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RESEARCH ARTICLE

Neuropathologic changes at age 90+ related to sleep duration 19 to 40 years earlier: The 90+ Study

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Abstract

INTRODUCTION: We investigated the association between sleep duration and neuropathologic changes 19 to 40 years later in oldest-old (age 90+) participants of The 90+ Study.

METHODS: Participants self-reported sleep duration and underwent neuropathologic evaluation. We categorized sleep duration as < 7, 7 to 8 = reference, > 8 hours and dichotomized neuropathologic changes as present/absent. We estimated odds ratio (OR) and 95% confidence intervals (CI) using logistic regression.

RESULTS: In 264 participants, mean age at sleep self-report was 69 years, mean age at autopsy was 98 years, and mean interval between sleep self-report and autopsy was 29 years (range: 19–40). Those reporting > 8 hours of sleep had lower likelihood of limbic-predominant age-related TDP-43 encephalopathy neuropathologic change (LATE-NC) inclusions (OR = 0.18; CI = 0.04–0.82) and amyloid beta deposits (OR = 0.34; 95% CI = 0.12–0.94).

DISCUSSION: Long self-reported sleep is associated with lower odds of neurodegenerative neuropathologic changes 19 to 40 years later in the oldest-old, suggesting a potential role of sleep in accumulation of dementia-related neuropathologies.

KEYWORDS
age 90+, neuropathologic change, oldest-old, self-reported sleep, sleep duration

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Highlights

- Association of self-reported sleep with non-Alzheimer's disease neuropathologic changes has not been explored.
- Whether sleep duration is related to dementia neuropathologic changes decades later is unclear.
- Long self-reported sleep is associated with lower odds of Alzheimer's disease neuropathologic change 19 to 40 years later in the oldest-old.
- Long self-reported sleep is associated with lower odds of limbic-predominant age-related TDP-43 encephalopathy neuropathologic change 19 to 40 years later in the oldest-old.

1 | BACKGROUND

With a projected 3-fold increase in the number of dementia cases in the next 30 years,[1] there is an urgent need to identify modifiable factors for dementia-related neuropathologic changes. One such modifiable factor, self-reported sleep duration, is associated with imaging and cerebrospinal fluid (CSF) markers of Alzheimer's disease (AD), but its association with neuropathologic changes on autopsy has not been studied. Moreover, the critically important question of whether sleep is an initiating or causal factor of dementia-related neuropathologic changes could not be explored in previous studies in which sleep and dementia biomarkers were measured proximate to each other. Most, but not all,[2] studies showed an association between short self-reported sleep duration (defined as ≤ 5 or ≤ 6 hours, depending on the study) with elevated biomarkers of AD, including positron emission tomography (PET) amyloid[3–5] and CSF total (t)-tau and phosphorylated (p)-tau concentrations.[6] These results support the hypothesis of amyloid clearance and low production during sleep. Studies that have analyzed neuropathologic changes on autopsy in relation to sleep have not analyzed self-reported sleep duration, but instead analyzed sleep architecture, sleep fragmentation, sleep disordered breathing, and mostly found the association of those sleep parameters with increased vascular neuropathologic changes (arteriolosclerosis, macroscopic infarcts, microinfarcts), Lewy body pathology, and substantia nigra neuronal loss.[7–9] Thus, understanding the association of sleep duration with neuropathologic changes remains a critical knowledge gap important for addressing the pressing public health issue of rising dementia prevalence. Additionally, understanding whether sleep duration is associated with neuropathologic changes decades later could inform on the potential role of sleep as a causal risk factor for diseases that cause dementia. Given the 10- to 20-year timeframe of pathological build-up before clinical symptom onset,[10] examining the associations between sleep and neuropathologic change across a longer time window is critical to inform on the causal nature of sleep as a modifiable risk or protective factor for dementia neuropathologic changes. Therefore, the aim of this study is to examine the associations between sleep duration self-reported 19 to 40 years earlier and dementia-related neuropathologic changes in oldest-old (age 90+) participants of The 90+ Study.

2 | METHODS

2.1 | Participants

We analyzed data from a subset of individuals who self-reported their sleep duration at one time point in the early 1980s as part of the population-based Leisure World Cohort Study (LWCS),[11] and had a neuropathological evaluation as part of The 90+ Study in 2003 or later.[12]

Of 1627 LWCS participants with sleep data who joined The 90+ Study, 956 were invited to the autopsy study, and 306 consented. Of those, 264 had neuropathologic evaluation as of March 2023 and were included in this analysis.

2.2 | The 90+ Study procedures

Cognitive diagnosis was assigned during a consensus conference after death using all available data[12] but blinded to neuropathological evaluation.

2.3 | Sleep duration self-reported as part of LWCS

The LWCS survey included one question about night sleep duration: "How many hours of sleep do you usually get each night? __hours." Participants reported sleep duration as an integer. Sleep duration was categorized as: < 7 (short), 7 to 8 (reference), > 8 (long) hours. We chose 7 to 8 hours as the reference because it is the most prevalent category in our analytic sample, is consistent with other relevant studies,[3,6] and corresponds to the recommendation of the National Sleep Foundation on optimal sleep duration for those ≥ 65 years.[13] No information on sleep quality, sleep medications, sleep apnea, or

usage of continuous positive airway pressure (CPAP) machine was collected.

2.4 | Neuropathologic changes on autopsy as part of The 90+ Study

Brains were obtained *post mortem* and fixed in formalin by the University of California Irvine Alzheimer's Disease Research Center Neuropathology Core and sent to the Department of Pathology at Stanford University, where pathological evaluations were performed with current consensus criteria, blinded to participant information. We considered 11 neuropathologic changes: 7 neurodegenerative and 4 vascular. The seven neurodegenerative neuropathologic changes included: (1) AD neuropathologic change (ADNC) based on the National Institute on Aging–Alzheimer's Association (NIA-AA) severity score,[14] (2) NIA-AA A score,[14] (3) Braak stage,[14] (4) NIA-AA C score,[15] (5) LATE-NC,[16] (6) age-related tau astrogliopathy (ARTAG),[17] and (7) Lewy body disease (LBD).[14] The four vascular neuropathologic changes included: (1) cerebral amyloid angiopathy (CAA),[18] (2) microvascular lesions,[14] (3) atherosclerosis,[19] and (4) arteriolosclerosis.[20] We dichotomized (present vs. absent) the 11 neuropathologic changes with 'present' neuropathologic change defined as: ADNC (intermediate/high), A score (2–3), Braak stage (tangle Braak stage III–VI), C score (sparse/moderate/frequent), LATE-NC (amygdala/hippocampus/frontal cortex), ARTAG (occasional/numerous), CAA (mild/moderate/severe), LBD (brainstem/amygdala/limbic/neocortical), microvascular lesions (≥ 3), atherosclerosis (severe), arteriolosclerosis (mild/moderate/severe).

The study was approved by the institutional review boards of the University of California Irvine (HS#2001–2029) and the University of Southern California (HS-815001). Research was conducted in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments. All participants or their surrogates provided written informed consent.

2.5 | Statistical analysis

To determine the association of sleep duration with each dichotomized neuropathologic change, we estimated the odds ratio (OR) and 95% confidence interval (CI) for short and long sleep relative to optimal sleep (7–8 hours) using logistic regression. ORs were adjusted for continuous age at self-reported sleep, age at death, sex, education (< college vs. college graduate). In two sensitivity analyses we repeated the above analysis using four sleep categories: < 7, 7, 8, and > 8; the reference group was 7 in the first analysis and 8 in the second. Participant characteristics were summarized as means, standard deviations, and ranges for continuous variables and as frequencies and percentages for categorical variables. Characteristics were compared between the three sleep duration groups using *t* test for continuous variables and chi-square test for categorical variables. Analyses were done using SAS 9.4 (SAS Institute Inc.).

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed the literature using PubMed as well as meeting abstracts and presentations. In most studies, self-reported sleep duration has been examined in relation to cerebrospinal fluid and imaging biomarkers of Alzheimer's disease that were measured close to sleep self-report.
2. **Interpretation**: Our findings are the first to demonstrate that self-reported sleep duration is related to neurodegenerative neuropathologic changes 19 to 40 years later, suggesting that sleep may play a role in accumulation of dementia neuropathologic change. Additionally, we are the first to demonstrate the association of self-reported sleep duration with limbic-predominant age-related TDP-43 encephalopathy neuropathologic change (LATE-NC).
3. **Future directions**: These findings need to be confirmed in larger studies in which sleep is measured repeatedly. It is important to investigate the potential mechanisms of the association of sleep with LATE-NC.

3 | RESULTS

Most participants were women (75%) and White (99%), and about half were college graduates (48%; Table 1). The mean age of participants was 69 years when they reported sleep, 98 years at time of death, and the mean interval between self-reported sleep duration and autopsy was 29 years (range: 19–40). Most participants (70%) slept 7 to 8 hours, 23% slept < 7 hours, and 7% slept > 8 hours. Participants from the three sleep duration groups, < 7, 7 to 8, > 8 hours, did not differ in terms of demographic and other health- and study-related variables, except for exercise and alcohol consumption, in that individuals with long sleep (> 8 hours) exercised less, compared to the other groups, and individuals with short sleep (< 7 hours) consumed less alcohol, compared to the other groups.

Participants with > 8 hours of sleep, compared to 7 to 8 hours, had significantly lower odds of amyloid beta (Aβ) deposits (A score) (OR = 0.34; CI: 0.12–0.94; P = 0.04) and LATE-NC (OR = 0.18; CI: 0.04–0.82; P = 0.03; Table 2). Although not statistically significant, the same pattern of lower (43%–58%) odds of neuropathologic change in people with > 8 hours of sleep was seen in most neurodegenerative neuropathologic changes: ADNC score, Braak stage, C score, and ARTAG. Sleep duration was not significantly associated with any vascular neuropathologic change; however, a U-shaped relationship in which both long and short sleep durations were associated with higher odds of vascular neuropathologic change is suggested.

The sensitivity analyses results are consistent with the main findings. Participants with > 8 hours of sleep, compared to either 7 or 8 hours, had significantly lower odds of Aβ deposits (A score;

TABLE 1 Characteristics of participants by sleep duration category and entire group.

	Sleep duration groups, hours				
	<7	7–8	>8		Total
N	61	185	18	*P* value	264
***N* (%)**					
Women	47 (77)	135 (73)	16 (89)	0.30	198 (75)
White	61 (100)	182 (98)	18 (100)	1.00	261 (99)
Education				0.93	
Less than college graduate	31 (51)	98 (53)	10 (56)		138 (52)
College graduate or higher	30 (49)	87 (47)	8 (44)		126 (48)
Case conference diagnosis				0.54	
Normal	15 (25)	43 (23)	5 (28)		63 (24)
CIND	17 (28)	45 (24)	7 (39)		69 (26)
Dementia	29 (48)	97 (52)	6 (33)		132 (50)
APOE ε4+	8 (14)	42 (23)	3 (19)	0.29	53 (21)
Hypertension	30 (52)	95 (53)	11 (61)	0.76	136 (54)
Diabetes	1 (2)	4 (2)	0	1.00	5 (2)
BMI				0.69	
Underweight or normal	43 (70)	131 (71)	11 (61)		185 (70)
Overweight or obese	18 (30)	54 (29)	7 (39)		79 (30)
Exercise				0.04	
0 hours/day	8 (13)	18 (10)	6 (33)		32 (12)
< 1 hours/day	26 (43)	67 (36)	6 (33)		99 (38)
≥1 hours/day	27 (44)	99 (54)	6 (33)		132 (50)
Alcohol				0.02	
0 drinks/ day	18 (30)	35 (19)	3 (17)		56 (21)
≤1 drinks/ day	26 (43)	53 (29)	6 (33)		85 (32)
> 1 drinks/ day	17 (28)	97 (52)	9 (50)		123 (47)
Caffeine				0.88	
< 50 mg/day	12 (20)	35 (19)	2 (11)		49 (19)
50–199 mg/day	26 (43)	74 (40)	7 (39)		107 (41)
≥200 mg/day	23 (38)	76 (41)	9 (50)		108 (41)
Mean (SD) [range]					
Age at self-reported sleep, years	69.2 (4.8) [59–79]	68.9 (5.1) [53–87]	67.1 (4.9) [56–75]	0.28	68.9 (5.0) [53–87]
Age at death, years	98.2 (3.5) [90–107]	97.9 (3.4) [91–106]	98.7 (4.0) [91–106]	0.52	98.0 (3.4) [90–107]
Years between sleep self-report and neuropathologic evaluation	29.1 (4.8) [20–40]	28.9 (4.5) [19–40]	31.6 (4.3) [25–39]	0.06	29.1 (4.6) [19–40]
Hours of night sleep	5.7 (0.6) [4–6]	7.6 (0.5) [7–8]	9.1 (0.2) [9–10]	–	7.2 (1.1) [4–10]

Notes: Underweight or normal is defined as BMI < 25 kg/m^2, overweight or obese is defined as BMI ≥ 25 kg/m^2. *P* values comparing the three sleep duration groups from *t* test for continuous variables and chi-square test for categorical variables.
Abbreviations: *APOE*, apolipoprotein E; BMI, body mass index; CIND, cognitive impairment no dementia; SD, standard deviation.

OR = 0.36; 95% CI = 0.13–1.06; *P* = 0.06, for 7 hours as reference; OR = 0.32; 95%CI = 0.11–0.92; *P* = 0.03, for 8 hours as reference) and LATE-NC (OR = 0.14; 95% CI = 0.03–0.65; *P* = 0.01, for 7 hours as reference, OR = 0.23; 95% CI = 0.05–1.09; *P* = 0.06, for 8 hours as reference; Table 3). Although not significant, the same pattern of lower (36%–78%) odds of neuropathologic change in people with > 8 hours of sleep is seen in most neurodegenerative neuropathologic changes: ADNC score, Braak stage, C score, and ARTAG. Again, sleep duration was not significantly associated with any vascular neuropathologic change, but a U-shaped relationship in which both long and short sleep durations are associated with higher odds of vascular neuropathologic change is suggested.

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TABLE 2 Odds of neuropathologic change by self-reported sleep duration category.

	OR	95% CI	*P* value
ADNC score			
< 7 hours	1.08	0.55, 2.11	0.82
7–8 hours	1.00	reference	–
> 8 hours	0.46	0.16, 1.29	0.14
A score			
< 7 hours	1.05	0.55, 2.03	0.87
7–8 hours	1.00	reference	–
> 8 hours	**0.34**	**0.12, 0.94**	**0.04**
Braak stage			
< 7 hours	1.04	0.20, 5.37	0.97
7–8 hours	1.00	reference	–
> 8 hours	0.42	0.04, 4.18	0.46
C score			
< 7 hours	0.88	0.43, 1.78	0.72
7–8 hours	1.00	reference	–
> 8 hours	0.42	0.15, 1.20	0.11
LATE-NC			
< 7 hours	0.71	0.38, 1.33	0.29
7–8 hours	1.00	reference	–
> 8 hours	**0.18**	**0.04, 0.82**	**0.03**
ARTAG			
< 7 hours	0.96	0.51, 1.81	0.91
7–8 hours	1.00	reference	–
> 8 hours	0.57	0.20, 1.58	0.28
Lewy body			
< 7 hours	1.41	0.70, 2.84	0.33
7–8 hours	1.00	reference	–
> 8 hours	1.76	0.57, 5.42	0.32
CAA			
< 7 hours	1.55	0.86, 2.79	0.15
7–8 hours	1.00	reference	–
> 8 hours	0.66	0.24, 1.80	0.41
MVL			
< 7 hours	1.37	0.32, 5.81	0.67
7–8 hours	1.00	reference	–
> 8 hours	1.23	0.13, 12.10	0.86
Atherosclerosis			
< 7 hours	1.53	0.55, 4.28	0.42
7–8 hours	1.00	reference	–
> 8 hours	1.72	0.34, 8.65	0.51
Arteriolosclerosis			
< 7 hours	2.12	0.89, 5.08	0.09
7–8 hours	1.00	reference	–
> 8 hours	2.30	0.49, 10.76	0.29

Note: ADNC score, A score, Braak stage, C score according to the NIA-AA criteria. OR, 95% CI, and *P* values from logistic regression with present versus absent neuropathologic changes as outcomes and self-reported sleep duration (< 7 hours, 7–8 hours = reference, > 8 hours) as predictor. Models adjusted for age at self-reported sleep, age at death, sex, education. Present neuropathologic change were defined as: ADNC (intermediate/high), A score (2–3), Braak stage (tangle Braak stage IV–VI), C score (sparse/moderate/frequent), LATE-NC (amygdala/hippocampus/frontal cortex), ARTAG (occasional/numerous), CAA (mild/moderate/severe), LBD (brainstem/amygdala/limbic/neocortical), microvascular lesions (≥3), atherosclerosis (severe), arteriolosclerosis (mild/moderate/severe).
Abbreviations: ADNC, Alzheimer's disease neuropathologic change; ARTAG, aging-related tau astrogliopathy; CAA, cerebral amyloid angiopathy; CI, confidence interval; LATE-NC, limbic-predominant age-related TDP-43 encephalopathy neuropathologic change; LBD, Lewy body disease; MVL, microvascular lesions; NIA-AA, National Institute on Aging–Alzheimer's Association; OR, odds ratio.

4 | DISCUSSION

We found that those who reported sleeping more than 8 hours at an average age of 69 had significantly lower odds of Aβ deposits (66% lower) and LATE-NC (82% lower) almost three decades later at age 90+, compared to those who reported sleeping 7 to 8 hours. The sensitivity analyses results are consistent with these main findings.

Our new finding is that we demonstrated that long (> 8 hours) self-reported sleep, compared to 7 to 8 hours of sleep, is associated with lower odds of Aβ on neuropathologic examination decades later. Although previous studies have not examined the association of self-reported sleep duration with neuropathologic changes, our finding concurs with the studies that examined the association of self-reported sleep duration with imaging and CSF AD biomarkers measured proximal to the sleep self-report. One study showed that long sleep was associated with lower PET Aβ in cognitively unimpaired older adults.[21] Other reports demonstrate the flip side of this mechanism in which short self-reported sleep is associated with high Aβ burden on PET or CSF.[3,4,6] Tapping more into mechanisms of these associations, studies that use experimental sleep manipulation have shown that unrestricted (or prolonged) sleep is associated with lower amyloid levels, whereas sleep restriction is associated with elevated levels of amyloid.[22–24] Thus, one night of unrestricted sleep has decreased CSF Aβ levels in healthy adults by 6%, and the magnitude of this decrease correlated with the total amount of sleep.[22] In an amyloid-developing mouse model increasing sleep time has resulted in the decrease of amyloid plaque pathology.[23] On the flip side, acute sleep deprivation during one night has increased CSF Aβ42, Aβ40, Aβ38 by 30% the following morning in healthy middle-aged and older adults.[22,24] Chronic sleep deprivation has increased amyloid plaque pathology

TABLE 3 Sensitivity analysis for odds of neuropathologic change by self-reported sleep duration category.

	7 hours reference			8 hours reference		
	OR	95% CI	*P* value	OR	95% CI	*P* value
ADNC score						
< 7 hours	1.06	0.49, 2.26	0.89	1.06	0.51, 2.23	0.87
7 hours	1.00	reference	–	1.01	0.52, 1.97	0.99
8 hours	0.99	0.51, 1.94	0.99	1.00	reference	–
> 8 hours	0.46	0.15, 1.36	0.16	0.46	0.16, 1.35	0.16
A score						
< 7 hours	1.11	0.53, 2.33	0.78	0.98	0.47, 2.01	0.94
7 hours	1.00	reference	–	0.88	0.46, 1.69	0.69
8 hours	1.14	0.59, 2.19	0.69	1.00	reference	–
> 8 hours	**0.36**	**0.13, 1.06**	**0.06**	**0.32**	**0.11, 0.92**	**0.03**
Braak stage						
< 7 hours	0.54	0.07, 4.19	0.55	1.51	0.27, 8.38	0.64
7 hours	1.00	reference	–	2.82	0.52, 15.29	0.23
8 hours	0.36	0.07, 1.93	0.23	1.00	reference	–
> 8 hours	0.22	0.02, 3.00	0.26	0.63	0.06, 6.73	0.70
C score						
< 7 hours	0.85	0.38, 1.92	0.70	0.88	0.40, 1.92	0.75
7 hours	1.00	reference	–	1.03	0.50, 2.14	0.93
8 hours	0.97	0.47, 2.01	0.93	1.00	reference	–
> 8 hours	0.41	0.14, 1.27	0.12	0.43	0.14, 1.29	0.13
LATE-NC						
< 7 hours	0.55	0.27, 1.12	0.10	0.94	0.47, 1.88	0.86
7 hours	1.00	reference	–	1.69	0.92, 3.13	0.09
8 hours	0.59	0.32, 1.09	0.09	1.00	reference	–
> 8 hours	**0.14**	**0.03, 0.65**	**0.01**	**0.23**	**0.05, 1.09**	**0.06**
ARTAG						
< 7 hours	0.86	0.41, 1.82	0.70	1.16	0.58, 2.32	0.67
7 hours	1.00	reference	–	1.34	0.71, 2.56	0.37
8 hours	0.74	0.39, 1.42	0.37	1.00	reference	–
> 8 hours	0.48	0.16, 1.43	0.19	0.64	0.22, 1.87	0.42
Lewy body						
< 7 hours	0.96	0.43, 2.12	0.92	1.80	0.79, 4.08	0.16
7 hours	1.00	reference	–	1.87	0.88, 3.99	0.10
8 hours	0.53	0.25, 1.14	0.10	1.00	reference	–
> 8 hours	1.28	0.40, 4.17	0.68	2.40	0.72, 7.97	0.15
CAA						
< 7 hours	1.59	0.81, 3.12	0.18	1.64	0.85, 3.15	0.14
7 hours	1.00	reference	–	1.03	0.57, 1.86	0.92
8 hours	0.97	0.54, 1.75	0.92	1.00	reference	–
> 8 hours	0.65	0.22, 1.87	0.42	0.67	0.23, 1.90	0.45
MVL						
< 7 hours	1.29	0.24, 6.78	0.76	1.45	0.27, 7.74	0.66
7 hours	1.00	reference	–	1.12	0.21, 5.89	0.89
8 hours	0.89	0.17, 4.70	0.89	1.00	reference	–
> 8 hours	1.17	0.10, 13.04	0.90	1.31	0.11, 15.05	0.83

(Continues)

TABLE 3 (Continued)

	7 hours reference			8 hours reference		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Atherosclerosis						
< 7 hours	1.13	0.36, 3.58	0.83	2.09	0.61, 7.21	0.24
7 hours	1.00	reference	–	1.84	0.56, 6.12	0.32
8 hours	0.54	0.16, 1.80	0.32	1.00	reference	–
> 8 hours	1.28	0.24, 6.94	0.77	2.36	0.41, 13.68	0.34
Arteriolosclerosis						
< 7 hours	1.86	0.71, 4.87	0.21	2.37	0.93, 6.03	0.07
7 hours	1.00	reference	–	1.28	0.62, 2.66	0.51
8 hours	0.78	0.38, 1.62	0.51	1.00	reference	–
> 8 hours	2.02	0.41, 9.95	0.39	2.59	0.53, 12.58	0.07

Notes: ADNC score, A score, Braak stage, C score according to the NIA-AA criteria. OR, 95% CI, and *P* values from logistic regression with present versus absent neuropathologic changes as outcomes and self-reported sleep duration (< 7 hours, 8 = reference or 7 hours = reference, > 8 hours) as predictor. Models adjusted for age at self-reported sleep, age at death, sex, education. Present neuropathologic change were defined as: ADNC (intermediate/high), A score (2–3), Braak stage (tangle Braak stage IV–VI), C score (sparse/moderate/frequent), LATE-NC (amygdala/hippocampus/frontal cortex), ARTAG (occasional/numerous), CAA (mild/moderate/severe), LBD (brainstem/amygdala/limbic/neocortical), microvascular lesions (≥3), atherosclerosis (severe), arteriolosclerosis (mild/moderate/severe).

Abbreviations: ADNC, Alzheimer's disease neuropathologic change; ARTAG, aging-related tau astrogliopathy; CAA, cerebral amyloid angiopathy; CI, confidence interval; LATE-NC, limbic-predominant age-related TDP-43 encephalopathy neuropathologic change; LBD, Lewy body disease; MVL, microvascular lesions; NIA-AA, National Institute on Aging–Alzheimer's Association; OR, odds ratio.

in amyloid-developing mice.[23] One of the drivers of the negative effect of sleep restriction might be disrupted slow wave sleep (SWS), which in a number of studies is associated with elevated plasma and CSF Aβ levels in healthy adults and in older adults with cognitive impairment.[25,26] Sleep, specifically SWS, is involved in clearance and reduced production of Aβ: increased exchange of CSF with interstitial fluid during SWS leads to an increased rate of Aβ clearance through glymphatic system;[27] higher microglia and its enhanced Aβ phagocytic activity during SWS reduces amyloid deposition;[28] and finally, reduced neurometabolic activity during SWS leads to decreased Aβ production/release from synapses.[23,29]

A major new finding is that we demonstrated that long (> 8 hours) self-reported sleep reported almost three decades earlier is associated with lower odds of LATE-NC in the oldest-old. One potential mechanism of this association might be through inflammatory pathways. Sleep loss activates inflammatory pathways leading to elevation of interleukin 6, tumor necrosis factor alpha, and other cytokines.[30] These inflammatory stimuli in turn promote cytoplasmic mislocalization and aggregation of TDP in glial and neuronal cells, which was shown in transgenic mice,[31] thus contributing to development or exacerbation of TDP proteinopathy. Consistent with the same directionality of the association of sleep duration with Aβ and LATE-NC in our study, there are data suggesting a connection between these two neuropathologic changes: late-stage AD patients have increased pathological cortical TDP-43[32] and TDP-43 neuropathology is associated with higher severity of AD neuropathologic changes.[33,34]

Cumulatively, the results suggest that long sleep might be protective against accumulation of dementia-related neuropathologic changes decades later in the oldest-old. This effect might be executed through a number of mechanisms including glymphatic clearance, decreased amyloid production, microglia phagocytic activity, and inflammation. Further research is needed to explore these mechanisms.

5 | STRENGTHS AND LIMITATIONS

Strengths of this study include this being the first report on sleep duration in relation to neuropathologic changes decades later; use of data from a well-characterized large autopsy cohort of individuals age 90+; and analysis of a wide range of neuropathologic changes, many of which have not been previously reported in the sleep literature. The interval of 19 to 40 years between sleep self-report and neuropathologic evaluation is longer than the 10 to 20 years of pathological build-up that precedes clinical manifestations; this allowed the exploration of the causal nature of sleep as a modifiable risk factor for dementia neuropathologic changes.

Limitations of the study include the small size of the long sleep duration category. Also, the lack of ethnic diversity in our sample may limit generalizability of our findings because of differences in the distributions of sleep duration and neuropathologic changes between Whites and individuals of other races and ethnicities. It is well established that extreme (short and long) sleep duration is more prevalent in non-White compared to White individuals.[35,36] Although limited, ethnoracial differences in neuropathological changes have been found. For example, AD, LBD, and cerebrovascular neuropathologies have been found to be more common, and TAR DNA-binding protein 43 (TDP-43) and frontotemporal lobar degeneration proteinopathies with tau inclusions (FTLD-tau) less common in Black individuals than in those

who areWhite.[37] Furthermore, AD-related neuropathologies in frontal and temporal cortices have been reported to be higher in individuals of Hispanic decent compared to White individuals.[38] Another limitation is that sleep duration was self-reported rather than objectively measured. However, this allows for data collection on a larger group of people and reduction in the rate of missing data. Finally, sleep was measured only once, so the stability of sleep duration is unknown.

6 | CONCLUSIONS

Using an exceptionally long interval of 19 to 40 years between self-reported sleep and neuropathological examination, we demonstrated that long sleep (> 8 hours) is associated with lower odds of LATE-NC and Aβ, supporting the hypothesis that long sleep may protect against dementia-related neuropathologic changes in the oldest-old.

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CONFLICT OF INTEREST STATEMENT

Z.A.M., C.H.K., A.P.-H, S.B., T.J.M., L.J., and M.M.C. have no conflict of interest to declare. B.A.M. has received consulting fees from Eisai. Author disclosures are available in the supporting information.

CONSENT STATEMENT

The study was approved by the institutional review boards of the University of California Irvine (HS#2001-2029) and the University of Southern California (HS-815001). Research was conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent.

DIVERSITY, EQUITY, AND INCLUSION STATEMENT

The 90+ Study participants included in this analysis are from a set cohort that was established in the early 1980s, and it largely reflected the demographic composition of 90-year-olds at that time. We have acknowledged and discussed this limitation of our study.

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SUPPORTING INFORMATION

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

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