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CLINICAL INVESTIGATION

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Associations of sleep timing and time in bed with dementia and cognitive decline among Chinese older adults: A cohort study

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Abstract

Background: The longitudinal associations of sleep timing and time in bed (TIB) with dementia and cognitive decline in older adults are unclear.

Methods: This population-based cohort study used data from 1982 participants who were aged ≥60 years, free of dementia, and living in rural communities in western Shandong, China. At the baseline (2014) and follow-up (2018) examinations, sleep parameters were assessed using standard questionnaires. Cognitive function was measured using the Mini-Mental State Examination (MMSE). Dementia was diagnosed following the DSM-IV criteria, and the NIA-AA criteria for Alzheimer disease (AD). Data were analyzed using restricted cubic splines, Cox proportional-hazards models, and general linear models.

Results: During the mean follow-up of 3.7 years, dementia was diagnosed in 97 participants (68 with AD). Restricted cubic spline curves showed J-shaped associations of sleep duration, TIB, and rise time with dementia risk, and a reverse J-shaped association with mid-sleep time. When sleep parameters were categorized into tertiles, the multivariable-adjusted hazard ratio (HR) of incident dementia was 1.69 (95%CI 1.01–2.83) for baseline sleep duration >8 hours (vs. 7–8 h), 2.17 (1.22–3.87) for bedtime before 9 p.m. (vs. 10 p.m. or later), and 2.00 (1.23–3.24) for mid-sleep time before 1 a.m. (vs. 1–1.5 a.m.). Early bedtime

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and mid-sleep time were significantly associated with incident AD (HR range: 2.25–2.51; $p < 0.05$). Among individuals who were free of dementia at follow-up, baseline long TIB, early bedtime and mid-sleep time, early and late rise time, and prolonged TIB and advanced bedtime and mid-sleep time from baseline to follow-up were associated with a greater decline in MMSE score ($p < 0.05$). These associations with cognitive decline were statistically evident mainly among men or participants who were aged 60–74 years.

Conclusions: Long TIB and early sleep timing are associated with an increased risk of dementia, and the associations with greater cognitive decline are evident only among older people aged 60–74 years and men.

KEYWORDS

Alzheimer disease, cognitive function, dementia, population-based cohort study, sleep

Key points

- Long time in bed and early sleep timing are associated with dementia, Alzheimer disease, and faster cognitive decline in rural older adults.
- The associations of sleep problems with greater cognitive decline are evident only among older people aged 60–74 years and men.

Why does this paper matter?

This cohort study showed that sleep problems such as long time in bed and early sleep timing may be risk factors of dementia and cognitive decline in rural-dwelling older adults. This suggests that cognitive function should be monitored in older adults who report prolonged time in bed and advanced sleep timing, especially in older individuals aged 60–74 years and men.

INTRODUCTION

China has the largest dementia population in the world, affecting ~5% of Chinese older adults.[1] Owing to lack of a curative therapy, identifying modifiable risk factors for dementia has become crucial for preventive interventions. Sleep is a complex physiological process of the human body. As people age, the sleep quantity, quality, and circadian rhythm change, characterized by decreased sleep duration and sleep efficiency, poor sleep quality, advanced sleep timing (i.e., bedtime, rise time, and mid-sleep time), and being more prone to excessive daytime sleepiness (EDS).[2] Several population-based studies have linked a range of sleep characteristics with cognitive disorders in older adults.[3–6] A meta-analysis suggested that extreme sleep duration, sleep fragmentation, and EDS were associated with cognitive decline or dementia.[7] However, the association of time in bed (TIB), a composite indicator of sleep duration, latency, and fragmentation, with dementia is poorly understood.[7] In addition, sleep timing, a behavior marker of circadian rhythms,[8] has been associated with hypertension and diabetes.[9,10] However, the longitudinal association of sleep timing with dementia and cognitive decline in older adults has been rarely explored. Furthermore, most cohort studies of sleep and dementia have been conducted among almost exclusively Caucasian populations in North America and Europe,[7,11] whereas the associations of sleep characteristics with dementia among rural older adults are not well-characterized. This is important because compared to western populations and urban residents, rural older adults in China usually go to bed earlier, rise earlier, have poorer sleep,[12,13] and are more susceptible to dementia,[1,14] partly due to differences in socioeconomic status, culture, education, and lifestyles.

In addition, sleep problems and cognitive aging phenotypes are known to be associated with demographics (age, sex, and education).[1,15] Furthermore, apolipoprotein E (*APOE*) ε4 allele, a well-established genetic risk factor

for dementia,[14] has been associated with shorter sleep duration.[16] However, whether the associations of sleep problems with cognitive phenotypes vary by demographics and *APOE* genotype remains unclear.

Therefore, in this population-based cohort study of rural-dwelling Chinese older adults, we sought to examine the associations of self-reported sleep characteristics (e.g., TIB, sleep timing, sleep duration, sleep quality, and EDS) with incident dementia, Alzheimer disease (AD), and cognitive decline, while taking into account their potential interactions with demographic features and *APOE* genotype.

METHODS

Study design and participants

This population-based cohort study included participants in the Shandong Yanggu Study of Aging and Dementia (SYS-AD) that targeted rural older residents in Yanlou Town, Yanggu County, western Shandong Province, as previously reported.[17] Briefly, in August–December 2014, 3274 participants (age ≥60 years) underwent face-to-face interviews, clinical examinations, and laboratory tests. Survivors of the SYS-AD baseline participants were invited for follow-up examination that was conducted in March–September 2018, as part of the baseline assessments of the Multimodal Interventions to Delay Dementia and Disability in Rural China (MIND-China).[18,19] We used three analytical samples to address our study aims, that is, we explored the associations of baseline sleep parameters with incident dementia (analytical sample 1, $n = 1982$) and cognitive decline (analytical sample 2, $n = 1845$) as well as the associations of changes in sleep parameters from baseline to follow-up with cognitive decline (analytical sample 3, $n = 1780$). Figure S1 and Text S1 provide the flowchart and detailed description of study participants in different analytical samples.

Research has been conducted in accordance with the Declaration of Helsinki. The SYS-AD Study and the MIND-China Study were approved by the Ethics Committee of Shandong Provincial Hospital in Jinan, Shandong. Written informed consents were obtained from all participants, or if the participants were not able to give the consent due to severe cognitive impairment, from the informants.

Data collection and assessments

At baseline, data were collected by trained staff via face-to-face interviews, clinical examinations, neuropsychological testing, and laboratory tests. Notably, data on depressive symptoms were not collected at baseline in 2014, instead, the 15-item Geriatric Depression Scale (GDS-15) was administered at the follow-up examination in 2018.[18] The presence of depressive symptoms was defined as a GDS-15 score ≥5. Text S1 provided detailed descriptions of data collection.

Sleep characteristics

We assessed sleep characteristics at both baseline and follow-up examinations via in-person interviews using the validated Chinese version of the Pittsburgh Sleep Quality Index (PSQI)[20] and Epworth Sleepiness Scale (ESS).[21] Poor sleep quality is defined as a total PSQI score >5.[22] EDS was defined as the total ESS score > 10.[23] Text S1 provided detailed descriptions.

Because there were no standard approaches in the literature for categorizing sleep duration, TIB, and sleep timing,[5,7,24–27] we divided participants according to tertiles of these sleep parameters. We used restricted cubic splines to explore their potential non-linear associations with incident dementia and AD. If the restricted cubic spline curve showed U- or J-shaped associations with incident dementia, we used the medium tertile of sleep parameters as reference group. Otherwise, we considered upper or lower tertile as reference group. Thus, based on tertiles, we categorized nocturnal sleep duration (hours) into short (<7), normal (7–8, reference), and long (>8) sleep duration; nocturnal TIB (hours) as short (<8), normal (8–9, reference), and long (>9) TIB; bedtime as early (before 9 p.m.), middle (9 p.m.–10 p.m.), and late (10 p.m. or later, reference) bedtime; rise time as early (before 5 a.m.), middle (5 a.m.–6 a.m., reference), and late (after 6 a.m.) rise time; and mid-sleep time (i.e., the mid-point between bedtime and rise time, which is a proxy for circadian phase) as early (before 1 a.m.), middle (1 a.m.–1.5 a.m., reference), and late (after 1.5 a.m.) mid-sleep time. Sleep latency was referred to as time (minutes) taken to fall asleep at night, and long sleep latency was defined as the latency >30 min.[26] Sleep efficiency was referred to as the percentage of time spent on actual sleep while in bed, and low sleep efficiency was defined as sleep efficiency ≤85%.[28]

Assessment of global cognition and diagnosis of dementia

At both baseline and follow-up examinations, we used a neuropsychological test battery to assess cognitive function.[17,18] Global cognitive function was assessed using the

MMSE.[29] Dementia was diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), criteria,[30] following a three-step diagnostic procedure, as previously reported.[17,18,31] In brief, trained medical staff first conducted the face-to-face interviews, clinical examinations, and assessments of cognitive and physical functioning, and recorded all information following structured questionnaires. Then, the neurologists reviewed all the records to screen participants who were suspected to have dementia or who had insufficient information for determining the dementia status for further evaluations. Finally, senior neurologists conducted additional face-to-face interviews with participants who were suspected to have dementia and their caregivers, and reassessed their medical history, cognitive status, daily living ability, and whenever available, neuroimaging data, and made a final diagnosis of dementia following the DSM-IV criteria.[30] Dementia was further classified into AD according to the National Institute on Aging-Alzheimer's Association (NIA-AA) criteria for probable AD[32] and vascular dementia (VaD) following the National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria for probable VaD.[33] Dementia cases that could not be classified as either AD or VaD were considered as other types of dementia.

Statistical analysis

The nonlinear associations of baseline self-reported sleep parameters with dementia were evaluated using restricted cubic splines, in which Cox proportional-hazards models were used with three knots at the 10th, 50th, and 90th percentiles of sleep parameters. The medians of sleep parameters (sleep duration: 7 h; TIB: 8 h; bedtime: 09:00 p.m.; rise time: 05:30 a.m.; and mid-sleep time: 01:30 a.m.) were used as the reference group. We also examined baseline sleep characteristics as tertiles in association with dementia. We used Schoenfeld residual test to verify the proportional-hazards assumption. We reported the main results from two models: Model 1 was adjusted for age, sex, and education, and Model 2 was additionally adjusted for body mass index (BMI), alcohol consumption, smoking, hypertension, diabetes, dyslipidemia, coronary heart disease, stroke, and *APOE* genotype.

General linear regression models were used to examine the associations of baseline sleep characteristics with MMSE score changes (follow-up MMSE score minus baseline MMSE score) among participants who were free of dementia at both baseline and follow-up. In the general linear models, we additionally adjusted for baseline MMSE score and follow-up time. We then tested the statistical interactions of sleep parameters with age (60–74 vs. ≥75 years), sex, education (illiteracy vs. non-illiteracy), and *APOE* ε4 allele (carriers vs. non-carriers) on MMSE score changes by simultaneously entering the independent variables and their cross-product term into Model 2. Stratified analyses were performed when statistical interactions were detected (p for interaction <0.05). We then used general linear models to examine the associations of changes in sleep parameters over the follow-up period with MMSE score decline among participants who remained free of dementia at follow-up.

In sensitivity analyses, we used the Fine-Gray subdistribution hazard models[34] to assess the potential impact of death on the observed associations between sleep characteristics and incident dementia, while considering death during the follow-up period as a competing event. In addition, we further controlled for the presence of depressive symptoms assessed at follow-up to evaluate the impacts of depressive symptoms on the associations of baseline sleep parameters with incident dementia and cognitive decline.

The R Statistical Software for Windows (version 4.0.4, R Foundation for Statistical Computing, Vienna, Austria) was used for all analyses. Two-tailed $p < 0.05$ was considered to be statistically significant.

RESULTS

Baseline characteristics of study participants

At baseline, the mean age of the 1982 participants was 70.05 (standard deviation [SD] = 4.76) years, 83.0% were aged 60–74 years, 59.6% were women, and 38.2% were illiterate (no formal schooling) (Table 1). During an average of 3.7 (SD = 0.3) years of follow-up, 97 individuals developed dementia, including 68 with AD.

Associations of baseline sleep characteristics with incident dementia and AD (analytical sample 1, $n = 1982$)

Adjusting for multiple confounders, restricted cubic spline curves showed J-shaped associations of sleep duration, TIB, and rise time with incident dementia, and a reverse J-shaped association between mid-sleep time and dementia risk (Figure 1). Long TIB and early mid-sleep time were significantly associated with an

TABLE 1 Characteristics of study participants at baseline ($n = 1982$)

Characteristics	Participants
Age (years), mean (SD)	70.05 (4.76)
Age groups, *n* (%)	
60–74 years	1646 (83.0)
≥75 years	336 (17.0)
Women, *n* (%)	1181 (59.6)
Education level, *n* (%)	
Illiteracy	758 (38.2)
Primary school	916 (46.2)
Middle school and above	308 (15.5)
BMI (kg/m^2), *n* (%)[a]	
<24	716 (40.2)
24–27.9	684 (38.4)
≥28.0	380 (21.3)
Alcohol consumption, *n* (%)	685 (34.6)
Ever smoking, *n* (%)	684 (34.5)
Hypertension, *n* (%)	1435 (72.4)
Diabetes, *n* (%)	280 (14.1)
Dyslipidemia, *n* (%)	530 (26.7)
Coronary heart disease, *n* (%)	377 (19.0)
Stroke, *n* (%)	172 (8.7)
APOE ε4 allele carrier, *n* (%)[a]	295 (15.5)
Sleep duration (hours), mean (SD)	7.09 (1.57)
Time in bed (hours), mean (SD)	8.25 (1.18)
Bedtime (hh:mm), mean (SD)	09:14 p.m. (00:52)
Rise time (hh:mm), mean (SD)	05:29 a.m. (00:46)
Mid-sleep time (hh:mm), mean (SD)	01:22 a.m. (00:35)
Sleep efficiency (%), mean (SD)	86.00 (16.00)
PSQI score, mean (SD)	5.73 (3.92)
ESS score, mean (SD)	4.57 (4.62)
MMSE score, mean (SD)	22.00 (5.35)

Abbreviations: *APOE*, apolipoprotein E gene; BMI, body mass index; ESS, Epworth Sleepiness Scale; MMSE, Mini-Mental State Examination; PSQI, Pittsburgh Sleep Quality Index.

[a]Numbers of participants with missing values were 202 for BMI, and 75 for *APOE* genotype. In subsequent analyses, a dummy variable was created for participants with missing data in each of the covariates.

increased risk of dementia. There was a linear association between bedtime and dementia risk. As a continuous variable, every 1-h advance in bedtime was associated with a 25% increased risk of dementia (95%CI 1.03–1.53). The associations of these sleep parameters with AD risk were similar to those with dementia. However, there was a reverse J-shaped association between rise time and AD risk, and a linear association between mid-sleep time and AD risk (Figure S2). As continuous variables, every 1-h advance in bedtime and mid-sleep time was associated with multivariable-adjusted hazard ratio (HR) of 1.27 (1.01–1.59) and 1.49 (1.05–2.12), respectively, for AD.

When sleep parameters were divided into tertiles, long sleep duration, early bedtime, and early mid-sleep time at baseline were significantly associated with an increased dementia risk, even in Model 2, except long TIB that showed marginally significant association with dementia risk ($p = 0.082$). We found no significant associations of rise time, sleep quality, sleep latency, sleep efficiency, or EDS with dementia risk (Table 2).

Similarly, early bedtime and mid-sleep time were significantly associated with increased AD risk, even in Model 2. There were no significant associations of sleep duration, TIB, rise time, sleep quality, sleep latency, sleep efficiency, or EDS with AD risk, although the association of early rise time with AD risk was marginally significant ($p = 0.055$) (Table 2). The associations of sleep timing with dementia and AD were present independent of sleep duration and TIB, except that early rise time became significantly associated with AD (data not shown). We did not detect statistical interactions of sleep parameters with demographic features and *APOE* genotype on risk of dementia and AD.

Associations between sleep characteristics and cognitive decline (analytical sample 2, $n = 1845$)

Long TIB, early bedtime and mid-sleep time, and early and late rise time at baseline were significantly associated with a greater decline in MMSE score, even in the fully adjusted models (Table 3). We did not detect any significant associations of sleep duration, sleep quality, sleep latency, sleep efficiency, or EDS with MMSE score changes.

There were statistical interactions of age (60–74 vs. ≥75 years) with TIB (<8 vs. 8–9 h), rise time (before 5 a.m. vs. 5 a.m.–6 a.m.), and mid-sleep time (before 1 a.m. vs. 1 a.m.–1.5 a.m.) on MMSE score changes (p for interactions = 0.029, 0.005, and 0.013 respectively). Further analyses stratified by age groups showed that, long TIB, early rise time, and early mid-sleep time were significantly associated with greater decline in MMSE score among participants aged 60–74 years, but not among those aged ≥75 years (Figure 2). In addition, there was a statistical interaction between sex and rise time (before 5 a.m. vs. 5 a.m.–6 a.m.) on MMSE score decline (p for

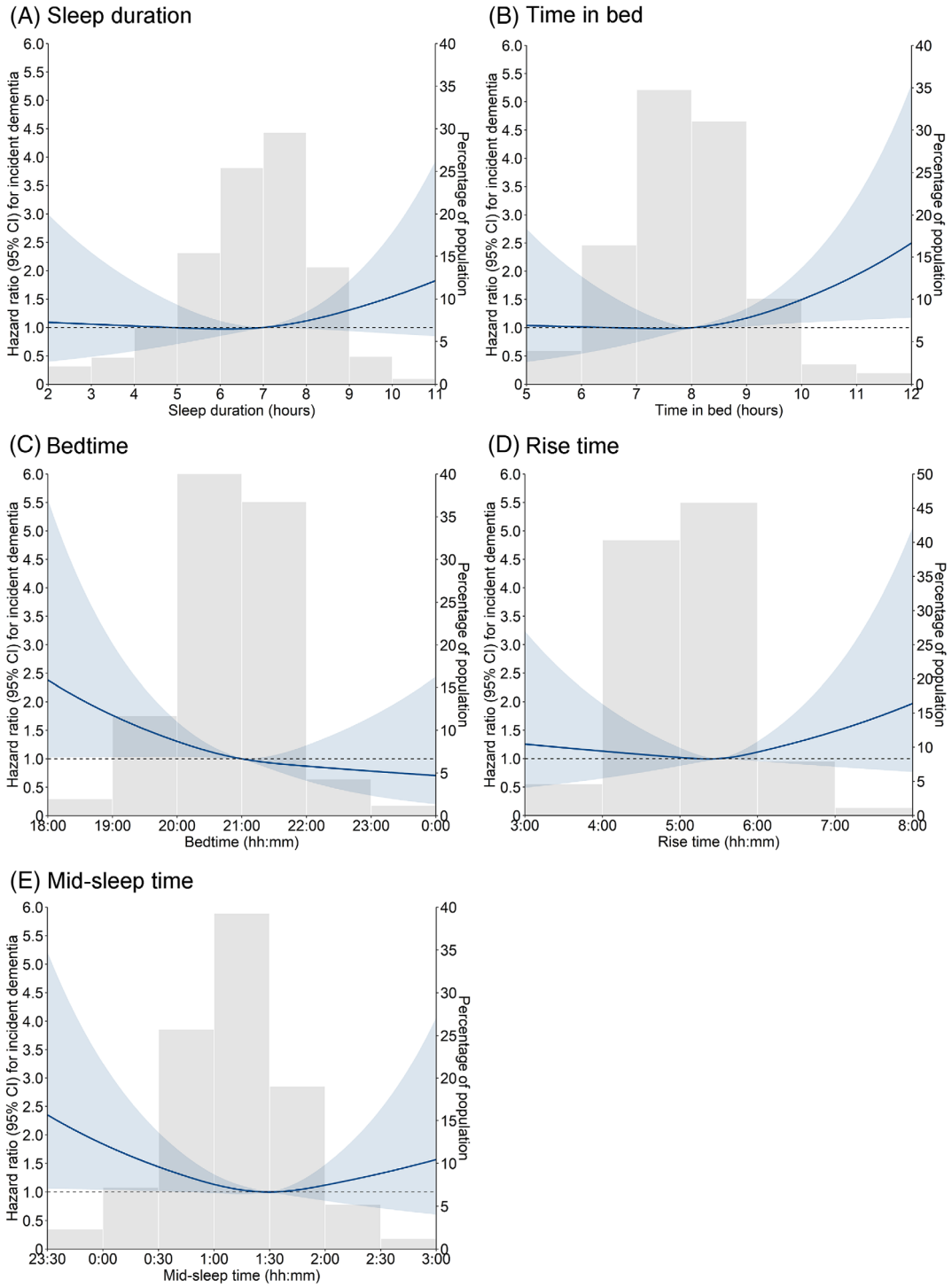

FIGURE 1 Multivariable-adjusted spline curves for associations of sleep characteristics with incident dementia ($n = 1982$). Solid lines represented hazard ratios of incident dementia, adjusting for age, sex, education, body mass index, alcohol consumption, smoking, hypertension, diabetes, dyslipidemia, coronary heart disease, stroke, and *APOE* genotype. The shaded areas represented the 95%CI. The histogram represented the distribution of study participants. CI, confidence interval.

interaction = 0.018), such that early and late rise time were associated with a greater decline in MMSE score in men but not in women (Figure 2). We did not detect statistical interactions of any other examined sleep characteristics with age, sex, education, or *APOE* genotype on cognitive decline.

TABLE 2 Associations of baseline sleep characteristics with incident dementia and Alzheimer disease ($n = 1982$)

Baseline sleep characteristics	No. of participants	All-cause dementia			Alzheimer disease		
		No. of cases	Hazard ratio (95% confidence interval)		No. of cases	Hazard ratio (95% confidence interval)	
			Model 1[a]	Model 2[a]		Model 1[a]	Model 2[a]
Sleep duration							
<7 h	646	34	1.24 (0.78–1.99)	1.21 (0.75–1.95)	25	1.23 (0.71–2.15)	1.17 (0.67–2.05)
7–8 h	979	36	1.00 (reference)	1.00 (reference)	25	1.00 (reference)	1.00 (reference)
>8 h	357	27	1.74 (1.05–2.88)*	1.69 (1.01–2.83)*	18	1.57 (0.85–2.89)	1.54 (0.82–2.87)
Time in bed							
<8 h	574	21	0.97 (0.58–1.62)	0.95 (0.56–1.60)	14	0.93 (0.50–1.73)	0.90 (0.48–1.70)
8–9 h	1130	48	1.00 (reference)	1.00 (reference)	34	1.00 (reference)	1.00 (reference)
>9 h	278	28	1.65 (1.02–2.66)*	1.53 (0.95–2.48)	20	1.47 (0.84–2.59)	1.35 (0.76–2.40)
Bedtime							
10 p.m. or later	642	19	1.00 (reference)	1.00 (reference)	13	1.00 (reference)	1.00 (reference)
9 p.m.–10 p.m.	941	43	1.49 (0.87–2.57)	1.53 (0.88–2.64)	29	1.48 (0.77–2.85)	1.55 (0.80–3.03)
Earlier than 9 p.m.	399	35	2.25 (1.27–3.97)**	2.17 (1.22–3.87)**	26	2.26 (1.15–4.46)*	2.25 (1.12–4.50)*
Rise time							
Earlier than 5 a.m.	160	9	1.29 (0.64–2.57)	1.19 (0.58–2.42)	9	1.83 (0.90–3.73)	2.04 (0.98–4.23)
5 a.m.–6 a.m.	1639	72	1.00 (reference)	1.00 (reference)	49	1.00 (reference)	1.00 (reference)
Later than 6 a.m.	183	16	1.45 (0.84–2.51)	1.38 (0.79–2.40)	10	1.23 (0.62–2.44)	1.09 (0.54–2.19)
Mid-sleep time							
Earlier than 1 a.m.	292	26	2.07 (1.28–3.34)**	2.00 (1.23–3.24)**	22	2.52 (1.47–4.33)***	2.51 (1.45–4.34)***
1 a.m.–1.5 a.m.	1184	48	1.00 (reference)	1.00 (reference)	33	1.00 (reference)	1.00 (reference)
Later than 1.5 a.m.	506	23	1.13 (0.69–1.86)	1.14 (0.69–1.89)	13	0.94 (0.49–1.78)	0.92 (0.48–1.76)
Sleep quality							
Good	1106	50	1.00 (reference)	1.00 (reference)	29	1.00 (reference)	1.00 (reference)
Poor	876	47	0.98 (0.65–1.46)	0.95 (0.63–1.43)	39	1.23 (0.76–2.01)	1.22 (0.75–2.00)
Sleep latency							
≤30 min	1343	58	1.00 (reference)	1.00 (reference)	37	1.00 (reference)	1.00 (reference)
>30 min	639	39	1.15 (0.76–1.74)	1.14 (0.75–1.73)	31	1.28 (0.79–2.07)	1.31 (0.80–2.14)
Sleep efficiency							
>85%	1321	58	1.00 (reference)	1.00 (reference)	40	1.00 (reference)	1.00 (reference)
≤85%	661	39	1.08 (0.72–1.63)	1.06 (0.70–1.60)	28	1.03 (0.64–1.68)	0.99 (0.60–1.62)
Excessive daytime sleepiness							
No	1748	84	1.00 (reference)	1.00 (reference)	56	1.00 (reference)	1.00 (reference)
Yes	234	13	1.24 (0.69–2.22)	1.06 (0.59–1.92)	12	1.69 (0.90–3.16)	1.63 (0.86–3.09)

Note: *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

[a]Model 1 was adjusted for age, sex, and education. Model 2 was additionally adjusted for body mass index, alcohol consumption, smoking, hypertension, diabetes, dyslipidemia, coronary heart disease, stroke, and *APOE* genotype.

TABLE 3 Associations of baseline sleep characteristics with MMSE score changes among participants who remained free of dementia at follow-up ($n = 1845$)

Baseline sleep characteristics	No. of participants	β coefficient (95% confidence interval)	
		Model 1[a]	Model 2[a]
Sleep duration			
<7 h	598	−0.01 (−0.40 to 0.38)	−0.06 (−0.45 to 0.33)
7–8 h	928	0.00 (reference)	0.00 (reference)
>8 h	319	−0.21 (−0.69 to 0.27)	−0.21 (−0.69 to 0.27)
Time in bed			
<8 h	548	0.29 (−0.09 to 0.68)	0.25 (−0.14 to 0.64)
8–9 h	1058	0.00 (reference)	0.00 (reference)
>9 h	239	−0.73 (−1.26 to −0.20)**	−0.75 (−1.29 to −0.22)**
Bedtime			
10 p.m. or later	616	0.00 (reference)	0.00 (reference)
9 p.m.–10 p.m.	876	−0.39 (−0.77 to 0.001)	−0.36 (−0.75 to 0.02)
Earlier than 9 p.m.	353	−1.17 (−1.66 to −0.67)***	−1.13 (−1.63 to −0.63)***
Rise time			
Earlier than 5 a.m.	150	−0.72 (−1.35 to −0.10)*	−0.76 (−1.39 to −0.13)*
5 a.m.–6 a.m.	1535	0.00 (reference)	0.00 (reference)
Later than 6 a.m.	160	−0.69 (−1.30 to −0.08)*	−0.77 (−1.38 to −0.15)*
Mid-sleep time			
Earlier than 1 a.m.	262	−0.85 (−1.35 to −0.35)***	−0.83 (−1.34 to −0.33)**
1 a.m.–1.5 a.m.	1107	0.00 (reference)	0.00 (reference)
Later than 1.5 a.m.	476	0.30 (−0.10 to 0.70)	0.27 (−0.13 to 0.67)
Sleep quality			
Good	1038	0.00 (reference)	0.00 (reference)
Poor	807	0.13 (−0.22 to 0.48)	0.10 (−0.26 to 0.45)
Sleep latency			
≤30 min	1258	0.00 (reference)	0.00 (reference)
>30 min	587	0.12 (−0.25 to 0.50)	0.12 (−0.26 to 0.49)
Sleep efficiency			
>85%	1328	0.00 (reference)	0.00 (reference)
≤85%	607	−0.20 (−0.57 to 0.17)	−0.22 (−0.60 to 0.15)
Excessive daytime sleepiness			
No	1631	0.00 (reference)	0.00 (reference)
Yes	214	−0.12 (−0.66 to 0.41)	−0.13 (−0.67 to 0.41)

Note: *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

[a]Model 1 was adjusted for age, sex, education, baseline MMSE score, and follow-up time. Model 2 was additionally adjusted for body mass index, alcohol consumption, smoking, hypertension, diabetes, dyslipidemia, coronary heart disease, stroke, and *APOE* genotype.

Associations of changes in sleep characteristics with cognitive decline (analytical sample 3, $n = 1780$)

Persistent long and prolonged TIB, persistent early and advanced bedtime and mid-sleep time from baseline to follow-up, and late rise time at both baseline and follow-up were accompanied by a greater decline in MMSE score (Figure S3).

Sensitivity analyses

We employed the Fine-Gray hazard models to examine the associations of baseline sleep parameters with incident dementia and AD by considering death during the follow-up period as a competing event, which yielded the results largely the same as those reported in Table 2 (Table S1). Furthermore, we additionally adjusted for the

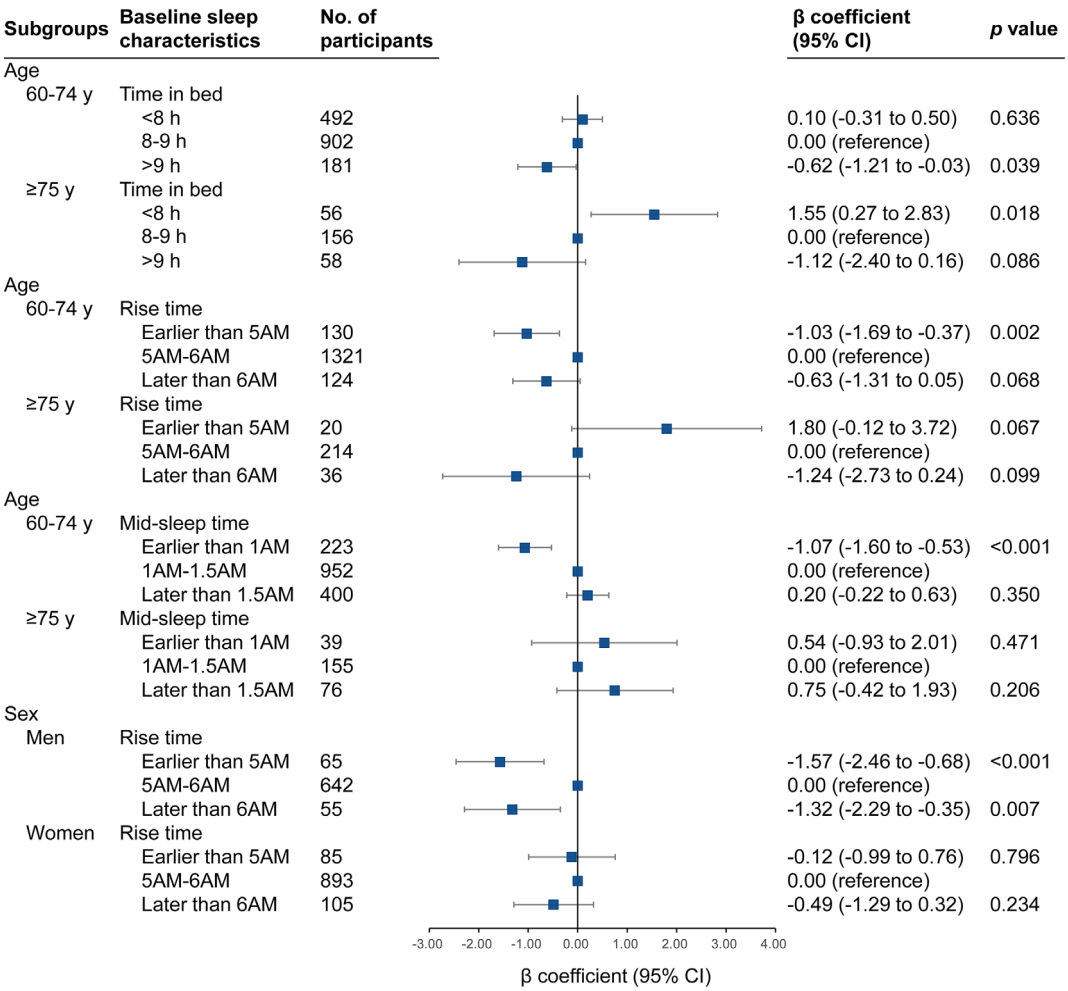

FIGURE 2 Associations of baseline sleep characteristics with MMSE score changes among participants who were free of dementia at follow-up, stratified by baseline age groups (60–74 vs. ≥75 years) and sex ($n = 1845$). Results were adjusted for age, sex, education, body mass index, alcohol consumption, smoking, hypertension, diabetes, dyslipidemia, coronary heart disease, stroke, *APOE* genotype, baseline MMSE score, and follow-up time.

presence of depressive symptoms at follow-up on the basis of Model 2, and the associations of baseline sleep parameters with incident dementia, AD, and changes in MMSE score were similar to those reported in Tables 2 and 3, Model 2 (data not shown).

DISCUSSION

In this population-based cohort study that targeted rural-dwelling older adults in western Shandong Province, China, we found J-shaped associations of sleep duration and TIB with incident dementia, and a reverse J-shaped association between mid-sleep time and dementia risk. Furthermore, long sleep duration, long TIB, and early sleep timing were associated with an increased risk of incident dementia, and their associations with greater cognitive decline were evident mainly among older adults aged 60–74 years and men. In addition, persistent long and prolonged TIB, persistent early and advanced bedtime and mid-sleep time from baseline to follow-up were associated with a greater decline in MMSE score.

Population-based studies have so far yielded mixed results regarding the associations between sleep problems and dementia. A meta-analysis of cohort studies showed that in addition to long sleep duration, short sleep duration was associated with an elevated risk of cognitive decline or dementia,[7] which was different from our study, however, the J-shaped relationship between nocturnal sleep duration and cognitive decline or dementia was in good agreement with our findings. This meta-analysis included studies mainly from the USA and Northern Europe, where people had relatively higher socioeconomic status and education, and longer sleep duration than Chinese rural residents.[35] Very few population-based studies have examined the associations

of TIB and sleep timing with dementia. The Rotterdam Study (age ≥ 55 years) showed that actigraphy-estimated longer TIB and earlier bedtime, but not extreme sleep duration, were associated with an increased risk of dementia and AD.[25] However, this study did not assess the potential nonlinear relationship between sleep parameters and dementia risk. Differences in demographics and sleep habits of study populations and assessment methods of sleep parameters might partly contribute to the inconsistent findings across studies. The Shanghai Aging Study that targeted urban Chinese older adults found that earlier bedtime, but not rise time, was associated with a higher risk of dementia.[27] These findings are similar to our results, although their study participants had later rise time and higher baseline mean MMSE score than ours (27.9 vs. 22.0). Late or early mid-sleep time indicates disrupted circadian rhythm. Population-based cohort studies have suggested that late mid-sleep time was associated with hypertension and diabetes,[9,10] two well-established risk factors for dementia. However, previous studies have rarely examined the relationship between mid-sleep time and incident dementia. We found that early but not late mid-sleep time was associated with dementia. This is in contrast with the Korean Longitudinal Study on Cognitive Aging and Dementia, which showed that late mid-sleep time (after 3 a.m.), but not early mid-sleep time (before 1 a.m.), was associated with reduced dementia risk.[26] It is worth noting that the mid-sleep time of our study participants was much earlier than that of those in the Korean study.

We further explored the relationship of sleep problems with cognitive decline among dementia-free older adults at follow-up. We found that prevalent and incident long TIB and early sleep timing anticipated accelerated cognitive decline even among dementia-free people at follow-up. TIB is a composite indicator of sleep duration, sleep latency, and sleep fragmentation. Thus, the association of long TIB with cognitive decline might reflect the combined effect of long sleep duration, long sleep latency, and low sleep efficiency. However, none of these individual sleep components alone was associated with MMSE score decline, suggesting that the composite measure of sleep problems (long TIB) is relevant for predicting global cognitive decline. Our data showed no associations of sleep quality with dementia or cognitive decline, consistent with a previous study.[7] Finally, we found no association of EDS with cognitive decline, which differed from the community-based cohort study of older adults in Japan.[36] However, the Japanese study only used a single question to assess EDS, which may partly contribute to the inconsistent findings. In addition, the rate of EDS in our study sample was relatively low (11.8%), which might be partly attributable to the fact that afternoon napping was common among rural older adults in China.[37,38] Unfortunately, we were not able to evaluate the impact of daytime napping owing to lack of relevant data.

Several potential mechanisms may explain the associations of sleep problems with dementia and cognitive decline. Long sleep duration has been associated with global brain atrophy,[39] more white matter hyperintensities,[40] and proinflammatory biomarkers (e.g., interleukin-6 and C-reactive protein),[41] which may be the pathways linking long sleep duration to dementia. Advanced sleep timing could be linked with dementia via its associations with amyloid-β accumulation,[42] medial temporal lobe atrophy,[43] and disruption of synaptic homoeostasis.[44]

The exact reasons for the age-varying associations of long TIB, early and late rise time, and early mid-sleep time with greater cognitive decline are unknown. Selective survival may play a part in the age-dependent associations because older age and sleep problems are both associated with mortality.[45] In addition, we found that early and late rise time were associated with greater cognitive decline only in men, which is in line with the previous reports.[5,46] The potential mechanisms underlining sex differences in the associations of sleep problems with cognitive outcomes are poorly understood, and merit further exploration.

Our population-based study targeted a rural area in China where older people had relatively low socioeconomic position and received no or limited education. Because most studies of sleep problems and cognitive aging have been conducted among urban residents in high-income countries, findings from our study may partly bridge the knowledge gap. In addition, we assessed a range of sleep characteristics including sleep timing, a marker of circadian rhythms. Nonetheless, our study has potential limitations. First, sleep characteristics were assessed through self-report, which might be subject to recall bias. Second, multiple testing could increase the possibility of detecting false positive associations, although the main analyses were driven primarily by our pre-defined research hypothesis. Third, although a wide range of confounders had been taken into account in the analysis, residual confounding might still exist due to lack of data on certain factors (e.g., sleep apnea and depressive symptoms) or imperfect measurements of some confounders (e.g., self-reported factors). Indeed, sleep apnea, characterized by EDS and poor sleep quality, has been associated with dementia.[47] Thus, the associations between the examined sleep characteristics and cognitive outcomes might be partly attributable to sleep apnea. However, the potential confounding effect of baseline depressive symptoms was confirmed to be minimal in the sensitivity analysis when the presence of

depressive symptoms at follow-up was taken into consideration. Fourth, we could not exclude the impact of potentially reverse causality on the observed associations due to relatively short follow-up period, given that sleep characteristics might be affected by brain pathologies in the preclinical phase of dementia.[48] Thus, cautiousness is needed when interpreting the observed associations. Finally, the study participants were recruited from only one rural region in western Shandong Province, which should be kept in mind when generalizing our findings to other populations.

In conclusion, our study shows that self-reported sleep problems such as long TIB and early sleep timing are independently associated with incident dementia and AD in Chinese rural older adults, and their associations with greater global cognitive decline vary by age and sex. This suggests that cognitive function should be monitored in older adults who report prolonged TIB and advanced sleep timing, especially in older individuals aged 60–74 years and men. Future intervention studies may help clarify whether moderately reducing TIB and delaying sleep timing can slow down cognitive decline and delay dementia onset in older adults.

AUTHOR CONTRIBUTIONS

Rui Liu, Shi Tang, Chengxuan Qiu, and Yifeng Du designed the study. Rui Liu, Shi Tang, Yifei Ren, Tingting Hou, Xiaoyan Liang, Yi Dong, Yongxiang Wang, Lin Cong, Xiang Wang, Yu Qin, and Juan Ren contributed to data collection. Rui Liu analyzed the data. Rui Liu drafted the manuscript. Yifeng Du and Chengxuan Qiu supervised the study. All authors made critical revisions for important intellectual content and approved the final manuscript.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

SPONSOR'S ROLE

The funding agency had no role in the study design, data collection and analysis, the writing of this manuscript, and in the decision to submit the work for publication.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

Text S1. Methods.

Table S1. Associations of baseline sleep characteristics with incident dementia and Alzheimer disease: Fine-Gray models ($n = 2180$)

Figure S1. Flowchart of the study participants in SYS-AD, 2014–2018

Figure S2. Multivariable-adjusted spline curves for associations of sleep characteristics with incident Alzheimer disease ($n = 1953$)

Figure S3. Associations of changes in sleep characteristics over the follow-up period with MMSE score changes among participants who remained free of dementia at follow-up ($n = 1780$)

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Editor's Note

Optimal sleep is an understudied factor that could potentially affect the prevalence and incidence of a number of different conditions. Some type of sleep disturbance is an almost ubiquitous complaint among older people—except for those enviable people who live into extreme old age in relatively good health and report falling asleep when their head hits the pillow and "sleeping like a baby." We know, for example, that poor sleep related to sleep apnea is associated with cardiovascular morbidity, and that progressively earlier bedtimes reflect altered circadian rhythms that are associated with many bodily functions such as immunity and urine production. Much of the basic and epidemiological research on sleep has, however, not found its way into general clinical knowledge or application.

In this issue of JAGS, a team of investigators from China and Sweden report an observational study in 1,982 people (60% women) suggesting that certain sleep patterns in older people may be associated with incident dementia over the course of 3–4 years. In particular they found that long self-reported sleep duration was associated with incident dementia. Some other longitudinal studies find similar associations over longer follow up periods: in the Framingham Study, including 2547 older people (57% women), long self-reported sleep (>9 h) was associated with incident dementia over 10 years in both men and women, and in the Women's Health Memory Study, with 7444 participants, both long (eight or more hours) and short (six or fewer hours) sleep were associated with incident cognitive impairment and dementia over 13 years. In these studies, the long follow up intervals support the possibility that changes in sleep may be an early marker of neurodegenerative processes in the brain, and experimental studies in animals suggest that central dysregulation of circadian rhythms could play a fundamental biological role in promoting neurodegeneration and cognitive decline.

The current study in JAGS reports an epidemiological survey of self-reported sleep and cognition among older adults living in China. Though findings are partially consistent with previous studies (all use self-report, rather than objective sleep measures), the association of long sleep with incident dementia (n = ~100) was found after a much briefer interval, and in a relatively modest sample of just under 2000 participants. The

statistics in the current study will be complicated to understand for most clinicians, and multiple comparisons were made on a relatively modest sample size. But, despite these limitations, this study adds to accumulating evidence that abnormal sleep patterns could be a clue to otherwise invisible neurodegeneration; whether "normalizing" sleep could be an important target for dementia prevention—in other words, for alleviating a physiological risk factor—requires large-scale, long-term clinical intervention trials. In the meantime, clinicians can safely be advised to inquire about sleep patterns as part of routine geriatric assessment and encouraged to track cognitive functioning in patients whose sleep deviates substantially from the recommended average.

-Joseph G. Ouslander, MD and ***Soo Borson, MD***