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Sleep, 24-Hour Activity Rhythms, and Cognitive Reserve: A Population-Based Study

Jendé L. Zijlmans[a], Mariska S. Riemens[a], Meike W. Vernooij[a,b], M. Arfan Ikram[a] and Annemarie I. Luik[a,*]
[a]*Department of Epidemiology, Erasmus MC University Medical Center, Rotterdam, the Netherlands*
[b]*Department of Radiology and Nuclear Medicine, Erasmus MC University Medical Center, Rotterdam, the Netherlands*

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Abstract.
Background: The cognitive reserve hypothesis aims to explain individual differences in susceptibility to the functional impact of dementia-related pathology. Previous research suggested that poor subjective sleep may be associated with a lower cognitive reserve.
Objective: The objective was to investigate if actigraphy-estimated sleep and 24-hour activity rhythms are associated with cognitive reserve.
Methods: This cross-sectional study included 1,002 participants from the Rotterdam Study (mean age: 65.0 years, standard deviation (SD): 7.1) who were assessed with actigraphy, five cognitive tests, and brain-MRI between 2009–2014. Sleep and 24-hour activity rhythms were measured using actigraphy (mean days: 6.7, SD: 0.5). Cognitive reserve was defined as a latent variable that captures variance across cognitive tests, while adjusting for age, sex, education, total brain volume, intracranial volume, and white matter hyperintensity volume. Associations of sleep and 24-hour activity rhythms with cognitive reserve were assessed using structural equation models.
Results: Longer sleep onset latency (adjusted mean difference: –0.16, 95%CI: –0.24; –0.08) and lower sleep efficiency (0.14, 95%CI: 0.05; 0.22) were associated with lower cognitive reserve. Total sleep time and wake after sleep onset were not significantly associated with cognitive reserve. After mutual adjustment, only the association of longer sleep onset latency remained significant (–0.12, 95%CI: –0.20; –0.04). The 24-hour activity rhythm was not significantly associated with cognitive reserve.
Conclusion: In conclusion, our study suggests that longer sleep onset latency is particularly associated with lower cognitive reserve. Future longitudinal work is needed to assess whether shortening the sleep onset latency could enhance cognitive reserve, in order to limit the susceptibility to the functional impact of dementia-related pathology.

Keywords: Actigraphy, circadian rhythm, cognitive reserve, cohort study, sleep

INTRODUCTION

Clinical symptoms of dementia can differ between patients, even if they are associated with a similar level of brain pathology [1]. The reserve hypothesis was developed to explain these individual differences in the susceptibility to the functional impact of dementia-related pathology [2]. Cognitive reserve is defined as "the adaptability (i.e., efficiency, capacity, flexibility) of cognitive processes that helps to explain differential susceptibility of cognitive abilities or day-to-day function to brain aging, pathology

*Correspondence to: Annemarie I. Luik, Department of Epidemiology, Erasmus MC University Medical Center Rotterdam, PO Box 2040, 3000 CA Rotterdam, the Netherlands. Tel.: +31 10 703 21 83; E-mail: a.luik@erasmusmc.nl.

or insult." [3]. Cognitive reserve cannot be measured directly and therefore studies have historically relied on proxies such as educational attainment to estimate cognitive reserve [3]. More recently, studies have developed the residual method to estimate cognitive reserve [4, 5]. In particular, global cognitive reserve, rather than domain-specific cognitive reserve, is a predictor of mild cognitive impairment and dementia [4, 5].

It has been posited that sleep and circadian rhythm disturbances may be associated with cognitive reserve [6], as there is a well-established link of sleep disorders with cognitive impairment [7, 8] and dementia [9]. We have previously demonstrated that a worse self-reported sleep quality is associated with lower cognitive reserve, although this association seems to be explained at least in part by concurrent depressive symptoms [10]. However, no population-based studies assessed the association of objectively estimated sleep and 24-hour rhythms, which may reflect the physiological aspect of sleep rather than the subjective experience of sleep [11], with general cognitive reserve.

Studies have assessed the association of objectively measured sleep and 24-hour activity rhythms with global cognitive functioning, which may be closely related to general cognitive reserve as these are partly based on the same neuropsychological test battery [4]. Previous work within the Rotterdam Study investigated actigraphy-estimated sleep parameters and 24-hour activity rhythms and found that a longer sleep onset latency and higher intradaily variability were associated with worse global cognition [12], suggesting that an association between sleep and 24-hour activity rhythms and cognitive reserve may also exist.

Sleep and 24-hour activity rhythms may be of particular interest with regards to cognitive reserve as they are also considered a potentially modifiable intervention target for dementia [13]. If improving sleep and 24-hour activity rhythms can impact cognitive reserve, it could slow age-related cognitive decline and prolong healthy aging. Therefore, we assessed the association of sleep (total sleep time, sleep efficiency, sleep onset latency, and wake after sleep onset) and 24-hour activity rhythms (interdaily stability, intradaily variability, and L5-onset) by means of actigraphy with cognitive reserve in a sample of middle-aged and elderly adults of the population-based Rotterdam Study.

METHODS

Study population

The current cross-sectional study is embedded within the Rotterdam Study, a population-based cohort study including 17,931 residents from the Ommoord district in Rotterdam, the Netherlands, aged 40 years and older [14]. Between January 2009 and July 2014, 1,932 participants who attended the research center for cognitive testing were invited for actigraphy and brain-MRI. We excluded participants who had no or incomplete data on cognition or educational attainment ($n = 325$), had no MRI-scan ($n = 137$) or an MRI-scan of insufficient quality ($n = 62$), had no actigraphy data ($n = 143$), or insufficient actigraphy data ($n = 249$), and who had prevalent dementia ($n = 14$). In total, 1,002 participants were included in this study (Supplementary Figure 1).

The Rotterdam Study has been approved by the Medical Ethics Committee of the Erasmus MC (registration number MEC 02.1015) and by the Dutch Ministry of Health, Welfare and Sport (Population Screening Act WBO, license number:1071272-159521-PG). The Rotterdam Study Personal Registration Data collection is filed with the Erasmus MC Data Protection Officer under registration number EMC1712001. The Rotterdam Study has been entered into the Netherlands National Trial Register (NTR; https://www.trialregister.nl) and into the WHO International Clinical Trials Registry Platform (ICTRP; https://www.who.int/ictrp/network/primary/en/) under shared catalogue number:NTR6831. All participants provided written informed consent to participate in the study and to have their information obtained from treating physicians.

Measurements

Sleep and 24-hour activity rhythms

Participants were asked to wear the actigraph for seven consecutive days and nights, while keeping a sleep diary at the same time. We used two types of actigraphs to estimate sleep and 24-hour activity rhythms: the Actiwatch (Actiwatch, model AW4; Cambridge Technology, Cambridge, UK) and the Geneactiv (Geneactiv, Activinsights Ltd, Kimbolton, UK). Recordings were sampled at 32 Hz (Actiwatch) or 50 Hz (GeneActiv), and were averaged into a score for each 30-s interval. To ensure comparability between the estimates of the two devices, we used

a validated algorithm to convert the triaxial GeneActiv to one-dimensional 30-s epoch data (using the z-axis), that was thereafter calibrated to Actiwatch counts using Passing-Bablok regression [15]. To determine sleep, a movement score taking into account weighted values of previous and following epochs was calculated. When the movement score exceeded a threshold of 20 activity counts, the epoch was scored as 'awake', otherwise as 'asleep' [16]. A minimum of four times 24 hours needed to be available to be included in the analyses, periods of 3 hours or more missing were deleted as 24-hour periods. Sleep diaries were used to capture additional information about the night [17]. For this study, we only used the questions which indicated the time at which participants tried to fall asleep and got out of bed in the morning.

We derived four parameters from the actigraph and the sleep diary: total sleep time, sleep efficiency, sleep onset latency, and wake after sleep onset. Total sleep time (min) was defined as the nightly sleep duration and calculated as the total duration of epochs scored as asleep between sleep start and sleep end. Time trying to fall asleep and get-up time were derived from the sleep diary. If these data were not present for a certain night, times indicated by a press of the button on the actigraph by the participant were used for all nights. Sleep start was defined using the first immobile period of at least 10 min after time trying to fall asleep with no more than one 30-s epoch of movement. Sleep end was defined as last period of at least 10 min of immobility before get-up time, which had no more than one 30-s epoch of movement. Sleep efficiency (%) reflected the ratio of total sleep time to time in bed. Time in bed was defined as the time between trying to fall asleep and get-up time. Sleep onset latency (min) indicated the time between trying to fall asleep and sleep start. Wake after sleep onset (min) was the time the participant was awake between sleep start and get-up time. The values used for data-analysis were calculated by averaging the scores for each variable over all available nights.

We additionally estimated 24-hour activity rhythms using non-parametric estimates. The nparACT R package was used to calculate interdaily stability, intradaily variability, and L5-onset time [18]. The interdaily stability indicates the stability of the activity rhythm over days, that is, the extent to which the profiles of individual days resemble each other. The intradaily variability quantifies alterations between an active and an inactive state lead relative to its 24-hour amplitude within the day, indicating the fragmentation of the activity rhythm relative to its 24-hour amplitude. Lastly, L5-onset indicates the average clock time the 5 consecutive hours with least activity of the day started.

Cognition

All participants completed a cognitive test battery of five cognitive tests, which assess multiple cognitive domains [14], at the research center. First, the 15-word verbal learning test (15-WLT) [19], a Dutch version of the Rey Auditory Verbal Learning task, measuring aspects of verbal memory. We used the total number of words named during the three trials of immediate recall test. The Stroop task [20] measures interference of automatic processes and attention. We used the time in seconds to complete the third task, which is the interference task. The Word fluency test (WFT) [21] measures searching efficiency in long-term memory. We used the total amount of correct and unique animals named. The Letter-digit substitution task (LDST) [22] measures processing speed. We used the number of correct matches of digits to letters. Lastly, the Purdue pegboard test (PPB) [23] measures fine motor skill. We used the number of correctly placed pins across the three conditions.

Brain volumes

Brain imaging was carried out with a 1.5 Tesla MRI scanner equipped with an 8-channel head coil at the research center [24]. The scans consisted of a T1-weighted sequence, a proton density sequence, and a fluid-attenuated inversion recovery (FLAIR) sequence. The T1-weighted and proton density sequence were used for the segmentation of cerebrospinal fluid, grey matter, and white matter, to be able to calculate intracranial volume and total brain volume. The FLAIR sequence was used to segment white matter lesions, to assess total white matter hyperintensity volume. Details regarding the MRI processing have been described extensively elsewhere [24].

Other variables

Multiple variables that were hypothesized to be associated with both sleep and cognitive reserve [10, 25] were measured. Sex and age were self-reported. Employment status was self-reported and categorized as paid employment, retirement, or no paid employment. Education was self-reported and categorized as primary education, lower/intermediate general education or lower vocational education, intermediate vocational education or higher general

education, and higher vocational education or university. Body mass index was calculated from length and weight (kg/m^2) measured on calibrated scales during a research center visit. Smoking status was self-reported and categorized as current, former, or never. Alcohol consumption was assessed using the Food Frequency Questionnaire [26] and calculated in grams per day, using an algorithm described elsewhere [27]. Coffee consumption during the week of actigraphy measurement was obtained through sleep diaries and defined as the average number of days coffee was consumed after 18 : 00; if data was missing for more than two days, the variable was set to missing. Use of sleep medication was obtained through the sleep diaries and defined as having used sleep medication (including over the counter medication) at least once during actigraphy measurement. If participants had more than two days missing, the variable was set as missing. Presence of possible sleep apnea was based on two questions from the Pittsburg Sleep Quality Index assessed during the home interview [28]. Possible sleep apnea was defined when participants experienced loud snoring for over two nights a week, and additionally had long pauses in breathing in at least one night a week. Hypertension was defined as use of antihypertensive medication during follow-up, or a systolic blood pressure greater than 140 mmHg or a diastolic blood pressure greater than 90 mmHg [29], measured at the research center. Diabetes was defined as use of antidiabetic medication, a fasting serum glucose level $\geq$7.1 mmol/L, or random serum glucose level $\geq$11.1 mmol/L [30]. Depressive symptoms were assessed during the home interview using the Center for Epidemiological Studies Depression Scale (CES-D), with higher scores indicating more depressive symptoms [31, 32]. A weighted average score was calculated; questionnaires with less than 15 answers were counted as missing. The number of APOE ε4 alleles was determined by DNA sequencing procedures which have been described elsewhere [33].

Statistical analysis

We used structural equation modeling to estimate cognitive reserve as a latent variable, based on the model of Petkus et al. [4] (Supplementary Figure 1). All continuous variables in the structural equations model were checked for normality and z-score standardized. The Stroop task and white matter hyperintensity volume were not normally distributed and therefore log-transformed before z-score standardization. To estimate cognitive reserve, each cognitive test score was adjusted for sex, age, educational status, total brain volume, and white matter hyperintensity volume. Total brain volume and white matter hyperintensity volume were chosen as global measures of brain pathology, and adjusted for sex, age, and intracranial volume as the total brain volume and white matter hyperintensity volume are dependent on these variables. The cognitive reserve latent variable was estimated as the residual variance of the five cognitive test scores after adjusting for these variables. A higher cognitive reserve score, i.e., a higher positive residual, therefore indicates a better cognitive functioning than expected, based on current level of cognition, age, sex, education, total brain volume, white matter hyperintensity volume, and intracranial volume.

Path coefficients were estimated to examine associations of actigraphy-estimated sleep and 24-hour activity rhythms with cognitive reserve in three separate models. In order to deal with outliers within the sleep parameters, scores exceeding four standard deviations from the mean were replaced with scores exactly four standard deviations from the mean. In Model 1, we examined the univariate association of the actigraphy-estimated sleep and 24-hour activity rhythm variables with cognitive reserve. In this model, we did not adjust for age and sex because the cognitive reserve latent variable is already adjusted for age and sex. In Model 2 we included employment status, body mass index, smoking habits, alcohol intake, coffee consumption, sleep medication, diabetes mellitus, hypertension, possible sleep apnea, depression, and time between measurements as covariables. These models were conducted separately for each sleep parameter. In Model 3, we included the four sleep variables to adjust each sleep parameter for the other sleep parameters in addition to all covariables.

Five sensitivity analyses were conducted. First, we investigated whether adjustment for *APOE* ε4 status (carrier $n = 249$ versus non-carrier $n = 690$, missing $n = 63$) affected our results by including it as a confounder in our models. Second, the analyses were stratified on sex. Third, the analyses were stratified on age (<65 years old and $\geq$ 65 years old). Fourth, the analyses were examined in a subsample of participants who had all measurements (actigraphy, cognitive testing, brain MRI) within six months of each other, to minimize any potential effect of time between the measurements on the associations. Fifth, the analyses were stratified for type of actigraphy device, as this might influence the sleep estimates.

Standard criteria of comparative fit index (CFI)>0.95, Tucker Lewis Index (TLI)>0.95, and root mean squared error of approximation (RMSEA)<0.06 were used to assess the model fit [34]. Full information maximum likelihood was used to handle missing values of covariables (range 0.1% to 2.0%). The robust maximum likelihood estimator was used because some of the covariables were not completely normally distributed. Path coefficients were described as the mean difference or the adjusted mean difference. We considered a p-value of < 0.05 as statistically significant. The structural equations models were fitted using the 'lavaan' package in R 4.0.4.

RESULTS

The mean age of our sample was 65.0 (SD: 7.1) years and 51.3% of the participants were women (Table 1). Table 2 shows the summary statistics for the actigraphy-estimated sleep and 24-hour activity rhythm variables, brain-MRI measures, cognitive reserve, and the time between the measurements.

A longer sleep onset latency (adjusted mean difference: –0.16, 95% CI –0.24; –0.08) and lower sleep efficiency (adjusted mean difference: 0.14, 95% CI 0.05; 0.22) were associated with a lower cognitive reserve after adjustment for covariables (Table 3), implying that for each –0.16 mean difference in SD of sleep onset latency, cognitive reserve was one SD lower. Total sleep time and wake after sleep onset were not significantly associated with cognitive reserve (Table 3). When additionally adjusting for the other actigraphy-estimated sleep variables, sleep onset latency remained associated with cognitive reserve (adjusted mean difference: –0.12, 95% CI –0.20; –0.04), whereas sleep efficiency did not (adjusted mean difference: 0.12, 95% CI –0.03; 0.27), see Table 3. We found no associations of interdaily stability, intradaily variability and L5-onset with cognitive reserve after adjustment for covariables (Table 3).

Additional adjustment for *APOE* ε4 status (carrier versus non-carrier) did not change any of the results (Supplementary Table 1). When stratifying the analyses on sex and age the effect estimates for sleep onset latency and sleep efficiency were somewhat larger in women and participants younger than 65 years old (Supplementary Tables 2 and 3). The effect estimates were in a similar direction as in the full sample when assessing the associations in a subsample of participants who had all measurements taken within six months ($n = 837$), see Supplementary Table 4. Effect estimates in the group with measurements within six months were larger for most sleep variables and smaller for the 24-hour activity rhythm variables compared to the full sample (Supplementary Table 4). Stratification for type of actigraphy device used (Geneactiv: $n = 618$, Actiwatch: $n = 384$) showed results in similar directions for both devices (Supplementary Table 5). The effect estimates in the Actiwatch group were larger for the sleep variables and smaller for the 24-hour activity rhythm variables when compared to the Geneactiv group. All structural equations models met the recommended values for CFI, TLI, and RMSEA.

DISCUSSION

In this study of community dwelling middle-aged and elderly persons, we found that a longer sleep onset latency and lower sleep efficiency were associated with a lower cognitive reserve with relatively small effect sizes. The association between sleep onset latency and cognitive reserve remained when adjusted for the other sleep variables, suggesting that sleep onset latency might be particular important. We found no associations between the 24-hour activity rhythm and cognitive reserve.

Longer sleep onset latency was associated with lower cognitive reserve, albeit with a relative small effect size for which clinical relevance remains to be determined. Although our study is cross-sectional, we might hypothesize that sleep onset latency affects cognitive reserve via the stress system, which may affect cognitive function and reserve [35] directly or lead to the formation of amyloid plaques, which in turn could be associated with cognitive decline or less cognitive reserve [36]. However, vice versa, amyloid plaques may also be a cause of poor sleep [36]. An association between brain amyloid-β burden and self-reported sleep onset latency has been previously been shown [37], potentially even present before cognitive impairment [38], suggesting it may well affect cognitive reserve. Yet, previous work from our group found no associations of actigraphy-estimated sleep onset latency with amyloid-β 40 and amyloid-β 42 and total-tau [39]. As opposed to possible structural underlying mechanisms of the association between sleep onset latency and cognitive reserve, there may also be functional mechanisms underlying the association. For example, if sleep onset latency lowers

Table 1
Descriptive characteristics of the study population ($N = 1{,}002$)

Variables	
Age, y, *mean (SD)*	65.0 (7.1)
Sex, women, *n (%)*	514 (51.3)
Education, *n (%)*	
Primary	55 (5.5)
Lower	350 (34.9)
Intermediate	309 (30.8)
Higher	288 (28.7)
Employment, *n (%)*	
Paid employment	329 (33.5)
Retired	513 (52.3)
No paid employment	139 (14.2)
Body mass index, kg/m2, *mean (SD)*	27.4 (4.1)
Smoking status, *n (%)*	
Current	107 (10.7)
Former	582 (58.0)
Never	313 (31.2)
Alcohol consumption, g/day, *mean (SD)*	7.9 (8.4)
Coffee consumption during actigraphy, days, *mean (SD)*	4.4 (2.9)
Sleep medication during actigraphy, *n (%)*	120 (12.0)
Possible sleep apnea, *n (%)*	97 (9.6)
Diabetes mellitus, *n (%)*	132 (13.2)
Hypertension, *n (%)*	648 (64.7)
Depressive symptoms, CES-D score, *mean (SD)*	5.3 (6.8)

SD, standard deviation; CES-D, Center for Epidemiological Studies Depression Scale. Missing: Employment $n = 21$; Body mass index $n = 1$; Alcohol consumption $n = 1$; Coffee consumption $n = 4$; Sleep medication $n = 6$; Diabetes mellitus $n = 2$; Depressive symptoms $n = 2$.

Table 2
Summary statistics for sleep, 24-hour activity rhythms, cognitive reserve, and time between the measurements ($N = 1{,}002$)

Measurement	
Sleep, *mean (SD)*	
Total sleep time, min/night	376.4 (50.9)
Sleep efficiency, %	77.6 (7.8)
Sleep onset latency, min/night	17.3 (13.6)
Wake after sleep onset, min/night	55.6 (23.3)
24-hour activity rhythms	
Interdaily stability, score, *mean (SD)*	0.74 (0.1)
Intradaily variability, score, *mean (SD)*	0.46 (0.1)
L5-onset, hour:min, *median (IQR)*	01 : 38 (00 : 57–2 : 36)[a]
Cognitive reserve, score, *mean (SD)*	0 (1)*
Time between measurements, *median (IQR)*	
Actigraphy and cognition, days	0 (56)
Actigraphy and MRI, days	47 (65)
MRI and cognition, days	56 (51)

[a]Missing $n = 9$, *This variable was standardized. Abbreviations: SD, standard deviation, IQR, interquartile range.

the amount of functional connectivity in the frontoparietal control network, a network that has been speculated to be a source for cognitive reserve [40], it would lead to a lower cognitive reserve. However, population-based studies found no associations of objective and subjective measures of sleep with functional connectivity between or within resting-state networks [41], suggesting this mechanism is unlikely.

Additionally, it is also possible that less healthy habits surrounding sleep are associated with less healthy habits in general (e.g., less exercise, intellectual pursuits, or social interaction), which may also be associated a lower cognitive reserve [6]. Additionally, longer sleep onset latencies are often seen in those with insomnia disorder. A previous meta-analysis ($n = 4{,}539$) found that insomnia disorder was

Table 3
Associations of actigraphy-estimated sleep and 24-hour activity rhythms with cognitive reserve ($n = 1{,}002$)

	Model 1 Mean difference (95%CI)	Model 2 Mean difference (95%CI)	Model 3 Mean difference (95%CI)
Sleep			
Total sleep time, per SD	0.07 (–0.02; 0.16)	0.08 (–0.01; 0.16)	–0.02 (–0.14; 0.10)
Sleep efficiency, per SD	**0.14 (0.06; 0.22)**	**0.14 (0.05; 0.22)**	0.10 (–0.04; 0.25)
Sleep onset latency, per SD	**–0.18 (–0.25; –0.11)**	**–0.16 (–0.24; –0.09)**	**–0.13 (–0.21; –0.04)**
Wake after sleep onset, per SD	–0.07 (–0.15; 0.01)	–0.06 (–0.14; 0.02)	0.02 (–0.08; 0.13)
24-hour activity rhythms			
Interdaily stability, per SD	**0.10 (0.02; 0.18)**	0.05 (–0.03; 0.14)	–
Intradaily variability, per SD	–0.08 (–0.17; 0.00)	–0.03 (–0.11; 0.06)	–
L5-onset, per SD	0.06 (–0.05; 0.18)	0.06 (–0.04; 0.17)	–

Model 1: Unadjusted; Model 2: Adjusted for employment status, body mass index, smoking habits, alcohol intake, coffee consumption, sleep medication, diabetes, hypertension, sleep apnea, depression and time between the cognition, MRI and actigraphy measurements; Model 3: As model 2, but also adjusted for the other sleep variables. All variables within the models have been standardized. Statistically significant results are in bold. CI, confidence interval.

associated with poorer overall cognitive performance [8], suggesting that the association we find with cognitive reserve might be in part driven by persons with insomnia, potentially via hyperarousal. Cognitive hyperarousal, in the context of insomnia, might cause both a longer sleep onset latency and a lower cognitive reserve [42, 43]. Unfortunately, we do not have information on insomnia diagnosis or hyperarousal available in our cohort to test this hypothesis. Further, the partly subjective nature of sleep onset latency, as a sleep diary question is used to determine the time a person wants to go to sleep, may have contributed to the association found, as estimating this time partly relies on cognitive function. Previous research suggested that data quality of questionnaires is affected in nursing home residents with moderate cognitive impairments [44], our population is however largely community dwelling. Nevertheless, if a causal relationship between sleep onset latency and cognitive reserve exists, intervening on sleep onset latency could potentially enhance cognitive reserve, and delay cognitive decline and Alzheimer's disease. Strategies to reduce sleep onset latency could for example be based on the principles of cognitive behavioral therapy for insomnia [45]. Future research is needed to investigate whether targeting sleep onset latency could enhance cognitive reserve.

A lower sleep efficiency was also associated with a lower cognitive reserve, but this association attenuated when adjusted for the other sleep parameters. As sleep onset latency and wake after sleep onset are part of sleep efficiency, and wake after sleep onset was not associated with cognitive reserve, we speculate that the association between sleep efficiency and cognitive reserve was at least partly explained by the association between sleep onset latency and cognitive reserve. However, it could again also be due to the partly subjective nature of the sleep efficiency measurement.

We found no associations of total sleep time and wake after sleep onset with cognitive reserve. This is in line with previous research in our cohort that also found no association between these constructs and global cognition [12]. Previous studies have however repeatedly reported an association between self-reported total sleep time and cognition [46], emphasizing that these associations may rely on the assessment methods or that other mechanisms may be at work for cognitive function and cognitive reserve. We also found no associations between the 24-hour activity rhythm and cognitive reserve, contrasting the previously found association between a higher intradaily variability and worse global cognition [12]. Previous studies have suggested circadian control of pathways, synchronization of local clocks, and neurogenesis as possible mechanisms through which circadian disturbances might affect cognition [47], but 24-hour activity rhythms do not seem to affect cognitive reserve via these or other mechanisms.

Our study has several limitations. First, as this was a cross-sectional study, it is not possible to infer causality or temporality from our findings. Second, the structural equation model for cognitive reserve could be lacking, as there might be unknown brain variables, associations or interactions [4]. Third, the sleep and 24-hour activity rhythm estimates are based on movement scores measured with actigraphy, rather than polysomnography or in-depth circadian rhythm measures. Strengths of this study include the large sample size, being able to adjust for a wide range

of covariables, and the observational design which allowed us to assess habitual sleep, which might be more relevant to pathologies that develop over longer periods over time.

In conclusion, we found associations of longer sleep onset latency and lower sleep efficiency with lower cognitive reserve. However, when adjusted for sleep onset latency, sleep efficiency was no longer associated with cognitive reserve. This may suggest that sleep onset latency, which is in part based on self-reported bedtimes in this study, may be a particular interesting construct to study further in relation to cognitive reserve. If evidence for a causal relationship can be found, targeting sleep onset latency might be a promising avenue to enhance cognitive reserve, in order to limit the susceptibility to the functional impact of dementia-related pathology.

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Authors' disclosures available online (https://www.j-alz.com/manuscript-disclosures/22-0714r1).

DATA AVAILABILITY

Data can be obtained upon request. Requests should be directed towards the management team of the Rotterdam Study (secretariat.epi@erasmusmc.nl), which has a protocol for approving data requests. Because of restrictions based on privacy regulations and informed consent of the participants, data cannot be made freely available in a public repository.

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: https://dx.doi.org/10.3233/JAD-220714.

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