

BACKGROUND

- Circadian rhythms drive optimal biological function
- Circadian disruption is linked to age-related diseases
- Rest-activity rhythms (RAR) are disrupted with aging and in dementia
- Disrupted RAR are early markers of dementia risk
- Actigraphy provides a non-invasive, real-world circadian assessment in naturalistic settings

METHODS

- Sample:
 - The Memory and Aging Project (MAP), a longitudinal clinical study at Rush Alzheimer's Disease Center [1]
 - Starting from 1997
 - Actigraphy added in 2005
 - Annual actigraphy follow-up for up to 19 years
 - Annual neuropsychological tests for cognition
 - Postmortem tissues to confirm AD
 - 1,201 cognitively normal participants (80.9 ± 7.3 years, 77% female, 19 years follow-up)
 - Actical wearable devices (Philips) were used to collect actigraphy signals from their non-dominant wrist (up to 10 days continuously)

- RAR extraction:
 - ~24-h rest-activity rhythm derived from the first 7 valid days using the Uniform-phased empirical mode decomposition (UP-EMD) method [2]

- RAR metrics:
 - Mean of ~24-h RAR amplitude
 - SD (variability) of ~24-h RAR amplitude

- Statistical analysis:
 - Cox proportional hazards model for incident AD (age, sex, education, and mean activity-adjusted)

RESULTS

- 374 participants developed AD, with a mean time to onset of 7.26 ± 4.23 years from baseline
- Higher mean RAR amplitude is associated with lower AD risk (per 1 SD increase, HR = 0.864, p = 0.011)
- Higher variability in RAR amplitude is associated with lower AD risk (per 1 SD increase, HR = 0.864, p = 0.015)

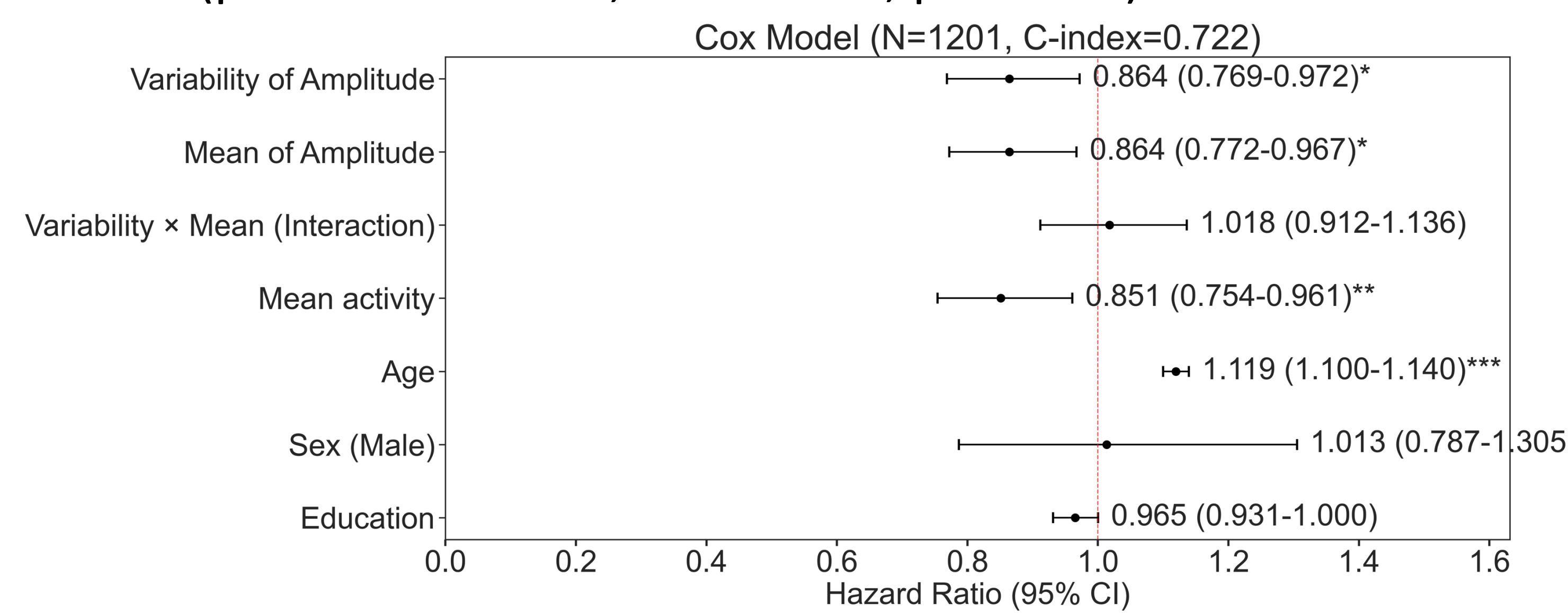


Figure 1. Cox model. Cox proportional hazards model for incident AD (age, sex, education, and mean activity-adjusted)

- Sensitivity analysis confirmed the results:
 - We excluded extreme values of mean and variability amplitude and categorized the sample into 2x2 (low/high, mean/variability) matched groups
 - Results hold for mean and variability, while the high mean and high variability group has the highest protective effect

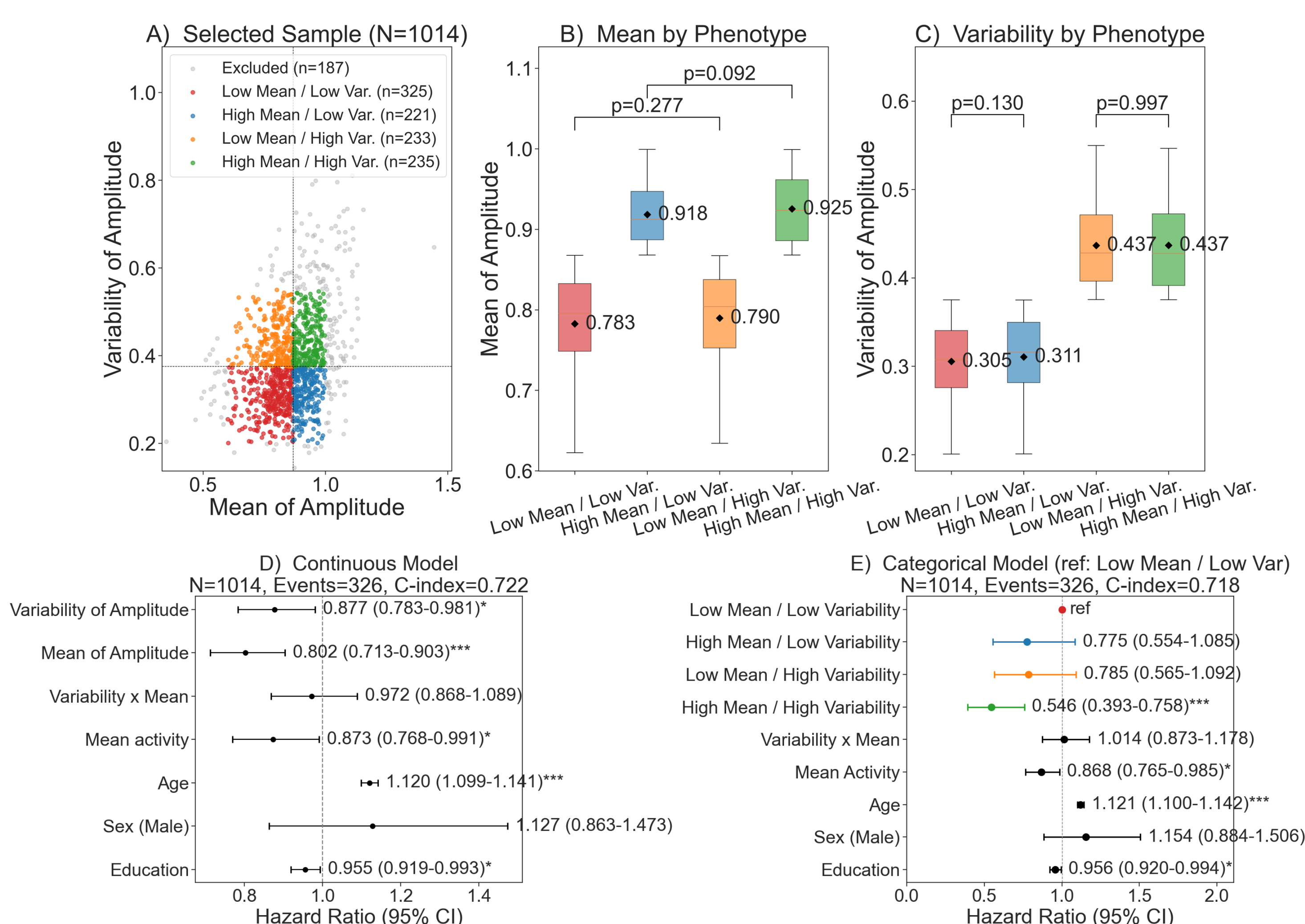


Figure 2. Sensitivity analysis. Subsample selection to test if the results are driven by outliers or an association between the mean and variability.

DISCUSSION

- Variability in 24-h RAR amplitude predicted incident AD, independent of mean amplitude, activity level, and demographics
- Both a higher mean amplitude of RAR and variability of RAR are protective against the incidence of AD
- The sensitivity analyses confirmed the importance of the variability of RAR
- Potential underlying mechanism:
 - Higher day-to-day variability of RAR may be linked to resting days
 - Activity-intensive days followed by rest days enable better recovery and reduced injury risk
 - Higher variability may reflect engaging in diverse activities across different days (e.g., social outings, grocery shopping, gardening)
- Future directions:
 - Validate in independent cohorts and in heterogeneous populations
 - Link RAR metrics with AD biomarkers (plasma, CSF, PET)

REFERENCES

1. Bennett DA, Schneider JA, Buchman AS, Barnes LL, Boyle PA, Wilson RS. Overview and Findings from the Rush Memory and Aging Project. *Curr Alzheimer Res.* 2012 Jul;9(6):646-63. doi: 10.2174/156720512801322663. PMID: 22471867; PMCID: PMC3439198.
2. Gao C, Haghayegh S, Wagner M, Cai R, Hu K, Gao L, Li P. Approaches for assessing circadian rest-activity patterns using actigraphy in cohort and population-based studies. *Curr Sleep Med Rep.* 2023 Dec;9(4):247-256. doi: 10.1007/s40675-023-00267-4. Epub 2023 Oct 31. PMID: 41585931; PMCID: PMC12829919.

ACKNOWLEDGEMENTS

Grant support: R01AG083799