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Daytime napping and Alzheimer's dementia: A potential bidirectional relationship

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Abstract

INTRODUCTION: Daytime napping is frequently seen in older adults. The longitudinal relationship between daytime napping and cognitive aging is unknown.

METHODS: Using data from 1,401 participants of the Rush Memory and Aging Project, we examined the longitudinal change of daytime napping inferred objectively by actigraphy, and the association with incident Alzheimer's dementia during up to 14-year follow-up.

RESULTS: Older adults tended to nap longer and more frequently with aging, while the progression of Alzheimer's dementia accelerates this change by more than doubling the annual increases in nap duration/frequency. Longer and more frequent daytime naps were associated with higher risk of Alzheimer's dementia. Interestingly, more excessive (longer or more frequent) daytime napping was correlated with worse cognition a year later, and conversely, worse cognition was correlated with more excessive naps one year later.

DISCUSSION: Excessive daytime napping and Alzheimer's dementia may possess a bidirectional relationship or share common pathophysiological mechanisms.

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1. Background

Excessive daytime napping is frequently seen in older adults, especially in those with Alzheimer's dementia [1]. A recently proposed mechanism is the arousal deficiency due to neuronal and neurotransmitter loss in wake-promoting neurons associated with tau tangles [2], one of the pathological hallmarks of Alzheimer's disease (AD), resulting in sleep-wake disturbances and a higher propensity for daytime napping. The other way around, excessive sleepiness during daytime, which may be a cause of longer and frequent naps, has also been linked to faster cognitive decline or AD pathology build-up [3–5].

However, there remains conflicting results regarding the effects of daytime napping on cognition in prior research. While some have shown benefits of napping on acute cognitive performance, mood, and alertness, particularly in younger adults [6,7], more naps have also been tied to adverse outcomes in long-term, including poor cognition [8–11]. For example, some cross-sectional studies reported associations between excessive self-reported napping and worse cognitive function [12–15]; a recent longitudinal study also showed an association between longer nap duration and faster cognitive decline in older men [1]. However, others also demonstrated the opposite way—self-reported napping was associated with lower odds of having cognitive impairment [16].

Nevertheless, all prior studies have performed only one single nap assessment within each participant. It remains unclear how daytime napping evolves with aging, particularly cognitive aging. In addition, these studies mostly employed subjective nap assessments that may not be reliable, especially in older adults given their cognitive status [17]. Longitudinal assessments of objective naps are required to understand the complex link between daytime napping and Alzheimer's dementia.

In the current work, we primarily tested two hypotheses: (1) participants nap longer and/or more frequently with aging, and this longitudinal change is exacerbated as participants progress from no cognitive impairment to mild cognitive impairment (MCI), and is further accelerated after the diagnosis of Alzheimer's dementia; and (2) participants with excessive objective daytime napping (i.e., longer and/or more frequent) are at increased risk of developing Alzheimer's dementia. Meanwhile, we also tested how daytime napping and cognitive performance drive each other's change longitudinally using a bivariate cross-lagged modelling. Testing these hypotheses will help clarify the relationship between daytime napping and Alzheimer's dementia by unraveling how the evolution of napping is intertwined with cognitive aging or the progression of Alzheimer's dementia.

2. Methods

2.1. Study design and subjects

We reported results from the on-going Rush Memory and Aging Project (MAP), a prospective, observational cohort study conducted at the Rush Alzheimer's Disease Center. MAP was approved by a Human Subjects Committee of Rush University Medical Center and was performed in accordance with the ethical standards laid down in the 1964

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Declaration of Helsinki and its later amendments. All participants signed an informed consent and a repository consent to allow data sharing.

The MAP project began in 1997. From 2005 and onwards, a watch-like device (Actical, Philips Respironics, Bend, OR) was introduced to record motor activity annually[18]. Subjects assessed with this Actical device were included in this work [N = 1,401; female: 1,065 (76.5%) age: 81.4 ± 7.5 (mean ± standard deviation, SD); see Table 1 for their demographics and clinical characteristics]. These subjects were also followed annually with assessments for cognitive function, comorbidities, and medication use. We used clinical data up until late April 2020.

2.2. Assessment of daytime napping using actigraphy

The Actical device was worn on the non-dominant wrist continuously for up to 14 days [mean±standard deviation (SD): 10±1 days; range: 2–14 days] during each visit. A daytime napping episode was identified as sleep during the common day light or daily active hours between 9AM and 7PM using a previously validated sleep scoring algorithm based on wrist activity counts [19,20]. Based on napping episodes identified, nap duration was calculated as the accumulated nap minutes per day, and nap frequency was calculated as the accumulated number of naps per day during the assessed days. Model details about this algorithm were summarized in Supplement Methods.

2.3. Annual assessment of cognition and clinical diagnoses

Cognitive function was assessed with a battery of 21 neuropsychological tests administered each year. Nineteen tests across a range of cognitive abilities were used to construct measures of five cognitive domains [21]. Individual tests were first z-score transformed based on the corresponding baseline means and SDs of all subjects in the cohort. A global composite cognitive measure was obtained by averaging the 19 z-scores. Details about the setup of the best batteries and the calculations of the global cognition have been published elsewhere [21] with cognitive data generated in that study directly available through the MAP to maintain the consistency and validity. For these cognitive measures, zero represents the mean, and one represents one SD of the baseline score of all MAP participants. Positive scores indicate better cognitive performance.

Diagnosis of Alzheimer’s dementia was based on the criteria recommended by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association (NINCDS/ADRDA) [22]. MCI was determined if persons were judged to have cognitive impairment by the neuropsychologist but did not meet the diagnostic criteria for dementia by the clinician [23].

2.4. Assessment of covariates

We grouped covariates in terms of (1) demographics (age, sex, and education), (2) nighttime sleep and circadian daily activity rhythm (total nighttime sleep duration, sleep fragmentation [24], wake after sleep onset (WASO), interdaily stability, and intradaily variability) [25], (3) co-morbidities and medications [depression, thyroid disease, vascular diseases, vascular disease risk factors, and medications that may affect sleep (anxiety and insomnia treatments,

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analgesics, anticonvulsants, or beta blockers)], and (4) *APOE* ε4 genotype. Detailed methods for assessing each covariate were summarized in Supplement Methods.

2.5. Statistical analysis

To examine how daytime napping evolved longitudinally during the progression of Alzheimer's dementia, we performed linear mixed-effects models with two change points anchored at the diagnoses of MCI and Alzheimer's dementia, respectively. Nap duration and frequency were included separately as a longitudinal outcome; time in years since baseline was a predictor; time in years since MCI diagnosis was included to estimate additional changes after MCI diagnosis; and time in years since Alzheimer's dementia diagnosis was included to estimate additional changes after the diagnosis of Alzheimer's dementia. Subject-specific random intercepts and random slopes were considered. These models were adjusted for age, sex, and education. Interaction items for each of the three time-lag variables and each of demographics were also included. Inclusion criterion for these analyses was that participants should had at least two instances of Actical assessments (regardless of baseline diagnoses; N = 1,065; see Fig. 1). These analyses were performed using MATLAB (Ver. R2019a, The MathWorks Inc., Natick, MA, USA).

To test the associations of baseline daytime napping with incident Alzheimer's dementia, a series of Cox-proportional hazards models were performed. The core models included nap duration or nap frequency separately as a predictor with adjustment of age, sex, and education. Nap duration and nap frequency were both square-root-transformed to correct for right-skewness. Adjusted models were subsequently used to control for groups of covariates step-wisely. The subjects who did not have follow-up clinical assessments (115) or were diagnosed with Alzheimer's dementia (83) at baseline were excluded, resulting in N = 1,203 participants who entered the analyses (see Fig. 1). These analyses were performed using JMP Pro (version 15, SAS Institute Inc., Cary, NC, USA).

As secondary analyses, we also performed bivariate cross-lagged linear mixed effect models based on structural equation modelling to examine how global cognition and nap duration/frequency drove each other longitudinally. Details of this modelling process were summarized in Supplement Methods and Supplement Fig. 1.

For all statistical tests described above, an alpha level of 0.05 (two-sided) was considered statistically significant.

3. Results

Table 1 summarizes the demographic and clinical characteristics of participants at analytical baseline. Nap duration and nap frequency were positively correlated (Spearman's $\rho = 0.91$; $p < 0.0001$). They were both positively correlated with age (using square root transformed napping measures: $r = 0.21$ and 0.23, respectively; both p's < 0.0001). There were no significant differences between men and women in nap duration $p = 0.946$) or nap frequency ($p = 0.627$). They were not significantly correlated with education ($r = -0.04$ and -0.01; $p = 0.177$ and 0.869, respectively).

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To examine the longitudinal changes in daytime napping, 1,065 participants who had at least two instances of actigraphy assessments were included (see Fig. 1 for a flowchart of selection of participants). Among them, 812 (75.7%) had no cognitive impairment (NCI) at baseline (384 had developed MCI and 146 had gone onto Alzheimer's dementia diagnosis); 209 (19.5%) had MCI at baseline (101 had developed Alzheimer's dementia); and 44 (4.1%) were diagnosed with Alzheimer's dementia at baseline. During NCI, nap duration increased over time with an annual increase of 11.31 ± 0.69 min [mean ± standard error (SE) unless otherwise indicated; $p < 0{\cdot}0001$]. The rate of increase doubled after the diagnosis of MCI (additional 13.35 min/year or total rate of 24.66 ± 1.49 min/year; $p < 0{\cdot}0001$) and a further near tripling after the diagnosis of Alzheimer's dementia (additional 43.69 min/year or total rate of 68.35 ± 6.47 min/year, $p < 0{\cdot}0001$; 68.35 min/year is over six times the rate during NCI) (Fig. 2A; Table 2). Similarly, participants took naps more frequently with aging at NCI (rate of frequency increase = 0.35 ± 0.02 times/year; $p < 0.0001$), and the rate doubled after the diagnosis of MCI (0.67 ± 0.04 times/year; $p < 0.0001$) and almost doubled again after the diagnosis of Alzheimer's dementia (1.25 ± 0.11 times/year; $p < 0.0001$) (Fig. 2B; Table 2).

To examine the association between daytime napping and incident Alzheimer's dementia, participants who did not have follow-up clinical assessments (115) or were diagnosed with Alzheimer's dementia (83) at baseline were excluded (see Fig. 1 for selection of participants). Of the remained 1,203 participants without Alzheimer's dementia at baseline, 290 (24%) developed Alzheimer's dementia within 6.0 years on average (range: 1–15; SD: 3.5) after baseline. A longer daytime nap was associated with higher risk of developing Alzheimer's dementia with a hazard ratio (HR) of 1.20 [95% confidence interval (CI): 1.06–1.35; $p = 0.004$; Table 3] per 1 SD higher nap duration variable. As an example, participants who napped ≥ 1 hour/day had a 1.4-fold increased risk compared to those who napped < 1 hour/day (Fig. 2C). The effect of 1 SD increase in higher nap duration was equivalent to that of being 1.6 years older at baseline [i.e., per 1 year older of age, the HR is 1.12; therefore, the HR 1.20 is corresponding to log(1.20)/log(1.12) = 1.6 years older of age; see Table 3]. More frequent naps were also associated with higher risk of incident Alzheimer's dementia, with a HR of 1.23 (95% CI: 1.08–1.39; $p = 0.001$) per 1 SD higher nap frequency variable, which was equivalent to the effect of being 1.9 years older (Table 4). Participants who napped once or more than once a day had 40% increased risk of developing Alzheimer's dementia compared with those who napped less than once a day (Fig. 2D). The associations were unchanged after further adjustment of covariates covering sleep and circadian daily activity rhythms, medical comorbidities and medications, and APOE ε4 genotype, separately or altogether (Tables 3 and 4).

To examine how daytime napping and cognition drive each other's change longitudinally, we applied a bivariate cross-lagged linear mixed effecting modelling to data of 1,003 participants who had both actigraphy and cognitive assessments in at least two visits. The bivariate models showed relatively satisfactory model fit (for nap duration: root mean square error of approximation = 0.055, comparative fit index = 0.910; for nap frequency, root mean square error of approximation = 0.056, comparative fit index = 0.909). Both models demonstrated a decline in global cognition overtime, with the rate of decline = −0.052 ± 0.004 unit per year in the model for nap duration, and = −0.051 ± 0.004 unit per year in the

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model for nap frequency (see “Cognition slope factor: Intercept” in Supplement Table 1). And consistently with the observations from the linear mixed effects change point models, nap duration increased by 0.207 ± 0.008 SD (SD of square room transformed nap duration = 3.528) per year, and nap frequency increased by 0.202 ± 0.008 SD (SD of square root transformed nap frequency = 0.606; “Nap slope factor: Intercept” in Supplement Table 1) per year. The slopes of global cognition and nap duration were negatively correlated (“Cognition slope, nap slope” in Supplement Table 1; $p = 0.011$), meaning that participants with faster cognitive decline tend to have increasing nap duration over time. However, this association was not observed for nap frequency ($p = 0.608$). Interestingly, there were significant bidirectional cross-lagged associations between nap duration and global cognition, as well as between nap frequency and global cognition (section C of Supplement Table 1). Specifically, global cognition was correlated with nap duration/nap frequency in the following year, and similarly, nap duration/nap frequency was correlated with global cognition in the subsequent year.

4. Discussion

To the best of our knowledge, this is the first cohort study demonstrating a bidirectional link between objectively measured, excessive daytime napping and Alzheimer’s dementia or cognitive impairment. These results show that participants tended to nap longer and more frequently with aging. Most importantly, the progression of Alzheimer’s dementia appeared to accelerate this aging effect by doubling or more than doubling the annual changes (increases) in nap duration/frequency. Our results also show that longer and more frequent daytime naps were associated with higher risk of developing Alzheimer’s dementia. In addition, our results directly demonstrate that longer or more frequent naps in a given year was correlated with lower level of cognitive performance one year later, and conversely, lower cognitive performance was correlated with subsequent longer and more frequent naps one year later.

This is also the first study examining the relationship between objectively measured daytime napping and incident Alzheimer’s dementia that involves both males and females. In a previous study, older men who napped more than 120 min/day had a higher odds of developing cognitive impairment compared with those who napped less than 30 min/day [1]. Our observation is in keeping with this. In addition, there was no interaction between nap duration and sex, implying no sex difference in the association between nap duration and the risk of Alzheimer’s dementia. This is also consistent with a prior study reporting cross-sectional evidence that older women who had long napping were more likely to have poor cognitive function or a diagnosis of dementia [14].

Nighttime sleep disturbances are known risk factors for developing cognitive impairment or dementia [26–28]. We found that the association between excessive daytime napping and incident Alzheimer’s dementia remained with similar effect sizes after adjustment of covariates for nighttime sleep quantity and quality including sleep duration, sleep fragmentation, and WASO, implying a role of daytime napping independent from changes in these nighttime sleep related characteristics. We further note that we did not observe direct associations between these nighttime sleep measures and incident Alzheimer’s dementia

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Therefore, it is unlikely that the increased duration and frequency of daytime napping were simply to compensate nighttime sleep loss; there might be other underlying disorders that affect, for example, the wake-promoting network that leading to lengthened sleep during both daytime and nighttime. Supporting this hypothesis, a recent postmortem study showed that patients with AD had decreased wake-promoting neurons in three brain regions (i.e., noradrenergic locus coeruleus neurons, orexin/hypocretin-producing neurons in the lateral hypothalamic area, and histaminergic neurons in the tuberomammillary nucleus) and the neuronal changes appear to be more linked to tau pathology (instead of amyloid plaque) [2], providing evidence for direct effect of AD-related degeneration on the arousal system. Altogether, the results indicate that there might be additional pathway(s) beyond the adverse effects of nighttime sleep disturbances; it is plausible that our observed associations of excessive daytime napping at baseline and increased risk for Alzheimer's disease during follow-up may reflect the effect of AD pathology at preclinical stages.

Alternatively, excessive daytime napping may change or reflect a change in the 24-hour circadian control, which has also shown to be prodromal to Alzheimer's dementia [29–31]. In our adjustment models, two circadian rest activity rhythm metrics were included, i.e., the interdaily stability that reflects the circadian robustness and the intradaily variability that reflects the fragmentation of rest activity rhythm. The adjustment did not attenuate the association of nap duration and nap frequency with incident Alzheimer's dementia. Note our previous study using the same cohort observed an association between intradaily variability and incident Alzheimer's dementia [30]; and we found that intradaily variability was no longer significantly associated with incident Alzheimer's dementia in the adjusted models, which may be due to the collinearity between intradaily variability and nap duration/frequency and the stronger effects of nap duration/frequency. Altogether, these results indicate that changes in daytime napping and circadian daily rhythms may have separate mechanisms to contribute to the risk of Alzheimer's dementia.

Other medical comorbidities that are associated with both daytime napping and risk of Alzheimer's dementia [32,33] may partially explain their associations. For example, in our adjusted models, depressive symptoms were significantly associated with the outcome, and the inclusion of depressive symptoms attenuated the HRs in nap duration and nap frequency by about 5%. Cardiovascular and vascular diseases are other potential pathways that may also explain the observed relationship [34,35]. Further studies examining how objectively measured daytime napping may lead to subsequent pathophysiological changes are warranted to scrutinize the nature of their relationships.

Previous cross-sectional studies have observed longer and more frequent daytime naps in older adults [36,37]. Our longitudinal design and repeated objective assessments of daytime napping based on actigraphy offer better suitability to capture these aging effects within each individual. In addition, we also demonstrated how the clinical progression of Alzheimer's dementia exerted influences on the longitudinal profiles of daytime napping. Specifically, the increased duration and frequency of daytime napping with aging became more pronounced during the stage of MCI, and these changes were further sped up after the diagnosis of Alzheimer's dementia. A potential mechanism that Alzheimer's accelerates the changes in daytime napping may be arousal deficiency due to pathological damage

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in wake-promoting neurons [2]. Prior knowledge also exists that Alzheimer's pathology leads to reduced nocturnal sleep quality [38,39] but not quantity [38]. Besides, changes in microstructural sleep patterns through electroencephalograph have also been showed in patients with clinical Alzheimer's dementia or MCI [40]. Our current study adds to this existing knowledge by demonstrating an effect of clinical Alzheimer's progression on the quantity of daytime napping (i.e., duration and frequency). Together with our finding that longer and more frequent daytime naps are prodromal to the development of Alzheimer's dementia, our results indicate a potential bidirectional relationship between them. This bidirectional relationship is further supported by our results that the one process was correlated with the other in the subsequent year.

Finally, objective assessment in this current study is likely to capture more naps than self-report used in previous research [34,41,42], or treats a long nap with certain interruptions as multiple naps. Self-reported napping habit can suffer from recall bias particularly in the elderly. So-called "snoozes" or periods of drowsiness are more likely to be detected by objective algorithm, but left out during self-report, which may further bias the evaluations of duration and frequency of napping. We also note that other aspects of napping habit require further examinations, too, for example, the timing of naps relative to the main sleep period and regularity/irregularity of napping events. Adding these aspects in future work may help refine the napping risk exposure.

There are limitations that are worth noting. First, caution should be exercised when translating our observations to younger cohorts, since the data we analyzed came from a very old cohort. Further studies are warranted to examine whether napping behaviors during middle life (e.g., before 65 years old) are associated with cognitive decline or incident Alzheimer's dementia in late life. Besides, studies using younger cohorts are also needed to better model the longitudinal profiles of nap duration and frequency in a wider period of life. Second, despite the observed longitudinal and cross-lagged associations, it is still unclear whether daytime napping and Alzheimer's dementia or cognitive decline are causally related. It is possible that daytime napping, as a behavior of older adults in free-living community, is partially a reflection of poorer health that could not be accounted for by traditional risk factors. Further studies may be required to establish a risk scoring scheme for Alzheimer's dementia or cognitive impairment based on the duration and frequency of daytime napping in older adults to facilitate the clinical applicability. Besides, future studies are also needed to examine whether a direct intervention in daytime sleep can lower risk. Third, although scoring sleep using actigraphy has been validated and has been widely used in field studies, we acknowledge that polysomnography is still the gold standard for sleep scoring. Besides, in a recent study [43], it has been reported that the Actical device and the newer version, ActiGraph provided significantly different estimates of physical activity. This raises the issue regarding the comparability of different types of actigraphy devices in sleep scoring. Large-scale studies are also warranted to valid or further optimize the actigraphy-based sleep scoring algorithm in older adults as well as for daytime sleep assessment. Finally, there could be unmeasured comorbidities that affect both daytime sleep and cognition, for example sleep apnea.[44] The MAP has started collecting SA risk scores (Berlin Questionnaire) since 2013, and only few MAP participants had this score available at

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the time of analysis (i.e., less than 300 participants).[45] This can be further examined later when new data become available.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Research in Context

1. Systematic review: Literature reviews via PubMed suggested daytime napping a common phenomenon in older adults, especially in people with Alzheimer's dementia, and associated with future risk of Alzheimer's dementia. Yet, it is unknown how daytime napping evolves over time in the context of cognitive aging.
2. Interpretation: Our findings suggested that progression of Alzheimer's dementia accelerated the aging-related changes in daytime napping. Our results also for the first time demonstrated directly that daytime napping and cognition may drive each other's changes bi-directionally.
3. Future direction: Future studies are warranted to examine: (1) the relationship between longer/more frequent daytime napping and Alzheimer's disease pathology, (2) whether earlier life (i.e., < 65 years old) daytime napping behavior is associated with late life cognition and cognitive outcomes, and (3) whether a direct intervention in daytime sleep can lower the risk of Alzheimer's dementia or cognitive decline.

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Highlights

- Daytime napping assessed objectively through actigraphy annually for up to 14 years
- Daytime napping modelled longitudinally with aging and Alzheimer's progression
- Longer/frequent daytime napping associated with higher Alzheimer's risk
- Alzheimer's progression sped up aging related changes in daytime napping
- Daytime napping and cognition drove each other's changes bi-directionally

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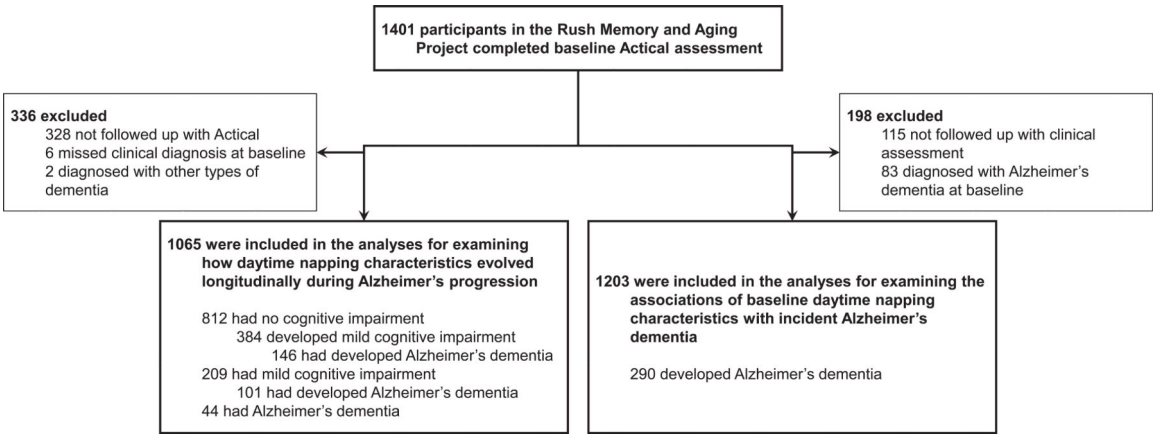

Fig. 1. Flow of participants through the study.

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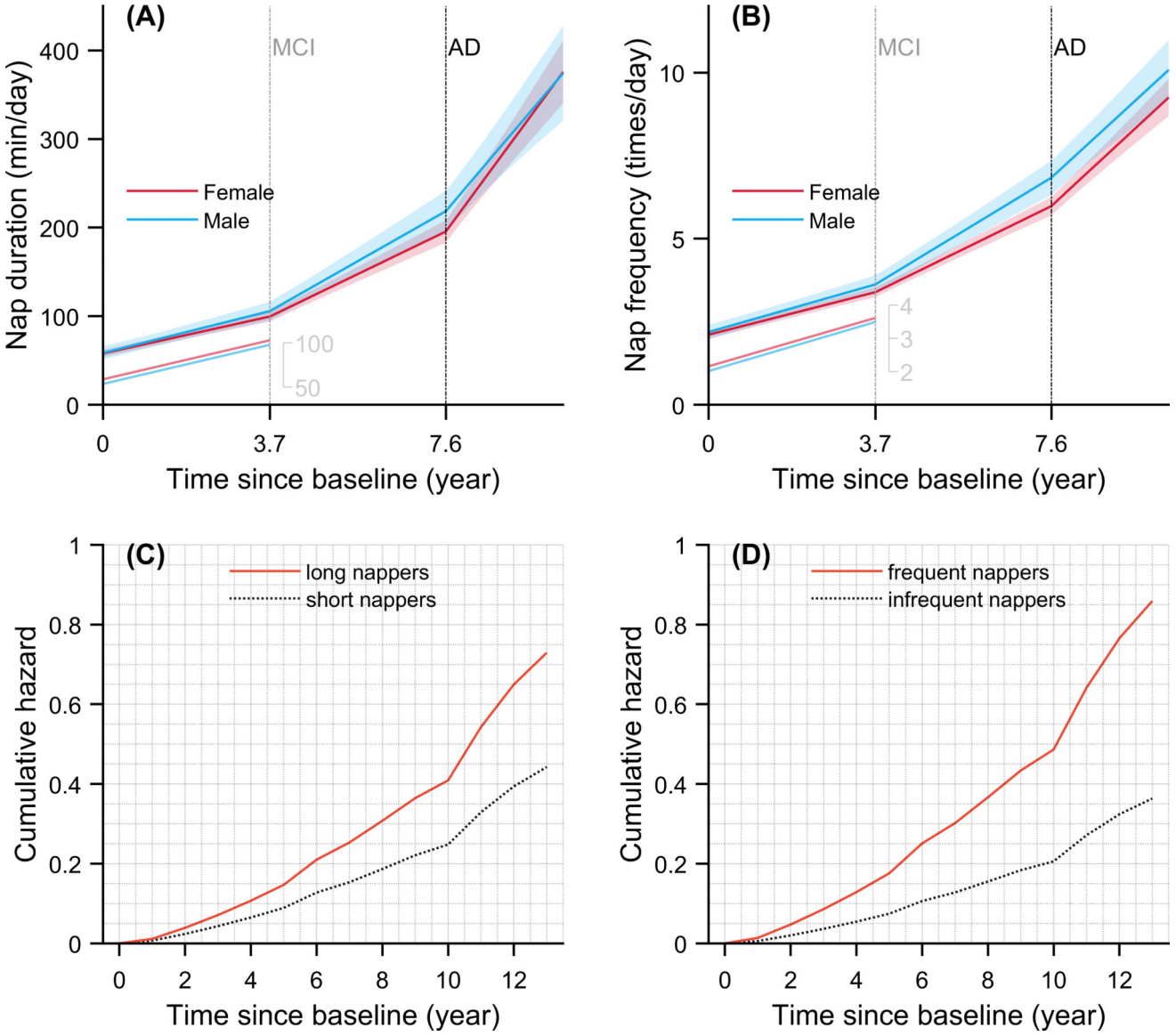

Fig. 2. Relationship between daytime napping and Alzheimer's dementia.

(A-B) Plots show predicted mean levels of nap duration (A) and nap frequency (B) based on mixed models for hypothetical female and male individuals with a mean age of 81 years (mean age of the cohort) who developed mild cognitive impairment (MCI) at 3.7 years after baseline and Alzheimer's dementia (AD) at 7.6 years after baseline. Predicted 95% confidence intervals are shown as shaded regions. The insets demonstrated the predicted mean levels of nap duration (A) and nap frequency (B) based on mixed models using a subset who never developed MCI during follow up. For better visualization, they are shifted downwards 30 and 1 units, respectively for (A) and (B). (C-D) Plots show cumulative hazard functions for nap duration (C) or nap frequency (D) for two representative individuals. Individuals who napped ≥ 1 hour/day (long nappers) had 1.4-fold increased risk compared to those who napped < 1 hour/day (short nappers). Participants who napped once or more than

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once a day (frequent nappers) had 40% increased risk of developing Alzheimer's dementia compared with those who napped less than once a day (infrequent nappers).

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Table 1.

Demographic and clinical characteristics of participants at baseline

Demographics	
Number of Participants	1401
Female	1065 (76.6%)
Age (years)	81.42 ± 7.47
Education (years)	15.04 ± 3.02
Daytime napping characteristics	
Nap duration (min/day)	46.60 [21.95–93.10]
Nap frequency (times/day)	1.80 [0.90–3.35]
Sleep and Circadian	
Total nighttime sleep duration (hour)	5.69 ± 1.45
Sleep fragmentation index (× 1E-2)	2.78 ± 0.70
Wake after sleep onset (min)	50.18 ± 16.00
Interdaily stability	0.52 ± 0.13
Intradaily variability	0.73 ± 0.20
Comorbidities and medications	
Depressive symptoms	0 [0–2]
Thyroid disease (yes)	323 (24%)
Vascular disease risk factors	1 [1–2]
Vascular disease burden	0 [0–1]
Anxiety (yes)	93(7%)
Insomnia (yes)	116 (8%)
Analgesic (yes)	1015 (73%)
Anticonvulsant (yes)	150 (11%)
Beta blocker (yes)	450 (33%)
APOE ε4 genotype	
APOE ε4 (carriers)	305 (23.00%)

Data expressed as a count (percentage %), mean ± SD, or median [inter-quartile range]. Depressive symptoms were assessed with a 10-item version of the Center for Epidemiologic Studies-Depression Scale.

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Table 2.

Longitudinal changes of daytime napping characteristics with respects to the progression of Alzheimer's dementia.

	Nap duration		**Nap frequency**	
	Estimate (SE)	***p***	**Estimate (SE)**	***p***
Intercept	57.69 (2.14)	< 0.0001	2.10 (0.06)	< 0.0001
Time since baseline (year)	11.31 (0.69)	< 0.0001	0.35 (0.02)	< 0.0001
Age (year)	1.39 (0.26)	< 0.0001	0.06 (0.01)	< 0.0001
Age * Time since baseline	0.422 (0.08)	< 0.0001	0.01 (0.00)	0.001
Sex (male)	0.38 (4.39)	0.931	0.08 (0.13)	0.559
Sex (male) * Time since baseline	1.42 (1.45)	0.329	0.04 (0.03)	0.257
Education (year)	0.36 (0.63)	0.565	0.01 (0.02)	0.102
Education * Time since baseline	−0.42 (0.21)	0.046	−0.01 (0.01)	0.017
Time since MCI (year)	13.35 (1.32)	< 0.0001	0.32 (0.03)	< 0.0001
Age * Time since MCI	0.51 (0.17)	0.003	0.01 (0.00)	0.0194
Sex * Time since MCI	2.89 (2.64)	0.273	0.12 (0.06)	0.045
Education * Time since MCI	−0.16 (0.39)	0.670	−2E-4 (0.009)	0.980
Time since dementia (year)	43.69 (6.30)	< 0.0001	0.58 (0.10)	< 0.0001
Age * Time since dementia	−0.78 (0.70)	0.266	0.004 (0.011)	0.734
Sex * Time since dementia	−14.31 (10.48)	0.172	−0.19 (0.16)	0.232
Education * Time since dementia	0.94 (1.50)	0.531	−5e-05 (0.023)	0.998

Abbreviation: dementia = Alzheimer's dementia; MCI = mild cognitive impairment.

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Table 3.

Daytime nap duration, covariates, and incident Alzheimer's dementia

	Models				
	A	**B**	**C**	**D**	**E**
Variables	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
	***p* value**	***p* value**	***p* value**	***p* value**	***p* value**
Age[a]	1.12 (1.10, 1.14)	1.12 (1.09, 1.14)	1.12 (1.10, 1.14)	1.12 (1.10, 1.15)	1.12 (1.09, 1.14)
	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Sex (female)	0.88 (0.67, 1.18)	0.95 (0.71, 1.29)	0.87 (0.65, 1.16)	0.87 (0.66, 1.17)	0.87 (0.64, 1.20)
	0.393	0.756	0.347	0.349	0.385
Education[b]	1.04 (1.00, 1.09)	1.05 (1.00, 1.09)	1.04 (1.00, 1.08)	1.06 (1.02, 1.11)	1.05 (1.01, 1.10)
	0.035	0.034	0.067	0.007	0.018
Nap duration (square root transformed)[c]	1.20 (1.06, 1.35)	1.23 (1.04, 1.44)	1.17 (1.03, 1.32)	1.20 (1.06, 1.35)	1.22 (1.02, 1.45)
	0.004	0.017	0.019	0.005	0.026
Sleep and Circadian					
Total nighttime sleep duration[a]	-	0.92 (0.82, 1.04)	-	-	0.94 (0.84, 1.06)
		0.172			0.340
Sleep fragmentation index[c]	-	1.02 (0.89, 1.16)	-	-	1.06 (0.92, 1.19)
		0.813			0.420
Wake after sleep onset[c]	-	0.99 (0.86, 1.13)	-	-	0.97 (0.85, 1.11_
		0.844			0.687
Interdaily stability[d]	-	0.92 (0.79, 1.07)	-	-	0.88 (0.75, 1.02)
		0.301			0.095
Intradaily variability[c]	-	1.11 (0.95, 1.30)	-	-	1.10 (0.94, 1.28)
		0.184			0.252
Comorbidities and medications					
Depression (square root transformed)[a]	-	-	1.45 (1.26, 1.69)	-	1.44 (1.23, 1.68)
			< 0.0001		< 0.0001
Thyroid disease (yes)	-	-	0.90 (0.69, 1.19)	-	0.99 (0.73, 1.32)

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	Models				
	A	**B**	**C**	**D**	**E**
Variables	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
	***p* value**	***p* value**	***p* value**	***p* value**	***p* value**
			0.476		0.934
Vascular disease risk factors	-	-	0.96 (0.83, 1.12)	-	0.94 (0.80, 1.10)
			0.625		0.418
Vascular disease burden	-	-	0.97 (0.82, 1.16)	-	0.99 (0.82, 1.19)
			0.746		0.912
Anxiety (yes)	-	-	0.73 (0.43, 1.25)	-	0.65 (0.35, 1.10)
			0.238		0.116
Insomnia (yes)	-	-	0.98 (0.66, 1.45)	-	1.27 (0.82, 1.87)
			0.907		0.274
Analgesic (yes)	-	-	0.96 (0.73, 1.27)	-	0.97 (0.72, 1.31)
			0.786		0.826
Anticonvulsant (yes)	-	-	1.12 (0.72, 1.74)	-	1.16 (0.69, 1.85)
			0.630		0.550
Beta blocker (yes)	-	-	0.81 (0.62, 1.06)	-	0.87 (0.65, 1.16)
			0.113		0.352
APOE ε4 genotype					
APOE ε4 (carriers)	-	-	-	2.22 (1.71, 2.85)	2.33 (1.76, 3.06)
				< 0.0001	< 0.0001

[a] Results for 1-unit increase.

[b] Results for 1-unit decrease.

[c] Results for 1-SD increase.

[d] Results for 1-SD decrease.

Abbreviations: CI = confidential interval; HR = hazard ratio; SD = standard deviation

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Table 4.

Daytime nap frequency, covariates, and incident Alzheimer's dementia

	Models				
	A	**B**	**C**	**D**	**E**
Variables	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
	***p* value**	***p* value**	***p* value**	***p* value**	***p* value**
Age[a]	1.12 (1.09, 1.14)	1.12 (1.09, 1.14)	1.12 (1.09, 1.14)	1.12 (1.10, 1.14)	1.12 (1.09, 1.14)
	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Sex (female)	0.89 (0.68, 1.18)	0.95 (0.70, 1.29)	0.87 (0.65, 1.16)	0.88 (0.67, 1.17)	0.87 (0.63, 1.19)
	0.411	0.749	0.357	0.371	0.380
Education[b]	1.05 (1.00, 1.09)	1.05 (1.00, 1.09)	1.04 (1.00, 1.08)	1.06 (1.02, 1.11)	1.05 (1.01, 1.10)
	0.0303	0.032	0.063	0.0053	0.015
Nap frequency (square root transformed)[c]	1.23 (1.08, 1.39)	1.26 (1.07, 1.48)	1.19 (1.05, 1.36)	1.22 (1.08, 1.39)	1.24 (1.04, 1.48)
	0.0013	0.008	0.0072	0.0023	0.019
Sleep and Circadian					
Total nighttime sleep duration[a]	-	0.92 (0.82, 1.03)	-	-	0.94 (0.84, 1.06)
		0.143			0.323
Sleep fragmentation index[c]	-	1.00 (0.88, 1.15)	-	-	1.05 (0.92, 1.19)
		0.966			0.511
Wake after sleep onset[c]	-	0.99 (0.87, 1.13)	-	-	0.98 (0.85, 1.11)
		0.901			0.718
Interdaily stability[d]	-	0.92 (0.80, 1.07)	-	-	0.88 (0.75, 1.02)
		0.301			0.098
Intradaily variability[c]	-	1.09 (0.93, 1.28)	-	-	1.08 (0.92, 1.27)
		0.292			0.360
Comorbidities and medications					
Depression (square root transformed)[a]	-	-	1.45 (1.25, 1.68)	-	1.44 (1.23, 1.68)
			< 0.0001		< 0.0001
Thyroid disease (yes)	-	-	0.91 (0.69, 1.20)	-	0.99 (0.74, 1.33)

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	Models				
	A	**B**	**C**	**D**	**E**
Variables	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
	***p* value**	***p* value**	***p* value**	***p* value**	***p* value**
			0.499		0.953
Vascular disease risk factors	-	-	0.96 (0.82, 1.12)	-	0.93 (0.79, 1.09)
			0.581		0.362
Vascular disease burden	-	-	0.97 (0.81, 1.15)	-	0.98 (0.82, 1.19)
			0.714		0.871
Anxiety (yes)	-	-	0.75 (0.44, 1.27)	-	0.65 (0.37, 1.16)
			0.283		0.125
Insomnia (yes)	-	-	0.99 (0.67, 1.48)	-	1.28 (0.85, 1.94)
			0.978		0.247
Analgesic (yes)	-	-	0.95 (0.72, 1.26)	-	0.96 (0.72, 1.29)
			0.720		0.790
Anticonvulsant (yes)	-	-	1.09 (0.70, 1.70)	-	1.15 (0.71, 1.88)
			0.704		0.578
Beta blocker (yes)	-	-	0.81 (0.62, 1.06)	-	0.89 (0.67, 1.18)
			0.121		0.411
APOE *ε*4 genotype					
APOE ε4 (carriers)	-	-	-	2.22 (1.71, 2.84)	2.33 (1.77, 3.07)
				< 0.0001	< 0.0001

[a] Results for 1-unit increase.

[b] Results for 1-unit decrease.

[c] Results for 1-SD increase.

[d] Results for 1-SD decrease.

Abbreviations: CI = confidential interval; HR = hazard ratio; SD = standard deviation