pii: sp-00785-14 http://dx.doi.org/10.5665/sleep.5352

SLEEP AND AGING

Impaired Sleep Predicts Cognitive Decline in Old People: Findings from the Prospective KORA Age Study

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Study Objectives: To investigate the association between sleep-related characteristics and cognitive change over 3 years of follow up in an aged population.
Methods: Sleep characteristics and covariates were assessed at baseline in a standardized interview and clinical examination of the population-based KORA Age Study (n = 740, mean age = 75 years). Cognitive score (determined by telephone interview for cognitive status, TICS-m) was recorded at baseline and 3 years later.
Results: At baseline, 82.83% (n = 613) of participants had normal cognitive status, 13.51% (n = 100) were classified with mild cognitive impairment (MCI), and 3.64% (n = 27) with probable dementia. The effect of three distinct patterns of poor sleep (difficulties initiating [DIS] or maintaining sleep [DMS], daytime sleepiness [DS] or sleep duration) were considered on a change in cognitive score with adjustments for potential confounders in generalized linear regression models. Cognitive decline was more pronounced in individuals with DMS compared to those with no DMS (β = 1.33, 95% CI = 0.41–2.24, P < 0.001). However, the predictive power of DMS was only significant in individuals with normal cognition and not impaired subjects at baseline. Prolonged sleep duration increased the risk for cognitive decline in cognitively impaired elderly (β = 1.86, 95% CI = 0.15–3.57, P = 0.03). Other sleep characteristics (DIS and DS) were not significantly associated with cognitive decline.
Conclusions: DMS and long sleep duration were associated with cognitive decline in normal and cognitively impaired elderly, respectively. The identification of impaired sleep quality may offer intervention strategies to deter cognitive decline in the elderly with normal cognitive function.
Keywords: elderly, sleep, cognitive decline, dementia
Citation: Johar H, Kawan R, Emeny RT, Ladwig KH. Impaired sleep predicts cognitive decline in old people: findings from the prospective KORA age study. *SLEEP* 2016;39(1):217–226.

Significance
Sleep-related characteristics are associated with an increased risk of cognitive decline. These characteristics are potentially modifiable risk factors that may offer strategies to improve cognitive function. However, prospective studies on the association between sleep-related characteristics and cognitive decline are sparse. No efforts to distinguish between cognitively intact and impaired individuals have been reported. We investigated the association between sleep-related characteristics and cognitive decline in older adults over 3 years of follow up and found that the individuals with normal cognition at baseline were at risk if they experienced difficulties maintaining sleep. This could be an early warning sign of increased risk of cognitive decline and should receive particular attention.

INTRODUCTION

Cognitive decline is a common problem in aging populations and is a major health concern that may confer serious challenges on daily activities of personal life and family functioning.[1] Thus, it is important to identify possible predictors of cognitive decline in order to develop effective preventive measures.

Recently, the sleep-cognition relationship has gained considerable attention in aging studies. As listed in Table 1, impaired sleep patterns under investigations have included prolonged or short sleep duration, excessive daytime sleepiness, snoring, as well as difficulties initiating (DIS) and maintaining sleep (DMS). Previous cross-sectional studies on the relation of sleep characteristics to cognition have predominantly focused on sleep duration and excessive daytime sleepiness, with most findings supporting an association between both self-reported long sleep duration and excessive daytime sleepiness with lower levels of cognitive function.[2–6] However, conflicting evidence was presented in a recent large scale cross-sectional study that emphasized the association of short sleep duration on cognitive decline.[4] In longitudinal studies, problems in initiating and maintaining sleep, excessive daytime sleepiness, and short and prolonged sleep duration were all associated with cognitive decline.[7–15] In contrast, evidence from other longitudinal studies failed to confirm a significant association between cognitive impairment and either sleep difficulties (DIS and DMS),[10,16] long sleep duration, or snoring.[16] Furthermore, several shortcomings of the previous published work includes study samples that are restricted to either male[7,9] or female[13,16] populations. To date, studies which reported significant associations between cognitive decline and problems maintaining sleep in both men and women remain sparse. Furthermore, none of these studies considered the influence of baseline cognitive status on the adverse effect of sleep on cognitive change.

Based on these mixed findings, the evidence for an association of various patterns of poor sleep and cognitive decline is still inconclusive. Despite extensive scientific work in sleep-cognition research in the recent years, there is still an unsatisfying research gap that demands further studies. Therefore, we aimed to investigate whether major patterns of poor sleep (difficulties in initiating sleep [DIS], difficulties in maintaining sleep [DMS] or both DIS and DMS, daytime sleepiness, and sleep duration) were associated with cognitive decline in a population-based sample of older adults (64–94 years) over 3 years of follow-up. Among the various risk factors of cognitive decline, baseline cognitive status has been shown to be one of the most important predictors. Several studies have demonstrated the predictive value of baseline cognitive function for further

Table 1—Prospective, population-based studies investigating sleep characteristics associations with cognitive decline.

References	Settings	n	Men/ Women (%)	Age (range/ mean)	Sleep Characteristics	Sleep Assessment	Cognitive Test	Main Findings	Confounders
CROSS-SECTIONAL STUDIES									
Ramos et al. (2013)	The Northern Manhattan Study (NOMAS)	2,266	39/61	75 ± 9	sleep duration, sleep disordered breathing, daytime sleepiness	Subjective	MMSE	Long sleep duration was associated with worse MMSE performance (or lower cognitive function).	age, sex, race-ethnicity, education, insurance status
Blackwell et al. (2006)	Community dwelling women	2,932	0/100	≥ 65	total sleep time, sleep efficiency, sleep latency, wake after sleep onset, total nap time	Objective	MMSE	Poor sleep was associated with impaired cognitive function in older women.	age, race, depression, education, health status, hypertension, smoking, alcohol use, physical activity
Blackwell et al.(2011)	The MrOS Sleep Study	3,132	100/0	≥ 65	total sleep time, sleep efficiency, wake after sleep onset, poor sleep, excessive daytime sleepiness	Subjective and objective	MMSE	Short sleep duration and excessive daytime sleepiness was not significantly associated with cognitive function.	age, race, BMI, co-morbidities, education, smoking, alcohol use, physical activity, depression
Merlino et al.(2010)	Community dwelling adults	750	39/61	≥ 65	Insomnia, snoring, sleep apneas, restless leg, sleep walking, daytime sleepiness	Subjective	MMSE	Daytime sleepiness was associated with dementia and cognitive decline	age, education, nervous system diseases, drugs
Elwood et al.(2010)	The Caerphilly Cohort Study		100/0	60–74	Insomnia, restless legs, snoring, sleep apnea, daytime sleepiness	Subjective		Sleep disturbance and daytime sleepiness was associated with vascular dementia.	age, social class, smoking, alcohol use, BMI, chest pain, drugs
PROSPECTIVE STUDIES									
Blackwell et al. (2014)	The MrOS Study	2,822	100/0	76 ± 5.3	sleep time, sleep onset, wake episodes	Subjective and objective	MMSE	Reduced sleep efficiency, DIS, DMS, poor sleep quality were associated with cognitive decline in older men.	depressive symptoms, comorbidities, medication use
Cricco et al. (2001)	The EPESE Study	6,444	75/35	> 65	symptoms of insomnia	Subjective	SPMSQ	Chronic insomnia was associated with incident cognitive decline in older men	age, race, education, smoking, alcohol consumption
Foley et al. (2001)	Honolulu Asia Aging Study (HAAS)	2,346	100/0	71–93	daytime sleepiness	Subjective	CASI	Daytime sleepiness was associated with 3-Year incident Dementia and cognitive decline in men.	age, education, hours of sleep, daytime napping, heart diseases
Jelicic et al. (2002)	Maastricht Ageing Study (MAAS)	838	52/48	> 50	sleep problems (falling asleep, waking up too early, disturbed sleep)	Subjective	MMSE	Subjective sleep problems was associated with cognitive decline	age, sex, cognitive function at baseline, education
Tworoger et al. (2006)	The NHS Cohort	1,844	0/100	70–81	sleep duration, difficulty sleeping, snoring	Subjective	TICS	Sleep duration, difficulty sleeping and snoring were not significantly associated with cognitive decline in women	age, education, smoking, physical activity, alcohol consumption, hypertension
Benito-leon et al. (2009)	The NEDICES Study	3,286	42/57	73	sleep duration	Subjective	MMSE	Long sleep duration was associated with risk for dementia	baseline age, educational level, smoking, alcohol consumption
Loerbroks et al.(2009)	The HeIDE Study	4,010	0/100	> 70	sleep duration	Subjective	TICS	Long sleep duration was significantly associated with cognitive impairment	hypertension, stroke, diabetes
Jaussent et al. (2012)	The French Three-City Study	4,894	43/57	> 65	excessive daytime sleepiness, difficulty in maintaining sleep	Subjective	MMSE	Excessive daytime sleepiness was associated with cognitive decline whereas poor sleep quality, DIS and early morning awakening were not	age ,sex, BMI, sleep medicines
Keage et al. (2012)	Cognitive Function and Ageing study	2,041	47/53	> 65	maintenance and onset of sleep	Subjective	MMSE	Napping at baseline, short sleep duration and excessive daytime sleepiness were associated with cognitive decline.	age, sex, BMI, education
Potvin et al. (2012)	ESA Study (Survey on Elder's Health	1,664	30/70	65–96	sleep duration, sleep quality	Subjective	MMSE	In men, short sleep duration and sleep efficiency was associated with cognitive impairment. In women, sleep disturbance and long sleep duration were associated with cognitive decline.	education, anxiety, chronic diseases, cardiovascular conditions
Benito-leon et al. (2013)	The NEDICES Study	2,715	43/57	73	sleep duration	Subjective	MMSE	Long sleep duration was associated with cognitive decline.	baseline age, gender, education, geographical area, depression
Virta et al. (2013)	Older Finnish Twin Cohort	2,336	52/48	> 65	sleep duration, sleep quality	Subjective	TICS	Short sleep duration, poor sleep quality and use of medications were associated with cognitive decline.	age, sex, education, follow up time
Devore et al. (2014)	Prospective Nurses' Health Study Cohort	15,385	0/100	> 70	sleep duration	Subjective	TICS	Long sleep duration was associated with cognitive decline.	age, education, smoking, physical activity, alcohol intake

CASI, cognitive abilities screening Instrument, SPMSQ, Short Portable Mental Status Questionnaire, MMSE, mini-mental status examination, TICS, telephone interview for cognitive status.

decline which provided the rationale for adjusting for baseline values in models of cognitive change in the current study.[17,18] Furthermore, the association between sleep and cognitive function was considered in the presence of potential confounders which have been acknowledged as risk factors of cognitive decline: age, sex, baseline cognitive score, smoking status, alcohol consumption, physical activity, depressive symptoms, hypertension, and somatic comorbidities.[9,10,12,13,15,19–21]

METHODS

Design and Setting and Participants

The data from the present investigation stem from the KORA-Age Study which is a population-based study that aimed to examine the prevalence and determinants of functioning, multi-morbidity and successful aging in men and women aged 64 to 94.[22,23] KORA-Age is a follow-up examination of

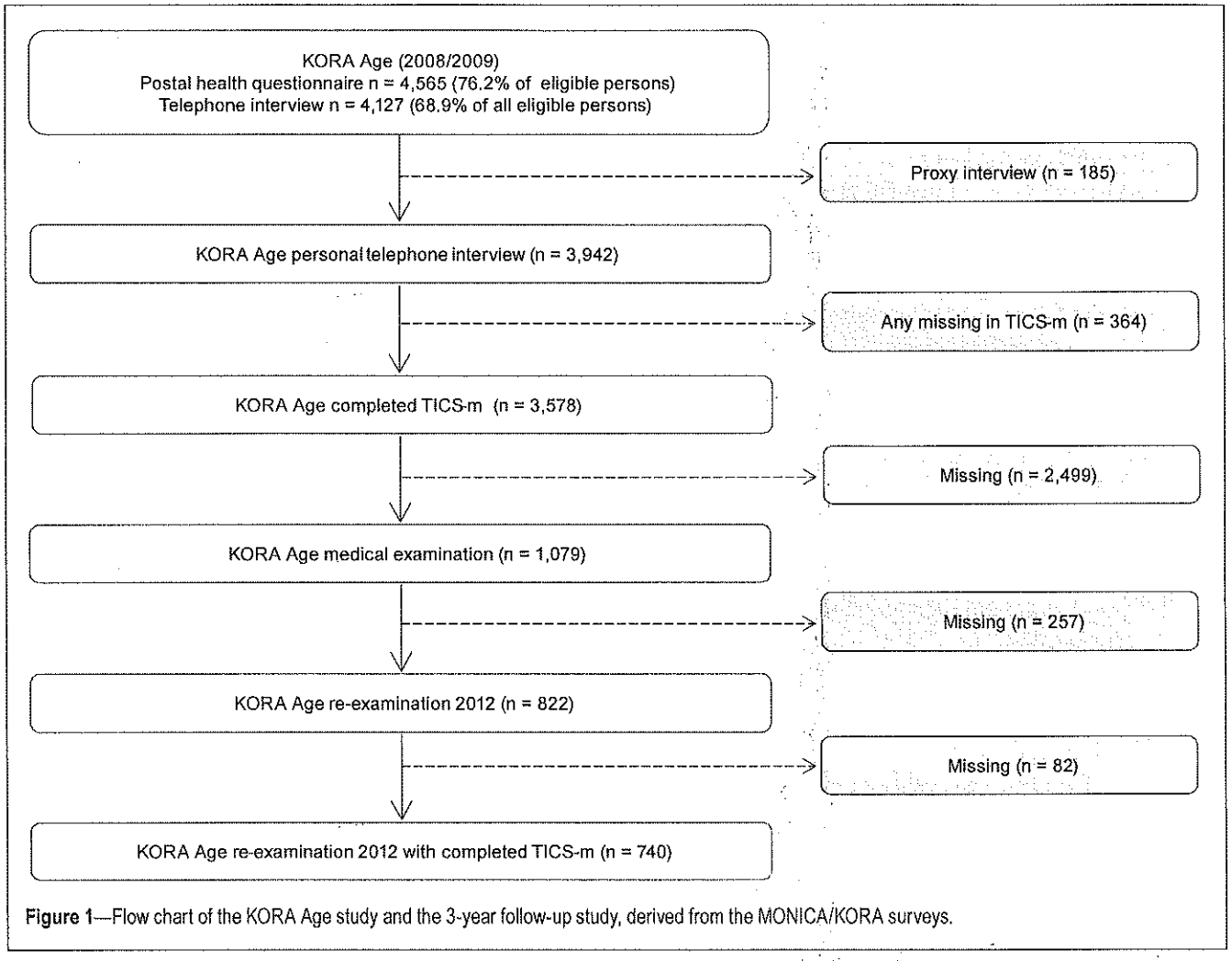

Figure 1—Flow chart of the KORA Age study and the 3-year follow-up study, derived from the MONICA/KORA surveys.

the participants (≥ 64 years) of the previous surveys of the MONICA/KORA (MONItoring of trends and determinants in CArdiovascular disease/Cooperative Research in the Region Augsburg) Study, which has collected data since 1984. Participants live in the city of Augsburg or its two surrounding counties in southern Germany.

In 2009, a clinical examination was performed in 1,079 participants in a gender- and age-stratified random sample of the MONICA cohort. In 2012, a re-examination was performed in 822 persons (84.3% of all eligible persons). Both baseline and follow-up surveys included a telephone and personal interview and a physical examination which assessed somatic and mental health related multi-morbidity. A total of 740 study participants (men = 49 %, n = 366, women 51%, n = 374, mean age = 75 years (range 64–94 years) with complete data on baseline covariates and cognitive status as well as cognitive status at follow-up were included in the study (Figure 1). In a drop-out analysis of the excluded participants, there were no significant age and sex differences observed (data not shown).

Quality control in the KORA Age study was assured by extensive operation manuals, training and certification of interview and examination personnel, a pilot study well in advance of the main study, and an external quality assurance audit. Internal quality control was performed to regularly monitor all relevant aspects of data acquisition. Written informed consent was obtained from each study participant and the study was approved by the ethics committee of the Bavarian Medical Association.

Endpoint: Cognitive Status

Cognitive status was measured by using the German language version of the Telephone Interview for Cognitive Status modified (TICS-m) which includes adjustment for years of education.[24] The TICS-m in German was administered according to published procedures.[24] The TICS-m includes 2 additional tasks: immediate and delayed verbal recall. The TICS-m contains the following items: (i) name, date, age and phone number (9 points); (ii) counting backward (2 points); (iii) first, a 10-word list learning exercise and then a delayed recall of that word list (20 points); (iv) serial sevens (5 points); (v) responsive naming (4 points); (vi) repetition (2 points); (vii) current German President and Chancellor (4 points); (viii) finger tapping (2 points); and (ix) word opposites (2 points). The instrument includes 4 cognitive domains: orientation; memory (registration, recent memory and delayed recall); attention/calculation; and language (semantic memory, comprehension and repetition). The TICS-m was administered according to

published procedures and followed a standardized script.[25] The TICS-m score ranges from of 0 to 50.[24] Normal cognitive function was defined as having a TICS-m score ≥ 31; mild cognitive impairment (MCI) was between 27–31; and a score ≤ 27 indicated probable dementia.[26]

Exposure: Sleep Characteristics

Sleep related characteristics were evaluated in the interview using the Uppsala Sleep Inventory (USI).[27] Two separate 3-category interview questions were asked concerning an individual's difficulties initiating sleep ("Do you have trouble falling asleep?") and difficulties maintaining sleep ("Do you wake up during the night?"). Individuals were considered to have difficulties if they answered "often" or "sometimes" and were compared to participants who answered "almost never" in response to the questions. Participants were grouped into those with difficulties initiating sleep (DIS), those with difficulties maintaining sleep (DMS), or those with difficulties in initiating or maintaining sleep (both DIS and DMS). Daytime sleepiness was assessed by the question, "Do you feel tired or exhausted during the day due to the sleeping problems in the night (often, sometimes, or almost never)." Sleep duration was assessed with the question "How many hours a day do you usually sleep? Please also think of nap habits." Participants were invited to answer in integer hours. Extreme sleep duration categories (short: ≤ 5 h, long: ≥ 9 h) were assessed based on the categories described in previous studies.[16,28]

Covariates Assessment

Sociodemographic Variables

Sociodemographic variables included age and sex.

Behavioral and Cognitive Risk Factors

Baseline information on sociodemographic variables, smoking habits, physical activity level, and alcohol consumption were gathered by trained medical staff during a standardized interview. Study participants provided information about whether they had ever smoked cigarettes regularly (never smoked, current smoker). Alcohol consumption was rated as "daily or almost daily," "once or several times a week," "no or very rarely alcohol." Each participant was questioned regarding his or her leisure time physical activity during the winter and summer. The questionnaire consisted of a 4-level graded scale for leisure time physical activity during summer and winter time (0, < 1, 1 to 2, and > 2 h/week). The winter and summer responses were combined to create one variable of leisure time physical activity level. Participants were classified as active if they regularly participated in sports ≥ 1 h/week in either season. Actual hypertension was defined as blood pressure values ≥ 140/90 mm Hg and/or use of antihypertensive medication. Multi-morbidity was defined as the co-occurrence of > 2 disease conditions based on the Charlson Comorbidity Index.[29]

Psychological Variables

Depressive symptoms were measured by the 15-item German version of the Geriatric Depression scale ([GDS-15] cutoff point > 5 for mild or moderate depression).[30]

Statistical Analysis

Baseline Descriptive Analysis

Study population characteristics were stratified by a cognitive status at baseline (normal versus cognitively impaired (probable dementia and MCI). Participants were classified as having no sleep problems (n = 159), having DIS (n = 52), DMS (n = 211) or both DIS and DMS (n = 318). Cognitive change (TICS-m1-TICS-m2) was defined as the difference between TICS-m score value at baseline and follow-up. Participants who had improved or declined in cognitive score at follow-up were based on a one point change per year (± 3). A negative value represents an improvement in cognitive function and a positive value represents cognitive decline. Bivariate associations of baseline variables with cognitive status were tested using the Kruskal-Wallis test for continuous variables with more than 2 groups. The χ^2 test was used to examine the associations between categorical variables.

Analytic Statistics

Linear regression was carried out to analyze the association between various patterns of poor sleep (main exposure) and cognitive change (continuous outcome). Three distinct patterns of poor sleep (sleep difficulties at night [DIS, DMS, and both], daytime sleepiness, and sleep duration) and the total sum score of all sleep domains were considered in separate models with 2 approaches. The association of poor sleep patterns and cognitive decline was considered in one "crude model" adjusted only for age and sex as well as in a "full model" adjusted additionally for the presence of known potential baseline confounders (age, sex, baseline cognitive score, smoking status, alcohol consumption, physical activity, depressive symptoms, hypertension, and somatic comorbidities[9,10,12,13,15,19–21]). Crude and fully adjusted models were calculated by using the GLM (generalized linear models) procedures. We then examined the interaction of the effect of any of the 3 patterns of poor sleep with baseline cognitive status on cognitive decline, by including the product of both variables in the fully adjusted model. Results are presented as parameter estimates of unstandardized (β) and 95% confidence intervals (CI). All statistical analyses were run in SAS version 9.2 (SAS Institute Inc., Cary, NC). The significance level was set at 0.05. The analysis and description followed the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guidelines for observational studies.[31]

RESULTS

Descriptive Analyses

The baseline study population consisted of 740 subjects including 49% (n = 366) men and 51% (n = 374) women. The median age of participants at baseline was 75 years (SD ± 6.18) ranging from 64–94 years. Among all participants, 82.83% (n = 613) had normal cognitive status, 13.51% (n = 100) showed indications of mild cognitive impairment (MCI), and 3.64% (n = 27) of participants had scores indicating probable dementia at baseline. Table 2 summarizes the sociodemographic characteristics and mental health related

Table 2—Population characteristics stratified by baseline cognitive status (n = 740).

Variables	Baseline Cognitive Status		P value
	Normal (n = 613)	Cognitively Impaired (n = 127)	
Age, mean ± SD (74.59 ± 6.18)	74.16 ± 6.16	76.77 ± 5.78	0.15
TICS-m score, mean (95% CI)	37.4 (37.1 to 37.7)	28.7 (28.3 to 29.1)	< 0.0001
Cognitive change score, mean (95% CI)	−1.28 (−2.10 to −0.45)	0.76 (0.42 to 1.10)	< 0.0001
Male	286 (46.66)	80 (62.99)	
Female	327 (53.34)	47 (37.01)	
Alcohol consumption			0.33
Daily or almost daily	175 (28.55)	45 (35.43)	
Once or Several times a week	176 (28.71)	30 (23.62)	
Smoking status			0.27
Current smoker	254 (41.44)	46 (36.22)	
Never smoked	359 (58.56)	81 (63.78)	
Physically inactive	234 (38.17)	64 (50.39)	0.01
Hypertension	444 (72.43)	94 (74.02)	0.71
Multi-morbidities			0.11
No somatic disease condition	69 (11.26)	8 (6.30)	
One condition	173 (28.22)	31 (24.41)	
≥ 2 conditions	371 (60.52)	88 (69.29)	
Sleep problems			0.45
Only DIS	46 (7.50)	6 (4.72)	
Only DMS	179 (29.20)	32 (25.20)	
Both DIS and DMS	260 (42.41)	58 (45.67)	
Daytime sleepiness			0.52
Often/sometimes	208 (33.93)	37 (29.36)	
Almost never	404 (66.01)	90 (70.87)	
Sleep duration, mean ± SD (7.67 ± 1.40)	7.62 ± 1.36	7.94 ± 1.56	0.98
Short sleep hours	39 (6.4)	9 (7.1)	0.60
Long sleep hours	147 (24.0)	43 (33.9)	0.06
Depressive symptoms	6 (0.98)	2 (1.57)	0.55

Values are presented as n (%), mean ± SD, or mean (95% CI). For continuous variables P values are derived by Kruskal-Wallis tests. For categorical variables P values are derived by χ^2 tests. SD, standard deviation; CI, confidence interval; DIS, difficulties in initiating sleep; DMS, difficulties in maintaining sleep.

variables stratified by cognitive status at baseline. Compared to cognitively impaired individuals, subjects with normal cognition were more likely to be female and to be physically active. However, at baseline, no significant differences between the 2 groups were observed in terms of age, lifestyle and cardiovascular risk factors (smoking status, alcohol intake, and hypertension), sleep characteristics (difficulties in maintaining sleep [DMS], difficulties in initiating sleep [DIS], daytime sleepiness [DS], and sleep duration), and depressive symptoms.

As displayed in Table 2, in all 613 study participants with normal cognitive function at baseline, a total of 21% (n = 128) were individuals without sleep problems, whereas a minority (8%, n = 46) reported having DIS, 29% (n = 179) reported DMS, and 42% (n = 260) had both DIS and DMS. Among 127 cognitively impaired subjects, 24% (n = 31) reported no sleep problems, whereas 5% (n = 6) reported having DIS, 25% (n = 32) had DMS, and 46% (n = 58) had both DIS and DMS.

Prospective Analysis

Cognitive Trajectories of the Study Participants

In the total population, the mean (± SD) TICS-m score at baseline and at 3-year follow up was quite similar (baseline = 35.9 ± 4.8 and follow-up = 35.5 ± 5.5). Almost half of the population (43%, n = 317) remained stable in their cognitive status. In 32% of participants (n = 236), a decline in cognitive score was observed, while in another 25% of participants (n = 189), > 3-point improvement in their TICS-m score was observed. Thus explaining the overall stability of TICS-m score in the population over 3 years.

In subjects with normal cognitive function (n = 615), 35% (n = 214) showed a decline after 3-year follow-up in cognitive score, 22% (n = 134) improved, and 43% (n = 267) remained stable in their cognitive score. From baseline to follow-up, the decline in cognitive score (mean, 95% CI) of participants with normal cognition was −1.28 (−2.10 to −0.45). However, the mean of change in score of the TICS-m

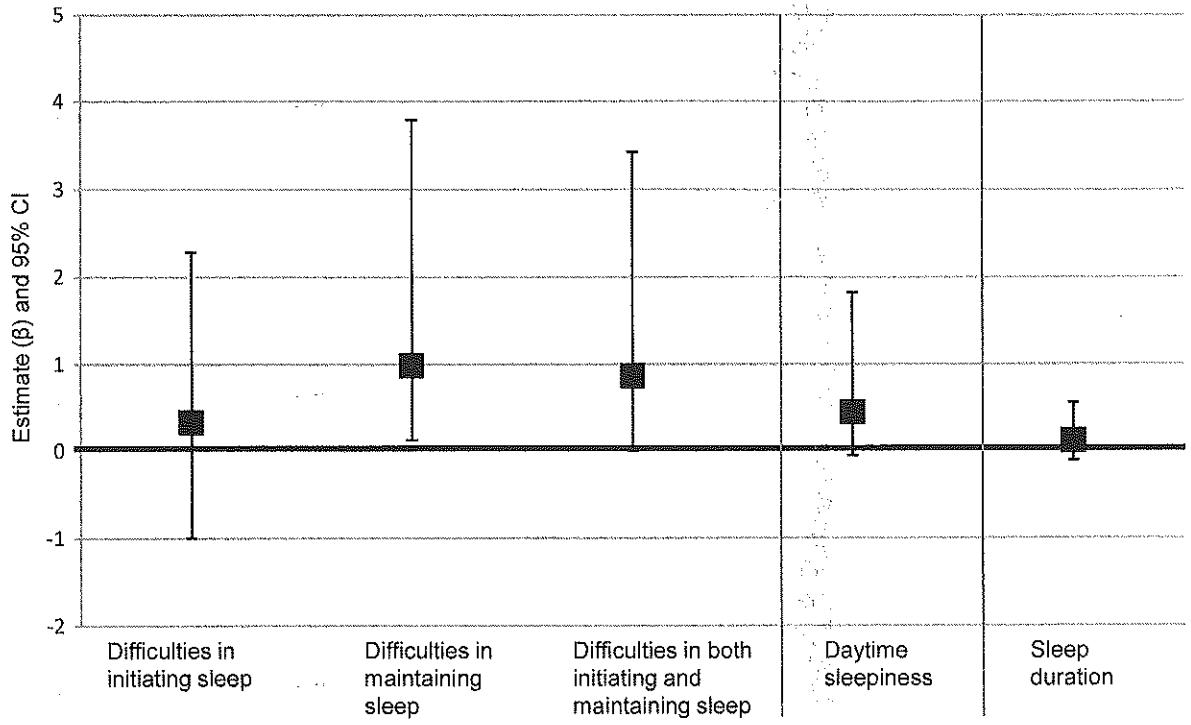

Figure 2—The effect (β-estimate and 95% confidence interval (CI)) of patterns of poor sleep on cognitive decline (n = 740). (Exposure of patterns of poor sleep on cognitive decline were assessed in 3 separate models; model 1: difficulties in initiating sleep, difficulties in maintaining sleep and both; model 2: daytime sleepiness; model 3: sleep duration). The effect of difficulties initiating, or maintaining sleep, or both, were referenced to no sleep difficulties. The effect of daytime sleepiness (often and sometimes) was referenced to almost never daytime sleepiness.

score for individuals with normal cognition remained within the normal range.

Out of 127 cognitively impaired participants, 17% (n = 22) showed a decline in cognitive score while 43% (n = 55) improved in their cognition and 39% (n = 50) remained stable. The mean of change in TICS-m score was 0.76 (0.42 to 1.10). Although the mean of change in score showed an improvement, the change in score remained within the cutoff for cognitive impairment.

Associations between Patterns of Poor Sleep and Cognitive Decline over Three Years

Participants who reported DMS at baseline (n = 211) were more likely to have a decline in their cognitive score after 3 years compared to those who reported no DMS at baseline (β = 0.85, 95% CI = 0.001 to 1.70, P value (P) = 0.049) (crude model adjusted for age, sex, and baseline cognitive score). The association between DMS and cognitive decline was slightly increased when models were additionally adjusted for physical activity, hypertension, smoking status, alcohol consumption, co-morbidities and depressive symptoms (full model, β = 0.88, 95% CI = 0.03 to 1.74, P = 0.04) as depicted in Figure 2.

However, difficulties in initiating sleep (DIS) (n = 52) or combined difficulties in maintaining and initiating sleep (both DIS and DMS) (n = 318) were not significantly associated with cognitive decline (DIS: β = 0.29, 95% CI = −1.01 to 1.59, P = 0.66, both DIS and DMS: β = 0.63, 95% CI = −0.19 to 1.44, P = 0.13), although the direction of association was similar. No other sleep characteristics (DIS, DIS and DMS, DS, or the continuous sleep duration variable) achieved statistically discernable effects. Daytime sleepiness and sleep duration were also assessed as main exposures in crude and full models (Figure 2). In a sensitivity analysis, extreme sleep duration categories (very short or very long sleep hours) were not significantly associated with cognitive decline in the total sample (data not shown).

Stratified Analysis: Associations between Sleep Disturbances and Cognitive Decline Stratified by Cognitive Status at Baseline

Based on the known confounding role of baseline cognitive status as well the significant interaction observed between cognitive decline and sleep disturbances (DMS*baseline cognitive status: P = 0.04), we further stratified our regression analyses according to normal or impaired cognitive status at baseline. DMS was significantly associated with cognitive decline only in participants with normal cognitive status and not in cognitively impaired individuals. In a fully adjusted model, cognitive decline was 1.3-points larger in cognitively normal individuals with DMS compared to individuals with no sleep disturbances (β = 1.26, 95% CI = 0.35 to 2.18, P = 0.007) whereas the effect in cognitively impaired participants with a 0.06-point change in TICS-m score, was not statistically significant in the model (β = 0.06, 95% CI = −2.23 to 2.35, P = 0.96) (Table 3).

Table 3—The effect of sleep-related characteristics (sleep disturbances, daytime sleepiness, and sleep duration) on cognitive decline stratified by baseline cognitive status (n = 740).

	Normal (n = 613)		Cognitively Impaired (n = 127)	
Sleep Characteristics (n)	**β (95% CI)**	**P value**	**β (95% CI)**	**P value**
No sleep problems	0	0	0	0
Only DIS (46/6)	0.58 (−0.78 to 1.94)	0.40	−1.40 (−5.39 to 2.58)	0.49
Only DMS (179/32)	1.26 (0.35 to 2.18)	0.007	0.06 (−2.23 to 2.35)	0.96
Both DIS and DMS (260/58)	0.77 (−0.11 to 1.66)	0.09	0.23 (−1.98 to 2.45)	0.83
No daytime sleepiness, DS	0	0	0	0
Often (64/10)	−1.05 (−2.22 to 0.11)	0.07	−1.82 (−5.29 to 1.65)	0.31
Sometimes (144/27)	0.11 (−0.67 to 0.89)	0.77	0.65 (−2.65 to 1.34)	0.52
Sleep duration, hours	0.006 (−0.23 to 0.24)	0.96	0.45 (−0.05 to 0.96)	0.08
6–8 h (38/9)	0	0	0	0
Short, ≤ 5 h (429/75)	0.66 (−0.68 to 2.01)	0.99	−0.14 (−3.38 to 3.09)	0.93
Long, ≥ 9 h (146/43)	0.37 (−0.38 to 1.13)	0.12	1.86 (0.15 to 3.57)	0.03
Sum of sleep score				
0 (78/19)	0	0	0	0
1 (164/28)	1.19 (0.11 to 2.27)	0.03	2.89 (0.21 to 5.58)	0.03
2 (179/38)	1.14 (0.07 to 2.22)	0.04	1.47 (−1.06 to 3.99)	0.25
3 (155/29)	1.16 (0.03 to 2.30)	0.04	1.06 (−1.73 to 3.84)	0.46
4 (39/13)	0.95 (−0.67 to 2.57)	0.25	3.36 (−0.23 to 6.95)	0.07

Adjusted for age, sex, baseline cognitive score, physical activity, hypertension, smoking status, alcohol consumption, comorbidities, and depressive symptoms. DIS, difficulties in initiating sleep; DMS, difficulties in maintaining sleep; DS, daytime sleepiness.

The impact of DMS was assessed in a sensitivity analysis as a single sleep complaint, adjusted additionally for DIS and other important confounders. As expected, DMS significantly increased the risk for cognitive decline in individuals with normal cognition (β = 0.89, 95% CI = 0.15 to 1.64, P = 0.02) while DIS did not (−0.23, −0.93 to 0.46, 0.52). Also no significantly discernable association was observed between either DMS or DIS and cognitive impairment in the cognitively impaired subjects (DMS: 0.47, −1.51 to 2.46, 0.64, DIS: −0.15, −2.04 to 1.74, 0.88). However, the accumulation of sleep complaints increased the risk for cognitive decline, as displayed in Table 3 in individuals with normal cognition. Here, a suggestive dose-response relationship was observed (1: β = 1.19, 95% CI = 0.11 to 2.27, P = 0.03, 2: 1.14, 0.07 to 2.22, 0.04, 3: 1.16, 0.03 to 2.30, 0.04). On the other hand, as also displayed in Table 3, prolonged sleep duration increased the risk for cognitive decline only in cognitively impaired participants (1.86, 0.15 to 3.57, 0.03) and not in subjects with normal cognition (0.37, −0.38 to 1.13, 0.12). No significant association between short sleep duration and cognitive decline was observed.

DISCUSSION

Insomnia comprises an impaired sleep pattern with difficulties in initiating sleep (DIS), maintaining sleep (DMS) or non-restorative sleep accompanies by significantly impaired daytime functioning.[32] Sleep problems are frequently reported in the elderly[33] and this is confirmed in the present study with only approximately 25% of participants reporting no sleep problems. To the best of our knowledge, here we present the first study in an older, community-based population that reports a significant association between DMS and cognitive decline in men and women with normal cognitive status over a 3 year of follow-up.

Even the adjustment for confounding risk factors (physical activity, hypertension, smoking status, alcohol intake and multi-morbidity) did not alter the strength nor the significance of the prospective association between DMS and cognitive decline in these subjects. This also holds true for depression, which is an established risk factor for cognitive decline[8] and is a key pattern of impaired sleep,[34] making it unlikely that the relationship between sleep and cognitive decline could be independent of depressive symptoms. However, the association between sleep disturbances and cognitive decline remained significant even after further adjustment for depressive symptoms. Hence, DMS appears to be a robust and independent predictor of cognitive decline particularly in subjects with normal cognitive function.

A positive association of DMS on cognitive decline has already been demonstrated in a few longitudinal studies, however, this evidence is mostly limited by sex-specific samples. The population-based MrOS study of 2,822 elderly men,[7] the male population in the Established Populations for Epidemiologic Studies of the Elderly (EPESE) study (n = 6,444, age 60 years and above),[8] and the elderly female population of the Survey on Elders' Health (ESA) study with 1,664 subjects (age range of 65 to 96 years)[28] showed an association between DMS and cognitive decline. In contrast, no association was observed between sleep disturbances and incident cognitive impairment in a female cohort of the Nurses' Health Study cohort (n = 1,844, age 70 to 81 years).[16] Thus, the present investigation confirms and extends these previous findings for both sexes in which DMS is associated with cognitive decline.

Furthermore, the previous studies of the EPESE study, the Maastricht Ageing Study (MAAS) and the Nurses' Health Study cohort, have combined DIS and DMS as part of insomnia-like features or subjective sleep complaints and did not assess DIS and DMS separately.[8,16,19] In this present study, we have shown that only DMS, and not DIS, nor both DIS and DMS, was associated with cognitive decline. DMS was still the only significant predictor of cognitive decline, even when assessed as a single sleep complaint in a model adjusted for DIS.

DMS has no measureable effect on cognitive decline in participants who were already compromised by lower cognitive functioning at baseline. No other study has comprehensively assessed the modifying role of the baseline cognitive status in the association of DMS and cognitive decline. The null effect in the cognitively impaired participants may be due to a "floor effect" resulting from little change in TICS-m score at baseline to follow-up because cognitively impaired subjects had already reached a lower cognitive function whereas individuals with normal cognition had a larger room for improvement/decline due to a wider range of TICS-m score in the normal cognitive status category. Secondly, we cannot exclude the possibility that cognitively impaired participants were not able to correctly answer the TICS-m questions.

Difficulties in initiating sleep (DIS) and daytime sleepiness (DS) were not associated with diminished cognition. As DIS has been associated in earlier studies with cognitive decline, it is most likely that our nonsignificant finding is due to the low number of subjects who reported DIS. The same holds true for daytime sleepiness (DS) which was recently demonstrated to be independently associated with cognitive decline in men and women of the French Three-City Study (n = 4,894 participants).[10] Additionally, in the Honolulu-Asia Aging study (n = 2,346) of men, daytime sleepiness (DS) was highlighted to be the only measurement that was reliably associated with cognitive decline over a 3-year follow-up.[9] On the contrary, in a British study of men and women (n = 2,041, aged 65 years and older), daytime napping was associated with lower risk of cognitive decline.[11] The present investigation contributes novel data to conflicting evidence published to date. A meta-analytic research strategy which could clarify the impact of DS in cognitive decline is urgently needed.

The third sleep feature assessed in this present investigation was sleep duration (in hours) that was neither associated with TICS-m score nor with cognitive decline; a result which is supported by a previous study.[16] In study participants with probable cognitive impairment at baseline, individuals who reported extremely long sleeping duration (≥ 9 h) had a significantly increased risk of continued cognitive decline. This was not observed with short sleep duration (≤ 5 h). However, it should be mentioned that both short[11] and prolonged sleep hours[12,13,15,20,28] have been shown to be associated with cognitive decline in other prospective analyses. Interestingly, long sleeping, as assessed by self-report and not from objective actigraph measurement, was significantly associated with cognitive decline in a cross-sectional male population study (n = 3,132, age 76.4 ± 5.6 years).[4] Thus, the current finding highlights the deleterious effect of prolonged sleep duration in cognitively impaired elderly men and women.

Potential Mechanisms

The present study was not designed to elucidate the psychobiological mechanism to explain the link between DMS and cognitive decline. However, insomnia is a sleep disorder associated with both cognitive-emotional and physiological hyperarousal. Dysregulated hypothalamic-pituitary-adrenal (HPA) axis[35] accompanied by hypersecretion of cortisol levels[36] and proinflammatory cytokines[37] were associated with increased risk for cognitive decline. Chronic exposure to cortisol[38,39] and blunted diurnal cortisol pattern[39] as well as central cholinergic dysfunction[40] with advancing age, may contribute to neurotoxicity effects on the hippocampus, which can affect memory performance and lead to cognitive impairment. It has been shown that the sleep maintenance zone is important for cognitive function[41] which occurs at the peak of REM when the body temperature is lowest.[42] Disruption of REM sleep has long been known to be associated with cognitive decline and a recent population-based study further identified specific stages within REM to be associated with cognitive decline in older men.[43] Our current analyses extend these findings in both sexes with evidence that DMS may be disrupting this essential phase of sleep that leads to memory failure. Future studies are warranted to assess disrupted sleep patterns with diurnal cortisol patterns to complete the link between HPA axis dysregulation, disrupted sleep patterns and cognitive decline.

Besides the detrimental effects of DMS on cognitive decline in elderly individuals with normal cognition, the findings that prolonged sleep hours have a negative impact on cognition appears somewhat counterintuitive. However, the fact that this was only observed in cognitively impaired participants may reflect a clinical symptom of deterioration with old age. It is not unlikely that this finding reflects a syndrome of vital exhaustion and general decline in somatic abilities and thus could also be a sign of a disease condition such as depression, frailty, or neurological disorders.

Study Strengths and Limitations

The study has several strengths and limitations. Among the strengths of the study is the extensive assessment of health risk factors in a large sample of elderly participants, enabling us to perform a comprehensive adjustment for potential confounders. The current study also has the advantage of using the TICS-m measurement that is sensitive for detecting early cognitive impairment and useful in large study settings[24] with a good test-retest reliability.[44] However, one needs to acknowledge that the TICS-m score is a screening instrument which does not substitute for a clinical diagnostic procedure but has significant probability to distinguish between normal and impaired cognition. The distribution of the TICS-m has been shown to have a more symmetric and normal-shaped distribution than the Mini-Mental State Examination (MMSE), suggesting that TICS-m is less subject to the ceiling effects.[24] Furthermore, both cognitively healthy and cognitively impaired individuals were phenotyped at baseline. The study participants were healthy enough to conduct a telephone interview and highest quality assurance was incorporated into the study to assure that each participant was independently answering each question.

A potential limitation of this study was the relatively short follow-up period of 3 years, which may have been too short to capture discrete levels of cognitive decline. Nonetheless, 3 years in old age may contribute to substantial changes in general health. Another limitation of this study was the assessment of sleep problems without a fixed time-frame and by self-report. However, only one prospective study assessed both objective and subjective sleep measurements and found no significant difference between both measurements.[7] Furthermore, we did not assess sleep apnea, which may be associated with limited oxygen supply that could have consequences on cognitive functioning.

CONCLUSION

This study presents evidence for the prospective association between longer nighttime wakefulness and cognitive decline over 3 years of follow-up even after adjustment for important confounders. In particular, individuals with normal cognition at baseline were at risk if they experienced difficulties maintaining sleep. These new findings may contribute to the development of appropriate preventive approaches in the identification of impaired sleep quality to avoid cognitive decline in elderly individuals with normal cognitive function. DMS in older adults could be an early warning sign of increased risk of cognitive decline and should receive particular attention from clinicians. Thus, it is important to include sleep quality assessment in health screening for older people. Identification of risk factors, combined with early diagnosis and intervention, is critically important to prevent individuals from cognitive decline that leads on a trajectory toward dementia. In this regard, disrupted sleep may be particularly detrimental for optimal maintenance of cognitive function. Thus, it is important to preserve sleep quality, particularly in the sleep maintenance zone.

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ACKNOWLEDGMENTS

Author contributions: Drs. Emeny and Ladwig designed the current analysis and proofread the manuscript. Drs. Emeny and Ladwig and Ms. Johar proofread the manuscript. Dr. Emeny and Ms. Johar advised on statistical analysis. Ms. Johar and Ms. Kawan managed the literature searches, statistical analysis and wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication December, 2014
Submitted in final revised form July, 2015
Accepted for publication July, 2015
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DISCLOSURE STATEMENT

This was not an industry supported study. The KORA research platform (KORA, Cooperative Research in the Region of Augsburg) was initiated and financed by the Helmholtz Zentrum München - German Research Center for Environmental Health, which is funded by the German Federal Ministry of Education and Research and by the State of Bavaria. The KORA-Age project was financed by the German Federal Ministry of Education and Research (BMBF FKZ 01ET0713) as part of the "Health in old age" program. The authors have indicated no financial conflicts of interest. The work was performed at Institute of Epidemiology II, Helmholtz Zentrum München, German Research Centre for Environmental Health, Ingolstädter Landstr. 1, 85764 Neuherberg, Germany.