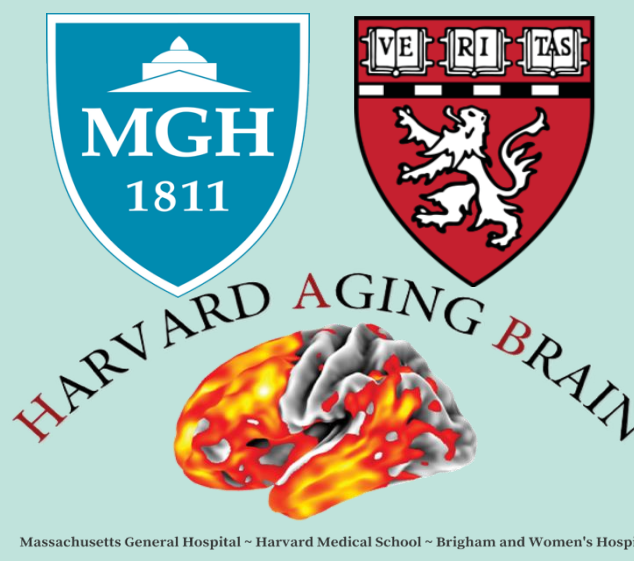


Tau but Not Neurodegeneration Mediates The Association Between Physical Frailty and Cognitive Decline in Preclinical Alzheimer’s Disease

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Background

Physical frailty is a known risk factor for dementia, including Alzheimer’s disease (AD). Our prior work from the Harvard Aging Brain Study (HABS) demonstrated a synergistic association between higher baseline physical frailty and β -amyloid (A β) burden with faster tau accumulation and cognitive decline in older individuals who were cognitively unimpaired at baseline. This suggests that physical frailty may be a potentially modifiable risk factor in preclinical AD progression. However, the relationship between physical frailty and neurodegenerative markers such as hippocampal volume remains unclear, a gap addressed in the current study. Using moderated mediation analysis, we further extend our prior work by examining whether the synergistic association between frailty and A β burden on cognitive decline is mediated through differences in tau accumulation (T) and/or neurodegeneration (N).

31-Item Frailty Index

Table 2. Frailty Index	Physical Health
1. Compared to other people your own age, how would you rate your physical health? (“much worse than average” = 1; “average” = 0.5; “better than average”, “much better than average” = 0)	20. Abnormal weight ($BMI \geq 30 = 1$ or $< 18.5 = 1$; $BMI \geq 25 = 0.5$)
2. How many times have you been hospitalized overnight in the last five years? (more than 2 = 1; 2 = 0.5; 1 or less = 0)	21. Stomach ulcers (y/n)
3. Cancer (other than skin cancer) (y/n)	22. Colitis (y/n)
4. Chronic liver disease (y/n)	23. Auto-immune disorders (y/n)
5. Diabetes (y/n)	Exhaustion
6. Elevated cholesterol (y/n)	24. During your waketime, do you feel tired or fatigued, or not up to par? (“almost every day”, “3-4 days/week” = 1; “1-2 times a week” = 0.5; “1-2 times a month”, “never or almost never” = 0)
7. Hearing problems (y/n)	25. How often do you feel tired or fatigued after your sleep? (“almost every day”, “3-4 days/week” = 1; “1-2 times a week” = 0.5, “1-2 times a month”, “never or almost never” = 0)
8. Heart attack or bypass surgery (y/n)	Shrinking
9. Angina or atrial fibrillation (y/n)	26. Weight loss (greater than or equal to 10lbs over 1 year)
10. Hypertension (y/n)	Inactivity
11. Arthritis/joint disease (y/n)	27. Pedometer step count (less than 3273 steps per day, 20 th percentile)
12. Kidney disease (y/n)	Slowness/mobility
13. Pulmonary embolism or blood clot (y/n)	28. Gait speed (20 th percentile, adjusted for height and sex)
14. Sleep disorder (y/n)	29. Gait abnormalities (y/n)
15. Spine disease (y/n)	30. Do you need help to walk? (y/n)
16. Stroke or TIA (y/n)	31. Have you fallen recently? (y/n)
17. Thyroid disease (y/n)	
18. Vision problems (y/n)	
19. Polypharmacy (medication count greater than 5)	

Methods

We examined 270 older adults from HABS (Table 1) who had baseline A β PET scans, frailty assessments, and were followed longitudinally with cognitive testing, tau PET (N=188), and MRI scans. Participant characteristics are described in Table 1. Physical frailty was assessed at baseline using a 31-item frailty index (FI; Table 2) as the primary measure. Sensitivity analyses were repeated using a modified Fried frailty phenotype consisting of four components: exhaustion, inactivity, shrinking, and slowness. Individuals with two or more of these components were classified as “frail”, one as “pre-frail”, and none as “robust”. Cognition was measured longitudinally using the Preclinical Alzheimer Cognitive Composite-5 (PACC-5). Global A β burden was measured longitudinally using C-Pittsburgh Compound-B (PIB) PET. Flortaucipir (FTP) PET was used for measuring longitudinal tau burden in the inferior temporal cortex (ITC). PET data used cerebellar gray as reference.

Neurodegeneration was assessed longitudinally using 3T MRI to measure intracranial volume (ICV)-adjusted hippocampal volume (HV). Analysis: We used linear mixed effects models to examine the effects of baseline physical frailty on longitudinal A β , tau, HV, and PACC5, adjusting for age, sex, APOE ϵ 4 carrier status, and education. We then extracted slopes of ITC tau, HV, and PACC5 changes for mediation analyses to examine whether changes in tau and/or HV mediated the interaction between baseline physical frailty and A β on PACC5 decline.

Table 1. Participant Characteristics	All Participants N=270	Longitudinal Tau Subgroup N=188
Age at baseline, yr mean (SD)	71.6 (7.8)	70.6 (7.9)
Females, n(%)	164 (61)	115 (61)
Education, yr, mean (SD)	16.0 (2.9)	16.1 (2.9)
APOE ϵ 4 carriers, n (%)	76 (28)	51 (27)
Frailty index, mean (SD)	0.15 (0.09)	0.14 (0.08)
Modified Fried frailty phenotype, n (%)	N=237 Robust: 127 (54) Prefrail: 83 (35) Frail: 27 (11)	N=162 Robust: 101 (62) Prefrail: 48 (30) Frail: 13 (8)
Baseline PiB PET FLR DVR, mean (SD)	1.2 (0.2)	1.2 (0.2)
Baseline A β positive, n (%)	62 (23)	40 (21)
Baseline PACC, mean (SD)	0.1 (0.6)	0.2 (0.6)
# longitudinal PACC assessments, median (IQR; range)	9 (7-12; 4-15)	9 (7-11; 3-14)
Duration of cognitive follow up, yr, median (IQR; range)	10.1 (7.1-12.4; 0.0-14.6)	11.1 (8.3-13.3; 3.4-15.0)
Baseline ITC tau PET SUVR, mean (SD)	---	1.2 (0.1)
Time between baseline and first tau PET, yr, mean (SD)	---	2.14 (1.6)
# longitudinal tau PET scans, median (IQR; range)	---	3 (2-3; 2-5)
Duration of tau PET follow up, yr, median (IQR; range)	---	5 (3-5; 1.25-10.5)
Baseline hippocampal volume, mm3, mean (SD)	7,531.1 (761.7)	7,564.3 (766.9)
# longitudinal MRI scans, median (IQR; range)	3 (2-4; 1-5)	4 (3-4; 2-5)
Duration of MRI follow up, yr, median (IQR; range)	6.9 (4.3-10.8; 2.3-14.5)	8.3 (5.3-11.0; 2.5-14.5)

Physical Frailty and Longitudinal A β , Tau, HV, and PACC5

A) A β : FI was not associated with longitudinal A β accumulation (β =-0.01 [-0.04 to 0.02], $p=0.42$). **B) Tau:** Higher baseline FI and elevated A β were synergistically associated with faster ITC tau accumulation (β =0.01 [0.00 to 0.02], $p=0.01$). **C) HV:** There were no independent or interactive (with A β) associations of FI with longitudinal HV ($p>0.87$). **D) PACC5:** Higher baseline FI and elevated A β were synergistically associated with faster PACC5 decline (β =-0.06 [-0.12 to -0.004], $p=0.04$). There was also an independent main effect of higher FI on faster PACC5 decline (β =-0.07 [-0.12 to -0.01], $p=0.01$).

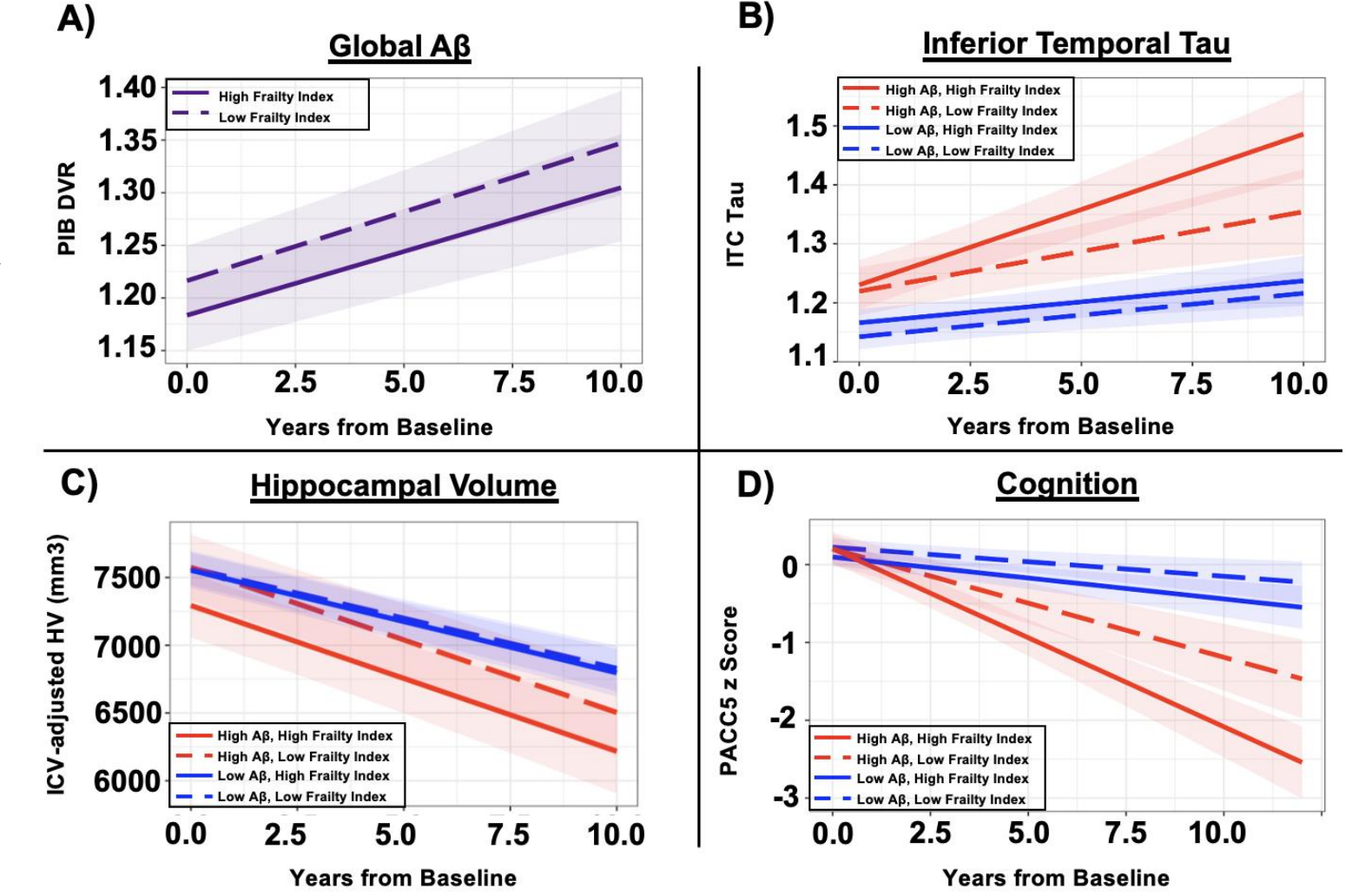
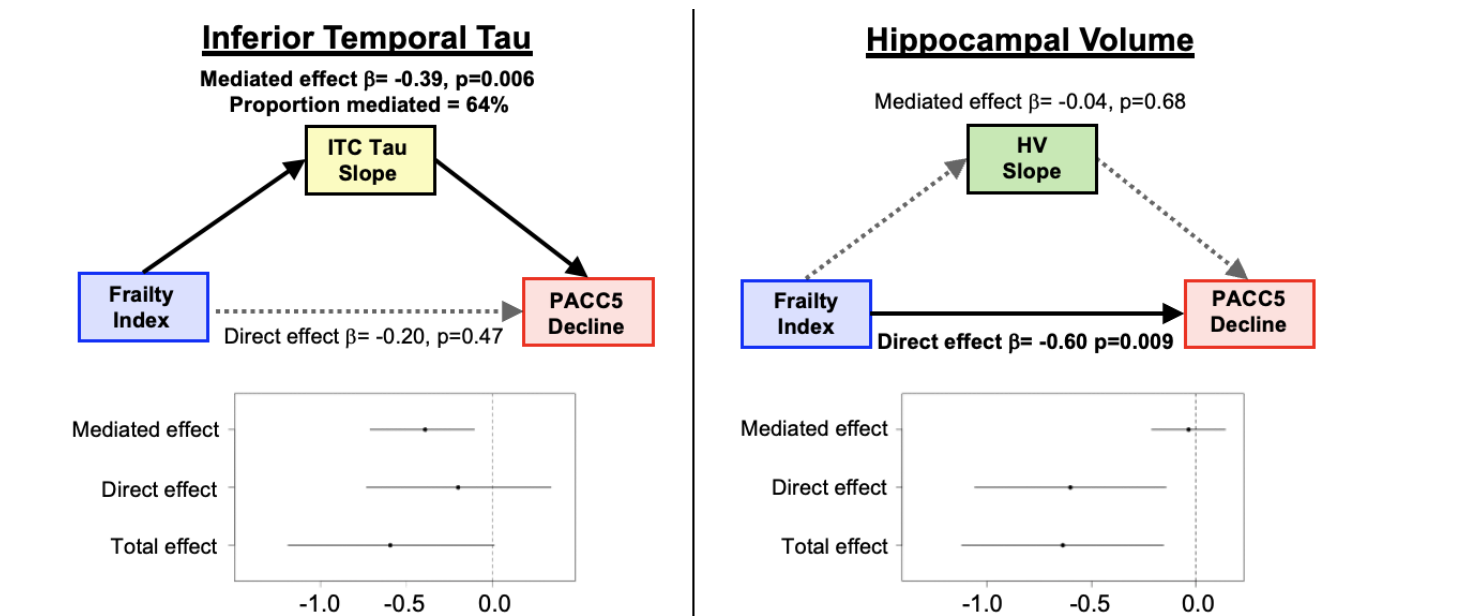


Figure Legend: Baseline FI and A β were modeled as continuous variables. To visualize the model results, estimated trajectories based on representative levels of low versus high baseline FI, and (for tau, HV, and PACC5 models) low versus high baseline A β are presented. Low FI: 0.07 [mean-1SD]; High FI: 0.27 [mean+1SD]; Low A β = 1.08 [mean of A β -negative individuals]; high A β = 1.46 [mean of A β -positive individuals]].

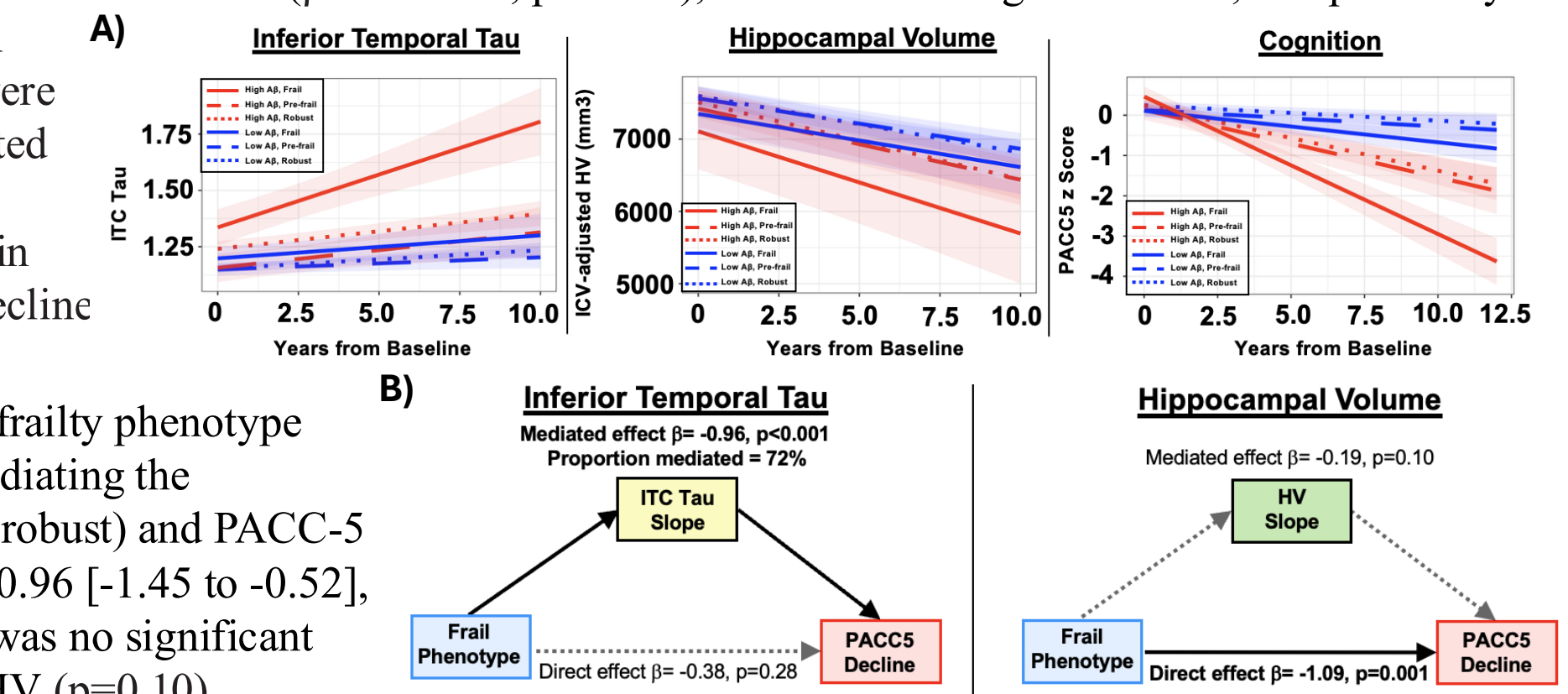
Tau (but not HV) Mediates Physical Frailty Effects on Cognitive Decline

Moderated mediation analyses revealed that, in individuals with elevated A β , faster ITC tau accumulation significantly mediated the association between higher FI and faster PACC-5 decline (β = -0.39 [-0.71 to -0.11], $p=0.006$, 64% mediated). There was no significant mediation of PACC-5 decline by changes in HV ($p>0.68$). In individuals with low A β (not shown), there were no significant total or mediated effects of FI on PACC5 decline ($p>0.4$), or mediation by ITC tau or HV changes ($p>0.11$).



Sensitivity Analyses with Frailty Phenotype

Sensitivity analyses were performed using a modified 4-criteria Fried frailty phenotype. **A) Tau:** Consistent with FI, frail phenotype (versus robust) and elevated A β were synergistically associated with faster ITC tau accumulation [β =0.01 [0.006 to 0.023], $p<0.001$]. **HV:** Frail phenotype was associated with lower baseline HV (β = -287.05, $p=0.045$), but not with longitudinal HV, independently or interactively with A β ($p>0.12$). **PACC5:** Frail phenotype (versus robust) and elevated A β were synergistically associated with faster A β -related PACC-5 decline [β = -0.07 [-0.12 to -0.018], $p=0.008$]. There was also an independent main effect of frail phenotype on faster PACC-5 decline [-0.025], $p=0.003$].



B) Our moderated mediation analyses using frailty phenotype identified consistent results, with ITC tau mediating the relationship between frail phenotype (versus robust) and PACC-5 decline in individuals with elevated A β (β = -0.96 [-1.45 to -0.52], $p<0.001$, 72% mediated). By contrast, there was no significant mediation of PACC5 decline by changes in HV ($p=0.10$).

Conclusion

In our cohort of baseline cognitively unimpaired older adults, we found an interactive association of higher baseline physical frailty (characterized by FI and frailty phenotype) and elevated A β on faster ITC tau accumulation and PACC-5 decline, but not on hippocampal atrophy. We further demonstrated that faster tau accumulation mediated the majority (64%) of FI effects on faster PACC5 decline in individuals with elevated A β . By contrast, there was no significant mediation of cognitive decline by hippocampal atrophy.

Our findings suggest that physical frailty may represent a modifiable risk factor that contributes to faster cognitive decline in preclinical AD through accelerated early neocortical tau accumulation. Future studies should investigate biological mechanisms (independent of hippocampal atrophy) that link physical frailty to tau-related cognitive decline in preclinical AD.

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