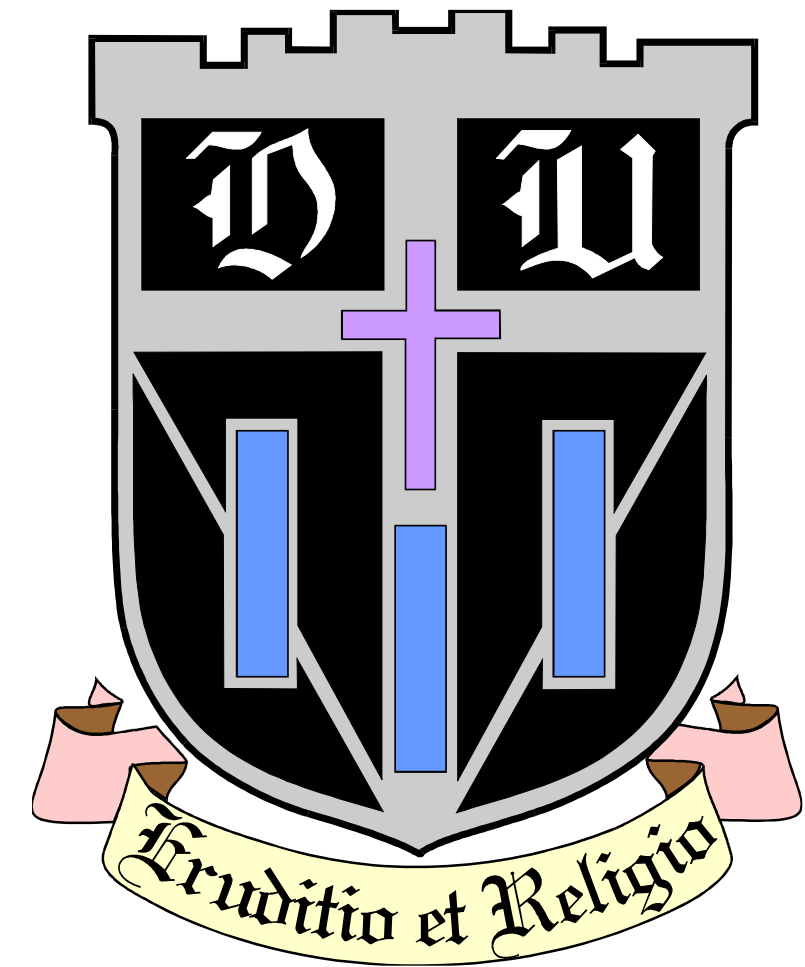


Cognitive Frailty Associates with Biomarkers for Alzheimer’s Disease
and Related Dementias and Prospective Cognitive Decline:
Data from the **Duke-UNC ADRC**



Patrick J. Smith¹, Kim Johnson², Heidi Roth¹, Guy Potter², Michael Devinney², Bethany Hsia², Sara Patillo², Weili Lin¹, Allen Song², Miles Berger², Richard O’Brien², Andy Liu², Michael Lutz², Sheng Luo¹, Andrea Bozoki¹, Kathleen Welsh-Bohmer², Gwenn Garden¹, Heather Whitson²
¹ University of North Carolina at Chapel Hill; ² Duke University Medical Center

Background

- Intra-individual variability (IIV) in cognitive performance across tests has been suggested as a marker of ‘**cognitive frailty**’, predicting cognitive decline over and above average performance
- Studies examining cognitive risk measures in parallel with ADRD biomarkers in middle-aged adults may have important implications for understanding their relevance for ADRD risk reduction
- Few studies have examined correlates of cognitive frailty, including ADRD biomarkers, chronic medical comorbidities, or other clinical characteristics
- Few studies have examined whether cognitive frailty predicts cognitive decline
- We examined the associations between demographic and clinical characteristics and ADRD biomarkers with cognitive frailty among participants in the Duke-UNC ADRC cohort, designed to investigate modifiable risk factors for ADRD across the lifespan.

DUKE-UNC ADRC COHORT

- Participants included 377 adults aged **25 to 80**, including 323 who had CSF assessments
- Inclusion criteria: 6th grade reading level and study partner. Exclusion Criteria: Unstable neuropsychiatric disorder, drug abuse, medical conditions or MRI contraindications
- Cognitive Function was assessed using the Unified Data Set (UDS) 3.0 and 4.0 with additional assessments of visuospatial function, memory, and language

Methods

- **Cognitive Frailty** was defined as the coefficient of variation (CoV), utilizing recently developed normative data developed using the UDS 3.0 test battery. CoV was analyzed as a continuous predictor and categorized for descriptive purposes ($z \leq -1.5$)
- Prospective 1-Year Cognitive Decline was examined as (i) mean RCI scores from all cognitive subtests and (ii) categorized (none, possible, or probable) using MCID changes in (a) mean RCI changes, (b) MoCA changes, and (C) CDR Sum of Boxes changes
- ADRD biomarker assessments were obtained from CSF:
 - Amyloid Beta 42/40 (A β 42/40)
 - Phosphorylated tau (p-tau)
 - Neurofilament light (NfL)
 - Glial fibrillar acidic protein
- Physical Frailty was assessed by gait speed and grip strength
- Sensory Function was assessed using a battery of visual and hearing tests
- Analyses: Linear and cumulative logistic egression models were examined using SAS 9.4 (Cary, NC), with age, gender, race, education, comorbidities, APOE genotype, and p-tau181 / A β 42 as covariates and as predictors.

Results

- Participant characteristics across individuals with and without cognitive frailty are presented in **Table 1**. Participants with cognitive frailty (n = 82 [22%]) were older, more often White, had worse ADRD biomarker levels, slower gait speed, and worse sensory function.
- The distribution of CoV across the cohort is shown in **Figure 1**.
- Lower cognitive frailty associated with less cognitive decline (B = 0.27, P<.001; **Figure 2**), more so than age (B = 0.17, P = .008), and only p-tau181 / A β 42 (B = -0.35, P < .001) was stronger
- Lower cognitive frailty was also protective against cognitive decline (OR = 0.68 [0.52, 0.91], P = .008). This association was weakened when p-tau181 / A β 42 was included (OR = 0.78 [0.57, 1.08], P = .140)
- Findings persisted when limited to cognitively normal participants

Conclusions

- We found that cognitive frailty associated with ADRD biomarkers and multiple clinical characteristics
- Cognitive frailty may provide prognostic information on risk of cognitive decline that is more informative than many other standard clinical risk markers
- Future studies should examine longitudinal associations of cognitive frailty and ADRD biomarker progression among middle-aged adults

Table 1. Clinical Characteristics of the sample

Variable	No Cognitive Frailty (n = 298)	Cognitive Frailty (n = 82)
Age**	57.3 (SD = 11.9)	62.3 (SD = 10.6)
Female Sex	186 (62%)	49 (59%)
White**	200 (73%)	73 (88%)
APOE-4 Allele	124 (43%)	41 (49%)
Education, yrs	16.9 (SD = 2.1)	17.1 (SD = 2.5)
ADRD Biomarkers		
A β 42/40**	0.082 (SD = 0.018)	0.068 (SD = 0.027)
P-tau 181 / A β 42**	0.053 (SD = 0.039)	0.158 (SD = 0.191)
P-tau 181**	32.3 (SD = 18.0)	62.5 (SD = 57.5)
NfL**	489 (SD = 417)	825 (SD = 811)
GFAP	10,970 (SD = 8,532)	13,546 (SD = 12,145)
Clinical Characteristics		
Body Mass Index, kg/m ²	28.2 (SD = 6.2)	27.3 (SD = 5.0)
Vision, z-score**	0.08 (SD = 0.55)	-0.3 (SD = 0.88)
Hearing, z-score**	0.09 (SD = 0.75)	-0.3 (SD = 0.9)
Gait Speed*	1.3 (SD = 0.2)	1.2 (SD = 0.3)
Grip Strength	27.4 (SD = 11.2)	27.8 (SD = 10.3)

Difference between sub-groups **P<.001; *P<.01

Figure 2. Cognitive frailty and one-year cognitive changes, adjusted for age, education, sex, race, comorbidities, and APOE genotype.

Cognitive Frailty and Prospective Cognitive Changes

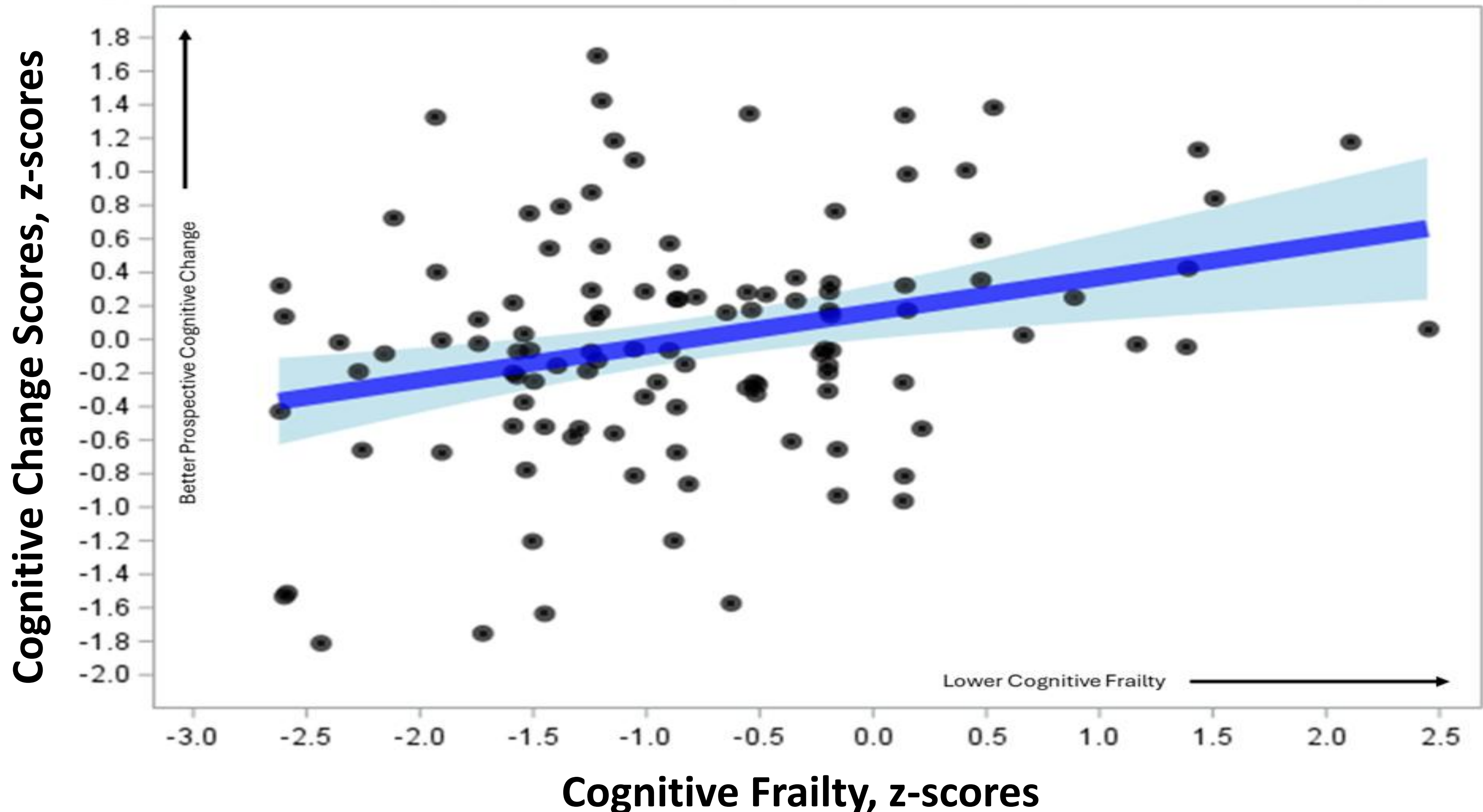


Figure 1. Distribution of cognitive frailty

