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Dose-response associations of device-measured sleep regularity and duration with incident dementia in 82391 UK adults

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Abstract

Background Sleep is a crucial lifestyle factor with impacts on mental and cognitive health. The associations between objectively measured sleep and risk of incident dementia are not yet fully understood. To evaluate the associations of device-measured sleep duration and regularity with incident dementia and explore whether sleep regularity moderates the association of sleep duration with dementia.

Methods Population-based prospective cohort study of 82,391 adults aged 43 to 79 years from the UK Biobank accelerometry subsample, collected between 2013 and 2015, followed up to 2022. Device-based sleep duration (h/day) and sleep regularity index (SRI), a metric ranging from 0-100 that quantifies a person's sleep regularity (with a greater value indicating higher consistency), were calculated from wrist-worn accelerometry data recorded over the course of one week. Incident all-cause dementia cases were obtained from national hospital admission, primary care and mortality data followed up to 30 November 2022. We used Cox proportional hazard models to estimate the hazard ratios (HRs) for incident dementia after adjustment for common demographic and clinical covariates.

Results Over a mean follow-up of 7.9 years, 694 incident dementia cases occurred. We observed a U-shaped association between sleep duration and incident dementia, with only short sleep (< 7 h) being significantly associated with a higher risk of dementia. The median sleep duration for short sleepers (< 7 h) of 6.5 h, compared to the reference point of 7.9 h was associated with HR of 1.19 (95%CI 1.01,1.40) for incident dementia. Sleep regularity was negatively associated with dementia risk in a near-linear fashion (linear $p = 0.01$, non-linear $p = 0.57$). When we dichotomized sleep regularity, those in the higher sleep regularity group (SRI ≥ 70) had an HR of 0.74 (95%CI 0.63, 0.87) compared to those with lower sleep regularity (SRI < 70). The beneficial associations between sleep regularity and incident dementia were present only among participants with short (< 7 h) and long (≥ 8 h) sleep duration.

Conclusions Assuming that the associations we observed are causal, maintaining a regular sleep pattern may help offset the deleterious association of inadequate sleep duration with dementia. Interventions aimed at improving sleep regularity may be a viable option for people not able to achieve the recommended hours of sleep.

Keywords Actigraphy, Sleep pattern, Sleep regularity, Sleep duration, Dementia, Public health, Epidemiology

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Background

Dementia is a non-communicable disease (NCD) with major consequences [1]. Cognitive decline and dementia in ageing raise critical societal and economic issues, with the World Health Organization (WHO) projecting that 141 million people will be affected by dementia by 2050 [2, 3]. While dementia shares common behavioral risk factors with other NCDs, such as physical activity (PA), diet, and mental health, the significance of sleep and its implementations of related guidelines are comparatively understated [4, 5]. Sleep plays a fundamental role in human physiology and is closely linked to numerous aspects of brain function, and cognitive and physical well-being [6]. A systematic review examining the relationship between sleep duration and a wide range of health outcomes in adults revealed that 7 to 8 h of sleep per day exhibited the most favorable associations with health [7]. However, 96% of the studies in this review paper used subjective sleep duration assessments [7]. Considerable evidence on the association between self-reported sleep duration and dementia showed that only short [8, 9] or long [10] sleep durations was associated with a higher risk of dementia amongst middle-aged to older adults. Other studies have found a U-shaped association between sleep duration and dementia [11, 12]. However, much of the existing evidence found to date on the association between sleep duration and dementia relied on questionnaire-based measurement of sleep characteristics [8–13]. These measurements are more imprecise than objective measures and have inherent biases such as social desirability and poor recall [14, 15].

There is a growing interest in how other dimensions of sleep, such as sleep regularity (i.e., consistency in sleep-wake patterns on a day-to-day basis), are associated with adverse health [16–19]. A recent report by the US National Sleep Foundation (NSF) and systematic reviews have shown that more irregular sleep is generally associated with adverse health and performance outcomes (e.g., mortality, cognitive performance, metabolic indicators, mental health, etc.), but comparatively fewer studies have focused on brain health [20, 21]. Night-to-night variability in sleep patterns has been found to be associated with higher levels of amyloid burden, which in turn is linked to cognitive decline and progression to dementia [16]. While a recent study showed that the association between sleep regularity and dementia can be independent of sleep duration [19], it remains unclear whether the adverse health effects of irregular sleep can be mitigated by healthy sleep duration, and vice versa. This understanding is critical for public health guidance and may offer practical means to improve health outcomes for individuals with unhealthy sleep patterns. Furthermore, those with insufficient sleep duration on weekdays may extend their sleep over the weekend ("catch-up sleep") to recover sleep debt, but this results in irregular sleep. Therefore, studies examining the association between sleep duration, sleep regularity, and dementia is critically important.

To date, no study has investigated whether sleep regularity mitigates the adverse health effects of insufficient sleep duration on dementia risk. Thus, the aim of this study was to examine the associations of device-measured sleep duration and regularity with incident dementia in adults. A secondary aim was to understand whether sleep regularity may modify the association of sleep duration with dementia.

Methods

Study participants and design

The UK Biobank enrolled over 500,000 participants between 2006 and 2010 [22]. The ethical approval was received from the UK National Health service (NHS) and National Research Ethics Service for the UK (No. 11/NW/0382) and participants provided written informed consent. Participants in the current study were drawn from the UK Biobank accelerometry sub-study, a prospective cohort of 103,104 participants aged 43 to 79 years. These participants were asked to wear a wrist accelerometer (Axivity AX3) on their dominant wrist to record daily rest–activity patterns for one week during June 2013 to January 2016 [23]. Participants with sufficient data from wrist accelerometers and non-missing information on all covariates were included. Accelerometer data were deemed sufficient if the participant provided at least three days of sleep data with at least one of those days being a weekend night of sleep. Non-wear periods and the distinction between non-wear and sleep periods were identified following standardized procedures [24]. We defined the start of the accelerometry period as the follow-up time onset [25]. We excluded participants with diagnosed dementia prior to accelerometer wear.

Sleep assessment

We used a validated sleep detection algorithm alongside a non-wear algorithm to determine sleep status and calculate sleep duration based on relative changes in wrist tilt angle between successive 5 s windows [24, 26, 27]. For each interval of 5 s, the average of the estimated wrist tilt angle was calculated and served as an input for the algorithm. Sleep periods were those with a tilt angle change of less than 5 degrees for 5 min or longer. We used the Sleep Regularity Index (SRI) to assess participants' sleep regularity [23, 28]. The SRI score quantifies day-to-day consistency in sleep–wake patterns derived from raw accelerometer data using procedures that have previously

been used in the UK Biobank [27, 29]. It captures day-to-day variation in bedtime, waketime, sleep durations, naps, and awakenings (wake after sleep onset, WASO), and is scaled from 0 to 100, representing the percentage probability of an individual being in the same sleep/wake state at any two time points 24 h apart (0 being random and 100 perfectly regular) (Supplementary Text 1). It is more advantageous compared to other measures of regularity in sleep timing by assessing sleep-wake patterns between successive days without assuming any specific structure of sleep, making it applicable to populations with highly fragmented sleep or naps [23, 30].

Outcome ascertainment

Incident dementia cases were obtained through data linkage with routinely-collected, coded national hospital admission, primary care and mortality data followed up to 30 November 2022 [31]. Primary care data were obtained through collaborations with data providers. Death information was obtained from the National Health Service (NHS) Digital of England and Wales, and NHS Central Register and National Records of Scotland. Across all outcome event sources, the earliest date of recorded dementia was considered the date of diagnosis. We identified incident cases of dementia using previously validated ICD-10 (International Classification of Diseases) primary and secondary diagnoses provided in Supplementary Table 1 [32].

Covariates

We selected covariates based on previous literature [8, 25, 27, 31]. These included common self-reported demographic and clinical covariates such as age, sex, ethnicity, fruit and vegetable consumption, smoking status, alcohol consumption, mental health issues, highest attained education level, coffee consumption, sleep problems including sleeplessness and insomnia, employment status, and device-based physical activity level, sedentary behavior, and body mass index (BMI).

Statistical analyses

We capped the range of sleep duration and SRI values both at the 2.5 and 97.5 percentile to minimize the influence of sparse data. Cox proportional hazard models were used to assess the independent association between sleep duration and regularity (independent variables), and the risk of incident dementia (outcome measure).

We carried out continuous dose–response analyses to investigate the potential linear and non-linear relationships between the exposures and the risk of incident dementia. Stratified analysis was used to explore the potential modification effect of sleep duration on sleep regularity. We stratified sleep duration into three groups, short (<7h), adequate (≥7 and <8 h), long (≥8 h) based on the sleep duration distribution within our sample. We classified participants with adequate sleep as optimal (≥7 and <8 h) sleepers, and participants with short or long sleep as non-optimal (<7 h and ≥8 h) sleepers. These categories were guided by the NSF sleep duration guidelines with modification considering our study used device-measured sleep whereas the guidelines were developed using self-reported sleep [33, 14]. The SRI cutoff of < 70 for irregular sleep was determined based on the bottom quintile of the SRI distribution within the sample [23, 34]. A recent UK Biobank accelerometry sub-study using the SRI score identified that an SRI < 70 corresponds to a SD > 1.9 h for sleep onset and offset variability and > 1.6 h for sleep duration variability [23].

In all dose-response analyses, we placed the knots at the 10th, 50th, and 90th percentiles of the exposure distribution [35], which is a common approach to avoid overfitting and account for data sparsity while ensuring adequate model flexibility and accuracy [29, 31]. The Wald test was used to assess non-linearity. For sleep duration, which we expected to have a U-shaped relationship with the outcome [36, 37], we first set the reference point to the lowest sleep data point. We estimated the optimal dose, which refers to the specific exposure value at which we observed the maximum significant risk reduction. We then set the reference point to the optimal dose for better graphical presentation. For sleep regularity, which had a monotonic relationship with the outcome, we set the reference point to the lowest SRI value observed in the data, and estimated the "minimum beneficial dose" [31] as the exposure value at which the risk reduction was 50% of the maximum risk reduction observed.

Proportional hazards assumptions were tested (and satisfied) using the Schoenfeld residuals. Models were adjusted for all covariates described above.

Sensitivity and additional analyses

We conducted sensitivity analyses: 1) excluding participants who developed dementia during the first two years of follow-up, 2) excluding participants who reported poor self-rated health to account for the potential influence of reverse causation [38], 3) excluding all participants who reported day or night shift work to remove the potential work schedule bias, 4) incorporating an additional adjustment for sleep apnea [39, 40] as a covariate in the model, 5) redefining the optimal sleep category of sleep duration with a wider range ≥ 7 and < 9 h and 6) excluding participants with self-reported sleeplessness and insomnia. We identified sleep apnea cases from hospitalizations (ICD-10 code G473), primary care data (Read Version 2 and 3 codes), and self-reported baseline data (and self-reported non-cancer illness code 1123 in the UK Biobank

data field 20002) (Supplementary Table 2). In a sensitivity analysis examining the associations of sleep regularity and dementia, we set the reference point to the optimal dose at which maximum risk reduction was observed. We conducted an additional stratified analysis to explore the potential modification effect of all three categories of sleep duration (short, adequate and long) on sleep regularity. For comparability with previous literature [8, 11, 13] we also conducted a categorical dose-response analysis of sleep duration, regularity, and incident dementia. We categorized sleep regularity into three distinct groups based on tertiles, and two groups using the SRI cutoff of 70.

All analyses were conducted in R version 4.3.0 and models were fitted using rms (version 6.7.0) and survival (version 3.5.5) packages.

Results

Sample and events

Supplementary Fig. 1 describes the sample derivation. Our analytic sample consisted of 82,391 participants with a mean (SD) age of 62.4 (7.7) years; 55.9% were female, and 93.6% were White. Among the participants, a total of 783 cases of incident dementia were recorded during a mean follow-up time of 7.9 (1.0) years. Following reductions due to data sparsity and outliers through the truncation of each sleep exposure, we observed 694 and 729 incident dementia events in the analyses for sleep duration and regularity, respectively. Detailed characteristics of participants stratified by sleep regularity and sleep duration are presented in Table 1 and Supplementary Table 3, respectively. A significant portion of participants (78.3%) had regular sleep, while 21.7% had irregular sleep.

Independent association of sleep duration and regularity with incident dementia

Figures 1 and 2 show the continuous dose-response association of sleep duration and regularity with incident dementia. In multivariable-adjusted analyses, there was a U-shaped relationship between sleep duration and the risk of incident dementia (Fig. 1). The dose-response curve shows a higher risk of dementia in both directions, with a steeper increase in risk as sleep duration decreases and the reference point set at the optimal dose, i.e., lowest hazard ratio (HR) for dementia. However, the association between long sleep duration and dementia risk did not reach statistical significance (Fig. 1). The optimal dose (based on the maximum incident dementia risk reduction) determined the reference point of 7.9 h sleep per day. Sleep regularity exhibited a monotonic inverse relationship with incident dementia (Fig. 2). At the highest measured SRI value of 94.2, we observed the maximum risk reduction of 46% (HR: 0.54 [0.40-0.73]), compared to the reference point at the lowest SRI value of 51.5. The minimum SRI dose (point estimate where the risk reduction was 50% of the maximum reduction observed) for sleep regularity was 66.1, corresponding to an HR of 0.77 (95%CI 0.63, 0.95). The HR corresponding to the median SRI value of 72.9 was 0.76 (95%CI 0.61,0.94).

Associations of sleep regularity with incident dementia by sleep duration

Figure 3 shows the dose-response relationship between sleep regularity and incident dementia modified by groups of sleep duration (optimal ≥7 and <8 h, non-optimal (<7h and ≥ 8h). For non-optimal sleepers, we observed a statistically significant inverse association between sleep regularity and incident dementia. The curve demonstrated a consistent decrease with increasing SRI, which started to level off after an SRI of around 80. The minimum sleep regularity dose for non-optimal sleepers was 61.6, corresponding to a HR of 0.75 (95% CI 0.63, 0.90). The HR corresponding to the median SRI value of 72.9 was 0.65 (96%CI 0.50, 0.85). For optimal sleepers, there was no evidence of an association until a value of approximately 80, after which the association became inverse but remained non-statistically significant. The statistical interaction tests between sleep duration and sleep regularity were non-statistically significant (all $p > 0.05$) (Supplementary Table 4).

Sensitivity and additional analyses

The results remained robust in all sensitivity analyses, such as excluding participants who developed dementia within the first two years of follow-up ($n = 69$) (Supplementary Figs. 2–4), excluding participants with self-reported poor health ($n = 2056$) (Supplementary Fig. 5–7), excluding participants employed in shift work ($n = 6221$) (Supplementary Fig. 8–10), additionally controlling for sleep apnoea (Supplementary Fig. 11–13) and redefining the sleep duration category (Supplementary Fig. 14). Excluding participants who experience frequent sleeplessness or insomnia ($n = 23{,}595$), the association between short sleep duration and dementia was attenuated to null due to the widened 95% CIs (Supplementary Fig. 15). However, the association of sleep regularity, including stratification by sleep duration, did not materially differ from the main analyses (Supplementary Fig. 16 and 17). The overall pattern of the dose-response curve between sleep regularity and incident dementia remained consistent after changing the reference point to an optimal SRI value of 94.2 (Supplementary Fig. 18). Continuous dose–response analysis with three groups of sleep duration (short, adequate, long) showed comparable inverse associations in the dose-response curves for

Table 1 Participants baseline characteristics by sleep regularity (*n*=82391)

	Overall	Irregular (SRI ≤70)	Regular (SRI>70)
n (%)	82391 (100.0)	17869 (21.7)	64522 (78.3)
Age, y (mean (SD))	62.4 (7.7)	62.7 (7.8)	62.3 (7.7)
Sex = Male, n (%)	36339 (44.1)	7065 (39.5)	29274 (45.4)
Ethnicity = White, n (%)	77088 (93.6)	16572 (92.7)	60516 (93.8)
BMI (mean (SD))	26.7 (4.5)	27.3 (4.9)	26.6 (4.4)
Fruit and vegetable consumption[a] (mean (SD))	8.0 (4.5)	8.0 (4.6)	8.0 (4.5)
Smoking, n (%)			
Current	5339 (6.5)	1490 (8.3)	3849 (6.0)
Never	47134 (57.2)	9663 (54.1)	37471 (58.1)
Previous	29918 (36.3)	6716 (37.6)	23202 (36.0)
Alcohol consumption[b] (mean (SD))	13.7 (15.4)	13.8 (16.3)	13.7 (15.1)
Coffee intake, cups per day (mean (SD))	2.0 (2.0)	2.0 (2.0)	2.0 (2.0)
Mental health issue[c] = Yes, n (%)	27005 (32.8)	6589 (36.9)	20416 (31.6)
Education[d], n (%)			
A/AS level	10618 (14.9)	2278 (15.1)	8340 (14.9)
College	35996 (50.6)	7257 (48.0)	28739 (51.3)
CSE	3225 (4.5)	772 (5.1)	2453 (4.4)
NVQ/HND/HNC	4583 (6.4)	1052 (7.0)	3531 (6.3)
O level	16696 (23.5)	3766 (24.9)	12930 (23.1)
Sleeplessness and insomnia[e] (%)			
Never/rarely	20515 (24.9)	3825 (21.4)	16690 (25.9)
Sometimes	38967 (47.3)	8228 (46.0)	30739 (47.6)
Usually	22909 (27.8)	5816 (32.5)	17093 (26.5)
Employment shift[f], n (%)			
Employed in day shift work	3285 (4.0)	799 (4.5)	2486 (3.9)
Employed in night shift work	2936 (3.6)	999 (5.6)	1937 (3.0)
Employed not in shift work	40817 (49.5)	8056 (45.1)	32761 (50.8)
Retired/not in workforce	35353 (42.9)	8015 (44.9)	27338 (42.4)
Light physical activity, mins per day (mean (SD))	118.4 (62.5)	114.0 (60.6)	119.7 (63.0)
Moderate physical activity, mins per day (mean (SD))	34.8 (28.2)	31.2 (26.7)	35.8 (28.5)
Vigorous physical activity, mins per day (mean (SD))	5.3 (6.3)	4.4 (5.6)	5.5 (6.5)
Sedentary behaviour, mins per day (mean (SD))	715.4 (106.1)	738.7 (111.2)	709.0 (103.7)
Dementia = Yes (%)	783 (1.0)	239 (1.3)	544 (0.8)

The columns breakdown corresponds to sleep regularity: irregular, 0~70 SRI; regular, 70~100 SRI. There were significant differences ($p<0.05$) across sleep score groups in all the characteristics shown in the table. Values represent mean (SD) unless specified otherwise

[a] Fruits and vegetable consumption is servings per day

[b] Alcohol consumption: above guidelines are >14 units per week, where 1 unit = 8 g of ethanol

[c] Had ever seen a doctor or psychiatrist for nerves, anxiety or depression

[d] A/AS level; Certificate of Secondary Education; National Vocational Qualification/Higher National Diploma/Higher National Certificate; O level

[e] Had trouble falling asleep at night or wake up in the middle of the night

[f] Shift work was defined as a work schedule that falls outside of the normal daytime working hours of 9am-5pm. Night shifts are identified when the corresponding work schedule involves working through the normal sleeping hours, for instance working through the hours from 12am to 6am

the short and long categories (Supplementary Fig. 19). Categorical analysis of sleep duration showed higher, but not statistically significant, risk of incident dementia for participants with short sleep durations with HR 1.18 (0.97,1.43) compared to those with adequate sleep (Supplementary Fig. 20). There was no significant association between long sleep duration and risk of incident dementia. Categorical analyses of sleep regularity by SRI cutoff of 70 (Supplementary Fig. 21) and population tertile-based groups (Supplementary Fig. 22) produced results consistent with the main analyses.

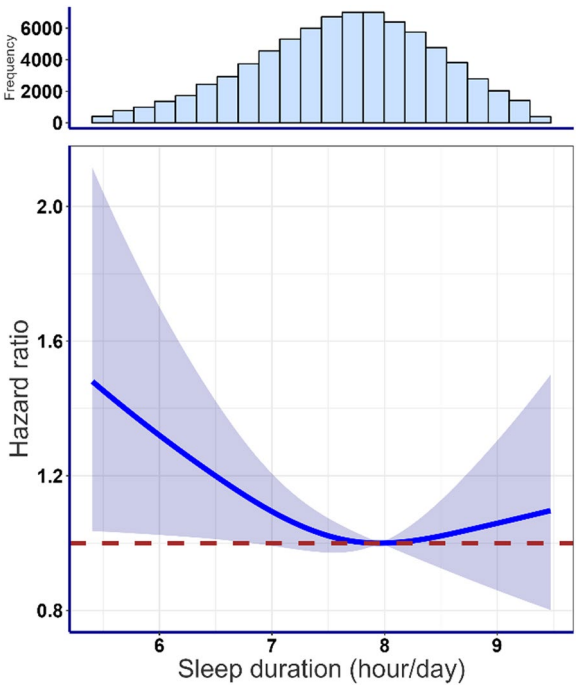

Fig. 1 Association of sleep duration with incident dementia ($n = 78256$, 694 events). Dose-response curves showing incident dementia hazard ratio associated with increasing daily sleep duration. Reference point set to the optimal data point (7.9 hazard ratios of sleep/day). Adjusted for age, sex, ethnicity, body mass index, fruit and vegetable consumption, smoking, alcohol consumption, coffee consumption, mental health issue, sleeplessness/insomnia, education, shiftwork, light-intensity physical activities, moderate-to-vigorous physical activity and sedentary behaviour. Data are shown for $n = 78256$ with 694 events and with a mean follow-up of 7.9 (1.0) years

Discussion

This study examined the association of device-measured sleep duration and sleep regularity with the risk of incident dementia. It is also the first study that investigated whether sleep duration moderates the association of sleep regularity with dementia. Our results suggest a U-shaped dose-response relationship of sleep duration with incident dementia, with only short sleep duration showing significantly higher risk. More regular sleep patterns were associated with lower dementia risk in a dose-response manner. The sample median SRI of approximately 73, representing the day-to-day consistency in sleep/wake patterns (with a greater value indicating higher consistency), was associated with 24% lower risk (95%CI 6-39%) for incident dementia. The beneficial associations between sleep regularity and incident dementia were present only among participants with short and long sleep.

Our findings are in line with previous literature that found short device-measured sleep duration to be associated with dementia, but not for long sleep duration [8]. Other recent meta-analyses suggest a significant U-shaped association between sleep duration and dementia risk, with a self-reported sleep duration of around 7 h being the most beneficial [36, 37]. Additionally, a meta-analysis of prospective cohort studies showed that there is a significant association between longer sleep duration and dementia risk [41]. However, one study suggested that the association between self-reported long sleep duration (> 9 h per night) and increased dementia risk might be due to reverse causation, as the association did not remain after exclusion of cases diagnosed within the first 5 or 10 years of follow-up [42].

Recent studies have indicated that sleep regularity is favorably associated with a wide range of health outcomes, including metabolic health, mortality, and mental health [20, 43–47]. While a recent device-based UK Biobank study found a U-shaped association between SRI and incident dementia [19], we report a novel finding of an inverse monotonic near-linear association between sleep regularity and incident dementia risk. Notably, our SRI distribution differs from that of the aforementioned study, aligning more closely with the established patterns derived from the UK Biobank [23] (Supplementary Fig. 23). Moreover, the U-shaped association identified in the previous study, suggesting that more regular sleep is associated with a higher dementia risk, lacks robust empirical support. Our finding is consistent with a longitudinal study on older women, which revealed that greater variability in sleep duration, measured by the standard deviation, was associated with higher risk of incident dementia [48]. It also aligns with studies associating variability of sleep parameters or circadian activity rhythms to dementia risk [18], Alzheimer's disease biomarkers [49], and cognitive impairment [50]. Our study used the SRI as a sleep regularity measurement, which captures variations in multiple dimensions of sleep patterns, covering not only sleep duration, but also sleep onset and offset, sleep-wake state within the sleep window and naps.

Our findings suggest that sleep regularity might help mitigate the deleterious association of sleep duration with dementia. It also suggests that sleep regularity may matter less for dementia risk when sleep duration is in the optimal range. Among participants with non-optimal sleep duration, we found a significant inverse association between sleep regularity and incident dementia. This suggests that more regular sleep was associated with lower dementia risk, especially when optimal sleep duration was not met. For example, participants with a median SRI score of 72 were associated with 35% lower dementia risk (95%CI 15-50%) compared to those with a lower SRI score of 52. However, this beneficial association of

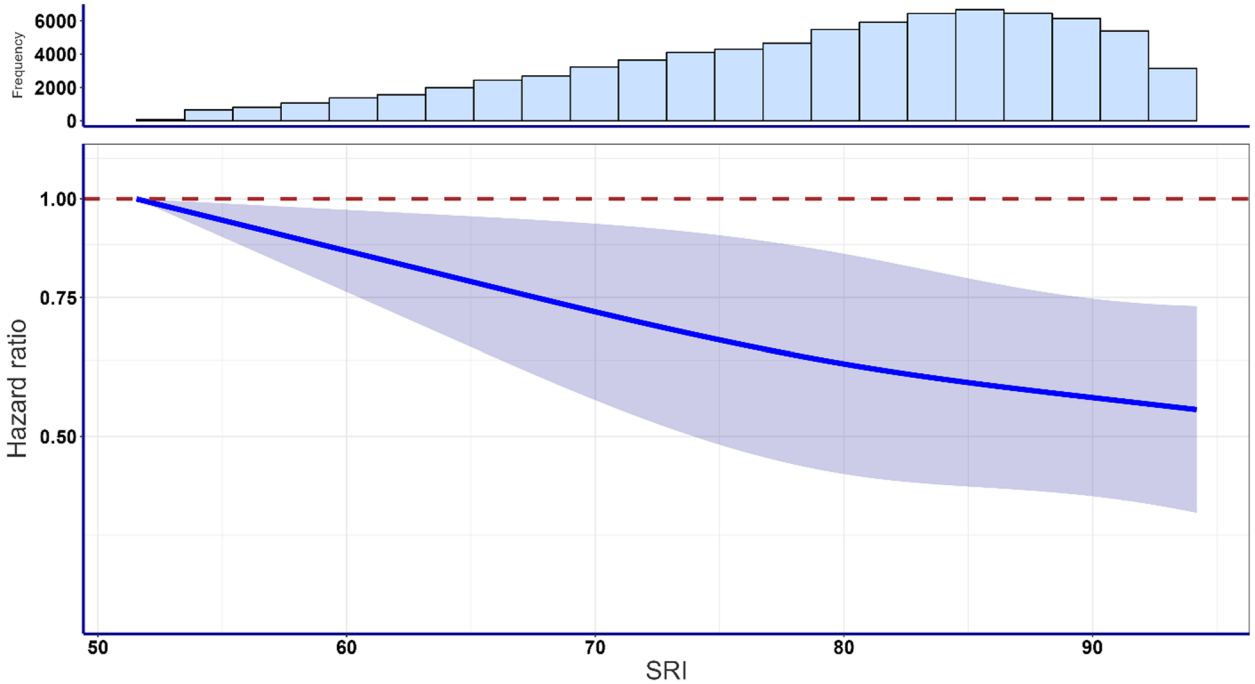

Fig. 2 Association of sleep regularity with incident dementia ($n = 78262$, 729 events). Dose-response curves showing incident dementia hazard ratio associated with increasing sleep regularity index (SRI) (linear $p = 0.013$, non-linear $p = 0.566$). Reference point set to the lowest data point (SRI = 51.5). Adjusted for age, sex, ethnicity, body mass index, fruit and vegetable consumption, smoking, alcohol consumption, coffee consumption, mental health issue, sleeplessness/insomnia, education, shiftwork, light-intensity physical activities, moderate-to-vigorous physical activity and sedentary behaviour. Data are shown for $n = 78262$ with 729 events and with a mean follow-up of 7.9 (1.0) years

regular sleep and dementia was not significantly evident among participants with optimal sleep of 7 to 8 h. A recent study using SRI scores from accelerometer data in the UK Biobank found that sleep regularity was more strongly associated with mortality risk than sleep duration [47]. Collectively, this body of evidence suggests that for those with non-optimal sleep duration, maintaining regular sleep patterns could potentially mitigate some risk of incident dementia.

Experimental and epidemiological studies provide a plausible mechanism linking poor sleep patterns and Alzheimer's disease (AD), which is the most common form of dementia [51, 52]. Sleep critically regulates AD-related proteins, such as amyloid-β (Aβ) and tau, preventing their accumulation resulting in aggregates critical in pathogenesis [53]. Epidemiological evidence using self-reported sleep duration demonstrated that short and long sleep duration were associated with greater Aβ burden [54]. Lack of sleep has specifically been linked to heightened production of Aβ at synapses during wakefulness compared to sleep, as well as a decrease in the clearance of Aβ from the brain's interstitial space [55, 56]. Sleep regularity is an indirect approach to assessing the degree of alignment between sleep and circadian timing (and light-dark cycles), which is known to have biological relationships with dementia [57–60]. Experimental studies on mice have shown that circadian disruption negatively affects the Aβ dynamics and speeds up the build-up of amyloid plaques in the brain [51]. Given that studies have indicated the circadian system's role in regulating amyloid-beta levels in the brain, it may partly explain the potential role of regular sleep in mitigating the adverse associations of unhealthy sleep duration on incident dementia.

The role of sleep regularity in dementia has not been extensively investigated in large cohorts with objective data. Our study assessed concurrently two important sleep dimensions, duration and regularity, providing a comprehensive understanding of the multidimensional nature of sleep and its association with dementia. Other strengths include the large sample size, device-based sleep measurements, the use of a novel sleep regularity metric [23], and the performance of both continuous and categorical analyses. Our study has several limitations, including its observational nature, which limits causal interpretation, and makes the possibility of some of our findings to be explained by residual or unmeasured confounding. The accelerometry data were collected 5.5 years after the baseline data collection, however covariates were relatively stable over time, with the exception of employment status [27, 29, 61]. The

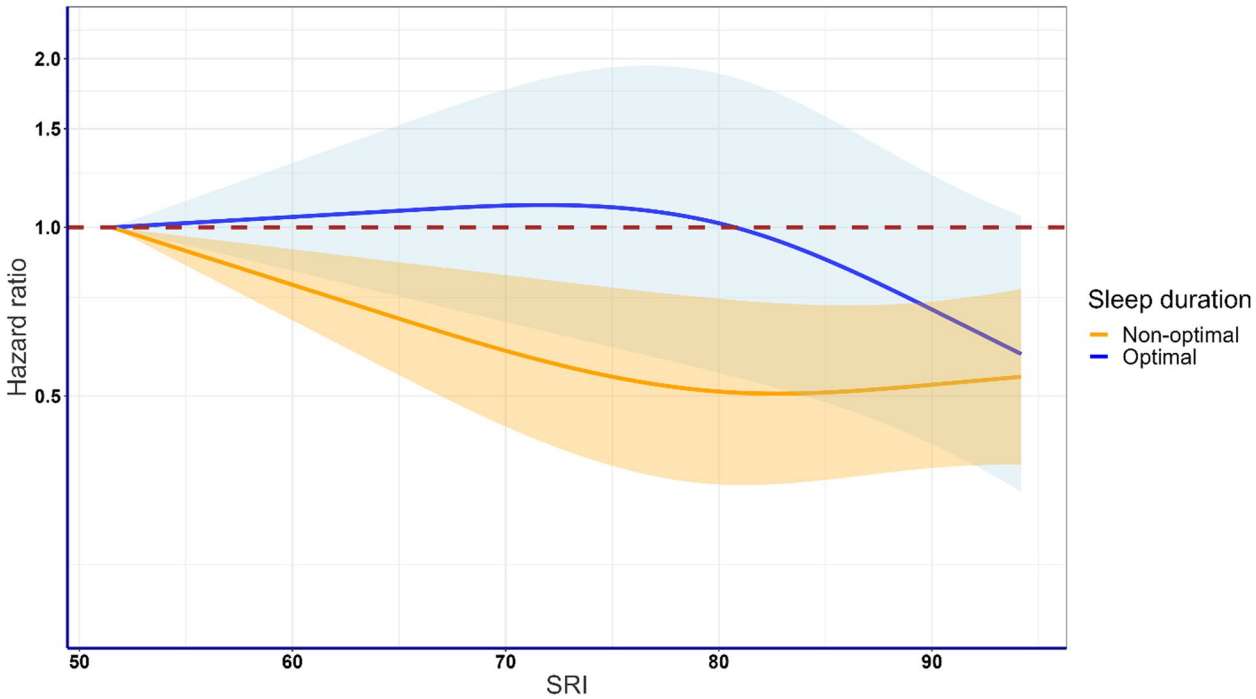

Fig. 3 Association of sleep regularity with incident dementia stratified by sleep duration ($n = 78262$, 729 events). Dose-response curves showing incident dementia hazard ratio associated with increasing sleep regularity index (SRI) stratified by two groups of sleep duration (optimal ≥ 7 and < 8 h/day, and non-optimal < 7 h/day and ≥ 8 h/day). Reference point set to lowest data point (SRI = 51.5). Adjusted for age, sex, ethnicity, body mass index, fruit and vegetable consumption, smoking, alcohol consumption, coffee consumption, mental health issue, sleeplessness/insomnia, education, shiftwork, light-intensity physical activities, moderate-to-vigorous physical activity and sedentary behaviour. Data are shown for $n = 78262$ with 729 events and with a mean follow-up of 7.9 (1.0) years

response rate in the UK Biobank was 5.5% [62], however a previous study suggested that the association of lifestyle exposures and long term health outcomes is not materially influenced by poor sample representativeness [63]. Our results pertain to an older age group predominantly consisting of individuals from a white background. To enhance generalizability of our findings, further research with other diverse cross-cultural cohorts is warranted.

Our study highlights the importance of integrating sleep regularity components into existing duration-focused public health guidelines to promote overall sleep health. Future clinical interventions could explicitly address regularity in addition to duration, such as implementing personalized behavioural strategies designed to promote consistent daily sleep-wake schedules, particularly for individuals unable to meet sleep duration recommendations due to personal, work or health related conditions.

Conclusions

Sleep duration and regularity were associated with risk of incident dementia. Sleep regularity showed an inverse association with incident dementia among those with non-optimal sleep duration, while no significant association was observed among those with optimal sleep duration. In the presence of insufficient sleep duration, maintaining regular sleep timing may reduce the risk of incident dementia. Considering the challenges of behavior change, future guidelines could place equal emphasis on sleep regularity and duration to expand intervention options and personalized advice.

Abbreviations

AD	Alzheimer's disease
Aβ	Amyloid-β
BMI	Body mass index
HR	Hazard ratio
NHS	National Health Service
NCD	Non-communicable disease
NSF	National Sleep Foundation
PA	Physical activity
SRI	Sleep regularity index
UKBB	UK Biobank
WASO	Wake after sleep onset
WHO	World Health Organization

Supplementary Information

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Supplementary Material 1.

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Authors' contributions
WB, RKB, MNA, and ES were major contributors in the design of the work, data analysis, and drafting the manuscript. YSB, SP, AJKP, NAK, JPC, SMWR, and PAC made substantial contributions to the interpretation of the data and manuscript revision. All authors read an approved the final manuscript.

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Data availability
The data that support the findings of this study are available from the UK Biobank, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with the permission of the UK Biobank.

Declarations

Ethics approval and consent to participate
The ethical approval was received from the UK National Health service (NHS) and National Research Ethics Service for the UK (No. 11/NW/0382) and participants provided written informed consent.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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