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RESEARCH ARTICLE

Age differences in the association between sleep and Alzheimer's disease biomarkers in the EPAD cohort

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Abstract

Introduction: We aimed to determine the independent association between sleep quality and Alzheimer's disease (AD) biomarkers, and whether the associations differ with age.

Methods: We included 1240 individuals aged ≥50, without dementia from the *European Prevention of Alzheimer's Disease* v1500.0 dataset. Linear regression was used to examine Pittsburgh Sleep Quality Index (PSQI) scores against cerebrospinal fluid (CSF) phosphorylated tau/β-amyloid ratio (p-tau/Aβ42) for the entire sample and via age tertiles. Models controlled for demographic, clinical, genetic, vascular, and neuroimaging variables.

Results: For the youngest age tertile, shorter sleep duration and higher sleep efficiency were associated with greater p-tau/Aβ42 ratio. For the oldest tertile, longer sleep latency was associated with greater p-tau/Aβ42.

Discussion: Differential relationships between sleep and AD pathology depend on age. Short sleep duration and sleep efficiency are relevant in middle age whereas time taken to fall asleep is more closely linked to AD biomarkers in later life.

KEYWORDS
Alzheimer's, Aβ42, biomarkers, EPAD, PSQI, p-tau, sleep, sleep duration, sleep efficiency, sleep latency

Highlights

- This study shows age differences in the link between sleep and AD biomarkers.
- Shorter sleep was associated with greater p-tau/Aβ42 ratio in middle age.
- The association was independent of genetic, vascular, and neuroimaging markers of AD.

1 | INTRODUCTION

An increasing number of epidemiological studies support an association between disturbances of sleep and risk for dementia. Using self-report measures, various parameters of sleep disturbance have been examined including overall sleep quality, sleep efficiency, and latency. For all-cause dementia, both short and long sleep duration may also confer greater risk.[1]

The mechanisms by which sleep disturbances may contribute to future dementia risk are not yet known. For Alzheimer's disease (AD) specifically, prior work using positron emission tomography (PET) in relatively small cognitively intact samples has shown that greater sleep latency[2] and duration[3] are linked to higher brain Aβ deposition. Using cerebrospinal fluid (CSF), a recent analysis of 736 cognitively intact participants in their sixties showed that both short and long self-reported sleep duration were associated with greater levels of Aβ (CSF Aβ42 and Aβ42/40).[4] While amyloid deposition is associated with low CSF Aβ42,[5] the ratio of CSF phosphorylated tau (p-tau)/Aβ (1-42) has also been associated with increased brain amyloid[6] and is superior to single biomarkers at predicting risk of decline and conversion to dementia.[7]

Whereas prior biomarker studies have variously controlled for contributors to Aβ accumulation such as age, sex, education, and apolipoprotein E ε4 (ApoE4) status, they have not simultaneously adjusted for concomitant factors linked to both sleep and dementia such as depression, cardiovascular risk, body mass index (BMI), smoking. or psychotropic use, as well as other known neurobiological correlates of dementia including white matter lesions and hippocampal volumes. In determining the specific and unique association of sleep with AD and dementia pathology, it is important to glean a clearer insight of the relative contribution of sleep disturbance beyond these other confounds and/or markers of disease, which in turn will advance our understanding of the pathophysiology of disease and also assist with directing screening approaches and the design of longitudinal studies to confirm these associative relationships.

Given dementia pathology begins to accumulate in the brain up to two decades before clinical symptoms,[8] it is important to elucidate if there are differential associations between sleep, age, and the presence of dementia biomarkers in midlife compared to in older aged or elderly samples. With regard to other key risks, systolic blood pressure[9] appears to be linked to cognitive decline only in the 6th decade (ages 50–59, but not in other age bands), the risk of atrial fibrillation is most pronounced in those younger than 67 years[10] and hypercholesterolemia also carries the strongest risk in midlife.[11] Prior work examining sleep, however, has tended to focus on older samples in their seventies, and no known studies have examined the sleep, age, and biomarker inter-relationships within the one sample. Longitudinal data from the Whitehall study[12] showed that the link between sleep duration and dementia 25 years later was evident from midlife and recent analysis of UK Biobank participants[13] found that higher genetic liability to AD influenced sleep duration only among those aged 55 years and older, implying potential age differences in the mechanistic pathways linking sleep disturbances and AD. Understanding the differential age associations between sleep and AD will have important implications for sleep screening and targeted interventions during midlife, potentially slowing cognitive decline and reducing the burden of dementia in later life.

In this study, we aimed to determine in a large sample of middle- to older-aged individuals without dementia, whether self-reported sleep duration, latency, and efficiency were associated with CSF AD biomarkers, and whether such relationships might differ by age.

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed the literature relating to the relationship between sleep disturbance and Alzheimer's disease (AD) pathology. Although these associations have been investigated in a handful of studies (cited as appropriate), studies in large well characterized samples remain limited and it is unclear whether the association differs by age.
2. **Interpretation**: The current findings from a large sample of older adults without dementia (n = 1240) demonstrate that self-reported sleep is related to AD pathology when accounting for known risk factors. Importantly, this effect differed by age, with sleep duration and sleep efficiency being more strongly associated with AD biomarkers among younger participants and sleep latency being more relevant for older groups. This has implications for the use of sleep measures as markers of AD risk and for targeting interventions.
3. **Future directions**: Longitudinal studies are required to elucidate relationships between sleep, cognition, and AD pathology as people age.

2 | METHODS

2.1 | Participants

Data were obtained from the European Prevention of Alzheimer's Disease (EPAD) Longitudinal Cohort Study (LCS)[14] data set v1500.0 [dataset].[15] The current study only included data from the first participant visit. Detailed inclusion/exclusion criteria are outlined elsewhere[14] but in brief participants were required to be $\geq$ 50 years of age, with at least 7 years of education and to have a study partner. Exclusion criteria were a diagnosis of any type of dementia, Clinical Dementia Rating (CDR $\geq$ 1), the presence of conditions associated with neurodegeneration or affecting cognition, cancer or history of cancer in the prior 5 years, contraindications to MRI or lumbar puncture or evidence of intracranial pathology. For the current study, we additionally excluded participants missing the CDR, CSF biomarkers, or data on the Pittsburgh Sleep Quality Index (PSQI) and one participant who had a CDR score of 1.

2.2 | Measures

CSF samples were collected according to harmonized preclinical protocol for measurement of p-tau and Aβ42 (analysis by automated Roche Elecsys System[14]), from which a p-tau/Aβ42 ratio was calculated.

Self-reported sleep quality was first assessed with the PSQI[16] total score, where a score > 5 is considered to be indicative of poor sleep

quality (score range 0–21). We also examined the PSQI component scores for sleep duration, latency, and efficiency.

Covariates of interest were age; sex; self-reported depressive symptoms (Geriatric Depression Scale – 30 item [GDS-30][17]); ApoE4 (positive/negative) and BMI. Based on available medical history coded according to Medical Dictionary for Regulatory Activities (MedDRA), we computed a dichotomous vascular risk index from high-level group terms defined as the presence of at least one of: current coronary artery disorder (angina, coronary artery disease, myocardial infarction, myocardial ischemia); lipid metabolism disorder (dyslipidemia, hypercholesterolemia); vascular hypertensive disorder (hypertension) glucose metabolism disorder (hyperglycemia, diabetes mellitus); or a history of smoking (never/past/current). Current psychotropic medication use was defined as current use of any antidepressant, antipsychotic, sedative medication, or melatonin.

Neuroimaging acquisition and processing procedures used in the EPAD study are detailed elsewhere.[18] Briefly, 3D T1w and FLAIR sequences were acquired across all sites to derive regional grey matter and white matter hyperintensity (WMH) volumes, respectively. Hippocampal volumes (left/right averaged and corrected for each participant's intracranial volume) and WMH volumes were automatically quantified via Learning Embeddings for Atlas Propagation (LEAP).[19]

For descriptive purposes, we report the percentage of participants reaching established cutoffs for p-tau and Aβ42 positivity,[20] along with cognitive scores on the MMSE[21] and Repeated Battery for Assessment of Neuropsychological Status.

2.3 | Statistical analysis

For linear regressions, the skewed p-tau/Aβ42 ratio was transformed to a normal distribution with ordered quantile normalization.[22] PSQI component scores of 2 or 3 were combined due to small numbers of scores of 3. Missing values in covariates (max 3.22%) were imputed with the median or mode for continuous or categorical variables, respectively.

In all models, the p-tau/Aβ42 ratio was included as the outcome variable, with age, sex, depressive symptoms, ApoE4 status, vascular risk, hippocampal volume, and WMH volume included as covariates. We first performed multiple linear regressions for the PSQI total score and p-tau/Aβ42 ratio (Table 2, Model 1) and repeated this with the inclusion of the interaction between age and the PSQI total score (Table 2, Model 2). We then examined the association between the component scores for sleep duration, latency, and efficiency and p-tau/Aβ42 ratio (Model 3, Table 3), followed by a model with all age × component score interactions (Model 4, Table 3).

Next, in order to examine the associations between sleep and AD pathology across age bands, the sample was split into age tertiles, and the relative contribution of each component was modeled after adjustment for other confounders or causal contributors to AD pathology (Models 5, 6, 7 Table 4). Although we a priori selected model variables based on their relationship to AD risk, sleep, or both, we considered that some of the variables (e.g., depressive symptoms or vascular risk) may be on the causal path between sleep and AD. To test if inclusion of these variables attenuated the relationships between sleep and AD, we performed the same analyses with only age, sex, and ApoE4 status as covariates.

The relative importance of the sleep variables and covariates was investigated by decomposition[23] of model R^2 using the LMG metric,[24] which captures both the direct effect of a regressor on the outcome and the effect adjusted for other covariates. Statistical analysis was completed in R (version 4.0.2).

3 | RESULTS

3.1 | Participants

After applying the study specific exclusion criteria, 1240/1500 participants were included for analysis. Characteristics of the included participants are presented in Table 1.

3.2 | Sleep quality

For the entire sample, Table 2 shows that the PSQI total score was not a significant predictor of p-tau/Aβ42 ratio after controlling for the covariates (Model 1) and there was no interaction between age and PSQI total score (Model 2).

3.3 | Component scores of sleep duration, latency, and efficiency

For the entire sample, Table 3 shows the regression models including covariates and PSQI component scores for sleep duration, latency, and efficiency after controlling for clinical covariates. In Model 3, both longer sleep latency and greater sleep efficiency were associated with higher p-tau/Aβ42 ratio in the whole sample. However, the distribution of component scores for sleep efficiency was severely unbalanced with only 6.5% of participants having a sleep efficiency component score of 0, indicative of sleep efficiency of at least 85%. Sleep duration was not associated with p-tau/Aβ42 ratio. Model 4 included all interactions. The interaction between age × sleep duration (both components 1 and 2/3) was significant. The interaction between age and sleep latency (component 2/3 only) reached $p = 0.05$.

To further explore the effect of age, we stratified the cohort by age into tertiles and again tested each component score and the covariates. These models are shown in Table 4 and Figure 1 displays relative proportions of each variable expressed as explained variance only (normalized to sum to 1).

For the youngest tertile (Model 5), aged 50–62 years, shorter sleep duration and higher sleep efficiency were significantly associated with higher p-tau/Aβ42 ratio (i.e., greater AD pathology). In this group, sleep efficiency had high relative importance or R^2 - greater than age,

TABLE 1 Baseline characteristics for all participants included in analysis

		Mean (SD)/*n* (%)/Median [IQR]		
	Whole sample	Younger	Middle	Older
n	1240	414	413	413
Age, years	65.34 (7.11)	57.41 (3.23)	65.48 (2.01)	73.15 (3.64)
Sex, male	538 (43.4%)	160 (38.6%)	181 (43.8%)	197 (47.7%)
CDR, 0.5	222 (17.9%)	42 (10.1%)	64 (15.5%)	116 (28.1%)
MMSE	29.00 [28.00, 30.00]	29.00 [28.00, 30.00]	29.00 [28.00, 30.00]	29.00 [27.00, 30.00]
RBANS total scale	103.97 (13.16)	106.73 (12.10)	103.44 (12.67)	101.75 (14.16)
p-tau/Ab42 ratio	0.01 [0.01, 0.02]	0.01 [0.01, 0.01]	0.01 [0.01, 0.02]	0.01 [0.01, 0.03]
CSF biomarker positive				
p-tau	171 (13.8%)	21 (5.1%)	48 (11.6%)	102 (24.7%)
Aβ42	399 (32.2%)	107 (25.8%)	123 (29.8%)	169 (40.9%)
ApoE4 status, positive	443 (35.7%)	168 (40.6%)	143 (34.6%)	132 (32.0%)
PSQI				
Total score	5.00 [3.00, 7.00]	4.00 [3.00, 7.00]	5.00 [3.00, 7.00]	5.00 [3.00, 7.00]
Sleep duration				
Score 0	303 (24.4%)	89 (21.5%)	105 (25.4%)	109 (26.4%)
Score 1	721 (58.1%)	234 (56.5%)	231 (55.9%)	256 (62.0%)
Score 2/3	216 (17.4%)	91 (22.0%)	59 (14.3%)	48 (11.6%)
Sleep latency				
Score 0	758 (61.1%)	253 (61.1%)	259 (62.7%)	246 (59.6%)
Score 1	325 (26.2%)	113 (27.3%)	95 (23.0%)	117 (28.3%)
Score 2/3	157 (12.7%)	48 (11.6%)	59 (14.3%)	50 (12.1%)
Sleep efficiency				
Score 0	81 (6.5%)	38 (9.2%)	21 (5.1%)	22 (5.3%)
Score 1	897 (72.3%)	290 (70.0%)	304 (73.6%)	303 (73.4%)
Score 2/3	262 (21.1%)	86 (20.8%)	88 (21.3%)	88 (21.3%)
GDS-30	4.00 [1.00, 7.00]	3.00 [1.00, 7.00]	3.00 [1.00, 6.00]	4.00 [2.00, 7.00]
BMI, kg/m^2	26.22 (4.30)	26.32 (4.47)	26.35 (4.36)	25.99 (4.05)
Vascular risk, yes	405 (32.7%)	117 (28.3%)	134 (32.4%)	154 (37.3%)
Smoking history				
Current	79 (6.4%)	38 (9.2%)	27 (6.5%)	14 (3.4%)
Never	557 (45.1%)	193 (46.6%)	181 (43.8%)	183 (44.3%)
Past	598 (48.5%)	183 (44.2%)	205 (49.6%)	216 (52.3%)
Psychotropic medication, yes	109 (8.8%)	33 (8.0%)	41 (9.9%)	35 (8.5%)
WMH volume, mm^3	3329.75 [1545.74, 8043.72]	2016.94 [995.13, 4375.60]	3226.31 [1535.06, 6364.61]	5719.15 [2875.93, 13291.63]
Hippocampal volume, mm^3	0.22 (0.02)	0.22 (0.02)	0.22 (0.02)	0.21 (0.02)

Note: CSF biomarker cut-offs were p-tau > 27 pg/mL and Aβ42 < 1000 pg/mL as previously validated in the EPAD cohort[13].
Abbreviations: ApoE4, apolipoprotein E ε4; BMI, body mass index; CDR, Clinical Dementia Rating Scale; CSF, cerebrospinal fluid; GDS-30, Geriatric Depression Scale - 30-item; Hippocampal volume, left and right mean, corrected for intracranial volume; MMSE, Mini-Mental State Examination; PSQI, Pittsburgh Sleep Quality Index; WMH, white matter hyperintensity.

depressive symptoms, and vascular risk. Depressive symptoms, ApoE4, and vascular risk also contributed to greater AD pathology (Figure 1, Table 4).

The association between component scores and p-tau/Aβ42 ratio for the middle tertile, aged 63–69 years, are presented in Model 6. There were no significant associations between sleep duration, sleep latency, or sleep efficiency in relation to AD pathology. Only ApoE4, depressive symptoms, and vascular risk showed significant relationships with AD pathology.

Finally, for the older group, aged 70–88 years, Model 7 shows that longer sleep latency was associated with higher p-tau/Aβ42 ratio, along with age, ApoE4 and hippocampal volume.

TABLE 2 Linear regression models of entire cohort – PSQI total score ($N = 1240$)

	Model 1: No interactions			Model 2: Age × PSQI		
Variables	**β (95% CI)**	***p***	**Decomp R^2**	**β (95% CI)**	***p***	**Decomp R^2**
PSQI total score	0 (−0.02, 0.01)	0.64	0.03%	−0.01 (−0.24, 0.04)	0.16	0.03%
Age	0.04 (0.03, 0.05)	<0.001	8.19%	0.03 (0.02, 0.05)	<0.001	8.21%
Sex (male)	0.13 (0.03, 0.23)	0.01	0.64%	0.13 (0.03, 0.23)	0.01	0.6%
ApoE4	0.63 (0.53, 0.74)	< 0.001	8.42%	0.63 (0.53, 0.74)	< 0.001	8.56%
GDS-30	0.02 (0.01, 0.03)	<0.001	0.72%	0.02 (0.01, 0.03)	<0.001	0.74%
Vascular risk	−0.18 (−0.29, −0.08)	<0.001	0.4%	−0.18 (−0.29, −0.08)	<0.001	0.46%
Hippocampal volume	−3.49 (−5.93, −1.06)	<0.001	1.46%	−3.55 (−5.99, −1.12)	<0.001	1.29%
Age × PSQI				0 (0, 0)	0.17	0.09%
Full model	**$F(7,1232) = 43.62$**	<0.001	19.86%	$F(8,1231) = 38.43$	<0.001	19.98%

Note: Dependent variable: p-tau/Aβ42.
Abbreviations: ApoE4, apolipoprotein E ε4; CI, confidence interval; Decomp R^2, decomposed model R^2 showing unique variance accounted for by each predictor; GDS-30, Geriatric Depression Scale – 30-item; PSQI, Pittsburgh Sleep Quality Index.

TABLE 3 Linear regression models of entire cohort for PSQI component scores of sleep duration, latency, and efficiency ($N = 1240$)

	Model 3: No interactions			Model 4: All interactions		
Variables	**β (95% CI)**	***p***	**Decomp R^2**	**β (95% CI)**	***p***	**Decomp R^2**
Duration	0.03 (−0.01, 0.15)	0.68	0.19%	1.56 (0.34, 2.79)	0.01	0.16%
Latency	0.19 (0.07, 0.31)	<0.001	0.52%	−0.98 (−2.08, 0.12)	0.08	0.51%
Efficiency	−0.3 (−0.51, −0.09)	0.01	0.61%	−1.01 (−2.93, 0.9)	0.3	0.66%
Age	0.04 (0.04, 0.05)	<0.001	8.26%	0.04 (0.01, 0.07)	0.01	8.29%
Sex (male)	0.12 (0.01, 0.22)	0.03	0.59%	0.12 (0.01, 0.22)	0.03	0.51%
ApoE4	0.63 (0.53, 0.74)	<0.001	8.42%	0.64 (0.53, 0.74)	<0.001	8.7%
GDS-30	0.02 (0.01, 0.03)	<0.001	0.84%	0.02 (0.01, 0.03)	<0.001	0.86%
Vascular risk	−0.18 (−0.28, −0.07)	<0.001	0.38%	−0.17 (−0.28, −0.07)	<0.001	0.47%
Hippocampal volume	−3.34 (−5.77, −0.9)	0.01	1.42%	−3.32 (−5.75, −0.89)	0.01	1.1%
Age × duration				−0.02 (−0.04, 0)	0.01	0.35%
Age × latency				0.02 (0, 0.03)	0.04	0.31%
Age × efficiency				0.01 (−0.02, 0.04)	0.46	0.3%
Full model	**$F(12,1227) = 27.57$**	<0.001	21.24%	**$F(18,1221) = 19.37$**	<0.001	22.21%

Note: Dependent variable: p-tau/Aβ42.
Abbreviations: ApoE4, apolipoprotein E ε4; CI, confidence interval; Decomp R^2, decomposed model R^2 showing unique variance accounted for by each predictor; GDS-30, Geriatric Depression Scale – 30-item; PSQI, Pittsburgh Sleep Quality Index.

As noted, given that some of the covariates (e.g., depressive symptoms, vascular risks) controlled for may exist on the causal pathway for dementia, we repeated the analyses to examine only minimally adjusted models (age, sex, and ApoE4 status). The resultant pattern of effects did not change with the minimally adjusted models (Tables S1–S3).

4 | DISCUSSION

In this study, we assessed whether self-reported sleep quality, and specific aspects of sleep disturbance are associated with AD pathology in a large sample of older adults without dementia while accounting for several factors including age, sex, depression, ApoE4, vascular risk, BMI, smoking status, use of psychotropics, white matter lesions, and hippocampal volumes. While there was no association between overall perceived sleep quality and p-tau/Aβ42 ratio, we found that in the overall sample of 1240 participants, the associations between sleep latency, duration, and sleep efficiency and AD pathology were dependent on age.

We examined these age interactions further with three specific analyses per age tertile. For the youngest tertile (age 50–62 years) of the EPAD cohort, both shorter sleep duration and higher sleep efficiency were associated with greater p-tau/Aβ42 ratio. However, for the oldest (age 70–88 years) tertile, longer sleep latency was associated with greater p-tau/Aβ42. There were no significant associations

TABLE 4 Linear regression models by age tertile for PSQI components of sleep duration, latency, and efficiency

	Age Tertile								
	Model 5: Age 50–62 years ($n = 414$)			Model 6: Age 63–69 years ($n = 413$)			Model 7: Age 70–88 years ($n = 413$)		
Variables	**β (95% CI)**	***p***	**Decomp R^2**	**β (95% CI)**	***p***	**Decomp R^2**	**β (95% CI)**	***p***	**Decomp R^2**
Sleep duration	0.26 (0.05, 0.46)	0.02	0.91%	−0.13 (−0.36, 0.1)	0.28	0.67%	−0.07 (−0.29, 0.16)	0.57	0.21%
Sleep latency	0.05 (−0.15, 0.24)	0.63	0.1%	0.2 (−0.03, 0.43)	0.08	0.59%	0.3 (0.09, 0.52)	0.01	1.3%
Sleep efficiency	−0.38 (−0.66, −0.09)	0.01	2.41%	−0.02 (−0.45, 0.4)	0.91	0.66%	−0.38 (−0.8, 0.05)	0.08	0.83%
Age	0.03 (0, 0.05)	0.02	1.04%	0.04 (0, 0.09)	0.07	0.49%	0.05 (0.02, 0.07)	<0.001	2.56%
Sex (male)	0.07 (−0.1, 0.24)	0.41	0.19%	0.08 (−0.1, 0.27)	0.39	0.3%	0.21 (0.02, 0.39)	0.03	1.21%
ApoE4	0.47 (0.31, 0.63)	<0.001	6.55%	0.68 (0.49, 0.87)	<0.001	10.3%	0.8 (0.6, 1)	<0.001	12.74%
GDS-30	0.02 (0.01, 0.04)	0.01	1.47%	0.03 (0.01, 0.05)	0.01	1.09%	0.02 (0, 0.04)	0.1	0.46%
Vascular risk	−0.28 (−0.45, −0.1)	<0.001	1.87%	−0.19 (−0.39, 0)	0.06	0.61%	−0.05 (−0.24, 0.14)	0.61	0.02%
Hippocampal volume	−1.85 (−5.79, 2.09)	0.36	0.29%	−1.72 (−6.14, 2.7)	0.44	0.3%	−5.06 (−9.43, −0.68)	0.02	2.34%
Full model R^2	**F (12,401) = 5.82**	<0.001	14.84%	F (12,400) = 5.89	<0.001	15.01%	F(12,400) = 9.22	<0.001	21.67%

Note: Dependent variable: p-tau/Aβ42.

Abbreviations: ApoE4, apolipoprotein E ε4; CI, confidence interval; Decomp R^2, Decomposed model R^2 showing unique variance accounted for by each predictor; GDS-30, Geriatric Depression Scale – 30-item; PSQI, Pittsburgh Sleep Quality Index.

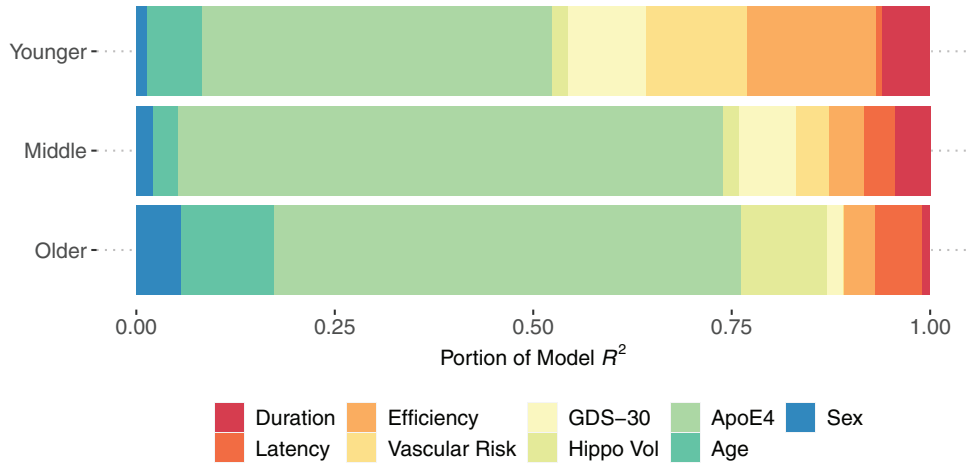

FIGURE 1 Decomposed model R^2 across age bands showing relative contribution of sleep component scores against other known risk and causal factors, expressed as a proportion of explained variance only (range 0–1). *Note*: Full model R^2: younger = 14.84%, middle = 15.01%, and older = 20.67% (also reported in Table 4). See *Statistical Analysis* for full description and references of R^2 decomposition. Duration, efficiency, latency, Pittsburgh Sleep Quality Index (PSQI) components for sleep duration, sleep efficiency, and sleep latency, respectively; GDS-30, Geriatric Depression Scale - 30 -item; ApoE4, apolipoprotein E ε4; Hippo vol, hippocampal volume, mm^3.

between sleep components and p-tau/Aβ42 ratio for the middle tertile, aged 63–69 years.

Our findings regarding sleep duration are consistent with recent large prospective studies which have shown short sleep in mid-life is linked to increased dementia risk 25 years later.[12] Although both short and long sleep duration have been linked to cognitive decline,[25,26] the follow-up period of these studies has been approximately 10 years or less. This area warrants further study. The findings regarding sleep efficiency in our study, were unexpected, as higher sleep efficiency was linked to greater AD pathology. It is possible that for middle aged adults with low sleep duration, their sleep deprivation is linked with more time spent in bed actually sleeping, however, this remains to be empirically examined or tested. For older adults aged over 69 years, our data suggest that sleep duration is no longer a predominant factor but instead the latency of sleep appears to be more critically linked to AD pathology. However, it is noted that longer sleep latency may be associated with daytime napping,[27] which is also associated with dementia[28] and napping was not examined in the EPAD cohort.

In addition to sleep, the association of other AD risk factors to p-tau/Aβ42 also varied by age. For instance, depressive symptoms and

vascular risk showed larger relative associations in the youngest group, which is aligned with neurobiological work linking these two risks to dementia.[29] By contrast, age, ApoE4 status, and hippocampal volumes showed larger relative associations with p-tau/Aβ42 ratio in the oldest group.

Overall, our results suggest that after controlling for many confounding factors, the relationship between self-reported sleep and markers of AD pathology may depend on age and this has implications for using sleep parameters as markers for AD risk or intervention targets in AD intervention trials. For example, short sleep duration at younger age may convey increased risk of developing AD while long sleep latency at older age may be a marker for ongoing AD pathogenesis. Establishing the contribution of various aspects of sleep disturbance to AD pathology relative to other AD risk factors will allow for a more personalized approach to both assessing AD risk and appropriately selecting individuals for sleep interventions. In addition, longitudinal studies measuring sleep, cognitive function, and AD biomarkers as well as other emerging biomarkers of neurodegeneration (e.g., neurofilament light, glial fibrillary acidic protein, or vascular dementia biomarkers) are critical to improving our understanding of these inter-relationships, and how they contribute uniquely to AD and other forms of dementia. Indeed, it is noted that for all models, with comprehensive modelling of a number of known risk and causal factors, explained variance was in the range of 15%–22%. Hence, there remains a large proportion of variance in AD pathology unexplained by these models. Additionally, the relative contribution of self-reported sleep to AD pathology was very small (up to a maximum of 2.4% across models), but notably was similar to other potentially modifiable risk factors such as depressive symptoms and vascular risk.

5 | LIMITATIONS AND FUTURE DIRECTIONS

The current study is limited by the use of self-report data, which can be impacted by recall inaccuracies. Subjective sleep measures, particularly of perceived sleep quality, have limited association with more objective sleep measures collected by actigraphy or polysomnography[30] and they do not capture key neurophysiological events integral for optimal sleep and which may provide greater insights into potential disease mechanisms. Additionally, our dataset did not capture obstructive sleep apnea, which is known to be prevalent in older people and linked to AD biomarkers and dementia risk.[31] It is noted that the data pertaining to sleep efficiency may have been driven by the inclusion of unbalanced groups. Finally, it is noted that these data are cross-sectional in nature. Future analyses seeking to support causal inferences may wish to consider the prospective associations between sleep duration, efficiency and latency in relation to the biomarkers for AD and other neurodegenerative diseases, and longitudinal cognitive decline or dementia trajectory.

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CONFLICT OF INTEREST

A/Prof Lucey has consulting agreements with Merck and Eli Lilly. Prof Naismith has a consulting agreement with Roche. A/Prof Leng and Dr Palmer have nothing to declare. Author disclosures are available in the supporting information.

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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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APPENDIX 1: Collaborators

Data used in preparation of this article were obtained from the Longitudinal Cohort Study (LCS), delivered by the European Prevention of Alzheimer's Disease (EPAD) Consortium. As such investigators within the EPAD LCS and EPAD Consortium contributed to the design and implementation of EPAD and/or provided data but did not participate in analysis or writing of this report.