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RESEARCH ARTICLE

# Actigraphy-estimated sleep and 24-hour activity rhythms and the risk of dementia

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## Abstract

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

**Methods:** We included 1322 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.

**Results:** During follow-up, 60 individuals developed dementia, of which 49 had Alzheimer's disease (AD). 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 AD. We found no associations of 24-hour activity rhythms with dementia risk.

**Discussion:** 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.

KEYWORDS
24-hour activity rhythms, actigraphy, Alzheimer's disease, cohort, dementia, epidemiology, longitudinal, population-based, prospective, rest-activity rhythms, sleep

## 1 | 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 (AD) 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, or as an early feature of disease before a diagnosis can be made.

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 AD.[13] Last, only a minority of population-based studies investigated 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 data from the population-based Rotterdam Study cohort. We followed 1322 middle-aged and elderly individuals (mean age 66 years) for more than 11 years. We compared sleep and 24-hour activity rhythm parameters using mutually adjusted models and investigated effect-modification by *APOE* ε4 status.

**RESEARCH IN CONTEXT**

1. Systematic review: We reviewed the literature through PubMed and references of relevant articles on the association of actigraphy-estimated sleep and 24-hour activity rhythms with incident cognitive decline or dementia: longitudinal studies were scarce. None investigated both sleep and 24-hour activity rhythm parameters or compared associations. Relevant potential interactions, such as those with apolipoprotein E4 (*APOE*-ε4), should be taken into account.
2. Interpretation: Findings indicate that actigraphy-estimated nighttime wakefulness, but not a fragmented or unstable 24-hour activity rhythm, plays a role in dementia etiology. A phase advance of sleep and "lights out" time may indicate prodromal dementia.
3. Future directions: Future studies may (a) focus on the role of actigraphy-estimated poor sleep, specifically nighttime wakefulness, in dementia etiology; (b) further investigate potential effect-modification by *APOE*-ε4; and (c) further investigate potential prodromal features such as a phase advance of sleep or earlier "lights out" time.

## 2 | METHODS

### 2.1 | Study setting and population

This study is embedded in the Rotterdam Study, a prospective population-based cohort starting in 1990. Participants were recruited from inhabitants of a representative suburban district of a large Dutch city, independent of health-care seeking.[17] Participants underwent a 2-hour interview at home, and subsequently underwent an extensive set of examinations (a total of 5 hours) during 2 visits to a dedicated research center strategically placed in the district center. Rounds are repeated every 4 to 5 years. In parallel, 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 Medical Center. All participants provided written informed consent for participation and to have medical information obtained from their treating physicians. We reported this study in line with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (see checklist in supporting information).

Between September 2004 and March 2007 (baseline of the current study), we invited participants who visited the research center and were deemed able to understand instructions to keep an actigraph for 7 days and also complete a daily sleep diary. A 7-day recording duration was chosen to balance an incrementally lower added value of extra days of recording[18] with a prolonged participant burden in this population-based study. For this first assessment of actigraphy in our cohort, we invited a subset of 2632 participants, of whom 2063 (78%) aged 62.4 ± 9.4 years accepted. We excluded participants with: (a) actigraph malfunctioning (n = 197); (b) less than 96 hours of consecutive recording (n = 109); (c) measurements during daylight savings (n = 23); (d) missing information on dementia status (n = 54). Last, we excluded persons aged <55 years at baseline, as those were considered not at risk for dementia in a population-based setting (n = 358; see Figure S1 in supporting information for a flowchart of participant selection).[19] The 1322 included individuals were on average 2.5 years younger, 8% less likely to be female, and had a 0.4 higher Mini-Mental State 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 until onset of dementia; loss to follow-up; death; or January 1, 2016. Follow-up totaled to 11,630 person-years (95% of the possible total without loss to follow-up[20]; 8.8 years per person on average).

### 2.2 | Sleep and 24-hour activity rhythms

Participants wore an actigraph around the wrist (ActiWatch model AW4, Cambridge Technology Ltd) for 138 ± 14 hours (median = 144) and completed a sleep diary during the same time period.[21] The Actiwatch is a research-grade actigraphy device, used to assess both sleep and 24-hour activity rhythms in a research and clinical setting, which has been validated against polysomnography.[22,23] Participants pressed a marker button on the device to denote "lights out" time (time intending to go to sleep) 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.[22] Counts were summed per 30-second epochs. We defined "sleep onset" as the midpoint of the first immobile period lasting ≥10 minutes after "lights out" with ≤1 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[24,25]: 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. We chose these non-parametric indicators of the 24-hour activity rhythm as these are thought to better represent the non-sinusoidal form of the rhythm in older adults.[26]

Correlations among sleep and 24-hour activity rhythm parameters at baseline in a similar study population have been reported previously.[27]

## 2.3 | 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. Regardless of attending the research center, for all participants we surveilled medical records of general practitioners and the regional institute for outpatient mental health care for dementia. As a result, dates of diagnoses were not centered around examination rounds but distributed throughout the follow-up. A consensus panel adjudicated diagnoses according to standard criteria. In this study, we considered the outcomes of all-cause dementia (Diagnostics and Statistical Manual of Mental Disorders—3rd Edition Revised [DSM-III-R]; hereafter: dementia), and AD (National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association [NINCDS—ADRDA]; including confirmed, probable, and possible AD).

## 2.4 | Covariates

For our etiological study, we selected potential confounders, or proxies for unmeasured confounders, based on theoretical knowledge as recommended in the disjunctive cause criterion.[28] We considered age, sex, education (categorized as primary, secondary/lower vocational, intermediate vocational, and higher vocational/university), paid employment, self-reported physical activity,[29,30] habitual alcohol consumption, body mass index, positive history of cardiovascular disease (transient ischemic attack [TIA], stroke, heart disease), smoking status, presence of hypertension, and presence of diabetes mellitus as potential confounders. Measurements of covariates took place during home interviews or at research center visits and are described in detail elsewhere.[31] For the sensitivity analyses we assessed depressive symptoms[32] (Centre for Epidemiological Studies–Depression Scale [CES-D]), possible sleep apnea (two questions of the Pittsburgh Sleep Quality Index [PSQI]),[33] napping (napping per day during daytime and evenings according to the sleep diary), and number of *APOE* ε4 alleles.[31]

## 2.5 | Statistical analysis

We used Cox proportional hazards regression models to associate sleep and 24-hour activity rhythm parameters (independent variable) with incident dementia and AD (dependent variable). We adjusted analyses for confounders by adding as independent variables age and sex in model 1, and 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 model 2. 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).

Post-hoc, we restricted analyses to persons without paid employment. Also, we presented stratified results for all parameters by *APOE* ε4 genotype (≥1 ε4 allele versus no ε4-alleles), age (≤75 vs >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 three stratifications ($P = .05/30$).

Last, we explored whether associations depended on follow-up time to provide some insight into possible reverse causation.[34] We performed analyses in increasingly longer epochs of follow-up time from baseline (eg, baseline to 2 years, baseline to 4 years, etc), using Firth's penalized Cox regression to account for the smaller number of events.[35]

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.[34]

Sleep variables were winsorized (ie, values of outliers changed toward the mean) to 3 standard deviations (SD) and subsequently standardized to facilitate comparison. Missing values on covariates (a median of 1% missing [interquartile range 0%-7%]) were imputed using five multiple imputations, except *APOE* genotype, performed with IBM SPSS Statistics version 24 (IBM Corp, Armonk, NY, USA). Statistical analyses were performed with R software (packages: survival, coxphf).

# 3 | RESULTS

We included 1322 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 AD.

**TABLE 1** Characteristics of study population at baseline

| Characteristic (unit) | Values (N = 1322) |
|---|---|
| Age at baseline (years) | 66.1 ± 7.6 |
| Female | 699 (53%) |
| Educational level<br>Primary education<br>Lower/intermediate or lower vocational<br>Higher or intermediate vocational<br>Higher vocational or university | 109 (8%)<br>585 (44%)<br>390 (30%)<br>238 (18%) |
| Paid employment | 274 (21%) |
| Physical activity (MET-hours/wk) | 62 (19-96) |
| Alcohol consumption (g/d) | 9 (1-20) |
| Smoking status<br>Never<br>Former<br>Current | 413 (31%)<br>695 (53%)<br>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[a] | 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 |

*Note*: Characteristics of the study population at baseline. 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.
Abbreviations: APOE, apolipoprotein E; CES-D, Center for Epidemiological Studies–Depression Scale; MET, metabolic equivalent of task; N, sample size.
[a]Missing 71 participants, including 3 persons with incident Alzheimer's disease.

## 3.1 | Associations of sleep and 24-hour activity rhythms with dementia risk

Longer sleep-onset latency (hazard ratio [HR] per 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 AD, 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 AD (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 AD 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 (Table S1 in supporting information). Also, restricting analyses to persons without clinically relevant depressive symptoms did not substantially affect estimates (Table S2 in supporting information). Post-hoc restriction to individuals without paid employment also showed no meaningful influence on our estimates (Table S3 in supporting information).

## 3.2 | Effect modification by *APOE* ε4, age, and sex

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* ε4 interaction term survived multiple testing.

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 (Table S4 in supporting information).

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 (Table S4). Yet, we found no statistically significant interactions with sex.

## 3.3 | Increasing epochs of follow-up time

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 AD. Overall, findings were similar for AD.

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

| | Dementia HR (95% CI) | | Alzheimer's disease HR (95% CI) | |
|---|---|---|---|---|
| | Cases/N = 60/1322 | | Cases/N = 49/1322 | |
| Determinant (per SD increase) | 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 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) |

*Note*: Hazard ratios (HRs) were obtained with Cox regression models. HRs above 1.00 denote that, with a higher value of the determinant, the hazards of dementia increases, while HRs below 1.00 indicate that dementia risk decreases. To compare HRs across determinants with different units, HRs are expressed per standard deviation increase. 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.
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) Cases/N = 60/1322 | Alzheimer's disease HR (95% CI) 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) |

*Note*: 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. Hazard ratios (HRs) above 1.00 denote that, with a higher value of the determinant, the hazards of dementia increases, while HRs below 1.00 indicate that dementia risk decreases. To compare HRs across determinants with different units, HRs are expressed per standard deviation increase. 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 <.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.

## 4 | 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, which may especially classify sleep-onset latency more accurately. 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 beta (A$\beta$) or tau pathology, which may affect sleep-wake regulating brainstem regions[36] years before dementia diagnosis,[37,38] confounded associations with dementia risk. Last, 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[9,11,13,39-41] 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,[9,39] 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

**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 *P* |
|---|---|---|---|
| | ε4 carriers Cases/ N[a] = 21/346 | ε4 non-carriers Cases/ N[a] = 36/905 | |
| Sleep | | | |
| Total sleep time | 1.04 (0.65-1.66) | 0.96 (0.68-1.35) | .89 |
| Sleep-onset latency | 1.28 (0.82-2.01) | 1.51 (1.10-2.06) | .38 |
| Wake after sleep onset | 0.83 (0.49-1.39) | 1.63 (1.19-2.25) | .01 |
| Time in bed | 1.14 (0.72-1.82) | 1.73 (1.16-2.57) | .02 |
| Sleep efficiency | 0.95 (0.57-1.56) | 0.61 (0.44-0.84) | .04 |
| Bedtimes | | | |
| "Lights out" time | 0.52 (0.31-0.87) | 0.42 (0.27-0.65) | .12 |
| Getting up time | 0.55 (0.31-0.98) | 0.84 (0.56-1.26) | .20 |
| 24-hour activity rhythm | | | |
| Intradaily variability | 0.75 (0.41-1.36) | 1.16 (0.85-1.60) | .03 |
| Interdaily stability | 1.36 (0.75-2.47) | 0.85 (0.62-1.18) | .07 |
| L5 onset | 0.70 (0.42-1.16) | 0.94 (0.69-1.29) | .48 |

*Note*: 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 *APOE* ε4 alleles.
Abbreviations: *APOE*, apolipoprotein E gene; CI, confidence interval; L5, least active consecutive 5 hours of the day; N, sample size.
[a]Missing data on *APOE* ε4 genotype for 71 individuals in total, of whom 3 had incident Alzheimer's disease.

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 AD pathology[42] in the brain seems to be a likely[43] substrate. Such confounding, however, is not in line with the 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.[43] Also, a previous study in a sample with the same age distribution and similar sociodemographic characteristics found that high intradaily variability was related strongest to a cerebrospinal fluid biomarker profile suggestive of preclinical AD.[44] Yet, intradaily variability was unrelated to incident dementia or AD in our study. Also arguing against confounding by preclinical pathology are the time-stratified analyses, which showed that poor sleep was not associated substantially more strongly with dementia risk in short versus longer follow-up durations. If preclinical pathology would drive these associations, one would expect to see stronger associations when sleep is measured closer to the diagnosis. 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 self-reported napping. Third, sleep disorders, particularly the presence of sleep-disordered breathing, may underlie some of the associations of poor sleep with dementia risk.[45] Sleep-disordered breathing may instigate neurodegenerative processes through intermittent hypoxia and oxidative stress, or through cardiovascular or proteostatic mechanisms.[46] We could only account for such effects by adjusting for an estimation of possible sleep apnea based on two PSQI questions regarding snoring and breathing pauses. In future work, sleep-disordered breathing should be taken into account by assessing these with respiratory sensors overnight. Further research to disentangle the specific roles of actigraphy-estimated nighttime wakefulness and sleep-disordered breathing in neurodegenerative or AD pathologies remains needed. Future studies may also consider relating changes in actigraphy-estimated sleep or 24-hour activity rhythms over repeated measurements, or specific measures of sleep fragmentation, with risk of dementia or related outcomes.

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, for example, through protein misfolding,[42] synaptic,[47] or hematopoietic effects.[4] The damage accumulated by carrying ε4 throughout life then marginalizes potential harmful effects that 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 AD only in *APOE* ε4-carriers, is not readily explained. Possibly, survival bias in this previous study[13] through including old (mean age >80)

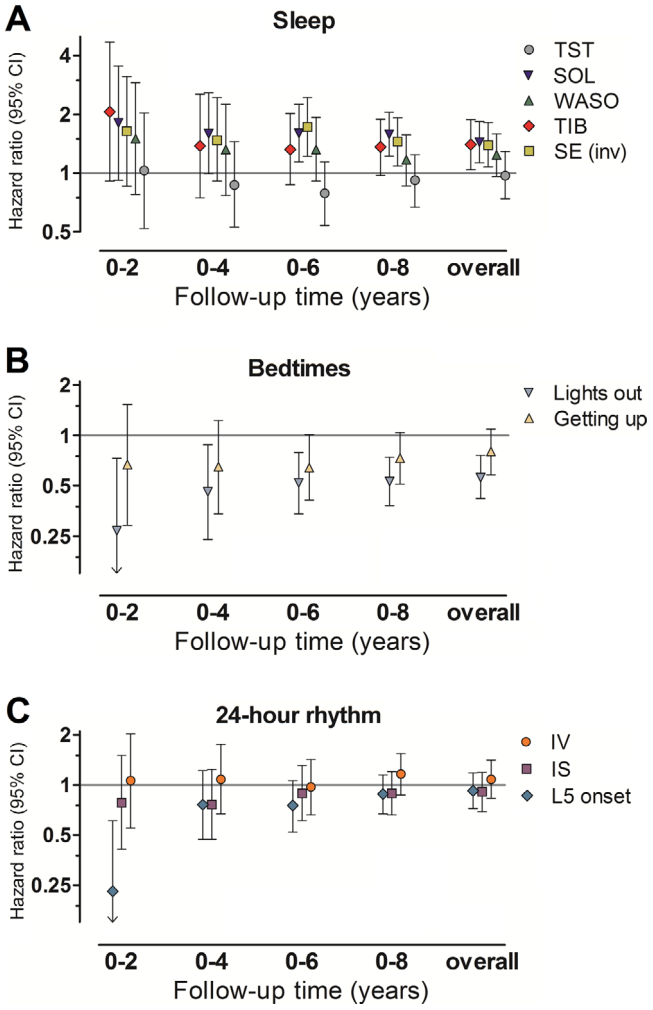


**FIGURE 1** Associations of sleep, bedtime, and 24-hour activity rhythm parameters with incident dementia, over increasing epochs of follow-up time. NOTE. Associations of (A) sleep, (B) bedtimes, and (C) 24-hour activity rhythm parameters with risk of dementia are shown for increasing epochs of follow-up 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 $\log_2$-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. 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

ε4-carriers,[48,49] 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[50] 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 AD. 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[11,51] should be further investigated.

We studied a relatively young age group (mean age 66 years), which we felt may provide insights particularly interesting for prediction or prevention. Importantly, age at baseline did not substantially modify our results, suggesting that our findings may be compared to that of previous studies that used samples with mean ages between 76 and 83 years.[9,11,13,39-41]

In conclusion, actigraphy-estimated nighttime wakefulness indicating an incapability to sleep is associated with an increased risk of dementia, especially AD. 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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Thom S. Lysen and M. Arfan Ikram had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

## AUTHOR CONTRIBUTIONS

Thom S. Lysen, Annemarie I. Luik, Henning Tiemeier, M. Arfan Ikram made substantial contributions to the conception and design of the work. Annemarie I. Luik, M. Kamran Ikram, Henning Tiemeier, M. Arfan Ikram supervised the acquisition of the data. Thom S. Lysen performed the data analysis. All authors contributed to interpreting the data. All authors contributed to drafting this manuscript and critically revising it for important intellectual content. All authors approved the final version to be published. All authors agree to be accountable for all

aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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## SUPPORTING INFORMATION

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

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