Circadian Rest-Activity Rhythms and Alzheimer Disease Biomarkers in Adults with Down Syndrome

Paul A. Chung, Victoria L. Fleming-Batayneh, Kathryn J. Reid, Daniela Grimaldi, David T. Plante, Christy L. Hom, Beau M. Ances, Benjamin L. Handen, Bradley T. Christian, Elizabeth Head, Mark Mapstone, Sigan L. Hartley, Phyllis C. Zee, for the Alzheimer's Biomarkers Consortium–Down Syndrome (ABC-DS) Investigators

BACKGROUND

- Our recent work demonstrated that greater rest-activity rhythm (RAR) fragmentation and lower peak daytime activity are associated with worse cognitive function and dementia symptoms in adults with Down syndrome (DS) (Chung et al., *Neurology,* 2026)
- Whether RAR disruption is similarly associated with AD plasma and imaging biomarkers in adults with DS is unknown

HYPOTHESIS

- Greater RAR fragmentation and lower peak daytime activity will be associated with a more adverse AD plasma and imaging biomarker profile.

METHODS

- Cross-sectional and longitudinal analysis
- Adults with DS aged 25 - 61 years enrolled in the Alzheimer Biomarker Consortium – Down Syndrome (ABC-DS)
- Wrist-worn actigraphy: Actigraph GT9x (ActiGraph, Pensacola, FL)
- Primary measures: intradaily variability (IV) and most active 10-hr activity counts (M10)
- Secondary measures: interdaily stability (IS), relative amplitude (RA), least active 5-hour activity counts (L5), coefficient of variation (CV) of total sleep time (TST) and sleep midpoint, and the sleep regularity index (SR)
- Primary outcome: pTau217
- Secondary outcomes: Aβ40, Aβ42, Aβ42/40 ratio, total-Tau, NfL
- Exploratory outcomes: amyloid and tau PET used for AD biological staging.
  - Amyloid PET+ (A+): centiloid ≥ 18
  - Tau PET+ (T+): SUVR ≥ 1.21
- Subgroup analysis: cognitively stable adults with DS (no mild cognitive impairment or dementia)
- Linear and logistic regression models adjusted for age, sex, intellectual disability level, site, and the apnea-hypopnea index (AHI)

RESULTS

Table 1. Sample Characteristics

	Whole Sample (N=114)	Cognitively Stable (N=99)
Demographics		
Age, years (mean ± SD)	39.8 ± 9.1	38.0 ± 8.1
Male sex, n (%)	64 (56.1%)	54 (54.5%)
Intellectual Disability Level, n (%)		
Mild	55 (48.2%)	48 (48.5%)
Moderate	49 (43.0%)	42 (42.4%)
Severe	10 (8.8%)	9 (9.1%)
Cognitive Status, n (%)		
Cognitively Stable	99 (86.8%)	99 (100.0%)
Mild Cognitive Impairment	10 (8.8%)	—
Dementia	5 (4.4%)	—
Sleep-Disordered Breathing		
pAHI (mean ± SD), (n)	19.8 ± 18.8, (106)	19.6 ± 19.2, (92)

Figure 1. Representative 7-Day Activity Profiles

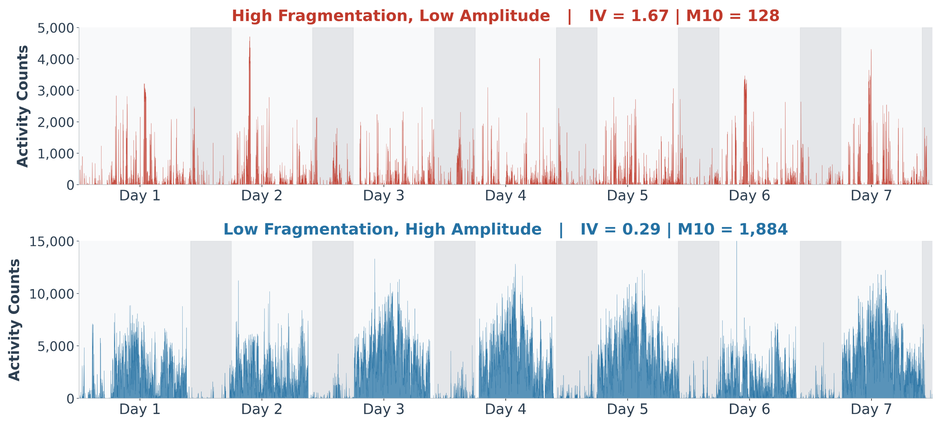
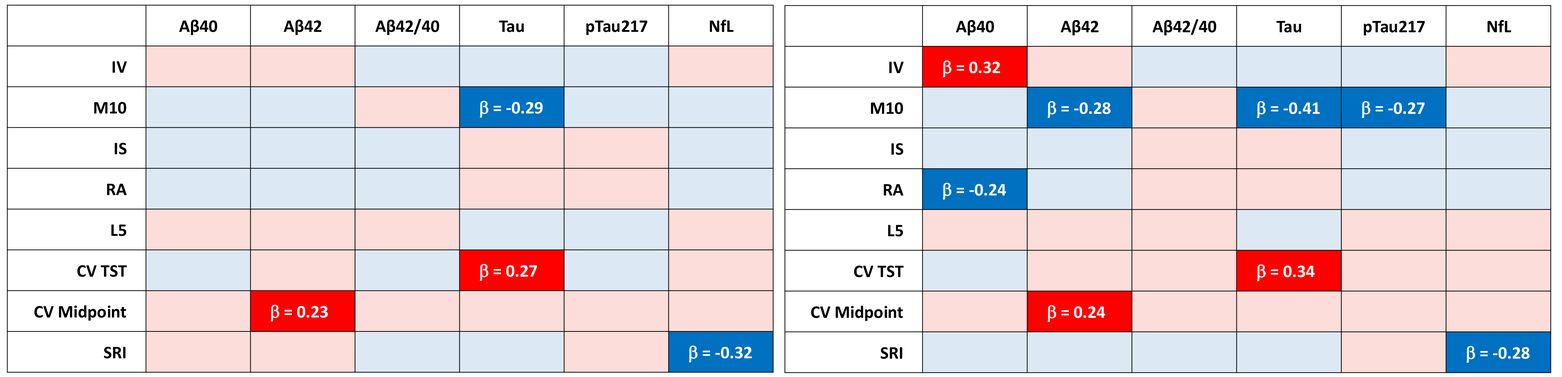


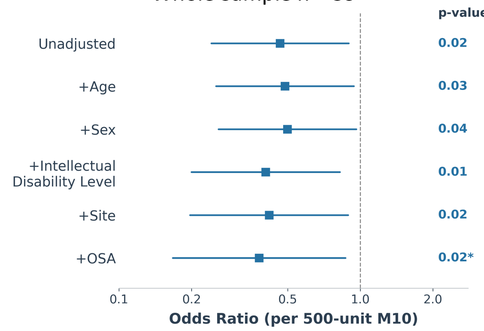
Figure 2. Heat Maps of Associations Between Actigraphy-Derived Measures and Plasma AD Biomarkers



Standardized β shown for significant associations ($p < 0.05$). Red = direct relationship; Blue = inverse relationship.

Figure 3. M10 and AD Biological Staging

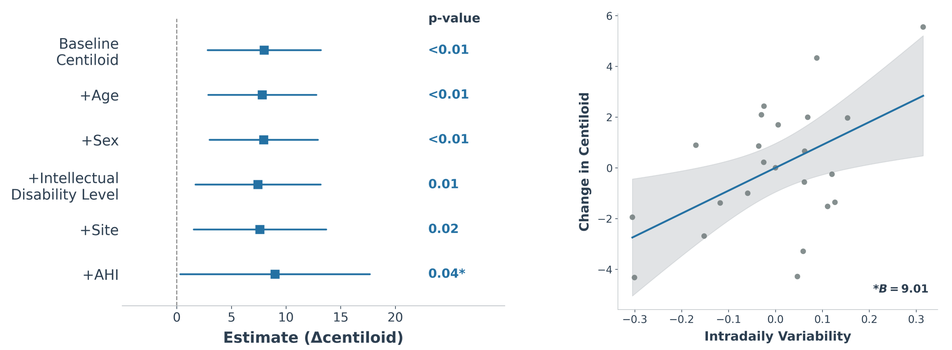
Whole Sample n = 59



Lower M10 associated with higher odds of A+/T- and A+/T+. Forest plot with incremental covariate adjustment. *Fully adjusted model: **OR = 0.38 (95% CI: 0.17 – 0.87)**.

Figure 4. IV and Change in Amyloid PET

Cognitively Stable n = 27



Higher IV associated with greater amyloid accumulation over 16 months. Forest plot with incremental covariate adjustment. Scatter plot depicts *fully adjusted model: ***B* = 9.01 (95% CI: 0.33 – 17.68)**.

SUMMARY/CONCLUSION

- Actigraphy-derived measures were associated with plasma AD biomarkers, with additional associations observed in cognitively stable adults with DS
- Lower M10 was associated with higher odds of AD biological staging. However, this should be interpreted cautiously as 50% of tau PET scans were not concurrent with actigraphy
- Higher IV was associated with longitudinal amyloid accumulation in cognitively stable adults with DS though confirmation with a larger sample size is needed
- These findings suggest that greater RAR fragmentation and lower peak daytime activity are associated with AD pathology in adults with DS, particularly in the preclinical stage

FUTURE DIRECTION

- Future work will investigate physiologic and molecular markers of circadian rhythm disruption in relation to AD pathology in adults with DS

KEY FINDINGS

Greater rest-activity rhythm fragmentation is associated with longitudinal amyloid accumulation in cognitively stable adults with DS

ACKNOWLEDGEMENTS

- This work was supported by NIA, NICHD, and the NIH INCLUDE Project (U01 AG051406, U01 AG051412, U19 AG068054, R01 AG070028, T32 HL007909, F31 AG085730).
- We thank the ABC-DS study participants, their families, care providers, and research staff

CONTACT

Paul A. Chung, DO
paul.chung@northwestern.edu