Association between Sleep Characteristics and Incident Dementia accounting for Baseline Cognitive Status: A Prospective Population-Based Study

Authors: Kathleen Bokenberger[1], Peter Ström[1], Anna K. Dahl Aslan[2,1], Anna L.V. Johansson[1], Margaret Gatz[3,1], Nancy L. Pedersen[1,3], Torbjörn Åkerstedt[4,5]

[1]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, 17177 Stockholm, Sweden

[2]Institute of Gerontology, School of Health and Welfare, Jönköping University, 55111 Jönköping, Sweden

[3]Department of Psychology, University of Southern California, Los Angeles CA 90089-1061, USA

[4]Stress Research Institute, Stockholm University, 10691 Stockholm, Sweden

[5]Department of Clinical Neuroscience, Karolinska Institutet, 17177 Stockholm, Sweden

Corresponding author:

Kathleen Bokenberger

Department of Medical Epidemiology and Biostatistics,

Karolinska Institutet, 17177 Stockholm, Sweden

Work:+46(0)8-5248-2225 Fax:+46(0)8-314-975

Email: kathleen.bokenberger@ki.se

Abstract

Background: While research has shown that sleep disorders are prevalent among people with dementia, the temporal relationship is unclear. We investigated whether atypical sleep characteristics were associated with incident dementia while accounting for baseline cognitive functioning.

Methods: Screening Across the Lifespan Twin Study (SALT) participants were 11,247 individuals from the Swedish Twin Registry who were at least 65 years at baseline (1998-2002). Sleep and baseline cognitive functioning were assessed via the SALT telephone screening interview. Data on dementia diagnoses came from national health registers. Cox regression was performed to estimate hazard ratios (HR) for dementia.

Results: After 17 years of follow-up, 1,850 dementia cases were identified. Short (≤ 6 hours) and extended (> 9 hours) time-in-bed (TIB) compared to the middle reference group (HR=1.40, 95% CI=1.06-1.85, HR=1.11, 95% CI=1.00-1.24, respectively) and rising at 8:00AM or later compared to earlier rising (HR=1.12, 95% CI=1.01-1.24) were associated with higher dementia incidence. Bedtime, sleep quality, restorative sleep, and heavy snoring were not significant predictors. Findings stratified by baseline cognitive status indicated that the association between short TIB and dementia remained in those cognitively intact at the start.

Conclusions: Short and extended TIB as well as delayed rising among older adults predicted increased dementia incidence in the following 17 years. The pattern of findings suggests that extended TIB and late rising represent prodromal features whereas short TIB appeared to be a risk factor for dementia.

Keywords: Dementia, cognitive impairment, incidence, sleep characteristics, prodromal sign, risk factor

Introduction

Research points to a connection between sleep abnormalities and dementia(1). Based mainly on cross-sectional studies, persons with cognitive impairment or dementia have been found to have sleep anomalies such as extreme sleep durations(1,2), sleep disturbance or poor sleep quality(1,3,4), circadian rhythm dysregulation and delayed phase shifts(5,6), and sleep-disordered breathing(7,8). While it is established that sleep-wake patterns often reflect physiologic changes with age or underlying neuropathological processes, there is growing attention to the idea that sleep could have a causal impact on cognitive decline and dementia susceptibility. Poor sleep quality and short sleep duration, for example, appear to induce neuropathology similar to that seen in Alzheimer's disease (AD) such as elevated concentrations of amyloid-β in the brain(9). Prospective studies that have the potential to examine characteristics of sleep as risk factors for future dementia development are fewer in number and have yielded mixed findings.

Many recent prospective studies, most of which were based on self-reported measures of sleep, have observed extreme sleep length to be associated with diminished cognition or dementia(1,10,11), though reports on short or long sleep duration, or both, as significant predictors were inconsistent across these studies. Other studies did not find an association(12-14). Reduced sleep quality predicted impaired cognition(10,15) and increased dementia risk(16-19) in 7 prospective studies, but was not linked to cognitive decline in other studies(13,20,21). No previous study seems to have used a measure of restorative sleep(22). Sleep-disordered breathing, characterized by chronic breathing difficulties during sleep which can be indicated by snoring(23), was related to worse cognitive function(12,24,25). Circadian disturbance and risk of cognitive decline represents an understudied area, but one earlier study observed that decreased

circadian activity rhythm and delayed phase rhythm were associated with poorer cognitive prognosis after 5 years follow-up(26).

Sufficient follow-up time is an important factor in epidemiologic studies examining sleep as a contributor to risk for cognitive decline and particularly for dementia, for which the most common subtype, AD, is suggested to have a preclinical phase extending for many years or even decades(27). Besides the Finnish study that followed participants for a median of 22 years(10), the follow-up period for the aforementioned prospective studies generally ranged between 1 to 10 years.

This study will add to the literature by using a longer follow-up time and by accounting for initial cognitive functioning, and by stratifying by groups with variable baseline cognitive status. This approach may clarify the relation between sleep duration and diagnosed dementia, as well as that between sleep quality and dementia. We also add a measure of restorative sleep, based on the assumption that not being restored by sleep may be relevant in the prediction of dementia. Specifically, we hypothesized that (a) anomalous sleep characteristics predict greater dementia incidence while taking into consideration baseline cognitive functioning, and (b) the association would be moderated by baseline cognitive status, because those with poorer baseline status may include preclinical or early dementia cases.

Methods

Participants

This register-based cohort study included individuals who were part of the Swedish Screening Across the Lifespan Twin study (SALT), which included all twins from the Swedish Twin Registry (STR) born in 1958 or earlier(28). Data collection for SALT occurred from March 1998

to December 2002, and was performed with a computer-assisted telephone interview that included questions about sleep as well as screening for cognitive function(28). To obtain follow-up information on dementia, the SALT cohort was linked at the individual level to national health registers using the personal identification number.

The present study included SALT participants who were 65 years or older at the time of interview (*n*=12,803, response rate = 71%), as only those 65 and over were given cognitive screening and subsequent clinical dementia workup if they screened poorly. The following were excluded from analysis: persons with missing cognitive screening (*n*=340); persons missing all sleep parameters (*n*=125); cases of dementia that occurred prior to or at the screening interview that were identified from the patient registers (*n*=49) or from the clinical dementia workup (*n*=150); and those with less than 3 years of follow-up time after the SALT interview (*n*=892) which included 125 dementia cases determined by patient register records. After these exclusions, altogether 11,247 participants were followed until dementia ascertainment, death, or the end of the study period (December 31, 2014). Data collection procedures were reviewed and approved by the Regional Ethics Board at Karolinska Institutet.

Sleep measures

All sleep measures were based on items from the Karolinska Sleep Questionnaire(29) that was included within the SALT interview. Rise time and bedtime were grouped according to the 75th percentile cut point of the response distribution (rising 8:00AM or later versus earlier rising; going to bed 11:00PM or later versus earlier bedtime, respectively) to detect delayed sleep phase. Calculated time in bed (TIB) was assessed as the difference between the reported bedtime and

rising time. TIB was categorized into 3 groups: ≤ 6 hours (short), between 6 and 9 hours (reference), and >9 hours (extended).

The sleep items included asking participants whether in the past 6 months they experienced the following: premature awakening (waking up too early in the morning), disturbed sleep, difficulties falling asleep, difficulties awakening (having trouble waking up in the morning), repeated nighttime awakenings, not feeling rested upon awakening, and heavy snoring. Response alternatives followed a 5-point scale ranging from 0 (never) to 4 (always). The first 3 listed items as well as rise and bedtime items were given to all participants (*N*=11,247 answered at least one of these 7 items), while the other items were administered by design to a smaller sample, identified randomly, and thus had fewer responses (*n*=4,716 answered all sleep items). A validated sleep quality index and restorative sleep index(29) used in sleep research previously(30) were created to capture aspects of sleep disturbance. The sleep quality index was the mean of 4 sleep items (difficulty falling asleep, disturbed sleep, repeated awakenings, and premature awakenings) and the restorative sleep index was the mean of 2 sleep items (difficulties awakening and not feeling rested upon awakening), with higher values indicating poorer or less restorative sleep, respectively. Heavy snoring (yes/no), examined as a separate parameter, was used as a marker of sleep-disordered breathing. A correlation matrix of 6 sleep parameters is presented in Supplementary Table S1.

Baseline cognitive screening

Cognitive screening administered in the SALT interview included the TELE(31), which provides a score indicating the total number of cognitive items answered correctly. If the participant performed poorly, an informant was interviewed with the Blessed Dementia Rating Scale

(BDRS)(31). The TELE and the BDRS were combined into an ordinal cognitive status scale, where a score of 0 indicated no cognitive dysfunction, 1 indicated that there were minor errors, 2 indicated poor cognitive performance but no confirmation of interference with daily functioning, and 3 indicated cognitive dysfunction sufficient to interfere with daily function(32). Participants who screened positive (scored a 3 on the ordinal cognitive status scale) and their twin were referred to a clinical workup for dementia(32). Among those assigned a "3", 46% were diagnosed with dementia based on a state-of-the-art clinical workup and hence excluded from the present study, with the balance generally having mild cognitive impairment insufficient to meet diagnostic criteria for dementia(32). The analyses used either the TELE score as a quantitative measure of baseline cognitive functioning or the ordinal categories as a measure of baseline cognitive status. For more details on the baseline cognitive screening, see Supplementary Materials.

Diagnoses of incident dementia

Three national registers were used to determine dementia ascertainment age: the National Patient Register (NPR), which includes both inpatient and outpatient records nationwide since 1987; the Cause of Death Register (CDR), which records death dates and underlying and contributing death causes since 1952; and the Prescription Drug Register (PDR), which began in 2005, wherein individuals with a prescription for dementia medication were defined as demented cases. Dementia diagnoses were identified based on the International Classification of Disease (ICD) version 10 codes.

Covariates

Covariate measures were based on self-reported data from the SALT interview. Covariates included baseline age, sex, highest educational attainment, night work status, smoking status, habitual alcohol consumption, physical exercise, body mass index, type II diabetes, sleep medication use, cancer history, depression, cardiovascular disease history, and chronic obstructive pulmonary disease (Supplementary Materials).

Statistical analysis

Differences in baseline characteristics between dementia cases and non-cases, as well as between responders and non-responders, were compared using chi-square tests and F-tests assuming equal variances. Cross-sectional associations between sleep parameters and baseline ordinal cognitive status were assessed using ordinal logistic regression with robust standard errors to estimate odds ratios (OR) with 95% CI, including adjustment for age, sex, and education.

Since chi-square tests and F-tests do not account for confounding and are not appropriate for assessing the risk of dementia with regards to sleep characteristics, hazard ratios (HR) with 95% CI were obtained from Cox proportional-hazards regression models with robust standard errors, with age as the underlying timescale and follow-up time as a time-varying covariate. HR point estimates may be interpreted in terms of effect size. The first Cox model was adjusted for age and follow-up time. The second model had additional adjustments for sex, education, and baseline TELE score. Aforementioned covariates besides those in the second model were included in additional models, but not the final model, so as to keep the model parsimonious, avoid model over-fitting, and to maintain study power as there was some degree of missing data for some covariates.

To assess if the relationship between the sleep parameters and dementia rates were modified by baseline cognitive status, Cox models adjusted for age, sex, and education, with robust standard errors, were stratified by the four ordinal cognitive status groups. Further, to adjust the associations between the sleep measures and dementia for genetic factors and shared environment, we performed a co-twin control analysis of twin pairs discordant for both exposure and outcome in adjusted Cox models stratified on pair membership. Additional sensitivity analyses are described in Supplementary Materials. All tests were two-sided and the significance level was 5%. Data analyses were conducted with SAS 9.4 and STATA version 13.

Results

Baseline characteristics of study population

Mean baseline age of the study participants was 72.5 years (standard deviation=5.9) and the median follow-up time was 14.3 years (range 3.0-17.7 years). Compared to dementia-free individuals, incident dementia cases were significantly older, more likely women, had poorer baseline cognitive functioning, higher depressive symptom scores, and lower proportions of ever smokers, habitual alcohol drinkers, and overweight ($p<.05$) (Supplementary Table S2). Characteristics of the sleep variables between persons with incident dementia and no dementia are reported in Supplementary Table S3. A comparison between responders (N=11,247) and non-responders (n=125) for the sleep items showed non-responders to be older and less educated. Non-responders also had worse baseline cognitive status, in which 60% scored a 2 (poor cognitive performance) and 30% scored a 3 (cognitive dysfunction) on the ordinal cognitive status scale ($p<.05$) (data not shown).

Sleep measures and baseline cognitive status

Extended TIB was significantly associated with poorer baseline cognitive status in the adjusted model (OR=1.13, 95% CI=1.03-1.23). Short TIB was not related to poorer cognitive status (OR=1.24, 95% CI=0.97-1.59). Later rise time (8:00AM or after) and later bedtime (11:00PM or after) was related to better baseline cognitive status (OR=0.88, 95% CI=0.81-0.96). The association between sleep quality and baseline cognitive status approached significance (OR=1.05, 95% CI=0.99-1.13). Baseline cognitive status was not associated with restorative sleep and snoring (Supplementary Table S4).

Sleep measures and incident dementia

TIB exhibited a U-shaped association with incident dementia, wherein short and extended TIB were related to higher incident dementia in multivariable adjusted models (Table 1). Later rise time, but not bedtime, was related to higher dementia risk. Differences between prospective and cross-sectional findings are discussed below. Other sleep measures were not associated with incident dementia. Findings were similar (change in estimates of association were less than 10%) even in additional analyses that were adjusted for additional covariates. Sensitivity analyses based on samples with different inclusion criteria yielded similar results.

Table 2 presents results from stratified analyses examining the effect of the sleep measures on dementia rates within the four ordinal cognitive strata. Within the group with no baseline cognitive dysfunction, both short and extended TIB remained predictive of greater dementia incidence. Among those with poorest baseline cognition, extended TIB and later rising were associated with higher rates of subsequent dementia.

Lastly, a co-twin control analysis was performed that included all twin pairs as well as only MZ pairs to assess possible confounding due to familial influences (Supplementary Table S5). We did not observe any significant associations, perhaps due to inadequate sample size.

Discussion

In this population-based study prospectively examining the association of sleep-related characteristics during late adulthood and subsequent dementia up to 17 years later, higher rates of incident dementia were associated with short (≤6 hours) and extended (>9 hours) TIB as well as with rise time at 8:00AM or later. Upon examination of the associations as a function of baseline cognitive status, short and extended TIB remained significant predictors of greater dementia risk among those cognitively intact at the start while late rise time was predictive only for the group with poorest baseline cognition. We did not find evidence of an association of increased dementia risk with bedtime, sleep quality, restorative sleep, or heavy snoring.

Cross-sectional findings showed that extended but not short TIB, was associated with poorer baseline cognition. This corresponds with the prospective findings showing that the impact of extended TIB on dementia risk was more pronounced among those with poorest baseline cognition, and that short TIB was shown to be a risk factor for dementia only among those with best baseline cognition. Our prospective findings on short and extended TIB being associated with increased dementia risk are in line with previous reports from some prospective studies(1,10,11), but depart from findings in other studies(12-14). The mechanism underlying the risk conferred by short TIB may be inefficient interstitial clearance of metabolic waste associated with insufficient time asleep, resulting in higher levels of extraneuronal β-amyloid(9,33). This argument, however, does not explain the adverse effect of extended TIB. Given that the pattern

of findings point to long TIB likely being a prodromal sign of dementia, it is plausible that different mechanisms underlie the link between short and long TIB with dementia. Long TIB may reflect existing neuropathological processes or be a sign of residual confounding due to comorbidity that is influencing such processes. Moreover, long sleep has been shown to be associated with impaired mobility(34) and increased mortality(35), but there have not been any studies demonstrating compelling evidence of a mechanism explaining the link between long sleep and poorer health status.

Late rise time and bedtime were associated with better baseline cognition since the cognitively intact group had the highest proportion of late risers and bedtime goers compared to the other groups with cognitive impairment. When we add dementia to the picture, the relative hazard of late versus early risers becoming demented was *lowest* in the baseline cognitively intact group and *highest* in the group with baseline dysfunction. Considering many of the late risers who converted to dementia had baseline cognitive impairment, late rising appears to be a dementia prodrome. There is a biological tendency to shift from eveningness to morningness with age, with older persons generally experiencing an internal circadian phase advance that is accompanied by a 1-hour advance in body temperature increase in the early morning due to changes in the circadian pacemaker(36). Late rising, which may imply delayed circadian rhythm, represents an atypical feature in the cognitively impaired elderly. Prior cross-sectional studies suggesting circadian timing irregularities(5), including phase-delayed circadian activity rhythm(6) in AD patients compared to controls, support our finding of late rising as prodromal of dementia. Similarly, increased odds of mild cognitive impairment and dementia development associated with delayed rhythms were observed in a cohort free of baseline cognitive impairment

or dementia when there was only a short follow-up time(26). Dementia incidence did not differ based on bedtime, contrary to expectations, and warrant further exploration.

Regarding characteristics of sleep disturbance, we noted that the association between sleep quality and baseline cognitive status approached significance, which agrees with previous cross-sectional findings(3). However, sleep quality was not predictive of subsequent risk for dementia, which is in line with reports from some studies(13,20,21), but not in others(16-19). Restorative sleep and heavy snoring were also not related to greater dementia incidence in this study. As previously mentioned, non-responders compared to responders of sleep items tended to be older, lower-educated, and had poorer baseline cognitive scores. Had the study sample included individuals with poorer cognition and worse sleep behavior, we may have seen more pronounced effects. Altogether, the pattern of findings demonstrate that tendencies of older adults to stay in bed longer and rise later may reflect prodromal features, and short TIB appeared to represent a risk factor of dementia.

Strengths & Limitations

One limitation of the study is that self-reported sleep may be prone to bias; however, polysomnography, which is considered the gold standard for measuring sleep, is not easily accessible in a clinical setting while informant questionnaires on sleep history are diagnostically pragmatic. Sleep measures and other covariates were assessed at only one occasion at baseline, which meant that the values for the variables were assumed as fixed over time in our models. As such, we were unable to measure intraindividual changes in sleep experiences across time. We note that measuring snoring via self-report is not ideal since people may be unaware that they snore(29), which may explain why heavy snoring did not predict dementia in this paper.

Relatedly, self-reported bedtime may not have been optimal for detecting tendencies for delayed sleep phase. There may have been problems with reliability of data obtained from those with baseline cognitive impairment, which would result in associations biased toward the null. However, results from a sensitivity analysis based on a sample that excluded persons with severe cognitive problems did not depart from the full cohort findings. One might argue that including individuals with initial poor cognitive status in the study may undermine arguments for causality between sleep behavior and dementia. Instead of excluding those cognitively impaired at baseline, we excluded participants who developed dementia within 3 years (or within 1 year, 2 years or 4 years in sensitivity analyses) proximal to baseline since all persons with cognitive impairment do not necessarily become dementia cases. Finally, multiple testing may have increased the probability of deriving a significant finding due to chance.

Strengths of this study include the long follow-up period of 17 years, the large study sample size, the use of a population-based prospective design utilizing registers with essentially complete follow-up and individual level data, the exclusion of persons who developed dementia soon after baseline, and the various sensitivity analyses done based on cohorts with different inclusion criteria to determine robustness of findings. Moreover, we had the possibility of adjusting for baseline cognitive function and examining if the association between sleep and subsequent dementia was dependent on baseline cognitive status.

Conclusions

Short and extended TIB (≤ 6 hours and > 9 hours) and late rising (8:00AM or later) among older adults predicted increased dementia incidence in the following 17 years, even when accounting for initial cognitive functioning. Upon examination of the associations by baseline cognitive

status, extended TIB and late rising seemed to be prodromal, whereas short TIB appeared to be a risk factor for dementia. Future prospective studies with sufficient follow-up on rise and bedtime in relation to dementia susceptibility are needed. Recognition of patients' sleep characteristics preceding and during the prodromal stage of dementia may allow for appropriate treatment earlier on and potentially delay cognitive impairment.

Funding

This work was supported by grants from the National Institute on Aging (R01-AG08724) and the Swedish Research Council for Health, Working Life and Welfare (FORTE).

Disclosure/ Acknowledgements

The authors have no conflicts of interest to declare.

References:

1. Yaffe K, Falvey CM, Hoang T. Connections between sleep and cognition in older adults. *Lancet Neurol.* 10// 2014;13(10):1017-1028.
2. Lo JC, Groeger JA, Cheng GH, Dijk D-J, Chee MWL. Self-reported sleep duration and cognitive performance in older adults: a systematic review and meta-analysis. *Sleep Med.* 1// 2016;17:87-98.
3. Nebes RD, Buysse DJ, Halligan EM, Houck PR, Monk TH. Self-Reported Sleep Quality Predicts Poor Cognitive Performance in Healthy Older Adults. *J. Gerontol. B Psychol. Sci. Soc. Sci.* 2009;64B(2):180-187.
4. Blackwell T, Yaffe K, Ancoli-Israel S, et al. Poor sleep is associated with impaired cognitive function in older women: the study of osteoporotic fractures. *J. Gerontol. A Biol. Sci. Med. Sci.* Apr 2006;61(4):405-410.
5. Bliwise DL, Tinklenberg JR, Yesavage JA. Timing of sleep and wakefulness in Alzheimer's disease patients residing at home. *Biol. Psychiatry.* Jun 1 1992;31(11):1163-1165.
6. Harper DG, Stopa EG, McKee AC, et al. Differential circadian rhythm disturbances in men with Alzheimer disease and frontotemporal degeneration. *Arch. Gen. Psychiatry.* Apr 2001;58(4):353-360.
7. Blackwell T, Yaffe K, Ancoli-Israel S, et al. Associations between sleep architecture and sleep-disordered breathing and cognition in older community-dwelling men: the Osteoporotic Fractures in Men Sleep Study. *J. Am. Geriatr. Soc.* Dec 2011;59(12):2217-2225.

8. Spira AP, Blackwell T, Stone KL, et al. Sleep-disordered breathing and cognition in older women. *J. Am. Geriatr. Soc.* Jan 2008;56(1):45-50.

9. Spira AP, Gamaldo AA, An Y, et al. Self-reported sleep and beta-amyloid deposition in community-dwelling older adults. *JAMA Neurol.* Dec 2013;70(12):1537-1543.

10. Virta JJ, Heikkila K, Perola M, et al. Midlife sleep characteristics associated with late life cognitive function. *Sleep.* Oct 2013;36(10):1533-1541, 1541A.

11. Benito-Leon J, Louis ED, Villarejo-Galende A, Romero JP, Bermejo-Pareja F. Long sleep duration in elders without dementia increases risk of dementia mortality (NEDICES). *Neurology.* Oct 21 2014;83(17):1530-1537.

12. Yaffe K, Laffan AM, Harrison SL, et al. Sleep-disordered breathing, hypoxia, and risk of mild cognitive impairment and dementia in older women. *JAMA.* Aug 10 2011;306(6):613-619.

13. Tworoger SS, Lee S, Schernhammer ES, Grodstein F. The association of self-reported sleep duration, difficulty sleeping, and snoring with cognitive function in older women. *Alz Dis Assoc Dis.* Jan-Mar 2006;20(1):41-48.

14. Loerbroks A, Debling D, Amelang M, Sturmer T. Nocturnal sleep duration and cognitive impairment in a population-based study of older adults. *Int. J. Geriatr. Psychiatry.* Jan 2010;25(1):100-109.

15. Potvin O, Lorrain D, Forget H, et al. Sleep quality and 1-year incident cognitive impairment in community-dwelling older adults. *Sleep.* Apr 2012;35(4):491-499.

16. Elwood PC, Bayer AJ, Fish M, Pickering J, Mitchell C, Gallacher JE. Sleep disturbance and daytime sleepiness predict vascular dementia. *J. Epidemiol. Community Health.* Sep 2011;65(9):820-824.

17. Lim AS, Kowgier M, Yu L, Buchman AS, Bennett DA. Sleep Fragmentation and the Risk of Incident Alzheimer's Disease and Cognitive Decline in Older Persons. *Sleep.* 2013;36(7):1027-1032.

18. Lim AS, Yu L, Kowgier M, Schneider JA, Buchman AS, Bennett DA. Modification of the relationship of the apolipoprotein E epsilon4 allele to the risk of Alzheimer disease and neurofibrillary tangle density by sleep. *JAMA Neurol.* Dec 2013;70(12):1544-1551.

19. Sterniczuk R, Theou O, Rusak B, Rockwood K. Sleep disturbance is associated with incident dementia and mortality. *Curr Alzheimer Res.* Sep 2013;10(7):767-775.

20. Lo JC, Loh KK, Zheng H, Sim SK, Chee MW. Sleep duration and age-related changes in brain structure and cognitive performance. *Sleep.* Jul 2014;37(7):1171-1178.

21. Jaussent I, Bouyer J, Ancelin ML, et al. Excessive sleepiness is predictive of cognitive decline in the elderly. *Sleep.* Sep 2012;35(9):1201-1207.

22. Riemann D. Nonrestorative Sleep: A New Perspective. *Sleep.* 2013;36(5):633-634.

23. Young T, Shahar E, Nieto F, et al. Predictors of sleep-disordered breathing in community-dwelling adults: The sleep heart health study. *Arch. Intern. Med.* 2002;162(8):893-900.

24. Cohen-Zion M, Stepnowsky C, Johnson S, Marler M, Dimsdale JE, Ancoli-Israel S. Cognitive changes and sleep disordered breathing in elderly: differences in race. *J. Psychosom. Res.* May 2004;56(5):549-553.

25. Osorio RS, Gumb T, Pirraglia E, et al. Sleep-disordered breathing advances cognitive decline in the elderly. *Neurology.* 2015;84(19):1964-1971.

26. Tranah GJ, Blackwell T, Stone KL, et al. Circadian activity rhythms and risk of incident dementia and mild cognitive impairment in older women. *Ann. Neurol.* Nov 2011;70(5):722-732.

27. Morris JC. Early-stage and preclinical Alzheimer disease. *Alzheimer Dis. Assoc. Disord.* Jul-Sep 2005;19(3):163-165.

28. Lichtenstein P, De faire U, Floderus B, Svartengren M, Svedberg P, Pedersen NL. The Swedish Twin Registry: a unique resource for clinical, epidemiological and genetic studies. *J. Intern. Med.* 2002;252(3):184-205.

29. Nordin M, Åkerstedt T, Nordin S. Psychometric evaluation and normative data for the Karolinska Sleep Questionnaire. *Sleep Biol. Rhythms.* 2013;11(4):216-226.

30. Akerstedt T, Knutsson A, Westerholm P, Theorell T, Alfredsson L, Kecklund G. Sleep disturbances, work stress and work hours: a cross-sectional study. *J. Psychosom. Res.* Sep 2002;53(3):741-748.

31. Gatz M, Reynolds CA, John R, Johansson B, Mortimer JA, Pedersen NL. Telephone screening to identify potential dementia cases in a population-based sample of older adults. *Int Psychogeriatr.* Sep 2002;14(3):273-289.

32. Gatz M, Fratiglioni L, Johansson B, et al. Complete ascertainment of dementia in the Swedish Twin Registry: the HARMONY study. *Neurobiol Aging.* Apr 2005;26(4):439-447.

33. Kang JE, Lim MM, Bateman RJ, et al. Amyloid-beta dynamics are regulated by orexin and the sleep-wake cycle. *Science.* Nov 13 2009;326(5955):1005-1007.

34. Stenholm S, Kronholm E, Sainio P, et al. Sleep-Related Factors and Mobility in Older Men and Women. *J. Gerontol. A Biol. Sci. Med. Sci.* 2010;65A(6):649-657.

35. Cappuccio FP, D'Elia L, Strazzullo P, Miller MA. Sleep Duration and All-Cause Mortality: A Systematic Review and Meta-Analysis of Prospective Studies. *Sleep.* 2010;33(5):585-592.

36. Dijk DJ, Duffy JF, Czeisler CA. Contribution of circadian physiology and sleep homeostasis to age-related changes in human sleep. *Chronobiol Int.* May 2000;17(3):285-311.

Table 1

Associations between sleep measures and incident dementia taking into account baseline cognitive functioning, based on Cox regression

		Model*
	Cases/Person-years	HR (95% CI)
Time in bed	1,844/138137	
≤ 6 hours	52/3043	1.40 (1.06-1.85)
Reference	1,255/101864	1.00
> 9 hours	537/33229	1.11 (1.00-1.24)
Rise time	1,844/138137	
Earlier than 8AM	1,304/100109	1.00
8AM or later	540/38027	1.12 (1.01-1.24)
Bedtime	1,844/138137	
Earlier than 11PM	1,201/84216	1.00
11PM or later	643/53920	0.99 (0.89-1.09)
Sleep quality index	980/66669	0.93 (0.85-1.01)
Restorative sleep index	984/66962	0.94 (0.80-1.09)
Heavy snoring	861/59615	
No	500/31853	1.00
Yes	361/27761	0.92 (0.80-1.06)

*Model is adjusted for follow-up time, sex, education, baseline cognitive functioning (TELE score), with age as the underlying timescale, with robust standard errors.

Note: Higher scores on the sleep quality index and restorative sleep index indicate poorer quality

and less restorative sleep, respectively. HR=hazard ratio. CI=confidence interval.

Table 2

Associations between sleep measures and incident dementia, stratified by baseline cognitive status

	Cognitively intact n=6,568	Minor cognitive problems n=2,728	Poor cognitive function n=1,332	Cognitive dysfunction n=619
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Time in bed				
≤ 6 hours	1.74 (1.19-2.55)	1.09 (0.61-1.93)	1.45 (0.72-2.90)	1.00 (0.47-2.13)
Reference	1.00	1.00	1.00	1.00
> 9 hours	1.18 (1.01-1.38)	1.02 (0.83-1.25)	0.90 (0.71-1.16)	1.47 (1.08-2.00)
Rise time				
Earlier than 8AM	1.00	1.00	1.00	1.00
8AM or later	1.05 (0.90-1.21)	1.13 (0.93-1.38)	1.10 (0.84-1.43)	1.59 (1.15-2.20)
Bedtime				
Earlier than 11PM	1.00	1.00	1.00	1.00
11PM or later	0.97 (0.85-1.12)	1.00 (0.83-1.21)	0.96 (0.74-1.24)	1.14 (0.80-1.62)
Sleep quality index	0.97 (0.86-1.09)	0.97 (0.81-1.14)	0.89 (0.73-1.09)	0.81 (0.63-1.04)
Restorative sleep index	0.97 (0.78-1.20)	0.95 (0.70-1.28)	0.88 (0.60-1.28)	0.95 (0.56-1.59)
Heavy snoring				
No	1.00	1.00	1.00	1.00
Yes	0.94 (0.77-1.15)	0.94 (0.71-1.25)	0.83 (0.58-1.18)	0.90 (0.55-1.48)

All models adjusted for follow-up time, sex, and education with age as the underlying timescale, with robust standard errors. HR=hazard ratio. CI=confidence interval.

Supplementary Materials

Appendix 1

Supplementary description of the methods

a) Baseline cognitive screening

The TELE cognitive screening instrument administered in the SALT interview to all participants aged 65 years and older included a 10-item mental status questionnaire, additional cognitive items, and questions about health and daily functioning.[1] The TELE score, based on the total sum of the cognitive items, has a range of 0 to 20, with a sensitivity of .86 and specificity of .90 for identifying dementia when using the cutoff score of 15/16.[2] Further, a previous Finnish study compared the TELE with the Mini Mental State Examination and reported a Pearson's correlation of 0.87 ($p < .0001$).[3]

b) Diagnoses of incident dementia

Dementia diagnoses from the National Patient Register and Cause of Death Register were identified based on the following International Classification of Disease (ICD) version 10 codes:F00, F01, F02, F03, F05.1, G30, G31.1, and G31.8A. Dementia diagnoses from the Prescription Drug Register were based on the following codes according to the Anatomical Therapeutic Chemical Classification System: N06DA, N06DA01, N06DA02, N06DA03, N06DA04, N06DA05, N06DX, N06DX01, N06DX02.

---

[1] Gatz M, Fratiglioni L, Johansson B, et al. Complete ascertainment of dementia in the Swedish Twin Registry: the HARMONY study. Neurobiol Aging. 2005;26(4):439-447.

[2] Gatz M, Reynolds CA, John R, Johansson B, Mortimer JA, Pedersen NL. Telephone screening to identify potential dementia cases in a population-based sample of older adults. Int Psychogeriatr. 2002;14(3):273-289.

[3] Jarvenpaa T, Rinne JO, Raiha I, et al. Characteristics of two telephone screens for cognitive impairment. Dement. Geriatr. Cogn. Disord. 2002;13(3):149-155.

c) Covariates

Demographic and socioeconomic covariates included sex (male/female), highest educational attainment (grouped as basic education, corresponding to 7 years or "folkskola", and more than basic education, reflecting the distribution of education among those in the study)[4], and night work status (yes/no).

Lifestyle and anthropometric covariates included smoking status (ever/never), habitual alcohol consumption (grouped as consumed alcohol during the last month versus no alcohol consumption during the last month), physical exercise (hardly any exercise, light exercise, moderate exercise, intense exercise), and body mass index (BMI) calculated as weight in kilograms divided by height in meters-squared (kg/m^2) and categorized as underweight (<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), and obese (≥30 kg/m^2).

Covariates related to medical conditions included: type II diabetes (yes/no), sleep medication use (ever/never), history of any cancer (yes/no), depression, cardiovascular disease history (CVD) (yes/no), and chronic obstructive pulmonary disease (COPD) (yes/no). For the sleep medication use measure, self-reported prescription drugs were coded to an ATC group. Ever users of sleep medication were defined as having used any medication with an ATC code of N05C for psycholeptics. If the specific drug name was not reported, open-ended responses that indicated use of sleeping tablets were considered. Depression was scored from the 11-item short form of Center for Epidemiologic Studies Depression Scale (CES-D)[5]. CVD was defined as ever having had angina pectoris, heart failure, high cholesterol, claudication or intermittent claudication, thrombosis, ischemic or hemorrhagic stroke, transient ischemic attack, cardiac

[4] Gatz M, Svedberg P, Pedersen NL, Mortimer JA, Berg S, Johansson B. Education and the risk of Alzheimer's disease: findings from the study of dementia in Swedish twins. J. Gerontol. B Psychol. Sci. Soc. Sci. 2001;56(5):P292-300.

[5] Kohout FJ, Berkman LF, Evans DA, Cornoni-Huntley J. Two shorter forms of the CES-D (Center for Epidemiological Studies Depression) depression symptoms index. J Aging Health. 1993;5(2):179-193.

valvular murmurs or narrowing of the carotid arteries, and irregular heartbeat. The binary COPD measure was derived based on whether one coughed with or without phlegm, or had bronchitis or emphysema.

d) Sensitivity analyses

Various sensitivity analyses were done to assess robustness of findings.

It was decided that individuals with less than 3 years of follow-up be excluded from the study so as to minimize reverse causality while maintaining study power. Sensitivity analyses were done based on data that included individuals according to alternative follow-up time stipulations (all follow-up time, or follow-up of at least 1 year, 2 years, 3 years, or 4 years) provided similar results.

Rise time and bedtime measures were dichotomized with the 75th percentile value as the cut-off point as a way to detect the association between delayed phase rhythms and incident dementia. Sensitivity analyses based on rise time and bedtime variables grouped according to70th, 75th, and 80th percentile cut points yielded similar OR and HR estimates, indicating the results were not spurious.

Additional analyses using the second Cox model (adjusted for age, follow-up time, sex, education, and TELE score, with robust standard errors) were performed on different samples based on certain inclusion/exclusion criteria, including: a sample in which all subjects were free of prevalent cognitive dysfunction at baseline (those with a score of 3 on the cognitive status scale), a sample excluding individuals who did not respond to all sleep items (N=4,716), and samples that included individuals with any follow-up time (N=12,192), follow-up of at least 1

year (*N*=12,074), follow-up of at least 2 years (*N*=11,743), and follow-up of at least 4 years (*N*=10,945). These analyses yielded estimates that were similar to estimates presented in Table 1.

Supplementary Table S1

Correlation matrix of sleep measures

	1	2	3	4	5	6
1. Time in bed	1.0					
2. Rise time	.62*	1.0				
3. Bedtime	-.53*	.39	1.0			
4. Sleep quality	.11*	.04	-.05	1.0		
5. Sleep restoration	.11*	.14*	.05*	.40*	1.0	
6. Heavy snoring	-.02	-.01	.07*	.04*	.14*	1.0

*p<.01. There were 11,193 observations for correlations between time in bed, rise time, and bedtime. For all other correlations, there were a minimum of 4,763 and maximum of 5,404 observations. Polychoric correlation coefficients are presented for correlations between categorical variables, and the Spearman correlation coefficient is presented for the correlation between sleep quality and sleep restoration.

Supplementary Table S2
Baseline characteristics of participants who did and did not develop incident dementia (*N* = 11,247)

	All (*N* = 11247)	No dementia (*n* = 9397)	Incident dementia (*n* = 1850)	Test statistic (df), *p*-value*
Baseline age (Mean ± SD)	72.5 ± 5.9	72.1 ± 5.8	74.3 ± 5.7	F(1) = 223, <.0001
Categories of baseline age	11247	9397	1850	$\chi^2(2)$=215.4,
65-69	4266 (37.9%)	3840 (40.9%)	426 (23.0%)	<.0001
70-79	5445 (48.4%)	4367 (46.5%)	1078 (58.3%)	
80-99	1536 (13.7%)	1190 (12.6%)	346 (18.7%)	
Sex	11247	9397	1850	$\chi^2(1)$=24.0,
Male	4903 (43.6%)	4192 (44.6%)	711 (38.4%)	<.0001
Female	6344 (56.4%)	5205 (55.4%)	1139 (61.6%)	
Highest education level	11247	9397	1850	$\chi^2(1)$=3.1, .07
≤ 7 years	5662 (50.3%)	4696 (50.0%)	966 (52.2%)	
> 7 years	4485 (49.7%)	4701 (50.0%)	884 (47.8%)	
Ordinal cognitive status	11247	9397	1850	$\chi^2(3)$=189.3,
0=intact	6,568 (58.4%)	5707 (60.7%)	861 (46.5%)	<.0001
1= minor errors	2,728 (24.3%)	2242 (23.9%)	486 (26.3%)	
2= performed poorly	1,332 (11.8%)	1011 (10.8%)	321 (17.3%)	
3=cognitive dysfunction	619 (5.5%)	437 (4.7%)	182 (9.8%)	
TELE score (M ± SD)	15.7 ± 2.2	15.8 ±2.1	15.0 ±2.5	F(1) = 209.8, <.0001
Smoking status	11221	9377	1844	$\chi^2(1)$=10.9,
Never	6026 (53.7%)	4971 (53.0%)	1055 (57.2%)	.0009
Ever	5195 (46.3%)	4406 (47.0%)	789 (42.3%)	
Alcohol Consumption	9634	8061	1573	$\chi^2(1)$=23.9,
No	5651 (%)	4641 (57.6%)	1010 (64.2%)	<.0001
Yes	3983 (%)	3420 (42.4%)	563 (35.8%)	
Physical exercise activity level	4474	3438	1036	$\chi^2(4)$=4.9, .18
Almost none	694 (15.5%)	552 (16.1%)	142 (13.7%)	
Light	2571 (57.5%)	1963 (57.1%)	608 (58.7%)	
Moderate	1165 (26.0%)	886 (25.7%)	279 (26.9%)	
Intense training	44 (1.0%)	37 (1.1%)	7 (0.7%)	

Body Mass Index	10701	8975	1726	$\chi^2(4)=15.7$, .001
Underweight	178 (1.7%)	151 (1.7%)	27 (1.6%)	
Normal weight	5342 (50.0%)	4405 (49.1%)	937 (54.3%)	
Overweight	4279 (40.0%)	3649 (40.7%)	630 (36.5%)	
Obese	902 (8.4%)	770 (8.5%)	132 (7.6%)	
Night work status	10969	9170	1799	$\chi^2(2)=0.2$, .68
Never	8018 (73.1%)	6696 (73.0%)	1322 (73.5%)	
Ever	2951 (26.9%)	2474 (27.0%)	477 (26.5%)	
Sleep medication use	11247	9397	1850	$\chi^2(2)=3.2$, .07
No	10627 (94.5%)	8895 (94.7%)	1732 (93.6%)	
Yes	620 (5.5%)	502 (5.3%)	118 (6.4%)	
Type 2 diabetes	11210	9364	1846	$\chi^2(2)=0.1$, .75
No	10211 (91.1%)	8533 (91.1%)	1678 (90.9%)	
Yes	999 (8.9%)	831 (8.9%)	168 (9.1%)	
CVD	11244	9394	1850	$\chi^2(2)=2.7$, .10
No	6399 (56.9%)	5378 (57.2%)	1021 (55.2%)	
Yes	4845 (43.1%)	4016 (42.8%)	829 (44.8%)	
Depression (Mean ± SD)	11229 (3.5 ± 4.0)	9384 (3.4 ± 4.0)	1845 (3.7 ± 4.2)	F(1) = 8.7, .003
COPD	11231	9383	1848	$\chi^2(1)=3.4$, .07
No	9847 (%)	8203 (87.4%)	1644 (89.0%)	
Yes	1384 (%)	1180 (12.6%)	204 (11.0%)	
Cancer	11243	9393	1850	$\chi^2(1)=0.2$, .64
No	10159 (90.4%)	8482 (90.3%)	1677 (90.6%)	
Yes	1084 (9.6%)	911 (9.7%)	173 (9.4%)	

* p-value for chi-square tests and F-tests assuming equal variances, whichever relevant.
† Reponses to sleep items grouped into 3 main groups as such: Never = Never, Sometimes = Seldom or Sometimes, Often = Usually or Always.

Supplementary Table S3
Baseline sleep characteristics of participants who did and did not develop incident dementia (*N* = 11,247)

	All (*N* = 11,247)	No dementia (*n* = 9397)	Incident dementia (*n* = 1850)	Test statistic (df), *p*-value*	Effect size
Time in bed (continuous) (Mean ± SD)	11193 8h 35m ± 1h 7m	9349 8h 34m ± 1h 6m	1844 8h 39m ± 1h 10m	F(1)=6.5, .01	R^2=.001
Time in bed	11193	9349	1844	χ^2(2)=17.2, <.0001	Φ=.04
≤ 6 hours	264 (2.4%)	212 (2.2%)	52 (2.8%)		
Reference	8059 (72.0%)	6804 (72.8%)	1255 (68.1%)		
> 9 hours	2870 (25.6%)	2870 (25.0%)	537 (29.1%)		
Rise time (continuous) (Mean ± SD)	11193 7:06AM ± 1:03	9349 7:06AM ± 1:02	1844 7:05AM ± 1:08	F(1)=0.3, .58	R^2=.00003
Rise time	11193	9349	1844	χ^2(1)=1.9, .17	Φ=.01
Earlier than 8AM	8061 (72.0%)	6757 (72.3%)	1304 (70.7%)		
8AM or later	3132 (28.0%)	2592 (27.7%)	540 (29.3%)		
Bedtime (continuous) (Mean ± SD)	11193 10:32PM ± 0:58	9349 10:32PM ± 0:58	1844 10:28PM± 1:02	F(1)=10.4, .001	R^2=.00002
Bedtime	11193	9349	1844	χ^2(1)=8.3, .004	Φ=-.03
Earlier than 11PM	6957 (62.0%)	5756 (61.6%)	1201 (65.1%)		
11PM or later	4236 (38.0%)	3593 (38.4%)	643 (34.9%)		
Sleep quality index (Mean ± SD)	11193 0.9 ± 0.8	4431 0.9 ± 0.8	980 0.9 ± 0.8	F(1)=0.1, .83	R^2=.00001
Difficulty falling asleep†	5474	4482	992	χ^2(2)=0.3, .86	Φ=.01
Never	2418 (44.2%)	1976 (44.1%)	442 (44.6%)		
Sometimes	2363 (43.2%)	1942 (43.3%)	421 (42.4%)		
Often	693 (12.6%)	564 (12.6%)	129 (13.0%)		

Disturbed sleep†	11162	9330	1832	$\chi^2(2)=3.7$, .16	Φ=.02
Never	6473 (58.0%)	5398 (57.9%)	1075 (58.9%)		
Sometimes	3810 (34.1%)	3177 (34.0%)	633 (34.6%)		
Often	879 (7.9%)	755 (8.1%)	124 (6.8%)		
Repeated nighttime awakening †	5472	4479	993	$\chi^2(2)=0.8$, .68	Φ=.02
Never	2489 (45.5%)	2026 (45.2%)	463 (46.6%)		
Sometimes	2432 (44.4%)	1997 (44.6%)	435 (43.8%)		
Often	551 (10.1%)	456 (10.2%)	95 (9.6%)		
Premature awakening†	11166	9335	1831	$\chi^2(2)=5.2$, .08	Φ=.02
Never	4622 (41.4%)	3852 (41.2%)	770 (42.1%)		
Sometimes	5214 (46.7%)	4395 (47.1%)	819 (44.7%)		
Often	1330 (11.9%)	1088 (11.7%)	242 (13.2%)		
Restorative sleep index (Mean ± SD)	5436 (0.3±0.4)	4452 (0.3±0.4)	984 (0.3±0.4)	F(1)=0.6, .45	R^2=.0001
Difficulty awakening†	5476	4479	997	$\chi^2(2)=0.7$, .72	Φ=.01
Never	4741 (86.6%)	3872 (86.4%)	869 (87.2%)		
Sometimes	668 (12.2%)	550 (12.3%)	118 (11.8%)		
Often	67 (1.2%)	57 (1.3%)	10 (1.0%)		
Not feeling rested upon awakening†	11136	9313	1823	$\chi^2(2)=4.2$, .12	Φ=.02
Never	5999 (53.9%)	4996 (53.6%)	1003 (55.0%)		
Sometimes	4008 (36.0%)	3349 (36.0%)	659 (36.2%)		
Often	1129 (10.1%)	968 (10.4%)	161 (8.8%)		
Snoring	4812	3951	861	$\chi^2(1)=4.8$, .03	Φ=-.03
No	2633 (54.7%)	2133 (54.0%)	500 (58.1%)		
Yes	2179 (45.3%)	1818 (46.0%)	361 (41.9%)		

* p-value for chi-square tests and F-tests assuming equal variances, whichever relevant.
† Reponses to sleep items were grouped into 3 main groups: Never = Never, Sometimes = Seldom or Sometimes, Often = Usually or Always.
R^2 = Correlation coefficient represents the effect size for t-test.
φ = Phi correlation coefficient represents the effect size for chi-square test.
Note: These analyses are not adjusted for confounding by age or other covariates. The sleep quality index was based on items for difficulty falling asleep, disturbed sleep, repeated nighttime awakening, and premature awakening. The restorative sleep index was based on items for difficulty awakening and not feeling rested upon awakening. Higher scores indicate poorer quality and less restorative sleep.

Supplementary Table S4
Cross-sectional associations between sleep measures and baseline cognitive status based on ordinal logistic regression

		Model 1[a]	Model 2[b]
	N	OR (95% CI)	OR (95% CI)
Time in bed	11,193		
≤ 6 hours	2,306	1.25 (0.98-1.61)	1.24 (0.97-1.59)
Reference	7,310	1.00 (ref)	1.00 (ref)
> 9 hours	1,577	1.12 (1.03-1.22)	1.13 (1.03-1.23)
Rise time	11,193		
Earlier than 8AM	8,061	1.00 (ref)	1.00 (ref)
8AM or later	3,132	0.83 (0.77-0.90)	0.88 (0.81-0.96)
Bedtime	11,193		
Earlier than 11PM	6,957	1.00 (ref)	1.00 (ref)
11PM or later	4,236	0.74 (0.67-0.82)	0.79 (0.71-0.87)
Sleep quality index	5,411	1.05 (0.99-1.12)	1.05 (0.99-1.13)
Restorative sleep index	5,436	1.04 (0.92-1.18)	1.07 (0.94-1.21)
Heavy snoring	4,812		
No	2,633	1.00 (ref)	1.00 (ref)
Yes	2,179	0.95 (0.84-1.06)	0.93 (0.83-1.04)

[a] Adjusted for age, with robust standard errors. [b] Model 1 + adjustment for sex, and education. The odds ratio (OR) refers to the effect of increasing one unit in poorer baseline cognitive status. CI = confidence interval. The model assumes proportional odds over all possible dichotomizations of the cognitive status categories, and estimated a combined OR of high compared to low values based on these dichotomizations.
Note: Higher scores on the sleep quality index and restorative sleep index indicate poorer quality and less restorative sleep, respectively.

Supplementary Table S5

Co-twin control analyses of the association between sleep parameters and dementia

		All twin pairs*		MZ twin pairs*
	N pairs	Discordant pairs	*N* pairs	Discordant MZ pairs
		HR (95% CI)		HR (95% CI)
Time in bed	292		66	
≤ 6 hours		0.84 (0.37-1.90)		0.49 (0.05-5.21)
Reference		1.00 (ref)		1.00 (ref)
> 9 hours		0.92 (0.69-1.23)		0.91 (0.51-1.61)
Rise time	276		62	
Earlier than 8AM		1.00 (ref)		1.00 (ref)
8AM or later		1.09 (0.82-1.44)		1.08 (0.60-1.93)
Bedtime	304		80	
Earlier than 11PM		1.00 (ref)		1.00 (ref)
11PM or later		0.90 (0.69-1.16)		1.15 (0.68-1.96)
Sleep quality index	425	0.51 (0.27-1.07)	94	0.91 (0.74-1.11)
Restorative sleep index	425	0.75 (0.50-1.13)	94	0.80 (0.56-1.12)
Heavy snoring	140		24	
No		1.00 (ref)		1.00 (ref)
Yes		0.81 (0.54-1.22)		0.88 (0.33-2.31)

*Adjusted for follow-up time, baseline cognitive functioning (TELE score), sex, and education, with age as the underlying time-scale, with robust standard errors. HR=hazard ratio. CI=confidence interval.

Note: Higher scores on the sleep quality index and restorative sleep index indicate poorer quality and less restorative sleep, respectively.