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Symptoms of sleep disturbance in persons with Alzheimer's disease and normal elderly

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SUMMARY

We retrospectively analyzed sleep time and sleep disturbance symptoms in 399 healthy, non-demented elderly (NDE) and 263 persons with a diagnosis of possible (n = 53) or probable (n = 210) Alzheimer's disease (AD). Our primary objective was to determine differences in subjective sleep disturbance between these samples. Secondary objectives were to determine if subjects with time in bed (TIB) ≤6 h per night reported more sleep disturbance and whether sleep complaints were associated with more severe cognitive and/or functional impairment. The prevalence of 'sleep problems' (a single item) was significantly lower in NDE (18.3%) than AD (27.6%), and the proportions of each cohort reporting TIB ≤6 h per night were very low (NDE: 6.0%; AD: 3.5%) and not significantly different. Less TIB was correlated with better cognitive function for AD (P < 0.01), and cognition and function were significantly worse for AD subjects with estimates of >6 h of TIB compared with those with estimates of ≤6 h (P < 0.05). Greater sleep disturbance was correlated with greater functional impairment in both cohorts; but only in AD did greater estimated TIB also correlate with greater functional impairment (all P < 0.05). In general, estimated TIB was not associated with mood in either cohort; however, in both cohorts depression was significantly associated with sleep disturbance symptoms and was significantly worse in those who reported having 'sleep problems'. There was no association between subjective perception of 'sleep problems', the number and frequency of sleep disturbance symptoms, and estimated TIB in either group.

Keywords

alzheimer's disease; healthy elderly; measurement; sleep; sleep disturbance

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INTRODUCTION

Sleep becomes more fragmented as we age, with more nighttime awakenings and greater tendency for daytime sleep (Bliwise, 1999). Alzheimer's disease (AD) causes further degeneration of sleep patterns (Bliwise, 1993; Bootzin *et al.*, 2000). Sleep-related problems generally increase as AD progresses (Moe *et al.*, 1995). More frequent nighttime awakenings develop, daytime sleep increases and both slow-wave sleep and REM sleep are decreased (Prinz *et al.*, 1982; Vitiello and Borson, 2001). Sleep disturbances may contribute to the behavioral, functional, and cognitive status of persons with AD, as well as to the burden and health status of the caregiver (Pollak and Perlick, 1991; Pollak and Stokes, 1997). For these reasons, sleep disturbance has recently been of particular interest in the AD population. For example, the Alzheimer's Disease Cooperative Study (ADCS; Thal, 1997), a federally sponsored consortium of AD research centers, recently completed a large (n = 157) clinical study of melatonin in the treatment of sleep disturbances in persons with AD (Singer *et al.*, 2003). The emergence of sleep disturbance in persons with AD as a research topic has gained momentum because of clarification of diagnostic criteria, namely, that six or fewer hours of sleep are one 'symptom' of sleep disturbance in this population (Yesavage *et al.*, 2003) and by extension, new instruments and methods to measure symptoms and changes in them in response to interventions (e.g. Tractenberg *et al.*, 2003).

In the present report, we describe the frequency and prevalence of 20 self- or caregiver-reported sleep disturbance symptoms in a cohort of persons diagnosed with probable or possible AD (McKhann *et al.*, 1984) and a normal elderly control group. Our primary objective was to address two key questions: (i) what are the prevalence rates of sleep disturbance symptoms in these two populations (and are the rates different)? (ii) Is cognitive status associated with greater prevalence, worse symptomatology, or a different range of symptoms? A secondary objective was to determine if more sleep disturbance was reported by AD patients with ≤6 h TIB versus those with >6 h TIB.

METHODS

Subjects

Subjects with AD presented with memory complaints on referral by either self, family or health care provider. Each subject's clinical history and exam findings were presented at a weekly case conference where a consensus diagnosis was reached by a team of neurologists, geriatric psychiatrists, and neuropsychologists. Cognitively intact participants [nondemented elderly (NDE)] were research subjects in a longitudinal study of normal aging. These subjects are known to have been cognitively intact at the time they completed the questionnaire based on the extensive neurological and neuropsychological assessment they received as per protocol of the Oregon Brain Aging Study (OBAS) (Howieson *et al.*, 2003; Kaye *et al.*, 1994). The analyses presented here focus on these NDE (n = 399) and on the clinic patients who met the NINCDS-ADRDA (National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association) criteria for probable (n = 210) or possible (n = 53) AD (McKhann *et al.*, 1984). Table 1 presents the characteristics of these participants with respect to demographics. Consent to include personal and clinical data in the research database used in this study was

signed by all participants at the time of their initial evaluation and enrollment. The data analyzed for this report include all AD patients and NDE subjects whose data were archived as of September 2002.

Instruments

Several instruments were administered at each participant's first visit to the clinic. The Mini-Mental State Exam (MMSE; Folstein *et al.*, 1975), ranging from 0 (worst) to 30 describes general cognitive functioning and is consistently used in dementia-related studies and clinical trials. The functional status questionnaire used in the assessments was a modified Activities of Daily Living/Instrumental Activities of Daily Living (ADL/IADL) questionnaire based on Older American Resources and Services Multidimensional Functional Assessment Questionnaire, an instrument that is sensitive to functional decline in people with dementia (Njegovan *et al.*, 2001). The questionnaire covers nine items of ADL function (eating, dressing/undressing, combing hair or shaving, walking, getting out of bed, bathing or showering, toileting, continence, and outside mobility) and seven items of IADL function (using telephone, traveling by car, bus or taxi, shopping for food or clothing, preparing meals, doing housework, taking own medicines and handling own money). All items are scored on a three-point scale of assistance required: none, slight or full; total ADL and IADL scores are separately derived as the sum of assistance-requirement ratings ranging from 0 (best) to 27 (worst, ADL) or 21 (worst, IADL).

The Cornell Depression Scale (Alexopoulos *et al.*, 1988a) comprised of 19 items covering mood or affect signs, behavioral disturbances, physical symptoms of depression, sleep and diurnal symptoms, and depressive thinking. This scale was completed by the clinician at the time of the initial clinic assessment. Higher scores indicate greater levels of depression. This instrument has been validated in both demented and NDE subjects (Alexopoulos *et al.*, 1988b).

The sleep disturbance symptom questionnaire (SDSQ, described below) is composed of questions covering 20 symptoms of sleep disturbance. The questions that comprise the SDSQ are part of a larger questionnaire (Personal and Family History Questionnaire) including personal and family medical histories, review of symptoms and functional status. The large questionnaire, including the 20 sleep-related items, was developed at the Oregon Health and Science University (OHSU) Layton Aging and Alzheimer's Disease Research Center for clinical assessment. The form is completed prior to the first clinic visit; cognitively intact participants fill it out themselves while persons with AD almost always have the assistance of a family member or caregiver.

In addition to the SDSQ, individuals included in the present analyses were also administered cognitive, functional, and depressive symptom instruments as part of their diagnostic evaluation in the Layton Aging and Alzheimer Clinic at OHSU and the Dementia Clinic of the Portland Veterans Affairs Medical Center. This report also describes data for non-demented controls who underwent identical assessments as part of an ongoing federally funded study of normal neurological aging.

In completing the questionnaire, subjects reported their 'usual' bed and wake times, from which we calculated their usual time in bed (TIB) each night. As the SDSQ did not include estimates of actual sleep time (such estimates are not likely to be accurate), we were not able to evaluate specific sleep time variables.

The SDSQ, as noted above, was completed by the participant prior to the first clinic visit. The questionnaires of the dementia patients were almost always completed by a family member, except in rare cases of very mild dementia in which the patients were able to complete the forms with little or no assistance. The subjects in the OBAS (NDE) cohort were able to complete the questionnaire on their own. The completion rates for the SDSQ and other items of the Personal and Family History Questionnaire were over 80% for the clinic (AD) cohort, and nearly 100% for the OBAS (NDE) cohort.

The 20 items of the SDSQ are rated for frequency 'in previous months' (i.e. an unspecified period of time), and are augmented by two additional queries: frequency of 'awakening feeling well-rested' and whether or not they considered themselves (or the patient) to have 'sleep problems'. These additional items are included in Table 2 (but were not included in the calculation of prevalence or total SDSQ scores). The inclusion of these two items allowed us to examine the subjective impact of the frequency of sleep disturbance symptoms on each respondent's sleep. In addition to summing the 20 frequency ratings to generate a total SDSQ score (0–80, higher scores suggesting more disturbance), we calculated the prevalence (endorsement) of each of the 22 items on the SDSQ.

The SDSQ also asks subjects to record their 'usual' bed and wake times. From this information, we calculated an estimate of their typical nighttime total TIB. As this is a questionnaire-based study that includes persons with dementia who in most cases would not be able to remember specific hours of sleep, we are not able to reliably determine actual sleep times or sleep duration. Fortunately, typical bed and wake times as reported on the SDSQ are likely to be known by family and caregivers and provide a reliable estimate of average TIB. For purposes of this analysis, this estimate of usual total TIB at night must serve as a surrogate for sleep time. We must emphasize that the reported values for TIB would likely overestimate sleep, and possibly even actual TIB, as there could be awakenings that might either be unknown to the caregiver or not reported in response to a question of bed and wake times.

Statistical methods

Correlations were calculated between the SDSQ scores (total score and endorsement rates) and TIB. To assess the impact of non-sleep variables on sleep symptoms, correlations were calculated between the SDSQ scores and all non-sleep related variables: age, AD duration, education level, MMSE, ADL, IADL, and Cornell Depression Scale. Finally, to evaluate the scope and breadth of the sleep disturbances observed in the two cohorts, mean frequency ratings and endorsement rates for each symptom were compared across cohorts by independent- samples *t*-tests. As our secondary objective was to validate a sleep duration criterion for sleep disturbance in AD that has recently been proposed for use in clinical trials (Yesavage *et al.*, 2003), we compared subjects with ≤6 h of TIB with those with >6 h TIB to determine if the time criterion correlates with SDSQ or TIB. (Tractenberg *et al.* (2003)

describe a similar comparison; in their study of 154 AD patients with ‘sleep disturbance’, only 43% of that sample met the <6-h criterion (p. 336); we altered the cutoff to include 6 h in this community-based sample in order to increase the number of individuals who might be considered in this group.)

All analyses were performed using SPSS v. 11.2 (2003; SPSS Inc., Chicago, IL, USA). Tests of the normality of the distributions of all continuous measures revealed significant skew and kurtosis in spite of essentially symmetrical distributions. Therefore, means and standard deviations for scores were calculated, along with modal values, for ratings of the 20 SDSQ symptoms. Nonparametric correlations (Spearman’s rho) and *t*-tests (Mann–Whitney), as well as chi-square tests were performed. *P*-values for the 22-item level tests were adjusted according to Holm (1979) and adjusted $P < 0.05$ were considered significant.

RESULTS

Cohort characteristics

The AD subjects ($n = 263$) averaged 74.0 ± 11.8 years of age. A small majority was female (54.0%) and well educated (average years of education = 13.6 ± 3.3). Average MMSE at the time of assessment was 19.2 ± 6.4, indicating a mild to moderate degree of dementia. The NDE in the OBAS ($n = 399$) were significantly older than patients with AD ($P < 0.001$), but had similar educational attainment ($P > 0.05$). There was a slightly higher proportion of females (60.1%) in the healthy group and the MMSE scores were all in the normal range (mean = 28.2 ± 1.5). As can be seen in Tables 1–5, not every subject had scores for every measure; therefore the total numbers in the tables and reported proportions may vary by 5–10 individuals.

SDSQ characteristics

Two values were calculated based on the SDSQ symptom responses. The ‘sleep disturbance score’ (sum of 20 frequency ratings, excluding ‘awakens feeling well rested’ and ‘sleep problems’) and the number of items (of 20) rated as having occurred at least once per month, or endorsed. On average, average total sleep disturbance scores were 17.1 (of a maximum of 80) in each cohort; and on average, just over five of the 20 items were endorsed in both groups. Both overall and at the symptom level, these two cohorts exhibited similar degrees and types of sleep disturbance. Table 2 presents the item-level descriptive statistics for the 20 SDSQ symptoms as well as the prevalence of the two additional items, ‘awakens feeling well rested’ and ‘sleep problems’.

For 13 of the 20 symptoms the most frequent response (modal frequency) in both cohorts was that they did not occur more than once a month. In addition to these 13 items (equivalent day and night sleep; lying awake tense/worried; snoring heavily; trouble breathing; breathing irregularly; twitch/jerk in sleep; wake with headache; wake up at night in pain; use medication or alcohol to get to sleep (two items); has bowel/bladder problems at night; has muscle cramps during sleep; and has restless legs during sleep) an additional three items had a modal response of zero for AD patients (takes >30 min to fall asleep; wake up at night for >1 h; wake up too early); however, in the non-demented cohort, the most frequent

ratings for these three items were once per month (1) or at least once per month (2) (see Table 2). Three other items (gets up at night; is drowsy during the day; and takes naps during the day) had modal frequency ratings of 2 in both cohorts, corresponding to occurring at least once per month. Also, both cohorts identified the same items as the most frequently occurring (wakes up during the night) and least frequently occurring (uses alcohol to get to sleep). Thus, in terms of reported specific symptoms of sleep disturbance, these cohorts appear fairly similar.

Sleep disturbance symptom differences

In terms of nighttime behaviors, the prevalence and frequency of half of the SDSQ items was greater in the NDE cohort than in AD, including number of wake ups per night, sleep latency (>30 min to fall asleep), waking up too early, and waking at night with pain (see Table 2). Conversely, two daytime behaviors were differentially exhibited in the AD cohort: napping during the day was marginally significantly more frequent (adjusted $P = 0.054$) and significantly more prevalent (adjusted $P = 0.045$) in the AD cohort than in NDE; drowsiness during the day was significantly more frequent (adjusted $P = 0.015$), but not more prevalent in the AD cohort than in NDE. Nighttime items where the AD cohort had greater prevalence or frequency include snoring heavily, breathing irregularly, twitching and waking up with a headache (see Table 2). Thus, in general, the NDE endorsed symptoms of insomnia with greater frequency and severity than did the AD patients, whereas symptoms of daytime sleepiness and symptoms suggestive of sleep disordered breathing, periodic leg movements, or a primary arousal disorder tended to be more common in the dementia group.

SDSQ and estimated sleep time

Correlation coefficients were calculated separately for persons with and without AD. For both groups, the association between the number of SDSQ symptoms endorsed and sum of frequency ratings (both excluding ‘awakens feeling well rested’ and ‘has sleep problems’) with our estimate of nighttime total sleep time (TIB) was positive and significant (i.e. all $P < 0.05$), suggesting that more TIB coincided with more symptoms of sleep disturbance. However, the correlation coefficients were <0.15 in every case, i.e. explaining <3% of the variance in estimated sleep time. The correlations between the sleep variables are given in Table 3.

SDSQ, TIB and non-sleep variables

In the non-demented individuals, no association was observed between MMSE and SDSQ (neither number endorsed nor total score) or TIB (all $P > 0.16$), and although MMSE was not associated with SDSQ in persons with AD, lower MMSE was significantly associated with a greater amount of TIB ($\rho = -0.276$, $P < 0.001$). In persons with AD, significantly worse functional impairment was associated with both SDSQ (ADL and total: $\rho = 0.378$; IADL and total: $\rho = 0.248$; ADL and number endorsed: $\rho = 0.356$; IADL and number endorsed: $\rho = 0.256$; all $P < 0.01$) and TIB (ADL: $\rho = 0.355$; IADL: $\rho = 0.395$, both $P < 0.01$). In NDE, while ADL was not associated with TIB ($\rho = 0.071$), IADL was ($\rho = 0.194$, $P < 0.01$) as was the case for the AD cohort. Like in the patient cohort, the associations in NDE between function and both sleep symptom variables were significant (ADL and total

SDSQ: $\rho = 0.260$, IADL and total SDSQ: $\rho = 0.169$; ADL and number endorsed: $\rho = 0.247$, IADL and number endorsed: $\rho = 0.171$; all $P < 0.01$). For both non-demented and AD cohorts, significant association was observed between depression scale scores and the two SDSQ variables (all $P < 0.01$), but not with TIB.

Respondent sex was associated with the number of symptoms endorsed for both non-demented and AD, but SDSQ scores and endorsement rates were higher for women than men in the non-demented cohort (F > M, $z = -2.4$, $P < 0.05$) and lower for women than men in the AD cohort (M > F, $z = -2.2$, $P < 0.05$). Age was positively associated with TIB in the nondemented cohort ($\rho = 0.125$, $P < 0.05$) and all three sleep variables were positively associated with age in the AD cohort (TIB: *rho* = 0.291, $P < 0.001$; sleep score: *rho* = 0.141, $P < 0.05$; number of sleep symptoms endorsed: *rho* = 0.183, $P < 0.01$). Education was not significantly associated with any sleep variable in either cohort (all $P > 0.06$).

Clinical/practical utility of sleep time and sleep symptoms

Each cohort was divided into two groups according to whether the time between reported 'usual bedtime' and 'usual wake time' reflected 0–6.0 h (≤6 h = disturbance) or at least 6.01 h (>6 h = no disturbance) recently proposed as one component in the diagnosis of sleep/wake disturbance in persons with AD (Yesavage *et al.*, 2003). Table 4 contains the mean values and standard deviations of SDSQ, TIB and non-sleep scores for the NDE and AD groups, broken down according to the 6-h criterion. Based on TIB, 3.5% of the AD cohort and 6.1% of the non-demented cohort had in-bed and wake times suggesting 6 h of sleep or less; these proportions were not different in the two groups ($P > 0.10$).

It can be seen in Table 4 that persons in the NDE cohort with TIB ≤6 h were no different from individuals with TIB >6 h in terms of the sleep and non-sleep variables. However, in the AD cohort, persons with TIB ≤6 h tended to be diagnosed with AD at a younger age and have higher MMSE scores (both $P < 0.05$) and required less assistance with ADLs ($P < 0.05$) and IADLs ($P < 0.01$) when compared with those who had TIB >6 h.

The cohorts were collapsed over the TIB criterion and then each was divided according to responses to the 'sleep problems' item. Table 5 presents the means and standard deviations of SDSQ, TIB and non-sleep scores for the NDE and AD groups, broken down according to endorsement of 'sleep problems'.

Significantly more of the AD cohort (27.6%) were reported to have 'sleep problems' when compared with the NDE cohort (18.3%) ($\chi^2 = 7.7$, $P < 0.01$). Within the AD cohort, persons with sleep problems had significantly more education, significantly longer duration of AD, and needed significantly more assistance with ADLs (all $P < 0.05$). Additionally, they had significantly more depressive symptoms and sleep disturbance symptoms (all $P < 0.01$). Less than 3% of those with sleep problems reported TIB ≤6 h; <4% of those without sleep problems reported this amount of TIB.

Within the NDE cohort, persons with sleep problems were significantly older ($P < 0.05$) and unlike the AD cohort, had significantly *less* education ($P < 0.01$) than those without sleep

problems. Similar to the AD cohort, significantly more depressive and sleep-disordered symptomatology were reported in persons with sleep problems (all $P < 0.01$).

To summarize Tables 4 and 5, the question about 'sleep problems' was endorsed for 27.6% of persons with probable or possible AD and of these, two (2.8%) had TIB ≤6 h. TIB estimates for this cohort were six or fewer hours in 3.5% of this cohort and of these 'short sleepers', two (22.2%) indicated that they 'had sleep problems'. That is, more caregivers of AD patients report that the subject has 'a sleep problem' than report that the subject is a short sleeper; very few caregivers reported both of these for any AD patient. This pattern was similar in the NDE: 18.3% indicated they had sleep problems, and 25% of these individuals estimated their TIB to be six or fewer hours. Of the 6.0% of this cohort who indicated TIB of six or fewer hours 8.2% also reported having sleep problems. Further analyses are underway to clarify the exact nature of the differences in prevalence and frequency of SDSQ symptoms reported by persons in each cohort with 'sleep problems' endorsed and not endorsed.

DISCUSSION AND CONCLUSIONS

These results indicate that the prevalence rates of specific sleep symptoms are similar in older, non-demented individuals (average age 80+) and slightly younger persons with mild to moderate AD (average age 74), slightly more NDE (6.0%) than AD (3.5%) were reported to be 'short sleepers' while a significantly greater proportion of AD subjects were reported to have 'sleep problems' (18.3% for NDE versus 27.6% for AD). The prevalence rate of 'sleep problems' in our AD subjects is remarkably consistent with another questionnaire-based estimate of 27.4% for sleep disturbance in an AD cohort (Lyketsos *et al.*, 2002), although higher prevalence rates have also been reported (43% by Chen *et al.*, 2000; 54% by Hart *et al.* 2003). Relative to the proportion endorsing 'sleep problems', the proportion of subjects in each cohort in bed six or fewer hours per night was only one-third as high for NDE (6.1% versus 18.5%), and just over one-tenth as high for persons with AD (3.5% versus 27.5%). We also found that 'short sleepers' are not the same people who have 'sleep problems'. In fact, prevalence of 'sleep disturbance' that was based on the presence of both would be estimated at<2%of NDE (6/399) and<1%of AD (2/261).

Not many caregivers of AD subjects reported short sleep, but many did report symptoms of sleep disturbance such as being drowsy during the day (67.9%), taking longer than 30 min to fall asleep (25.5%), waking up at night for more than 1 h (24.1%) waking too early (36.0%) or having restless sleep (33.1%). Given such high percentages, it is curious that only 27.6% endorsed 'sleep problem' for the AD subjects; it also suggests that caregivers and NDE alike do not consider short sleeping to be a problem. It is possible that although symptoms such as daytime sleepiness, long sleep latency and others are common in AD patients, caregivers may not report a sleep problem unless their own sleep is disturbed. This is a major weakness of questionnaire-based studies of sleep disturbance prevalence in AD patients.

The fact that our NDE subjects were describing their own sleep may be a reason they reported higher levels of sleep symptomotology than the AD subjects; conversely the finding that the two groups were very similar in terms of the symptoms endorsed might

reflect some commonality between the caregivers and the NDE in addition to similarities between the sleep disturbances experienced by NDE and persons with AD. Any comparisons between these two groups (NDE and AD), however, must be tempered by the fact that the NDE subjects completed the questionnaires on their own, whereas most of the AD subjects' caregivers completed the SDSQ for them. Whether an observer is more or less likely to report sleep symptoms might affect the sleep symptom endorsements, although exactly how is unclear. The validity of most rating scales in studies of AD hinge on this issue and it therefore deserves more study.

Our data also suggest that a time or sleep duration-based criterion for sleep disturbance significantly underestimates prevalence of sleep disturbance. Although we observed statistically significant associations between TIB and the two SDSQ variables (total ratings and number of symptoms endorsed), the amount of variance in TIB explained by either SDSQ score was <3% in both cohorts. This result is similar to our previous report of small (6%) but significant explanatory power for an actigraphy-based estimate of nighttime sleep time and assessed sleep disturbance; we recently reported on sleep disturbance symptoms for a cohort of AD patients using an instrument called the Sleep Disorders Inventory (SDI; Tractenberg *et al.*, 2003). The SDI is a seven-symptom inventory of sleep disturbance symptoms developed for a large multicenter clinical trial of melatonin for the treatment of sleep disturbance in AD (Singer *et al.*, 2003). Derived from a well-known instrument, the Neuropsychiatric Inventory (Cummings *et al.*, 1994; Mega *et al.*, 1996), the SDI was adapted for standardized use with demented patients after the present data had already begun collection. Tractenberg *et al.* (2003) reported that, although greater sleep disturbance was reported by the AD subjects with less sleep time, this negative association was statistically significant but not particularly strong. This conflicts with the findings presented here (of a small, but significant positive association between sleep time and sleep disturbance), although in both studies, the associations were weak (even if statistically significant). Three important distinctions between the two studies are: (i) the clinical trial subjects were individuals whose caregivers reported both short sleep and sleep disturbance symptomatology; and (ii) the SDI has seven symptoms, thus a smaller potential range for scores, whereas the range of the SDSQ is 0–80; and (iii) sleep time in the clinical trial was estimated using actigraphy whereas in our community-based study we relied on TIB. The conflict further supports our contention that persons with both short sleep and sleep disturbance symptoms are different from those with one or the other, and could readily be resolved by replicating these analyses in an independent community cohort with more carefully measured sleep times.

The consistency between those results and ours here, in terms of sleep duration being a poor predictor of symptoms of sleep disturbance, reinforces the conclusion by Yesavage *et al.* (2003) that a definition of sleep disturbance in AD patients should not rely only on a threshold of total sleep time as this will not reflect the caregiver's major perception of sleep disturbance in AD patients. Requiring both short sleep and the presence of disturbance symptomatology will make recruitment into trials more difficult than necessary and make recruitment of what are clearly atypical subjects more likely (Tractenberg *et al.*, 2003); although the results we describe in this report are based on a sleep questionnaire, they

certainly support the concept that a time-based sleep disturbance criterion alone is not adequate for either clinical diagnosis or clinical trial design. In fact, Yesavage *et al.* (2003) proposed the criterion of sleep duration <6 h as one of four types of sleep disturbance patterns (along with prolonged wakefulness after sleep onset, excessive daytime sleep, and altered circadian pattern of sleep) to be typical of AD sleep disturbance. They propose that two of these four sleep disturbance patterns in AD patients need to be present to fulfill criteria for a sleep disorder diagnosis (Yesavage *et al.*, 2003). Our results suggest that subjective perception of the presence of a 'sleep problem' might also be included for this diagnosis, as well as supporting the inclusion of some sort of assessment of the reporter's own sleep.

While MMSE scores were not correlated with SDSQ scores, more TIB was cross-sectionally associated with worse dementia (cognition and function scores) in this AD cohort; similar results were reported by Maggi et al. (1998) based on a survey of 2398 community-dwelling elderly (non-demented) Italians. Several investigators have reported that nighttime sleep fragmentation worsens as AD progresses (McCurry *et al.*, 1999; Moe *et al.*, 1995; Pat-Horenczyk *et al.*, 1998; Vitiello *et al.*, 1990). Investigators also report daytime sleepiness increases as dementia progresses (Ancoli-Israel *et al.*, 1989; Prinz *et al.*, 1982). An association between more TIB and lower MMSE scores may indicate more nighttime sleep fragmentation, leading to lower sleep efficiency and therefore more TIB, or it could actually reflect longer sleep periods. Declines in sleep efficiency may be indicative of worse sleep-related breathing problems and periodic leg movements in more severe dementia (Vitiello and Borson, 2001). On the contrary, it could also indicate hypersomnia secondary to impaired daytime arousal in AD, as has been suggested in earlier reports (Pat-Horenczyk *et al.*, 1998). Apathy may be more pronounced as AD progresses (Cummings and Kaufer, 1996) and this also could conceivably lead to more TIB in severely impaired patients. There are many conditions that can account for longer times in bed; as we did not measure actual sleep time, apathy, or other potentially explanatory variables formally, we cannot comment further on the finding. However, we still have many options for further analyses of the data we have collected; future research needs to clarify these issues. Sleep research in AD needs to emphasize not only insomnia (short sleepers) but hypersomnia (long sleepers) as well.

The SDSQ scores were associated with respondent sex in our data, and this association was different depending on the cognitive status of the cohort. Studies of sleep and circadian rhythms in older adults and those with dementia have only inconsistently shown gender differences in daytime sleepiness, insomnia, and circadian phase (Bliwise, 1989); Tractenberg *et al.* (2003) and Voderholzer *et al.* (2003) independently found neither objective nor subjective reports of sleep disturbance to be associated with respondent sex. In this study, endorsement of 'sleep problems' and the prevalence of an estimated TIB ≤6 h were not different for men and women in either cohort. Our sex effects were observed in terms of both summaries of subjective ratings: the number of 20 sleep disturbance symptoms endorsed and in the total sleep disturbance score. It is possible that some of the differences across reports may be due to whether the respondent answers for him or herself, or describes a sleep partner; the meaning of our apparently conflicting results is uncertain.

In conclusion, we have shown that very old but healthy older adults report nearly as much sleep disturbance as seen in patients with AD, although this may reflect reporter bias that is inherent to our methodology. Short times in bed at night do not account for the presence of sleep complaints in either group. Our results support the basic concept incorporated in recently proposed diagnostic criteria for sleep disturbance in AD, in that short sleep alone is an inadequate marker of sleep disorder in these patients; long sleep might also be of concern. These data also suggest that the recently published definition of sleep disturbance in persons with AD (Yesavage *et al.*, 2003) might actually also pertain to individuals who are cognitively intact.

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References

Alexopoulos GS, Abrams RC, Young RC, Shamolan CA. Cornell scale for depression in dementia. Biol Psychiatr. 1988a; 23:271–284.

Alexopoulos GS, Abrams RC, Young RC, Shamolan CA. Use of the Cornell Scale in nondemented patients. J Am Ger Soc. 1988b; 36:230–236.

Ancoli-Israel S, Parker L, Sinaee R, Fell RL, Kripke DF. Sleep fragmentation in patients in a nursing home. J Gerontol. 1989; 44:M18–M21. [PubMed: 2910988]

Bliwise, D. Sleep and circadian rhythm disorders in aging and dementia. In: Turek, FW.; Zee, PC., editors. Regulation of Sleep and Circadian Rhythms. Marcel Decker, Inc; New York: 1989. p. 487-525.

Bliwise D. Sleep in normal aging and dementia. Sleep. 1993; 16:40–81. [PubMed: 8456235]

Bootzin, RR.; Manber, R.; Lowey, DH.; Kuo, TF.; Franzen, PL. Sleep Disorders. In: Adams, HE.; Sutker, PB., editors. Comprehensive Handbook of Psychopathology. 3. Plenum Press; New York: 2001. p. 671-711.

Chen UC, Borson S, Scanlan JM. Stage-Specific prevalence of behavioral symptoms in Alzheimer's disease in a multi-ethnic community sample. Am J Geriatr Psychiatr. 2000; 8(2):123–133.

Cummings JL, Kaufer D. Neuropsychiatric aspects of Alzheimer's disease: the cholinergic hypothesis revisited. Neurology. 1996; 47(4):876–883. [PubMed: 8857712]

Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. Neurology. 1994; 44:2308–2314. [PubMed: 7991117]

Folstein MF, Folstein SE, McHugh PR. 'Mini-Mental State': a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975; 12:189–198. [PubMed: 1202204]

Hart DJ, Craig D, Compton SA, Critchlow S, Kerrigan BM, McIlroy SP, Passmore AP. A retrospective study of the behavioural and psychological symptoms of mid and late phase Alzheimer's disease. Int J Geriatr Psychiatry. 2003; 18(11):1037–1042. [PubMed: 14618556]

Holm S. A simple sequentially rejective multiple test procedure. Scand J Stat. 1979; 16:65–70.

Howieson DB, Camicioli R, Quinn J, Silbert LC, Care B, Moore MM, Dame A, Sexton G, Kaye JA. Natural history of cognitive decline in the old. Neurology. 2003; 60:1489–1494. [PubMed: 12743237]

Kaye J, Howiesson D, et al. Neurological evaluation of the optimally healthy oldest old. Arch Neuro. 1994; 51:1205–1211.

Lyketsos CG, Lopez O, Jones B, Fitzpatrick AL, Breitner J, De Kosky S. Prevalence of neuropsychiatric symptoms in dementia and mild cognitive impairment: results from the Cardiovascular Health Study. JAMA. 2002; 288:1475–1483. [PubMed: 12243634]

McCurry S, Logsdon R, et al. Characteristics of sleep disturbance in community-dwelling Alzheimer's disease patients. J Geriatr Psychiatr Neurol. 1999; 12:53–59.

McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA work group under the auspices of the Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology. 1984; 34:939–944. [PubMed: 6610841]

Maggi S, Langlois JA, Minicuci N, Grigoletto F, Pavan M, Foley DJ, Enzi G. Sleep complaints in community dwelling older persons: prevalence, associated factors, and reported causes. J Am Geriatr Soc. 1998; 46(2):161–168. [PubMed: 9475443]

Mega MS, Cummings JL, Fiorello T, Gornbein J. The spectrum of behavioral changes in Alzheimer's disease. Neurology. 1996; 46:130–135. [PubMed: 8559361]

Moe KE, Vitiello MV, Larsen LH, Prinz PN. Symposium: cognitive processes and sleep disturbances: sleep/wake patterns in Alzheimer's disease: relationships with cognition and function. J Sleep Res. 1995; 4:15–20. [PubMed: 10607136]

Njegovan V, Hing MM, Mitchell SL, Molnar FJ. The hierarchy of functional loss associated with cognitive decline in older persons. J Gerontol A Biol Sci Med Sci. 2001; 56:M638–643. [PubMed: 11584037]

Pat-Horenczyk R, Klauber MR, Shochat T, et al. Hourly profiles of sleep and wakefulness in severely versus mild-moderately demented nursing home patients. Aging (Milano). 1998; 10:308–315. [PubMed: 9825022]

Pollak CP, Perlick D. Sleep problems and institutionalization of the elderly. J Geriatr Psychiatry Neurol. 1991; 4:204–210. [PubMed: 1789908]

Pollak CP, Stokes PE. Circadian rest-activity rhythms in demented and nondemented older community residents and their caregivers. J Am Geriatr Soc. 1997; 45:446–452. [PubMed: 9100713]

Prinz P, Peskind E, et al. Changes in the sleep and waking EEGs of nondemented and demented elderly subjects. J Am Ger Soc. 1982; 30:86–92.

Singer C, Tractenberg RE, Kaye J, Gamst A, Grundman M, Thomas RG, Thal LJ. A multicenter clinical trial of melatonin for sleep disturbance in Alzheimer's disease. Sleep. 2003; 26:893–901. [PubMed: 14655926]

Thal LJ. Development of the Alzheimer's Disease Cooperative Study. Int J Geriatr Psychopharmacol. 1997; 1:6–9.

Tractenberg RE, Singer CS, Cummings JL, Thal LJ. The Sleep Disorders Inventory (SDI): an instrument for studying sleep disturbance in persons with Alzheimer's disease. J Sleep Res. 2003; 12:331–337. [PubMed: 14633245]

Vitiello M, Borson S. Sleep disturbances in patients with Alzheimer's disease: epidemiology, pathophysiology and treatment. CNS Drugs. 2001; 15:777–796. [PubMed: 11602004]

Vitiello M, Prinz P, et al. Sleep disturbances in patients with mild-stage Alzheimer's disease. J Gerontol. 1990; 45:M131–M138. [PubMed: 2365965]

Voderholzer U, Al-Shajlawi A, Weske G, Feige B, Riemann D. Are there gender differences in objective and subjective sleep measures? A study of insomniacs and healthy controls. Depress Anxiety. 2003; 17:162–172. [PubMed: 12768650]

Yesavage JA, Friedman L, Ancoli-Israel S, Bliwise D, Singer C, Vitiello MV, Monjan AA, Lebowitz B. Development of diagnostic criteria for defining sleep disturbance in Alzheimer's disease. J Geriatr Psychiatry Neurol. 2003; 16:131–139. [PubMed: 12967054]

Table 1

Descriptive statistics for study participants by cognitive status

Score/value	Non-demented elderly (n = 399)	Poss/prob AD (n = 263)
Age (years)***	81.9 ± 8.5	74.0 ± 11.8
Sex (% female)	60.1%	54.0%
Education (years)	13.9 ± 2.7	13.6 ± 3.3
Duration of AD (years)	NA	4.6 ± 2.9
Mini-Mental State Exam (MMSE)***	28.2 ± 1.5	19.2 ± 6.4
ADL***	0.18 ± 0.65 (*n* = 280)	2.6 ± 3.2
IADL***	0.17 ± 0.68	6.9 ± 4.6
Cornell Depression Scale**	1.5 ± 1.6 (*n* = 202)	3.7 ± 3.4
Sleep score (sum of frequency ratings)†	17.1 ± 7.9	17.1 ± 8.9
Number of endorsed symptoms†	5.5 ± 3.0	5.3 ± 3.0
Estimated nighttime total time in bed (h) (TIB)	8.1 ± 1.2	9.1 ± 1.5
Percent of group with ≤6 h TIB	6.1%	3.5%
Percent of group with ‘sleep problems’**‡	18.3%	27.6%

Non-demented elderly, healthy elderly subjects with normal cognitive function at the time of initial assessment in the Oregon Brain Aging Study; Poss/prob AD, individuals met NINCDS-ADRDA criteria for possible or probable Alzheimer’s disease; ADL, activities of daily living; IADL, instrumental activities of daily living.

*$P < 0.05$;

**$P < 0.01$;

***$P < 0.001$.

†All symptom ratings were included except ‘awaken feeling well rested’ and ‘have sleep problems’.

‡Tested using chi-squared contingency test; for all other score values, Mann–Whitney non-parametric comparisons of mean values was used.

Table 2

Sleep symptoms: endorsement rates and mean frequency ratings by group

	Frequency		Endorsement	
Symptom	**Non-demented**	**Poss/prob AD**	**Non-demented**	**Poss/prob AD**
Number of wake-ups per night*	2.4 ± 1.2; 2	2.0 ± 1.1; 2	87.5%	82.3%
Drowsy during the day*	1.8 ± 1.1; 2	2.0 ± 1.1; 2	61.5	67.9
Takes naps during the day†	1.8 ± 1.2; 2	2.2 ± 1.2; 2	59.7	71.3
Equal sleep time (day = night)*†	0.15 ± 0.52; 0	0.41 ± 0.90; 0	2.6	9.8
Takes >30 min to fall asleep*†	1.4 ± 1.1; 1	0.95 ± 1.1; 0	42.4	25.5
Wake up during night for >1 h*†	1.3 ± 1.0; 1	0.90 ± 0.95; 0	42.4	24.1
Wake up too early	1.4 ± 1.1; 2	1.2 ± 1.1; 0	44.6	36.0
Restless sleep	1.1 ± 0.9; 1	1.2 ± 1.0; 1	32.0	33.1
Lies awake tense/worried	0.84 ± 0.84; 0	0.93 ± 1.0; 0	20.4	25.8
Snores heavily*	0.86 ± 1.2; 0	1.3 ± 1.3; 0	27.8	39.4
Has trouble breathing	0.27 ± 0.64; 0	0.41 ± 0.89; 0	6.3	11.3
Breathes irregularly*	0.30 ± 0.78; 0	0.54 ± 0.98; 0	8.1	15.4
Twitches/jerks in sleep*†	0.53 ± 0.84; 0	1.1 ± 1.3; 0	15.1	35.2
Wakes up with headache	0.38 ± 0.75; 0	0.55 ± 0.88; 0	9.7	14.7
Wake at night with pain*	0.67 ± 0.89; 0	0.47 ± 0.81; 0	19.2	12.5
Uses medication to help get to sleep	0.46 ± 0.85; 0	0.43 ± 0.96; 0	15.2	12.1
Uses alcohol to help get to sleep	0.06 ± 0.29; 0	0.04 ± 0.34; 0	1.1	0.8
Has bowel/bladder problems at night*	1.6 ± 1.4; 0	1.2 ± 1.3; 0	48.9	35.0
Has muscle cramps during sleep	1.2 ± 1.0; 0	0.84 ± 0.92; 0	39.8	25.2
Has restless legs during sleep*†	1.0 ± 1.1; 0	0.66 ± 1.0; 0	35.4	19.6
Awakes feeling well rested	3.1 ± 1.0; 4	3.0 ± 1.1; 4	91.6	87.1
Has sleep problems			18.5	27.5

Values are given as mean ± SD; mode.

Frequency ratings (in previous months): 0 = never; 1 = less than once per month; 2 = at least once per month; 3 = at least once per week; 4 = nearly every day/night).

Endorsement ratings of 0 or 1 (less than once per month) = ‘unendorsed’; ratings of at least once per month = ‘endorsed’.

Frequency ratings were compared by Mann–Whitney nonparametric comparison;

*Holm-adjusted $P < 0.05$.

Endorsement was compared by chi-square test;

†Holm-adjusted $P < 0.05$.

Table 3

Nonparametric correlations by cohort: SDSQ total, number of SDSQ symptoms endorsed (0–20), and estimated nighttime total sleep time (TIB) with each other and non-sleep variables

	SDSQ		No. of symptoms endorsed		TIB	
	NDE	AD	NDE	AD	NDE	AD
Age (years)	0.066	0.141*	−0.079	0.183**	0.125*	0.291**
Education (years)	0.025	0.045	−0.036	0.014	−0.004	0.117
Duration of AD (years)		0.232**		0.195**		0.165*
Age of AD onset		0.070		0.127*		0.228**
MMSE	0.047	−0.057	−0.028	−0.070	−0.070	−0.276**
ADL	0.260**	0.378**	0.247**	0.366**	0.071	0.355**
IADL	0.169**	0.248**	0.171**	0.256**	0.194**	0.395**
Cornell Depression Scale	0.283**	0.315**	0.272**	0.352**	0.007	0.052
SDSQ†			0.904**	0.923**	0.124*	0.128*
Number of endorsed symptoms†					0.114*	0.138*

NDE, non-demented elderly; AD, probable or possible Alzheimer's disease; ADL, activities of daily living; IADL, instrumental activities of daily living; SDSQ, sleep disturbance symptom questionnaire sum of ratings; TIB, estimated nighttime total sleep time.

*$P < 0.05$;

**$P < 0.01$.

†All symptom ratings were included except 'awaken feeling well rested' and 'have sleep problems'.

Table 4

Comparison of sleep and non-sleep variables by cohort for subjects with ≤6 h or >6 h TIB

	NDE		AD	
	≤6 h (n = 24)	**>6 h (n = 369)**	**≤6 h (n = 9)**	**>6 h (n = 249)**
Age (years)	80.3 ± 8.3	82.0 ± 8.5	63.3 ± 9.9	74.4 ± 11.5**
Gender (% female)	45.8%†	61.2%	66.7%‡	53.4%
Education (years)	14.0 ± 3.3	13.9 ± 2.7	12.3 ± 2.7	13.6 ± 3.2
Duration of AD (years)			4.8 ± 3.3	4.6 ± 2.9
Age at AD onset			59.4 ± 9.6	69.2 ± 11.3*
Mini Mental State Exam	28.3 ± 1.4	28.2 ± 1.5	23.8 ± 4.1	19.1 ± 6.4*
ADL	0.20 ± 0.62	0.17 ± 0.63	0.88 ± 1.8	2.6 ± 3.2*
IADL	0.04 ± 0.20	0.17 ± 0.70	1.9 ± 2.8	7.0 ± 4.5**
Cornell Depression Scale	1.8 ± 1.9	1.4 ± 1.5	5.0 ± 3.6	3.7 ± 3.4
SDSQ¶	17.9 ± 10.2	17.0 ± 7.5	14.2 ± 6.9	17.1 ± 9.0
Number of endorsed symptoms¶	5.3 ± 3.2	5.5 ± 3.0	4.0 ± 2.9	5.3 ± 3.0
% with sleep problems	6/24 (25.0%)§	67/369 (18.2%)	2/9 (22.2%)	70/249 (28.1%)

Values are given as mean ± SD or %.

NDE, non-demented elderly; AD, probable or possible Alzheimer's disease; SDSQ, sleep disturbance symptom questionnaire sum of ratings; TIB, estimated nighttime total sleep time.

*$P < 0.05$;

**$P < 0.01$.

†45.8% of NDE with TIB ≤6 h were female.

‡66.7% of AD with TIB≤6 h were female.

§25% of NDE with TIB ≤6 h reported 'sleep problems'.

¶All symptom ratings were included except 'awaken feeling well rested' and 'have sleep problems'.

Table 5

Comparison of subjects by cohort with/without ‘have sleep problems’

	NDE		AD	
	Yes (n = 73)	**No (n = 320)**	**Yes (n = 72)**	**No (n = 186)**
Age (years)	83.6 ± 7.3	81.5 ± 8.7*	74.8 ± 12.6	73.7 ± 11.5
Gender (% female)	68.9%†	58.8%	53.4%‡	54.2%
Education (years)	13.2 ± 2.7	14.1 ± 2.7**	14.2 ± 3.3	13.4 ± 3.3*
Duration of AD (years)			5.2 ± 3.0	4.4 ± 2.8*
Age at AD onset			69.0 ± 12.1	68.9 ± 11.4
Mini Mental State Exam	28.0 ± 1.5	28.2 ± 1.5	18.7 ± 7.2	19.4 ± 6.0
ADL	0.27 ± 0.67	0.17 ± 0.65	3.5 ± 3.7	2.2 ± 2.9*
IADL	0.12 ± 0.44	0.18 ± 0.72	7.6 ± 5.1	6.6 ± 4.3
Cornell Depression Scale	2.2 ± 1.7	1.3 ± 1.6**	5.2 ± 3.3	3.2 ± 3.2**
SDSQ§	22.6 ± 6.8	15.9 ± 7.6**	23.3 ± 8.6	14.7 ± 7.8**
Number of endorsed symptoms§	7.6 ± 2.6	5.0 ± 2.9**	7.4 ± 2.9	4.5 ± 2.6**
Percent sleeping ≤6 h	6/73 (8.2%)‡	18/320 (5.6%)	2/72 (2.8%)	7/186 (3.8%)

Values are given as mean ± SD or %.

NDE, non-demented elderly; AD, probable or possible Alzheimer’s disease; SDSQ, sleep disturbance symptom questionnaire sum of ratings; TIB, estimated nighttime total sleep time.

*$P < 0.05$;

**$P < 0.01$.

†68.9% of NDE with sleep problems were female.

‡8.2% of NDE endorsing ‘sleep problems’ had TIB ≤6 h.

§All symptom ratings were included except ‘awaken feeling well rested’ and ‘have sleep problems’.