Sleep and Circadian Rhythm Disorders in Human Aging and Dementia

M V Vitiello, University of Washington, Seattle, WA, USA

General Introduction

In 2007, approximately 12% of the United States population consisted of people 65 years of age or older. By 2030, this proportion will rise to 20%. Because the older portion of the population is increasing twice as fast as other age groups, the number of people 65 year of age or older in the United States will effectively double, to 72 million, by 2030.

Alzheimer's disease (AD) is a progressive neurodegenerative disorder, common in older adults, that accounts for approximately two-thirds of all dementias worldwide. In the United States, it has recently been estimated that between 2 and 4 million older adults have AD. Further estimates suggest that this number is likely to quadruple over the next 50 years.

Among older adults, one of the major changes that commonly accompany the aging process is an often profound disruption of an individual's daily sleep–wake cycle. This disruption is often further exacerbated in older individuals suffering from neurodegenerative disorders, such as AD. Here we review what is known about sleep and circadian rhythms in normal aging and in AD.

Normal Aging

As many as 50% of older individuals complain about sleep problems, including disturbed or light sleep, frequent awakenings, early morning awakenings, and undesired daytime sleepiness. Such disturbances are often associated with impaired daytime function and compromised quality of life. The most striking change in the sleep in older adults is the frequent interruption of nighttime sleep by periods of wakefulness, possibly the result of an age-dependent intrinsic lightening of sleep homeostatic processes. Further, older adults are more easily aroused from nighttime sleep by auditory stimuli, suggesting that their sleep may be more easily disrupted by exogenous stimuli. Both of these changes are indicative of impaired sleep maintenance and depth and contribute to the characterization of the sleep of older adults as lighter, or more fragile, than that of younger adults.

These age-associated increases of nighttime wakefulness are mirrored by increases in daytime fatigue, excessive daytime sleepiness, and increased likelihood of napping or falling asleep during the day. Aging is also associated with a tendency to both fall asleep and awaken earlier. That is, a tendency for older individuals to be larks rather than owls. Older individuals also tend to be less tolerant of phase shifts in time of the sleep–wake schedule such as those produced by jet lag and shift work. These changes suggest an age-related breakdown of the normal adult circadian sleep/wake rhythm.

Polysomnographic (PSG) studies of sleep architecture have consistently demonstrated four age-related changes in nighttime sleep quality: reductions in total sleep time, reductions in sleep efficiency, reductions in slow wave sleep, and increases in waking after sleep onset. Nevertheless, age-related changes in numerous other PSG sleep measures remain unclear. Sleep onset latency, stages 1 and 2, and rapid-eye movement (REM) have all been reported to change with age, whereas other studies have observed no such age-related changes.

It is important to note that even carefully screened older adults who do not complain of sleep disturbance and who have minimal medical burdens show the changes described when compared to younger adults. This suggests that at least some of the sleep disturbance seen in older adults is part of the aging process *per se*, apparently independent of any medical or psychiatric illnesses or primary sleep disorders and often referred to as age-related sleep change. As to whether this age-related decline in the ability to generate sleep equates with a decreased need for sleep in the later years of the human life span remains unclear. Nevertheless, the available scientific evidence suggests that it is important to remember that as individuals age, they make need to modify their expectations about the duration and quality of their nighttime sleep.

Sleep in Normal Aging

Clearly sleep changes with advancing age, but an important question remains: exactly when during the adult life span do these changes occur? It has typically been assumed that the age-related sleep changes that characterize the sleep of older adults begin to appear in early adulthood and progress steadily across the full continuum of adult human life span, including the older adult years, so that, for example, the sleep of the typical 75-year-old was assumed to be worse than that of the typical 65-year-old.

However, the results of a recent and comprehensive meta-analysis of objective sleep measures across the

human life span demonstrated that the bulk of the age-related changes seen in adult sleep patterns do not occur continuously across the human adult life span but, rather, occur between early adulthood, beginning at age 19, and that after age 60 changes in sleep macroarchitecture becomes effectively asymptote, declining only minimally from age 60 to age 102. These sleep changes across adult life-span are summarized in Table 1. When the full adult life span is examined (2391 adults, ages 19–102 years), such analyses confirmed the four most consistently reported age-related changes in PSG studies of sleep macroarchitecture: decreases in total sleep time (TST), decreases in sleep efficiency (SE), decreases in slow wave sleep (SWS), and increases in waking after sleep onset (WASO). Also confirmed were less consistently reported age-related sleep changes; increases in stage 1 (S1) and stage 2 (S2) sleep and decreases in REM sleep were all observed in their meta-analyses. Conversely, age-related changes in both sleep latency (SLAT) and REM latency (REMLAT) were minimal.

It is crucial to note that all these significant age changes in objectively assessed sleep architecture were found only when the full adult life span of 19–102 years was examined. When the sleep of only older adults (1142 adults, ages 60–102 years) was examined, the meta-analyses demonstrated that no sleep measures showed any significant age-related change within the older adult portion of the study sample, with the single exception of SE, which declined significantly but at a modest rate of ∼3% per decade.

Table 1 Summary of significant findings from meta-analyses examining the association between various sleep measures and age

	Adults 19–102 years[a]	Older adults 60–102 years[b]
Total sleep time	⇓	⇔
Sleep latency	⇔	⇔
WASO	⇑	⇔
Sleep efficiency	⇓	⇓
Stage 1 (%)	⇑	⇔
Stage 2 (%)	⇑	⇔
SWS (%)	⇓	⇔
REM (%)	⇓	⇔
REM latency	⇔	⇔

[a]n = 2391 adults.
[b]n = 1142 adults.
From Ohayon MM, Carskadon M, Guilleminault C, and Vitiello MV (2004) Meta-analysis of quantitative sleep parameters from childhood to old age in healthy individuals: Developing normative sleep values across the human lifespan. *Sleep* 27(7): 1255–1273. ⇓, decreased; ⇑, increased; ⇔, unchanged; REM, rapid-eye movement sleep; SWS, slow wave sleep; WASO, waking after sleep onset.

These findings were comparable for both older men and older women.

These findings seem counterintuitive and fly against our commonly held concepts of sleep changes with aging. However, it is important to remember that Ohayon and colleagues used very rigorous selection criteria, such that the subjects involved in the studies analyzed were not representative of the older population *per se* but, rather, were in excellent health and more likely represented individuals who were optimally or successfully aging. That is, these findings represent normative age-related changes in sleep architecture and not average sleep changes of the entire aging population. When various medical and psychiatric comorbidities that typically accompany the aging process were controlled for and optimal aging was examined, the bulk of age-related sleep changes occurred in early and middle adulthood (ages 19–60 years); after age 60, assuming the individual remained in good health, further age-related sleep changes were likely to be, at most, modest. Conversely, if such comorbidities were present, these minimal age-related sleep changes might well be exacerbated, consistent with the level of sleep-related complaints seen in the general aging population.

Circadian Rhythms in Normal Aging

Not only does the quality of sleep change across the human life span, but the timing of when that sleep occurs also apparently changes with aging. Circadian rhythms are those that occur within a period of 24 h (from the Greek about (*circa*) a day (*dies*)), such as the adult human sleep–wake cycle. Interestingly, as with sleep, there is a considerable disparity in the conventional wisdom concerning circadian rhythms and aging and which evidence is supports or does not support these conventionally held beliefs. The conventional wisdom regarding what happens to human circadian processes with aging holds that (1) the circadian amplitude is reduced; (2) the circadian phase is advanced (i.e., the circadian rhythm moves earlier relative to the environment); (3) the circadian free-running period (tau) is shortened; and (4) the ability to tolerate rapid phase shifts, such as those experienced in shift work or rapid transmeridian travel (jet lag), declines.

However, the available evidence convincingly supports only two of these beliefs: that older people tend to have earlier circadian phases, with a corresponding tendency to go to bed and arise from bed earlier than younger adults; and that they have more trouble than younger adults adjusting to the rapid phase shifts due to shift work and jet lag, at least in terms of sleep quality, subjective complaint, and performance measures. Interestingly, the data in support of

diminished circadian amplitudes and shortened circadian taus in healthy older adults are, at best, equivocal. Again, it is important to note that these circadian changes are those seen in normal, or more accurately normative, aging, in which age-related health comorbidities have been carefully screened out.

Excessive Daytime Sleepiness and Napping in Normal Aging

Two other commonly held assumptions about sleep and aging are that older adults typically report more excessive daytime sleepiness (EDS) and nap more than younger adults. Few community-based epidemiological studies have reported the prevalence of regular napping and its association with sleep complaints and other mental and physical health problems, especially in relation EDS. Somewhat counterintuitively, although epidemiological studies typically show a significant increase in the prevalence of regular napping with advancing age, EDS does not demonstrate a similar increase in prevalence among older adults. Consistent with the findings already described for nighttime sleep measures, very recent findings indicate that the presence of comorbidities (medical illness, depression, etc.) is highly associated with the likelihood of an older adult reporting regular napping or EDS. That is, healthy older adults, even those complaining of significant nighttime sleep disturbance, are much less likely to report regular napping or EDS than their more health-burdened cohorts.

There is considerable debate as to whether regular napping among older adults, particularly those in good health, may be beneficial to daytime wakefulness or perhaps detrimental to their nighttime sleep propensity. Studies of naps in healthy noncomplaining older adults demonstrated that napping had only a mild to moderate impact on nighttime sleep quality and may even result in improved postnap cognitive performance. However, these results should be interpreted with caution because, again, it is important to emphasize that the subjects involved were carefully screened healthy older adults. It is unclear if similar results would be obtained, for example, with a sample of older insomniacs.

Causes of Sleep and Circadian Disturbances in Older Adults

It is often repeated that epidemiological studies report that as much as 50% of older adults complain of significant, chronic sleep disturbance. However, it is important to keep in mind that the other 50% of older adults do not so complain. As previously reviewed, the sleep of very healthy older adults changes only very slowly across the later human life span. Conversely it has also been shown that older adults who do not complain of any sleep problems nevertheless have objective sleep quality that is markedly compromised (e.g., less TST, less SE, less SWS, and more WASO) compared to that of healthy, non-sleep-complaining, younger adults. Nevertheless, there are many factors in addition to the age-related sleep and circadian changes already discussed that contribute to the significant sleep disturbance reported by half of all older adults. These include (1) medical and psychiatric comorbidities and their treatments, such as cardiovascular disease, arthritis, depression, or AD and many of the drugs used to treat them; (2) primary sleep disorders, many of which, such as sleep apnea, restless legs syndrome, and REM behavior disorder, tend to occur with increasing frequency in older adults; (3) the many behavioral, environmental, and social factors, often collectively referred to as sleep hygiene, that have the potential to maximize or compromise an individual's sleep quality; and (4) some combination of these factors. A more comprehensive list of such contributing factors with specific examples appears in Table 2.

Table 2 Causes of poor sleep in older adults

Cause/problem	Examples
Physiological	Age-related sleep change
	Age-related circadian rhythm change (phase advance)
Medical illnesses	Arthritis or other conditions causing chronic or intermittent pain
	Chronic cardiac or pulmonary disease
	Gastro-esophageal reflux disorder
Psychiatric illnesses	Depression
	Alzheimer's disease
Medications	Diuretics (leading to nocturnal awakenings)
	Inappropriate use of OTC medications
Primary sleep disorders	Sleep disordered breathing (sleep apnea)
	Restless legs syndrome
	REM behavior disorder
Behavioral/social	Retirement/lifestyle change reducing need for regular bed and rise times
	Death of a family member or friend
	Inappropriate use of social drugs
	Transmeridian air travel
	Napping
Environmental	Bedroom environment (e.g., ambient noise, temperature, light, bedding)
	Moving to a new home or downsizing to a smaller space or a retirement community or related facility
	Institutionalization

OTC, over-the-counter; REM, rapid-eye movement.
Reproduced from Vitiello MV (2006) Sleep in normal aging. *Sleep Medicine Clinics* 1(2): 171–176, with permission from Elsevier.

Alzheimer's Dementia

Both normal aging and AD are associated with disturbances in the daily sleep–wake cycle, although the disturbances in AD are typically much more severe. Within the AD population itself, significant sleep disturbances are quite common, affecting as much as half of community- and clinic-based samples.

For AD patients, sleep disturbance adds an additional burden to the compromised function and quality of life directly attributable to dementia. For AD caregivers, disturbances in patients' sleep and nighttime behavior, particularly the reduced nighttime sleep time, increased nighttime wakefulness, and wandering that commonly require considerable caregiver attention, with a subsequent chronic sleep loss for the caregivers themselves, are a significant source of physical and psychological burden and are often cited as one of the principal reasons for a family's decision to institutionalize a demented person.

The Biological Bases of Sleep Disturbances in AD

The sleep disturbances that accompany early-stage or mild dementia are remarkable in that they appear as exacerbations of the sleep changes found in normal aging rather than as unique disease-related phenomena. The sleep of AD patients is marked by an increased duration and frequency of awakenings, decreased SWS and REM sleep, and more daytime napping. Damage to neuronal pathways that initiate and maintain sleep is the most likely cause of the acceleration of these age-related sleep changes in AD patients. These compromised neural structures, including the suprachiasmatic nucleus (SCN) of the hypothalamus and neuronal pathways originating in subcortical regions, also regulate arousal and the sleep–wake cycle. Recent work suggested that at least some of the sleep disruption seen in AD many be an inherent trait, probably linked to apolipoprotein E (APO E) status, such that AD patients positive for the APO E ε4 allele show greater sleep disruption over time.

There is considerable evidence that sleep disturbance grows more severe with increasing severity of AD. However, the moderate, or intermediate, stages of the disease are typically when most other behavioral disturbances occur with peak frequency. The breakdown of the basic circadian sleep–wake rhythm of dementia patients can be severe and in extreme cases may lead to an extremely fragmented sleep–wake pattern or nearly complete day–night sleep pattern reversals. In end-stage AD, patients may appear to sleep throughout most of the day and night, awakening only for brief periods. However, as of this time there have been no prospective longitudinal studies of sleep in AD that would inform an accurate understanding of both the course and the individual differences of these sleep disturbances. This remains an important gap in both the biology and therapeutics of sleep disturbances in demented patients.

The current standard of care for treating cognitive disorders in AD is the use of oral acetylcholinesterase inhibitors. These drugs may improve sleep patterns in some AD patients, particularly by increasing REM sleep. Because they act by enhancing cholinergic transmission in the brain, the involvement of both forebrain and brain stem cholinergic nuclei in regulating sleep–wake cycles and arousal forms the rationale for expecting both positive and negative sleep effects with use of these agents.

Circadian Rhythm Disorder in AD

AD patients commonly manifest a breakdown of their circadian sleep–wake rhythm. Termed irregular sleep–wake rhythm disorder (ISWRD), this perturbation of circadian rhythmicity is commonly associated with neurological impairment in older adults, such as the deficits experienced by AD patients. ISWRD is characterized by the relative absence of a circadian pattern in the sleep–wake cycle. Total sleep time can well be comparatively normal, but, instead of being consolidated into a single long relatively continuous major sleep period, sleep times are shortened and, in extreme cases, relatively brief sleep periods are distributed almost randomly throughout the day and night. The cause, or more likely the causes, of this association are unknown, but AD-related damage to the SCN, locus of the circadian pacemaker, is clearly implicated as an important, if not a major, etiological factor. Experimental ablation of the SCN in animals produces a loss of circadian rhythmicity that strongly resembles the sleep–wake pattern typically seen in older adults with dementing disorders, particularly in the later stages of the dementia. However, it is important to note that clinical studies, the bulk of which have been carried out in older adults with dementia (particularly AD), have rarely used formal sleep diagnostic criteria for ISWRD.

Although complaints of nighttime sleep fragmentation and daytime napping have been consistently reported to increase with age, the weight of the available evidence strongly indicates that, although the prevalence of ISWRD increases with age, this increase is secondary to the increased prevalence of associated medical disorders with advancing age. Age is apparently not an independent risk factor for ISWRD; rather, it is probably the age-related medical comorbidities which constitute the main risk factors

for sleep pathology, including both increasing disturbances in sleep architecture and the increase in prevalence of ISWR with advancing age. ISWRD is particularly associated with neurological impairment in older adults, most significantly AD.

Although there is no direct evidence for a genetic basis for ISWRD, there are several lines of evidence that suggest that the sleep disturbance seen in AD is at least partially based on genetic factors. Actigraphic studies of AD patients have demonstrated longitudinal deterioration of sleep quality, and most of this longitudinal variance in sleep appears to be related to an inherent trait of the individual patient. This suggests that genetic factors may help determine the ultimate course and level of sleep deterioration seen in a given AD patient, a hypothesis consistent with research indicating that much circadian variation in physiological systems is controlled by a limited number of similar genes across species. Regardless, the tentative relationship of genetic factors as a risk for ISWRD remains to be fully explored.

Older adults are exposed to reduced light levels in their daily lives relative to younger individuals. This reduction may be exacerbated by disorders of vision, which are common in older adults and which many further attenuate the impact of ambient light on the SCN. Finally, the SCN itself is adversely impacted by age. The impact of each of these factors is magnified in patients with AD, including those who are community dwelling, who have been shown to be exposed to less light than age-matched healthy normal controls. Furthermore, the retina and the optic nerve can both be compromised in AD. Older adults, especially those who are institutionalized, are exposed to less intense light than younger people, but questions remains as to the importance of reduced light exposure as an etiological factor in ISWRD.

Other Causes of Sleep and Circadian Disturbances in AD

Population-based studies examining the causes, incidence, and persistence of sleep disturbances in AD patients are lacking; consequently, little is known about the risk factors for their development. Therefore, we must look to the literature concerning sleep disturbance in the nondemented elderly and factor this with clinical assessments of individual patients to make informed inferences about the AD population. Certainly the same neurodegenerative mechanisms that result in the evolving cognitive deficits seen in AD are a potential primary cause of the sleep disruption seen in this population. However, it is important to recognize that sleep can be disrupted for many other reasons as well. The likely major

causes of sleep disruption in AD, as with normal aging, include (1) physiological changes that arise as part of normal nonpathological aging; (2) sleep problems due to comorbid physical or mental health conditions, including AD, and possibly their treatments; (3) primary sleep disorders; (4) poor sleep hygiene or sleep-related habits; or (5) commonly, some combination of these factors.

Studies of patients living in institutional settings provide much of the available information about sleep and circadian disturbance in cognitively impaired patients. Environmental factors that promote circadian dysregulation in dementia patients living in such settings include light, noise, activity schedules, and the needs of staff. Ambient light levels are typically too low in many congregate care facilities to support natural light-dependent internal rhythms, and noisy conditions, especially during the night, are both common and inimical to sleep. The staffing schedules and timing of specific activities in many facilities that care for demented people may be driven less by the needs of the patients than by compliance with federal and state requirements governing nursing-home operations. Regulatory requirements in general fail to incorporate many of the positive evidence-based practices found to be beneficial for demented residents, focusing more attention on feeding and bathing schedules, injury prevention, and detection of medical problems than on sleep and other issues related to quality of life.

Conclusion

Previously it was assumed that sleep and circadian rhythms decline inexorably with advancing age. However, recent research shows that, at least for health older adults, most of the age changes in sleep that have typically been thought to progress steadily across the adult human life span actually occur before age 60 and that adults over age 60 who remain healthy can expect their sleep quality to remain relatively stable as they age. Similarly age-related changes in circadian changes, again in older adults free of comorbid illnesses, are not as marked as was previously assumed. However, even healthy older adults tend to have earlier circadian phases, with a corresponding tendency to go to bed and arise from bed earlier than younger adults and to experience more trouble than younger adults adjusting to the rapid phase shifts such as those experienced in shift work and jet lag, at least in terms of sleep quality, subjective complaint, and performance measures.

Although sleep quality and circadian rhythms are apparently relatively well preserved in healthy older

adults, the negative impact of age-related comorbid illnesses on sleep and circadian rhythms is also clear. AD is a classic example of this negative impact, with AD patients typically demonstrating progressively fragmented sleep and irregular circadian rhythms with increasing severity of the disease.

Nevertheless, there is a growing body of evidence that the sleep quality and circadian rhythmicity of AD patients can, like those of other less-than-healthy older adults, be improved through nonpharmacological treatment approaches, whether the AD patients are community dwelling or institutionalized. Such groundbreaking work offers a firm foundation for future efforts to improve the sleep and related circadian rhythms of older adults, regardless of their health status.

See also: Aging of the Brain and Alzheimer's Disease; Alzheimer's Disease: An Overview; Alzheimer's Disease: Molecular Genetics; Alzheimer's Disease: Transgenic Mouse Models; Animal Models of Alzheimer's Disease; Brain Glucose Metabolism: Age, Alzheimer's Disease and ApoE Allele Effects; Genetics of Circadian Disorders in Humans; Psychiatric Disorders Associated with Disturbed Sleep and Circadian Rhythms; Shift Work and Circadian Rhythms.

Further Reading

Alessi CA, Martin JL, Webber AP, Cynthia Kim E, Harker JO, and Josephson KR (2005) Randomized, controlled trial of a non-pharmacological intervention to improve abnormal sleep/wake patterns in nursing home residents. *Journal of the American Geriatrics Society* 53: 803–810.

Alessi CA and Schnelle JF (2000) Approches to sleep disorders in the nursing home setting. *Sleep Medicine Reviews* 4(1): 45–56.

Ancoli-Israel S, Gehrman P, Martin JL, et al. (2003) Increased light exposure consolidates sleep and strengthens circadian rhythms in severe Alzheimer's disease patients. *Behavioral Sleep Medicine* 1: 22.

Bonnefond A, Harma M, Hakola T, Sallinen M, Kandolin I, and Virkkala J (2006) Interaction of age with shift-related sleep-wakefulness, sleepiness, performance, and social life. *Experimental Aging Research* 32(2): 185–208.

Campbell SS, Murphy PJ, and Stauble TN (2005) Effects of a nap on nighttime sleep and waking function in older subjects. *Journal of the American Geriatrics Society* 53: 48–53.

Cajochen C, Munch M, Knoblauch V, Blatter K, and Wirz-Justice A (2006) Age-related changes in the circadian and homeostatic regulation of human sleep. *Chronobiology International* 23(1–2): 461–474.

Dijk DJ, Duffy JF, and Czeisler CA (2001) Age-related increase in awakenings: Impaired consolidation of nonREM sleep at all circadian phases. *Sleep* 24(5): 565–577.

Dijk DJ, Duffy JF, Riel E, Shanahan TL, and Czeisler CA (1999) Ageing and the circadian and homeostatic regulation of human sleep during forced desynchrony of rest, melatonin and temperature rhythms. *Journal of Physiology* 516: 611–627.

Duffy JF, Zeitzer JM, Rimmer DW, Klerman EB, Dijk DJ, and Czeisler CA (2002) Peak of circadian melatonin rhythm occurs later within the sleep of older subjects. *American Journal of Physiology, Endocrinology and Metabolism* 282(2): E297–E303.

Foley DJ, Ancoli-Israel S, Britz P, and Walsh J (2004) Sleep disturbances and chronic disease in older adults: Results of the 2003 National Sleep Foundation Sleep in America Survey. *Journal of Psychosomatic Research* 56: 497–502.

Foley DJ, Monjan AA, Brown SL, Simonsick EM, Wallace RB, and Blazer DG (1995) Sleep complaints among older persons: An epidemiological study of three communities. *Sleep* 18: 425–432.

Foley DJ, Monjan AA, Simonsick EM, Wallace RB, and Blazer DG (1999) Incidence and remission of insomnia among elderly adults: An epidemiologic study of 6,800 persons over three years. *Sleep* 22(supplement 2): S366–S372.

Foley DJ, Vitiello MV, Bliwise DL, Ancoli-Israel S, Monjan AA, and Walsh JK (2007) Frequent napping is associated with excessive daytime sleepiness, depression, pain and nocturia in older adults: Findings from the national sleep foundation "2003 sleep in America" poll. *American Journal of Geriatric Psychiatry* 15: 344–350.

Hoffman MA and Swaab DF (2006) Living by the clock: The circadian pacemaker in older people. *Ageing Research Review* 5(1): 33–51.

Martin JL, Webber AP, Alam T, Harker JO, Josephson KR, and Alessi CA (2006) Daytime sleeping, sleep disturbance, and circadian rhythms in the nursing home. *American Journal of Geriatric Psychiatry* 4: 121–129.

McCurry SM, Gibbons LE, Logsdon RG, Vitiello MV, and Teri L (2005) Nighttime insomnia treatment and education for Alzheimer's disease: A randomized, controlled trial. *Journal of the American Geriatrics Society* 53: 793–802.

McCurry SM, Logsdon RG, Teri L, and Vitiello MV (2007) Evidence-based psychological treatments for older adult sleep disorders. *Psychology and Aging* 22(1): 18–27.

Monk TH (2005) Aging human circadian rhythms: Conventional wisdom may not always be right. *Journal of Biological Rhythm* 20(4): 366–374.

Monk TH, Buysse DJ, Carrier J, Billy BD, and Rose LR (2001) Effects of afternoon "siesta" naps on sleep, alertness, performance, and circadian rhythms in the elderly. *Sleep* 24(6): 680–687.

Ohayon MM, Carskadon MA, Guilleminault C, and Vitiello MV (2004) Meta-analysis of quantitative sleep parameters from childhood to old age in healthy individuals: Developing normative sleep values across the human lifespan. *Sleep* 27(7): 1255–1273.

Rybarczyk B, Stepanski E, Fogg L, Lopez M, Barry P, and Davis A (2005) A placebo-controlled test of cognitive behavioral therapy for comorbid insomnia in older adults. *Journal of Consulting Clinical Psychology* 73(6): 1164–1174.

Van Someren EJ (2000) Circadian and sleep disturbances in the elderly. *Experimental Gerontology* 35(9–10): 1229–1237.

Van Someren EJ, Riemersma RF, and Swaab DF (2002) Functional plasticity of the circadian timing system in old age: Light exposure. *Progress in Brain Research* 138: 205–231.

Vitiello MV (2000) Effective treatment of sleep disturbances in older adults. *Clinical Cornerstone* 2(5): 16–27.

Vitiello MV (2006) Sleep in normal aging. Sleep Medicine Clinics 1(2): 171–176.

Vitiello MV and Borson S (2001) Sleep disturbances in patients with Alzheimer's disease: Epidemiology, pathophysiology and management. *CNS Drugs* 15(10): 777–796.

Vitiello MV, Larsen LH, and Moe KE (2004) Age-related sleep change: Gender and estrogen effects on the subjective-objective

sleep quality relationships of healthy, non-complaining older men and women. *Journal of Psychosomatic Research* 56(5): 503–510.

Vitiello MV, Moe KE, and Prinz PN (2002) Sleep complaints co-segregate with illness older adults: Clinical research informed by and informing epidemiological studies of sleep. *Journal of Psychosomatic Research* 53: 555–559.

Vitiello MV, Prinz PN, Williams DE, Frommlet MS, and Ries RK (1990) Sleep disturbances in patients with mild-stage Alzheimer's disease. *Journal of Gerontology* 45(4): M131–M138.

Wu YH and Swaab DF (2005) The human pineal gland and melatonin in aging and Alzheimer's disease. *Journal of Pineal Research* 38: 145–152.

Yesavage JA, Friedman L, Kraemer H, et al. (2004) Sleep/wake disruption in Alzheimer's disease: APOE status and longitudinal course. *Journal of Geriatric Psychiatry and Neurology* 17(1): 20–24.

Yesavage JA, Taylor JL, Kraemer H, Noda A, Friedman L, and Tinklenberg JR (2002) Sleep/wake cycle disturbance in Alzheimer's disease: How much is due to an inherent trait? *International Psychogeriatrics* 14(1): 73–81.