의학박사 학위논문

The Associations of Subjective and Objective Sleep Measures with Cognitive Decline in Cognitively Normal Elderly

정상인지기능 노인에서
주관적 및 객관적 수면 지표와 인지저하의 관계

2020년 2월

서울대학교 대학원

의학과 정신과학전공

서 승 완

The Associations of Subjective and Objective Sleep Measures with Cognitive Decline in Cognitively Normal Elderly

지도 교수 김 기 웅

이 논문을 의학박사 학위논문으로 제출함
2019년 10월

서울대학교 대학원
의학과 정신과학전공
서 승 완

서승완의 의학박사 학위논문을 인준함
2020년 1월

위 원 장 _____ (인)

부위원장 _____ (인)

위 원 _____ (인)

위 원 _____ (인)

위 원 _____ (인)

The Associations of Subjective and Objective Sleep Measures with Cognitive Decline in Cognitively Normal Elderly

by

Seung Wan Suh, M.D.

A Thesis Submitted to the Department of Medicine in Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy in Medicine (Psychiatry) at Seoul National University College of Medicine

January 2020

Approved by thesis committee:

Professor _____ **Chairman**

Professor _____ **Vice Chairman**

Professor _____

Professor _____

Professor _____

Abstract

The Associations of Subjective and Objective Sleep Measures with Cognitive Decline in Cognitively Normal Elderly

Suh, Seung Wan

Department of Psychiatry, College of Medicine

The Graduate School

Seoul National University

Background and Objectives: There have been numerous studies on the relationship between subjective/objective sleep measures and cognitive decline at the group level. However, subjective sleep characteristics have never been examined in a single, full model. Furthermore, objective sleep markers have never been examined in the aspect of the complementary roles of NREM and REM sleep in the memory consolidation process. Although the association of sleep and the risk of cognitive decline has been repeatedly reported, the validity of sleep measures for predicting cognitive decline at the individual level is still in question. This study examines four hypotheses. First, we investigated whether subjective sleep disturbances induce cognitive decline, i.e. becoming mild cognitive impairment (MCI) or dementia, over 4 years in cognitively normal elderly using a full-model fit (Hypothesis I). Second, in the subsample of this cohort, we explored whether NREM/REM sleep cycles and their associated sleep architecture are associated with the risk of cognitive decline using polysomnography

in cognitively normal elderly (Hypothesis II). Third, we investigated whether the subjective sleep parameters were correlated with the polysomnographic findings, both of which were found to be associated with the risk of cognitive decline (Hypothesis III). Fourth, we examined whether the logistic regression model using subjective sleep parameters can predict cognitive decline with a satisfactory level of performance (Hypothesis IV).

Methods: For the hypothesis I, data were acquired from a nationwide, population-based, prospective cohort of Korean elderly whose cognitive function was normal (NC, N = 2,238) at baseline. We excluded individuals with major psychiatric/neurological disorders or taking sleeping pills at baseline, and followed them for 4 years. Subjective sleep characteristics (midsleep time, sleep duration, sleep latency, subjective sleep quality, sleep efficiency, and daytime dysfunction) and cognitive status were measured using the Pittsburgh Sleep Quality Index (PSQI) and Consortium to Establish a Registry for Alzheimer's Disease Assessment (CERAD), respectively, at baseline and 4-year follow-up assessments. We used logistic regression models adjusted for covariates including age, sex, education, apolipoprotein E genotype, Geriatric Depression Scale, Cumulative Illness Rating Scale, and physical activity.

For the hypothesis II, we enrolled 235 cognitively normal subsamples from the cohort used above who underwent overnight polysomnography at baseline. A NREM/REM cycle is a sequence of NREM and REM sleep, uninterrupted by a waking period of >2 min. After 4 years, the development of MCI or dementia was related to the measures of sleep architecture, including NREM/REM cycle parameters by logistic regression analyses.

For the hypothesis III, we used data from participants with NC (N = 235) who completed 4 years of follow-up and provided baseline PSQI scores and polysomnographic measures. We performed Kendall's rank correlation analyses to

evaluate the correlation between subjective sleep measures and NREM/REM sleep cycle parameters that turned out to be significantly related to cognitive decline in the prior analyses.

For the hypothesis IV, we randomly divided the cognitively normal baseline cohort (N = 2,238) dataset into training and testing datasets in a 4:1 ratio after which a 10-fold cross-validation analysis was conducted. We developed a predictive model for the cognitive decline after 4 years using binary logistic regression analysis in the training datasets and examined their predictive validity for the same outcome in the testing datasets using ROC analyses. Subsequently, we performed two additional analyses; 1) a prediction model for the progression to dementia after 4 years in the baseline NC group, and 2) a prediction model for the progression to dementia after 4 years in the merged dataset composed of the baseline NC or MCI (N = 2,893) group.

Results: Regarding hypothesis I, long sleep latency (>30 minutes), long sleep duration (≥ 7.95 hours), and late mid-sleep time (after 3:00 AM) at baseline were associated with the risk of cognitive decline at 4-year follow-up assessment in cognitively normal participants; odds ratios (OR) was 1.40 (95% CI, 1.03–1.90; p = 0.03) for long sleep latency, 1.67 (95% CI, 1.18–2.35; p = 0.004) for long sleep duration, and 0.61 (95% CI, 0.41–0.90; p = 0.03) for late mid-sleep time. Newly developed long sleep latency during the follow-up period also doubled the risk of cognitive decline (OR, 1.95 [95% CI, 1.36–2.81]; p = 0.002).

Regarding hypothesis II, a short average cycle length was significantly associated with cognitive decline (OR, 0.97 [95% CI, 0.94–0.99]; p = 0.02). When its substructure and NREM and REM sleep outside of cycles were considered simultaneously, the average REM sleep duration per cycle was significantly related to the outcome (OR, 0.87 [95% CI, 0.76–0.98]; p = 0.03).

Regarding hypothesis III, Sleep latency was found to be negatively

correlated with average cycle length (τ = -0.11, p = 0.04) and NREM periods in each cycle (τ = -0.16, p = 0.002).

Regarding hypothesis IV, we were able to predict incident cognitive decline after 4 years in the baseline NC group with area under the curve (AUC) of 0.65 (sensitivity = 0.60; specificity = 0.66) using a binary logistic regression model made of subjective sleep characteristics, APOE ε4 allele status, and other demographic and lifestyle factors. The additional analyses revealed that we predicted incident dementia after 4 years with AUC of 0.62 (sensitivity = 0.66; specificity = 0.73) in the same baseline subjects, and also predicted incident dementia in the baseline NC or MCI group with AUC of 0.85 (sensitivity = 0.89; specificity = 0.75).

Interpretation: Subjective sleep complaints such as long sleep latency (>30 minutes) and long sleep duration ($\geq$ 7.95 hours) may predict the higher risk of cognitive decline while late mid-sleep time (after 3:00 AM) may predict the lower risk of cognitive decline in the cognitively normal elderly. Furthermore, subjective long sleep latency showed a significant association with the short average duration of NREM/REM cycles measured by polysomnography which was also associated with the future risk of cognitive decline in these populations. Subjective sleep measures may not be a random expression of a habitual sleep pattern but a reliable measure verifiable by objective markers reflecting sleep macrostructures related to cognitive decline. We observed that the predictive performance for the incident cognitive decline using only cognitively normal elderly populations was not satisfying. However, our findings indicated that it might be possible to develop a prediction model for dementia using subjective sleep measures in nondemented elderly.

Part of this work was previously published on:
-Suh, Seung Wan, et al. "Sleep and Cognitive Decline: A Prospective Nondemented Elderly Cohort Study." Annals of Neurology 83.3 (2018): 472-482.

-Suh, Seung Wan, et al. "Short Average Duration of NREM/REM Cycle Is Related to Cognitive Decline in an Elderly Cohort: An Exploratory Investigation." Journal of Alzheimer's Disease 70.4 (2019): 1123-1132.

Keyword: Sleep, Elderly, Subjective, Objective, Polysomnography, Dementia, Longitudinal

Student Number : 2014-21984

Table of Contents

Figure

Tables

Chapter 1. Introduction

1.1. Study Background

It had been a focus of earlier studies that the principal role of sleep might be protection from interfering environmental stimuli (1). However, observations of the system and synaptic consolidation in slow-wave sleep (SWS) and rapid eye movement (REM) sleep, respectively, have led researchers to consider sleep as a contributor to both qualitative and quantitative changes of memory representations (1). Furthermore, sleep is reported to have a bidirectional relationship with amyloid-β (Aβ) in the brain (2). SWS reduced Aβ production, expanded the extracellular fluid in the brain, and increased Aβ clearance (2). In contrast, Aβ brain deposition disrupted sleep architecture, and Aβ immunotherapy reversed sleep disturbances (2). Therefore, sleep disturbances may be related to the risk of cognitive decline or dementia, and subjective and objective markers of sleep have been investigated from this perspective.

As for the subjective sleep characteristics, a multitude of sleep parameters including long sleep latency, poor sleep efficiency or quality, excessive daytime sleepiness, sleep-disordered breathing (3), delayed sleep phase, and long sleep duration were reported, corroborated by recent meta-analyses (4, 5), to be associated with cognitive impairments in late life. However, to date, findings on these associations were inconsistent. For example, there was a report that sleep latency was not associated with cognitive decline (6), while other studies reported an association with advanced sleep phase (7), with short sleep duration (6), with both long and short sleep duration (8), or no associations (9, 10). We identified several factors that contribute to these conflicting results. First, they did not adopt a full-model fit for diverse sleep parameters in the multivariate analyses due to

limited sample size, thus unable to capture the confounding effects of these parameters. Second, a considerable portion of previous studies relied their evaluation of cognitive functions on tests such as Mini-Mental Status Examination (MMSE) and Telephone Interview for Cognitive Status (TICS), which are not sensitive to mild cognitive impairments. Third, lots of previous studies did not properly subdivide baseline cognitive status when analyzing the influence of sleep parameters on cognition, only adjusting for the baseline screening scores. Furthermore, the different impacts of prevalent and incident sleep disturbances on the cognitive decline and its reversibility have scarcely been investigated.

On the other hand, cognitive impairment has also been studied in the context of objective markers of sleep, including its macrostructures. Several cross-sectional studies showed that Alzheimer's disease patients, even in the early stages of the disease, showed lower SWS and REM sleep percentage, and reduced sleep efficiency (11). A recent prospective cohort study demonstrated that lower REM sleep percentage and longer REM sleep latency, but not SWS percentage, were associated with an increased risk of incident dementia (12). However, sleep is not a static or homogeneous state but a dynamic process with cyclic electrophysiological changes (13). According to the "sequential hypothesis," the consolidation of explicit and implicit memory can occur optimally when SWS and REM sleep take place successively (14). In this respect, Mazzoni and colleagues demonstrated that the average duration of successive non-REM (NREM) sleep - REM sleep cycles defined according to their own criteria, and the proportion of total cycle time (TCT) in total sleep time (TST) were positively correlated with the number of recalled words presented before sleep in the elderly (15). Sonni found that average NREM/REM cycle length, TCT, and the proportion of TCT in TST were all significantly greater in young adults than in elderly individuals (16). However, to the best of our knowledge, there have been no prospective studies that investigated

the relationship between NREM/REM cycles and the risk of future cognitive decline in the elderly.

Meanwhile, these prospective studies examining the relationship between sleep measures and cognitive function can only provide evidence at the group level. As dementia research communities have faced with several failures of drug development over the past decades (17), however, it is increasingly important to identify those who have intact cognitive function and, at the same time, who are vulnerable to cognitive decline in the near future in order to select subjects that would be most benefited by primary preventive strategies. In this respect, it is the calling of the times to construct a valid and reliable prediction model for dementia at the individual level employing cost-effective biomarkers that have been investigated intensively so far. Though a multitude of these markers including magnetic resonance imaging (MRI) measures and neuropsychological test scores have been used in previous literature (18, 19), subjective sleep characteristics have not been studied in this type of prediction model yet. However, the reliability and validity of subjective sleep measures are still in question and many researchers have expressed doubt about using these measures as a predictor in a statistical model.

1.2. Purpose of Research

First, we investigated whether the baseline subjective sleep parameters (mid-sleep time, sleep duration, sleep latency, sleep quality, sleep efficiency, and daytime dysfunction) and their changes over 4 years induce cognitive decline in a large, randomly sampled, community-dwelling, cognitively normal elderly cohort.

Second, from a subsample of the elderly cohort describe above, we explored whether objective sleep measures including NREM/REM sleep cycles and

their associated sleep architectures were related to the future risk of cognitive decline (becoming MCI or dementia) in the cognitive normal participants.

Third, we investigated the validity of the subjective sleep parameters by examining their correlation with corresponding polysomnographic findings and NREM/REM sleep cycle parameters that found to be associated significantly with cognitive decline in the prior analyses.

Fourth, we examined the predictive performance of the logistic regression model for the progression to dementia after 4 years using these subjective sleep parameters as independent variables.

Chapter 2. Methods

2.1. Study population

2.1.1. Main cohort for subjective sleep measures

We conducted this study as a part of the Korean Longitudinal Study on Cognitive Aging and Dementia (KLOSCAD) (20). In KLOSCAD, we randomly sampled 30 villages and towns from 13 specific districts across South Korea. Based on residential rosters and data on people aged 60 years or above, we randomly selected 10% of the elderly adults from urban areas and 20% from rural areas. All participants lived at home during the study period. We conducted the baseline assessment of the cohort from 2011 – 2012, and two other follow-up assessments in 2013 – 2014 and 2015 – 2016 periods. We excluded the participants with following conditions at the baseline assessment; serious psychiatric disorders including dementia according to the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders Text Revision (DSM-IV-TR) (21), mild cognitive impairment (MCI) following the consensus criteria proposed by the International Working Group on MCI (22), serious neurologic disorders including Parkinson's disease, use of sedatives during the past 1 month, or any missing data on sleep parameters and covariates. All participants provided a written informed consent. This study was approved by the Institutional Ethics Review Board (IRB) of the Seoul National University Bundang Hospital.

2.1.2. Subcohort for objective sleep measures

We conducted this study as an addendum to the KLOSCAD using its subpopulation who were enrolled from the Jukjeon district of Yongin city (Figure 2). From the 6,959 residents aged 60 or above in that area, we selected 696

individuals (10%) via systemic random sampling using the residential roster and invited them to the baseline evaluation between 2011 and 2012. Among them, 348 subjects (50.0%) completed the baseline evaluation including overnight polysomnography of which 282 were cognitively normal (NC) after excluding those diagnosed with MCI and dementia. Among these NC participants, 235 completed a 4-year follow-up evaluation between 2015 and 2016. All participants provided written informed consent and this study protocol was approved by the Institutional Review Board of SNUBH.

2.2. Assessment of cognitive disorders

Geriatric psychiatrists administered a face-to-face standardized diagnostic interview, physical and neurological examinations to each participant using the Korean version of the Consortium to Establish a Registry for Alzheimer's Disease Assessment Packet Clinical Assessment Battery (CERAD-K-C) (23) and the Korean version of the Mini International Neuropsychiatric Interview (MINI) (24). Trained research neuropsychologists or nurses administered the CERAD-K Neuropsychological Assessment Battery (CERAD-K-N) (23, 25), Digit Span Test (26), and Frontal Assessment Battery (27) to every participant. Laboratory tests including complete blood cell counts, chemistry profiles, a serologic test for syphilis, and apolipoprotein E genotyping were conducted as well. We confirmed the final diagnosis of them through consensus diagnostic conferences involving four geriatric research psychiatrists. We diagnosed dementia according to the DSM-IV-TR diagnostic criteria (21), while MCI was diagnosed following the consensus criteria proposed by the International Working Group on MCI (22). We defined NC as a state that is able to function independently in the community and without any impairment in objective neuropsychological tests.

2.3. Assessment of sleep parameters

2.3.1. Subjective sleep measures

We estimated the subjective sleep parameters (mid-sleep time, sleep duration, sleep latency, sleep quality, sleep efficiency, and daytime dysfunction) at the baseline and 4-year follow-up evaluations for the main cohort using the Korean version of the Pittsburgh Sleep Quality Index (PSQI) (28). For statistical purposes, we categorized sleep variables into two groups using the component scores of PSQI to accommodate them in a single model. Detailed descriptions of these variables can be found in Table 1. While "sleep quality" is a subjective rate of overall quality of sleep reflecting various aspects of it during the past one month, "sleep efficiency" is a more of a calculated measure, defined as the ratio of the subjectively reported actual sleep duration to the total time spent in bed. We defined "poor sleep efficiency" group as having its value below 75% (component scores *2* or *3*). "Daytime dysfunction" group was defined as having the component score *1* or more because the number of individuals in the main cohort with this component score 2 or 3 was only 67 among 2,238 people with NC at baseline. We defined mid-sleep time as the mid-point between the bedtime and the waking time reflecting when the sleep took place, while sleep duration is about how long one slept. For mid-sleep time and sleep duration, it has been reported that the association between these variables and health outcomes including the cognitive function is likely to be U- or J- shaped (7). Therefore, we defined an "average group" for each of these variables whose respective values were within one standard deviation of the median derived from the NC group (from AM 1:00 to AM 3:00 for mid-sleep time and from 5 h 3 min to 7 h 57 min for sleep duration). If the value was below the range, it fell into the "early mid-sleep time" or "short sleep duration" groups. If the value was above the range, it was defined as "late mid-sleep time" or "long sleep duration" groups. We employed these criteria, and

not the conventional standard of average sleep duration ranged from 6 to 9 because previous studies reported that sleep characteristics are dependent on the ethnicity of subjects, and generally short sleep duration was reported for the Asian (29).

2.3.2. Polysomnographic data and NREM/REM sleep cycles

Participants from the subcohort underwent overnight polysomnography in a sleep laboratory at SNUBH using Embla N7000 (Embla, Reykjavik, Iceland) with simultaneous video recordings. Following the guidelines of Rechtschaffen and Kales (30), we scored sleep stages in 30-s epochs, and placed electroencephalography (EEG) electrodes at the C3/A2, O1/A2, and O2/A1 areas and two electrooculographic electrodes at the sides of both eyes to assess vertical and horizontal ocular movements. Additionally, we placed submental electromyographic electrodes at the submentalis muscle and for recording limb movements, at both anterior tibialis muscles. We examined chest and abdominal respiratory movements by strain gauges. Nasal pressure cannulas were employed to study airflow, and a pulse oximeter was applied on an index finger to measure arterial oxygen saturation. Participants were allowed to choose their own bedtime and wake-up time around PM 10:30 and AM 6:00, respectively. Using the criteria set by Mazzoni (15), a NREM/REM cycle was defined as a sequence of NREM and REM sleep stages, both >2 min, and not interrupted by >2 min of a waking period. REM periods <2 min were subsumed under the previous sleep stage. If a sequence of NREM stages was intervened by a waking period >2 min, it was not considered to be a part of the NREM/REM cycle. Independent variables of our analysis included the percentage of time spent in S1, S2, SWS, and REM sleep. In addition, other secondary sleep measures such as sleep period time (SPT, elapsed time from sleep onset to the last epoch of sleep), TST (time spent in S1, S2, SWS, and REM sleep during SPT), sleep onset latency (SOL), REM sleep latency

(REML), sleep efficiency (SE, percentage of total sleep time over total recording time), and wake time after sleep onset (WASO) were also considered as exposures and were evaluated. NREM/REM cycle-related parameters selected in this study included the percentage of time spent in S1, S2, SWS, and REM sleep during NREM/REM cycles, SOL (elapsed time from lights-out to the first epoch of NREM/REM cycle), REML (elapsed time from lights-out to the first epoch of REM sleep of NREM/REM cycle), SE and WASO during NREM/REM cycles, TCT, TCT/SPT, TCT/TST, NREM and REM time in TCT, average cycle length (TCT divided by the number of cycles), average NREM and REM per cycle, and NREM and REM periods outside of cycles.

2.4. Assessment of confounding factors

From the main and sub- cohort, baseline data on age, sex, years of education, presence of apolipoprotein E ε4 allele, Geriatric Depression Scale (GDS) score, Cumulative Illness Rating Scale (CIRS), socioeconomic status, employment status, presence of cohabitants, degree of smoking and drinking, physical activity measured in calorie/week, REM sleep behavior disorder screening questionnaire score, and STOP-BANG score were all collected by trained research nurses during the evaluation. CIRS (31) is a measure for evaluating the overall burden of comorbid illnesses, rating on a 5-point scale over each of 13 relatively independent body systems. For the subjective sleep characteristics study, we excluded participants with major depressive disorder at baseline, and further evaluated the Korean version of the GDS (32) to adjust for the effects of subsyndromal depression. We considered the amount of smoking and alcohol consumption quantified as pack/day and standard unit/week, respectively, over the past year (33). The degree of physical activity (total energy expenditure in consumed kilo-calories/week) was calculated using a formula with a metabolic equivalent task and

a relative metabolic rate (34). Poor economic status was determined if a participant was covered by the National Medicaid Program. STOP-BANG questionnaire is a measure to detect those with high risk of obstructive sleep apnea by assessing snoring (S), tiredness (T) during daytime, observed apnea (O), high blood pressure (P), body mass index (B), age (A), neck circumference (N), and gender (G) of subjects (35). We selected these variables as confounding factors of our models because they are found to be associated with sleep habits and causally related to cognitive function based on previous studies (36).

2.5. Statistical analyses

2.5.1. Subjective sleep measures from the main cohort

We compared the differences between groups using independent sample t-test and χ^2 test for continuous and categorical variables, respectively. We analyzed the impact of sleep on cognitive changes over 4 years using logistic regression models. In these models, we incorporated mid-sleep time, sleep duration, sleep latency, sleep quality, sleep efficiency, and daytime dysfunction as independent variables under a full-model fit to properly reflect key components of the circadian rhythm, including phase, amplitude, and stability (37), and adjusted the aforementioned covariates. For the NC group at baseline, we defined the outcome, cognitive decline, as the incidence of MCI or dementia over the follow-up period. We also examined the effect of the changes in the sleep parameter over the follow-up period if this parameter, at the baseline, was found to be associated with the cognitive decline in the full-model. To estimate the level of explained variances of a regression model, we presented Nagelkerke's R^2. Lastly, we conducted a sensitivity analysis excluding those who were reported to have taken sedatives in the past one month by PSQI during the study period.

2.5.2. Objective sleep measures from the subcohort

We compared baseline demographic variables, cognitive test scores, and sleep measures between the participants with cognitive decline and those without cognitive decline after 4 years using the Mann-Whitney U test for continuous variables and the $\chi 2$ or Fisher's exact test for categorical variables. For cognitive test scores such as MMSE and CERAD-total score (38), we further compared them using analysis of covariance (ANCOVA) adjusted for covariates described below. In addition, CERAD-total scores were prospectively compared in each group at baseline and at follow-up using repeated measures ANCOVA with the same adjustments in order to confirm the progression of cognitive decline. Shapiro-Wilk test (39) assured the normality of the distribution of dependent variables in our analyses.

We related sleep stage or NREM/REM cycle parameters to the risk of cognitive decline using univariate and multivariate binary logistic regression analyses adjusted for age, sex, years of education, presence of APOE ε4 allele, body mass index, presence of major depressive disorder according to DSM-IV-TR, amount of smoking and alcohol consumed over the last 1 year, total score of CIRS, physical activity measured in total energy expenditure in consumed calories/week, presence of sleep-disordered breathing (SDB), whether taking sedatives in the previous month reported in the Korean version of the PSQI, and the duration of awakenings measured in WASO at the baseline evaluation. We calculated the amount of physical activity from a formula using a relative metabolic rate and a metabolic equivalent task (34). We defined the presence of SDB as having the apnea-hypopnea index (AHI) of 15 events or more per hour following the American Academy of Sleep Medicine Manual for the Scoring of Sleep and Associated Events (40). Additionally, we adjusted the model for WASO to

examine the association between NREM/REM cycles and cognitive decline independent of the duration of awakenings.

We then explored the factors that might contribute to the relationship between NREM/REM cycles and cognitive decline. Adjusted with covariates mentioned above, NREM/REM cycle parameters are related to the risk of cognitive decline after excluding 1) those with REM sleep behavior disorder (RBD) (41), 2) those with restless legs syndrome (RLS) (Definite RLS on Cambridge-Hopkins questionnaire for RLS (42), 3) those with alcohol use disorder (Alcohol Use Disorder Identification Test-Korean version (43) score $\geq$20), 4) those with extreme chronotypes (earliest 5% [<1 AM] and latest 5% [>4 AM] of mid-sleep time) where usual bedtimes and wake times were acquired from the PSQI, or 5) those taking sedatives in the past one month by PSQI during the study period. We ran these sensitivity analyses because each of these states has profound relationships with sleep architecture (44). The assumption of linearity between continuous predictors and log odds was verified using the Box- Tidwell test (45).

2.5.3. Correlation between subjective and objective sleep measures

For this analysis, we used data from the elderly participants from the polysomnography subcohort who completed 4 years of follow-up, had baseline cognitive function as NC, and provided baseline PSQI scores. We performed Kendall's rank correlation analysis (46) to examine the degree of correlation between subjective and objective sleep measures because of the non-normal distribution of included variables. First, three baseline subjective sleep characteristics in their raw, continuous form (i.e. sleep latency in minutes, sleep efficiency in %, and sleep duration in minutes) were cross-sectionally correlated with corresponding polysomnographic findings, namely, SOL, SE, and TST, respectively. Second, to evaluate its validity, each of the subjective sleep

characteristics in its continuous form was correlated with NREM/REM sleep cycle-related parameters which were found to be significantly associated with cognitive decline after 4 years. The pattern of distribution of included variables was assessed using Shapiro-Wilk test (39).

2.5.4. Predictive performance of subjective sleep measures

To assess the predictive performance of the binary logistic model for the cognitive decline after 4 years, we randomly divided the cognitively normal baseline cohort (N = 2,238) into training and testing datasets in a 4:1 ratio for 10-fold cross-validation analyses. From the training dataset, a binary logistic regression equation was derived with the dependent variable being whether or not diagnosed with MCI or dementia after 4 years. Independent variables included all of the six sleep parameters and were adjusted for the same confounders described above. These equations were then applied to corresponding testing datasets for their validation. Subsequently, we performed two additional analyses based on the same method as above; 1) a prediction model for the progression to dementia after 4 years in the baseline NC group, and 2) a prediction model for the progression to dementia after 4 years in the merged dataset composed of the baseline NC or MCI (N = 2,893) group. Receiver operating characteristic (ROC) curves were estimated to identify discriminatory cut-off values, their area under the curve (AUC), sensitivity, and specificity. Analyses employed 2-sided significance at the 0.05 level. All statistical analyses were performed using the R Statistical Software (version 3.2.3; R Foundation for Statistical Computing, Vienna, Austria).

Chapter 3. Results

3.1. Subjective sleep measures from the main cohort

As summarized in Figure 1, 3,307 out of 6,818 participants in the baseline assessment of the KLOSCAD were enrolled at the inception of the study, and 2,238 cognitively normal participants completed the 4-year follow-up assessment.

At the 4-year follow-up assessment, 246 (11.0%) were converted to MCI (147 to amnestic and 99 to non-amnestic MCI) and 19 (0.8%) to dementia (16 to Alzheimer's disease, 2 to vascular dementia, and 1 to mixed dementia).

Compared to the non-decliners after 4 years, cognitive decliners were older, less educated, more depressive, poorer, more likely to live alone, physically inactive, and had fewer female individuals (Table 2). Over the 4-year follow-up period, 89 (2.7%) passed away, 12 (0.4%) was institutionalized, 964 (29.2%) refused to participate, and 4 (0.1%) had incomplete PSQI assessments. These dropouts were older (mean age [SD], 69.9 [6.6] vs 68.7 [5.9]; $p < 0.001$), less educated (years of education [SD], 8.0 [5.1] vs 9.2 [5.2]; $p < 0.001$), more depressive (GDS score [SD], 9.4 [6.1] vs 9.0 [6.0]; $p = 0.019$), and poorer (% with Medicaid [SD], 4.4 vs 2.9; $p = 0.016$) compared to participants who completed 4-year follow-up.

In the cognitively normal participants at baseline, long baseline sleep duration and long baseline sleep latency were associated with about 70% and 40% higher chances of cognitive decline while late baseline mid-sleep time was associated with about 40% lower chances of cognitive decline over the 4-year follow-up period (Nagelkerke's $R^2 = 0.13$, Table 3). As shown in Table 4, long sleep latency or long sleep duration at both the baseline and 4-year follow-up assessments were associated with about 2 times higher risk of cognitive decline

over the 4-year follow-up period. Prolongation of sleep latency (not long sleep latency at the baseline assessment but long sleep latency at the 4-year follow-up assessment) was also associated with about 2 times higher risk of cognitive decline over the 4-year follow-up period. In contrast, late mid-sleep time at both the baseline and 4-year follow-up assessments was associated with about 50% lower risk of cognitive decline over the 4-year follow-up period. In addition, we found that after excluding 137 participants (6.1 %) who took sedatives during the study period, there was no difference in the significant results described above.

3.2. Objective sleep measures from the subcohort

The demographic and clinical characteristics of the participants are summarized in Table 5. The participants were followed for 4.01 ± 0.24 years. Among the 235 NC participants, 13 had MCI (eight with amnestic and five with non-amnestic MCI) and 1 had dementia (dementia with Lewy bodies) at the 4-year follow-up evaluation. We found that the CERAD-total score of participants without cognitive decline did not change over 4 years (mean [SD]; from 74 [9] to 74 [10], F [1, 219] = 6.241, $p = 0.758$), while it decreased significantly for those with cognitive decline during the same period (mean [SD]; from 70 (7) to 64 (11), F [1, 12] = 27.486, $p = 0.035$). The final sample had 4 individuals with RBD, 5 with definite RLS, 2 with alcohol use disorder, and 19 with extreme habitual chronotypes (earliest 5%, N = 8; latest 5%, N = 11) at the time of baseline evaluation. Between participants and those who refused at baseline, we found no observable difference in sex ratio (p = .943), though the latter was significantly older than participants (mean age [SD]; 71.6 [8.7] vs. 68.4 [6.2]; $p < 0.001$).

The participants with cognitive decline at the 4-year follow-up evaluation were older, less educated, less likely to be depressed, less physically active, and had more comorbidities at the baseline evaluation than those without cognitive

decline. They also showed poorer cognitive test scores in terms of MMSE and CERAD-total score at baseline than the cognitively intact group, although their differences disappeared when the comparison was adjusted for the confounding factors using ANCOVA (F [1, 233] = 10.745, p = 0.061 for MMSE; F [1, 233] = 2.835, p = 0.094 for CERAD-total score). Among these cognitive decline group, 2 participants (14 %) reported to had taken clonazepam, alprazolam, or zolpidem, while 24 participants (11 %) from non-decliners had used clonazepam, diazepam, lorazepam, alprazolam, triazolam, zolpidem, or trazodone in the study period. None of the participants took cholinesterase inhibitors during the study period.

As shown in Table 6, the sleep architectures of total sleep were comparable between the participants with cognitive decline and those without cognitive decline. However, when we compared the sleep architectures during NREM/REM cycles, the participants with cognitive decline showed a larger proportion of S1, a smaller proportion of S2 and shorter average sleep cycle length than those without cognitive decline. The average lengths of both NREM and REM sleep per cycle were shorter in the participants with cognitive decline compared to those without cognitive decline.

When each sleep stage parameter was related separately to the cognitive decline after 4 years, none of the sleep variables produced any significant result (Table 7). However, several NREM/REM cycle-related parameters revealed several significant outcomes as shown in Table 8. We found that, in an unadjusted model, a larger proportion of time spent in S1 sleep and a smaller proportion of time spent in S2 sleep during NREM/REM cycles are associated with higher odds of cognitive decline after 4 years, though these associations became insignificant after adjustments. In addition, a unit increase (in minutes) in average cycle length was related to an approximately 3% lower chance of cognitive decline during the follow-up period. We also found that the average duration of both NREM and REM periods per cycle was associated with a significantly lower chance of

cognitive decline. We found that each of the sensitivity analyses excluding those with RBD, RLS, alcohol use disorder, extreme chronotypes at baseline, or sedative-users did not change these significant relationships.

Model 1 in Table 9 showed that if the average duration of NREM and REM periods per cycle are entered into the adjusted model, a unit increase in average REM per cycle was related to about a 14% lower chance of cognitive decline, while average NREM per cycle was insignificant. After accounting for the NREM and REM periods outside of cycles, the adjusted model (Model 2 in Table 9) revealed that a unit increase in only REM periods in the average cycle is associated with a lower chance of cognitive decline with a similar magnitude. These findings also remained significant for each sensitivity analysis. There was no evidence of multicollinearity among independent variables in all of our models with the maximum variance inflation factor being 3.234.

3.3. Correlation between subjective and objective sleep measures

In the same participants who were cognitively normal and had baseline PSQI and polysomnographic measures, subjective sleep latency, efficiency and duration were all positively correlated with polysomnographically-assessed SOL, SE, and TST, respectively, with a statistical significance (Table 10). In addition, we found that subjective sleep latency was negatively correlated with average cycle length, especially NREM periods in each cycle. However, it did not reach a statistical significance with average REM sleep periods per cycle. No other subjective sleep characteristics that showed significant association with cognitive function after 4 years was correlated with NREM/REM sleep cycle parameters. Only subjective sleep quality, a component score of PSQI with its increasing score indicating an

aggravation of the symptoms, showed a significant negative correlation with average NREM periods per cycle.

3.4. Predictive performance of subjective sleep measures

As for the prediction model for the progression to cognitive decline after 4 years in cognitively normal elderly using subjective sleep measures at baseline, it showed a poor (0.6 – 0.7) discrimination in terms of AUC values based on the criteria by Kleinbaum and Klein (47) (Model 1 in Table 11). The additional analyses revealed that we also predicted the progression to dementia after 4 years in cognitively normal elderly with a poor (0.6 – 0.7) classification performance (Model 2 in Table 11) while we predicted the same outcome in the baseline NC + MCI group with a good (0.8 – 0.9) performance (Model 3 in Table 11, Figure 3)

Chapter 4. Discussion

4.1. Subjective sleep measures from the main cohort

We found that, over 4 years, prevalent long sleep latency, incident or sustained alike, increased the risk of incident cognitive decline (MCI or dementia) in the participants with NC. Previous studies including meta-analyses also reported that difficulty in initiating sleep was associated with cognitive impairment in individuals with NC (4, 9, 10). In addition, we found that shortening sleep latency did not reduce the odds of cognitive decline in the NC group. These results indicate that long sleep latency may not be a risk factor for cognitive decline, rather an early marker of neurodegeneration in the cognitively normal elderly. A recent study using florbetapir-PET showed that the sleep latency was positively associated with deposition of Aβ in the prefrontal cortex in healthy old people (48). As this area is reported to be affected at an early stage of Alzheimer's disease (49), it might explain the increased sleep latency in this population.

We also found that long sleep duration increased the risk of incident cognitive decline by 1.7 times in those with NC after 4 years. Several previous studies (36, 50), including meta-analyses (4, 5), advocated our results on the association between long sleep duration and the risk of cognitive decline, although not consistently (6, 9, 10). These conflicting results seemed to suffer from incomprehensive adjustment for the impact of other sleep parameters. In particular, some studies adjusted, at most, for the brief cognitive test scores, without considering the essential difference of baseline cognitive function between MCI and NC. Recent prospective studies (36, 50) reported an association of prolonged sleep duration with the risk of cognitive decline in people with MCI, but not with NC. However, our findings indicate that after taking into account how well one did

sleep and what time the sleep took place, the NC group might be a cognitively vulnerable group to prolonged sleep. It has been reported that a substantial amount of Aβ begins to accumulate before an individual is diagnosed with MCI (51), and inflammatory cytokines such as C-reactive protein and interleukin-6 induced by these pathologic proteins are associated with increased habitual sleep durations (52) which might explain our findings.

Interestingly, prevalent and sustained late mid-sleep time showed protective effects against cognitive decline in the NC population after 4 years. A cross-sectional study (7) showed that earlier bedtime and earlier waking time were associated with lower MMSE while other researchers (53, 54) demonstrated that incident MCI or dementia was associated with a delayed acrophase, an actigraphically measured value of the peak of activity. However, again, we propose that these findings might have been confounded by other sleep parameters, for example, quality of sleep and duration, or baseline cognitive status (NC or MCI) of the very population researchers intended to investigate. It has been suggested that, from a neurobehavioral perspective, two interacting processes work in opposition or in synchrony to each other;1) the circadian pacemaker driving an endogenous oscillatory signal and 2) homeostatic sleep pressure increasing with the time spent awake (55). If this circadian pacemaker is deteriorated early and cannot oppose the accumulated homeostatic sleep pressure, an individual can experience early sleepiness in the evening, leading to a gradual advance of the circadian phase (56).

To our knowledge, this is the first prospective cohort study that incorporated diverse aspects of sleep such as mid-sleep time, latency, duration, quality, efficiency, and daytime dysfunction into a single model to evaluate their impact on cognitive decline. It was suggested that to construct a mathematical model of a circadian rhythm, the effect of fundamental properties of circadian time structures should be considered (57). These characteristics include amplitude, stability, and phase (37, 58). According to a recently published report (59), the

circadian rhythm amplitude reflected languidness (difficulty to overcome sleepiness and lethargy due to a lack of sleep) or vigorousness, and was related to "daytime sleepiness." They also reported that the stability of rhythm is either flexible (adaptable to sudden changes in the internal rhythm) or rigid, which corresponds to the degree of satisfaction from sleep. This dimension includes the sleep latency, duration, efficiency, and subjective quality (59). Finally, a sleep phase is defined as the relative angular displacement of the oscillation from a reference angle, which has been seldom appreciated in previous studies on the relationship between sleep and cognition. Studies on the circadian sleep-wake cycle have often associated this property with dim light melatonin onset of which the midphase of sleep, i.e. mid-sleep time, was found to be a good proxy (60). In addition, Roenneberg et al. (61) proposed that a chronotype of an individual is best estimated by the midphase of sleep. These findings have led us to construct a logistic regression model into which all these biologically relevant parameters were entered, assumably making our analysis more reliable than previous studies.

An important issue when administering PSQI to the elderly is whether the memory deficits in this population distorted the results substantially. Moreover, some might argue that a single subjective report of a sleep pattern, even from the cognitively normal participants, is quite arbitrary in its nature, and rather reliable and objective measures including repeated actigraphy over two to seven consecutive nights can only have a meaningful implication for the sleep pattern (62). Previous studies (63, 64) using polysomnography or actigraphy showed that people with MCI overestimated their subjective sleep latency while there were no remarkable discrepancies between subjective and objective measures with regard to sleep duration, bedtime, and wake time. However, they also suggested that, in the cognitively healthy elderly population, there was no significant difference between a single subjective sleep report and an overnight polysomnographic finding conducted on the same day (63) which fact leads us to surmise that our PSQI data

from the NC group could hold valuable information. In addition, we observed from our cohort that subjective measures such as sleep duration, latency, and efficiency were all significantly correlated with the corresponding polysomnographic measures, and even with NREM/REM sleep cycle markers in case of subjective sleep latency. Though the absolute values of the Kendall's correlation coefficient of these analyses were relatively low ranging from 0.11 to 0.16, it is important to note that their corresponding values of Spearman's ρ and Pearson's *r* are ranging from 0.16 to 0.24 and 0.17 to 0.25, respectively, seemingly higher effect sizes (65). Besides, abundant studies argue that subjective sleep measures itself are clinical constructs that are fundamentally different from polysomnographic measures, reflecting long-standing physiological characteristics and other internal factors related to cognitive function (64, 66). Therefore, we believe that habitual sleep patterns obtained from a single report of PSQI can have its own significance at least for the cognitively normal elderly population.

Other limitations in the present study are worth noting. First, the 4-year follow-up period was relatively short, possibly leading to false-negative outcomes for some sleep parameters. Second, we were not able to identify whether an individual's job is of the night or shift type, though we managed to adjust our model for employment status. Third, entering an excessive number of variables into a single logistic model may lead to an over-fit model (67). To avoid this problem, large sample size is required to make the ratio of the number of the less commonly occurring event of dichotomous outcomes to the number of predictors greater than 10 (68). The fact that all of the models in our regression analysis have this number greater than 20, coupled with sufficiently low variance inflation factors of every predictor, confirms the statistical validity of our model. Fourth, we could not examine the impact of sleep parameters on the risk of dementia and MCI separately in the participants with NC because there was only a small number of incident dementia cases during the follow-up.

4.2. Objective sleep measures from the subcohort

Our exploratory analyses revealed that a short average NREM/REM cycle length was associated with an increased risk of cognitive decline in cognitively normal elderly individuals. However, other primary and secondary measures of sleep architecture were not associated with cognitive decline. Previous prospective studies concerning sleep architecture and cognitive function have primarily focused on individual sleep measures per se, without considering the relative position or the complementary role of NREM and REM sleeps in their analyses (1). Of note, the definition of the NREM/REM cycle in the previous literature was not unanimous, with the majority of works denoting it as a simple continuum of NREM and REM sleep which necessitates a clear distinction from the NREM/REM cycle used in this paper. Our results suggest that it is not simply the total NREM or REM sleep duration, but the time spent in these stages in a successive manner with each NREM/REM cycle longer, especially REM sleep duration in these cycles, that may play an important role in maintaining cognitive function in the elderly. Their neurobiological mechanism and clinical implications are remained to be elucidated by succeeding studies.

According to the "dual-process hypothesis" (1), NREM sleep, including light sleep (stage S1 and S2) (69), mainly supports declarative, hippocampus-dependent memory through reactivation, redistribution, and reorganization of encoded memory representations (system consolidation), while REM sleep facilitates non-declarative, that is, procedural or emotional memory, by promoting enduring synaptic changes to stabilize memories (synaptic consolidation). On top of that, the "sequential hypothesis" proposed that NREM sleep may initialize long-term potentiation and prime the associated network for ensuing synaptic consolidation in REM sleep through thalamo-cortical spindles and hippocampal

sharp wave-ripples (69). Therefore, this hypothesis claims that the optimal consolidation of declarative and non-declarative memory can be achieved when NREM and REM sleep occur successively. Besides, previous studies found that these thalamo-cortical spindles which constitute the integrity of NREM/REM cycle showed an increase in their density and activity in the prefrontal cortex after learning (70, 71) and their reduced activity was correlated with poor performance in abstraction and working memory task (72). Therefore, NREM/REM cycles might be associated with the frontal lobe function as well as with memory consolidation. This may partly explain why the numbers of people who developed amnestic MCI (57.1%) and non-amnestic MCI (42.9%) over the follow-up period were comparable and those 6 participants who developed non-amnestic MCI exhibited impairments in FAB and DSTs but not in the domains of visuospatial or language functions.

In contrast to several previous prospective studies asserting that a longer REM sleep latency, a lower REM sleep percentage, or a higher level of sleep fragmentation was associated with incident cognitive decline (12, 73), conventional primary and secondary sleep measures were not related to the risk of cognitive decline in this study. It is possible to assume that the follow-up duration of 4 years employed in our study was not sufficient to reveal these relationships but could be enough to unveil how NREM/REM cycles are associated with cognitive decline, although we cannot provide direct evidence based on adequately long follow-up data. In addition, there is a possibility that inaccurate assessment of sleep measures, caused by home-based polysomnography of previous literature compared to our laboratory-based study, might have contributed to these discrepant results. Adjustments for extensive confounding factors in the current analysis, including APOE ε4 allele, CIRS, and especially amount of drinking which was not addressed before, could also explain why the results we obtained were not in agreement with previous findings. Rigorous evaluation of cognitive function using standardized

diagnostic procedures for every available participant and use of a community-based cohort with systemic random sampling are other distinctive features of our study.

This study had several limitations. First, we collected the polysomnography data in the laboratory within a single night. Therefore this study was unable to capture the variability of sleep architecture over time, and vulnerable to the "first night effect" (74). However, previous studies have shown that sleep architecture, especially SWS, may reflect individual traits since its between-subject similarity (variation) was low, while within-subject similarity (stability) was high (75). In addition, a recent paper suggested that the structural organization and amount of REM periods may be a trait-like nature linked to genetic determinants (76). Given that sleep spindle activities connecting NREM and REM periods also clearly show reproducible and disparate individual patterns, with negligible night-to-night variation (77), it seems plausible to suppose that NREM/REM cycle parameters and other sleep measures addressed in this study have inter-individual variability and can be considered as exposures in our analysis model. Second, because we followed the guidelines of Rechtschaffen and Kales, and not those of American Academy of Sleep Medicine (78) at the time of polysomnographic assessment, the electrode montages we applied did not cover the frontal area and may not sufficiently detect delta waves (79), though we placed two adjunctive occipital electrodes (O1/A2 and O2/A1) particularly for evaluating sleep onset and arousals. Third, we did not exclude those with SDB in the analyses, but rather, adjusted our models for its presence. Previous studies reported that the prevalence of clinically significant SDB with AHI level $\geq$15 in the elderly group was as high as 49% (80), and thus, the exclusion of this population (N = 86, 37%) from our cohort would substantially compromise the generalizability of our findings. Fourth, the statistical power was limited due to a relatively short duration of follow-up and the small number of participants (N = 14) that developed the outcome of interest at

follow-up. Fifth, the percentage of participants who showed cognitive decline for about 4 years was relatively low (6.0%). However, it had been known that the incidence of MCI increases with age (81) and is as low as 9.70–35.9 per 1,000 person-year in individuals aged <75 years (82). Because participants of our cohort were fairly young (age 68±5 years), we concluded that the proportion of those who developed cognitive decline in our study is reasonable. Lastly, compared to an age-related trend of normative sleep values of people in the late 60s (83), our cohort showed a higher percentage of S1 sleep (17% vs. 7%), longer REM sleep latency (123 min vs. 68 min), and longer WASO (89 min vs. 60 min). These findings might be affected by the 86 participants (37%) in this cohort who experienced moderate to severe SDB (84) because this disorder was associated with an increased percentage of S1 sleep and a high arousal index (85). It is also likely that long REM sleep latency is affected by the first night effect (86).

4.3. Correlation between subjective and objective sleep measures

We found that, in cognitively normal elderly, subjective sleep characteristics were well correlated with corresponding polysomnographic measures. Furthermore, subjective sleep latency was negatively correlated with average cycle length and average NREM periods per cycle which were found to be associated with cognitive decline in our previous analyses. Based on these findings, we believe that subjective sleep characteristics obtained from PSQI are not a random expression of a habitual sleep pattern, but a reliable measure verifiable by objective markers, and even able to reflect sleep macrostructures related to cognitive decline.

Some previous studies on the difference between subjective sleep and polysomnographic markers in insomnia patients had reported that people tended to underestimate sleep duration (87, 88) or overestimate sleep latency (89) than the

laboratory findings. For those without sleep disorders, Hita-Yanez and colleagues (63) showed that TST was not different between these two measures in cognitively healthy and MCI participants alike, while subjective sleep onset latency was overestimated in MCI subjects compared to polysomnographic findings, and cognitively healthy subjects provided comparable sleep onset latency between these two measures. These results were largely in accordance with ours.

As Harvey and Tang had lined out in their review (90), the mismatch between subjective and objective sleep markers might be explained by a person's predisposition for worry and selective attention which leads to chronic physiological arousal and misperception of sleep as a wake. In addition, mood (91-93) and memory (94, 95) had also been contemplated to exert an influence on this discrepancy. Although we excluded those with any form of cognitive disorders and psychiatric problems at baseline, the subject's personality has not been accounted for in our work.

Other methodological issues deserve mention. First, polysomnography was conducted only once which can cause a first-night effect and a distortion of objective sleep markers. Second, we had no information on whether the working schedule, if present, of participants was of night type or involved weekends as these factors could affect both the subjective and objective sleep measures (62).

4.4. Predictive performance of subjective sleep measures

Using subjective sleep characteristics, baseline cognitive function status, APOE ε4 allele status, and other demographic and lifestyle factors, we were able to predict, after 4 years, incident cognitive decline in the baseline NC group with AUC of 0.65 (sensitivity 0.60, specificity 0.66), incident dementia in the baseline NC group with AUC of 0.62 (sensitivity 0.66, specificity 0.73), and incident dementia in the baseline NC or MCI group with AUC of 0.85 (sensitivity 0.89, specificity 0.75).

The level of performance shown by the last model indicated a meaningful prediction as suggested by a biomarker working group (96).

To the best of our knowledge, this is the first study that investigated the usefulness of subjective sleep characteristics for predicting cognitive deterioration after 4 years at the individual level. At the group level, abundant previous studies had already reported the risk of, or association with cognitive decline using diverse biomarkers that include magnetic resonance imaging (MRI) measures, cerebrospinal fluid, APOE genotype, and sleep measures (12, 50, 97-99). Recently, several studies had attempted to predict cognitive decline at the individual level. Albert and colleagues (18) showed that by employing the cerebrospinal fluid domain (amyloid-β and phosphorylated-τ), the MRI domain (right hippocampus volume and right entorhinal cortex thickness), the cognitive domain (paired associates immediate recall test and digit symbol substitution test scores), and the APOE 4 ε4 allele status, a Cox proportional hazards model predicted progression to MCI from NC (N = 224 with baseline mean age of 57) after 5 years with AUC 0.85, sensitivity 0.80, and specificity 0.75. In addition, Korolev and colleagues (19) demonstrated that, based on morphometric MRI measures and functional and cognitive markers, a probabilistic, kernel-based pattern classification predicted Alzheimer's disease from MCI (N = 259, with baseline mean age of 75) after 3 years with AUC 0.87, sensitivity 0.83, and specificity 0.76. We found that none of these studies had ever incorporated sleep measures in their prediction models. Moreover, our prediction model composed of substantially quick, easy to administer, and inexpensive subjective sleep measures compared to MRI or CSF biomarkers that make it practical for clinical or research purposes.

Our study has several limitations. First, our first two models using only cognitively normal participants yielded a poor performance, though after including both baseline NC and MCI group the prediction model gave a good classification performance. As mentioned earlier, these two groups might have a different

association with, or vulnerability to sleep disturbances thus putting them together in a single model can impair its validity. However, because of the small number of individuals with dementia at follow-up, 19 cases out of 2,238 baseline NC participants (0.5 %), we decided to secure the statistical power by putting these two groups in the analyses together. Moreover, considering the fact that a significant portion of MCI participants reverted to NC after 4 years in our cohort (data not shown), it could be inappropriate to have MCI status as an outcome variable for a prediction model. Second, we followed participants for 4 years which periods might be not enough to have enough number of dementia cases at follow-up. However, it had been postulated that the neurobiological changes related to dementia may not be significant 7 to 10 years before the onset of symptoms (18), thus it is possible that lengthening follow-up periods can lead to a paradoxical decrease in the performance of the prediction model. Third, we included a total of 14 covariates in the prediction model including demographic information and lifestyle factors. These wide-ranging adjustments can contribute to improved performance but at the same time, reduce its usability in clinical or research settings. Fourth, though our model predicted the progression to dementia with a meaningful performance, it still is not substantially superior to the previous prediction models. Though our findings implicate that subjective sleep measures are useful in this regard, adding more variables such as MRI indexes or amyloid β measures from positron emission tomography (PET) would enhance the value of this model.

4.5. Comprehensive discussion and conclusion

At the group level, we identified that subjective sleep complaints such as long sleep latency (>30 minutes) and long sleep duration (≥ 7.95 hours) may predict the higher

risk of cognitive decline while late mid-sleep time (after 3:00 AM) may predict the lower risk of cognitive decline in the cognitively normal elderly. As for the objective measures the, short average duration of NREM/REM cycles, especially average REM sleep duration in each cycle, in cognitively normal elderly might also be used as an early marker of cognitive decline. We subsequently ascertained that subjective long sleep latency showed a significant association with the short average duration of NREM/REM cycles measured by polysomnography which fact led us to conclude that these subjective sleep measures are not a random expression of a habitual sleep pattern, but a reliable measure verifiable by objective markers reflecting sleep macrostructures related to cognitive decline. We observed that the predictive performance for the incident cognitive decline using only cognitively normal elderly populations was not satisfying. However, our findings indicated that it might be possible to develop a prediction model for dementia using subjective sleep measures in nondemented elderly.

These results suggest that subjective sleep measures obtained from PSQI, a relatively quick, easy, and inexpensive measure, in nondemented elderly could be used to predict which person will develop dementia after 4 years. Therefore, if enhanced by adding more variables such as MRI and amyloid-PET indexes in the future, our model can provide useful information for selecting individuals who are at high risk of cognitive decline and might be used for the targeted primary prevention strategy for dementia for those who would be most benefited. In addition, as a multitude of variables included in our model can also be candidates for subject inclusion criteria of a clinical trial, it could be employed as a screening tool for many of the researches aimed at preclinical Alzheimer's disease.

Future research is warranted to confirm our findings with a longer follow-up period, a larger sample size, and a more robust and reliable polysomnographic assessment. Additionally, if our results are cross-validated, it is important to

explore whether interventional strategies to restore or stabilize a short sleep latency or a long average NREM/REM cycle can protect against cognitive decline.

Acknowledgment

This work was supported by a grant from the Korean Health Technology Research and Development Project of the Ministry of Health, Welfare, and Family Affairs, Republic of Korea (Grant No. A092077).

Potential Conflicts of Interest

Nothing to report.

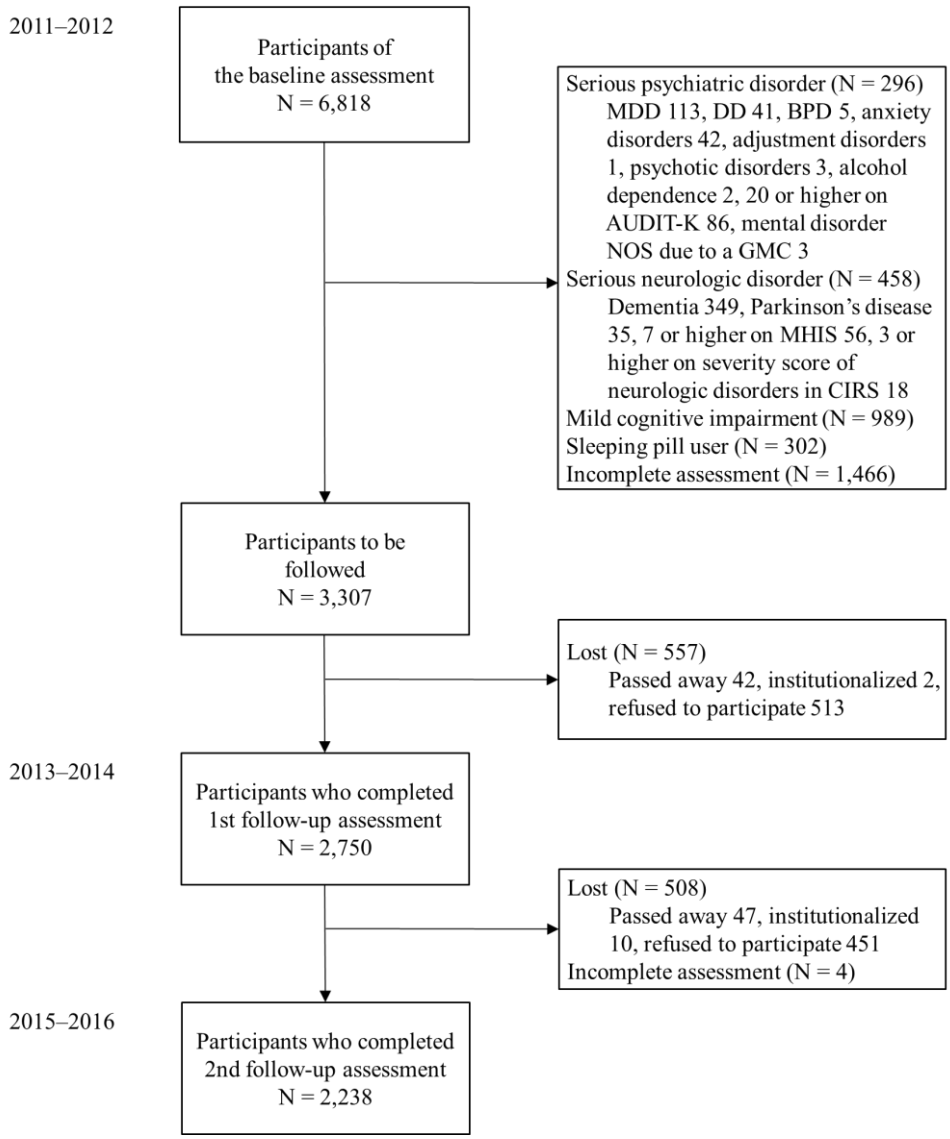

Figure 1. Flow chart of the subjective sleep characteristics study
MDD = major depressive disorder; DD = dysthymic disorder; BPD = bipolar disorders; AUDIT-K = alcohol use disorders identification test-Korean version; NOS = not otherwise specified; GMC = general medical condition; MHIS = modified Hachinski ischemic score; CIRS = cumulative illness rating scale

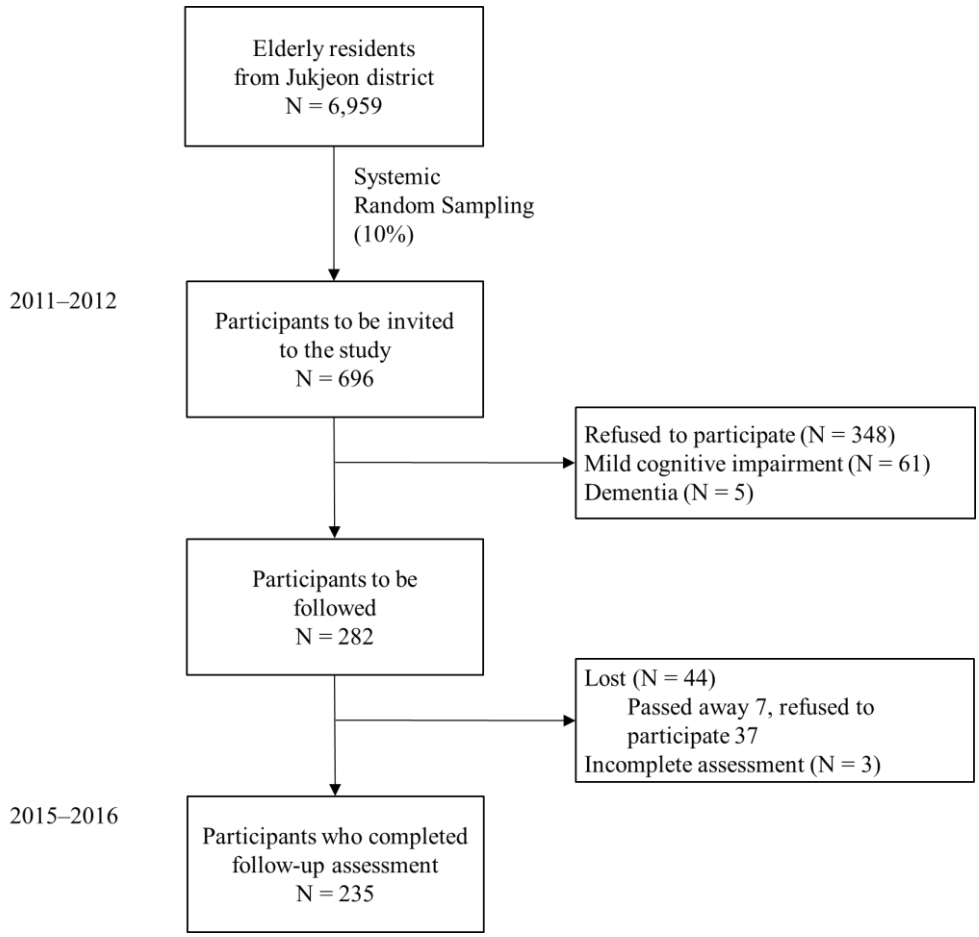

Figure 2. Flow chart of the NREM/REM sleep cycle study

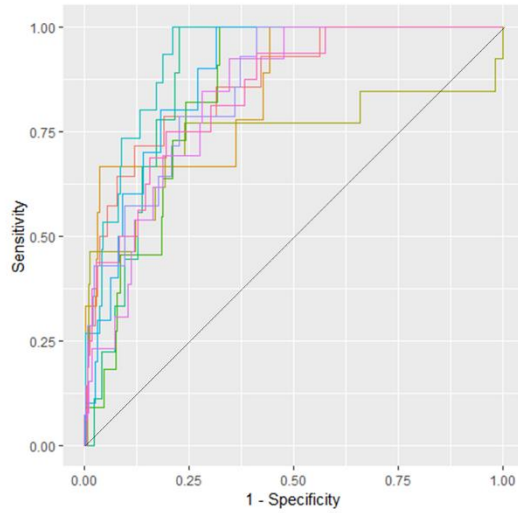

Figure 3. Receiver operating characteristics (ROC) curves of the binary logistic regression model for the progression to dementia after 4 years in individuals with normal cognition or mild cognitive impairment at baseline.

Table 1. Summary of each of sleep parameters derived from the Pittsburgh Sleep Quality Index

Variables	Definition[a]	Rate
Mid-sleep time	The mid-point between the self-reported bedtime and the waking time.	**Average**, between AM 1:00 and AM 3:00 **Early**, before AM 1:00 **Late**, after AM 3:00
Sleep duration	Subjectively reported total duration of actual sleep.	**Average**, between 5 hr 3min and 7 hr 57 min **Short**, less than 5 hr 3 min **Long**, more than 7 hr 57 min
Sleep latency	Sum of two scores; Self-reported time spent awake in bed before falling asleep; <15 min (0), 16-30 min (1), 31-60 min (2), >60 min (3). And the frequency of nights with sleep latency more than 30 minutes; Not during the past month (0), < 1 per week (1), 1 or 2 per week (2), ≥ 3 per week (3). If the sum is equal to 0 = 0 (component score); 1-2=1; 3-4=2, 5-6=3.	**Short**, component score 0 or 1 **Long**, component score 2 or 3, i.e. sleep latency > 30 min occurring at least every month
Sleep quality	Subjective rate of overall quality of sleep; very good (0), fairly good (1), fairly bad (2), very bad (3)	**Good**, component score 0 or 1 **Poor**, component score 2 or 3
Sleep efficiency	The ratio of the subjectively reported actual sleep duration to the total time spent in bed; ≥ 85% (0), 75-84% (1), 65-74% (2), < 65% (3)	**Good**, component score 0 or 1 **Poor**, component score 2 or 3, i.e. self-reported sleep efficiency < 75 %
Daytime dysfunction	Sum of two scores; Whether having a problem keeping up the enthusiasm to get things done; No problem at all (0), Only a very slight problem (1), Somewhat of a problem (2), A very big problem (3). And how often having a trouble staying awake while driving, eating meals, or engaging in social activity; Not during the past month (0), < 1 per week (1), 1 or 2 per week (2), ≥ 3 per week (3). If the sum is equal to 0 = 0 (component score); 1-2=1; 3-4=2, 5-6=3.	**Absent**, component score 0 **Present**, component score 1, 2, or 3

[a]All self-reports are based on the experience over the last one month.

Table 2. Characteristics of the participants at the baseline evaluation

	Cognitive decline (-) N = 1,973	Cognitive decline (+)[a] N = 265	p[b]
Age (years, mean ± SD)	67.8 ± 5.5	70.9 ± 6.4	<0.001
Women (%)	47.0	37.0	0.002
Education (years, mean ± SD)	9.9 ± 5.2	7.7 ± 5.0	<0.001
GDS (points, mean ± SD)	8.2 ± 5.6	9.8 ± 6.0	<0.001
CIRS (points, mean ± SD)	4.2 ± 2.6	4.5 ± 2.7	0.071
APOE ε4 allele positivity (%)	20.5	20.0	0.847
Low socioeconomic status[b] (%)	2.3	4.5	0.030
Currently working (%)	33.4	35.1	0.592
Living alone (%)	10.8	17.4	0.002
Smoking (pack/day, mean ± SD)	0.10 ± 0.74	0.06 ± 0.24	0.399
Drinking (SU/week, mean ± SD)	4.1 ± 12.6	3.7 ± 10.2	0.631
Physical activity (kcal/week, mean ± SD)	85.9 ± 175.8	56.4 ± 96.0	0.007
High risk of RBD[c] (%)	7.6	9.8	0.205
High risk of OSA[d] (%)	10.1	7.5	0.185

[a]Student t-test for continuous variables and chi-square test for categorical variables
[b]Covered by the National Medicaid Program
[c]Scored 5 or higher on REM sleep behavior disorder screening questionnaire
[d]Scored 5 or higher on STOP-BANG
NC, normal cognition; GDS, Geriatric Depression Scale; CIRS, Cumulative Illness Rating Scale; SU, standard unit; RBD, REM sleep behavior disorder; OSA, obstructive sleep apnea

Table 3. Impact of sleep on the risk of cognitive decline in the cognitively normal participants

Characteristics	No.events/total n	OR (95% CI)
Mid-sleep time		
Average	168/1407	1.000
Early	60/339	1.280 (0.911–1.798)
Late	37/492	**0.606 (0.410–0.895)**[b]
Sleep duration		
Average	146/1400	1.000
Short	59/479	0.862 (0.590–1.260)
Long	60/359	**1.665 (1.180–2.350)**[c]
Sleep latency		
Short	164/1579	1.000
Long	101/659	**1.397 (1.026–1.904)**[b]
Sleep quality		
Good	216/1877	1.000
Poor	49/361	0.994 (0.677–1.461)
Sleep efficiency		
Good	233/2005	1.000
Poor	32/233	0.902 (0.563–1.444)
Daytime dysfunction		
Absent	164/1489	1.000
Present	101/749	1.145 (0.859–1.525)

Binary logistic regression analysis adjusted for age, sex, education, presence of apolipoprotein E ε4 allele, Geriatric Depression Scale score, Cumulative Illness Rating Scale, socioeconomic status, employment status, presence of cohabitants, smoking, drinking, physical activity, REM sleep behavior disorder screening questionnaire score, and STOP-BANG score.
[a]After excluding those taking sedatives during the previous 1 month from baseline.
[b]$p < 0.05$, [c]$p < 0.01$

Table 4. Impact of change of sleep-parameters on the risk of cognitive decline in the cognitively normal participants

Pattern of change	No.events/total n	OR (95% CI)
Change in mid-sleep time over 4 years[c]		
Not late at both baseline and follow-up	203/1543	1.000
Changed from not late to late	25/205	0.866 (0.549–1.365)
Changed from late to not late	16/206	0.878 (0.545–1.412)
Late at both baseline and follow-up	21/284	**0.560 (0.336–0.932)[a]**
Change in sleep latency over 4 years[d]		
Short at both baseline and follow-up	105/1237	1.000
Changed from short to long	59/342	**1.951 (1.356–2.808)[b]**
Changed from long to short	41/306	1.160 (0.869–1.548)
Long at both baseline and follow-up	60/353	**2.001 (1.344–2.980)[b]**
Change in sleep duration over 4 years[e]		
Not long at both baseline and follow-up	171/1631	1.000
Changed from not long to long	34/248	1.376 (0.912–2.074)
Changed from long to not long	38/226	1.143 (0.857–1.524)
Long at both baseline and follow-up	22/133	**1.976 (1.180–3.308)[b]**

Binary logistic regression analysis adjusted for age, sex, education, presence of apolipoprotein E ε4 allele, Geriatric Depression Scale score, Cumulative Illness Rating Scale, socioeconomic status, employment status, presence of cohabitants, smoking, drinking, physical activity, REM sleep behavior disorder screening questionnaire score, and STOP-BANG score.

[a]$p < 0.05$, [b]$p < 0.01$

[c]Additionally adjusted for sleep duration, latency, quality, efficiency, and daytime dysfunction.

[d]Additionally adjusted for mid-sleep time, sleep duration, quality, efficiency, and daytime dysfunction.

[e]Additionally adjusted for mid-sleep time, sleep latency, quality, efficiency, and daytime dysfunction.

Table 5. Baseline characteristics of the participants

	Cognitive decline (-) N = 221	Cognitive decline (+)[a] N = 14	p[b]
Age, y	67 (5)	71 (6)	0.022
Women, n (%)	132 (60)	9 (64)	0.619
Education, y	13 (4)	10 (6)	0.027
Body mass index, kg/m^2	24 (3)	24 (2)	0.303
Smoking, pack/day	0.05 (0.20)	0.07 (0.27)	0.712
Drinking, SU/week	3 (9)	0.8 (3)	0.132
Apolipoprotein E ε4 allele, n (%)	53 (22.4)	49 (22.5)	0.578
Major depressive disorder, n (%)	7 (3)	0 (0)	1.000
CIRS, points	5 (3)	7 (3)	0.008
Physical activity (kcal/week)[c]	107 (125)	41 (51)	0.049
Sleeping medication use[d], n (%)	24 (11)	2 (14)	0.390
Sleep-disordered breathing[e], n (%)	80 (36)	6 (43)	0.616
MMSE, points	27 (2)	25 (3)	<0.001[f]
CERAD-Total score[g], points	74 (9)	70 (7)	<0.001[f]

Values are mean (SD) unless specified otherwise.
[a]Development of mild cognitive impairment or dementia at the 4-year follow-up evaluation
[b]Mann-Whitney U test for continuous variables, and χ^2 test or Fisher's exact test for categorical variables.
[c]Total energy expenditure in consumed kilocalories per week.
[d]Use of any sleeping medication during the previous month.
[e]Apnea-hypopnea index ≥15 events/h
[f]Became nonsignificant when compared using analysis of covariance.
[g]Summation of subtest scores of CERAD neuropsychological battery including verbal fluency, modified Boston naming test, word list learning, constructional praxis, word list recall, and word list recognition discriminability.
SU, standard unit; CIRS, Cumulative Illness Rating Scale; MMSE, Mini–Mental State Examination; CERAD, Consortium to Establish a Registry for Alzheimer's Disease

Table 6. Baseline objective sleep measures

	Total sleep			Sleep in NREM/REM cycles		
	Cognitive decline (-)	Cognitive decline (+)	p^b	Cognitive decline (-)	Cognitive decline (+)	p^b
Midsleep time	2:10 (0:44)	2:10 (0:40)	0.969	2:21 (1:03)	2:56 (1:34)	0.057
Sleep stages						
S1, min	63 (34)	74 (35)	0.265	29 (23)	35 (32)	0.346
Time in S1, %	17 (9)	21 (11)	0.141	**11 (7)**	**16 (9)**	**0.012**
S2, min	218 (57)	204 (63)	0.375	131 (87)	99 (74)	0.174
Time in S2, %	57 (11)	55 (13)	0.454	**48 (14)**	**40 (15)**	**0.032**
SWS, min	30 (25)	36 (34)	0.373	18 (20)	15 (22)	0.554
Time in SWS, %	8 (7)	10 (9)	0.320	7 (7)	6 (8)	0.481
NREM sleep duration, min	311 (54)	314 (45)	0.849	184 (103)	155 (111)	0.295
Time in NREM sleep, %	82 (6)	85 (9)	0.061	69 (14)	64 (17)	0.207
REM sleep duration, min	72 (27)	66 (34)	0.489	70 (28)	64 (33)	0.438
Time in REM sleep, %	19 (6)	17 (8)	0.351	31 (14)	36 (17)	0.207
Secondary sleep measures						
SPT, min	463 (47)	467 (41)	0.709	–	–	
TST, min	383 (65)	374 (67)	0.608	–	–	
Sleep onset latency, min	18 (29)	20 (24)	0.802	481 (312)	446 (314)	0.683
REM sleep latency, min	121 (77)	154 (130)	0.154	145 (88)	174 (150)	0.248
Sleep efficiency, %	79 (13)	77 (15)	0.660	97 (2)	97 (3)	0.818
WASO, min	88 (60)	97 (70)	0.624	7 (6)	7 (7)	0.693
Cycle-related parameters						
Number of cycles, n	–	–		3.7 (1.4)	4.5 (2.4)	0.060
TCT, min	–	–		255 (117)	218 (128)	0.267
Average cycle length[c], min	–	–		**71 (33)**	**47 (26)**	**0.010**
Average NREM length per cycle, min	–	–		**51 (31)**	**33 (22)**	**0.031**
Average NREM proportion per cycle, %	–	–		69 (14)	64 (17)	0.207
Average REM length per cycle, min	–	–		**20 (8)**	**14 (7)**	**0.011**
Average REM proportion per cycle, %	–	–		31 (14)	36 (17)	0.207

Values are mean (SD) unless specified otherwise.
[a]Developing mild cognitive impairment or dementia after 4 years of follow-up.
[b]Mann-Whitney U test for continuous variables.
[c]TCT divided by the number of cycles.
SWS, slow wave sleep; SPT, sleep period time; TST, total sleep time; WASO, wake time after sleep onset; TCT, total cycle time.

Table 7. Association between individual sleep stage parameters and the risk of developing mild cognitive impairment or dementia

	Unadjusted		Adjusted	
Characteristics[a]	OR (95% CI)	*p*	OR (95% CI)	*p*
Sleep stages				
Time in S1, %	1.034 (0.988, 1.081)	0.149	1.033 (0.966, 1.104)	0.346
Time in S2, %	0.981 (0.933, 1.032)	0.452	0.969 (0.920, 1.020)	0.231
Time in SWS, %	1.038 (0.964, 1.118)	0.322	1.075 (0.988, 1.168)	0.092
Time in NREM sleep, %	1.092 (0.971, 1.196)	0.124	1.044 (0.950, 1.147)	0.374
Time in REM sleep, %	0.959 (0.878, 1.047)	0.351	1.000 (0.908, 1.101)	0.998
Secondary sleep measures				
SPT, min	1.002 (0.990, 1.015)	0.708	1.002 (0.989, 1.015)	0.773
TST, min	0.998 (0.990, 1.006)	0.637	1.000 (0.991, 1.008)	0.920
Sleep onset latency, min	1.002 (0.986, 1.019)	0.801	0.999 (0.976, 1.022)	0.910
REM sleep latency, min	1.004 (0.998, 1.009)	0.161	1.001 (0.996, 1.007)	0.676
Sleep efficiency, %	0.991 (0.953, 1.031)	0.659	1.001 (0.959, 1.046)	0.951
WASO, min	1.002 (0.994, 1.010)	0.623	1.000 (0.991, 1.010)	0.938

Binary logistic regression analysis adjusted for age, sex, education, presence of apolipoprotein E ε4 allele, body mass index, presence of major depressive disorder, amount of smoking and alcohol consumed over the last 1 year, total score of Cumulative Illness Rating Scale, amount of physical activity, presence of sleep-disordered breathing (apnea-hypopnea index ≥15), and whether taking sedatives in the previous month.

[a]Each variable is related separately to the cognitive decline.

SWS, slow wave sleep; SPT, sleep period time; TST, total sleep time; WASO, wake time after sleep onset

Table 8. Association between individual NREM/REM cycle-related parameters and the risk of developing mild cognitive impairment or dementia

	Unadjusted		Adjusted	
Characteristics[a]	OR (95% CI)	*p*	OR (95% CI)	*p*
Sleep in NREM/REM cycles				
Time in S1, %	**1.077 (1.013, 1.145)**	**0.017**	1.082 (0.998, 1.174)	0.057
Time in S2, %	**0.961 (0.927, 0.997)**	**0.035**	0.973 (0.935, 1.012)	0.171
Time in SWS, %	0.971 (0.895, 1.054)	0.481	0.994 (0.915, 1.080)	0.886
Time in NREM sleep, %	0.979 (0.948, 1.012)	0.211	0.990 (0.951, 1.029)	0.602
Time in REM sleep, %	1.021 (0.988, 1.055)	0.211	1.011 (0.971, 1.051)	0.602
Secondary measures in NREM/REM cycles				
Sleep onset latency, min	1.000 (0.998, 1.001)	0.682	1.000 (0.998, 1.002)	0.920
REM sleep latency, min	1.003 (0.998, 1.008)	0.252	1.000 (0.995, 1.005)	1.000
Sleep efficiency, %	0.974 (0.779, 1.218)	0.817	0.974 (0.765, 1.240)	0.830
WASO, min	0.980 (0.890, 1.081)	0.691	1.009 (0.911, 1.117)	0.868
TCT, min[b]	0.997 (0.992, 1.002)	0.258	0.999 (0.993, 1.006)	0.838
Average cycle length[c], min[b]	**0.962 (0.937, 0.987)**	**0.003**	**0.965 (0.937, 0.993)**	**0.016**
Average NREM per cycle, min[b]	**0.963 (0.935, 0.991)**	**0.010**	**0.958 (0.925, 0.991)**	**0.014**
Average NREM proportion per cycle, %[b]	0.979 (0.948, 1.012)	0.211	0.986 (0.944, 1.030)	0.535
Average REM per cycle, min[b]	**0.875 (0.791, 0.967)**	**0.009**	**0.845 (0.751, 0.949)**	**0.005**
Average REM proportion per cycle, %[b]	1.021 (0.988, 1.055)	0.211	1.014 (0.971, 1.059)	0.535
TCT/SPT, %[b]	0.228 (0.022, 2.316)	0.211	0.719 (0.032, 16.239)	0.836
TCT/TST, %[b]	0.186 (0.020, 1.715)	0.138	0.511 (0.032, 8.125)	0.635
NREM in TCT, min[b]	0.997 (0.991, 1.003)	0.282	0.999 (0.992, 1.006)	0.772
REM in TCT, min[b]	0.992 (0.974, 1.012)	0.437	1.002 (0.979, 1.026)	0.847

Binary logistic regression analysis adjusted for age, sex, education, presence of apolipoprotein E ε4 allele, body mass index, presence of major depressive disorder, amount of smoking and alcohol consumed over the last 1 year, total score of Cumulative Illness Rating Scale, amount of physical activity, presence of sleep-disordered breathing (apnea-hypopnea index ≥15), and whether taking sedatives in the previous month.

[a]Each variable is related separately to the cognitive decline.

[b]Additionally adjusted for WASO

[c]TCT divided by the number of cycles.

SWS, slow wave sleep; WASO, wake time after sleep onset; TCT, total cycle time.

Table 9. Association between multiple NREM/REM cycle-related parameters and the risk of developing mild cognitive impairment or dementia

	Unadjusted		Adjusted	
Variables[a]	OR (95% CI)	*p*	OR (95% CI)	*p*
Model 1				
Average NREM per cycle, min	0.969 (0.939, 0.999)	**0.043**	0.965 (0.929, 1.003)	0.069
Average REM per cycle, min	0.901 (0.815, 0.996)	**0.041**	0.859 (0.759, 0.973)	**0.017**
Model 2				
Average NREM per cycle, min	0.968 (0.930, 1.006)	0.100	0.955 (0.908, 1.005)	0.080
Average REM per cycle, min	0.900 (0.813, 0.996)	**0.042**	0.865 (0.761, 0.982)	**0.026**
NREM outside of cycles, min	1.000 (0.990, 1.009)	0.938	0.996 (0.984, 1.008)	0.515
REM outside of cycles, min	0.993 (0.926, 1.065)	0.852	1.013 (0.930, 1.104)	0.767

Binary logistic regression analysis adjusted for age, sex, education, presence of apolipoprotein E ε4 allele, body mass index, presence of major depressive disorder, amount of smoking and alcohol consumed over the last 1 year, total score of Cumulative Illness Rating Scale, amount of physical activity, presence of sleep-disordered breathing (apnea-hypopnea index ≥15), whether taking sedatives in the previous month, and wake after sleep onset in minutes.

[a]All variables included in a single model are related simultaneously to the outcome.

Table 10. Kendall's rank correlation coefficient (τ) between subjective sleep characteristics and polysomnographic findings in cognitively normal elderly

Subjective measures	Corresponding PSG findings[a]		Average cycle length		Average NREM per cycle		Average REM per cycle	
	τ	*p*	τ	*p*	τ	*p*	τ	*p*
MS	N/A		-0.013	0.799	0.013	0.797	-0.050	0.316
SD	**0.143**	**0.005**	0.039	0.448	0.078	0.125	-0.048	0.352
SL	**0.124**	**0.016**	**-0.107**	**0.037**	**-0.162**	**0.002**	0.070	0.175
SQ	N/A		-0.100	0.070	**-0.153**	**0.006**	0.069	0.212
SE	**0.108**	**0.027**	0.071	0.149	0.087	0.075	-0.008	0.865
DF	N/A		0.075	0.194	0.042	0.463	0.083	0.148

[a], Total sleep time for subjective sleep duration, sleep onset latency for subjective sleep latency, and percentage of total sleep time over total recording time for subjective sleep efficiency.

PSG, polysomnography; NREM, non-rapid eye movement; REM, rapid eye movement; MS, mid-sleep time; SD, sleep duration; SL, sleep latency; SQ, sleep quality; SE, sleep efficiency; DF, daytime dysfunction; N/A, not applicable

Table 11. Predictive performance of binary logistic regression models

Iteration	Cut-off	AUC	Sensitivity (%)	Specificity (%)
Model 1. Prediction for the cognitive decline[a] after 4 years in the baseline NC group				
1	0.107	0.668	72.7	57.3
2	0.111	0.613	56.9	67.3
3	0.121	0.634	58.3	64.8
4	0.106	0.670	59.6	67.0
5	0.125	0.619	68.8	54.2
6	0.148	0.677	44.4	82.9
7	0.116	0.640	51.0	76.6
8	0.105	0.653	64.0	63.6
9	0.113	0.650	65.5	63.2
10	0.111	0.628	61.1	60.7
Mean (SD)	0.116 (0.012)	0.645 (0.021)	60.2 (7.9)	65.8 (8.1)
Model 2. Prediction for the progression to dementia after 4 years in the baseline NC group				
1	0.123	0.580	34.5	82.6
2	0.003	0.793	100.0	60.1
3	0.012	0.707	66.7	76.1
4	0.024	0.732	85.7	61.3
5	0.018	0.711	77.8	71.9
6	0.045	0.456	25.0	99.3
7	0.009	0.670	75.0	86.0
8	0.012	0.527	60.0	69.8
9	0.005	0.361	100.0	33.8
10	0.013	0.704	33.3	92.0
Mean (SD)	0.026 (0.034)	0.624 (0.131)	65.8 (25.9)	73.3 (17.8)
Model 3. Prediction for the progression to dementia after 4 years in the baseline NC + MCI group				
1	0.019	0.867	78.6	81.0
2	0.030	0.853	66.7	96.5
3	0.016	0.841	100.0	67.7
4	0.018	0.737	76.9	76.1
5	0.015	0.877	100.0	77.5
6	0.022	0.846	75.0	80.6
7	0.013	0.879	100.0	68.4
8	0.016	0.857	100.0	59.0
9	0.018	0.833	92.3	65.4
10	0.015	0.925	100.0	78.8
Mean (SD)	0.018 (0.005)	0.852 (0.045)	89.0 (12.5)	75.1 (10.0)

a, becoming MCI or dementia; AUC, area under the curve; NC, normal cognition; MCI, mild cognitive impairment; SD, standard deviation

Bibliography

1. Diekelmann S, Born J. The memory function of sleep. Nature Reviews Neuroscience. 2010;11(2):114-26.
2. Musiek ES, Xiong DD, Holtzman DM. Sleep, circadian rhythms, and the pathogenesis of Alzheimer disease. Experimental & molecular medicine. 2015;47(3):e148.
3. Haba-Rubio J, Marti-Soler H, Tobback N, Andries D, Marques-Vidal P, Waeber G, et al. Sleep characteristics and cognitive impairment in the general population The HypnoLaus study. Neurology. 2017;88(5):463-9.
4. Bubu OM, Brannick M, Mortimer J, Umasabor-Bubu O, Sebastião YV, Wen Y, et al. Sleep, Cognitive impairment and Alzheimer's disease: A systematic review and meta-analysis. Sleep. 2016.
5. Kim H-B, Myung S-K, Lee S-M, Park YC, Group KM-AS. Longer duration of sleep and risk of cognitive decline: a meta-analysis of observational studies. Neuroepidemiology. 2016;47(3-4):171-80.
6. Keage HAD, Banks S, Yang KL, Morgan K, Brayne C, Matthews FE. What sleep characteristics predict cognitive decline in the elderly? Sleep medicine. 2012;13(7):886-92.
7. Auyeung TW, Lee JSW, Leung J, Kwok T, Leung PC, Woo J, et al. Cognitive deficit is associated with phase advance of sleep–wake rhythm, daily napping, and prolonged sleep duration—a cross-sectional study in 2,947 community-dwelling older adults. Age. 2013;35(2):479-86.
8. Lo JC, Groeger JA, Cheng GH, Dijk D-J, Chee MW. Self-reported sleep duration and cognitive performance in older adults: a systematic review and meta-analysis. Sleep medicine. 2016;17:87-98.
9. Tworoger SS, Lee S, Schernhammer ES, Grodstein F. The association of self-reported sleep duration, difficulty sleeping, and snoring with cognitive function in older women. Alzheimer Disease & Associated Disorders. 2006;20(1):41-8.
10. Blackwell T, Yaffe K, Ancoli-Israel S, Schneider JL, Cauley JA, Hillier TA, et al. Poor sleep is associated with impaired cognitive function in older women: the study of osteoporotic fractures. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences. 2006;61(4):405-10.
11. Mander BA, Winer JR, Jagust WJ, Walker MP. Sleep: a novel mechanistic pathway, biomarker, and treatment target in the pathology of Alzheimer's disease? Trends in neurosciences. 2016;39(8):552-66.
12. Pase MP, Himali JJ, Grima NA, Beiser AS, Satizabal CL, Aparicio HJ, et al. Sleep architecture and the risk of incident dementia in the community. Neurology. 2017;89(12):1244-50.
13. Czeisler CA, Klerman EB. Circadian and sleep-dependent regulation of

hormone release in humans. Recent progress in hormone research. 1999;54:97-130; discussion -2.
14. Giuditta A, Ambrosini MV, Montagnese P, Mandile P, Cotugno M, Zucconi GG, et al. The sequential hypothesis of the function of sleep. Behavioural brain research. 1995;69(1-2):157-66.
15. Mazzoni G, Gori S, Formicola G, Gneri C, Massetani R, Murri L, et al. Word recall correlates with sleep cycles in elderly subjects. Journal of sleep research. 1999;8(3):185-8.
16. Sonni A, Spencer RM. Sleep protects memories from interference in older adults. Neurobiology of aging. 2015;36(7):2272-81.
17. Wang Y-J. Alzheimer disease: Lessons from immunotherapy for Alzheimer disease. Nature Reviews Neurology. 2014;10(4):188.
18. Albert M, Zhu Y, Moghekar A, Mori S, Miller MI, Soldan A, et al. Predicting progression from normal cognition to mild cognitive impairment for individuals at 5 years. Brain. 2018;141(3):877-87.
19. Korolev IO, Symonds LL, Bozoki AC, Initiative AsDN. Predicting progression from mild cognitive impairment to Alzheimer's dementia using clinical, MRI, and plasma biomarkers via probabilistic pattern classification. PloS one. 2016;11(2):e0138866.
20. Han JW, Kim TH, Kwak KP, Kim K, Kim BJ, Kim SG, et al. Overview of the Korean longitudinal study on cognitive aging and dementia. Psychiatry investigation. 2018;15(8):767.
21. Diagnostic and statistical manual of mental disorders. 4th ed. Washington, DC: American Psychiatric Association. 2000.
22. Winblad B, Palmer K, Kivipelto M, Jelic V, Fratiglioni L, Wahlund LO, et al. Mild cognitive impairment–beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. Journal of internal medicine. 2004;256(3):240-6.
23. Lee JH, Lee KU, Lee DY, Kim KW, Jhoo JH, Kim JH, et al. Development of the Korean Version of the Consortium to Establish a Registry for Alzheimer's Disease Assessment Packet (CERAD-K) Clinical and Neuropsychological Assessment Batteries. The Journals of Gerontology Series B: Psychological Sciences and Social Sciences. 2002;57(1):P47-P53.
24. Yoo S-W, Kim Y-S, Noh J-S, Oh K-S, Kim C-H, NamKoong K, et al. Validity of Korean version of the mini-international neuropsychiatric interview. Anxiety and Mood. 2006;2.
25. Lee DY, Lee KU, Lee JH, Kim KW, Jhoo JH, Kim SY, et al. A normative study of the CERAD neuropsychological assessment battery in the Korean elderly. Journal of the International Neuropsychological Society. 2004;10(01):72-81.
26. Wechsler D. Instruction Manual for the Wechsler Memory Scale Revised. New York, NY: Psychological Corporation. 1987.
27. Kim TH, Huh Y, Choe JY, Jeong JW, Park JH, Lee SB, et al. Korean version

of frontal assessment battery: psychometric properties and normative data. Dementia and geriatric cognitive disorders. 2010;29(4):363-70.
28. Sohn SI, Kim DH, Lee MY, Cho YW. The reliability and validity of the Korean version of the Pittsburgh Sleep Quality Index. Sleep and Breathing. 2012;16(3):803-12.
29. Whinnery J, Jackson N, Rattanaumpawan P, Grandner MA. Short and long sleep duration associated with race/ethnicity, sociodemographics, and socioeconomic position. Sleep. 2014;37(3):601-11.
30. Rechtschaffen A, Kales A. A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects. Washington, DC: US Government Printing Office; 1968.
31. Miller MD, Paradis CF, Houck PR, Mazumdar S, Stack JA, Rifai AH, et al. Rating chronic medical illness burden in geropsychiatric practice and research: application of the Cumulative Illness Rating Scale. Psychiatry research. 1992;41(3):237-48.
32. Kim JY, Park JH, Lee JJ, Huh Y, Lee SB, Han SK, et al. Standardization of the Korean version of the Geriatric Depression Scale: reliability, validity, and factor structure. Psychiatry investigation. 2008;5(4):232-8.
33. Global status report on alcohol and health 2014. Geneva, Switzerland: World Health Organization; 2014.
34. Nishihara T, Katsuki F, Hori M, Kagawa C, Okuda S, Utsu T, et al. Estimation of energy expenditure and daily activity index on 185 subjects by a new personal computer system. The Japanese Journal of Nutrition and Dietetics. 1988;46(2):73-84.
35. Chung F, Elsaid H. Screening for obstructive sleep apnea before surgery: why is it important? Current Opinion in Anesthesiology. 2009;22(3):405-11.
36. Johar H, Kawan R, Emeny RT, Ladwig K-H. Impaired Sleep Predicts Cognitive Decline in Old People: Findings from the Prospective KORA Age Study. Sleep. 2015;39(1):217-26.
37. Golden SS, Canales SR. Cyanobacterial circadian clocks—timing is everything. Nature Reviews Microbiology. 2003;1(3):191-9.
38. Chandler MJ, Lacritz L, Hynan L, Barnard H, Allen G, Deschner M, et al. A total score for the CERAD neuropsychological battery. Neurology. 2005;65(1):102-6.
39. Shapiro SS, Francia R. An approximate analysis of variance test for normality. Journal of the American Statistical Association. 1972;67(337):215-6.
40. American Academy of Sleep Medicine Task Force. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. Sleep. 1999;22:667-89.
41. Kang S-H, Yoon I-Y, Lee SD, Han JW, Kim TH, Kim KW. REM sleep behavior disorder in the Korean elderly population: prevalence and clinical

characteristics. Sleep. 2013;36(8):1147-52.
42. Allen RP, Burchell BJ, MacDonald B, Hening WA, Earley CJ. Validation of the self-completed Cambridge-Hopkins questionnaire (CH-RLSq) for ascertainment of restless legs syndrome (RLS) in a population survey. Sleep medicine. 2009;10(10):1097-100.
43. Kim KW, Choi EA, Lee SB, Park JH, Lee JJ, Huh Y, et al. Prevalence and neuropsychiatric comorbidities of alcohol use disorders in an elderly Korean population. International journal of geriatric psychiatry. 2009;24(12):1420-8.
44. Thakkar MM, Sharma R, Sahota P. Alcohol disrupts sleep homeostasis. Alcohol. 2015;49(4):299-310.
45. Box GE, Tidwell PW. Transformation of the independent variables. Technometrics. 1962;4(4):531-50.
46. Kendall M, Gibbons J. Rank Correlation Methods, New York: Oxford Univ. Press; 1990.
47. Kleinbaum DG, Klein M. Assessing discriminatory performance of a binary logistic model: ROC curves. Logistic Regression: Springer; 2010. p. 345-87.
48. Branger P, Arenaza-Urquijo EM, Tomadesso C, Mézenge F, André C, De Flores R, et al. Relationships between sleep quality and brain volume, metabolism, and amyloid deposition in late adulthood. Neurobiology of aging. 2016;41:107-14.
49. Thal DR, Rüb U, Orantes M, Braak H. Phases of Aβ-deposition in the human brain and its relevance for the development of AD. Neurology. 2002;58(12):1791-800.
50. Westwood AJ, Beiser A, Jain N, Himali JJ, DeCarli C, Auerbach SH, et al. Prolonged sleep duration as a marker of early neurodegeneration predicting incident dementia. Neurology. 2017;88(12):1172-9.
51. Jack CR, Knopman DS, Jagust WJ, Petersen RC, Weiner MW, Aisen PS, et al. Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. The Lancet Neurology. 2013;12(2):207-16.
52. Irwin MR, Olmstead R, Carroll JE. Sleep disturbance, sleep duration, and inflammation: a systematic review and meta-analysis of cohort studies and experimental sleep deprivation. Biological psychiatry. 2016;80(1):40-52.
53. Tranah GJ, Blackwell T, Stone KL, Ancoli-Israel S, Paudel ML, Ensrud KE, et al. Circadian activity rhythms and risk of incident dementia and mild cognitive impairment in older women. Annals of Neurology. 2011;70(5):722-32.
54. Wang JL, Lim AS, Chiang WY, Hsieh WH, Lo MT, Schneider JA, et al. Suprachiasmatic neuron numbers and rest–activity circadian rhythms in older humans. Annals of Neurology. 2015;78(2):317-22.
55. Rogers NL, Dorrian J, Dinges DF. Sleep, waking and neurobehavioural

performance. Frontiers in Bioscience. 2003;8:s1056-s67.
56. A Putilov A. Age-associated Advance of Sleep Times Relative to the Circadian Phase of Alertness-Sleepiness Rhythm: Can it be Explained by Changes in Ratios Between Strengths of the Underlying Oscillatory Processes? Current aging science. 2016;9(1):44-56.
57. Refinetti R, Cornélissen G, Halberg F. Procedures for numerical analysis of circadian rhythms. Biological Rhythm Research. 2007;38(4):275-325.
58. Di Milia L, Smith PA, Folkard S. Refining the psychometric properties of the circadian type inventory. Personality and Individual differences. 2004;36(8):1953-64.
59. Jafari Roodbandi A, Choobineh A, Daneshvar S. Relationship between circadian rhythm amplitude and stability with sleep quality and sleepiness among shift nurses and health care workers. International journal of occupational safety and ergonomics. 2015;21(3):312-7.
60. Crowley SJ, Acebo C, Carskadon MA. Sleep, circadian rhythms, and delayed phase in adolescence. Sleep medicine. 2007;8(6):602-12.
61. Roenneberg T, Wirz-Justice A, Merrow M. Life between clocks: daily temporal patterns of human chronotypes. Journal of Biological Rhythms. 2003;18(1):80-90.
62. Aili K, Åström-Paulsson S, Stoetzer U, Svartengren M, Hillert L. Reliability of actigraphy and subjective sleep measurements in adults: the design of sleep assessments. Journal of Clinical Sleep Medicine. 2017;13(01):39-47.
63. Hita-Yañez E, Atienza M, Cantero JL. Polysomnographic and subjective sleep markers of mild cognitive impairment. Sleep. 2013;36(9):1327-34.
64. Westerberg CE, Lundgren EM, Florczak SM, Mesulam M-M, Weintraub S, Zee PC, et al. Sleep influences the severity of memory disruption in amnestic mild cognitive impairment: results from sleep self-assessment and continuous activity monitoring. Alzheimer disease and associated disorders. 2010;24(4):325.
65. Gilpin AR. Table for conversion of Kendall's Tau to Spearman's Rho within the context of measures of magnitude of effect for meta-analysis. Educational and psychological measurement. 1993;53(1):87-92.
66. Argyropoulos SV, Hicks JA, Nash JR, Bell CJ, Rich AS, Nutt DJ, et al. Correlation of subjective and objective sleep measurements at different stages of the treatment of depression. Psychiatry Research. 2003;120(2):179-90.
67. Concato J, Feinstein AR. Monte Carlo methods in clinical research: applications in multivariable analysis. Journal of investigative medicine: the official publication of the American Federation for Clinical Research. 1997;45(6):394-400.
68. Bagley SC, White H, Golomb BA. Logistic regression in the medical literature:: Standards for use and reporting, with particular attention to one

medical domain. Journal of clinical epidemiology. 2001;54(10):979-85.
69. Genzel L, Kroes MC, Dresler M, Battaglia FP. Light sleep versus slow wave sleep in memory consolidation: a question of global versus local processes? Trends in neurosciences. 2014;37(1):10-9.
70. Schmidt C, Peigneux P, Muto V, Schenkel M, Knoblauch V, Münch M, et al. Encoding difficulty promotes postlearning changes in sleep spindle activity during napping. Journal of Neuroscience. 2006;26(35):8976-82.
71. Clemens Z, Fabo D, Halasz P. Overnight verbal memory retention correlates with the number of sleep spindles. Neuroscience. 2005;132(2):529-35.
72. Buchmann A, Dentico D, Peterson MJ, Riedner BA, Sarasso S, Massimini M, et al. Reduced mediodorsal thalamic volume and prefrontal cortical spindle activity in schizophrenia. Neuroimage. 2014;102:540-7.
73. Lim AS, Kowgier M, Yu L, Buchman AS, Bennett DA. Sleep fragmentation and the risk of incident Alzheimer's disease and cognitive decline in older persons. Sleep. 2013;36(7):1027.
74. Littner M, Hirshkowitz M, Kramer M, Kapen S, Anderson WM, Bailey D, et al. Practice parameters for using polysomnography to evaluate insomnia: an update. Sleep. 2003;26(6):754-60.
75. Israel B, Buysse DJ, Krafty RT, Begley A, Miewald J, Hall M. Short-term stability of sleep and heart rate variability in good sleepers and patients with insomnia: for some measures, one night is enough. Sleep. 2012;35(9):1285-91.
76. Adamczyk M, Ambrosius U, Lietzenmaier S, Wichniak A, Holsboer F, Friess E. Genetics of rapid eye movement sleep in humans. Translational psychiatry. 2015;5(7):e598.
77. De Gennaro L, Ferrara M, Vecchio F, Curcio G, Bertini M. An electroencephalographic fingerprint of human sleep. Neuroimage. 2005;26(1):114-22.
78. Iber C. The AASM manual for the scoring of sleep and associated events: Rules. Terminology and Technical Specification. 2007.
79. Himanen S-L, Hasan J. Limitations of rechtschaffen and kales. Sleep medicine reviews. 2000;4(2):149-67.
80. Senaratna CV, Perret JL, Lodge CJ, Lowe AJ, Campbell BE, Matheson MC, et al. Prevalence of obstructive sleep apnea in the general population: a systematic review. Sleep medicine reviews. 2017;34:70-81.
81. Gao S, Unverzagt FW, Hall KS, Lane KA, Murrell JR, Hake AM, et al. Mild cognitive impairment, incidence, progression, and reversion: findings from a community-based cohort of elderly African Americans. The American Journal of Geriatric Psychiatry. 2014;22(7):670-81.
82. Roberts RO, Geda YE, Knopman DS, Cha R, Pankratz V, Boeve BF, et al. The incidence of MCI differs by subtype and is higher in men: the Mayo Clinic Study of Aging. Neurology. 2012;78(5):342-51.

83. Ohayon MM, Carskadon MA, Guilleminault C, Vitiello MV. Meta-analysis of quantitative sleep parameters from childhood to old age in healthy individuals: developing normative sleep values across the human lifespan. Sleep. 2004;27(7):1255-73.
84. Flemons W. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The Report of an American Academy of Sleep Medicine Task Force. Sleep. 1999;22:667-89.
85. Redline S, Kirchner HL, Quan SF, Gottlieb DJ, Kapur V, Newman A. The effects of age, sex, ethnicity, and sleep-disordered breathing on sleep architecture. Archives of internal medicine. 2004;164(4):406-18.
86. Toussaint M, Luthringer R, Schaltenbrand N, Carelli G, Lainey E, Jacqmin A, et al. First-night effect in normal subjects and psychiatric inpatients. Sleep. 1995;18(6):463-9.
87. Fernandez-Mendoza J, Calhoun SL, Bixler EO, Karataraki M, Liao D, Vela-Bueno A, et al. Sleep misperception and chronic insomnia in the general population: the role of objective sleep duration and psychological profiles. Psychosomatic medicine. 2011;73(1):88.
88. Manconi M, Ferri R, Sagrada C, Punjabi NM, Tettamanzi E, Zucconi M, et al. Measuring the error in sleep estimation in normal subjects and in patients with insomnia. Journal of sleep research. 2010;19(3):478-86.
89. Carskadon MA, Dement WC, Mitler M, Guilleminault C, Zarcone VP, Spiegel R. Self-reports versus sleep laboratory findings in 122 drug-free subjects with complaints of chronic insomnia. American Journal of Psychiatry. 1976;133(12):1382-8.
90. Harvey AG, Tang NK. (Mis) perception of sleep in insomnia: A puzzle and a resolution. Psychological bulletin. 2012;138(1):77.
91. Bonnet MH, Arand D. Physiological activation in patients with sleep state misperception. Psychosomatic medicine. 1997;59(5):533-40.
92. Edinger JD, Fins AI, Glenn DM, Sullivan Jr RJ, Bastian LA, Marsh GR, et al. Insomnia and the eye of the beholder: are there clinical markers of objective sleep disturbances among adults with and without insomnia complaints? Journal of consulting and clinical psychology. 2000;68(4):586.
93. Lakshminarayana Tadimeti M, Caruana-Montaldo B, Wallace B, Mendelson M. Sleep latency and duration estimates among sleep disorder patients: variability as a function of sleep disorder diagnosis, sleep history, and psychological characteristics. Sleep. 2000;23(1):1.
94. Perlis M, Giles D, Mendelson W, Bootzin RR, Wyatt J. Psychophysiological insomnia: the behavioural model and a neurocognitive perspective. Journal of sleep research. 1997;6(3):179-88.
95. Wyatt JK, Bootzin RR, Allen JJ, Anthony JL. Mesograde amnesia during the sleep onset transition: replication and electrophysiological correlates. Sleep. 1997;20(7):512-22.

96. Ronald T, Group NIoAW. Consensus report of the working group on:“Molecular and biochemical markers of Alzheimer’s disease”. Neurobiology of Aging. 1998;19(2):109-16.
97. Roe CM, Fagan AM, Grant EA, Hassenstab J, Moulder KL, Dreyfus DM, et al. Amyloid imaging and CSF biomarkers in predicting cognitive impairment up to 7.5 years later. Neurology. 2013;80(19):1784-91.
98. Soldan A, Pettigrew C, Lu Y, Wang MC, Selnes O, Albert M, et al. Relationship of medial temporal lobe atrophy, APOE genotype, and cognitive reserve in preclinical A lzheimer's disease. Human brain mapping. 2015;36(7):2826-41.
99. Vos SJ, Gordon BA, Su Y, Visser PJ, Holtzman DM, Morris JC, et al. NIA-AA staging of preclinical Alzheimer disease: discordance and concordance of CSF and imaging biomarkers. Neurobiology of aging. 2016;44:1-8.

초 록

배경 및 목적: 그 동안 집단 수준에서 주관적/객관적 수면 지표와 인지저하의 관계를 살핀 연구들이 무수히 이루어져 왔음. 그러나 다양한 주관적 수면 지표를 하나의 모델에 통합하여 분석한 연구는 수행된 바 없음. 나아가 객관적 수면지표를 기억 강화와 관련된, 비렘과 렘수면의 상호 보완적 맥락에서 분석한 과거 연구 또한 수행된 바 없음. 수면과 인지저하의 관계에 대한 여러 보고는 있었지만, 개인 수준에서 인지저하를 예측하는 데에 있어 수면지표의 타당성에는 많은 의문이 있는 실정임. 본 연구는 아래와 같은 4가지 가설을 검증하고자 함. 첫째, 정상인지기능 노년 코호트에서 다양한 기저 주관적 수면지표가 4년후 인지저하, 즉, 경도인지장애 (MCI) 또는 치매 발생과 관련이 있을 것이다 (가설 I). 둘째, 상기 코호트의 하위표본에서 수면다원검사 (PSG)를 통해 NREM/REM 수면주기 및 이와 연관된 수면 구조가 인지저하와 관련이 있을 것이다 (가설 II). 셋째, 앞선 연구에서 인지저하와 연관되었다고 밝혀진 주관적 수면 지표와, 역시 인지저하와 연관되었다고 분석된 수면다원검사지표 사이에 상관관계가 있을 것이다 (가설 III). 넷째, 개인 수준에서 주관적 수면지표가 4년후 인지저하를 만족할 만한 검증력으로 예측할 수 있을 것이다 (가설 IV).

방법: 가설 I의 분석을 위해, 자료는 한국 노인을 대표할 수 있는 전국적 인구기반의 전향적 코호트에서 기저 인지기능이 정상 (normal cognition, NC, N = 2,238)인 대상자를 모집함. 심각한 정신과적, 신경과적 질환이

있거나 수면제를 복용하는 대상자를 배제하였으며, 4년간 추적관찰 하였음. 주관적 수면 지표 (중간수면시간, 수면길이, 수면잠복기, 수면질, 수면효율, 및 주간기능장애)는 피츠버그수면질척도 (PSQI)를 통하여, 인지기능은 Consortium to Establish a Registry for Alzheimer's Disease Assessment (CERAD)를 사용하여 기저와 4년 추적 시점에서 각각 이루어짐. 분석에는 로지스틱 회귀모형이 사용되었으며, 나이, 성별, 교육연수, APOE 유전형, 노인우울척도, 누적질환평가점수, 및 신체활동량으로 보정하였음.

가설 II의 분석을 위해, 앞선 분석에서 사용된 코호트의 하위표본으로부터 기저에 PSG를 시행한, 235명의 기저 NC 노인의 자료를 사용하였음. 하나의 비렘/렘 수면주기는 2분 초과의 각성시기에 의해 단절되지 않은, 연속되어 순차적으로 나타나는 비렘과 렘 수면 단위로 정의됨. 로지스틱 회귀 모형을 사용하여, 비렘/렘 수면주기 및 이와 연관된 수면구조와, 4년후 인지저하 사이의 연관성을 분석함.

가설 III의 분석을 위해, 기저에서 PSG 및 PSQI를 모두 시행하고 4년 추적을 완료한 기저 NC 노인 235명의 자료를 사용함. 켄달의 순위 상관분석을 통해 앞선 연구에서 인지저하와 관련있다고 알려진 주관적 수면 지표 및 비렘/렘 수면주기의 상관관계를 규명함.

가설 IV의 분석을 위해, NC로 구성된 전체 기저 코호트 자료 (N = 2,238)를 4:1 비율로 훈련데이터셋과 검증데이터셋으로 나눠 10겹 교차검증을 수행함. 훈련데이터셋에 이분형 로지스틱 회귀 분석을 사용하여 4년 후 인지저하 예측 모델을 수립하고, 이의 예측 타당도를 분석하기위해 검증데이터셋에서 ROC 곡선을 얻음. 추가 분석으로, 1) 기저 NC 대상자에서 4년 후 치매 발생에 대한 예측 모델을, 2) 기저 NC 또는 MCI인 대상자를 통합 (N = 2,893)하여 데이터 분할 후 위와

같은 방법으로 4년 후 치매발생에 대한 예측 모델을 수립함.

결과: 가설 I과 관련하여, 기저의 긴 수면잠복기 (30분 초과), 긴 수면길이 (7.95시간 이상), 늦은 수면중간시간 (새벽 3시이후)이 기저 NC 집단에서 4년후 인지저하와 연관되었음 (우도비, 긴 수면잠복기 1.40 [95% CI, 1.03–1.90], $p = 0.03$; 긴 수면길이 1.67 [95% CI, 1.18–2.35], p = 0.004; 늦은 수면중간시간 0.61 [95% CI, 0.41–0.90], $p = 0.03$). 이 지표들이 추적기간동안 동일한 상태를 유지하였을 때, 이 연관관계는 통계적 유의성을 유지하였으며, 동일 기간 동안 새로 발생한 긴 수면잠복기 또한 2배 높은 인지저하 위험성과 관련이 있었음 (우도비, 1.95 [95% CI, 1.36–2.81], $p = 0.002$).

가설 II와 관련하여, 짧은 평균 주기시간이 인지저하와 연관되어 있었음 (우도비, 0.97 [95% CI, 0.94–0.99], $p = 0.02$). 주기의 하위 구조와, 주기 밖의 비렘, 렘수면이 분석에 모두 포함되었을 때에는, 주기 당 렘수면 길이가 짧을수록 인지저하와 연관되어 있다는 결과가 관찰됨 (우도비, 0.87 [95% CI, 0.76–0.98], $p = 0.03$).

가설 III과 관련하여, 수면잠복기가 비렘/렘 수면주기 평균길이와 음의 상관관계가 있었으며 ($\tau = -0.11$, $p = 0.04$), 주기 당 비렘 수면 길이와도 음의 상관관계가 관찰되었음 ($\tau = -0.16$, $p = 0.002$).

가설 IV와 관련하여, 주관적 수면 지표, APOE 유전자형과 인구학적, 생활습관 인자들을 사용하여 이분형 로지스틱 모델을 구축하였음. 이를 통해 정상인지기능 노인의 4년 후 인지저하를 곡선아래면적 (AUC) 0.65, 민감도 0.60, 특이도 0.66으로 예측하였음. 이어서 정상인지기능 노인의 4년 후 치매 발생에 대해서는 AUC 0.62, 민감도 0.66, 특이도 0.73으로 예측을 하였으며, 기저인지기능이 NC인

대상자와 MCI인 대상자를 통합하여 분석했을 경우, 이 집단에서 4년후 치매 발생 예측에 대한 성능은 AUC 0.85, 민감도 0.89, 특이도 0.75로 분석됨.

결론 및 해석: 정상인지기능 노인의 긴 수면 잠복기 (30분 초과)와 긴 수면시간 (7.95시간 이상)과 같은 주관적 수면 호소가 인지저하의 높은 위험을 예측 할 가능성이 있으며, 정상인지노인의 늦은 수면 중간시간 (새벽 3시 이후)은 인지저하의 낮은 위험을 예측할 가능성이 있음. 더불어, 주관적으로 긴 수면 잠복기는, 정상인지노인의 높은 인지저하 위험과 연관된, 수면다원검사의 짧은 비렘/렘 수면주기 평균시간과 유의한 연관관계가 있었음. 주관적 수면 지표는 수면습관의 무작위적인 표현이 아니라, 인지저하와 연관된 수면구조를 반영하는 객관적 지표로 확인 가능한, 신뢰할 수 있는 지표일 가능성이 있음. 본 분석에서 정상인지기능 노인을 활용한 4년후 인지 저하 예측 모델의 성능은 만족스럽지 않았음. 그러나 비치매 노인을 대상으로 수면인자를 포함한 치매 발생 예측 모델의 개발 가능성은 확인됨.

본 연구의 일부는 아래 잡지에 기 게재된 바 있음:

−Suh, Seung Wan, et al. "Sleep and Cognitive Decline: A Prospective Nondemented Elderly Cohort Study." Annals of Neurology 83.3 (2018): 472−482.

−Suh, Seung Wan, et al. "Short Average Duration of NREM/REM Cycle Is Related to Cognitive Decline in an Elderly Cohort: An Exploratory Investigation." Journal of Alzheimer's Disease 70.4 (2019): 1123−1132.

주요어 : 수면, 노인, 주관적, 객관적, 수면다원검사, 치매, 전향적

학　　번 : 2014-21984