Supplementary Online Content

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eAppendix. Participants and Actigraphy Analysis

eTable 1. Effect of pTau:Aβ42 Ratio on Circadian Variables

eTable 2. Correlations Between Circadian and Sleep Variables

This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix

METHODS:

Participants: The longitudinal studies included the Adult Children Study, in which all volunteers were age 45-75 years at baseline and 50% have a parental history of sporadic AD, and the Memory and Aging Project, a community volunteer cohort in which all were age >60 years and healthy at baseline.

Actigraphy analysis: The sleep diary queried for naps the previous day, bedtime, sleep latency, nighttime awakenings, waketime, and open-ended comment. Participants were instructed to press a time stamp button on the actigraph when getting into bed to go to sleep, or getting out of bed after awakening in the morning. Actigraphy data were collected in 30-second epochs. All actigraphy records were first scored manually by blinded scorer as previously described [56]. Briefly, time stamp data were used to score bedtime and waketime if they corresponded to a drop-off or increase in activity levels. If time stamp data were missing or did not appear to correspond to activity levels, then sleep diary information was used. Sleep variables were derived using Actiware™ (Philips-Respironics, Murrysville, PA) software using the high-sensitivity low threshold wake cutoff of 20. Naps were week were calculated by counting number of daytime naps recorded in diary over 2 weeks. Raw activity counts in30-second epochs were used for circadian analysis. The first seven continuous days of data, starting at midnight, without a >3 hour period of zero activity count (indicating actigraph was removed), were extracted for analysis. Two scorers, blinded to biomarker status, separately determined the seven days included in analysis. For participants with discrepancies in the days selected by the two scorers, the entire actigraphic recordings were manually examined by two additional scorers, who adjudicated which time period would be analyzed. Light exposure was recorded by actigraphs, but were not analyzed because participants were not consistently instructed on leaving the light monitor uncovered. Since the

actigraphs were worn on the wrist and are often covered by long sleeves, participants having actigraphy recording during colder months would have had artifactually low or irregular light exposure.

eTable 1: Effect of pTau:Aβ42 ratio on circadian variables. All participants with CSF biomarkers were included (N=148). Standardized β and p values are shown for unadjusted analyses and after adjustment for age and sex.

	Unadjusted β	**p unadjusted**	**β after adjustment for age and sex**	**p adjusted**
Mesor	-0.025	0.767	0.044	0.600
Acrophase	-0.167	**0.042**	-0.136	0.122
F	0.066	0.424	0.011	0.901
Alphacount	-0.045	0.590	0.033	0.699
IV	0.251	**0.002**	0.231	**0.008**
IS	0.044	0.594	-0.026	0.750
EMD amplitude	-0.025	0.759	0.012	0.887
EMD Period	-0.060	0.468	-0.089	0.315

eTable 2: Correlations between circadian and sleep variables. Sleep variables, derived from a combination of nighttime actigraphy data and sleep diaries are shown in rows, and circadian variables are shown in columns. Pearson correlations and p values between each sleep variable and each circadian variable are shown in intersecting cells. Measures of sleep timing include bedtime and waketime. Measures of sleep quantity include time in bed (time between bedtime and waketime) and total sleep time. Standard deviation of total sleep time is a measure of regularity of sleep quantity, with higher values indicating more irregular sleep quantity. Measures of sleep quality include sleep efficiency and wake time after sleep onset. Naps per week are the number of daytime naps per week recorded by sleep diary. Notably, naps per week is the only sleep variable that is correlated with IV, with greater number of naps being correlated with more fragmentation. No other measures of sleep quality, timing, regulariy, or quantity was associated with IV. This suggests that IV is capturing rest-activity fragmentation during the daytime rather than duplicating measures of sleep fragmentation.

	Mesor	**Acrophase**	**F**	**Alphacount**	**IV**	**IS**	**EMD Amplitude**	**EMD period**
Bedtime	-.068 p=.351	**.324** **p=.000**	**-.158** **p=.030**	-.117 p=.109	.015 p=.840	**-.183** **p=.012**	-.137 p=.059	.010 p=.895
Waketime	-.126 p=.083	.386 p<.001	.047 p=.523	**-.177** **p=.015**	-.035 p=.635	-.063 p=.385	-.018 p=.811	-.082 p=.259
Time in bed	-.129 p=.077	.117 p=.109	**.182** **p=.012**	-.140 p=.055	.007 p=.927	.061 p=.401	.081 p=.269	-.121 p=.097
Total sleep time	-.104 p=.153	.066 p=.364	**.240** **p=.001**	-.075 p=.303	-.085 p=.246	.128 p=.079	**.174** **p=.016**	-.116 p=.112
Standard Deviation of Total sleep time	**-.146** **p=.045**	.128 p=.080	**-.171** **p=.019**	**-.189** **p=.009**	.010 p=.892	**-.255** **p<.001**	**-.172** **p=.018**	-.054 p=.461

Sleep efficiency	-.007 p=.926	-.040 p=.589	.110 p=.132	.045 p=.536	-.112 p=.124	.094 p=.199	.136 p=.063	-.020 p=.790
Wake time after sleep onset	.050 p=.494	.039 p=.598	.004 p=.961	-.002 p=.975	.062 p=.398	.029 p=.694	-.005 p=.943	-.028 p=.706
Naps per week (n=187)	-.006 p=.935	-.063 p=.393	**-.153** **p=.037**	-.040 p=.591	**.152** **p=.037**	-.119 p=.106	-.059 p=.425	.059 p=.421