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Sleep, hippocampal volume, and cognition in adults over 90 years old

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Abstract

Background: Several lines of research support associations between sleep and cognition in older adults. However, there is a paucity of data regarding sleep and cognition in nonagenarians and centenarians.

Aims: The current study examined self-reported sleep quantity and sleep quality in relation to hippocampal volume and cognition in adults aged 90 and older.

Methods: A total of 144 participants of The 90+ Study completed The Medical Outcomes Study sleep questionnaire. Participants reported subjective sleep duration in hours and three sleep quality factors: sleep problems, adequacy, and somnolence. Neuropsychological assessments of memory, global cognition, language, and executive function were completed, on average, 61 days from the questionnaire. Hippocampal volume on 3T MRI, adjusted for intracranial volume, was obtained in 82 participants. We performed multiple linear regressions, controlling for age, sex, education, sleep medication, and depression, to examine sleep characteristics in relation to hippocampal volume and cognitive performance in all subjects and then stratified by cognition.

Results: Sleep duration >8 hours was associated with lower scores in tests of global cognition, memory, and executive function compared to sleep duration of 7–8 hours when collapsing across

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cognitive status, but only with memory in cognitively impaired subjects, and not in cognitively normal subjects.

Discussion and Conclusions: Long sleep duration is associated with poorer global cognition, memory, and executive function in the oldest-old, and is only associated with memory in cognitively impaired oldest-old. Additional research is necessary to determine if sleep duration is a risk factor or a result of poor cognition in advanced age.

Keywords

geriatric; oldest-old; neurology; sleep; aging; cognition

Introduction

Adults over the age of 90 are the fastest proliferating demographic in the United States, and have considerable sleep complaints and the highest rates of cognitive difficulties [1,2]. However, there is a remarkable dearth of data on the relationship between sleep and cognition in this age group. A rapidly growing body of research suggests intriguing relationships between subjective sleep characteristics and cognitive functioning in the elderly. Sleep duration and measures of sleep quality have been implicated in cognitive decline and dementia [3,4]. For example, several studies using subjective measures of sleep have reported that poorer cognitive functioning in the elderly are associated with either long nocturnal sleep duration [5–8], short nocturnal sleep duration [9,10],or both long and short sleep duration [11,12]. For example, an investigation in the Northern Manhattan Study cohort noted an association between sleep duration ≥ 9 hours and poorer global cognition in a mostly cognitively normal sample of 927 stroke-free older adults (mean age 75 ± 9) [5]. A study investigating 2012 cognitively unimpaired adults at baseline, aged 65 to 94 years, found that subjects who slept ≤ 6.5 hours had an increased risk of cognitive decline at 10 years [9]. A study in 28,670 Chinese older adults without dementia aged 50 to 85 years found that 3–4 hours or ≥ 10 hours of sleep was associated with a higher likelihood of memory impairment [11]. The literature most commonly demonstrates that extreme long or short sleep durations are related to poor cognitive functioning in older adults. This finding is supported by a meta-analysis of sleep studies showing that self-reported extremes of sleep duration are related to poorer cognitive functioning in older adults [13]. These investigations raise the possibility that sleep may be a potentially modifiable risk factor and could provide a potentially useful strategy for amelioration of cognitive decline inaging. Our study aims to examine this relationship in adults over 90 years old, an understudied, but fastest-growing segment of the elderly population.

The association between sleep and cognition merits investigation in adults over 90 years old as the current literature characterizes clear age-mediated changes in sleep across the lifespan [14]. Aging is accompanied by a myriad of changes in sleep patterns [15]. Decreased sleep quality, reduction in hours of nocturnal sleep, excessive daytime sleepiness, and sleep disorders are frequent in older adults [16]. The differential impact of nocturnal sleep quantity in different age groups has been demonstrated in the extant literature. A study found that a reduction of self-reported hours of night sleep from 8 hours to 6 hours was associated with impaired performance on memory tasks in adolescents (mean age 15.0

± 0.8) but not young adults (mean age 18.9 ± 0.6 years) [17]. A cross-sectional study found that both subjectively reported short (<6 hrs) and long (>8 hrs) sleep were associated with poorer amnestic and non-amnestic cognition in adults aged 50–64 with and without dementia. However, only long sleep (>8 hrs) was associated with poorer amnestic and non-amnestic cognition in adults over 65 with and without dementia [18]. A study conducted in young adults aged 17 to 30 years old, found that self-reported short sleep duration (<7 hours) was related to worse self-rated health than those who slept 7–8 hours, when there was no associations with long sleep duration (>8 hours), suggesting that short sleep is of more concern than long sleep in young adults [19]. Due to the differences in sleep characteristics across the lifespan, age of the study population is an important determinant of the results.

Characteristics of sleep quality that could affect cognitive functioning in older people include excessive daytime sleepiness [20] and sleep disturbance [4]. The Medical Research Council Cognitive Function and Ageing Study investigated a sample of 2012 individuals 65 years and older and found that daytime sleepiness was longitudinally associated with incident cognitive impairment, assessed by the Mini Mental State Examination (MMSE) [21], over 10 years [9]. One cross-sectional study conducted in China reported that poor self-reported sleep quality, assessed by the Pittsburgh Sleep Quality Index (PSQI) [22], was related to lower MMSE scores and to a greater prevalence of dementia in a sample of 660 nonagenarians and centenarians with normal cognitive function, mild cognitive impairment, or dementia (mean age 93.52 ± 3.37, 67.3% female, 32.7% male) [23]. However, this study did not find a link between sleep duration and the MMSE, a global measure of cognitive functioning and the sole cognitive test assessed. Although this study did not find a relationship between sleep duration and the MMSE, it is possible that sleep duration could be associated with poorer performance in some cognitive domains, but not others [12] in adults over 90. Similarly, sleep quality could be related to global cognition, or possibly, specific domains of cognition such as memory, language, and executive function in adults over 90 years old.

Reductions in hippocampal volume are characteristic of many neurodegenerative diseases in older adults [24, 25]. The high prevalence of these disorders, including those with preclinical disease, provides challenges and opportunities to better understand the relationships between sleep, cognition and the brain. Several investigations have noted hippocampal volumes to be associated with lower scores on cognitive testing [26, 27]. In one study, smaller hippocampal volumes were associated with lower scores on both the Montreal Cognitive Assessment (MoCA) [28] and the NIH Toolbox-Cognitive Battery (NIHTB-CB) [29] in 93 healthy older adults (mean age 71.9 ± 9.3 years) [26]. Extending this line of research, some investigations have suggested that sleep characteristics may be related to hippocampal volume. In one study, investigators found that excessive daytime sleepiness assessed by the Epworth Sleep Questionnaire [30] was associated with reduced hippocampal volumes in 232 cognitively normal older adults (mean age 75 ± 0.9 years) who had sleep disordered breathing, but cognitive functioning was not examined in relation to these variables [31]. Similarly, another study found excessive daytime sleepiness (EDS) to be related to reduced hippocampal volume in 22 cognitively normal adults aged 28–60 years with obstructive sleep apnea [32]. In contrast, a large study of 1374 cognitively normal adults, in which 208 subjects had EDS (mean age 74.5 ± 8.6 years) did not find a relationship [33]. Another sleep quality

characteristic, sleep efficiency, was investigated in a sample of 218 older adults (mean age 67.28 ± 8.1 years). In this study, lower subjective sleep efficiency, assessed by the PSQI, was associated with reduced hippocampal volumes [34]. However, in a study of 147 middle-aged adults, (mean age 53.9 ± 15.5 years), investigators found no association between sleep quality assessed by the PSQI and hippocampal volume [35].The current literature has not extensively investigated the impact of subjective or objective sleep characteristics on hippocampal volume in older adults, and has not explored this relationship in people over 90 years of age. Hippocampal atrophy has been shown to predict cognitive decline in aging populations [36, 37]. Therefore, the association between sleep and hippocampal volume in the oldest-old warrants further investigation.

Given the dearth of information in people over 90 years old and the public health impact of this rapidly growing segment of the population, the current study aimed to explore the relationship between self-reported sleep quantity and quality, cognitive functioning, and hippocampal volume in the oldest-old. To that end, the goal of the present cross-sectional study was twofold. The first aim of the study was to investigate the relationship between self-reported sleep quantity (average hours of nocturnal sleep) and sleep quality (sleep adequacy, sleep somnolence, and sleep problems) and global cognitive functioning and three cognitive domains in adults over 90 years old. The second aim was to investigate the relationship between self-reported sleep quality and sleep quantity and hippocampal volume in adults over 90. We have chosen to independently investigate sleep quantity and sleep quality in relation to cognitive functioning and hippocampal volume. Self-reported sleep quality and sleep quantity may track different constructs. One study has shown that in older adults, short or long sleep duration is related to different dimensions of sleep quality. Short sleep duration was related to sleep complaints and feeling unrested in the morning whereas long sleep duration was associated with daytime sleepiness, independent of health status [38]. Therefore, it is possible that self-reported sleep quality and sleep quantity might result in different consequences in terms of cognitive decline. However, the pathway from these measures to cognitive decline is unclear and needs further investigation. Thus, the current study will explore the role of subjective reports of nocturnal sleep duration, sleep adequacy, sleep somnolence, and overall sleep problems in cognitive aging and age-related hippocampal changes in the oldest-old. It was hypothesized that oldest old participants who self-reported short sleep or long sleep, poorer sleep adequacy, greater sleep somnolence, or more sleep problems, would have worse cognitive scores and smaller hippocampal volumes.

Methods

Study Participants

Participants were recruited from The 90+ Study, an ongoing longitudinal investigation of the oldest-old based in Laguna Woods, California. The 90+ Study investigates factors that affect longevity and health, including the maintenance of cognitive function. The 90+ Study also directly investigates the following cognitive domains: global cognition, memory, language, executive function, psychomotor speed, visual-spatial, and attention/working memory. Researchers visit the study participants every six months to conduct neuropsychological evaluations, neurological examinations, informant questionnaires, and other investigations.

Participants who do not agree to an in-person evaluation may designate an informant to provide information via mail or telephone about demographics, medical history, medication use, and complete a questionnaire about the participant's cognitive status and functional abilities, as outlined in a previous manuscript detailing the recruitment, enrollment, and clinical assessment procedures of the 90+ Study [39]. All procedures of The 90+ Study have been approved by the Institutional Review Board of the University of California, Irvine and all participants have signed written informed consent. The Medical Outcomes Study (MOS) sleep questionnaire was mailed to all 90+ Study participants being actively followed in person (n=192) regardless of cognitive status (no dementia, cognitive impairment no dementia (CIND), and dementia), with 144 participants (75%) completing the questionnaire (95.15±3.45 years). Thirty-seven individuals did not reply (19.27%) and 11 (5.73%) were deceased. Given that The 90+ Study includes people from varying cognitive status, we investigated people with both normal aging and pathological aging. Participants who had completed a neuropsychological assessment within six months of completing the sleep questionnaire and had a geriatric depression scale (GDS) score [40] within 18 months of completing the sleep questionnaire were included in analysis. The GDS score was used to assess depression. The GDS-15 is a questionnaire that consists of questions pertaining to participants' feelings over a week. Participants answer yes or no to the questions. Thus, the final sample included 138 participants (95.12±3.40). Eighty-two of these individuals had brain imaging data and were included for analysis of hippocampal volume.

Sleep Quantity and Sleep Quality Indices

The MOS sleep questionnaire is a self-administered questionnaire that was utilized to obtain measures for sleep quantity (hours of nocturnal sleep) and quality (sleep adequacy, sleep somnolence, and sleep problems). The MOS questionnaire contains 12 items and measures different dimensions of sleep over the past four weeks [41].The MOS questionnaire measures nocturnal sleep duration and the following sleep quality indices: sleep disturbance, snoring, sleep short of breath or headache, sleep adequacy, sleep somnolence, sleep problems index I, and sleep problems index II. Its validity and reliability has been consistently demonstrated in multiple studies and within different populations [42, 43]. One study confirmed the validity and reliability of the MOS Sleep Questionnaire in a nationally representative sample of 1011 US adults, aged 18–94 years, and in a sample of 173 adults with neuropathic pain participating in a clinical drug trial, aged 31–100 years [43]. The sleep scales validity and reliability has also been demonstrated in a population of patients aged 63.6 ± 10.6 years with painful diabetic neuropathy [42], adults over 18 years old with restless leg syndrome [44], and middle aged adults with rheumatoid arthritis [45]. We modified the questionnaire to include a yes/no question on the use of medications as a sleeping aid over the past month as well as a more readable format with larger font. This question was added in order to control for the use of sleep medications during analysis and to characterize the research participants. Two questions measured quantitative aspects of sleep: average hours of nocturnal sleep and sleep latency. In the present study, sleep quantity was measured as average hours of nocturnal sleep, which was categorized into short sleep (defined as < 7 hours per night), optimal sleep (defined as 7–8 hours per night), and long sleep (defined as >8 hours per night). Sleep quantity was categorized based on recommendations by The National Sleep Foundation. The National Sleep Foundation

recommends that adults over 65 years old should sleep between 7 to 8 hours. Therefore, in our study, we have considered 7–8 hours of sleep as optimal sleep [46]. Optimal sleep was used as the reference group for statistical analysis. Sleep latency was included as an item in the calculation of sleep problem index II, an aspect of subjective sleep quality. The remaining ten questions related to sleep quality, asked participants to report the frequency of the query as “all of the time,” “most of the time,” “a good bit of the time,” “some of the time,” “a little of the time,” or “none of the time.” Responses were averaged to generate three sleep scales using a standardized scoring approach for the MOS questionnaire [47]. The following three sleep scales were used to assess multiple distinct aspects of the participants’ subjective sleep quality: sleep adequacy, sleep somnolence, and sleep problems index II.Sleep adequacy is a 2-item measure that subjectively evaluates how restorative or sufficient an individual’s sleep is. Sleep somnolence is a 3-item measure that subjectively evaluates daytime sleepiness and difficulties staying awake during the day. Sleep problems index II is a 9-item measure that subjectively evaluates overall sleep quality and encompasses sleep difficulties. A higher number on the 0 to 100 scale indicates a greater occurrence of that particular measure (greater adequacy of sleep, greater sleep somnolence, and greater sleep problems).

Neuropsychological Battery and Neurological Examination

Cognitive test scores were obtained from neuropsychological tests from the visit closest to the date of completion of the questionnaire (61.83±42.14 days). The cognitive test scores reflected different cognitive domains, including global cognition, assessed by the MMSE [21], memory, by the short form California Verbal Learning Test (CVLT) Long Delay [48], the Boston Naming Test (BNT) [49], and executive function by the Trail Making Test B (TMT B) [50], as summarized in a previous study [51].

The MMSE is a screening tool for cognitive impairment in geriatric populations, which consists of 15 questions that assess five domains of cognition. It is scored on a 0 to 30 scale, with a higher score reflecting better cognition. The short form CVLT is a test of memory using free recall of a list of 9 words. A higher score indicates recall of more words from the list and thus better performance. BNT consists of 15 items assessing word retrieval. A higher score indicates better performance. TMT B consists of letters and numbers that must be connected in the proper order, akin to connect the dots. The TMT B score is the amount of time taken to complete the test. Therefore, a higher score indicates poorer performance.

Cognitive status was assessed during a structured neurological examination at the time the participants underwent neuropsychological examination. The neurologic examiner assigned a diagnosis of dementia based on the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria for dementia [52]. Participants without dementia were characterized as ‘normal cognition’ or ‘cognitive impairment no dementia’ (CIND). Individuals in this category showed cognitive losses in one or more domains but did not meet criteria for dementia.

Hippocampal Volume

Hippocampal volume was obtained from Magnetic Resonance Imaging (MRI). 82 participants underwent 3T MRI. Volumetric T1 volumes were acquired from 164 × 1 mm slices using 3D SPGR sequence with the following parameters: inversion time (TI); 400ms, echo time (TE), 3100 ms; repetition time (TR), 7200 ms; acquisition matrix, 256 × 256 pixels; flip angle, 11 degrees; field of view (FOV), 26.0cm. Following image acquisition, all MRI scans were processed using a standard pipeline involving brain extraction followed by tissue and hippocampal segmentation. Hippocampal segmentation was performed semi-automatically using an atlas-based method combined with label fusion [53,54].Briefly, our implementation involves diffeomorphic matching of 10 hippocampal atlases to the target image, followed by a consensus algorithm evaluation among all the matches as to the identity of hippocampal locations. Human analysts check the end results for visual quality of segmentation and apply minor cleanup as needed. The obtained hippocampal volumes were adjusted for intracranial volume. The adjusted volume was calculated using a proportions approach by calculating the ratio between the hippocampal volume and the intracranial volume to produce a unitless value between 0 and 1.

Statistical Analysis

Chi-squared tests were used to compare categorical values and independent samples t-tests were used for continuous variables in order to compare the characteristics (sex, education, age, MMSE score, adjusted hippocampal volume, and cognitive status) of study participants who returned a completed sleep questionnaire and those who did not. Chi-squared tests were used to compare categorical values and F-tests were used for continuous variables in order to compare the characteristics (sex, education, age, MMSE score, adjusted hippocampal volume, sleep medication use, sleep quantity, sleep adequacy, sleep somnolence, and sleep problems index II) of study participants based on cognitive status (normal, CIND, dementia). Chi-squared tests were also obtained to compare cognitive status by sleep quantity category. Short, optimal, and long sleepers were compared based on use of sleep medications. Participants' education levels were dichotomized into less than a bachelor's degree vs greater than or equal to a bachelor's degree. Participants who replied to the sleep questionnaire were also characterized based on sex. Multiple linear regression, controlling for age, sex, education, sleep medication and depression, was performed to examine the relation between sleep (quality and quantity) and cognitive function. The control was accomplished by including those terms as covariates in the multiple linear regression models.Sleep quality, measured by sleep adequacy, sleep somnolence, and sleep problems index II, and quantity were the independent variables, and cognition, measured by MMSE, CVLT, BNT, and TMT B, were the dependent variables. Sleep quantity was classified as short sleep (<7 hours), optimal sleep (7–8 hours), and long sleep (>8 hours). Multiple linear regression, controlling for age, sex, education, sleep medication, depression, and MMSE, was performed to examine the relation between sleep (quality and quantity) and hippocampal volume. Sleep quantity and quality were the independent variables and hippocampal volume was the dependent variable. In addition to running this analysis on the study population as a whole, multiple linear regression analyses were run accordingly for the cognitively normal and cognitively impaired (CIND and dementia) groups. Since few participants with dementia had cognitive test scores, with the majority reporting long sleep,

the cohort was not properly balanced or powered to examine associations in participants with dementia alone. Therefore, participants with dementia and CIND were grouped together to form a “cognitively impaired” group. Statistical analyses were performed using JMP Pro Version 13. Relationships were considered significant if the *p* value was less than or equal to 0.05.

Results

Characterization of Participants by Response

It is helpful to understand the differences between those who returned their completed questionnaires and those who did not in order to better characterize the study participants. The characteristics of the study participants by sleep questionnaire response status are presented in Table 1. Study participants who replied were younger (p=0.004), had higher MMSE scores (p=0.006), were more likely to have normal cognition (p<0.001), and had larger hippocampal volumes (p=0.01) compared to study participants who did not reply. Sex and education did not significantly differ between participants who replied and those who did not reply. Comparing participants based on response status was of interest in order to look for potential differences between those who returned the questionnaire and those who did not. We assumed that the latter group would be cognitively less fit than the former, and as expected, this was the case. Stratification of characteristics by response revealed that our study captures a more cognitively intact population of nonagenarians and centenarians from the 90+ Study cohort.

Subjective Sleep Measures in Nonagenarians and Centenarians

Study participants slept an average of 7.82±1.43 hours, had an average sleep adequacy of 46.45±13.33, an average sleep somnolence of 34.35±24.43, and an average sleep problems index II score of 23.96±14.73. 17.9% were in the short sleep group, 48.5% in the optimal sleep group, and 33.6% in the long sleep group. The majority of participants (77.37%) who replied did not report taking any medications to help them sleep. Not surprisingly, individuals who slept less than 7 hours during the night reported using the most sleep medications (33.33%) compared to optimal sleepers (20.00%) and long sleepers (22.22%). Of the sleep measures, males had significantly greater sleep somnolence scores, 42.04±26.39, than females, 30.11±22.32 (t-ratio: - 2.68, p=0.009). The other sleep measures did not significantly differ by sex (all p>0.05). Participants with dementia slept more (9.55±1.04 hours) than those with normal cognition (7.58±1.35 hours) and those with cognitive impairment no dementia (7.90±1.43 hours). None of the short sleepers had dementia, 22.73% of long sleepers had dementia, and 1.61% of optimal sleepers had dementia (Chi: 17.53, p<0.001).

The characteristics of participants by cognitive status are presented in Table 2. The majority of cognitively normal participants had optimal sleep (54%), of CIND participants, 43% had optimal sleep and 40% reported long sleep. Lastly, almost all participants with dementia had long sleep (91%). CIND participants had the greatest mean sleep adequacy (49.1±11.0) with participants with dementia having the least mean sleep adequacy (40.9±8.3). Participants with dementia had the greatest mean sleep somnolence (43.6±27.7), with cognitively normal

participants having the least mean sleep somnolence (32.6±24.1). Participants with dementia had the greatest mean sleep problems index II score (25.0±15.0) and cognitively normal participants had the lowest mean sleep problems index II score (23.9±15.2).

Subjective Sleep Measures and Cognitive Functioning

Sleep quantity was associated with global cognition (MMSE), memory (CVLT), and executive function (TMT B) scores (see Table 3), after controlling for age, sex, education, sleep medication, and GDS. Long sleep (>8 hours) was associated with poorer MMSE (p=0.01), CVLT (p=0.004), and TMT B (p=0.02) scores compared to optimal sleep (7–8 hours). No significant association was found between long sleep and BNT (p=0.96). Short sleep (<7 hours) was not significantly associated with any of the cognitive test scores compared to optimal sleep (all p>0.05). No significant relationships were found between the sleep quality measures and cognitive test scores (all p>0.05). These results demonstrate that nocturnal sleep of greater than eight hours was associated with poorer global cognition, memory, and executive function but not with language (naming). When stratified by cognitive status, a trend between long sleep and worse performance on MMSE, CVLT, and TMT B was observed in the cognitively normal group, but these associations did not reach significance (all p>0.05) (see Table 4). In the cognitively impaired group (CIND and dementia), long sleep duration was significantly associated with poorer performance on CVLT (p=0.02) (see Table 4). No significant relationships were found between the sleep quality measures and cognitive test scores when collapsing across cognitive status and when stratifying by cognitive status. When comparing the cognitively normal and cognitively impaired groups (CIND and dementia), the magnitude of the estimates between long sleep duration and cognitive test scores in the cognitively impaired subjects were much greater than in the cognitively normal subjects.

Subjective Sleep Measures and Hippocampal Volume

Individuals with MRIs were included for analysis of hippocampal volume and sleep variables. Of these 82 people, only 79 reported sleep quantity, and 20.25% of participants were in the short sleep group, 49.37% in the optimal sleep group, and 30.38% in the long sleep group. As seen in Table 5 and 6, no significant relationships were found between any sleep measures and hippocampal volume in the participants (all p>0.05), even when stratified by cognitive status (all p>0.05).

Discussion

The current study investigated the association between subjective sleep quantity and subjective sleep quality with hippocampal volume and cognition in adults over 90. This is the only study to investigate multiple sleep measures in relation to global cognition, memory, executive function, and language in the oldest-old. Our study showed that long sleep duration (>8 hours) in adults over 90 years old, was associated with poorer performance on measures of global cognition, memory, and executive function but not language (naming), after adjusting for sex, age, education, depression, and sleep medication use. In contrast, we did not find any associations between sleep adequacy, sleep somnolence, sleep problems index II and cognition. Such findings illustrate the importance of examining

sleep duration in the last decades of life, as it may be relevant to cognitive health in this vulnerable population.

As in all cross-sectional studies, we do not know the directionality of the relationship between sleep and cognition [55]. Similarly, we do not know the underlying mechanisms through which sleep may impact cognition and health, or cognition and health may impact sleep. Several possible explanations could be underlying this association. Long sleep could be compensation for poor sleep quality, such as excessive daytime sleepiness and sleep fragmentation, which have been shown to be associated with poor cognition [56, 57]. To support this notion, several studies suggest relationships between long sleep and indicators of poor sleep quality. For instance, long sleep has been associated with sleep fragmentation [58, 59]. Another study found that 1649 patients with sleep apnea and excessive daytime sleepiness were characterized by longer sleep duration compared to the 1233 subjects who did not have excessive daytime sleepiness [60]. Long sleep may also be an indicator of other comorbidities or chronic illnesses. For example, one longitudinal study found that history of stroke, diabetes, cancer, hip fracture and older age were all independently associated with an increased likelihood of developing long sleep duration in adults [61]. Participants of The Northern Manhattan study who reported nocturnal sleep duration of ≥ 9 hours had higher frequencies of hypertension and diabetes [5]. However, long sleep duration was independently associated with poorer cognition after adjusting for these comorbidities in the study. Similarly, a longitudinal study in 3286 participants (mean age 73.2 ± 6.3 years) of the Neurological Disorders in Central Spain cohort found a positive relationship between long sleep duration and dementia after adjusting for comorbidities including hypertension, diabetes mellitus, and depressive symptoms [62].Both of these studies were conducted in adults in their seventies and eighties. It is highly likely that individuals over 90 years old who sleep longer may have specific health issues related to age. Research from The 90+ study has shown that adults over 90 years old are more likely to suffer from frailty, fatigue, psychoactive medication usage, and various medical comorbidities [63]. Research from The 90+ study (mean age= 94) has also shown that most participants without functional disability had at least one major medical illness and 62% had two or more [64]. The association between long sleep duration and poor cognition demonstrated in our study may be due to the high prevalence of medical comorbidities in adults over 90 years old.

When stratifying the analyses by cognitive status, we found a significant association between long sleep duration and CVLT. In cognitively normal participants, the same trend was observed between long sleep and worse MMSE, CVLT, and TMT B, but it was not significant. This finding is inconsistent with the current literature in cognitively normal younger elderly, which suggests an association between long sleep quantity and poorer cognition [3,6,7]. Our results may have differed because of our relatively small sample size or perhaps because our study population exclusively included adults over 90 years old. The only other study to examine sleep duration in adults over 90 years with and without dementia also did not find a relationship between sleep duration and MMSE [23]. Therefore, it is possible that sleep quantity is unrelated to cognitive functioning in cognitively normal nonagenarians and centenarians. In cognitively impaired (CIND and dementia) participants, long sleep was significantly related to CVLT. Our results suggest that long sleep duration is associated with poorer memory in oldest old with CIND or dementia, but not in cognitively

healthy oldest old. Long sleep duration was more prevalent in participants with cognitive impairment and dementia. Long sleep duration may be a result of cognitive decline and may be symptomatic of subclinical and clinical dementia in this age group, rather than a cause of cognitive decline. Participants with CIND or dementia in this study were older, which may indicate a higher prevalence of medical comorbidities than the cognitively normal participants. Furthermore, all but one of the participants with dementia were long sleepers, making it is possible that long sleep may be a manifestation rather than a cause of dementia. In line with this possibility, The Framingham Heart Study found that although long sleep duration in the past was not related to dementia risk, an increase of sleep duration to greater than 9 hours over a mean period of 13 years predicted an increased risk of incident dementia in 2457 older adults (mean age 72 ± 6 years) [3]. Consequently, it is important to investigate this relationship longitudinally in nonagenarians and centenarians in order to better understand the directionality of the association.

Our study did not find any associations between hippocampal volume and sleep quantity or quality. The majority of studies examining sleep and hippocampal volume were conducted among cognitively normal adults in their seventies and younger with specific sleep disorders, such as insomnia and sleep apnea [31, 65, 66]. One study in 232 cognitively normal older adults with sleep-disordered breathing found that excessive daytime sleepiness was associated with a small but significant reduction in the bilateral hippocampal volume (mean age 75 ± 0.9 years) [31]. When studies were performed in cognitively healthy older adults with no reported sleep disorders, several investigations noted a relationship between sleep and cortical gray matter, but not between sleep and hippocampal volume [67, 68, 69].

The current study has several limitations. Due to the cross-sectional design of the study, we cannot determine the directionality of the observed associations. Furthermore, the study utilized subjective sleep measures and the incorporation of objective sleep measures such as actigraphy or polysomnography in future studies could provide more information and capture other facets of sleep. The mean interval between questionnaire completion and date of cognitive assessment was 61 days and since the MOS questionnaire reflected the subjective sleep quality over the past month, there could be a change in perception of sleep quality with time in the participants. In our current study, we did not measure the presence of specific sleep disorders among our participants or cortical gray measures which may be relevant in the oldest-old. Despite these limitations, the strengths of our study include our high response rate from an understudied age demographic. Furthermore, we were able to control for depression and sleep medication use, factors that have been associated with sleep quantity and quality [70].

Overall, sleep duration greater than 8 hours, was significantly related to global cognition, memory, and executive function in adults over the age of 90 encompassing all levels of cognition. In those who were cognitively normal, no significant associations were observed between sleep duration and cognitive functioning, but sleep duration greater than 8 hours was significantly related to memory in adults over 90 years with CIND and dementia. In addition, the majority of those afflicted with dementia slept greater than 8 hours. Although the directionality of this relationship cannot be determined in this study, these results demonstrate a relationship between sleep and cognitive health. Better understanding of these

relationships can provide potential strategies for improving sleep and cognitive health in aging. Since nonagenarians are the fast-growing segment of the population and have the highest rates of cognitive impairment it is important to further investigate the role of sleep in this age group.

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Table 1.

Characteristics of Study Participants by Response

Characteristics	Did not reply (n=37)	Replied (n=138)[a]	χ^2	t-ratio	*p*-value
Sex			2.56		0.11
Female, n (%)	29 (78%)	89 (64%)			
Male, n (%)	8 (22%)	49 (36%)			
Education, n (%)			3.77		0.05
< Bachelor's	23 (62%)	61 (44%)			
≥ Bachelor's	14 (38%)	77 (56%)			
Age (years), mean (SD)	97.2 (3.75)	95.1 (3.40)		−3.05	0.004*
MMSE (points), mean (SD)	23.9 (4.92)	27.1 (3.29)		3.73	0.006*
Adjusted hippocampal volume, mean (SD)	0.0045 (0.0004)	0.0048 (0.0005)		2.77	0.01*
Cognitive status, n (%)			19.99		<0.0001*
Normal	15 (44%)	90 (67%)			
CIND	6 (18%)	33 (25%)			
Dementia	13 (38%)	11 (8%)			
Sleep Medication, n (%)					
Yes		31 (23%)			
No		106 (77%)			
Sleep Quantity, n (%)					
<7 hours		24 (18%)			
7–8 hours		65 (49%)			
>8 hours		45 (34%)			

Abbreviations: MMSE, mini-mental state examinations; CIND, cognitive impairment no dementia; SD, standard deviation

* $p<0.05$ indicates significance

Note:

[a] Although 144 individuals replied, only 138 were included in analysis.

Table 2.

Characteristics of Study Participants by Cognitive Status

Characteristics	Normal (n=90)	CIND (n=33)	Dementia (n=11)	χ^2	F-ratio	*p*-value
Sex				2.82		0.24
Female, n (%)	56 (62%)	24 (73%)	5 (45%)			
Male, n (%)	34 (38%)	9 (27%)	6 (55%)			
Education, n (%)				2.05		0.36
< Bachelor's	37 (41%)	18 (55%)	4 (36%)			
≥ Bachelor's	53 (59%)	15 (45%)	7 (64%)			
Age (years), mean (SD)	94.8 (3.27)	95.3 (3.48)	96.5 (3.79)		1.30	0.28
MMSE (points), mean (SD)	28.4 (1.60)	25.8 (2.6)	20.8 (5.2)		56.59	<0.001*
Adjusted hippocampal volume, mean (SD)	0.0049 (0.0005)	0.0047 (0.0004)	0.0046 (0.0006)		3.73	0.03*
Sleep Medication, n (%)				0.42		0.81
Yes	18 (20%)	8 (25%)	2 (18%)			
No	72 (80%)	24 (75%)	9 (82%)			
Sleep Quantity, n (%)				19.88		<0.001*
<7 hours	19 (21%)	5 (17%)	0 (0%)			
7–8 hours	48 (54%)	13 (43%)	1 (9%)			
>8 hours	22 (25%)	12 (40%)	10 (91%)			
Sleep Adequacy	46.9 (13.6)	49.1 (11.0)	40.9 (8.3)		1.72	0.18
Sleep Somnolence	32.6 (24.1)	36.0 (23.5)	43.6 (27.7)		1.12	0.33
Sleep Problems Index II	23.9 (15.2)	24.5 (14.3)	25.0 (15.0)		0.04	0.96

Abbreviations: MMSE, mini-mental state examinations; CIND, cognitive impairment no dementia; SD, standard deviation

* p<0.05 indicates significance

Table 3.

Sleep Quantity and Quality Measuresin Relation to Cognitive Test Scores

Cognitive Test	Sleep Measure	Estimate [f]	Std. Error	*p* value
MMSE (points) [a]	Sleep quantity [e]			
	Short (<7 hours)	0.624	0.495	0.21
	Long (>8 hours)	−1.141	0.433	<0.01 *
	Sleep somnolence	−0.016	0.013	0.19
	Sleep problems index II	0.006	0.020	0.75
	Sleep adequacy	−0.009	0.021	0.67
CVLT (words) [b]	Sleep quantity [e]			
	Short (<7 hours)	0.400	0.390	0.31
	Long (>8 hours)	−0.992	0.342	<0.01 *
	Sleep somnolence	0.002	0.011	0.85
	Sleep problems index II	0.007	0.016	0.68
	Sleep adequacy	−0.017	0.017	0.32
BNT (items) [c]	Sleep quantity [e]			
	Short (<7 hours)	0.077	0.339	0.82
	Long (>8 hours)	0.015	0.304	0.96
	Sleep somnolence	0.009	0.009	0.34
	Sleep problems index II	0.015	0.013	0.25
	Sleep adequacy	−0.007	0.015	0.61
TMT B (seconds) [d]	Sleep quantity [e]			
	Short (<7 hours)	−4.859	16.039	0.76
	Long (>8 hours)	34.969	14.479	0.02 *
	Sleep somnolence	0.345	0.467	0.46
	Sleep problems index II	−0.084	0.689	0.90
	Sleep adequacy	−0.422	0.680	0.54

Abbreviations: MMSE, mini-mental state examinations; CVLT, California verbal learning test; BNT, Boston naming test;TMT B, trails making test B

* p<0.05 indicates significance

Notes:

[a] Scored as number of points, with higher score indicating better performance.

[b] Scored as number of words recalled, with higher score indicating better performance.

[c] Scored as number of items correct, with higher score indicating better performance.

[d] Scored as time to completion in seconds, with lower score indicating better performance.

[e] Participants in the short sleep (<7 hours) and long sleep (>8 hours) categories are compared to participants in the optimal sleep group (7–8 hours).

[f] Every unit increase in the sleep measure is associated with an increase or decrease (−) in units of the cognitive measure.

Table 4.

Sleep Quantity and Quality Measures in Relation to Cognitive Test Scores for Cognitively Normal Subjects compared to Subjects with CIND/Dementia

		Normal			CIND/Dementia		
Cognitive Test	**Sleep Measure**	**Estimate**[f]	**Std. Error**	***p* value**	**Estimate**[f]	**Std. Error**	***p* value**
MMSE (points) [a]	Sleep quantity [e]						
	Short (<7 hours)	0.073	0.291	0.80	0.676	1.228	0.59
	Long (>8 hours)	−0.098	0.287	0.73	−1.712	0.911	0.07
	Sleep somnolence	0.004	0.008	0.65	−0.014	0.025	0.58
	Sleep problems index II	0.008	0.012	0.52	0.024	0.040	0.55
	Sleep adequacy	−0.003	0.013	0.84	−0.002	0.057	0.98
CVLT (words) [b]	Sleep quantity [e]						
	Short (<7 hours)	−0.081	0.351	0.82	1.119	0.989	0.27
	Long (>8 hours)	−0.361	0.342	0.29	−1.727	0.722	0.02 *
	Sleep somnolence	0.003	0.010	0.75	−0.008	0.022	0.72
	Sleep problems index II	0.010	0.015	0.49	−0.012	0.033	0.71
	Sleep adequacy	−0.005	0.016	0.77	−0.006	0.048	0.91
BNT (items) [c]	Sleep quantity [e]						
	Short (<7 hours)	−0.373	0.283	0.19	1.760	1.056	0.11
	Long (>8 hours)	0.315	0.278	0.26	−0.764	0.788	0.34
	Sleep somnolence	0.010	0.008	0.25	0.003	0.023	0.91
	Sleep problems index II	0.005	0.012	0.71	0.033	0.032	0.32
	Sleep adequacy	−0.005	0.014	0.71	0.014	0.048	0.78
TMT B (seconds) [d]	Sleep quantity [e]						
	Short (<7 hours)	9.281	14.708	0.53	−145.257	111.114	0.25
	Long (>8 hours)	8.047	14.495	0.58	119.057	77.375	0.18
	Sleep somnolence	0.395	0.424	0.36	2.958	1.470	0.08
	Sleep problems index II	0.688	0.617	0.27	−3.127	2.331	0.22
	Sleep adequacy	−0.938	0.634	0.14	0.978	3.471	0.79

Abbreviations: MMSE, mini-mental state examinations; CVLT, California verbal learning test; BNT, Boston naming test;TMT B, trails making test B; CIND, cognitive impairment no dementia

* p<0.05 indicates significance

Notes:

[a] Scored as number of points, with higher score indicating better performance.

[b] Scored as number of words recalled, with higher score indicating better performance.

[c] Scored as number of items correct, with higher score indicating better performance.

[d] Scored as time to completion in seconds, with lower score indicating better performance.

[e] Participants in the short sleep (<7 hours) and long sleep (>8 hours) categories are compared to participants in the optimal sleep group (7–8 hours).

[f] Every unit increase in the sleep measure is associated with an increase or decrease (−) in units of the cognitive measure

Table 5.

Sleep Quantity and Quality Measures in Relation to Hippocampal Volume.

Sleep Measure	Estimate[b]	Std Error	*p* value
Sleep quantity[a]			
Short (<7 hours)	2.582e-5	9.386e-5	0.78
Long (>8 hours)	−8.700e-5	8.364e-5	0.30
Sleep somnolence	−1.196e-6	2.371e-6	0.62
Sleep problems index II	−7.859e-7	3.627e-6	0.83
Sleep adequacy	−1.148e-6	3.927e-6	0.77

[a]Participants in the short sleep (<7 hours) and long sleep (>8 hours) categories are compared to participants in the optimal sleep group (7–8 hours).

[b]Every unit increase in the sleep measure is associated with an increase or decrease (−) in units of hippocampal volume.

Note: Hippocampal volume was adjusted for intracranial volume.

Table 6.

Sleep Quantity and Quality Measures in Relation to Hippocampal Volume for Cognitively Normal Subjects compared to Subjects with CIND/Dementia

	Normal			CIND/Dementia		
Sleep Measure	**Estimate[b]**	**Std. Error**	***p* value**	**Estimate[b]**	**Std. Error**	***p* value**
Sleep quantity [a]						
Short (<7 hours)	5.604e-6	1.130e-4	0.96	−3.826e-5	2.260e-4	0.87
Long (>8 hours)	−5.300e-5	1.170e-4	0.65	2.424e-5	1.620e-4	0.88
Sleep somnolence	−4.116e-6	3.146e-6	0.20	5.869e-6	3.581e-6	0.12
Sleep problems index II	−3.458e-6	4.939e-6	0.49	7.653–6	5.543e-6	0.18
Sleep adequacy	−2.120e-7	4.851e-6	0.96	−9.182e-6	6.814e-6	0.19

Abbreviations: CIND, cognitive impairment no dementia

[a]Participants in the short sleep (<7 hours) and long sleep (>8 hours) categories are compared to participants in the optimal sleep group (7–8 hours).

[b]Every unit increase in the sleep measure is associated with an increase or decrease (−) in units of hippocampal volume.

Note: Hippocampal volume was adjusted for intracranial volume.