts for education (<high school, high school graduate, or >high school), household income (less than or equal to $30,000/ $30,000-50,000/more than 50,000), nativity (non-US-born <10 years in country, non-US-born ≥ 10 years in country, US-born), heritage (Mexican, Puerto Rican, Cuban, Dominican, Central American, South American, or Mixed/Other), smoking status (never/former/current), alcohol use (never/former/current). [c] Additionally adjusts for duration of moderate-to-vigorous physical activity (minutes) and body mass index (continuous in kg/m2).

†Sleep duration categories were broadened for the long sleepers to also include individuals with 8 hours and 45 minutes of sleep per night, since the sample size dropped dramatically among individuals who slept 8 hours and 45 minutes compared to 9 hours.

‡The reference groups for the following model are indicated for each covariate: alcohol use (ref=current drinker), body mass index (ref=Normal to Underweight), center (refe=San Diego), cigarette use (ref=never), household income (ref=<30k), nativity status (ref=Non-US Born and 10<=YRSUS <20), education (ref=high school), gender (ref=woman), marital status (ref=married), ethnicity (ref=Mexican).

Table A.2. Incidence Ratio Ratios between Self-Reported Sleep Measures and the Charlson Co-Morbidity Index in Tertiles in Sueno from Survey-Weighted, Zero-Inflated Poisson Model

	Model 1[a]‡		Model 2[b]‡		Model 3[c]‡	
	IRR (95% CI)	P	IRR (95% CI)	P	IRR (95% CI)	P
Insomnia (n=1,825)		0.0001		0.0004		0.001
T1: 0-4	Ref		Ref		Ref	
T2: 5-10	1.33 (1.06 - 1.67)		1.30 (1.04 - 1.63)		1.27 (1.02 - 1.59)	
T3: 11-20	1.76 (1.37 - 2.26)		1.64 (1.28 - 2.10)		1.60 (1.25 - 2.04)	
Excessive Daytime Sleepiness (n=1,824)		0.004		0.005		0.006
T1: 0-3	Ref		Ref		Ref	
T2: 3-7	1.29 (0.99 - 1.68)		1.33 (1.03 - 1.72)		1.33 (1.03 - 1.71)	
T3: 7-24	1.42 (1.15 - 1.77)		1.42 (1.13 - 1.79)		1.40 (1.12 - 1.75)	

*The logit section of the zero-inflated model modeled the probability of having non-zero and zero CCIs the same (e.g., only including an intercept term), whereas the count model included all of the confounding covariates. [a] Adjustment for field center (Bronx, Chicago, Miami, and San Diego), age (continuous), and gender (male/female). [b] Additionally adjusts for education (<high school, high school graduate, or >high school), household income (less than or equal to $30,000/ $30,000-50,000/more than 50,000), nativity (non-US-born <10 years in country, non-US-born ≥ 10 years in country, US-born), heritage (Mexican, Puerto Rican, Cuban, Dominican, Central American, South American, or Mixed/Other), smoking status (never/former/current), alcohol use (never/former/current). [c] Additionally adjusts for duration of moderate-to-vigorous physical activity (minutes) and body mass index (continuous in kg/m2).

†Sleep duration categories were broadened for the long sleepers to also include individuals with 8 hours and 45 minutes of sleep per night, since the sample size dropped dramatically among individuals who slept 8 hours and 45 minutes compared to 9 hours. ‡The reference groups for the following model are indicated for each covariate: alcohol use (ref=current drinker), body mass index (ref=Normal to Underweight), center (refe=San Diego), cigarette use (ref=never), household income (ref=<30k), nativity status (ref=Non-US Born and 10<=YRSUS <20), education (ref=high school), gender (ref=woman), marital status (ref=married), ethnicity (ref=Mexican).

Table A.3. Interaction P-Values between Sleep Rest-Activity Metrics and Charlson Co-Morbidity Index

	Nativity	Gender	Age Group
Categorical			
Insomnia	<0.0001	0.03	0.009
Excessive Sleepiness	0.07	0.91	0.01
Sleep Duration	0.006	0.99	0.89
Midsleep Timepoint	0.07	0.50	0.14
Weekday Bedtime	0.33	0.98	0.47
Weekend Awaketime	0.57	0.45	0.40

APPENDIX B: Supplementary Materials to Chapter 3

Supplementary Methods

Sleep Data Processing for Rest-Activity Rhythm Metrics

Sleep/wake classification was obtained from the Cole-Kripke algorithm using the vector magnitude (VM) [96]. VMs were also used to derive rest-activity rhythm (RAR) characteristics, using non-parametric approaches after discarding the first day of wear. Non-wear periods were imputed in two stages; first, the dominant sleep/wake classification is used to fill in non-wear periods if there are at least 30 minutes of sleep or wakefulness within a day and hour. Otherwise, the awake/sleep classification was be based on the dominant classification from the hour for VM and sleep/wake status, respectively. Mean imputation was performed on VM for non-wear periods of activity in this same two-step process.

Form 155 Sleep Questionnaire

The daytime napping question stated the following: "Please pick the answer that best describes how often you experienced the situation in the past 4 weeks. Did you nap during the day?". The daytime sleepiness related to light activities stated the following: "Please pick the answer that best describes how often you experienced the situation in the past 4 weeks. Did you fall asleep during quiet activities like reading, watching TV, or riding in a car?". Each of the questions were converted into an ordinal category starting at 0, and the value increased with improved daytime alertness or satisfaction. The daytime alertness questions had the following response options, and the associated values are shown: "No, not in past 4 weeks" (0), "Yes, less than once a week" (1), "Yes, 1 or 2 times a week" (2), "Yes, 3 or 4 times a week" (3), "Yes, 5 or more times per week" (4). The sleep satisfaction question stated: "Overall, was your typical night's sleep during the past 4 weeks." This sleep satisfaction measure was also converted from

numeric to ordinal for the following response options: "very restless" (0), "restless" (1), "average quality" (2), "sound or restful" (3), and "very sound or restful" (4). Each of these questionnaire measures were converted from categorical to numeric measures, in order to allow for them to be used in defining sleep clusters/profiles in later clustering analyses.

Mapping of Individual Sleep and Rest-Activity Rhythm Measures to the RUSATED model

Inter-daily stability represented the sleep regularity dimension of the RUSATED model; sleep duration, WASO, sleep latency, number of awakenings, length of awakenings, and sleep efficiency represented sleep duration and continuity/efficiency dimensions. The remaining RUSATED dimensions of daytime sleepiness/alertness and sleep satisfaction were represented by the following sleep parameters: objectively measured intra-daily stability, self-reported daytime napping, daytime sleepiness during light activities, and sleep quality. Sleep timing was presented by the start and midpoint of M10 and L5 periods, average waketime, and average bedtime.

Sleep Cluster Enrichment: Visualization of Participant-Level Heterogeneity within Clusters

As a sensitivity analysis, we performed sample heterogeneity assessments of the distinct clusters (see Supplementary Methods) [175] to visualize cluster enrichment for age group (<80 years, >80 years), race-ethnicity (White, Black, Hispanic), diabetes status (yes/no), CVD (yes/no) and depression (yes/no). Differences in cluster enrichment may identify a latent factor that is describing differences in sleep patterns and subsequently sleep-fall risk associations; we further evaluated whether sleep-fall associations could be explained by these potential latent factors by adding an interaction term for latent factor * clusters into fall models and reporting models stratified by this potential latent factor.

The term "sample heterogeneity" arises from the cellular and genomic literature [175], which we will refer to as "participant-level heterogeneity," since we are studying heterogeneity between participant-level sleep profiles. In exploring this heterogeneity, we calculated the enrichment of each cluster for clinically meaningful classes (e.g., disease outcomes) and visualize these labels with the pre-defined clusters. While this approach is being increasingly explored in the literature to uncover underlying potential causes [175], we used this approach to inform whether we tested for effect modification in the existing statistical models by this clinically meaningful class. Additionally, we also visualized mortality (yes/no) during subsequent follow-up of this population, although it would be theoretically inappropriate to evaluate mortality as an effect modifier. Additionally, we also looked for the presence of frequent fallers (>2 falls per year) within these clusters. Lastly, we visualized outliers for each individual sleep feature within the clusters to inform understanding of classification of these OPACH participants who had extreme sleep profiles.
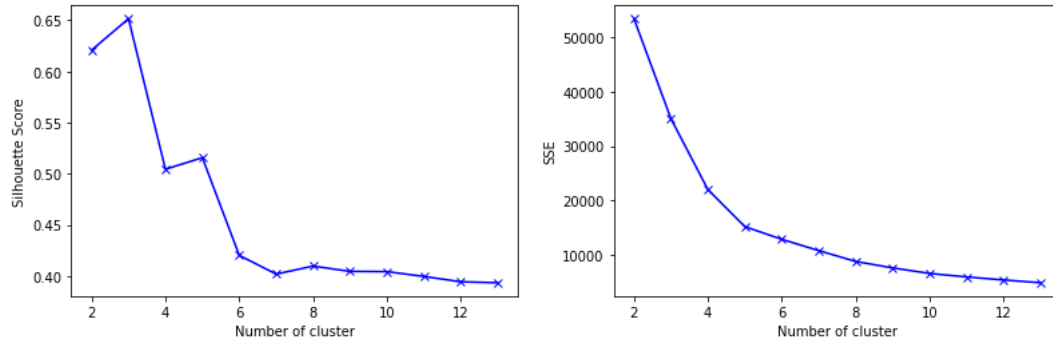
Figure B.1. Elbow plot of silhouette scores and SSE plot for cluster selection for the hyperparameters used in the final clustering model

This silhouette plot indicates that clusters 2-5 from K-Means had cluster scores above the model selection criteria of 0.50.
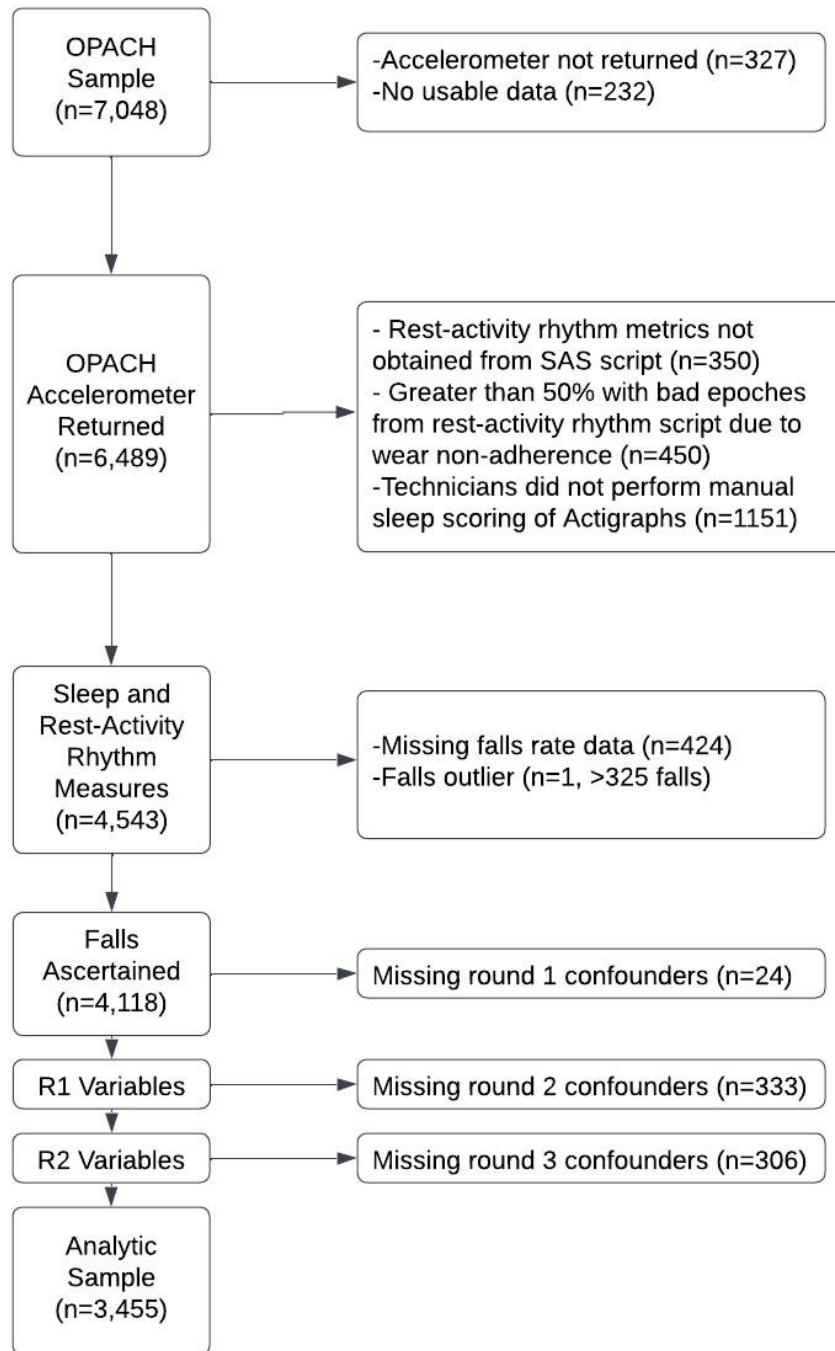
Figure B.2. Flow chart for the complete-case analysis in this Women's Health Initiative analysis of sleep and fall risk

Table B.1. Multiply Imputed (m=25), Linear Regression Models of Sleep-Circadian Cluster with Physical Functioning Markers using UMAP and K-Means (k=5; n=4,543)

Physical Functioning Marker	Sleep Clusters	Model 1		Model 2		Model 3	
		Beta (95% CI)	P-value	Beta (95% CI)	P-value	Beta (95% CI)	P-value
EPESE SPBB Score (0-12)	C2: "Healthy"	Ref	1.99E-09	Ref	0.03	Ref	0.13
	C1: "Sleep Disturbed"	-0.63 (-0.84--0.41)		-0.32 (-0.53--0.12)		-0.26 (-0.47--0.05)	
	C3: "Mild Fragmentation"	-0.06 (-0.26-0.14)		-0.02 (-0.21-0.17)		-0.01 (-0.21-0.18)	
	C4: "Earlier L5 midpoint"	-0.75 (-1.30--0.21)		-0.27 (-0.79-0.26)		-0.24 (-0.77-0.28)	
	C5: "C1 with Shorter, Less Disrupted Sleep"	-0.31 (-0.53--0.08)		-0.10 (-0.31-0.12)		-0.07 (-0.28-0.15)	
Balance Test Score (0-4)	C2: "Healthy"	Ref	2.41E-06	Ref	0.008	Ref	0.02
	C1: "Sleep Disturbed"	-0.20 (-0.29--0.10)		-0.13 (-0.22--0.03)		-0.11 (-0.21--0.02)	
	C3: "Mild Fragmentation"	-0.03 (-0.11-0.06)		-0.02 (-0.10-0.07)		-0.01 (-0.10-0.07)	
	C4: "Earlier L5 midpoint"	-0.39 (-0.61--0.17)		-0.28 (-0.51--0.06)		-0.28 (-0.50--0.06)	
	C5: "C1 with Shorter, Less Disrupted Sleep"	-0.09 (-0.19-0.01)		-0.04 (-0.14-0.05)		-0.04 (-0.14-0.06)	
Chair Stand Score (0-4)	C2: "Healthy"	Ref	1.81E-08	Ref	0.04	Ref	0.18
	C1: "Sleep Disturbed"	-0.28 (-0.38--0.17)		-0.14 (-0.25--0.04)		-0.11 (-0.21-0.00)	
	C3: "Mild Fragmentation"	-0.07 (-0.17-0.03)		-0.05 (-0.14-0.05)		-0.04 (-0.14-0.05)	
	C4: "Earlier L5 midpoint"	-0.32 (-0.58--0.06)		-0.10 (-0.36-0.16)		-0.08 (-0.34-0.17)	
	C5: "C1 with Shorter, Less Disrupted Sleep"	-0.17 (-0.28--0.06)		-0.08 (-0.18-0.03)		-0.06 (-0.17-0.04)	
Gait Speed Score (0-4)	C2: "Healthy"	Ref	0.009	Ref	0.29	Ref	0.36
	C1: "Sleep Disturbed"	-0.19 (-0.30--0.09)		-0.09 (-0.19-0.01)		-0.08 (-0.18-0.03)	
	C3: "Mild Fragmentation"	0.01 (-0.08-0.11)		0.03 (-0.06-0.12)		0.03 (-0.06-0.13)	
	C4: "Earlier L5 midpoint"	-0.03 (-0.28-0.22)		0.14 (-0.11-0.38)		0.14 (-0.11-0.39)	
	C5: "C1 with Shorter, Less Disrupted Sleep"	-0.03 (-0.14-0.07)		0.04 (-0.07-0.14)		0.04 (-0.06-0.15)	

Abbreviations: C1-5: Clusters between 1-5. The crude model (M1) was adjusted for age, race-ethnicity, and education. Model 2 was adjusted for the following covariates including age, race-ethnicity, education, self-rated health, alcohol consumption, smoking status, total minutes spent in physical activity, cardiovascular disease, diabetes, and cancer. The fully adjusted model (M3) was adjusted for the same model covariates as model 2 and was additionally adjusted for sleep medication, depression, and body mass index.

Table B.2. Baseline Characteristics in OPACH (2012-2018) for Full Sample (n=6,489), Analytic Sample (n=4,4543), and Multiply Imputed Sample (n=4,543) with m=25 imputations

	Full, Unrestricted Sample	Multiply Imputed with Complete Accelerometry	Analytic Sample without Imputation	Excluded from Analytic Sample	P-value for Analytic vs. Excluded
	n=6,489	n=4,543	n=4,543	n=1,946	n=6,489
Age, yrs.; *mean (sd)*	78.70 (6.70)	78.69 (6.74)	78.69 (6.74)	78.72 (6.60)	0.85
Age Groups, ≥80 Years; n (%)	3223 (49.7)	2267 (49.9)	2267 (49.9)	956 (49.1)	0.59
Race-ethnicity; n (%)					0.02
White	3205 (49.4)	2288 (50.36)	2288 (50.4)	917 (47.1)	
Black	2187 (33.7)	1519 (33.44)	1519 (33.4)	668 (34.3)	
Hispanic	1097 (16.9)	736 (16.2)	736 (16.2)	361 (18.6)	
Education; n (%)					0.33
High School/GED	1316 (20.4)	926 (20.38)	920 (20.4)	396 (20.5)	
Some College	2496 (38.7)	1784 (39.28)	1774 (39.3)	722 (37.4)	
College Graduate+	2634 (40.9)	1833 (40.34)	1822 (40.3)	812 (42.1)	
Self-Rated Health; n (%)					0.26
Excel./Very Good	3235 (50.1)	2275 (50.08)	2269 (50.1)	966 (50.0)	
Good	2574 (39.8)	1826 (40.20)	1820 (40.2)	754 (39.0)	
Poor/Very Poor	651 (10.1)	441 (9.71)	439 (9.7)	212 (11.0)	
Physical Activity, total steps per day; *mean (sd)*	334.05 (98.91)	340.76 (98.36)	340.78 (98.37)	317.47 (98.33)	<0.001
Physical Function; *mean (sd)*	68.43 (26.09)	68.51 (26.11)	68.59 (26.08)	68.05 (26.12)	0.45
Smoker Status, Smoker; n (%)	164 (2.8)	131 (2.88)	118 (2.8)	46 (2.7)	0.76
Sleep Medication; n (%)					0.009
Not in the past month or less	4309 (73.6)	3393 (74.68)	3097 (74.7)	1212 (70.8)	
Less than once per week	527 (9.0)	393 (8.65)	358 (8.6)	169 (9.9)	
1+ times per week	1020 (17.4)	758 (16.68)	690 (16.6)	330 (19.3)	
Alcohol Frequency; n (%)					0.75
Non-Drinker	2230 (37.9)	1720 (37.86)	1563 (37.6)	667 (38.5)	
<1 per Week	2008 (34.1)	1560 (34.35)	1429 (34.4)	579 (33.4)	
≥1 per Week	1651 (28.0)	1263 (27.80)	1165 (28.0)	486 (28.1)	
BMI; *mean (sd)*	28.17 (5.77)	28.08 (5.69)	28.04 (5.68)	28.47 (5.96)	0.008
Diabetes, yes; n (%)	1350 (20.8)	925 (20.36)	925 (20.4)	425 (21.8)	0.19
Cardiovascular disease, yes; n (%)	637 (9.8)	437 (9.62)	437 (9.6)	200 (10.3)	0.44
Cancer, yes; n (%)	1090 (16.8)	780 (17.17)	780 (17.2)	310 (15.9)	0.24
Depression, no ; n (%)	5238 (93.3)	4223 (92.95)	3700 (93.2)	1538 (93.7)	0.54

Table B.3. Complete Case Analysis, Negative Binomial Models of Fall Rate with Sleep-Circadian Cluster Risk Factors derived from K-Means (k=5) following UMAP data reduction (n=3,455)

Sleep Exposure	Categories	Model 1 IRR (95% CI)	Model 1 P-value	Model 2 IRR (95% CI)	Model 2 P-value	Model 3 IRR (95% CI)	Model 3 P-value
ML-Derived Clusters	C1 "Sleep Disturbed"	1.22 (1.04-1.42)	6.75E-04	1.16 (0.99-1.36)	5.25E-03	1.14 (0.97-1.35)	1.69E-03
	C2 "Healthy"	Ref		Ref		Ref	
	C3 "Mild Fragmentation"	1.16 (1.00-1.33)		1.13 (0.98-1.30)		1.15 (1.00-1.33)	
	C4 "Earlier L5 midpoint"	1.99 (1.41-2.86)		1.83 (1.29-2.63)		1.97 (1.38-2.84)	
	C5 "C1 with Shorter, Less Disrupted Sleep"	1.06 (0.90-1.25)		1.03 (0.87-1.21)		1.02 (0.87-1.21)	
Inter-Daily Variability (IS)	Q1	Ref	0.02	Ref	0.12	Ref	0.18
	Q2	0.92 (0.79-1.07)		0.95 (0.82-1.11)		0.95 (0.82-1.11)	
	Q3	0.96 (0.83-1.12)		0.98 (0.84-1.15)		0.95 (0.81-1.12)	
	Q4	0.79 (0.68-0.92)		0.84 (0.72-0.99)		0.84 (0.71-0.99)	
Intra-Daily Variability (IV)	Q1	Ref	0.01	Ref	0.08	Ref	0.27
	Q2	1.23 (1.06-1.43)		1.2 (1.03-1.4)		1.12 (0.96-1.31)	
	Q3	1.10 (0.94-1.28)		1.07 (0.91-1.26)		1.07 (0.91-1.26)	
	Q4	1.26 (1.08-1.47)		1.18 (0.99-1.4)		1.18 (0.99-1.42)	
L5	Q1	Ref	0.07	Ref	0.06	Ref	0.09
	Q2	0.97 (0.84-1.13)		0.97 (0.84-1.12)		0.92 (0.79-1.07)	
	Q3	0.90 (0.78-1.04)		0.91 (0.79-1.06)		0.91 (0.79-1.06)	
	Q4	1.10 (0.95-1.28)		1.12 (0.96-1.29)		1.09 (0.93-1.27)	
M10	Q1	Ref	1.95E-04	Ref	0.049	Ref	0.29
	Q2	0.88 (0.76-1.02)		0.88 (0.75-1.04)		0.90 (0.76-1.06)	
	Q3	0.85 (0.73-0.99)		0.87 (0.72-1.05)		0.92 (0.76-1.11)	
	Q4	0.70 (0.6-0.82)		0.72 (0.57-0.91)		0.80 (0.63-1.02)	

Abbreviations: IS – inter-daily stability; IV – intra-daily variability; L5 – activity count for least active 5 hours of the day; M10 – activity count most active 10 hours of the day. C1-5: Clusters between 1-5. The crude model (M1) was adjusted for age, race-ethnicity, and education. Model 2 was adjusted for the following covariates including age, race-ethnicity, education, self-rated health, alcohol consumption, smoking status, total minutes spent in physical activity, cardiovascular disease, diabetes, and cancer. The fully adjusted model (M3) was adjusted for the same model covariates as model 2 and was additionally adjusted for sleep medication, depression, and body mass index.

APPENDIX C: Supplementary Materials to Chapter 4

<u>Supplementary Methods</u>

<u>Mediation Analysis of Rest-Activity Metrics, M10, and Cognitive Outcomes.</u>

<u>Supplementary Results</u>

<u>Bayesian Network of Sleep, Dementia, and AD</u>

In this study, we present two Bayesian Network models that characterize the structure of the relationship between sleep-RAR factors and incident dementia and Alzheimer's disease (Figures 1-2). This derived network can be described as a product of the conditional probability distributions of the variables that comprise the network's nodes (e.g., joint probability distribution). By decomposing each model described, a complex model can be simplified to highlight the factors that directly influence each variable in the sleep-cognition models. We highlight differences in the conditional probabilities between sleep-dementia and sleep-AD networks in bold.
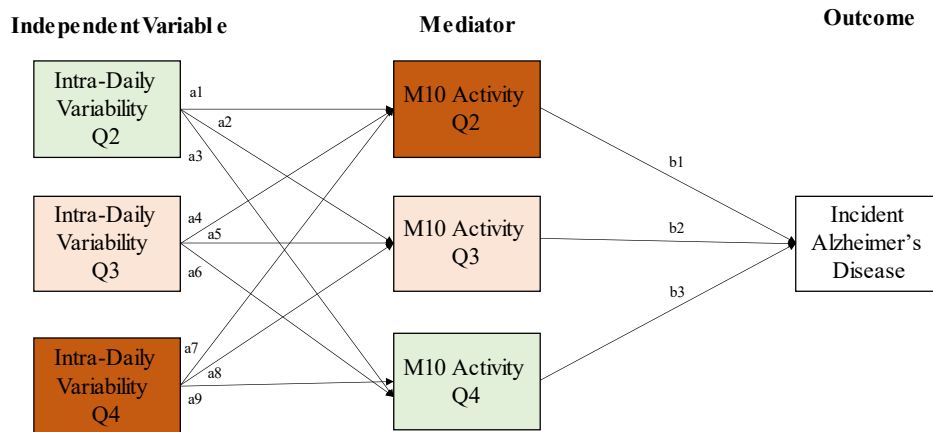
Overview. Mediation Model of Non-Parametric Sleep Parameters (Intra-Daily Variability), M10 Activity, and Incident Alzheimer's Disease
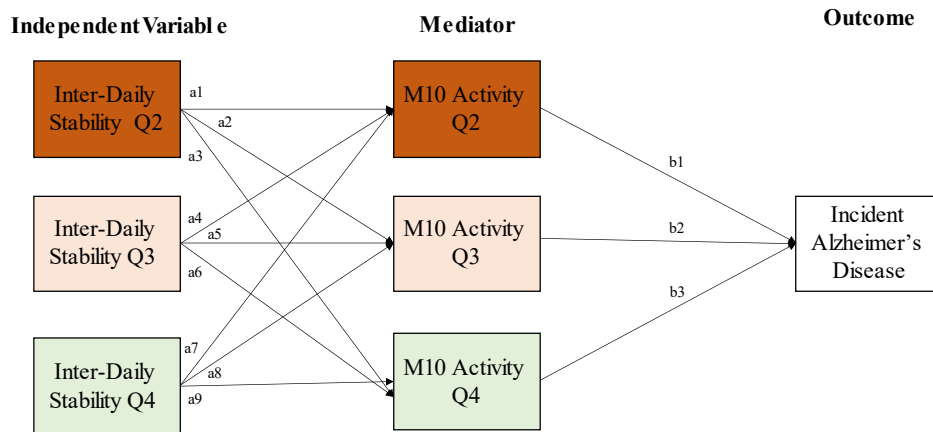
Figure C.1. Mediation visualization of intra-daily variability, M10 activity, and AD

The network diagram identified from the Bayesian Network model identified an indirect effect for intra-daily variability and Alzheimer's Disease that is mediated by M10 activity. Structural equation modeling was performed with the lavaan package to identify the indirect effect; no direct effect was modeled between intra-daily variability and incident Alzheimer's Disease due to the absence of an edge in the network model, in addition to the absence of an association from survival analyses. Logistic regression models were fit for the mediation and outcome models. Each mediation model separately regressed the dummy variables coded using indicator coding for M10 quartile levels 2-4 on the independent variable (intra-daily variability). These mediation models were adjusted for inter-daily stability and race-ethnicity, since these variables were identified as confounding variables based on the BN model. The outcome model regressed Alzheimer's Disease on the mediator, and the outcome model was also adjusted for inter-daily stability and race-ethnicity. Bootstrapped confidence intervals were estimated for the indirect effects based on 1,000 samples.

The mediation models were identified based on an existing work focused on conducting mediation analyses with multiple category, unordered variables [176].

For example, the indirect effect for intra-daily variability quartile 2 vs. quartile 1 is indicated by the following equations:

Indirect Effect for IV quartile 2 vs. 1 = a1*b1+a2*b2+a3*b3

Overview. Mediation Model of Non-Parametric Sleep Parameters (Inter-Daily Stability), M10 Activity, and Incident Alzheimer's Disease

Figure C.2. Mediation Visualization of Inter-Daily Stability, M10 Activity, and Alzheimer's Disease

Table C.1. Bynum Algorithm Definition of Alzheimer's Disease and Related Disorder or Senile Dementia

The Bynum-standard algorithm was implemented using ICD-9 codes and ICD-10 codes to identify dementia in the CMS claims database. Additional dementia and AD cases were identified using a list of medications, specifically the generic name. The diagnosis codes used for the dementia and AD diagnoses are indicated below. Prescription records for the following medications (identified using the generic name) were used to identify additional dementia and AD cases. The same list of medications (based on generic names) were used to identify dementia and Alzheimer's Disease cases, which included Memantine, Donepezil, Rivastigmine, and Galantamine.

ICD Code	Description	ICD Version
2900	Senile dementia, uncomplicated	9
29010	Presenile dementia, uncomplicated	9
29011	Presenile dementia with delirium	9
29012	Presenile dementia with delusional features	9
29013	Presenile dementia with depressive features	9
29020	Senile dementia with delusional features	9
29021	Senile dementia with depressive features	9
2903	Senile dementia with delirium	9
29040	Vascular dementia, uncomplicated	9
29041	Vascular dementia, with delirium	9
29042	Vascular dementia, with delusions	9
29043	Vascular dementia, with depressed mood	9
2940	Amnestic disorder in conditions classified elsewhere	9
29410	Dementia in conditions classified elsewhere without behavioral disturbance	9
29411	Dementia in conditions classified elsewhere with behavioral disturbance	9
29420	Dementia, unspecified, without behavioral disturbance	9
29421	Dementia, unspecified, with behavioral disturbance	9
3310	Alzheimer's disease	9
33111	Pick's disease	9
33119	Other frontotemporal dementia	9
3312	Senile degeneration of brain	9
3317	Cerebral degeneration in diseases classified elsewhere	9
33182	Dementia with Lewy bodies	9
797	Senility without mention of psychosis	9

Table C.1. Bynum Algorithm Definition of Alzheimer's Disease and Related Disorder or Senile Dementia, Continued.

ICD Code	Description	ICD Version
F0150	Vascular dementia, unspecified severity, without behavioral disturbance, psychotic disturbance, mood disturbance, and anxiety	10
F0151	Vascular dementia with behavioral disturbance	10
F0280	Dementia in other diseases classified elsewhere, unspecified severity, without behavioral disturbance, psychotic disturbance, mood disturbance, and anxiety	10
F0281	Dementia in other diseases classified elsewhere with behavioral disturbance	10
F0390	Unspecified dementia, unspecified severity, without behavioral disturbance, psychotic disturbance, mood disturbance, and anxiety	10
F0391	Unspecified dementia with behavioral disturbance	10
F04	Amnestic disorder due to known physiological condition	10
G138	Systemic atrophy primarily affecting central nervous system in other diseases classified elsewhere	10
G300	Alzheimer's disease with early onset	10
G301	Alzheimer's disease with late onset	10
G308	Other Alzheimer's disease	10
G309	Alzheimer's disease, unspecified	10
G3101	Pick's disease	10
G3109	Other frontotemporal neurocognitive disorder	10
G311	Senile degeneration of brain, not elsewhere classified	10
G312	Degeneration of nervous system due to alcohol	10
R4181	Age-related cognitive decline	10

Table C.2. Alzheimer's Disease Bynum Definition

ICD Code	Description	ICD Version
3310	Alzheimer's disease	9
G300	Alzheimer's disease with early onset	10
G301	Alzheimer's disease with late onset	10
G308	Other Alzheimer's disease	10
G309	Alzheimer's disease, unspecified	10

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