BIOCARD

Relationship of physical activity to longitudinal rates of change in AD-specific and AD non-specific blood biomarkers

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Introduction

- **Alzheimer's disease (AD)** is a progressive neurodegenerative disorder characterized by changes in brain pathology, including amyloid accumulation, tau-related neurodegeneration, and neuroinflammation. Identifying lifestyle factors that may slow or prevent these pathological changes is a critical area of research.
- **Physical activity** has been associated with cognitive health benefits, but its relationship with changes in blood-based biomarkers of AD and neurodegeneration remains unclear.

Study Objectives

- **Primary Goal:**
  - Assess whether physical activity is associated with the rate of change in blood-based biomarkers of AD over time.
- **Secondary Goal:**
  - Determine whether APOE-ε4 genetic status (the strongest genetic risk factor for late-onset AD) or sex modifies the relationship between physical activity and biomarker changes.
- **Physical Activity Measurement:**
  - Self-reported activity frequency: Measured via the CHAMPS activity questionnaire.
  - Objective activity volume: Assessed through actigraphy-based monitoring.
- **Data Source:**
  - The BIOCARD Study, a longitudinal study designed to identify early biomarkers of cognitive decline and AD.

CHAMPS Measure

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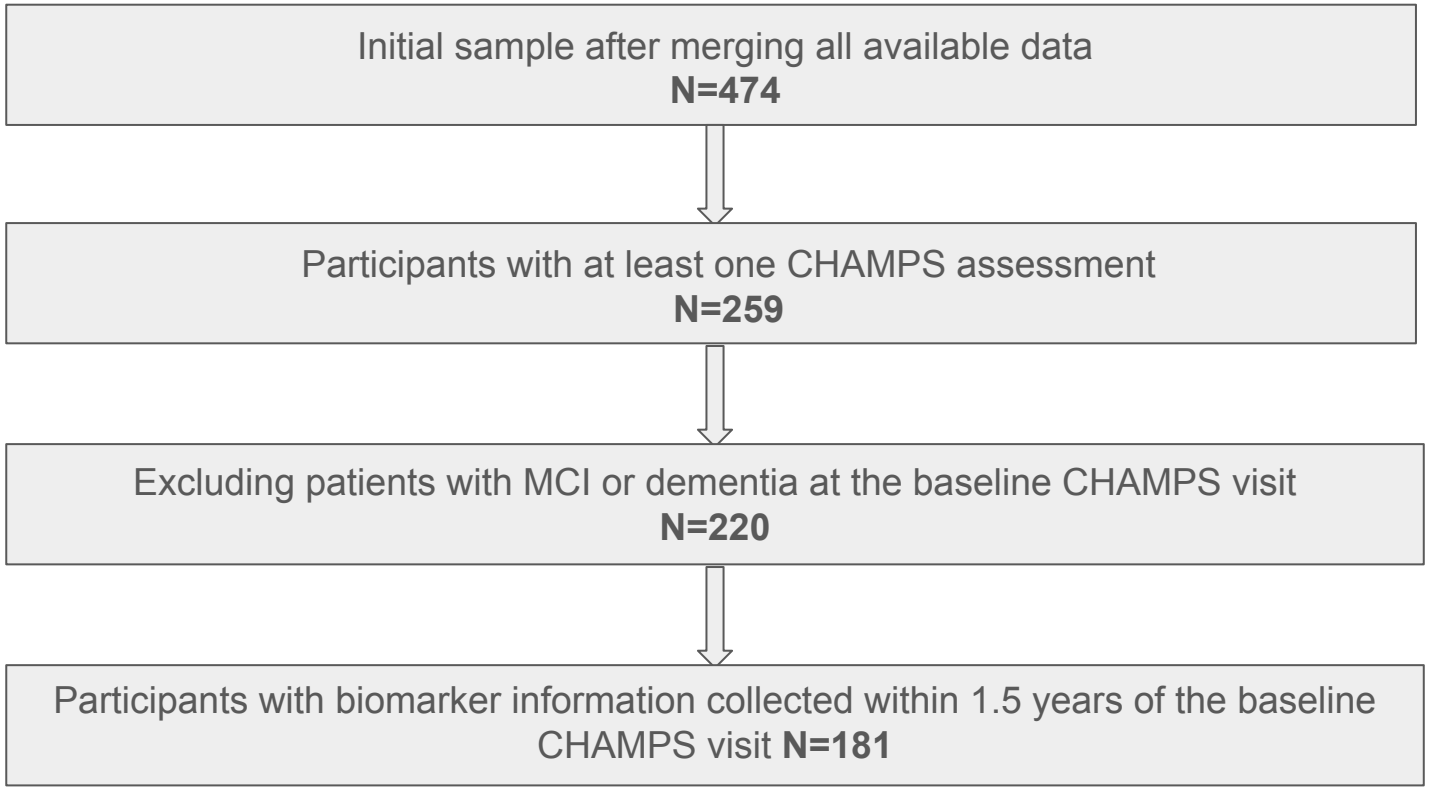
CHAMPS Data

- The **Community Healthy Activities Model Program for Seniors (CHAMPS)** questionnaire is a self-report activity questionnaire that asks about a subject's engagement in physical, cognitive, and social activities. The CHAMPS measures used in this study are:
  - **LOW_INT_FREQ**: Low-intensity physical activity score, which includes activities such as walking, light household chores, and stretching exercises.
  - **HIGH_INT_FREQ**: High-intensity physical activity score, which includes vigorous activities such as playing tennis, running, or heavy gardening.
  - **ALL_INT_FREQ**: Total physical activity score, representing a combination of both low- and high-intensity activities.

Study Inclusion and Exclusion Criteria

- **Baseline**: age at the first available CHAMPS assessment defined as **Age_CHAMPS.**
- **Inclusion Criteria**:
  - Include participants with **at least** one CHAMPS assessment.
  - Include participants with biomarkers collected within 1.5 years of their baseline CHAMPS assessment.
- **Exclusion Criteria**
  - Exclude visits with biomarker values identified as extreme outliers.
  - Exclude patients with a diagnosis of *Mild Cognitive Impairment (MCI)* or *Dementia* at baseline CHAMPS assessment.

Sample Size


Initial sample after merging all available data
N=474
Participants with at least one CHAMPS assessment
N=259
Excluding patients with MCI or dementia at the baseline CHAMPS visit
N=220
Participants with biomarker information collected within 1.5 years of the baseline CHAMPS visit **N=181**

Descriptive Statistics

Mean (SD) Age_CHAMPS	69.65 (8.27)
Range (min, max) Age_CHAMPS	(34.40, 92.51)
N (%) Female sex	115 (63.54%)
Mean (SD) years of education	17.35 (2.23)
N (%) White race	180 (99.45%)
N (%) APOE4 carriers	58 (32.04%)
Mean (SD) years of follow-up (baseline CHAMPS to last blood biomarker measure)	3.54 (1.26)
Range (min, max) years of follow-up (baseline CHAMPS to last blood biomarker measure)	(0.00, 6.32)

Mean (SD) number of blood biomarker measures over time	4.14 (1.25)
Range (min, max) number of blood biomarker measures over time	(1.00, 7.00)
Mean (SD) time (in years) between baseline CHAMPS and associated baseline blood biomarker measure	0.01 (0.15)
Range (min, max) time (in years) between baseline CHAMPS and associated baseline blood biomarker measure	(-1.13, 1.07)
Mean (SD) LOW_INT_FREQ	11.26 (7.98)
Mean (SD) HI_INT_FREQ	10.76 (11.19)
Mean (SD) ALL_INT_FREQ	22.02 (15.21)
Mean (SD) BMI	26.54 (4.93)

Model Predictors

- **Time:** Represents the years elapsed from baseline to a given follow-up visit.
- **Sex_F:** A binary variable indicating sex: Female = 1; Male = 0.
- **APOE4:** A binary variable representing the presence of the APOE ε4 allele.
    - APOE4 = 0 if no copies of the ε4 allele; APOE4 = 1 if one or two copies of the ε4 allele.
    - The presence of one or two copies of the ε4 allele is associated with an increased risk of AD compared to those with no ε4 copies, with two copies conferring greater risk than one.
- **Age_CHAMPS:** Represents the standardized age at the first available or baseline CHAMPS assessment.
- **BMI:** Standardized body mass index (BMI), which may influence blood biomarker values and correlate with physical activity levels.
    - Measured BMI is used preferentially; self-reported BMI is used if measured values are unavailable.
- **CHAMPS:** Represents the standardized physical activity score derived from the CHAMPS questionnaire.
    - Modeled separately for: low-intensity activity; high-intensity activity; total activity.

Model Outcomes

- AD-Specific Measures
  - **PTAU181**: Phosphorylated tau, a biomarker that increases in AD and reflects tau pathology.
  - **AB42AB40**: The ratio of amyloid beta 42 to amyloid beta 40, which serves as an indicator of amyloid protein accumulation in the brain. Lower levels in blood are associated with AD.
- AD Non-Specific Measures
  - **NFL (Neurofilament Light Chain)**: A marker of axonal injury, with elevated levels observed in AD and other neurodegenerative diseases.
  - **YKL-40 (Chitinase-3-like Protein 1)**: An inflammatory biomarker; higher levels are associated with increased neuroinflammation and tend to rise in AD.
  - **sTREM2 (Soluble Triggering Receptor Expressed on Myeloid Cells 2)**: A biomarker of microglial activation and inflammation; higher levels are observed in AD.
  - **GFAP (Glial Fibrillary Acidic Protein)**: A marker of astrocyte activation, with increased levels indicating a greater cellular response to nervous system damage, commonly elevated in AD.

Model Specification

The linear mixed-effects model used in this analysis is specified as follows:

$$Y_{ij} = \beta_0 + \beta_1 \text{time}_{ij} + \beta_2 \text{Age\_CHAMPS}_i + \beta_3 \text{Sex\_F}_i + \beta_4 \text{APOE4}_i + \beta_5 \text{BMI}_i + \beta_6 \text{CHAMPS}_i + \beta_7 (\text{time}_{ij} \times \text{Age\_CHAMPS}_i) + \beta_8 (\text{time}_{ij} \times \text{Sex\_F}_i) + \beta_9 (\text{time}_{ij} \times \text{APOE4}_i) + \beta_{10} (\text{time}_{ij} \times \text{BMI}_i) + \beta_{11} (\text{time}_{ij} \times \text{CHAMPS}_i) + u_{0i} + u_{1i} \text{time}_{ij} + \epsilon_{ij}$$

Where:

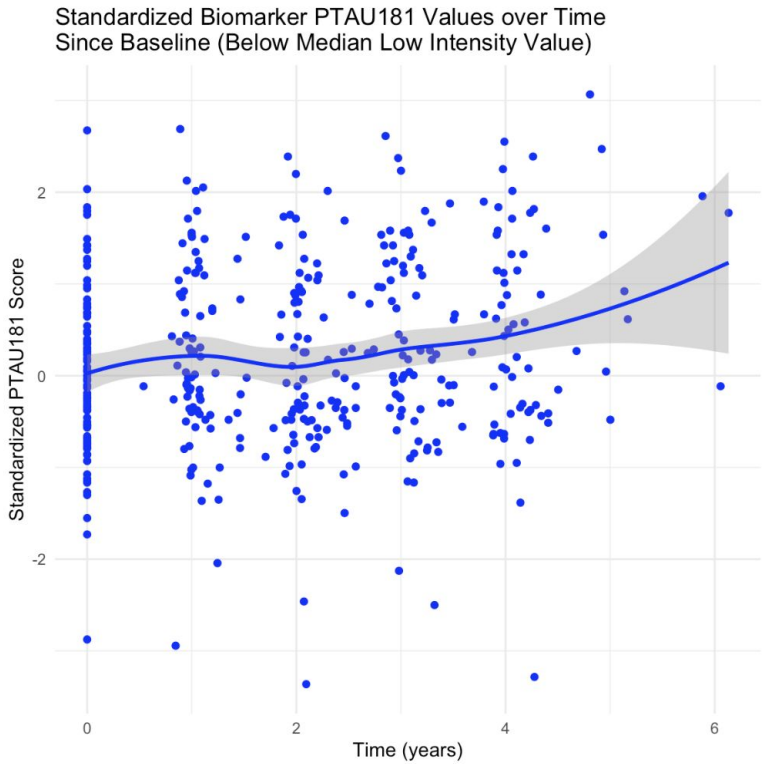
- Y_{ij} is the biomarker outcome for participant i at time j.
- β_0 is the fixed intercept.
- $\beta_1, \ldots, \beta_{11}$ are the fixed effect coefficients.
- $u_{0i} \sim N(0, \sigma_u^2)$ is the random intercept for subject i.
- $u_{1i} \sim N(0, \sigma_v^2)$ is the random slope for time for subject i.
- $\epsilon_{ij} \sim N(0, \sigma^2)$ is the residual error.

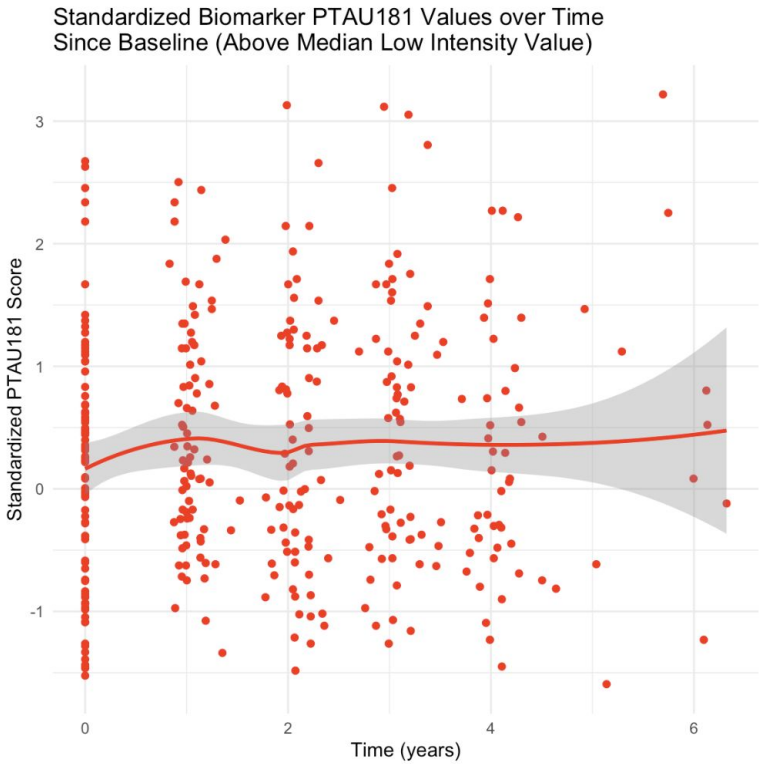
Results

Biomarker	Variable	Estimate	Std.Error	t value	P-value
GFAP	Low Intensity	-0.0289662	0.0574372	-0.5043105	0.6146886
	Low Intensity * Time	-0.0007803	0.0132549	-0.0588695	0.9531225
NFL	Low Intensity	0.0477200	0.0564632	0.8451522	0.3991845
	Low Intensity * Time	-0.0113304	0.0123235	-0.9194091	0.3591130
PTAU181	Low Intensity	0.1342135	0.0655286	2.0481660	0.0420656
	Low Intensity * Time	-0.0119012	0.0135064	-0.8811515	0.3793452
AB42AB40	Low Intensity	-0.0489567	0.0696969	-0.7024227	0.4833635
	Low Intensity * Time	0.0103859	0.0141289	0.7350820	0.4632990
sTREM2	Low Intensity	0.0166356	0.0714148	0.2329429	0.8160836
	Low Intensity * Time	0.0105445	0.0117510	0.8973297	0.3705382
YKL40	Low Intensity	0.0502821	0.0685055	0.7339862	0.4639523
	Low Intensity * Time	-0.0189569	0.0160042	-1.1844941	0.2380269

Results

In PTAU181 analysis, low intensity CHAMPS value is a predictor with a significance of 0.05.



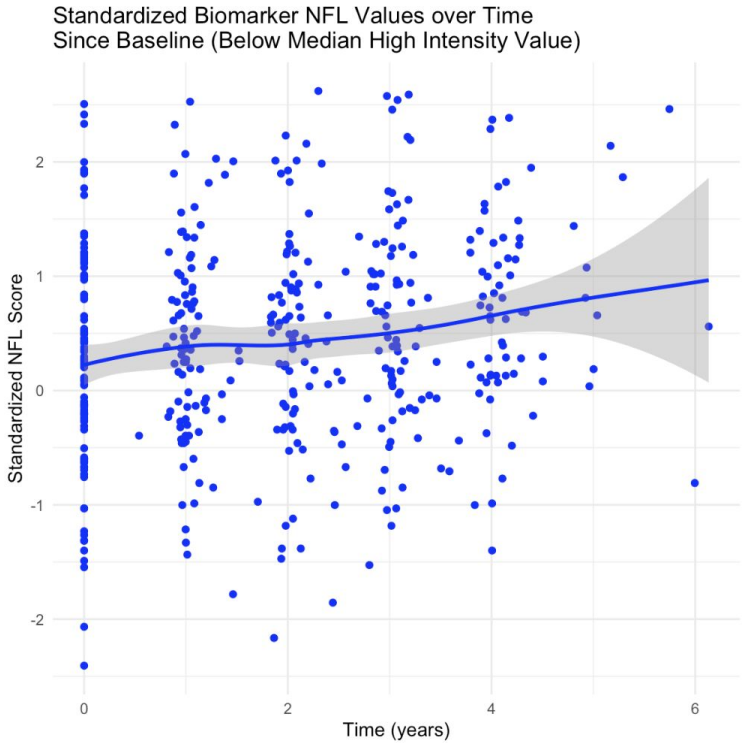


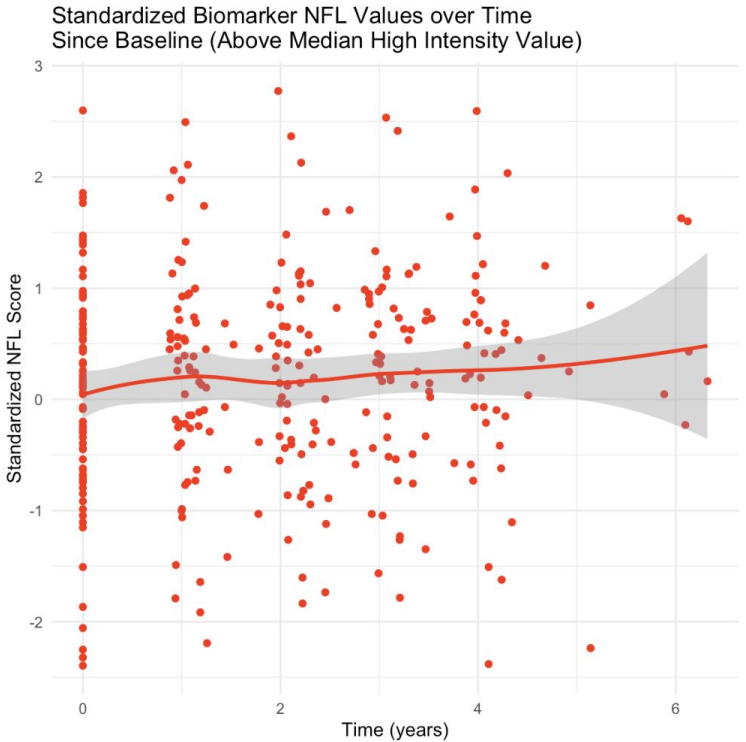
Results

Biomarker	Variable	Estimate	Std.Error	t value	P-value
GFAP	High Intensity	0.0316689	0.0564676	0.5608323	0.5756611
	High Intensity * Time	-0.0164456	0.0116857	-1.4073259	0.1616855
NFL	High Intensity	-0.0622563	0.0555790	-1.1201411	0.2642349
	High Intensity * Time	-0.0300337	0.0106269	-2.8262004	0.0054012
PTAU181	High Intensity	-0.0015278	0.0654838	-0.0233306	0.9814143
	High Intensity * Time	-0.0168690	0.0118943	-1.4182396	0.1582763
AB42AB40	High Intensity	-0.0220533	0.0690807	-0.3192396	0.7499387
	High Intensity * Time	0.0114879	0.0128032	0.8972613	0.3712649
sTREM2	High Intensity	0.0751529	0.0704844	1.0662339	0.2878411
	High Intensity * Time	0.0009407	0.0103645	0.0907637	0.9277902
YKL40	High Intensity	0.0458244	0.0675979	0.6778964	0.4987696
	High Intensity * Time	-0.0139454	0.0143331	-0.9729486	0.3326452

Results

In NFL analysis, the interaction of high intensity CHAMPS value with time is a predictor with a significance of 0.01.



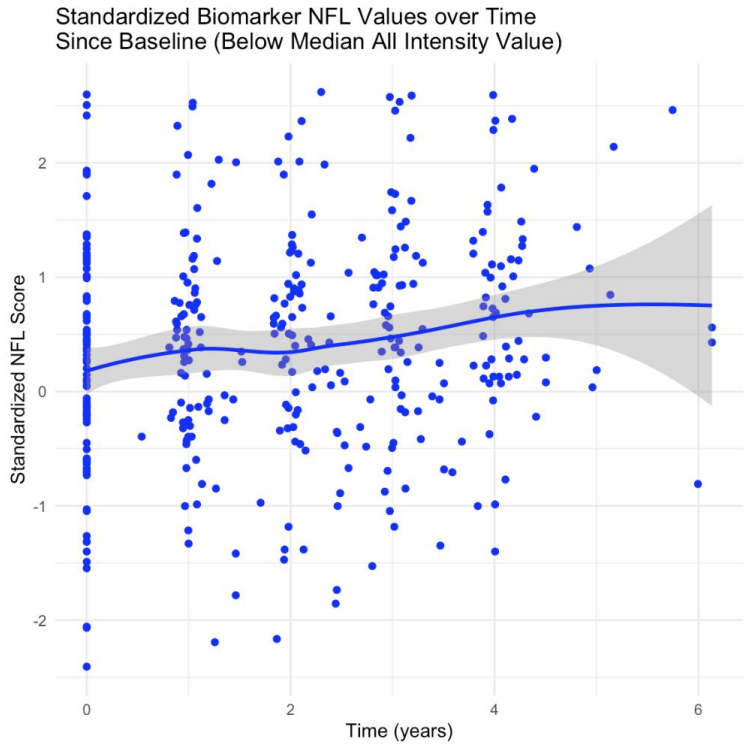


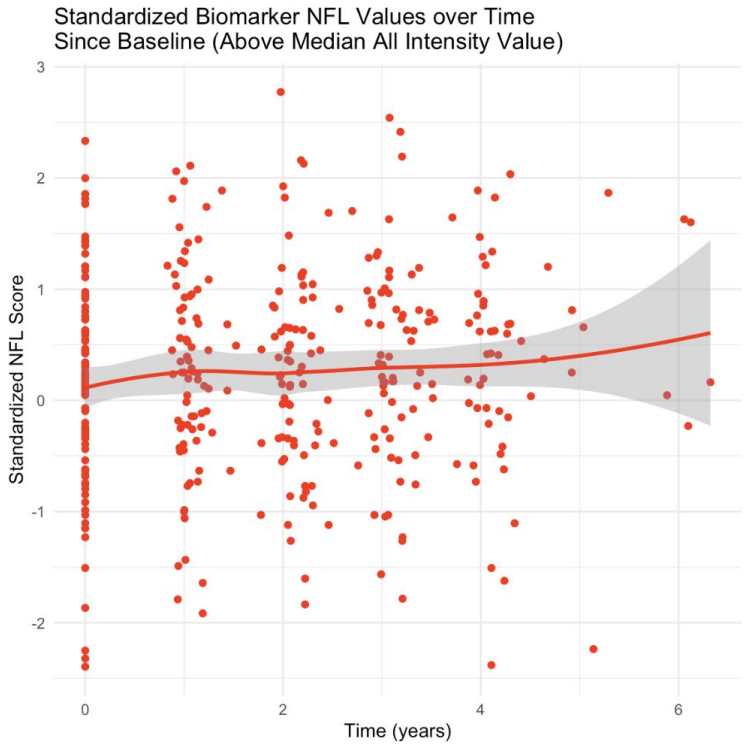
Results

Biomarker	Variable	Estimate	Std.Error	t value	P-value
GFAP	All Intensity	0.0093363	0.0569699	0.1638811	0.8700206
	All Intensity * Time	-0.0134611	0.0121818	-1.1050185	0.2710031
NFL	All Intensity	-0.0202448	0.0561278	-0.3606917	0.7187744
	All Intensity * Time	-0.0297523	0.0110924	-2.6822192	0.0081280
PTAU181	All Intensity	0.0688774	0.0657215	1.0480180	0.2961258
	All Intensity * Time	-0.0188194	0.0123802	-1.5201291	0.1304822
AB42AB40	All Intensity	-0.0420066	0.0694536	-0.6048149	0.5461074
	All Intensity * Time	0.0139368	0.0132417	1.0524996	0.2943790
sTREM2	All Intensity	0.0649220	0.0709184	0.9154477	0.3612564
	All Intensity * Time	0.0054628	0.0108207	0.5048430	0.6142836
YKL40	All Intensity	0.0601112	0.0680111	0.8838443	0.3780302
	All Intensity * Time	-0.0197565	0.0148470	-1.3306766	0.1857176

Results

In NFL analysis, the interaction of all intensity CHAMPS value with time is a predictor with a significance of 0.01.





Actigraphy Measure

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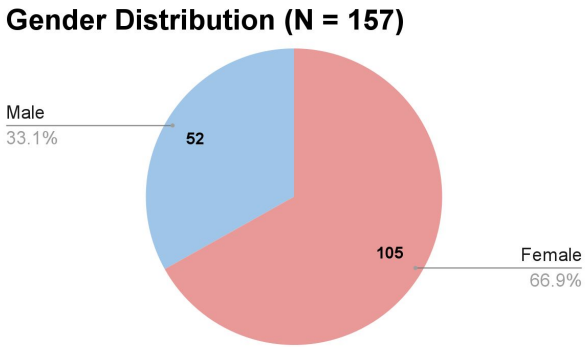
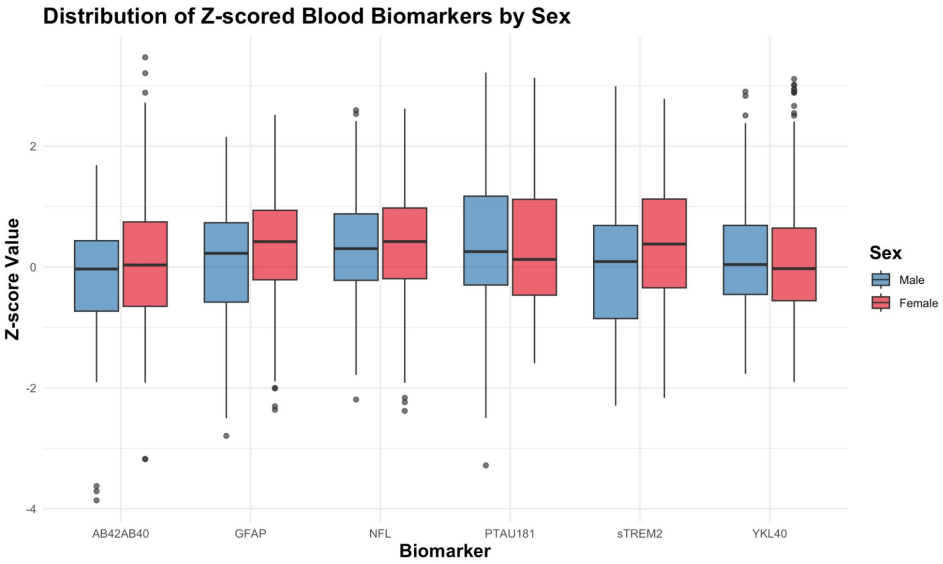
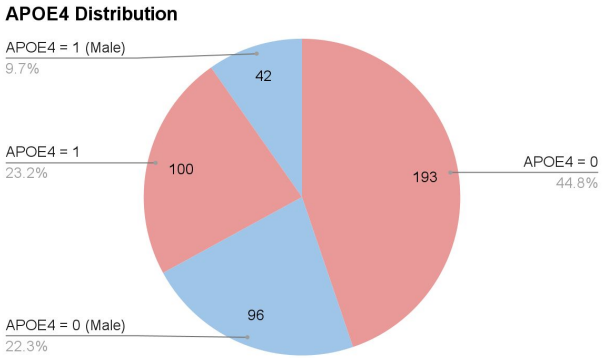
Actigraphy Data Filter

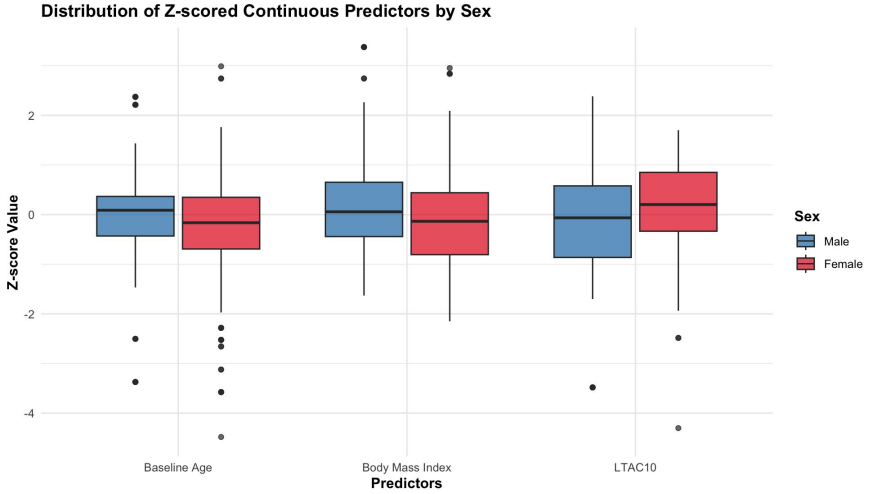
- **Actigraphy Data (LTAC10)**
  - Total volume of physical activity, as measured objectively using actigraphy
- Subset of processed CHAMPS data **with** Actigraphy measures
  - Number of patients: 157; Number of observations: 431
- Similar filter condition:
  - Include patients with **at least** one actigraphy assessment within 1.5 years
  - **Baseline**: the age with first available actigraphy assessment
  - Only include visits from baseline forward for each patient
  - Exclude patients with a diagnosis of *Mild Cognitive Impairment (MCI)* or *Dementia* at baseline Actigraphy assessment
  - Replace blood biomarker z-score values with NA if recognized as outlier
    - If outlier, {Blood Biomarker}_outlier = 1; If not, {Blood Biomarker}_outlier = 0



Actigraphy Data Visualizations







Actigraphy Model Variables

Standardized Blood Biomarkers measures: **AB42AB40, PTAU181, NFL, YKL40, sTREM2, GFAP** (numeric)

Predictors:

- Actigraphy Measure: **LTAC10** (numeric)
- Baseline variable: **Age_Act** (numeric)
  - the age with first available actigraphy assessment
- Gender: **Sex_F** (categorical)
  - Female: Sex_F = 1; Male: Sex_F = 0
- APOE genetic status: **APOE4** (categorical)
  - 0 if APOECODE = 2.2, 2.3, or 3.3;
  - 1 if APOECODE = 2.4, 3.4, or 4.4
  - NA if APOECODE is blank
- Body Mass Index: **BMI** (numeric)
- **Time** = AgeAtVisit - Age_Act (numeric)

⚠️: **All continuous variables (except for Time) are standardized by z-score**

Actigraphy Model Result

Model: Linear Mixed Effect Regression Model - lmer() from lmerTest package

Blood Biomarker	Variable	Estimate	Std. Error	t-value	Pr(>|t|)
AB42AB40	LTAC10	0.009034	0.082821	0.109	0.913294
	LTAC10 : Time	-0.029499	0.027272	-1.082	0.281972
PTAU181	LTAC10	0.008093	0.07822	0.103	0.9177
	LTAC10 : Time	-0.027097	0.023909	-1.133	0.2585
NFL	LTAC10	-0.071843	0.065945	-1.089	0.277702
	LTAC10 : Time	-0.014923	0.024718	-0.604	0.546574
YKL40	LTAC10	-0.13069	0.08413	-1.553	0.122482
	LTAC10 : Time	-0.0157	0.0315	-0.498	0.619798
sTREM2	LTAC10	4.12E-02	8.46E-02	0.487	0.6269
	LTAC10 : Time	3.45E-03	2.92E-02	0.118	0.9063
GFAP	LTAC10	0.060422	0.062802	0.962	0.3376
	LTAC10 : Time	-0.040283	0.025681	-1.569	0.12144

Table1. Estimated Effects of LTAC10 and LTAC10:time on Blood Biomarker Levels from Linear Mixed-Effects Models.

Limitations

- Time
- Data
  - Missingness
  - Complex and unstructured format, making merging slow due to mismatched details
  - Filtering criteria
- Model
  - Linear regressions
  - Fewer models tested than initially proposed due to time constraints
  - Few yielded significant results, requiring further analysis for stronger conclusions

❓ What we have done?

🎉 Done well

- 🔄 **Consistent and Productive Communication**
- 📑 **Clear and Well-Structured Analysis Plan**
- ❓ **Effective Q&A Sessions**
- ⚖️ **Fair and Balanced Contribution**
- 🎯 **Commitment to Defined Goals**
- 🤝 **Mutual Respect**
- 😊 **Maintaining a Positive and Motivated Atmosphere**

⬆️ Need better

- 🔍 **Conduct Error Checks Before Each Meeting**
- 🗣️ **Speak Clearly and at a Steady Pace**
- ⏳ **Manage Time Constraints Effectively**
- 💡 **Provide More Professional Insights**

Thanks for Listening!