Sleep Habits in Mild Cognitive Impairment

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Abstract: We explored the relationship between sleep disturbances and mild cognitive impairment (MCI) in community-dwelling seniors. Recent evidence suggests that sleep habits are differentially compromised in different subtypes of MCI, but the relationship between sleep disruption and MCI remains poorly understood. We gathered daily objective measures of sleep disturbance from 45 seniors, including 16 with MCI (mean age, 86.9 ± 4.3 y), over a 6-month period. We also collected self-report measures of sleep disturbance. Although there were no differences between groups in any of our self-report measures, we found that amnestic MCI (aMCI) volunteers had less disturbed sleep than both nonamnestic MCI (naMCI) and cognitively intact volunteers, as measured objectively by movement in bed at night ($F_{2,1078} = 4.30$, $P = 0.05$), wake after sleep onset ($F_{2,1078} = 41.6$, $P < 0.001$), and number of times up at night ($F_{2,1078} = 26.7$, $P < 0.001$). The groups did not differ in total sleep time. In addition, the aMCI group had less day-to-day variability in these measures than the intact and naMCI volunteers. In general, the naMCI volunteers showed a level of disturbed sleep that was intermediate to that of aMCI and intact volunteers. These differences in sleep disruption between aMCI and naMCI may be related to differences in the pathology underlying these MCI subtypes.

Key Words: MCI (mild cognitive impairment), assessment of cognitive disorders/dementia, sleep habits, cohort studies

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Disrupted sleep, including nighttime awakenings, difficulty falling asleep, and early awakening, are common in the elderly.[1–4] Estimates of the prevalence of sleep disturbances in the elderly range from 21% to 54%. One of the most important functional aspects of sleep in the elderly is a strong association between poor sleep and cognitive impairment. There is ample evidence of sleep disturbance in Alzheimer disease compared with normal elderly,[5] including increased daytime sleepiness,[6,7] longer duration of nighttime sleep,[8,9] poor sleep efficiency,[10] and more frequent awakening at night.[5] There is also increasing evidence that sleep disturbances play an important role in mild cognitive impairment (MCI) in seniors,[9,11–15] and some studies have suggested that disruptive nighttime behaviors are the most common clinically significant neuropsychiatric symptom in patients with MCI.[14,15]

MCI is used to describe a syndrome of cognitive impairment in the absence of functional impairment. However, MCI is a heterogenous construct, with the long-term prognosis for patients varying depending on their MCI subtype. Amnestic MCI (aMCI) refers to those patients with a primary complaint of declining memory, whereas patients with nonamnestic MCI (naMCI) have no complaint of memory deficits but show impairment in ≥ 1 other cognitive domains. Recently, evidence from screening questions about sleep disturbances has suggested that the frequency[16,17] and severity[18] of nighttime disturbances may be greater in naMCI than in aMCI patients. This is consistent with recent actigraphy studies examining the relationship between sleep disturbances and performance on tests of executive function. For example, Naismith et al[12] used actigraphy to follow 15 seniors with naMCI over 14 days and looked at the correlation between the number and duration of arousals [wake after sleep onset (WASO)] and scores on executive function tests. They found a negative correlation between WASO and sorting and attention tasks, and a positive correlation to response inhibition tasks. Similarly, Blackwell et al[19] used actigraphy to assess sleep measures in cognitively healthy seniors in the MrOS study over a 5-night period, and found that WASO >90 minutes was associated with poorer performance on a test of executive function (trails B). In another study, they found a correlation between less time spent in REM sleep and performance on trails B.[20] In contrast, Westerberg and colleagues looked at the relationship between wrist-worn actigraphy measures of sleep over 14 nights in 10 aMCI patients and 10 controls for 2 memory tasks completed each day. They found that the night-tonight variability in sleep latency, WASO, and total sleep time (TST) were correlated with performance on the next-day memory tests.[21] It could be expected that WASO might be increased in naMCI patients as compared with controls and to aMCI patients; however, such a study has not been done.

Polysomnography (PSG) studies have also revealed more subtle changes in sleep measures in aMCI patients. Although most studies find no difference between aMCI patients and healthy controls on typical measures of sleep disruption, such as WASO and TST, the use of electroencephalography and surface electromyography in PSG has shown an increase in the number of periodic leg movement (PLM) arousals[22,23] and slow wave sleep (SWS) arousals[24] in aMCI patients. Interestingly, the latter study also showed that aMCI APoE4 carriers had less REM sleep and fewer SWS arousals than non-ApoE4 carriers, leading the investigators to hypothesize that increased wake duration caused by SWS fragmentation in aMCI patients may contribute to the production of toxic amyloid. Similar studies have not been done in naMCI patients.

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The objective of the present study was 2-fold. First, we wanted to determine whether sleep patterns assessed using objective measures differ between aMCI and naMCI volunteers. We hypothesized that we would see more disrupted sleep in MCI volunteers as compared with controls, and in naMCI volunteers as compared with aMCI volunteers. Second, we want to further examine the question of night-to-night variability in sleep measures across these groups. On the basis of Westerberg's findings, we expected to see increased variability in our aMCI cohort, but also wanted to know if this variability was typical of naMCI volunteers as well. Thus, using in-home sensors to collect objective sleep measures over an extended period of time,[25] we explored the relationship between sleep disturbances and MCI in community-dwelling seniors.

METHODS

Participants

Forty-five ambulatory community-dwelling elderly volunteers (mean age, 86.9 ± 4.3 y; 40 female) currently being monitored in their homes as part of an Oregon Center for Aging and Technology (ORCATECH) longitudinal study[26] were included in this analysis. All volunteers were recruited from the Portland, Oregon metropolitan area and provided written informed consent before participating in study activities. The protocol was approved by the OHSU Institutional Review Board (IRB#2353). Inclusion criteria were a score <5 on the short version of the Geriatric Depression Scale[27] (not depressed), a Mini-Mental State Examination[28] score of >23, and a Clinical Dementia Rating scale[29] score ≤ 0.5 (not demented). In addition, all MCI participants had to have had a diagnosis of aMCI or naMCI in ≥ 2 consecutive annual visits to be included (see the Independent variables section below). Medical illnesses with the potential to limit physical participation (eg, wheelchair bound) or likely to lead to untimely death over the monitoring period (such as certain cancers) were exclusions for the original study; for the current analysis, participants for whom >6 weeks of monitoring data were missing (due to travel, or to sensor outages) during the 26-week monitoring period were also excluded. All volunteers included in the current analysis lived alone.

Procedures

Volunteers were clinically assessed in their home at baseline upon their enrollment in the study, at 6 months (by telephone), and during annual in-home visits with research personnel who administered standardized health and function questionnaires and physical and neurological examinations. In addition, volunteers completed weekly questionnaires concerning medication changes, falls, injuries, health changes, emergency room visits, depression, changes to living space, vacations, and visitors. The Sleep Disturbance Symptom Questionnaire (SDSQ[5]) was administered online every 6 months.

To detect movement on a continuous basis, wireless passive infrared motion sensors (MS16A; http://X10.com) were placed in each room of the home (bedroom, bathroom, kitchen, living rooms, and hallway-entry areas). These sensors fire when a person moves in their vicinity, creating an event-based time series identifying when and where activity is taking place in the home. In addition, wireless magnetic contact sensors (DS10A, http://X10.com) were placed on each door of the home to track door openings and closings, allowing us to determine when the participant left the home. Data from all sensors were sent wirelessly to a dedicated research laptop computer placed in the volunteer's home, then time-stamped and stored in an SQL database. All data were encrypted and securely uploaded to a central database on a daily basis. The sensor data was used to derive nighttime activity measures, as described below, using algorithms that we developed previously.[25] Briefly, the nighttime activity measures are based on a determination of the individual's status at any given moment in time. Each time a sensor fires, the timing and sequence of the previous 15 sensor firings are considered and the status of the person is identified as out-of-bed, in-bed, or in-bed-asleep. Thus, the data are not only similar to that collected using actigraphy, but also give information about what the person does when they get up (eg, go to the bathroom). In a recent study comparing nighttime activity in 21 seniors measured using both our system and wrist-worn actigraphy over 12 days, we found a 76% ($\pm$ 11%) correlation between the measures. Similar to actigraphy, estimations of sleep are necessarily based on periods of no movement for at least 20 minutes, and so the algorithms will overestimate sleep and underestimate sleep latency in cases of insomnia where the person is lying still but awake. Thus, rather than calculate sleep latency, we instead use "settling time" (see below), which more accurately reflects that the person has ceased movement after going to bed.

As the algorithms assumed that the individual was alone at night, we necessarily excluded periods of data when the volunteer had visitors, and periods when sensor data could not be collected due to sensor malfunction or power outages or when the subject was away from home. For each volunteer, we selected the earliest 26-week period in which there were reliable sensor data for every week and included those data in the current analysis. For each volunteer, their clinical assessment within that 26-week period was used to determine cognitive status, and the SDSQ questionnaire within that period was used for the self-report responses.

Variables

Control Variables

A number of possibly confounding factors were examined to identify possible health differences between groups. Functional status was assessed using the Functional Activities Questionnaire.[30] This questionnaire assesses the participant's ability to independently perform key functional activities such as medication management, managing money, and traveling by car, bus, or taxi. The presence of comorbidities was assessed using the Cumulative Illness Rating Scale (CIRS).[31] The CIRS assesses chronic illness burden, and is significantly correlated with physician's estimates of medical burden.[32] Body mass index was calculated using the participant's weight in kilograms divided by their height (in meters) squared. This was examined because body mass index is correlated with the incidence of sleep disorders. Finally, to assess potential medication impact on patterns of sleep, we recorded the number of stimulant and sedative medications taken by each volunteer.

Dependent Variables

Subjective Assessment of Sleep Quality: The SDSQ was used to assess self-reported quality of sleep. This

questionnaire was administered every 6 months, and included 20 questions about sleep habits coded by frequency of occurrence (never, seldom, occasionally, frequently, always) on a 5-point scale (0 to 4), with higher scores reflecting that the problem occurred more frequently. Three of the questions were combined to create a subjective insomnia score (take >30 min to fall asleep, wake up at night for more than an hour, wake up too early), 3 questions were combined to create a subjective restlessness measure (have restless sleep, twitch or jerk during sleep, have restless legs at night), and 3 questions were combined to create a subjective daytime sleepiness score (feel drowsy during the day, take naps, do not wake up feeling well rested). Finally, 1 question (how many times do you get up at night: 0 = zero, 1 = once or twice, 2 = 3 or 4 times, 3 = ≥ 5 times) was used as the subjective measure of number of times up at night.

Objective Measurements of Sleep: The timing and location of the sensor firings were used to estimate a number of sleep variables that are commonly used to assess sleep. Note that as with all movement-based estimates of sleep measures, including actigraphy and bed mats, variables such as TST must be inferred from periods of inactivity. However, we have validated the algorithm used to derive these measures against ground truth measures of movement on the bed.[25] The variables we examined for this study were WASO (time spent awake after initial sleep onset until the last wakening in the morning), TST (wake time subtracted from total time in bed), settling time (time from getting into bed until the start of the first 20 min period of no movement), number of times up at night (when the participant actually got out of bed), and total movement in bed at night (number of bedroom sensor firings while the participant was in bed, a measure of restlessness). As noted, the objective measures used in this study were collected on a daily basis for a 26-week period. Because episodic activity outliers may skew the data (eg, up more frequently at night due to illness, increased restlessness due to unusual levels of daytime activity), the median of each measure was taken for each week, together with the interquartile range to assess variability within each week. These measures provide more robust estimates in the presence of outliers than do mean and variance. Thus, for each objective measure we obtained 26 weekly summaries of central tendency and variability.

Independent Variables

MCI Status: MCI status was determined using operationalized Petersen criteria.[33] Volunteers were classified as having no MCI (intact), aMCI, or naMCI based on the evaluation closest to the middle of the 26-week objective sleep recording. aMCI is characterized by a memory deficit ≥ 1.5 SD below the age-adjusted and education-adjusted norms, a subjective memory complaint usually corroborated by an informant, and essentially preserved general cognitive function and functional activities. naMCI is characterized by compromised cognitive function in other domains such as language, attention, or executive function but not in memory, without dementia or functional impairment.

Data Analysis

We used an overall MANOVA and then applied univariate ANOVA for significant results to compare the clinical status (control variables) of the volunteers across MCI groups. Similarly, the composite subjective measures were compared across groups using a MANOVA. Individual subjective measures were analyzed using a Kruskal-Wallis test to determine if any specific responses differed by MCI status. Objective measures were analyzed individually using a mixed-effects ANOVA model with time (repeated measure) as the within-subject random effect and group (intact, aMCI, naMCI) as the fixed effect. The Tukey HSD was used to control for multiple comparisons. Finally, ordinal logistic regression was used to determine if the objective measure of times up at night predicted the self-report of this measure. All analyses were done using the Matlab Statistics Toolbox.

RESULTS

Subject Characteristics

In our sample of older adults, 6 volunteers (13%) were classified as aMCI and 10 (22%) were classified as naMCI. Table 1 shows the demographic features and the means across groups for the control measures. MANOVA showed no differences between groups in any of these measures, indicating that these measures were not likely the source of differences in sleep behaviors between the groups.

Cross-Sectional Comparisons Between Healthy and MCI Participants

Subjective Measures

Very few of the participants reported substantial sleep disturbances (those that occurred frequently or always). Although in general the aMCI group reported less insomnia and restlessness than the other groups, there were no significant differences between groups in any of the individual self-report scores. Similarly, there were no differences in the self-report of the subjective insomnia score, subjective restlessness score, subjective daytime sleepiness score, or number of times up at night (Table 2). On average, volunteers reported that they slept well and got up only once a night. However, 33% of volunteers reported that they never

TABLE 1. Comparison of Demographic and Control Measures Across Groups

	Intact	aMCI	naMCI
Age (y)	87.5 ± 4.0	84.8 ± 6.6	86.5 ± 3.4
Female/male	26/3	5/1	9/1
FAQ	0.07 ± 0.26	0.67 ± 1.21	0.10 ± 0.32
CIRS	21.9 ± 2.42	20.5 ± 2.66	22.8 ± 2.53
GDS	0.86 ± 1.30	0.83 ± 0.75	1.60 ± 1.96
MMSE	28.3 ± 2.06	27.2 ± 1.48	28.0 ± 1.89
BMI	27.0 ± 3.91	26.5 ± 3.35	27.8 ± 4.87
BMI range	19.5-33.8	21.0-29.8	21.1-38.3
Medications (%)			
None	59	33	50
Stimulants	21	33	40
Sedatives	3	0	0
Mixed	17	33	10

MANOVA revealed no differences between groups. Although the FAQ scores were higher for aMCI volunteers than for the other groups, these differences were not significant after adjustment for multiple comparisons.

aMCI indicates amnestic MCI; BMI, body mass index; CIRS: Cumulative Illness Rating Scale; FAQ: Functional Activities Questionnaire; GDS: Geriatric Depression Scale; MCI, mild cognitive impairment; MMSE: Mini-Mental State Exam; naMCI, nonamnestic MCI.

TABLE 2. Means and SDs of Self-reported Sleep Measures for Each Group

Measure	Intact (29)	aMCI (6)	naMCI (10)	*P*
SDS	1.80 ± 0.15	1.50 ± 0.32	1.97 ± 0.25	0.69
SIS	1.27 ± 0.15	0.76 ± 0.32	1.64 ± 0.25	0.21
SRS	1.02 ± 0.14	0.38 ± 0.29	0.70 ± 0.23	0.34
No. times up at night	1.13 ± 0.14	1.00 ± 0.29	1.00 ± 0.23	0.77

MANOVA revealed no differences between groups.
Numbers of participants in each group are shown in parentheses.
SDS indicates subjective daytime sleepiness score; SIS, subjective insomnia score; SRS, subjective restlessness score.

or seldom woke up feeling rested, and 27% reported that they frequently or always took naps.

Objective Measures

Figure 1 shows an example of the longitudinal data collected using the in-home sensors over the 26-week period, across the 3 groups. In general, there was marked week-to-week variability in the median weekly measures over the 26 weeks for all measures and for most volunteers. There were no significant effects of time on the objective measures, nor were there group × time interactions. Overall, the aMCI group showed significantly less sleep disturbance than the other groups: less movement in bed at night ($F_{2,1078} = 4.30$, $P = 0.05$), less time for WASO ($F_{2,1078} = 41.6$, $P < 0.001$), and fewer number of times up at night ($F_{2,1078} = 26.7$, $P < 0.001$). However, their TST was not different than the other groups. In contrast, the naMCI group showed greater settling time at night than the other groups ($F_{2,1078} = 59.17$, $P < 0.001$).

Similar trends were seen in the weekly interquartile ranges; both the WASO IQR ($P < 0.003$) and number of times up at night IQR ($P = 0.0004$) were significantly smaller for the aMCI group, indicating that they had less day-to-day variability in these measures than the intact and naMCI volunteers. Despite this intersubject variability, the between-subject variability was greatest for aMCI subjects and least for the intact subjects. Table 3 summarizes the results of the analysis of the objective measures.

Both the average number of times up at night over the past 26 weeks and the median number of times up in the week immediately preceding the questionnaire were fitted using ordinal logistic regression to determine if these values predicted the self-report estimate of number of times up at night. Both objective measures predicted the self-report measure (previous 26 wk: $\chi^2 = 8.15$, $P = 0.017$; previous week: $\chi^2 = 8.65$, $P = 0.013$). Sixty-five percent of volunteers got up once or twice at night. However, 47% of volunteers misreported their number of times up at night, with approximately equal numbers overreporting and underreporting. However, there were no differences across groups in this ability to report how often they got up at night.

DISCUSSION

Using in-home sensors to collect ongoing objective measures of sleep and nighttime behaviors, we found that

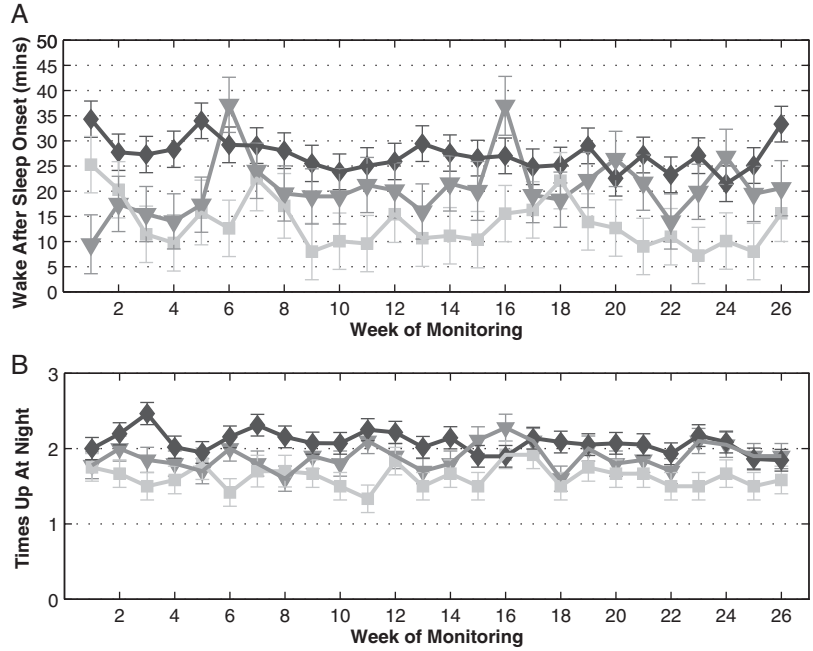

FIGURE 1. Example of the 26-week longitudinal data across groups. Group means were calculated from the median of the daily measures for the week for each volunteer. Black diamonds: intact volunteers; light gray squares: aMCI; dark gray triangles: naMCI. Top plot: wake after sleep onset; bottom plot: times up at night. Statistical significance bars calculated using the pooled variance across weeks for each group.

TABLE 3. Means and SDs of Objective Sleep Measures Across Groups

Measure	Intact (29)	aMCI (6)	naMCI (10)
Movement in bed (in sensor firings)‡	9.40 ± 0.40	7.81 ± 0.88	10.85 ± 0.68
Wake after sleep onset (min)*	27.22 ± 1.19	13.51 ± 2.62	20.64 ± 2.02
Total sleep time (h)	8.34 ± 0.04	8.50 ± 0.09	8.45 ± 0.07
Settling time (min)§	2.5 ± 0.07	2.32 ± 0.15	3.07 ± 0.11
No. times up at night (# times)*	2.08 ± 0.04	1.63 ± 0.10	1.89 ± 0.08

All *P*-values after correction for multiple comparisons.
Number of participants in each group are shown in parentheses.
*$P < 0.001$ for aMCI < intact, naMCI.
‡$P < 0.05$ for aMCI < naMCI.
§$P < 0.001$ for naMCI > intact, aMCI.

aMCI, naMCI, and cognitively intact volunteers show different patterns of sleep disturbances. In particular, aMCI volunteers had less disturbed sleep than both naMCI and cognitively intact volunteers, as measured by movement in bed at night, WASO, and number of times up at night. In general, the naMCI volunteers showed a level of disturbed sleep that was intermediate to that of aMCI and intact volunteers. The 1 exception was movement in bed, which measured restlessness at night, and which was greater in naMCI volunteers than in aMCI volunteers. These differences were seen even though the self-report of sleep behaviors did not differ between groups. Interestingly, the TSTs were equivalent across groups, which is consistent with the few reports of this measure in patients with MCI.[34] The relationship between sleep and MCI status is challenging to untangle given the evidence that poor sleep can lead to compromised cognitive function.[21,35,36] A recent study by Westerberg et al[21] suggested that poorer scores on next-day word and face recall were associated with less time in bed and with lower subjective sleep quality in aMCI volunteers but not in intact volunteers. However, they did not see an influence of TST or WASO on the next-day scores, nor did they see differences in objective sleep measures derived from actigraphy between intact and aMCI volunteers.

In contrast with past studies, our findings suggest that aMCI volunteers typically experience less sleep disruption during the night than cognitively intact volunteers. Some studies using objective measures of sleep, such as PSG[37] or actigraphy data,[21] found no differences between aMCI patients and healthy controls in sleep measures such as WASO, TST, and sleep latency. Other PSG studies have reported a greater number of SWS arousals,[24] shifts from non-REM sleep,[38] and arousals due to PLMs[22,23] in aMCI and demented patients. One possible reason for the difference in our findings is that SWS arousals and shifts from non-REM sleep, measurable only with PSG, may occur more frequently in aMCI patients. Even PLMs may be small enough so that our sensors do not capture them. As actigraphy also does not capture PLMs, this would also explain why this increase has been reported in PSG but not in actigraphy studies. However, PSG is known to be disruptive to sleep,[39] with a strong "firstnight effect." As our data are collected continuously over 6 months, our approach provides data about individual's "typical" night rather than a single night in a PSG clinic. This would be consistent with Westerberg's finding that the variability in sleep latency, WASO, and TST were correlated with performance on the memory tests for aMCI patients—that is, these measures may be highly variable in an aMCI population.[21] Our measures capture differences in night-to-night sleep disruption that are not seen with PSG.

Of great interest is the recent observation in humans that suggests that those with less disrupted sleep have lower CSF β-amyloid concentrations,[40] a CSF profile associated with AD. Although we do not have CSF β-amyloid concentrations for our participants, given the greater association of aMCI with AD, it is plausible that the sleep metrics we have observed may reflect underlying amyloid production dynamics regulated in part by activity cycles associated with the development of AD.

It is notable that only about half of the volunteers were able to reliably report how often they got up at night. Accurate measures of nighttime behaviors such as number of times up at night are particularly important for medication studies, where reliable measures are needed to determine if a medication intended to improve, for example, nocturia is effective. This difficulty in self-report may be in part due to the significant night-to-night variability that is revealed by the objective measures. When reporting sleep behavior during a clinic visit, patients will undoubtedly vary in what experience they choose to emphasize. For example, they may report the most recent night's sleep, or their general impression of the past couple of weeks.

The fact that self-report measures did not differentiate the groups—even for a measure that was well correlated with its equivalent objective measure (number of times up at night)—underscores the value of collecting frequent in-home measurements. Over a 26-week period, all of the measures showed marked variability for most volunteers, reflecting the many influences such as life events (eg, illness or death of friends or family) on sleep in a geriatric population. Some volunteers showed periods or bursts of increased disruption over the 6-month period. We did not treat these periods differently, but this variability over the 6-month period is a likely factor in the lack of an effect of time in our current models.

Although there were no differences between groups in their use of stimulants and sedatives, we did not record caffeine consumption and therefore this may have varied across the groups. If so, this could account for differences in restlessness. In addition, our sample size was small, and a larger study is needed to verify these results. However, the differences between groups were quite large even in this small sample. Another limitation of this study is that it was a cohort of the oldest old, and due to their age the participants were mostly women; thus a younger cohort may show different patterns of sleep disturbances.

Future work needs to take into account factors such as life events, seasonality, and holidays that may disrupt sleep at different time scales. Unobtrusive capture of continuous measures of sleep collected over extended periods of time provide important insights into the sleep patterns of healthy and cognitively impaired individuals, and enable the conduct of longitudinal studies. More in-depth analyses may identify specific factors resulting in acute changes in sleep patterns as well as long-term trends and their implications for declines over time in specific neurocognitive domains, as well as the risk of developing dementia and other critical health outcomes.

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