

The Longitudinal Association Between Plasma pTau217, Sleep, and Speech Rate in Adults at Increased Risk for Cognitive Decline



Phoebe Crumpton¹, Kristin Basche^{2,3}, Anikka Baker¹, Bruce P. Hermann^{2,4}, Jessica Z.K. Caldwell², Ramiro Reyes², Rachael E. Wilson², Nathaniel C. Chin^{2,5}, Barbara B. Bendlin^{2,5}, Henrik Zetterberg², Sterling Johnson^{2,5}, Kimberly Diggle Mueller^{1,2}
¹Communication Sciences and Disorders, University of Wisconsin-Madison, Madison WI, USA, ²University of Wisconsin-Madison, Madison, WI, USA, ³Division of Geriatrics, School of Medicine and Public Health, University of Wisconsin-Madison, Department of Neurology, School of Medicine and Public Health, University of Wisconsin – Madison, Wisconsin Alzheimer's Disease Research Center, School of Medicine and Public Health, University of Wisconsin – Madison

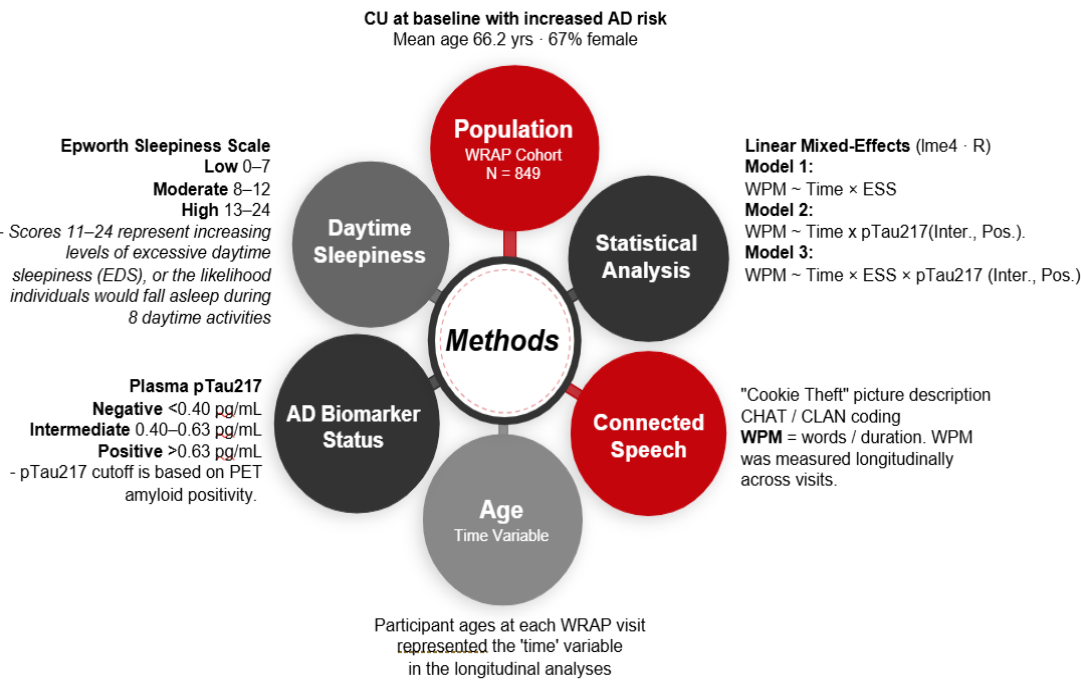
BACKGROUND

- Alzheimer's disease (AD) is a growing public health concern, with prevalence rising as the population ages, creating urgency to identify modifiable risk factors that could slow or prevent disease onset.
- Sleep is a potential modifiable risk factor for AD and cognitive decline.
- Poor sleep quality may accelerate cognitive decline in those with underlying AD pathology and is associated with excessive daytime sleepiness (EDS).
- Connected speech analysis is sensitive to subtle cognitive decline across the AD continuum, offering a low-cost, low-burden detection tool.
- No prior studies have examined the relationship among EDS, AD biomarkers, and connected speech over time.

OBJECTIVES

- To determine if a subjective measure of EDS and connected speech could serve as a combined, sensitive tool for early identification of AD pathology.
- Evaluate whether EDS interacts with plasma pTau217 status to predict longitudinal change in speaking rate (words per minute [WPM]) among adults at increased risk for cognitive decline from the Wisconsin Registry for Alzheimer's Prevention (WRAP) cohort.

METHODS



Models were adjusted for age, sex, education, total speech duration and depression symptoms measures by the Center for Epidemiologic Studies Depression Scale (CES-D).

RESULTS

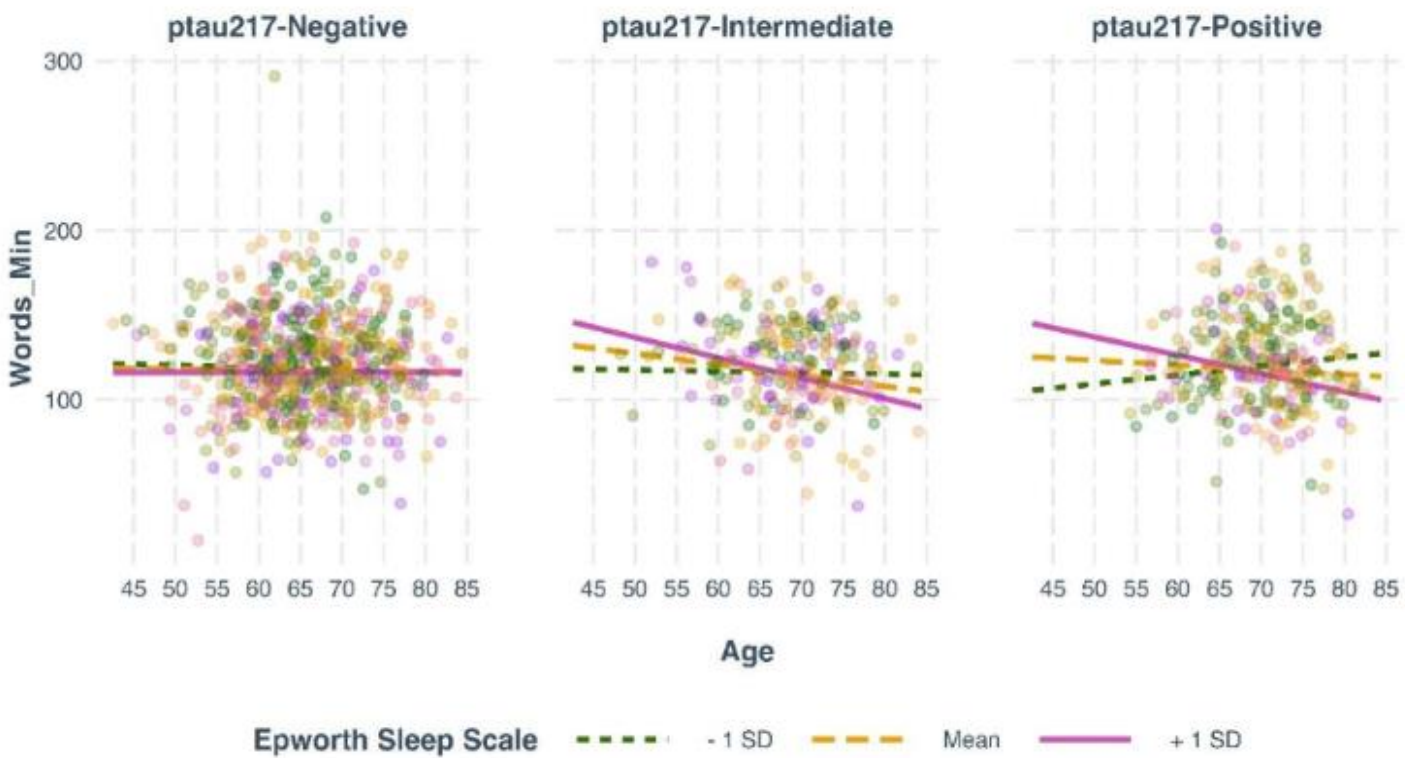


Figure 1. Age-Related Decline in Words Per Minute by Epworth Sleep Score and pTau217 Status. A three-way interaction among time (age), EDS (measured by the Epworth Sleep Scale [ESS] taken from the first available visit), and pTau217 status showed that increased daytime sleepiness predicted reduced words per minute overtime compared to less daytime sleepiness in the pTau217 positive ($\beta = -0.25$, $p = .006$) and pTau217 intermediate groups ($\beta = -0.18$, $p = .035$). However, this relationship is not observed in the negative group. *Notes: Participant baselines were defined as the earliest WRAP visit with available speech samples and complete ESS assessment. Plasma pTau217-ALZpath status was taken from the most recent visit, with cut-offs at 0.40 pg/mL and 0.63 pg/mL. ESS was used as a continuous measure in all mixed effects models (range 0 - 24); however, for visual purposes in Figure 1, ESS was assigned to 3 standard deviation categories.*

Increased daytime sleepiness (measured by ESS) → lower WPM over time

Intermediate pTau217 → lower WPM over time

Significant 3-way interaction (time × EDS × pTau217 positive, intermediate)

CONCLUSIONS

- EDS was associated with greater decline in speaking rate over time, with accelerated decline among intermediate and positive pTau217 groups versus biomarker-negative participants.
- Our findings suggest that increased daytime sleepiness and AD-related pathology may jointly contribute to changes in connected speech over time.
- Overall, sleep may be a modifiable target for AD intervention.
- Speech-based measures and subjective measures of sleep may serve as sensitive, low-burden tools for detecting individuals at increased risk for cognitive-linguistic decline related to AD; further investigation of these measures are needed.

TABLES

Table 1: Demographics & Clinical Characteristics Stratified by Epworth Sleepiness Scale Category

	Overall	Low ESS (0–7)	Medium ESS (8–13)	High ESS (14–24)	p-value
	N = 849	N = 583	N = 219	N = 47	
Age at Baseline, Mean (SD)	66.2 (6.89)	66.3 (6.81)	66.2 (7.19)	64.6 (6.38)	0.483
Sex, Female; N (%)	574 (67.6%)	419 (71.9%)	133 (60.7%)	22 (46.8%)	<0.001
Years of Education, Mean (SD)	16.4 (2.71)	16.4 (2.73)	16.4 (2.71)	15.8 (2.55)	0.508
CES-D Score, Mean (SD)	6.38 (6.87)	5.44 (6.11)	7.98 (7.71)	10.6 (8.65)	<0.001
Words Per Minute (WPM), Mean (SD)	123 (28.4)	124 (28.0)	120 (28.8)	117 (30.9)	0.164
Age at AD Plasma pTau217, Mean (SD)	69.8 (7.24)	69.9 (7.23)	69.9 (7.29)	67.6 (6.93)	0.216
MMSE Baseline, Mean (SD)	29.4 (1.01)	29.3 (1.02)	29.4 (0.983)	29.3 (0.939)	0.829
Consensus Diagnosis, Mean (SD)					
Cognitively Unimpaired-Stable	710 (83.6%)	498 (85.4%)	179 (81.7%)	33 (70.2%)	0.304
Cognitively Unimpaired-Declining	115 (13.5%)	69 (11.8%)	35 (16.0%)	11 (23.4%)	
Mild Cognitive Impairment	22 (2.6%)	14 (2.4%)	5 (2.3%)	3 (6.4%)	
Dementia	2 (0.2%)	2 (0.3%)	0 (0%)	0 (0%)	

Plasma pTau217 Cutoff Category, Mean (SD)				
Negative	480 (56.5%)	327 (56.1%)	124 (56.6%)	29 (61.7%)
Intermediate	162 (19.1%)	104 (17.8%)	49 (22.4%)	9 (19.1%)
Positive	201 (23.7%)	148 (25.4%)	45 (20.5%)	8 (17.0%)

Table 1. Notes: ¹Mean, SD; n (%); ²P-values from one-way ANOVA for continuous variables and chi-square test for categorical variables. Abbreviations and Definitions: ESS=Epworth Sleepiness Scale (Johns, 1991); CES-D = Center for Epidemiologic Studies Scale for Depression (Radloff, 1977), Plasma p-Tau217-ALZpath cut-offs at 0.40 pg/mL and 0.63 pg/mL (Ashton et al, 2024). *ESS was used as a continuous measure in all models (range 0-24). For ease of interpretation, we created three groups according to the following score distributions: 0-7=low daytime sleepiness, 8-12=moderate daytime sleepiness, 13-24=high daytime sleepiness; for clinical cutoffs for the ESS, see (Johns, 1991). **Models were run with and without participants with dementia and results remained the same. ***Participants' first visit containing a speech transcript was made concurrent with their ESS measure. ****Participants' p-Tau217 cutoff category was made concurrent with their final WPM measure.

Table 2: Model 3 Output Showing 3-Way Interaction Among Sleep, pTau217, Time on Words Per Minute

Predictor	Model 3 - WPM		
	Est.	CI	p
Sex (female)	8.31	4.38–12.25	<0.001
Education	1.07	0.40–1.75	0.002
CES-D	–0.36	–0.60–0.12	0.003
Age	–0.07	–0.39–0.24	0.658
Sleep (ESS)	–0.19	–0.83–0.44	0.549
Age × ESS	0.02	–0.06–0.10	0.595
pTau217 [Intermediate]	–1.30	–6.07–3.47	0.593
pTau217 [+]	1.23	–3.42–5.88	0.604
Age × pTau217 [Intermediate]	–0.56	–1.21–0.09	0.089
Age × pTau217 [+]	–0.19	–0.87–0.49	0.584
pTau217 [Intermediate] × ESS	0.06	–1.14–1.27	0.917
pTau217 [+] × ESS	0.04	–1.17–1.25	0.946
Age × pTau217 [Intermediate] × ESS	–0.18	–0.35–0.01	0.035
Age × pTau217 [+] × ESS	–0.25	–0.42–0.07	0.006

Table 2. Abbreviations, Definitions, and Notes: ESS=Epworth Sleepiness Scale (Johns, 1991); CES-D = Center for Epidemiologic Studies Scale for Depression (Radloff, 1977), Plasma pTau217-ALZpath cut-offs at 0.40 pg/mL and 0.63 pg/mL (Ashton et al, 2024), reference group=negative. *ESS was used as a continuous measure in all models (range 0-24).

ACKNOWLEDGEMENTS

This work was supported by grants from the NIH National Institute on Aging: R01 AG082052 (Mueller), R01 AG070940 (Mueller), and R01 AG027161 (Johnson). The funding sources had no role in study design, data collection, management, or analysis. This study's content are solely those of the authors and do not reflect the official positions of the NIH. We would like to thank all WRAP participants, as well as WAI and ADRC staff whose ongoing contributions made this research possible.