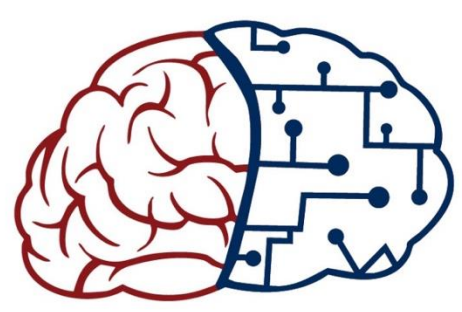




Longitudinal Prevalence And Severity Of Nighttime Behaviors Across Pathologic Cohorts

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BACKGROUND

Sleep is a restorative process critical for synaptic plasticity, memory consolidation, cellular metabolism and clearance of metabolic waste¹. There are documented changes in slow wave sleep and increased sleep fragmentation with age¹. Changes in sleep may be both a symptom and a driver of neuropathology and may serve as a potential non-invasive biomarker for disease². Sleep disturbances can have a significant impact on quality of life for patients and caregivers. Prior studies in behavioral variant frontotemporal dementia have shown more frequent transitions between wakefulness and light sleep (N1) and fewer transitions to restorative slow wave sleep (N3)³, but did not account for the heterogeneity of underlying pathologies.

METHODS

- Participants were selected from the University of Pennsylvania Integrated Neurodegenerative Diseases Database⁴
- Autopsy cases with at least one neuropsychiatric inventory questionnaire (NPI-Q) were included in the analyses
- Prevalence and severity of sleep disturbances were compared across three neuropathologically defined cohorts:
 - Alzheimer's disease (AD), Frontotemporal lobar degeneration (FTLD) -Tau (Tau), and FTLD-TDP (TDP)
 - AD cases with neuronal alpha-synuclein or limbic predominant age related TDP-43 encephalopathy co-pathologies were excluded
 - Sleep disturbance was captured by the NPI-Q⁵ prompt:
 - Does the patient awaken during the night, rise too early in the morning, or take excessive naps during the day?
 - Measured as an ordered four level variable: absent, mild, moderate, or severe

Table 1. Cohort Description				
	AD N = 61	Tau N = 71	TDP N = 57	p-value
Age at Onset	68.5 ± 11.4	63.4 ± 8.4	59.7 ± 8.8	<0.001
Education	16.0 ± 3.4	15.9 ± 2.7	15.9 ± 2.5	0.8
Age at Death	78.9 ± 11.1	71.5 ± 7.9	67.7 ± 9.7	<0.001
Sex (% Female)	28 (46%)	31 (44%)	23 (40%)	0.8
Follow up (mean yrs)	3.73 ± 3.98	1.56 ± 1.88	2.22 ± 2.82	

- Kruskal-Wallis rank sum and Pearson's Chi-squared tests were used for demographic comparisons
- Bayesian cumulative logit mixed-effects model with flexible thresholds and a participant-level random intercept was fit to model severity over time with fixed effects for disease duration, cohort, their interaction, and age at onset.
- Pairwise cohort contrasts were obtained from posterior marginal estimates
- NITE ~ Disease Duration * Cohort + Age at Onset + (1 | Participant)

RESULTS

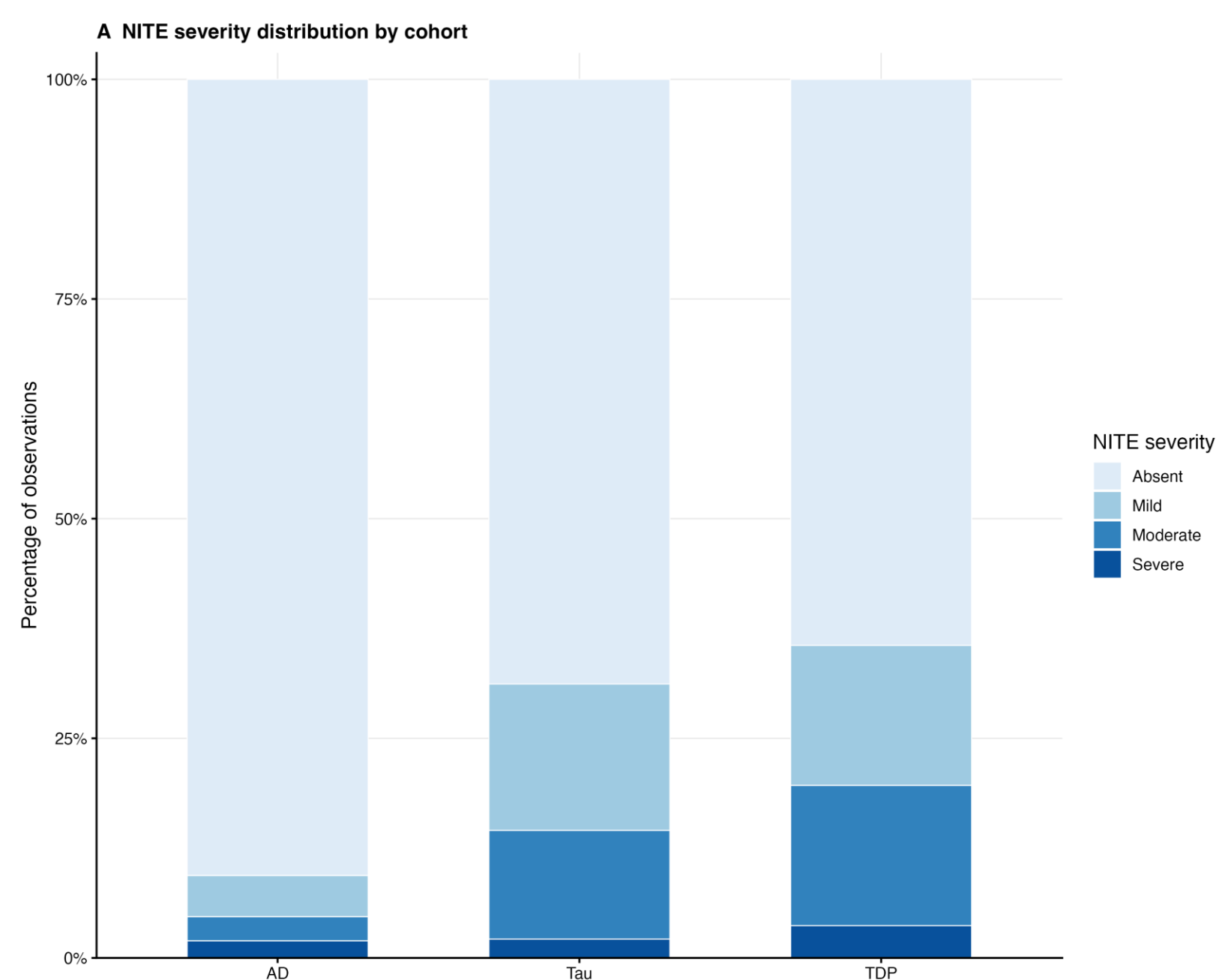


Figure A. Percent prevalence and distribution of sleep disturbances by cohort.

Table 2. Pairwise Cohort Comparisons		
Group	Estimate (log-OR)	95% HPD
AD vs Tau	-1.86	-3.04 to -0.58
AD vs TDP	-2.30	-3.67 to -1.02
Tau vs TDP	-0.45	-1.61 to 0.69

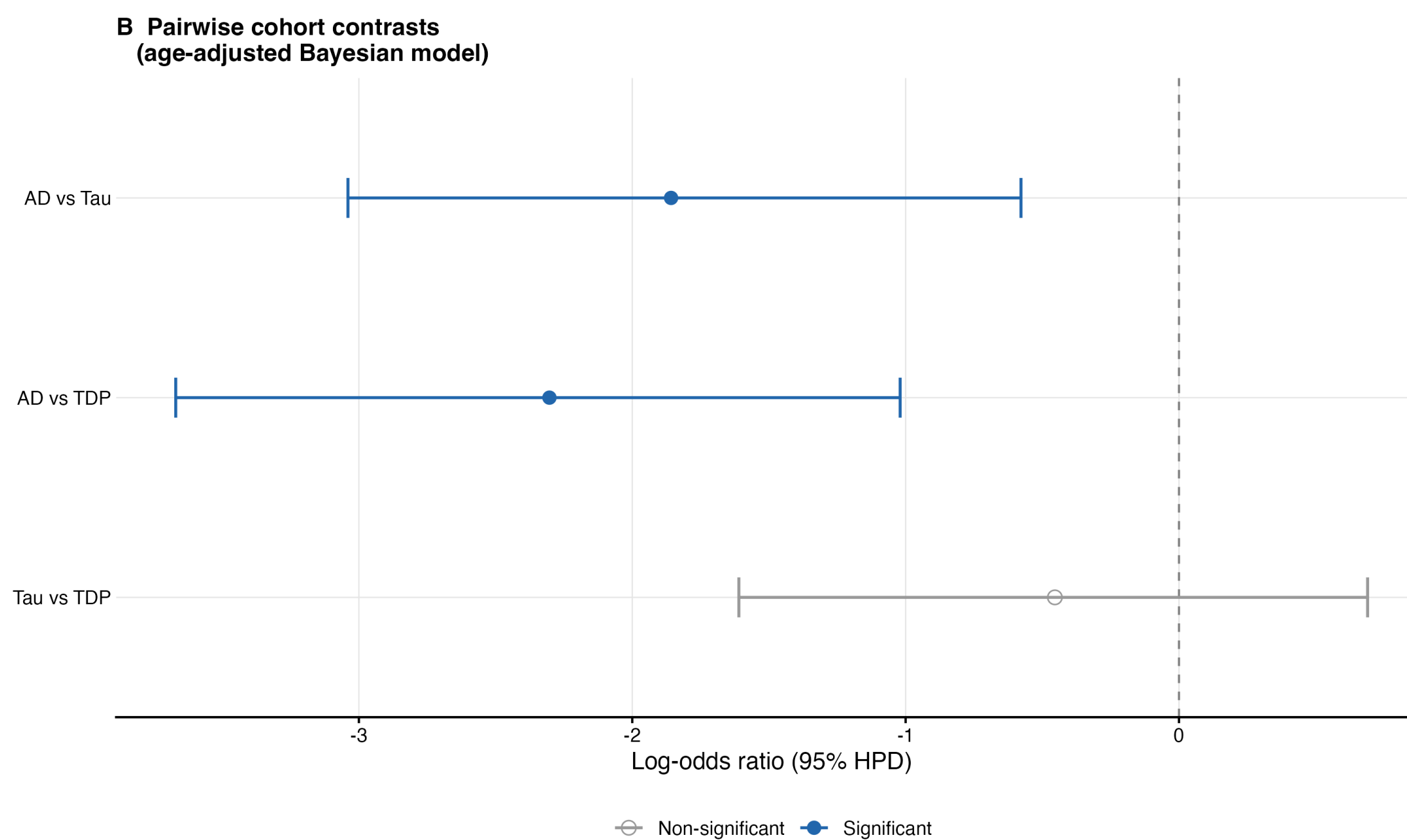


Figure B. Age-adjusted Bayesian cumulative logit mixed-effects model pairwise comparison of sleep disturbances between cohorts indicating that both FTLD Tau and TDP cohorts have higher odds of sleep disturbances compared to AD, but there were no significant differences between FTLD subgroups (Table 2).

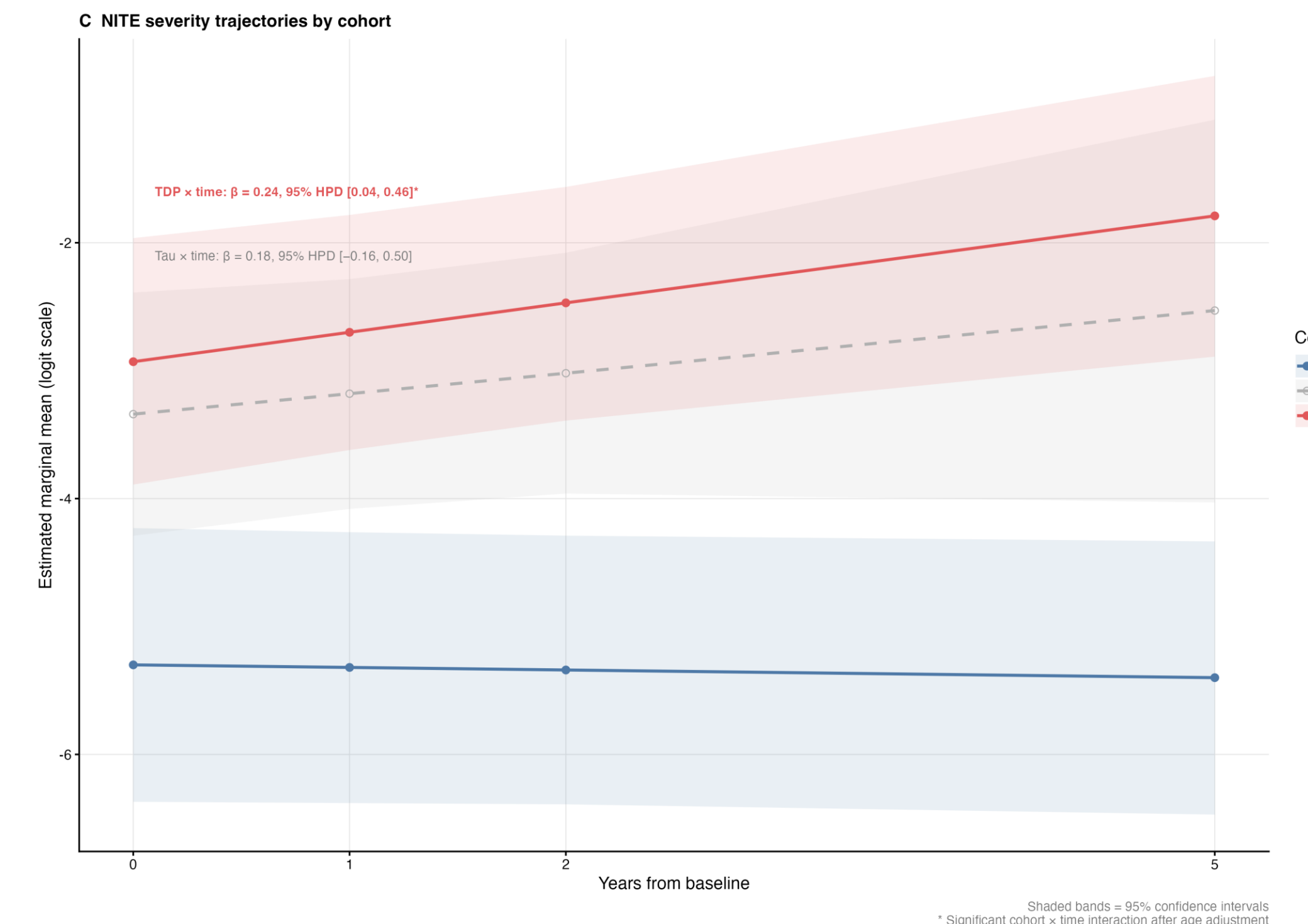


Figure C. Bayesian cumulative logit mixed-effects model of sleep disturbances over time indicating that FTLD Tau and TDP have higher baseline prevalence. There were no significant differences in prevalence in the AD cohort over time. The TDP cohort had significant increases in sleep disturbances over time ($\beta = 0.24$, 0.04-0.46); this was not significant in the Tau cohort but followed a similar trend ($\beta = 0.18$, -0.16-0.50) (Table 3). Random intercept SD was 2.59.

Table 3. Trajectory of Nighttime Behavior				
Time point	Est AD vs Tau	p-value	Est AD vs TDP	p-value
Baseline	-1.96	0.0025	-2.37	0.0009
Year 1	-2.14	0.0006	-2.62	0.0001
Year 2	-2.32	0.0004	-2.87	<0.0001
Year 5	-2.87	0.0021	-3.61	<0.0001

CONCLUSIONS

In an autopsy defined cohort, we investigated whether the prevalence of sleep disturbances differed by primary pathology, comparing Alzheimer's disease (AD), frontotemporal lobar degeneration (FTLD) Tau and TDP-43 proteinopathies. Compared to AD, there were significantly higher odds of sleep disturbances in both FTLD-Tau and TDP, with the highest odds observed in FTLD-TDP. Longitudinal modeling demonstrated higher baseline prevalence of sleep disturbances in both FTLD cohorts, with a significant increase in sleep disturbance over time in FTLD-TDP and a similar, but non-significant trend in FTLD-Tau, while sleep disturbances in AD did not change over time. These pathology-associated differences held after adjusting for age, suggesting that these findings are not simply a phenomenon of aging. Substantial inter-individual variability in sleep disturbances was observed independent of age and cohort, indicating that factors beyond primary neurodegenerative pathology, such as region pathology burden, network involvement, or other conditions, may influence sleep as well. Although limited by use of the care partner-reported, double-barreled item of NPI nighttime behavior, these findings suggest that sleep disturbances in FTLD, particularly FTLD-TDP, may be underappreciated. If validated using objective sleep metrics, sleep disturbances may represent a clinically accessible marker of disease severity or progression. Future studies will examine the relationship between regional pathology and sleep disturbances in neurodegenerative diseases.

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