DEMENTIA – ACTIGRAPHY-ESTIMATED SLEEP AND 24-HOUR ACTIVITY RHYTHMS

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ABSTRACT

We investigated and compared associations of objective estimates of sleep and 24-hour activity rhythms using actigraphy with risk of dementia.

We included 1,322 non-demented participants from the prospective, population-based Rotterdam Study cohort with valid actigraphy data (mean age 66±8 years, 53% women), and followed them for up to 11.2 years to determine incident dementia.

During follow-up, 60 individuals developed dementia, of which 49 had Alzheimer's disease. Poor sleep as indicated by longer sleep latency, wake after sleep onset, and time in bed and lower sleep efficiency, as well as an earlier 'lights out' time, were associated with increased risk of dementia, especially Alzheimer's disease. We found no associations of 24-hour activity rhythms with dementia risk.

Poor sleep, but not 24-hour activity rhythm disturbance, is associated with increased risk of dementia. Actigraphy-estimated nighttime wakefulness may be further targeted in etiologic or risk prediction studies.

INTRODUCTION

Sleep is essential to the brain as it supports learning and memory, regulates synaptic plasticity, and enhances waste clearance from the brain.[1,2] Conversely, disturbed sleep may harm the brain through increased neuro-inflammation[3] or atherosclerosis,[4] or by accumulation of detrimental proteins involved in Alzheimer's disease pathology.[1,5] Against this background, sleep disturbances have been associated with incident dementia[6,7] and as such may be regarded as a potential risk factor, a prodromal disease feature, or as signaling presence of preclinical brain pathology.

Sleep is closely related to the circadian timing system,[8] functioning of which is reflected behaviorally in 24-hour rhythms of physical activity. Disturbed 24-hour activity rhythms have also been linked to dementia risk.[9-11] Yet, it remains unknown how sleep and 24-hour activity rhythms compare with respect to dementia risk, and to what extent these aspects contribute to risk independent from each other.[12] Also, we need to consider relevant interactions, such as that of sleep disturbances with presence of the Apolipoprotein E ε4 (*APOE* ε4) allele on risk of Alzheimer's disease.[13] Lastly, only a minority of population-based studies studied objectively measured sleep in relation to dementia risk, while most studies[6,7,14] measured sleep using self-report measures as these are feasible to obtain in large study populations. Although important for evaluating sleep,[15] self-report measures may hamper attributing associations to sleep per se as they rely on cognitive and affective factors that determine the subjective appraisal of sleep.[16]

Sleep and 24-hour activity rhythms may be independently inferred from physical activity measurements over multiple days using actigraphy. In this study, we investigated associations of actigraphy-derived sleep and 24-hour activity rhythm parameters with the risk of dementia, using over 11 years of follow-up data from the population-based Rotterdam Study cohort. We compared sleep and 24-hour activity rhythm parameters using mutually adjusted models, and investigated effect-modification by *APOE* ε4 status.

METHODS

Study setting and population

This study is embedded in the Rotterdam Study, a prospective population-based cohort in a Dutch suburban district starting in 1990.[17] Examination rounds are repeated every 4-5 years. Incident disease is assessed continuously with electronic linkage between the study database and medical records. The Rotterdam Study has been approved by the Medical Ethics Committee of the Erasmus MC. All participants provided written informed consent for participation and to have medical information obtained from their treating physicians.

Between 2004 and 2007 (baseline of the current study), 2063 participants (78% of 2632 invited) aged 62.4±9.4 years wore an actigraph for ≥4 days and also completed a daily sleep diary. We excluded participants with: i) Actigraph malfunctioning (n=197); ii) Less than 96 hours of consecutive recording (n=109); iii) Measurements during daylight savings (n=23); iv) Missing information on dementia status (n=54). Lastly, we excluded persons aged <55 years at baseline, as those were considered not at risk for dementia in a population-based setting (n=358).[18] The 1,322 included individuals were on average 2.5 years younger, 8% less likely to be female, and had a 0.4 higher Mini-mental status examination score, but did not differ in questionnaire-assessed sleep or bedtimes compared to invited persons aged >55 who did not participate (n=768). Included participants were followed for 11,630 person-years (95% of possible total if no loss to follow-up[19]) until onset of dementia, loss to follow-up, death, or 1 January 2016.

Sleep and 24-hour activity rhythms

Participants wore an actigraph (ActiWatch model AW4, Cambridge Technology Ltd) for 138 ± 14 hours (median=144) and completed a sleep diary during the same time period.[20] Participants pressed a marker button on the device to denote 'lights out' time and getting up time. Missing marker times (21% of all time values) were imputed from the sleep diary, or estimated by inspecting actigraphy recordings when sleep diaries were missing. Within the defined time in bed, total sleep time and wakefulness were estimated using a validated algorithm with a threshold of 20 activity counts.[21] We defined 'sleep onset' as the midpoint of the first immobile period lasting ≥10 minutes after 'lights out' with ≤one epoch of movement. Sleep onset latency was calculated as the time from 'lights out' to sleep onset, and wake after sleep onset was calculated as the wakefulness after sleep onset. Sleep efficiency was calculated as total sleep time / time in bed * 100%.

We calculated the following indicators of the 24-hour activity rhythm[22,23]: Intradaily variability which quantifies the amount of alterations of activity-inactivity, interdaily stability which quantifies how activity profiles across days resemble each other, and the average time of day when the least active 5 consecutive hours started (L5 onset) indicating phase of most inactivity.

Correlations amongst sleep and 24-hour activity rhythm parameters at baseline in a similar study population have been reported previously.[24]

Dementia

Diagnosing dementia involved cognitive screening for all participants visiting the research center. We further assessed individuals scoring a Mini-mental state examination<26 or Geriatric Mental Schedule organic level>0 with the Cambridge Mental Disorders of the Elderly Examination, including a spouse or informant interview. Simultaneously, for all participants we surveilled medical records of general practitioners and the

regional institute for outpatient mental health care for dementia. A consensus panel adjudicated diagnoses according to standard criteria. In this study, we considered the outcomes of all-cause dementia (DSM-III-R; hereafter: dementia), and Alzheimer's disease (NINCDS–ADRDA).

Covariates

Using the disjunctive cause criterion,[25] we considered age, sex, education (categorized as primary, secondary/lower vocational, intermediate vocational and higher vocational/university), paid employment, self-reported physical activity,[26,27] habitual alcohol consumption, body mass index, positive history of cardiovascular disease (TIA, stroke, heart disease), smoking status, presence of hypertension, and presence of diabetes mellitus as potential confounders or appropriate proxies for unmeasured confounders.[25] Measurements took place during home interviews or at research center visits and are described in detail elsewhere.[28] For the sensitivity analyses we assessed depressive symptoms[29] (Centre for Epidemiological Studies - Depression Scale [CES-D]), possible sleep apnea (2 questions of the Pittsburgh Sleep Quality Index,[30] napping (napping per day during daytime and evenings according to the sleep diary), and number of *APOE* ε4 alleles.[28]

Statistical analysis

We used Cox proportional hazards regression models to associate sleep and 24-hour activity rhythm parameters with incident dementia and Alzheimer's disease, adjusted for age/sex and additionally for abovementioned confounders. We also investigated non-linearity in associations for total sleep time and time in bed by modeling a quadratic term. We additionally adjusted all associations of sleep and bedtime parameters observed in the main analysis for the 24-hour activity rhythm variables, to evaluate their independence. In sensitivity analysis, we separately adjusted analyses for possible sleep apnea, napping, and number of *APOE* ε4 alleles, and restricted analyses to persons without clinically relevant depressive symptoms (CES-D ≤16).

Also, we presented stratified results for all parameters by *APOE* ε4 genotype (≥1 ε4-allele versus no ε4-alleles), age (≤75 versus >75), and sex on risk of dementia, and formally tested multiplicative interaction by modeling a product term. We evaluated statistical significance of interaction terms at P<.0016, defined by applying a Bonferroni correction for testing 10 parameters across 3 stratifications (P=.05/30).

Lastly, we explored whether associations depended on follow-up time to provide some insight into possible reverse causation.[31] We performed analyses in increasingly longer epochs of follow-up time from baseline (e.g. baseline to 2 years, baseline to 4 years, etc.), using Firth's penalized Cox regression to account for the smaller number of events.[32]

Testing the proportional hazards assumption of the main analyses using Schoenfeld residuals indicated a violation for L5 onset. Please note that this non-proportionality was not removed, but made insightful with aforementioned analysis.[31]

Sleep variables were winsorized (i.e. values of outliers changed towards the mean) to 3 SD and subsequently standardized to facilitate comparison. Missing values on covariates (except *APOE*-genotype) were imputed using five multiple imputations, performed with IBM SPSS Statistics version 24 (IBM Corp, Armonk, NY). Statistical analyses were performed with R software (packages: survival, coxphf).

RESULTS

We included 1,322 participants at baseline (Table 1) aged 66.1±7.6 years. During 11.2 years of follow-up (median=9.5), 60 individuals developed dementia, including 47 with Alzheimer's disease.

Longer sleep onset latency (hazard ratio [HR] per standard deviation [SD] increase 1.44, 95% confidence interval [CI] 1.13-1.83) and longer time in bed (HR 1.40, 95% CI 1.04-1.88) were associated with an increased risk of dementia. A higher sleep efficiency (HR 0.72, 95% CI 0.55-0.93) and later 'lights out' time were associated with decreased dementia risk (HR 0.56, 95% CI 0.41-0.76). For Alzheimer's disease, aforementioned associations were stronger, including an association for longer wake after sleep onset (Table 2). In contrast, total sleep time was not associated with the risk of dementia (HR 0.97, 95% CI 0.74-1.29) or Alzheimer's disease (HR 0.92, 95% CI 0.68-1.26, Table 2). Estimates were not meaningfully different when only adjusted for age and sex (Table 2).

We found no statistically significant non-linearity after fitting quadratic terms for the associations of total sleep time (P value=.95) or time in bed (P value=.27) with dementia risk, nor with Alzheimer's disease risk (P value=.44; P value=.30, respectively).

The 24-hour activity rhythms were not associated with dementia risk (Table 2). Aforementioned associations of sleep parameters with dementia risk were also not affected by further adjustment for 24-hour activity rhythm parameters (Table 3).

Estimates remained similar after separate further adjustment for possible sleep apnea, number of naps, or number of *APOE* ε4 alleles (Supplementary Table 1). Also, restricting analyses to persons without clinically relevant depressive symptoms did not substantially affect estimates (Supplementary Table 2).

Stratifying by *APOE* ε4 suggested that associations of sleep parameters with increased risk of dementia were present only in ε4-negative individuals (Table 4), but when formally tested no sleep-by-*APOE* interaction term survived multiple testing.

Table 1. Characteristics of study population at baseline

Characteristic (unit)	Values (N=1,322)
Age at baseline (years)	66.1 ± 7.6
Female	699 (53%)
Educational level	
Primary education	109 (8%)
Lower/intermediate or lower vocational	585 (44%)
Higher or intermediate vocational	390 (30%)
Higher vocational or university	238 (18%)
Paid employment	274 (21%)
Physical activity (MET-hours/week)	62 (19-96)
Alcohol consumption (grams/day)	9 (1-20)
Smoking status	
Never	413 (31%)
Former	695 (53%)
Current	214 (16%)
Body mass index (kg/m^2)	28.0 ± 4.0
History of cardiovascular disease	1.1 (0.3 – 32.0)
Presence of hypertension	888 (67%)
Presence of diabetes mellitus	104 (8%)
Depressive symptoms (CES-D score)	3 (1-7)
Possible sleep apnea	369 (28%)
Napping (number of naps)	1 (0-3)
Presence of ≥1 *APOE* ε4 allele*	346 (26%)
Total sleep time (hours)	6.4 ± 0.9
Sleep efficiency (%)	79 (74-83)
Wake after sleep onset (hours)	1.1 (0.9-1.4)
Sleep latency (minutes)	13 (7-22)
Time in bed (hours)	8.2 ± 0.9
Bedtime ('lights out') (hh:mm)	23:50 ± 00:50
Time getting up (hh:mm)	08:05 ± 00:50
Intradaily variability (score)	0.40 (0.33-0.49)
Interdaily stability (score)	0.83 (0.76-0.88)
Onset least active consecutive 5 hours (hh:mm)	01:50 ± 01:08

Values are expressed as No. (%) for categorical variables and mean ± standard deviation or median (1st quartile – 3rd quartile) for continuous variables, unless specified otherwise. Includes imputed values for covariates.

*Missing 71 participants, including 3 persons with incident Alzheimer's disease

Abbreviations: CES-D=Center for Epidemiological Studies – Depression Scale; MET=Metabolic equivalent of task; N=sample size.

Table 2. Associations of sleep, bedtime and 24-hour activity rhythm parameters with incident dementia and Alzheimer's disease

Determinant (per SD increase)	Dementia HR (95% CI)		Alzheimer's disease HR (95% CI)	
	Cases/N=60/1322		Cases/N=49/1322	
	Model 1	Model 2	Model 1	Model 2
Sleep				
Total sleep time	0.99 (0.76-1.30)	0.97 (0.74-1.29)	0.95 (0.70-1.28)	0.92 (0.68-1.26)
Sleep onset latency	1.38 (1.10-1.74)	1.44 (1.13-1.83)	1.42 (1.11-1.83)	1.45 (1.11-1.89)
Wake after sleep onset	1.17 (0.92-1.51)	1.23 (0.95-1.59)	1.30 (1.00-1.70)	1.38 (1.05-1.81)
Time in bed	1.34 (1.00-1.80)	1.40 (1.04-1.88)	1.40 (1.01-1.95)	1.49 (1.06-2.10)
Sleep efficiency	0.78 (0.60-1.00)	0.72 (0.55-0.93)	0.72 (0.54-0.94)	0.66 (0.50-0.87)
Bedtimes				
Time 'lights out'	0.57 (0.42-0.76)	0.56 (0.41-0.76)	0.55 (0.40-0.76)	0.53 (0.37-0.74)
Time getting up	0.79 (0.59-1.06)	0.79 (0.58-1.08)	0.81 (0.58-1.13)	0.79 (0.56-1.13)
24-hour activity rhythm				
Intradaily variability	1.06 (0.82-1.38)	1.07 (0.82-1.40)	1.04 (0.78-1.40)	1.05 (0.78-1.41)
Interdaily stability	0.93 (0.71-1.22)	0.92 (0.70-1.20)	0.90 (0.67-1.21)	0.87 (0.65-1.17)
L5 onset	0.88 (0.69-1.13)	0.92 (0.72-1.17)	0.85 (0.65-1.12)	0.88 (0.67-1.16)

Hazard ratios were obtained with Cox regression models. Model 1 is adjusted for age and sex. Model 2 is additionally adjusted for educational level, employment status, physical activity, alcohol consumption, body mass index, smoking status, history of cardiovascular disease, presence of hypertension, and presence of diabetes mellitus. Abbreviations: CI=Confidence interval; HR=Hazard ratio; L5=Least active consecutive 5 hours of the day; N=sample size; SD=Standard deviation

Table 3. Associations of sleep parameters with incident dementia and Alzheimer's disease, additionally adjusted for 24-hour activity rhythm parameters

Determinant (per SD increase)	Dementia HR (95% CI)	Alzheimer's disease HR (95% CI)
	Cases/N=60/1322	Cases/N=49/1322
Sleep		
Total sleep time	1.00 (0.74-1.34)	0.93 (0.67-1.29)
Sleep onset latency	1.52 (1.17-1.97)	1.53 (1.14-2.05)
Wake after sleep onset	1.25 (0.95-1.64)	1.42 (1.07-1.90)
Time in bed	1.44 (1.06-1.95)	1.52 (1.07-2.15)
Sleep efficiency	0.70 (0.52-0.93)	0.63 (0.46-0.86)

Hazard ratios were obtained with Cox regression models, adjusted for main analysis confounder and additionally for intradaily variability, interdaily stability, and time of onset of the least active consecutive 5 hours of the day. Confounders included age, sex, educational level, employment status, physical activity, alcohol consumption, body mass index, smoking status, history of cardiovascular disease, presence of hypertension, and presence of diabetes mellitus. In all models, no 24-hour activity rhythm parameter was statistically significant at P value<0.05. We observed no multicollinearity: All variance inflation factors were lower than 2. Abbreviations: CI=Confidence interval; HR=Hazard ratio; N=sample size; SD=Standard deviation

Table 4. Effect-modification of associations of sleep, bedtime and 24-hour activity rhythm parameters with risk of dementia by *APOE* ε4

Determinant (per SD increase)	Dementia HR (95% CI), *APOE*-stratified		Interaction
	ε4 carriers	ε4 non-carriers	
	Cases/N*=21/346	Cases/N*=36/905	P value
Sleep			
Total sleep time	1.04 (0.65-1.66)	0.96 (0.68-1.35)	0.89
Sleep onset latency	1.28 (0.82-2.01)	1.51 (1.10-2.06)	0.38
Wake after sleep onset	0.83 (0.49-1.39)	1.63 (1.19-2.25)	0.01
Time in bed	1.14 (0.72-1.82)	1.73 (1.16-2.57)	0.02
Sleep efficiency	0.95 (0.57-1.56)	0.61 (0.44-0.84)	0.04
Bedtimes			
'Lights out' time	0.52 (0.31-0.87)	0.42 (0.27-0.65)	0.12
Getting up time	0.55 (0.31-0.98)	0.84 (0.56-1.26)	0.20
24-hour activity rhythm			
Intradaily variability	0.75 (0.41-1.36)	1.16 (0.85-1.60)	0.03
Interdaily stability	1.36 (0.75-2.47)	0.85 (0.62-1.18)	0.07
L5 onset	0.70 (0.42-1.16)	0.94 (0.69-1.29)	0.48

Hazard ratios were obtained from Cox regression models, adjusted for age and sex (if applicable), and educational level, employment status, physical activity, alcohol consumption, body mass index, smoking status, history of cardiovascular disease, presence of hypertension, and presence of diabetes mellitus. We tested interaction through modeling a product term of the unstandardized determinant with the number of ε4-alleles. *Missing data on *APOE* ε4 genotype for 71 individuals in total, of whom 3 had incident Alzheimer's disease. Abbreviations: *APOE*=Apolipoprotein E gene; CI=Confidence interval; L5=Least active consecutive 5 hours of the day; N=sample size

Age-stratified analyses did not show a consistent pattern of differences in associations across age, and we found no statistically significant multiplicative interactions with age (Supplementary Table 3).

Sex-stratified analyses showed shorter total sleep time was associated with lower dementia risk in women, opposite to the direction of the point estimate in men. Vice versa, longer time in bed was associated with increased dementia risk only in men (Supplementary Table 3). Yet, we found no statistically significant interactions with sex.

For the sleep parameters, hazard ratio estimates remained mostly similar over increasing follow-up time (Figure 1A). The strong association of later 'lights out' with lower dementia risk in the first 2 years of follow-up (HR 0.27, 95% CI 0.10-0.73) attenuated with increasing follow-up time (Figure 1B). Later L5 onset was associated with lower dementia risk in the first 2 years of follow-up only (HR 0.23, 95% CI 0.09-0.61) (Figure 1C). Incident cases in this period all had Alzheimer's disease. Overall, findings were similar for Alzheimer's disease.

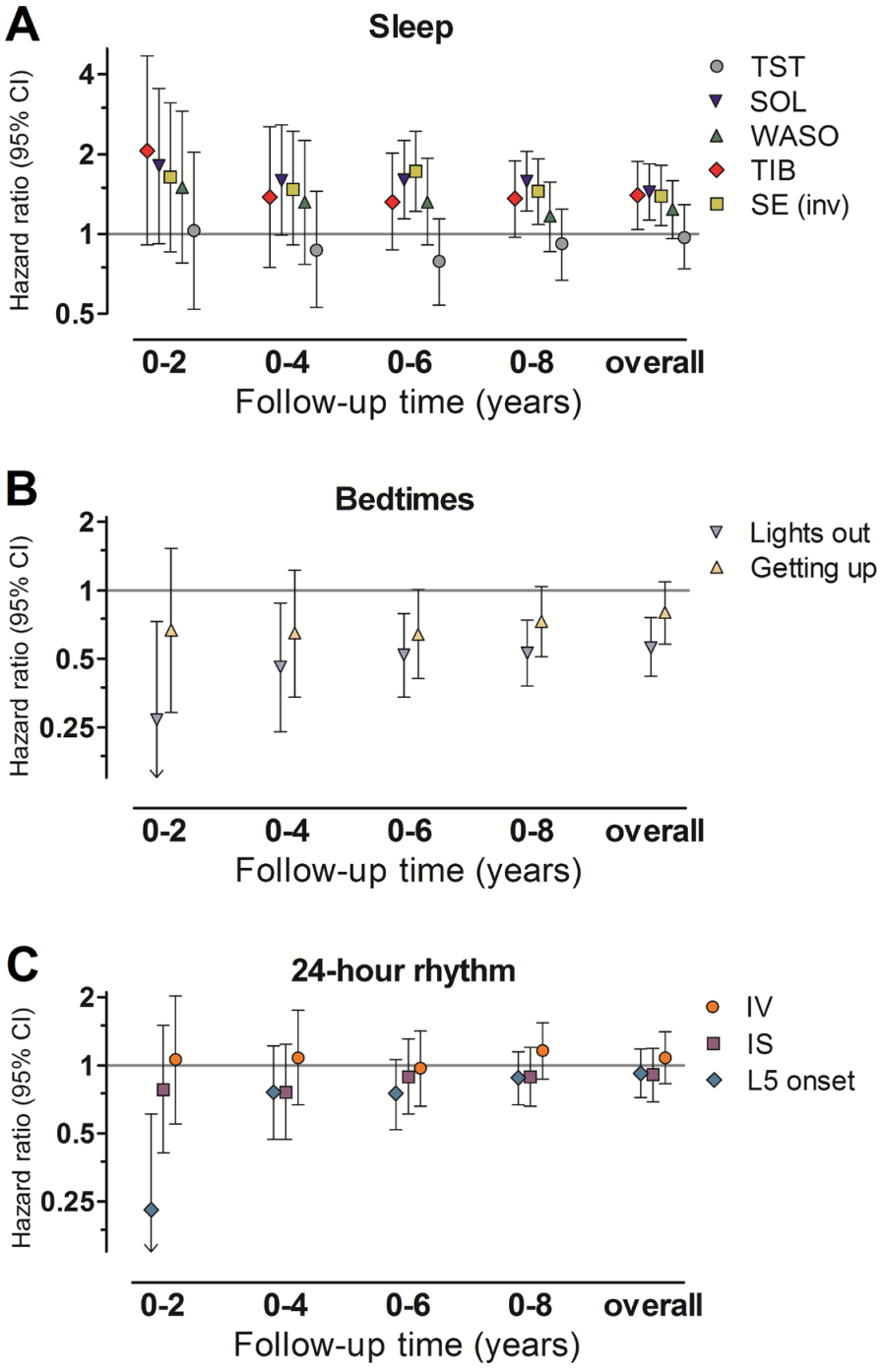

Figure 1. Associations of sleep, bedtime and 24-hour activity rhythm parameters with incident dementia, over increasing epochs of follow-up time

Associations of (A) sleep, (B) bedtimes and (C) 24-hour activity rhythm parameters with risk of dementia are shown for increasing epochs of follow-up time within the study timeframe. Hazard ratios for epochs in shorter follow-up time were obtained using multivariate Firth's penalized Cox regression models. We obtained estimates after censoring all participants still at risk at 2 years (8 incident dementia cases), 4 years (15 cases), 6 years (28 cases), 8 years (47 cases), and after the total follow-up of 11.2 years after baseline (60 cases). Hazard ratios are adjusted for age, sex, educational level, employment status, physical activity, alcohol consumption, body mass index, smoking status, history of cardiovascular disease, presence of hypertension, and presence of diabetes mellitus, are expressed per standard deviation increase in the parameter, and plotted at a log2-scale. Please note that estimates obtained for sleep efficiency were inversed (transformed as 1/estimate depicting sleep 'inefficiency') for graphical comparison of effect sizes of sleep parameters.
Abbreviations: CI=Confidence interval; IS=Interdaily stability; IV=Intradaily variability; L5=Least active consecutive 5 hours of the day; SE=Sleep efficiency; SOL=Sleep onset latency; TIB=Time in bed; TST=Total sleep time; WASO=Wake after sleep onset

DISCUSSION

In the general population, actigraphy-estimated longer sleep onset latency, longer wake after sleep onset, longer time in bed, and lower sleep efficiency, as well as earlier 'lights out' time, were associated with a higher risk of dementia. In contrast, 24-hour activity rhythm fragmentation or stability did not influence dementia risk.

Several methodological considerations should be mentioned. Actigraphy-derived behavioral rhythms do not necessarily equate to the endogenous circadian rhythm. Additionally, the gold standard for measuring sleep is polysomnography. Potential misclassification of sleep and circadian rhythms, and the low number of incident cases in this study, may have reduced our power to detect small effect sizes. Also, we could not assess the extent to which preclinical amyloid β (Aβ) or tau pathology, which may affect sleep-wake regulating brainstem regions[33] years before dementia diagnosis,[34,35] confounded associations with dementia risk. Lastly, selection bias may have influenced our findings, although characteristics of included and non-included participants were largely similar.

Our study adds to previous actigraphy-based studies[9,11,13,36-38] by showing that disturbed sleep is more predictive of developing dementia than disrupted 24-hour activity rhythms. Instead of total sleep time, it was rather an increased amount of wakefulness when in bed, in line with previous findings,[9,36] and an advanced 'lights out' time that determined dementia risk. We speculate that this indicates that a reduced capability to sleep when in bed drives dementia risk, rather than for example deliberate lifestyle choices to curtail sleep. Our findings suggest that individuals may have tried to adapt to such an 'incapability' to sleep by increasing time in bed, mainly by advancing 'lights out' time, to maintain a sufficient amount of sleep. Several mechanisms could underlie this incapability to sleep.

First, associations may indicate presence of an underlying disease process that both increases dementia risk and impairs sleep, for which accumulation of Alzheimer's disease pathology[39] in the brain seems to be a likely[40] substrate. Such confounding, however, is not in line with finding that associations for poor sleep seemed restricted to *APOE* ε4 non-carriers, and not ε4-carriers who are at increased risk of having more brain Aβ deposition at this age.[40] Also, a previous study found that high intradaily variability was related strongest to an increased cerebrospinal fluid biomarker profile suggestive of preclinical Alzheimer's disease.[41] Yet, intradaily variability was unrelated to incident dementia or Alzheimer's disease in our study. Also arguing against confounding by preclinical pathology are the time-stratified analyses, showing that poor sleep was not associated substantially stronger with dementia risk in short versus longer follow-up durations, in contrast to early 'lights out' and early L5 onset. Second, the slowly progressing dementia process may impair sleep not directly but through emergence of prodromal features such as behavioral or neuropsychiatric symptoms. This mechanism may be less likely as associations were also present in persons without depressive symptoms, and independent of napping. Third, sleep disorders, particularly the presence of sleep-disordered breathing, may underlie some of the associations of poor sleep with dementia risk.[42] Sleep-disordered breathing may instigate neurodegenerative processes through intermittent hypoxia and oxidative stress, or through cardiovascular or proteostatic mechanisms.[43] We could only account for such effects by adjusting for a self-reported proxy of sleep-disordered breathing, which might have been insufficient. Further research to disentangle the specific roles of actigraphy-estimated nighttime wakefulness and sleep-disordered breathing in neurodegenerative or Alzheimer's disease pathologies remains needed.

Another remark regarding our *APOE*-stratified findings is that, interestingly, associations of sleep with dementia risk seemed restricted to *APOE* ε4 non-carriers, although we found no statistically significant interactions after correcting for multiple testing. Possibly, disturbed sleep and carrying *APOE* ε4 impact dementia risk similarly, e.g. through protein misfolding,[39] synaptic[44] or hematopoietic effects.[4] The damage accumulated by carrying ε4 throughout life then marginalizes potential harmful effects disturbed sleep, or what underlies it, may have on dementia risk. The discrepancy of our findings with previous work,[13] reporting that sleep fragmentation increases risk of Alzheimer's disease only in *APOE* ε4-carriers, is not readily explained. Possibly, survival bias in this previous study[13] through including old (mean age >80) ε4-carriers,[45,46] or modeling poor sleep differently may have played a role.

We could not confirm the hypothesis that circadian disturbances, reflected by variability and stability of activity rhythms, are implicated[47] in dementia etiology. Yet, the association of earlier L5 onset with increased dementia risk in the next 2 years suggests a phase advance of nighttime inactivity as a prodromal feature of dementia and

Alzheimer's disease. Heterogeneity of activity rhythm findings in dementia risk, including ours, with regard to the direction of a prodromal phase shift[10] and use of different modeling strategies[11,48] should be further investigated.

In conclusion, actigraphy-estimated nighttime wakefulness indicating an incapability to sleep is associated with an increased risk of dementia, especially Alzheimer's disease. At the same time, circadian disturbances as reflected in 24-hour activity rhythms played a limited role in dementia risk in this population of middle-aged and elderly persons.

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SUPPLEMENTARY TABLES

Supplementary Table 1. Associations of sleep, bedtime and 24-hour activity rhythm parameters with risk of dementia, additionally adjusted for sleep apnea, napping and *APOE*-ε4 genotype

Determinant (per SD increase)	Dementia HR (95% CI), after additionally adjusting for:		
	Possible sleep apnea	Napping	No. of *APOE*-ε4 allele(s)
	Cases/N=60/1,322	Cases/N=60/1,322	Cases/N=57/1,251
Sleep			
Total sleep time	1.01 (0.76-1.35)	1.03 (0.77-1.37)	0.95 (0.72-1.27)
Sleep onset latency	1.44 (1.12-1.85)	1.44 (1.13-1.84)	1.45 (1.14-1.84)
Wake after sleep onset	1.23 (0.94-1.61)	1.23 (0.95-1.60)	1.24 (0.96-1.60)
Time in bed	1.43 (1.06-1.93)	1.50 (1.11-2.04)	1.39 (1.03-1.87)
Sleep efficiency	0.73 (0.55-0.96)	0.72 (0.55-0.94)	0.71 (0.55-0.92)
Bedtimes			
'Lights out' time	0.56 (0.41-0.76)	0.54 (0.40-0.73)	0.56 (0.41-0.76)
Getting up time	0.79 (0.57-1.10)	0.82 (0.60-1.13)	0.79 (0.58-1.08)
24-hour activity rhythm			
Intradaily variability	1.05 (0.79-1.40)	0.98 (0.73-1.33)	1.08 (0.82-1.41)
Interdaily stability	0.93 (0.70-1.23)	0.95 (0.72-1.25)	0.90 (0.68-1.19)
L5 onset	0.92 (0.72-1.19)	0.92 (0.72-1.19)	0.92 (0.72-1.18)

Hazard ratios were obtained from Cox regression models, adjusted for age, sex, educational level, employment status, physical activity, alcohol consumption, body mass index, smoking status, history of cardiovascular disease, presence of hypertension, and presence of diabetes mellitus.
Abbreviations: *APOE*= Apolipoprotein E gene; CI=Confidence interval; HR=Hazard ratio; N=sample size.

Supplementary Table 2. Associations of sleep, bedtime and 24-hour activity rhythm parameters with risk of dementia, in persons without clinically relevant depressive symptoms

Determinant (per SD increase)	Dementia HR (95% CI)
	Cases/N=56/1,209
Sleep	
Total sleep time	0.95 (0.72-1.25)
Sleep onset latency	1.46 (1.14-1.88)
Wake after sleep onset	1.28 (0.99-1.64)
Time in bed	1.39 (1.03-1.88)
Sleep efficiency	0.70 (0.54-0.91)
Bedtimes	
'Lights out' time	0.55 (0.40-0.74)
Getting up time	0.77 (0.56-1.06)
24-hour activity rhythm	
Intradaily variability	1.00 (0.76-1.33)
Interdaily stability	0.95 (0.72-1.26)
L5 onset	0.82 (0.63-1.07)

Clinically relevant depressive symptoms were defined as a score ≥16 on the Center for Epidemiologic Studies – Depression Scale. Hazard ratios were obtained from Cox regression models, adjusted for age, sex, educational level, employment status, physical activity, alcohol consumption, body mass index, smoking status, history of cardiovascular disease, presence of hypertension, and presence of diabetes mellitus.
Abbreviations: CI=Confidence interval; N=sample size

Supplementary Table 3. Effect-modification of associations of sleep, bedtime and 24-hour activity rhythm parameters with risk of dementia by age and sex

Determinant (per SD increase)	Dementia HR (95% CI), age-stratified			Dementia HR (95% CI), sex-stratified		
	Age ≤ 75 years	Age > 75 years		Men	Women	
	Cases/ N=29/1,129	Cases/ N=31/193	P_{INT}	Cases/ N=29/623	Cases/ N=31/699	P_{INT}
Sleep						
Total sleep time	1.18 (0.80-1.75)	0.74 (0.49-1.11)	0.14	1.39 (0.94-2.04)	0.66 (0.44-1.00)	0.02
Sleep onset latency	1.22 (0.83-1.78)	1.54 (1.11-2.16)	0.16	1.28 (0.85-1.92)	1.57 (1.16-2.14)	0.22
Wake after sleep onset	1.34 (0.97-1.84)	1.03 (0.66-1.62)	0.77	1.24 (0.87-1.75)	1.21 (0.82-1.79)	0.81
Time in bed	1.63 (1.09-2.44)	1.00 (0.62-1.63)	0.28	2.07 (1.33-3.22)	0.99 (0.65-1.50)	0.02
Sleep efficiency	0.75 (0.52-1.07)	0.68 (0.45-1.01)	0.40	0.83 (0.57-1.23)	0.64 (0.44-0.91)	0.29
Bedtimes						
'Lights out' time	0.60 (0.40-0.89)	0.48 (0.28-0.83)	0.50	0.53 (0.36-0.79)	0.61 (0.38-0.98)	0.61
Getting up time	0.97 (0.63-1.49)	0.61 (0.37-0.99)	0.77	0.93 (0.59-1.45)	0.68 (0.43-1.06)	0.46
24-hour activity rhythm						
Intradaily variability	1.46 (0.99-2.14)	0.93 (0.64-1.35)	0.12	0.79 (0.52-1.21)	1.35 (0.93-1.96)	0.08
Interdaily stability	0.88 (0.61-1.26)	0.94 (0.61-1.43)	0.27	1.13 (0.73-1.75)	0.82 (0.57-1.18)	0.42
L5 onset	0.89 (0.59-1.33)	0.87 (0.62-1.21)	0.34	0.69 (0.47-1.02)	1.10 (0.77-1.55)	0.06

Hazard ratios were obtained from Cox regression models, adjusted for age and sex (if applicable), and educational level, employment status, physical activity, alcohol consumption, body mass index, smoking status, history of cardiovascular disease, presence of hypertension, and presence of diabetes mellitus. The age cut-off of 75 years was chosen to balance dementia incidence between strata. We tested interaction through modeling a product term of the unstandardized determinant with age or sex.
Abbreviations: CI=Confidence interval; N=sample size; $P_{INT=}$ P-value for multiplicative interaction