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Plasma ADRD Biomarkers, MCI/Dementia, and Cognitively Healthy Longevity in WHIMS

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Plasma Alzheimer's Biomarkers:
Blood Tests to Detect Alzheimer's Disease Pathology

Key Plasma Biomarkers & What They Indicate:

Phosphorylated Tau (p-tau):

- **p-tau217 & p-tau181:** Highly specific to Alzheimer's
- **p-tau217:** Most accurate for predicting AD.

Amyloid Beta (Aβ):

- **Aβ42/Aβ40 Ratio:** Indicates amyloid plaque buildup.

Neurofilament Light (NfL):

- Marker of neurodegeneration.

Glial Fibrillary Acidic Protein (GFAP):

- Signals astrogliosis in the brain.

Clinical Significance:

Early Detection	Reduced Invasiveness	Monitoring & Prognosis	Trial Efficiency
Identify AD before symptoms.	Less costly than CSF or PET scans.	Track disease progression.	Improve patient selection.

Current Status:

p-tau217: Strong potential for routine use.

Plasma ADRD Biomarkers in WHIMS

- Measured p-tau217, p-tau181, GFAP, NfL, and Aβ42:Aβ40 at baseline in 2,836 women
- Measured these biomarkers at baseline and LLS in 1,000 women (15 years apart)
- **Data resource to study how plasma biomarkers of ADRD pathology relate to various factors and outcomes in WHIMS**

JAMA Network Open

Original Investigation | Neurology

Plasma Phosphorylated Tau 217 and Incident Mild Cognitive Impairment and Dementia in Older Women

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Abstract

IMPORTANCE There is limited research on the long-term associations of plasma phosphorylated tau 217 (p-tau217) with mild cognitive impairment (MCI) and dementia. No study has evaluated whether such associations vary by race or hormone therapy (HT) use.

OBJECTIVE To examine associations of baseline plasma p-tau217 with incident MCI and dementia and determine whether associations vary by age, race, *APOE* ε4 carrier status, or HT use.

DESIGN, SETTING, AND PARTICIPANTS This cohort study examined women recruited from 39 US clinical sites between 1996 and 1999 into the Women's Health Initiative Memory Study who were randomized to either estrogen alone vs placebo or estrogen plus progestin vs placebo. Women were assessed for up to 25 years through 2021. Baseline plasma p-tau217 was measured in 2024 and analyzed between February and August 2025. Women aged 65 to 79 years who were cognitively unimpaired at baseline were included for this analysis.

EXPOSURE Plasma p-tau217, quantified using the ALZpath Simoa assay.

MAIN OUTCOMES AND MEASURES The primary outcome was the combined end point of incident MCI or probable dementia. Secondary outcomes included MCI and dementia examined separately. Cause-specific hazard ratios (HRs) and 95% CIs for the association of p-tau217 with MCI or dementia were estimated using Cox proportional hazards regression models.

RESULTS Among 2766 participants (mean [SD] age, 69.9 [3.8] years; 486 [17.9%] Black, 196 [7.1%] Hispanic, and 2007 [73.9%] White), 1311 developed the combined end point of MCI or dementia (849 participants with MCI and 752 participants with dementia). Every 1-SD increase in $\log_2$-transformed p-tau217 was associated with incident MCI or dementia (HR, 2.43; 95% CI, 2.18-2.71) and each individual outcome (MCI: HR, 1.94; 95% CI, 1.72-2.20; dementia: HR, 3.17; 95% CI, 2.79-3.61). Associations of p-tau217 with dementia were larger in magnitude for women randomized to estrogen plus progestin (HR, 4.18; 95% CI, 3.41-5.13) vs placebo (HR, 3.07; 95% CI, 2.41-3.91) (*P* for interaction = .04) but did not significantly vary by estrogen alone vs placebo. P-tau217 associations with MCI or dementia were larger in magnitude for women older than 70 years (*P* for interaction = .04), *APOE* ε4 carriers (*P* for interaction = .02), and White women compared with Black women (*P* for interaction < .001). However, the combination of p-tau217 and age performed similarly in White women (area under the curve = 72.0%; 95% CI, 70.3%-73.6%) and Black women (area under the curve = 70.4%; 95% CI, 64.0%-78.0%). P-tau217 was not associated with incident MCI in Black women.

(continued)

Key Points

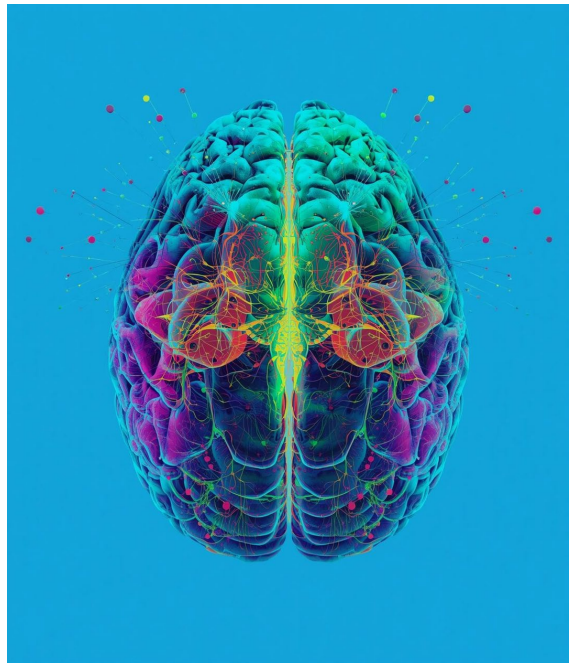
Question Do associations of plasma phosphorylated tau 217 (p-tau217) with incident mild cognitive impairment (MCI) and dementia vary by race, hormone therapy, age, or *APOE* ε4 carrier status?

Findings In this cohort study among 2766 older women, associations of p-tau217 with incident dementia were larger in magnitude among women assigned to estrogen plus progestin vs placebo but did not vary for estrogen alone vs placebo. P-tau217 associations with MCI or dementia were larger in magnitude for women older than 70 years, *APOE* ε4 carriers, and White compared with Black women.

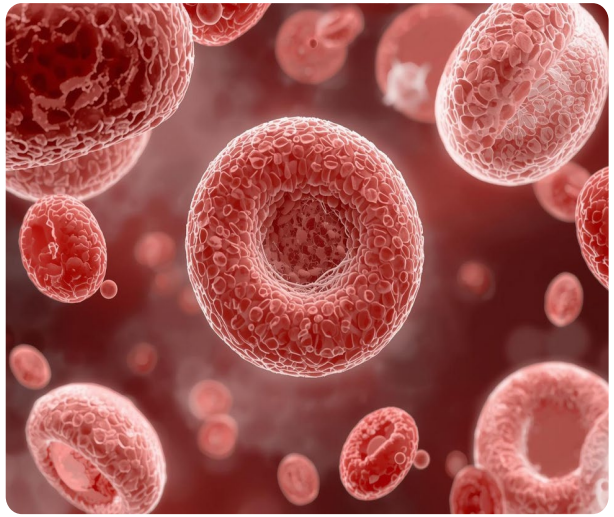
Meaning These findings underscore the value of p-tau217 and show that many factors should be considered when examining its associations with cognitive outcomes.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.



Plasma p-tau217 has greater accuracy in detecting AD pathology relative to other biomarkers



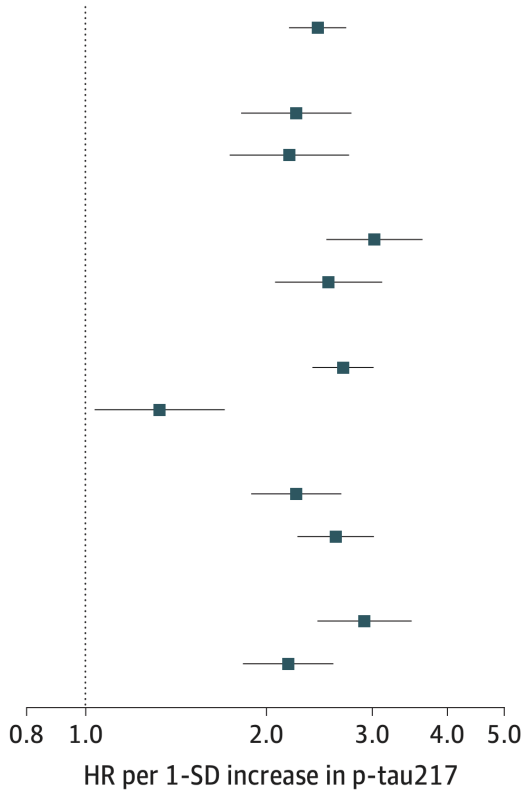
Limited data on its ability to predict dementia in cognitively healthy people

Baseline Characteristics

N=2,766	No. (%) or Mean (SD)
Age	69.9 (3.8)
College graduate	31.2%
White	73.9%
Current smoker	5.4%
BMI, kg/m^2	28.6 (5.6)
Diabetes	6.9%
Cardiovascular disease	4.8%
APOE e4 carrier	26.8%

Figure 1. Forest Plot of the Association of Baseline Plasma Phosphorylated Tau 217 (P-Tau217) With Mild Cognitive Impairment or Dementia

Contrast	No. of events/ No. at risk	HR (95% CI)	*P* value
Overall	1295/2694	2.43 (2.18-2.71)	
Estrogen alone trial			
Intervention	276/553	2.24 (1.81-2.77)	.86
Placebo	267/553	2.18 (1.74-2.74)	
Estrogen plus progestin trial			
Intervention	392/804	3.02 (2.52-3.64)	.19
Placebo	360/784	2.54 (2.07-3.12)	
Race			
White	1120/2007	2.68 (2.38-3.01)	<.001
Black	141/486	1.33 (1.04-1.70)	
Age, y			
≤70	667/1628	2.24 (1.89-2.66)	.04
>70	628/1066	2.61 (2.25-3.02)	
APOE ε4			
Carrier	338/486	2.91 (2.43-3.49)	.02
Noncarrier	690/1328	2.17 (1.83-2.58)	

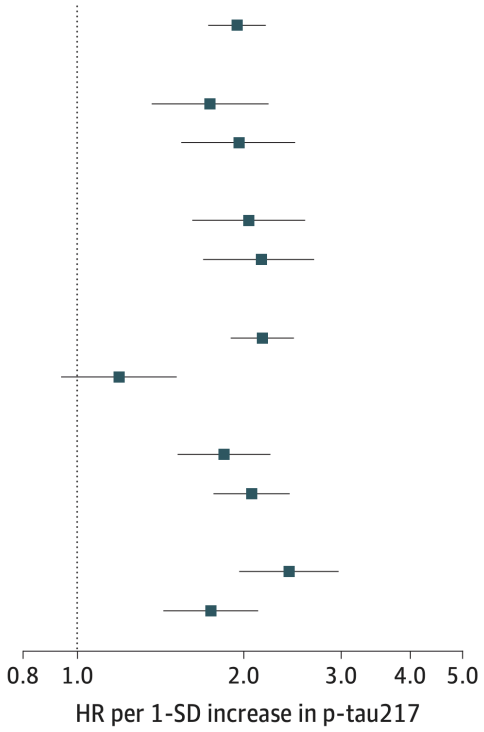


Plasma p-tau217 associated with 2-fold higher risk of MCI/dementia

Stronger associations in White women, >70 yrs, APOE e4 carriers

Figure 2. Forest Plot of the Association of Baseline Plasma Phosphorylated Tau 217 (P-Tau217) With Incident Mild Cognitive Impairment

Contrast	No. of events/ No. at risk	HR (95% CI)	*P* value
Overall	837/2694	1.94 (1.72-2.20)	
Estrogen alone trial			
Intervention	197/553	1.74 (1.37-2.22)	.49
Placebo	177/553	1.96 (1.54-2.48)	
Estrogen plus progestin trial			
Intervention	235/804	2.05 (1.62-2.59)	.80
Placebo	228/784	2.13 (1.69-2.69)	
Race			
White	693/2007	2.16 (1.90-2.47)	<.001
Black	119/486	1.19 (0.94-1.52)	
Age, y			
≤70	436/1628	1.85 (1.52-2.24)	.53
>70	401/1066	2.07 (1.77-2.43)	
APOE ε4			
Carrier	185/486	2.42 (1.97-2.98)	.02
Noncarrier	448/1328	1.75 (1.43-2.13)	

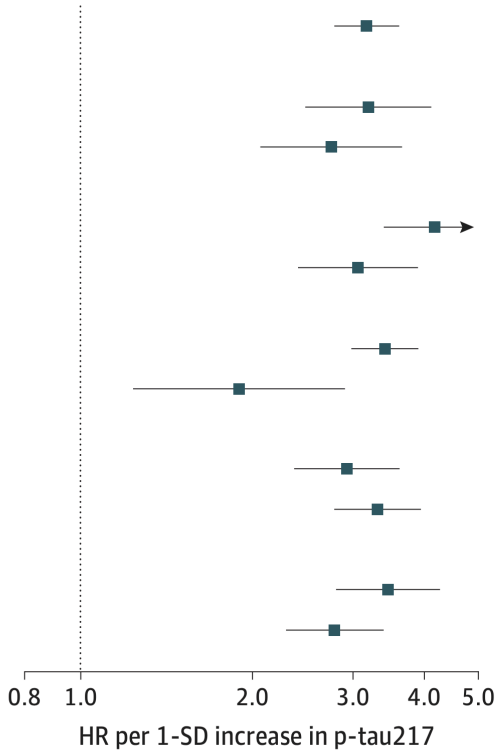


Plasma p-tau217 associated with 2-fold higher risk of MCI

Stronger associations in White women and APOE e4 carriers

Figure 3. Forest Plot of the Association of Baseline Plasma Phosphorylated Tau 217 (P-Tau217) With Incident Dementia

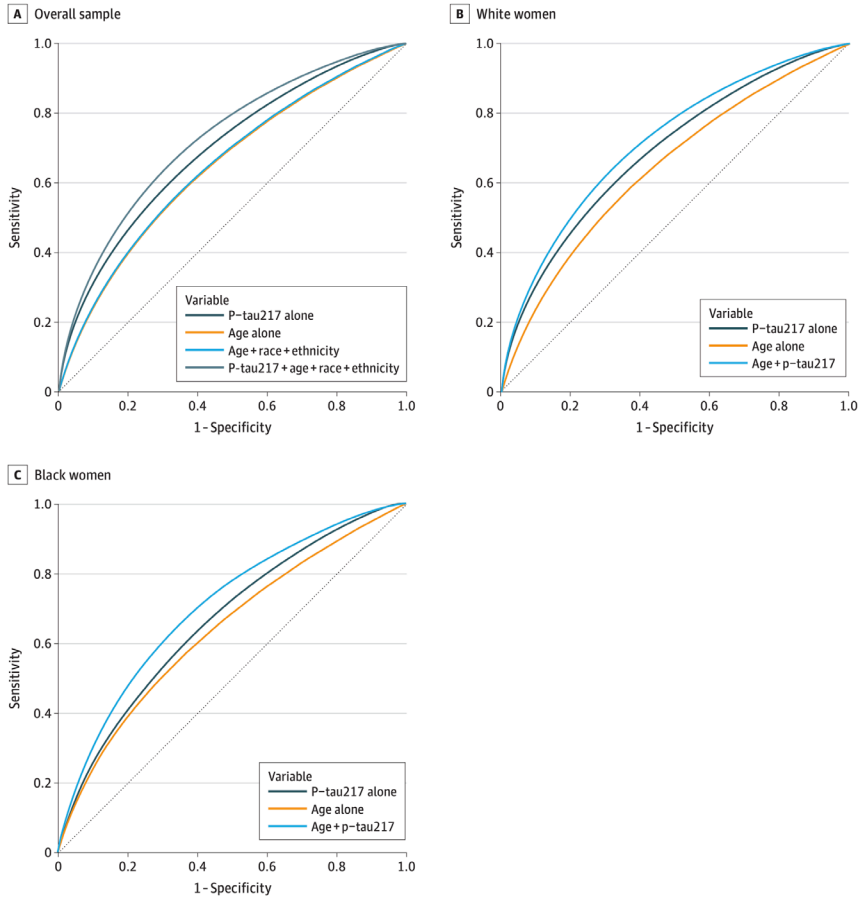
Contrast	No. of events/ No. at risk	HR (95% CI)	*P* value
Overall	744/2694	3.17 (2.79-3.61)	
Estrogen alone trial			
Intervention	150/553	3.20 (2.49-4.13)	.44
Placebo	136/553	2.76 (2.08-3.67)	
Estrogen plus progestin trial			
Intervention	249/804	4.18 (3.41-5.13)	.04
Placebo	209/784	3.07 (2.41-3.91)	
Race			
White	666/2007	3.42 (2.99-3.92)	.01
Black	61/486	1.90 (1.24-2.92)	
Age, y			
≤70	371/1628	2.94 (2.38-3.63)	.04
>70	373/1066	3.33 (2.79-3.96)	
APOE ε4			
Carrier	224/486	3.47 (2.81-4.27)	.13
Noncarrier	394/1328	2.80 (2.30-3.41)	



Plasma p-tau217 associated with 3-fold higher risk of dementia

Stronger associations in women assigned to estrogen plus progestin, White women, >70 yrs

Figure 4. Discriminative Accuracy of Plasma Phosphorylated Tau 217 (p-tau217) for Incident Dementia in the Overall Sample, White Women, and Black Women



- P-tau217 showed better discrimination than demographics for dementia
- Combination of p-tau217 and demographics outperformed either alone w/ AUC of 72.7%
- **Similar performance in Black and White women**

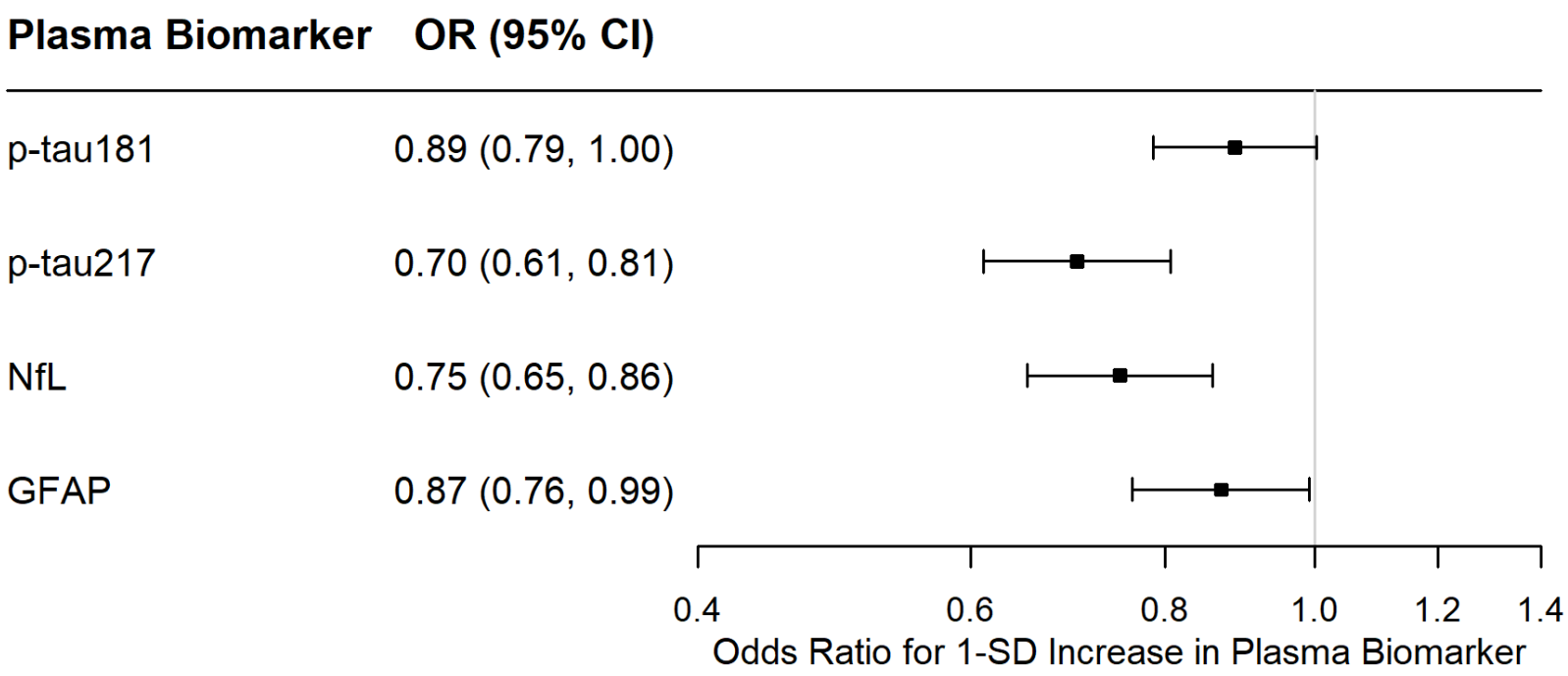
Conclusions

- Among cognitively healthy women, plasma p-tau217 associated with incident MCI/dementia during 25-y follow-up
- P-tau217 and dementia HR was stronger in women assigned to estrogen plus progestin vs placebo but not e-alone vs placebo
- Similar discriminative accuracy for dementia in White and Black women when combining p-tau217 with age

Associations of Plasma ADRD Biomarkers with Lifespan and Healthspan

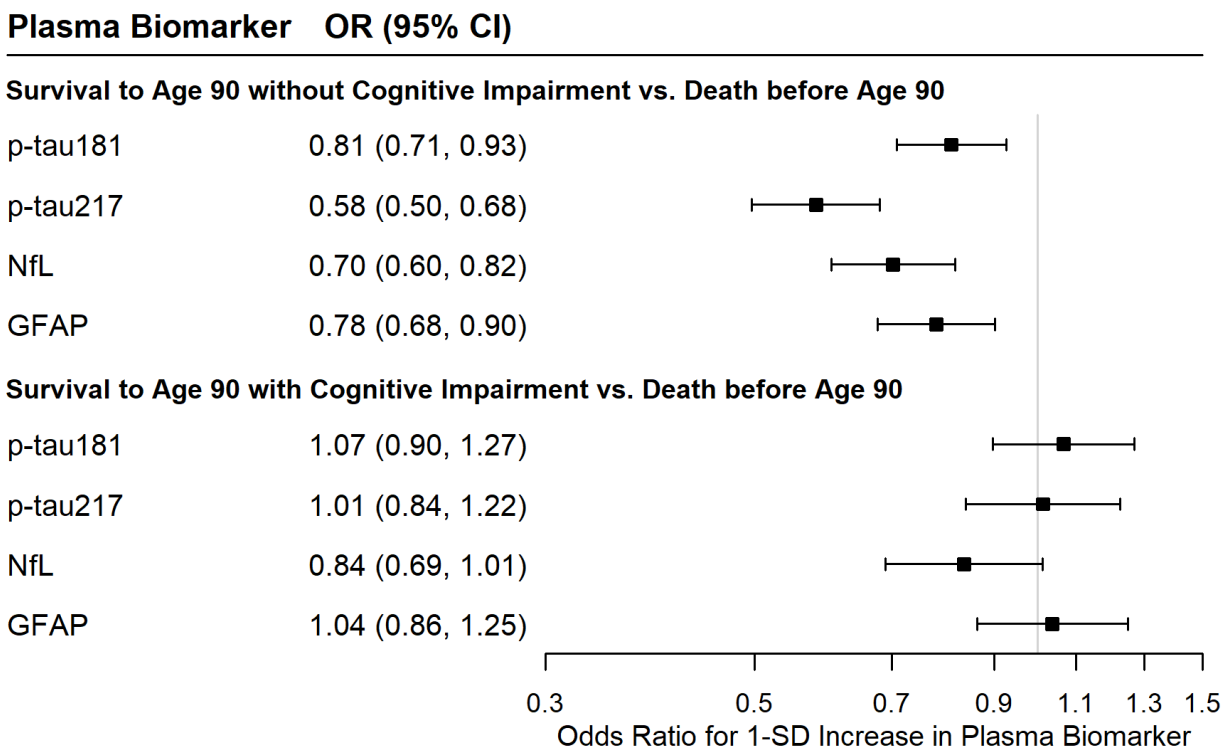
Bowei Zhang, MS

Plasma ADRD Biomarkers and Exceptional Longevity



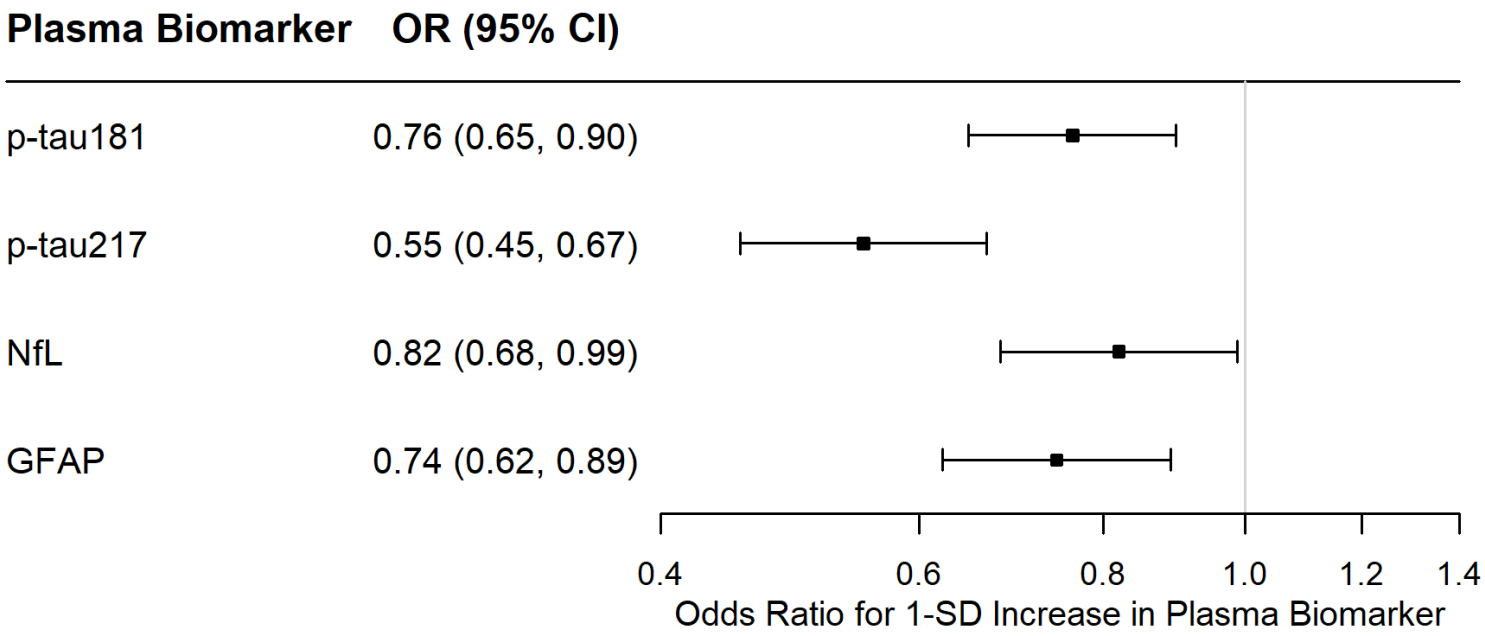
Elevated p-tau217, p-tau181, NfL, and GFAP associated with lower odds of survival to age 90 vs dementia-free death

Plasma ADRD Biomarkers and Cognitively Healthy Longevity



Elevated p-tau217, p-tau181, NfL, and GFAP associated with lower odds of survival to age 90 without MCI/dementia vs dementia-free death

Plasma ADRD Biomarkers and Cognitively Healthy Longevity



Elevated p-tau217, p-tau181, NfL, and GFAP associated with lower odds of survival to age 90 without MCI/dementia vs with MCI/dementia

Conclusions

- Higher levels of all plasma ADRD biomarkers associated with lower odds of survival to age 90 without MCI/dementia
- Plasma ADRD biomarkers may serve as indicators of healthspan and identify those less likely to be cognitively healthy age 90
- Plasma biomarkers may be novel biomarkers of aging and potentially surrogate endpoints in anti-aging interventions

Thank You

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161,808 WHI Participants

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Cardiovascular Risk Factors and 15-Year Changes in Plasma Biomarkers of ADRD Pathology in WHIMS

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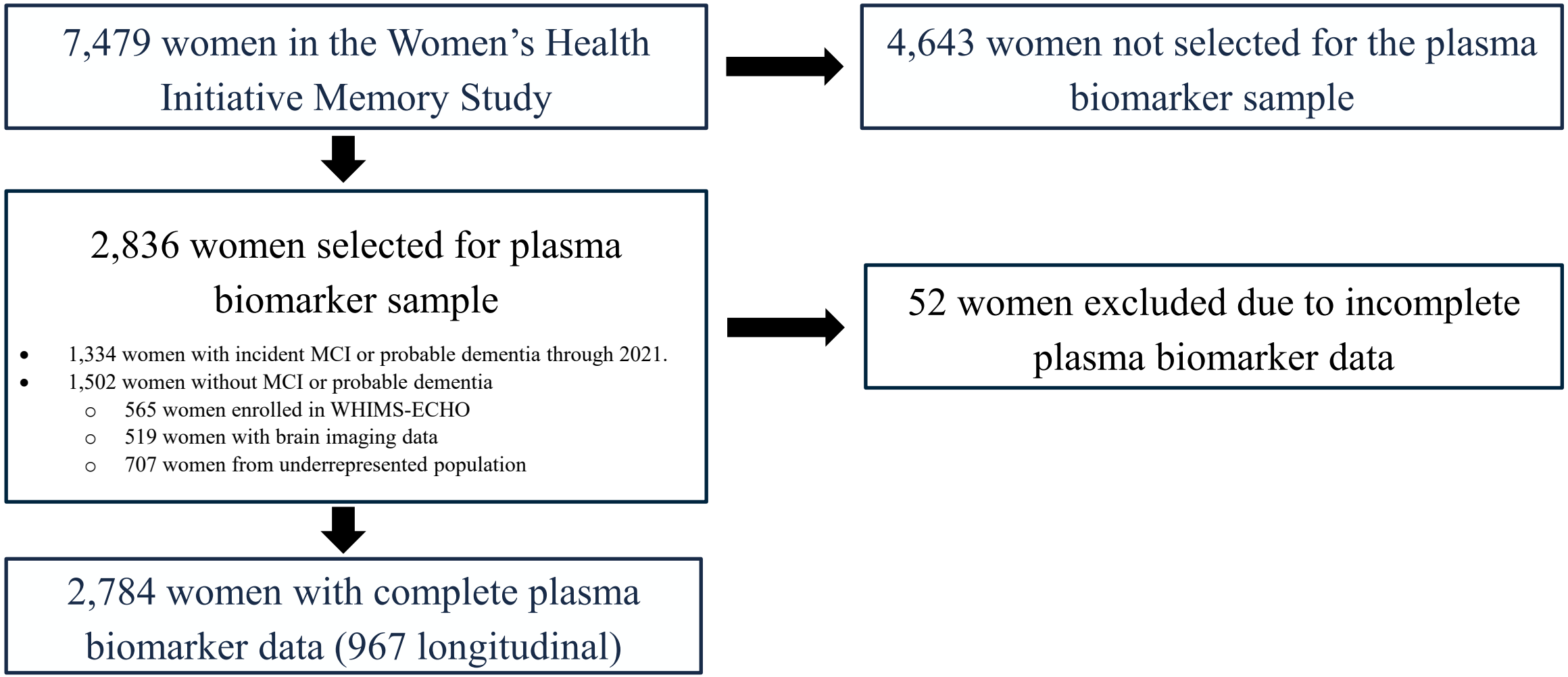
Background

- Alzheimer's disease prevalence is rapidly increasing, with disproportionate burden in women
- Blood-based biomarkers enable minimally invasive assessment of AD-related pathology
- Cardiovascular (CV) risk factors are modifiable risk factors of dementia
- Limited studies have assessed their associations with changes in plasma biomarkers

Objectives

- Assess temporal changes in plasma ADRD biomarkers
- Examine associations of modifiable CV risk factors with baseline levels and longitudinal changes in plasma ADRD biomarkers

Study Population



Plasma Biomarkers of ADRD

Measured at baseline (1996-1999) and second time visit (2012 - 2013) with a mean (SD) of 15.13 (0.60) years between visits

- Phosphorylated tau at threonine 217 (**p-tau217**)
- Amyloid beta 42:40 ratio (**Aβ42:Aβ40**)
- Phosphorylated tau at threonine 181 (**p-tau181**)
- Neurofilament light chain (**NfL**)
- Glial fibrillary acidic protein (**GFAP**)

Cardiovascular Risk Factors

Comorbidities

- Diabetes
- Hypertension
- Total cholesterol (≥ 200 mg/dL)
- HDL cholesterol (< 50 mg/dL)
- LDL cholesterol (≥ 160 mg/dL)

Cardiovascular Risk Factors

Lifestyle behaviors

Smoking status:

- Never smoked
- Past smoker
- Current smoker

Alcohol use:

- Never
- Past drinker
- Current drinker (< 7 drinks per week)
- Current drinker (≥ 7 drinks per week)

Sleep duration:

- < 7 hours
- 7-8 hours (reference)
- > 8 hours

Moderate-to-vigorous physical activity (MVPA):

- Under guidelines (< 7.5 MET-hours/week),
- Meets guidelines (≥ 7.5 MET-hours/week)

Baseline Characteristics and Cardiovascular Risk Factors of Analytic Sample

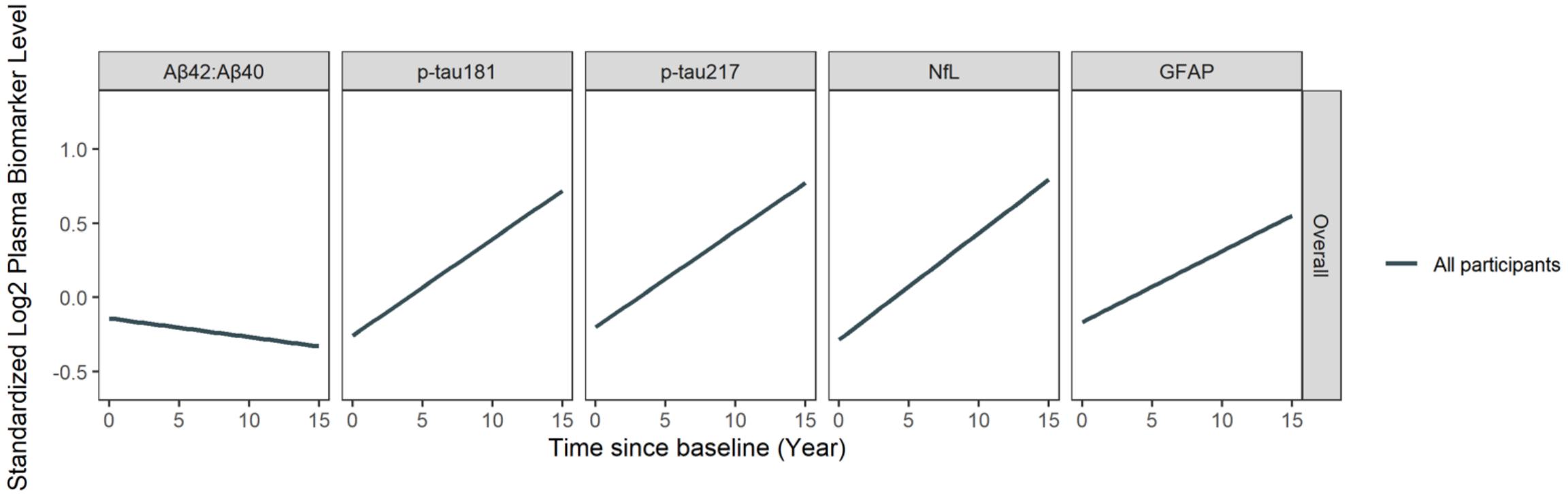
N = 2,784	No. (%) or Mean (SD)
Age	69.9 (3.8)
White	1,993 (73.1%)
Hispanic or Latino	202 (7.3%)
College graduate or higher	861 (31.0%)
BMI at Baseline (kg/m²)	28.6 (5.6)
eGFR at Baseline (ml/min/1.73 m²)	83.6 (13.6)
APOE	
ε2 carrier	193 (12.5%)
ε4 carrier	403 (26.2%)
Cardiovascular disease	135 (4.8%)

Baseline Characteristics and Cardiovascular Risk Factors of Analytic Sample

N = 2,784	No. (%) or Mean (SD)
Diabetes	196 (7.1%)
Hypertension	1,874 (67.3%)
Total cholesterol ≥ 200 mg/dL	2,043 (81.3%)
HDL cholesterol < 50 mg/dL	1,015 (40.4%)
LDL cholesterol ≥ 160 mg/dL	914 (39.6%)
Current smoker	150 (5.5%)
Alcohol use	
Current drinker (< 7 drinks per week)	1,473 (53.5%)
Current drinker (≥ 7 drinks per week)	259 (9.4%)
Sleep duration (hours)	
< 7	1,136 (41.1%)
7 - 8	1,519 (55.0%)
> 8	109 (3.9%)
MVPA Meets Guidelines (≥ 7.5 MET/wk)	677 (24.4%)

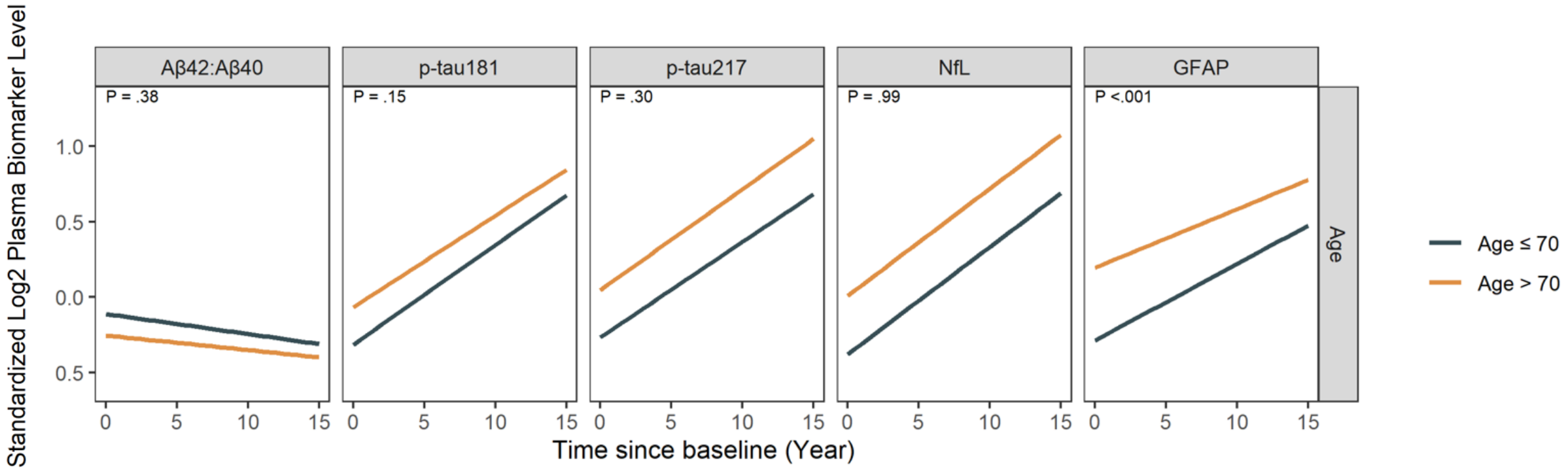
Longitudinal Changes in Plasma ADRD Biomarkers

- Aβ42:Aβ40 declined over time, while p-tau181, p-tau217, NfL, and GFAP increased



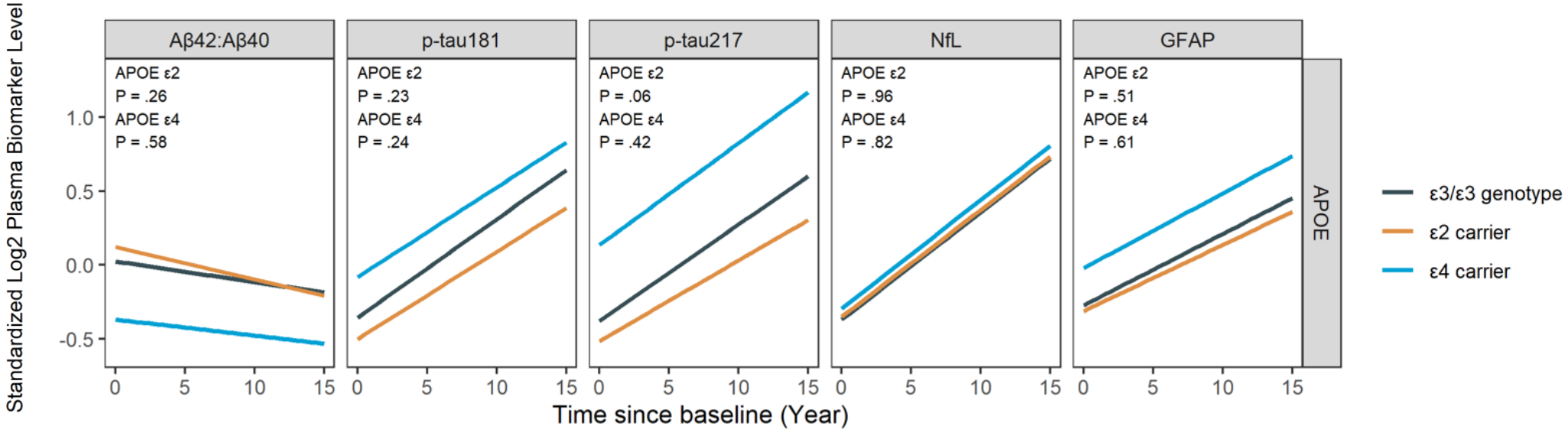
Longitudinal Changes in Plasma ADRD Biomarkers

- Women >70 years had higher of levels of pathology, with a slower increase in GFAP only



Longitudinal Changes in Plasma ADRD Biomarkers

- APOE ε4 carriers vs. ε3/ε3 carriers showed more adverse baseline biomarker levels
- APOE ε2 carriers vs. ε3/ε3 carriers did not differ in biomarker levels
- Longitudinal changes did not differ by APOE genotype

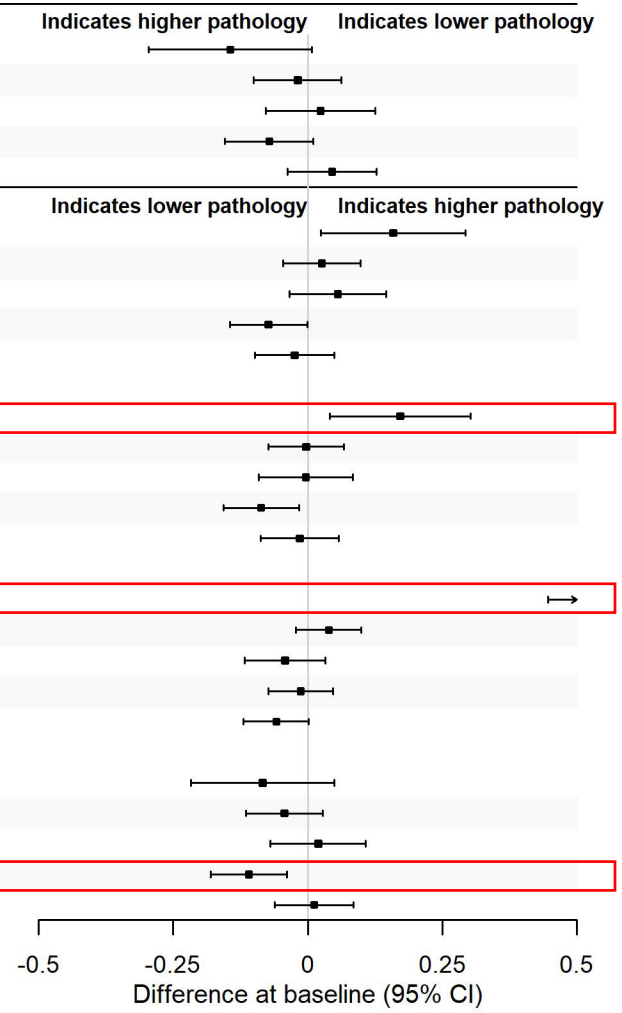


Associations of Baseline Comorbidities with Baseline Levels of Plasma ADRD Biomarkers

At baseline,

- No significant association was observed for Aβ42:Aβ40
- Diabetes was associated with higher levels of p-tau217 and NfL
- Unexpectedly, an at-risk level of HDL cholesterol was associated with lower GFAP

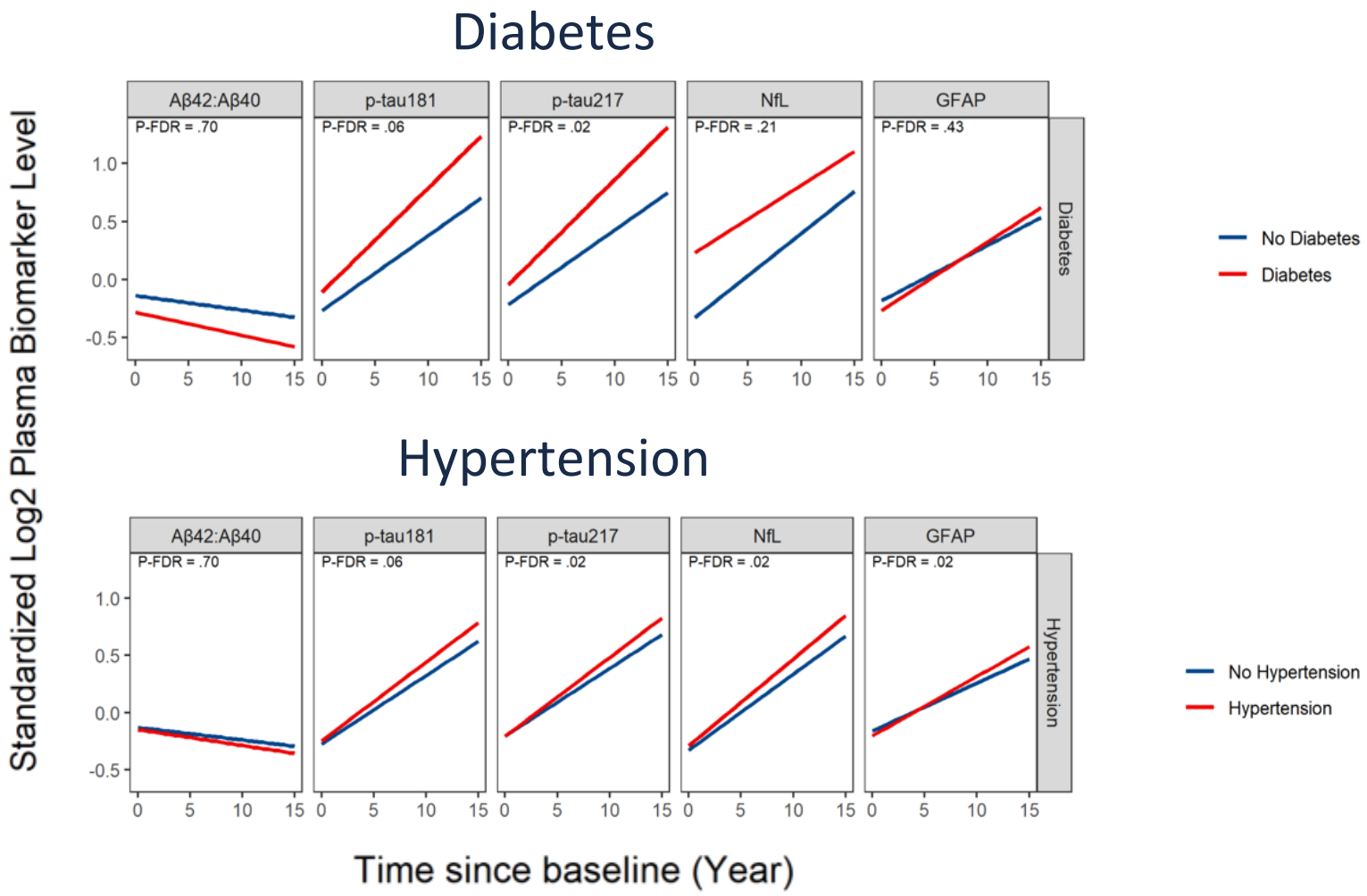
Cardiovascular Risk Factor	Baseline Effect β (95% CI)	FDR-adjusted P-value
Aβ42:Aβ40		
Diabetes	-0.144 (-0.296, 0.008)	.38
Hypertension	-0.019 (-0.100, 0.063)	.81
Total Cholesterol ≥ 200 mg/dL	0.024 (-0.078, 0.126)	.81
HDL Cholesterol < 50 mg/dL	-0.071 (-0.153, 0.010)	.38
LDL Cholesterol ≥ 160 mg/dL	0.045 (-0.038, 0.128)	.62
p-tau181		
Diabetes	0.159 (0.024, 0.293)	.07
Hypertension	0.026 (-0.046, 0.098)	.58
Total Cholesterol ≥ 200 mg/dL	0.056 (-0.034, 0.145)	.44
HDL Cholesterol < 50 mg/dL	-0.073 (-0.145, -0.001)	.12
LDL Cholesterol ≥ 160 mg/dL	-0.024 (-0.098, 0.049)	.58
p-tau217		
Diabetes	0.171 (0.041, 0.302)	.04
Hypertension	-0.003 (-0.073, 0.067)	.93
Total Cholesterol ≥ 200 mg/dL	-0.004 (-0.091, 0.084)	.93
HDL Cholesterol < 50 mg/dL	-0.087 (-0.157, -0.017)	.05
LDL Cholesterol ≥ 160 mg/dL	-0.015 (-0.087, 0.057)	.81
NfL		
Diabetes	0.558 (0.446, 0.669)	<.001
Hypertension	0.039 (-0.021, 0.100)	.50
Total Cholesterol ≥ 200 mg/dL	-0.042 (-0.117, 0.033)	.50
HDL Cholesterol < 50 mg/dL	-0.013 (-0.073, 0.046)	.72
LDL Cholesterol ≥ 160 mg/dL	-0.058 (-0.119, 0.002)	.19
GFAP		
Diabetes	-0.084 (-0.217, 0.049)	.38
Hypertension	-0.043 (-0.115, 0.028)	.38
Total Cholesterol ≥ 200 mg/dL	0.019 (-0.069, 0.108)	.79
HDL Cholesterol < 50 mg/dL	-0.109 (-0.180, -0.039)	.02
LDL Cholesterol ≥ 160 mg/dL	0.012 (-0.061, 0.085)	.82



Associations of Baseline Comorbidities with Changes in Plasma ADRD Biomarkers over an Average of 15 Years

Longitudinally,

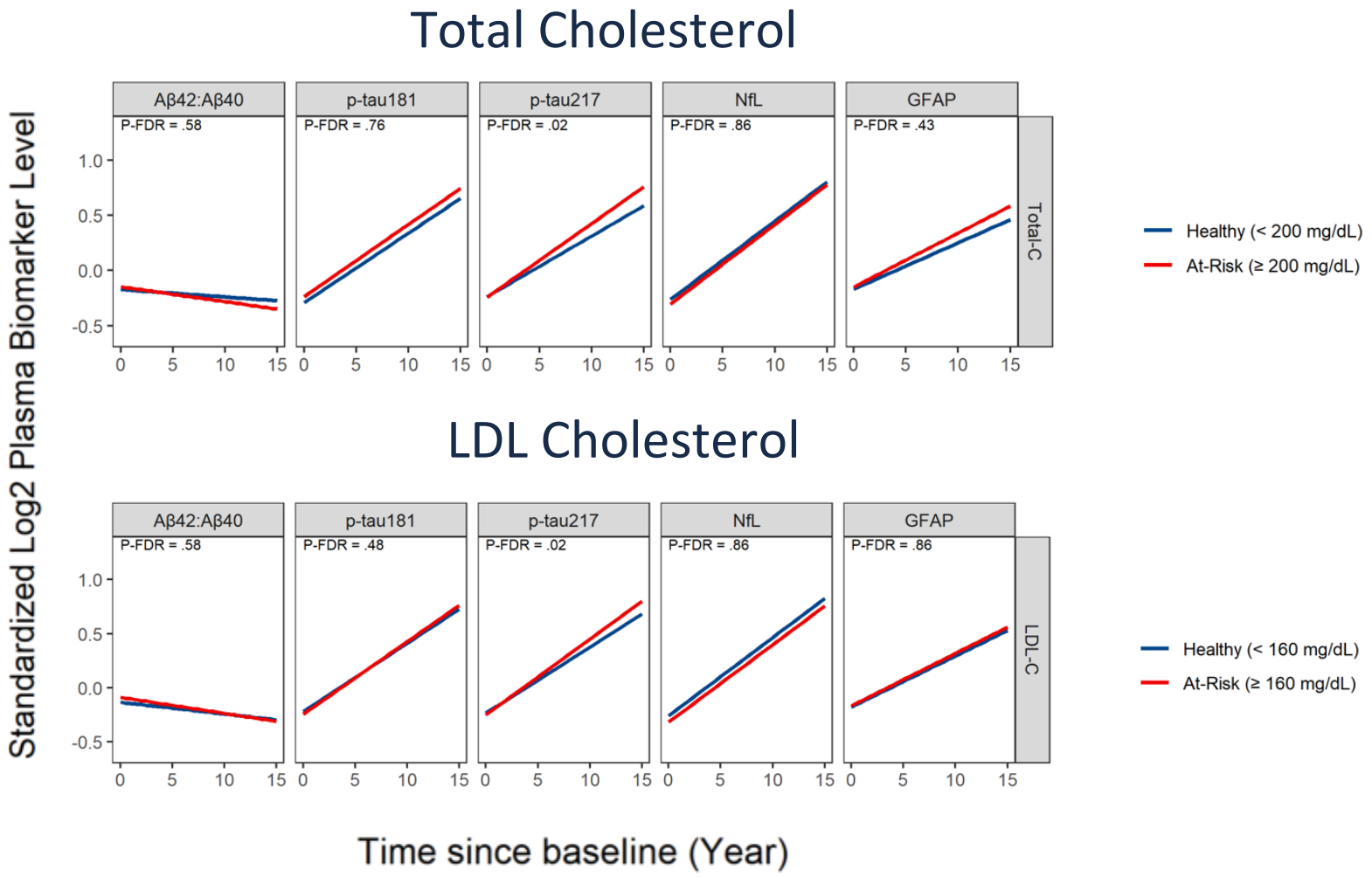
- Diabetes was associated with a faster increase in p-tau217 (P-FDR = 0.02)
- Hypertension was associated with faster increases in p-tau217, NfL, and GFAP (P-FDR = 0.02)



Associations of Baseline Comorbidities with Changes in Plasma ADRD Biomarkers over an Average of 15 Years

Longitudinally,

- At-risk levels of both total cholesterol and LDL cholesterol were each associated with a faster increase in p-tau217 (P-FDR = 0.02)

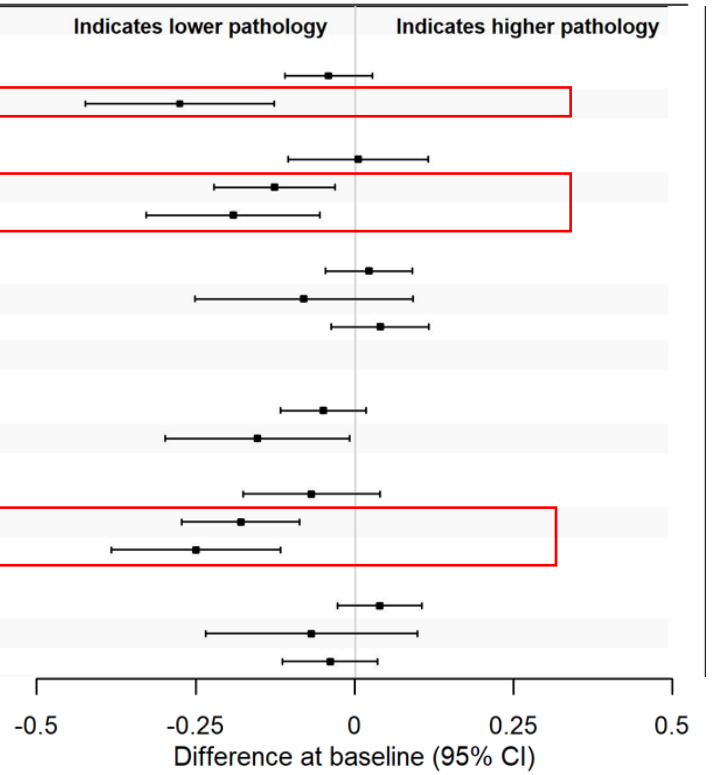


Associations of Baseline Lifestyle Behaviors with Baseline Levels of Plasma ADRD Biomarkers

At baseline,

- Current smoking was associated with lower p-tau181 levels
- Current drinking was associated with lower p-tau181 and p-tau217 levels

Cardiovascular Risk Factor	Baseline Effect β (95% CI)	FDR-adjusted P-value
p-tau181		
Smoking status		
Past smoker	-0.042 (-0.112, 0.028)	.44
Current smoker	-0.280 (-0.432, -0.129)	.004
Alcohol use		
Past drinker	0.005 (-0.107, 0.118)	.92
Current drinker (< 7 drinks per week)	-0.129 (-0.225, -0.032)	.04
Current drinker (≥ 7 drinks per week)	-0.195 (-0.334, -0.056)	.04
Sleep duration		
<7 hours	0.022 (-0.048, 0.092)	.58
>8 hours	-0.082 (-0.256, 0.093)	.52
MVPA (≥ 7.5 MET-hours/week)	0.040 (-0.038, 0.119)	.50
p-tau217		
Smoking status		
Past smoker	-0.051 (-0.119, 0.018)	.32
Current smoker	-0.156 (-0.304, -0.009)	.10
Alcohol use		
Past drinker	-0.070 (-0.179, 0.040)	.39
Current drinker (< 7 drinks per week)	-0.183 (-0.277, -0.089)	.002
Current drinker (≥ 7 drinks per week)	-0.255 (-0.390, -0.119)	.002
Sleep duration		
<7 hours	0.040 (-0.028, 0.107)	.41
>8 hours	-0.070 (-0.239, 0.100)	.55
MVPA (≥ 7.5 MET-hours/week)	-0.040 (-0.116, 0.036)	.44

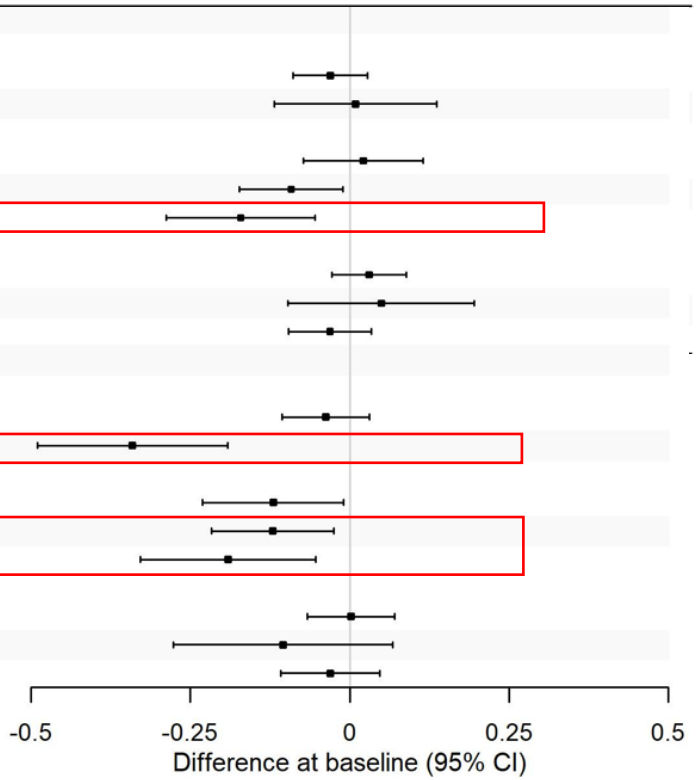


Associations of Baseline Lifestyle Behaviors with Baseline Levels of Plasma ADRD Biomarkers

At baseline,

- Current smoking was associated with lower GFAP levels
- Current drinking was associated with lower NfL and GFAP levels

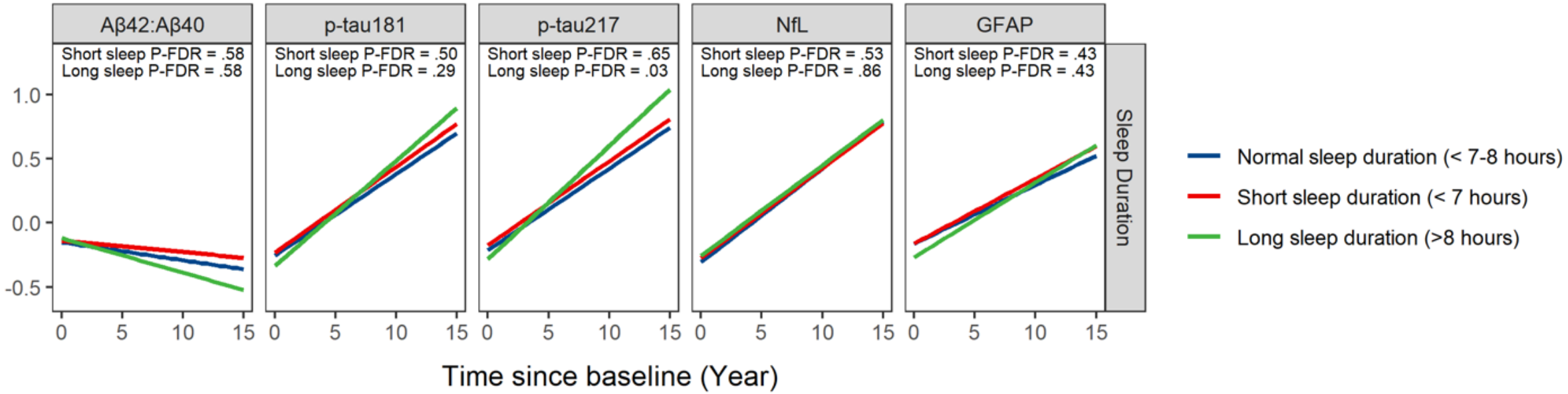
Cardiovascular Risk Factor	Baseline Effect β (95% CI)	FDR-adjusted P-value
NfL		
Smoking status		
Past smoker	-0.031 (-0.089, 0.028)	.50
Current smoker	0.009 (-0.118, 0.136)	.89
Alcohol use		
Past drinker	0.022 (-0.072, 0.115)	.72
Current drinker (< 7 drinks per week)	-0.092 (-0.172, -0.011)	.11
Current drinker (≥ 7 drinks per week)	-0.171 (-0.287, -0.055)	.03
Sleep duration		
<7 hours	0.030 (-0.028, 0.088)	.50
>8 hours	0.050 (-0.096, 0.196)	.66
MVPA (≥ 7.5 MET-hours/week)	-0.031 (-0.096, 0.034)	.51
GFAP		
Smoking status		
Past smoker	-0.038 (-0.106, 0.031)	.41
Current smoker	-0.341 (-0.490, -0.191)	<.001
Alcohol use		
Past drinker	-0.120 (-0.230, -0.009)	.09
Current drinker (< 7 drinks per week)	-0.121 (-0.216, -0.025)	.04
Current drinker (≥ 7 drinks per week)	-0.191 (-0.328, -0.053)	.03
Sleep duration		
<7 hours	0.002 (-0.067, 0.071)	.96
>8 hours	-0.105 (-0.277, 0.067)	.38
MVPA (≥ 7.5 MET-hours/week)	-0.031 (-0.108, 0.047)	.57



Associations of Baseline Lifestyle Behaviors with Changes in Plasma ADRD Biomarkers over an Average of 15 Years

Longitudinally,

- Long sleep duration (>8 hours) was associated with a faster increase in p-tau217 (P-FDR = 0.03)
- No other significant association was observed in lifestyle behaviors



Summary

We observed that at baseline:

- Diabetes was associated with higher levels of p-tau217 and NfL
- At-risk levels of HDL cholesterol were associated with lower GFAP
- Current smoking was associated with lower levels of p-tau181 and GFAP
- Current drinking was associated with lower levels of p-tau181, p-tau217, NfL, and GFAP

Summary

In terms of changes over time:

- Hypertension was associated with faster increases in p-tau217, NfL, GFAP
- Several comorbidities (diabetes, hypertension, at-risk levels of total and LDL cholesterol) were associated with a faster increase in p-tau217
- Among lifestyle behaviors, only long sleep duration was associated with a faster increase in p-tau217

Conclusions

- Levels of pathology reflected in plasma ADRD biomarkers increased over time
- Some comorbidities, particularly diabetes, were associated with baseline levels of plasma biomarkers and increases over time
- Among lifestyle behaviors, only long sleep duration was associated with a faster increase in p-tau217

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Statistical Analyses

Sensitivity Analyses

- Effect modification evaluated across age group (≤ 70 vs > 70) and APOE categorized as ε3/ε3 (reference), ε2 carriers (ε2/ε2, ε2/ε3), and ε4 carriers (ε2/ε4, ε3/ε4, ε4/ε4).
- We did not stratify findings by race
- Sensitivity analyses
  - Excluding women with CVD diagnosed at baseline
  - Removing extreme outliers (5-SD above the mean) instead of using winsorization
  - Excluding women with eGFR < 60 mL/min/1.73m^2

Association of Baseline Comorbidities with Changes in Plasma Biomarkers of ADRD over an Average of 15 Years

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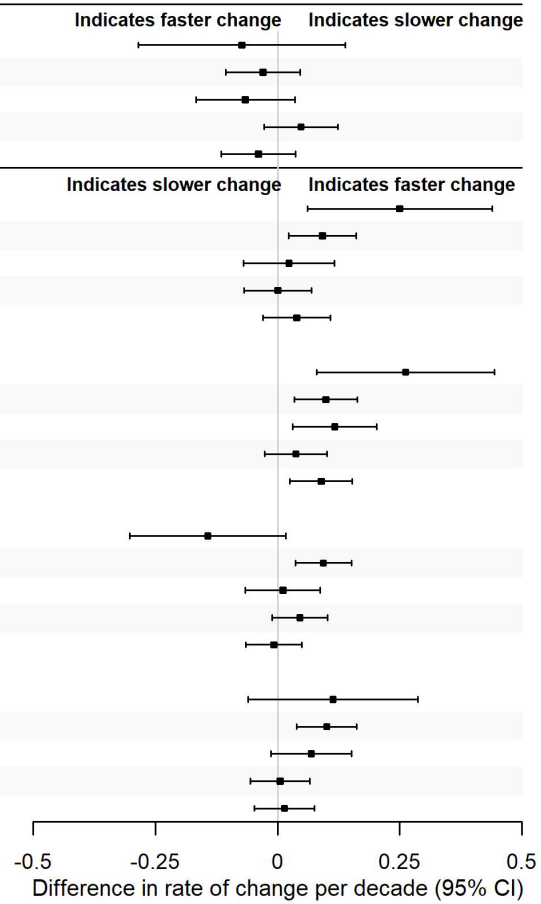
Cardiovascular Risk Factor	Exposure × time β (95% CI)	FDR-adjusted P-value
Aβ42:Aβ40		
Diabetes	-0.073 (-0.284, 0.138)	.70
Hypertension	-0.030 (-0.106, 0.046)	.70
Total Cholesterol ≥ 200 mg/dL	-0.066 (-0.167, 0.035)	.58
HDL Cholesterol < 50 mg/dL	0.048 (-0.028, 0.123)	.58
LDL Cholesterol ≥ 160 mg/dL	-0.039 (-0.115, 0.037)	.58
p-tau181		
Diabetes	0.250 (0.061, 0.438)	.06
Hypertension	0.092 (0.022, 0.161)	.06
Total Cholesterol ≥ 200 mg/dL	0.023 (-0.069, 0.116)	.76
HDL Cholesterol < 50 mg/dL	0.001 (-0.068, 0.070)	.98
LDL Cholesterol ≥ 160 mg/dL	0.039 (-0.030, 0.109)	.48
p-tau217		
Diabetes	0.262 (0.080, 0.443)	.02
Hypertension	0.098 (0.034, 0.163)	.02
Total Cholesterol ≥ 200 mg/dL	0.117 (0.031, 0.203)	.02
HDL Cholesterol < 50 mg/dL	0.037 (-0.027, 0.101)	.41
LDL Cholesterol ≥ 160 mg/dL	0.089 (0.025, 0.153)	.02
NfL		
Diabetes	-0.143 (-0.302, 0.017)	.21
Hypertension	0.094 (0.036, 0.151)	.02
Total Cholesterol ≥ 200 mg/dL	0.011 (-0.066, 0.087)	.86
HDL Cholesterol < 50 mg/dL	0.046 (-0.011, 0.103)	.22
LDL Cholesterol ≥ 160 mg/dL	-0.008 (-0.065, 0.050)	.86
GFAP		
Diabetes	0.113 (-0.060, 0.287)	.43
Hypertension	0.100 (0.039, 0.162)	.02
Total Cholesterol ≥ 200 mg/dL	0.069 (-0.013, 0.151)	.43
HDL Cholesterol < 50 mg/dL	0.005 (-0.056, 0.067)	.96
LDL Cholesterol ≥ 160 mg/dL	0.014 (-0.048, 0.076)	.86

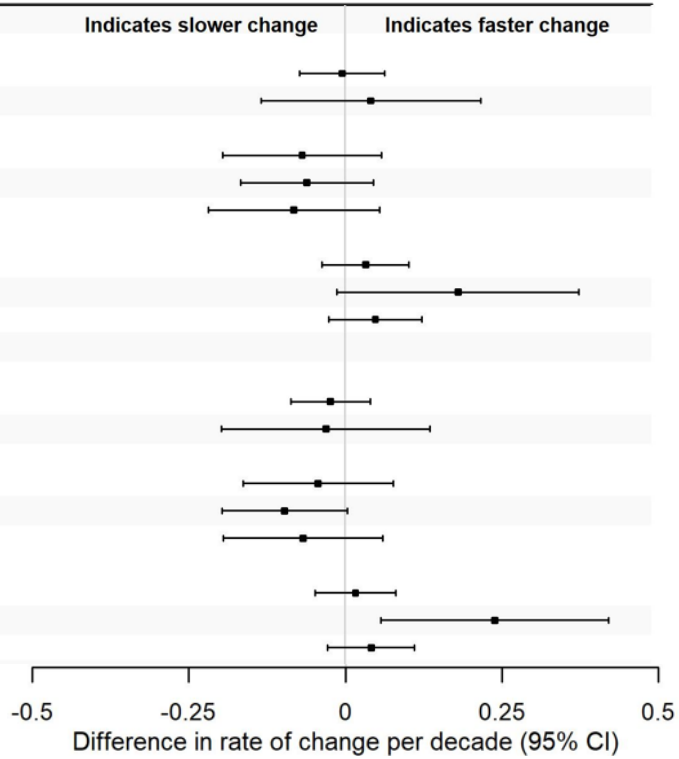


Association of Baseline Lifestyle Risk Factors with Changes in Plasma Biomarkers of ADRD over an Average of 15 Years

Longitudinally,

- Long sleep duration (>8 hours) was associated with a faster increase in p-tau217.

Cardiovascular Risk Factor	Exposure × time β (95% CI)	FDR-adjusted P-value
p-tau181		
Smoking status		
Past smoker	-0.004 (-0.074, 0.066)	.98
Current smoker	0.043 (-0.137, 0.222)	.76
Alcohol use		
Past drinker	-0.069 (-0.199, 0.060)	.48
Current drinker (< 7 drinks per week)	-0.062 (-0.170, 0.047)	.48
Current drinker (≥ 7 drinks per week)	-0.083 (-0.223, 0.057)	.48
Sleep duration		
<7 hours	0.034 (-0.037, 0.105)	.50
>8 hours	0.185 (-0.012, 0.383)	.29
MVPA (≥ 7.5 MET-hours/week)	0.050 (-0.026, 0.126)	.48
p-tau217		
Smoking status		
Past smoker	-0.023 (-0.088, 0.042)	.58
Current smoker	-0.031 (-0.201, 0.140)	.72
Alcohol use		
Past drinker	-0.043 (-0.166, 0.079)	.58
Current drinker (< 7 drinks per week)	-0.098 (-0.200, 0.004)	.13
Current drinker (≥ 7 drinks per week)	-0.068 (-0.198, 0.062)	.44
Sleep duration		
<7 hours	0.018 (-0.049, 0.084)	.65
>8 hours	0.246 (0.060, 0.431)	.03
MVPA (≥ 7.5 MET-hours/week)	0.043 (-0.027, 0.114)	.41

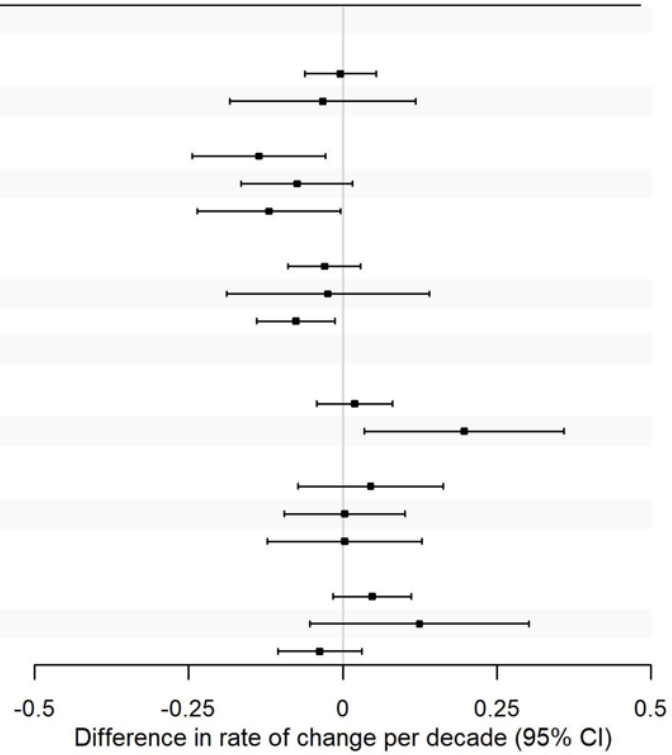


Association of Baseline Lifestyle Risk Factors with Changes in Plasma Biomarkers of ADRD over an Average of 15 Years

Longitudinally,

- No lifestyle risk factor was associated with changes in NfL or GFAP

Cardiovascular Risk Factor	Exposure × time β (95% CI)	FDR-adjusted P-value
NfL		
Smoking status		
Past smoker	-0.004 (-0.062, 0.054)	.90
Current smoker	-0.033 (-0.183, 0.118)	.86
Alcohol use		
Past drinker	-0.136 (-0.244, -0.028)	.08
Current drinker (< 7 drinks per week)	-0.074 (-0.165, 0.016)	.22
Current drinker (≥ 7 drinks per week)	-0.120 (-0.236, -0.004)	.14
Sleep duration		
<7 hours	-0.030 (-0.089, 0.029)	.53
>8 hours	-0.024 (-0.188, 0.140)	.86
MVPA (≥ 7.5 MET-hours/week)	-0.076 (-0.139, -0.013)	.08
GFAP		
Smoking status		
Past smoker	0.019 (-0.043, 0.081)	.78
Current smoker	0.197 (0.035, 0.358)	.11
Alcohol use		
Past drinker	0.045 (-0.072, 0.162)	.73
Current drinker (< 7 drinks per week)	0.003 (-0.095, 0.101)	.96
Current drinker (≥ 7 drinks per week)	0.003 (-0.122, 0.129)	.96
Sleep duration		
<7 hours	0.048 (-0.016, 0.111)	.43
>8 hours	0.124 (-0.053, 0.301)	.43
MVPA (≥ 7.5 MET-hours/week)	-0.037 (-0.105, 0.031)	.52



Effect Modification

- Associations of cardiovascular risk factors and changes in plasma GFAP were modified by age group.

	Age ≤ 70 yrs		Age > 70 yrs		
Risk Factors	**β (95% CI)**	**P-value**	**β (95% CI)**	**P-value**	**P-Interaction**
Hypertension	0.092 (0.017, 0.166)	.02	0.151 (0.042, 0.260)	.007	<.001
Total Cholesterol ≥ 200 mg/dL	0.001 (0.000, 0.002)	.05	0.000 (-0.001, 0.002)	.63	<.001
LDL Cholesterol ≥ 100 mg/dL	0.001 (0.000, 0.002)	.04	0.000 (-0.001, 0.002)	.59	<.001
Smoking Status					
Past Smoker	0.016 (-0.059, 0.091)	.68	0.006 (-0.100, 0.112)	.91	.009
Current Smoker	0.197 (0.024, 0.370)	.03	-0.071 (-0.578, 0.435)	.78	
Sleep Duration					
<7 hours	0.096 (0.018, 0.174)	.02	-0.042 (-0.148, 0.065)	.44	<.001
>8 hours	0.167 (-0.061, 0.396)	.15	0.076 (-0.197, 0.350)	.58	

Effect Modification

- Associations of cardiovascular risk factors with changes in plasma biomarkers did not significantly vary by APOE genotype.

Sensitivity Analyses

Results were consistent with the primary analyses after

- Excluding women with CVD at baseline
- Removing extreme outliers (5-SD above the mean) instead of using winsorization
- Excluding women with eGFR < 60 mL/min/1.73m^2

Discussion

Strengths

- Large sample size with longitudinal measurements of plasma ADRD biomarkers spanning an average of 15 years.
- Comprehensive set of modifiable cardiovascular risk factors and plasma ADRD biomarkers, including p-tau217 which few studies have examined.

Limitations:

- Included cognitively unimpaired women 65 years or older only.
- Plasma ADRD biomarkers were measured up to two time points.

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Plasma ADRD biomarkers and all-cause and cause-specific mortality in WHIMS

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WHI Meeting May 8, 2026

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Plasma Biomarkers of AD-Related Pathology

- have shown promise for detecting latent AD pathology and for predicting cognitive decline and dementia
- associations with mortality are less well understood

Objective: Determine the association of AD-specific biomarkers (Aβ42/Aβ40, p-tau181, p-tau217) and non-specific biomarkers (NfL, GFAP) with all-cause and cause-specific mortality among WHIMS women.

Study Population

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7,479 women in the Women's Health Initiative Memory Study

→ 4,643 women not selected for the plasma biomarker sample

↓

2,836 women selected

- 1,334 with incident MCI or probable dementia through 2021.
- 1,502 women without MCI or probable dementia
  - 565 women enrolled in WHIMS-ECHO
  - 519 women with brain imaging data
  - 707 women from underrepresented population

→ 52 women excluded due to incomplete plasma biomarker data

↓

2,784 women with complete plasma biomarker data

Shadyab & McEvoy R01AG079149

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Ascertainment of Cause of Death

Cause of death was determined by centralized review of medical records and death certificates at each WHI clinical center

All-cause mortality: death from any cause

- **Dementia mortality:** deaths attributed to any form of dementia
- **CVD mortality:** deaths from possible or definite coronary heart disease, cerebrovascular disease, other cardiovascular conditions, or unknown cardiovascular causes
- **Cancer mortality:** deaths due to any type of cancer
- **Other-cause mortality:** deaths not classified as dementia, cancer, or CVD

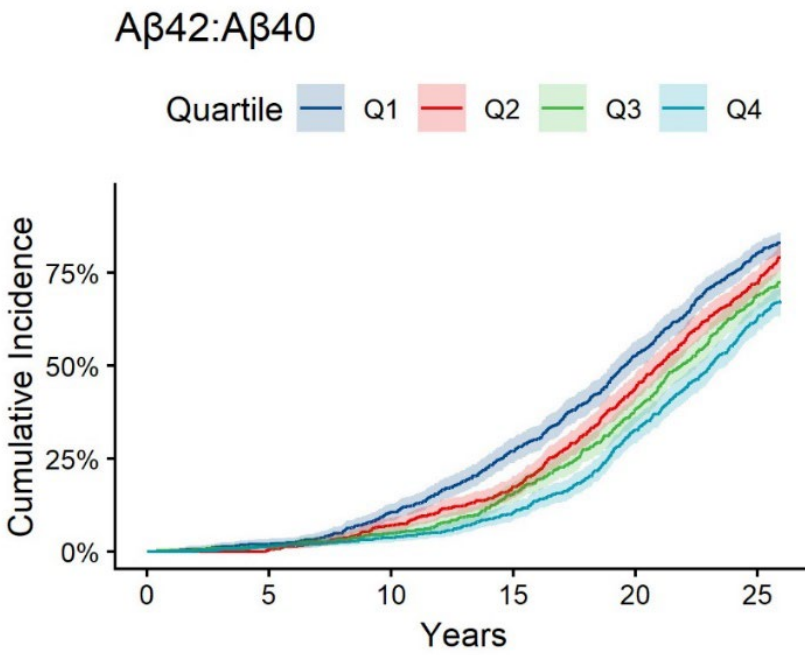
Statistical Approach

- Biomarker values were winsorized at the 99th percentile, log_2-transformed, then z-scored
- Kaplan-Meier methods to estimate cumulative incidence of all-cause mortality
- Cox proportional hazards models to estimate association of each biomarker with all-cause mortality, incorporating weights to account for the sampling design
- Models adjusted for race, ethnicity, hormone therapy trial arm, education, BMI, and eGFR
- In secondary analyses, Fine-Gray subdistribution hazard models were used to estimate associations of each plasma biomarker with cause-specific mortality, treating other causes of death as competing events

Sample Characteristics at Baseline Among 2784 WHIMS Women

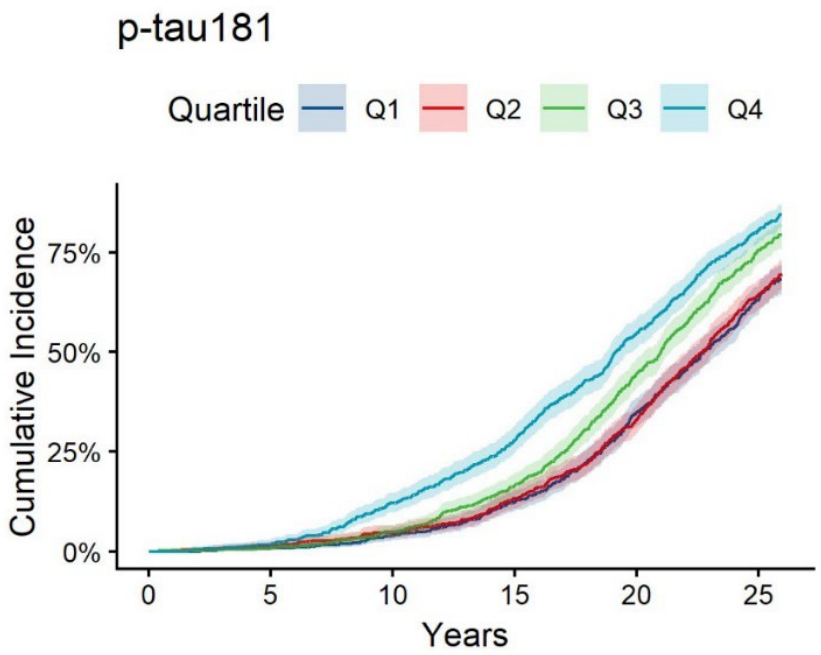
Characteristic	Mean (SD) or No. (%)
Age	70 (4)
College Graduate or Higher	861 (31%)
Race:	
Asian	127 (5%)
Black	505 (19%)
White	1,993 (73%)
Hispanic or Latina	202 (7%)
BMI (kg/m^2)	29 (6)
eGFR (ml/min/1.73 m^2)	84 (14)
APOE ε4 Carrier	486 (27.0%)

Cumulative Incidence of All-Cause Mortality by Biomarker Quartiles



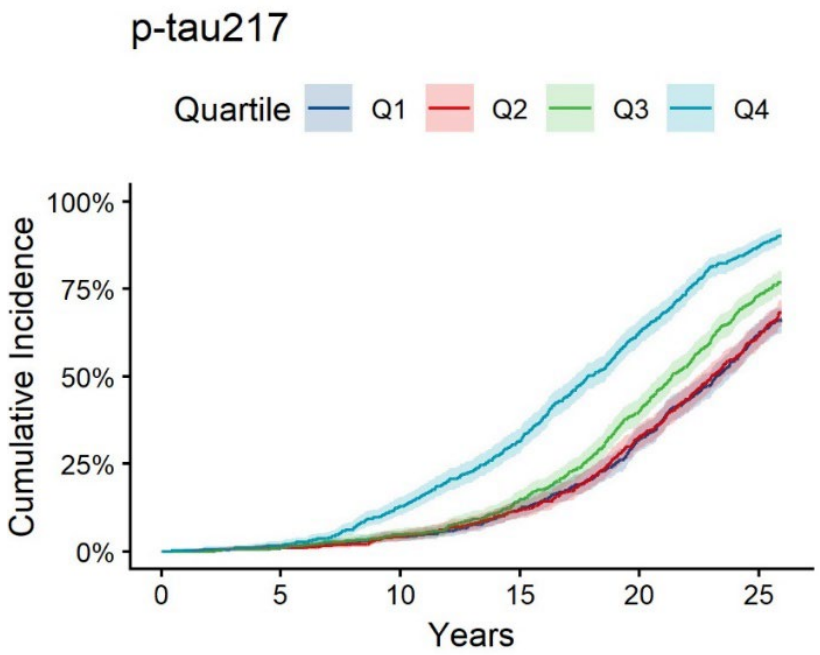
Event: All-cause Mortality

Q1	0	13	70	182	356	541
Q2	0	2	47	116	297	485
Q3	0	8	32	104	259	464
Q4	0	8	24	70	220	425



Event: All-cause Mortality

Q1	0	5	27	83	234	425
Q2	0	9	31	87	220	427
Q3	0	6	33	114	309	520
Q4	0	11	82	188	369	543



Event: All-cause Mortality

Q1	0	6	27	80	215	417
Q2	0	7	28	80	223	417
Q3	0	7	32	100	271	493
Q4	0	11	86	212	423	588

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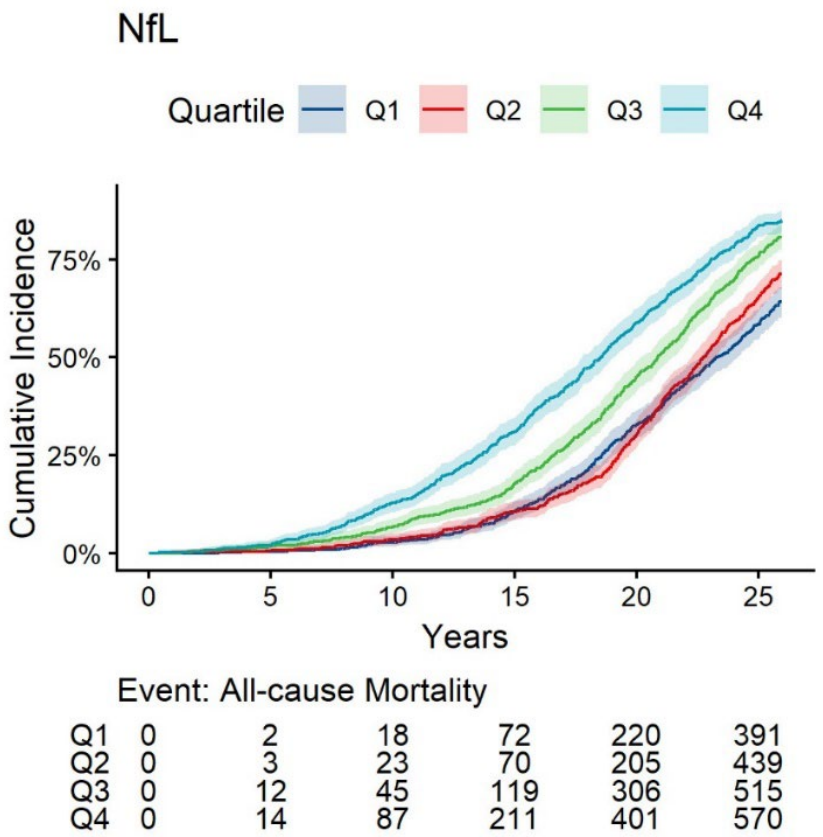
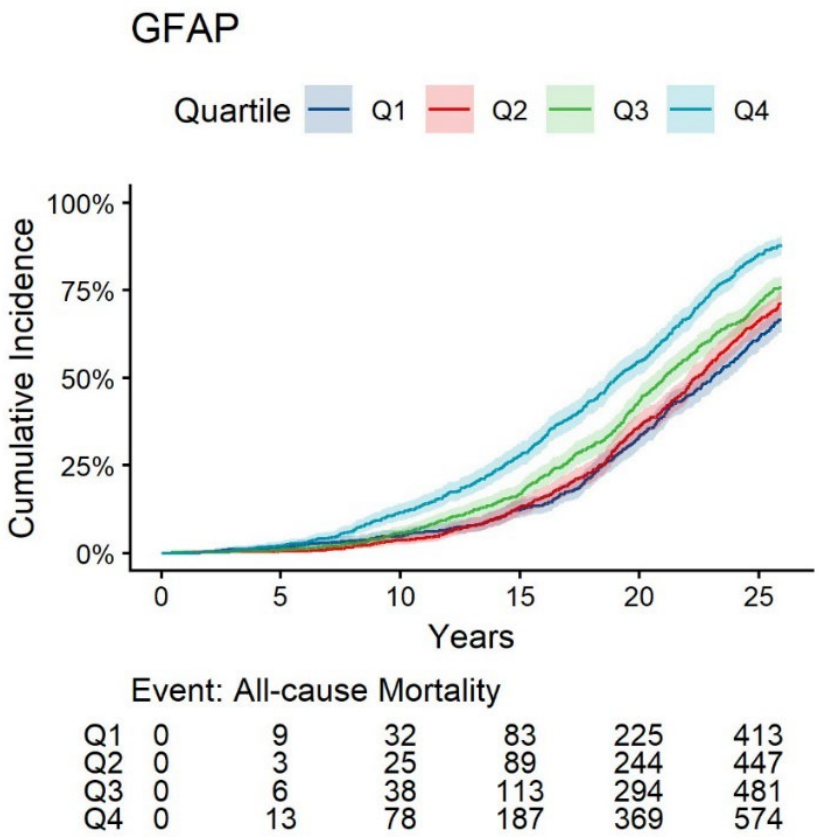
Cumulative Incidence of All-Cause Mortality by Biomarker Quartiles





Associations of Plasma Biomarkers with All-Cause Mortality

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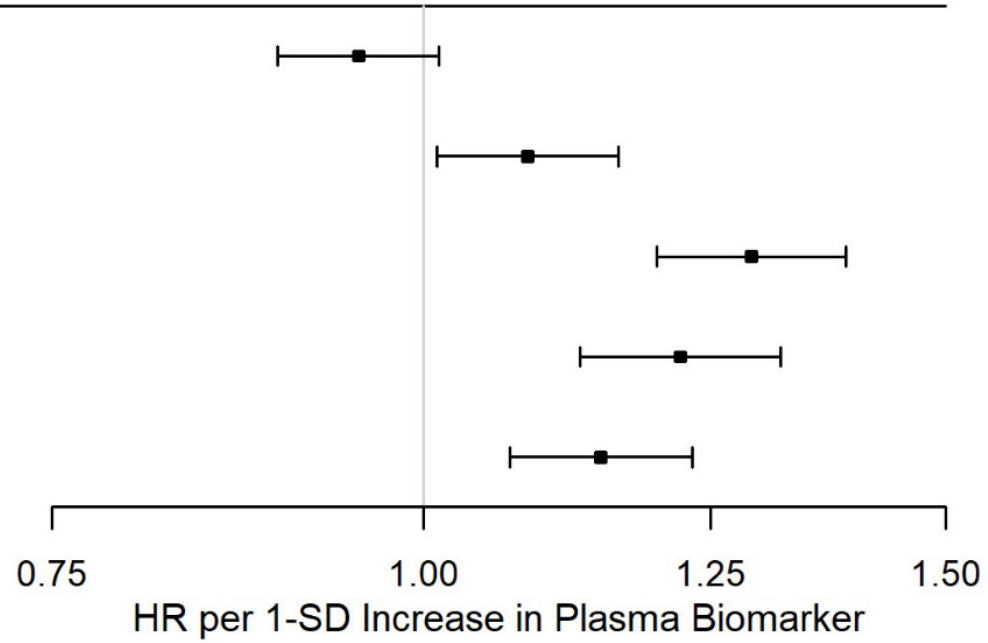
Plasma Biomarker	HR (95% CI)	FDR P-value
Aβ42:Aβ40	0.95 (0.89, 1.01)	.12
p-tau181	1.08 (1.01, 1.16)	.03
p-tau217	1.29 (1.20, 1.39)	<.001
NfL	1.22 (1.13, 1.32)	<.001
GFAP	1.15 (1.07, 1.23)	<.001



Cox proportional hazards regressions models, adjusted for age, race, ethnicity, hormone therapy trial group, education, BMI, and eGFR. Models were weighted to account for biomarker sample selection. The analytic sample included 2700 women after removing those with missing race or ethnicity.

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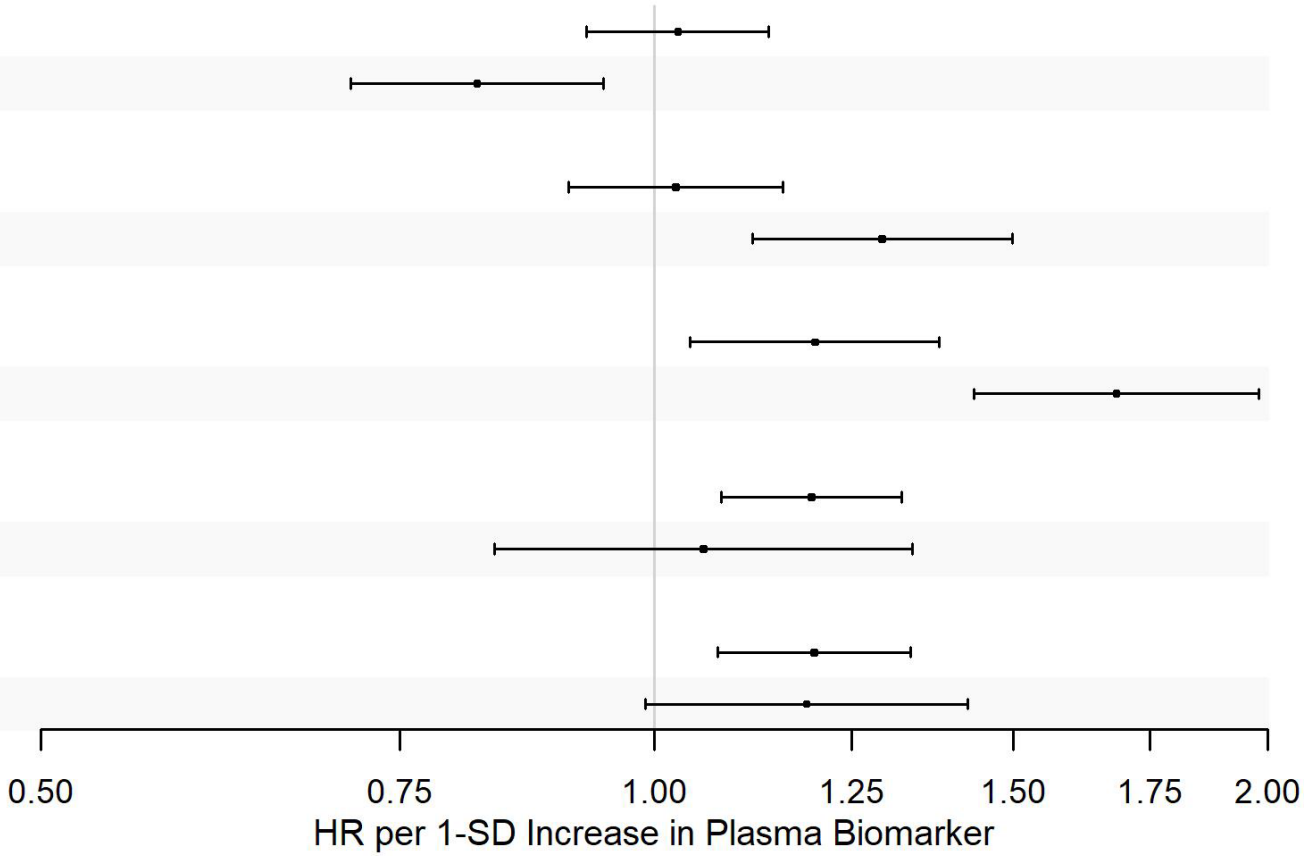
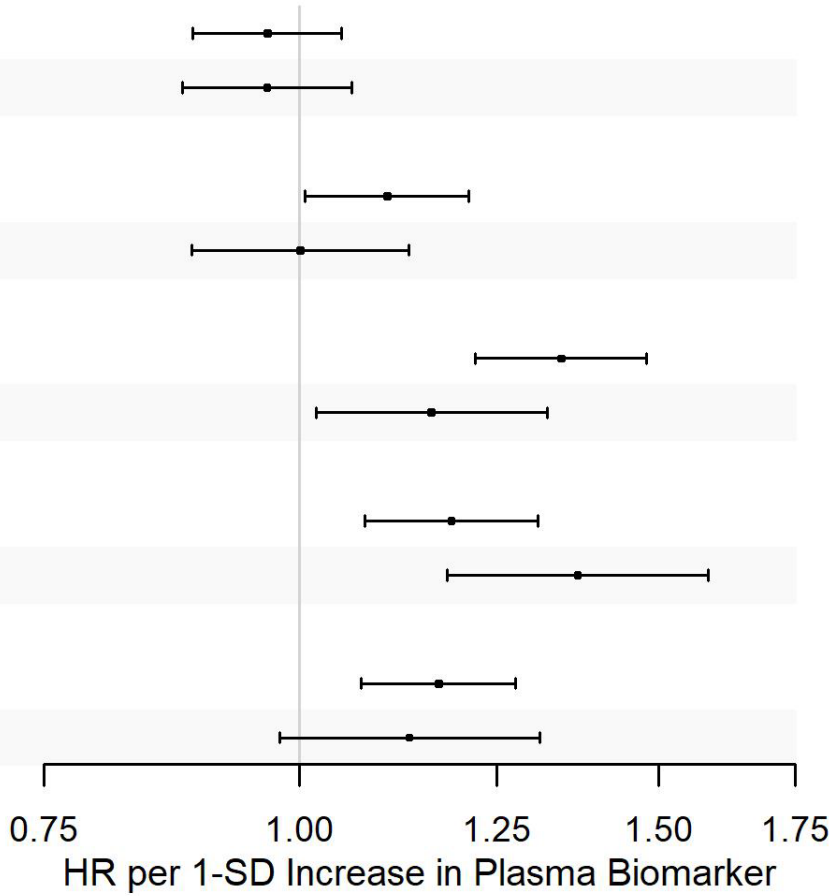
Modification by APOE ε4 Carrier Status

Contrast	HR (95% CI)	P-Interaction
Aβ42:Aβ40		
Non-carrier	1.03 (0.93, 1.14)	.01
Carrier	0.82 (0.71, 0.94)	
p-tau181		
Non-carrier	1.02 (0.91, 1.16)	.007
Carrier	1.29 (1.12, 1.50)	
p-tau217		
Non-carrier	1.20 (1.04, 1.38)	<.001
Carrier	1.69 (1.43, 1.98)	
NfL		
Non-carrier	1.19 (1.08, 1.32)	.14
Carrier	1.06 (0.83, 1.34)	
GFAP		
Non-carrier	1.20 (1.07, 1.34)	.93
Carrier	1.19 (0.99, 1.42)	



Modification by Race

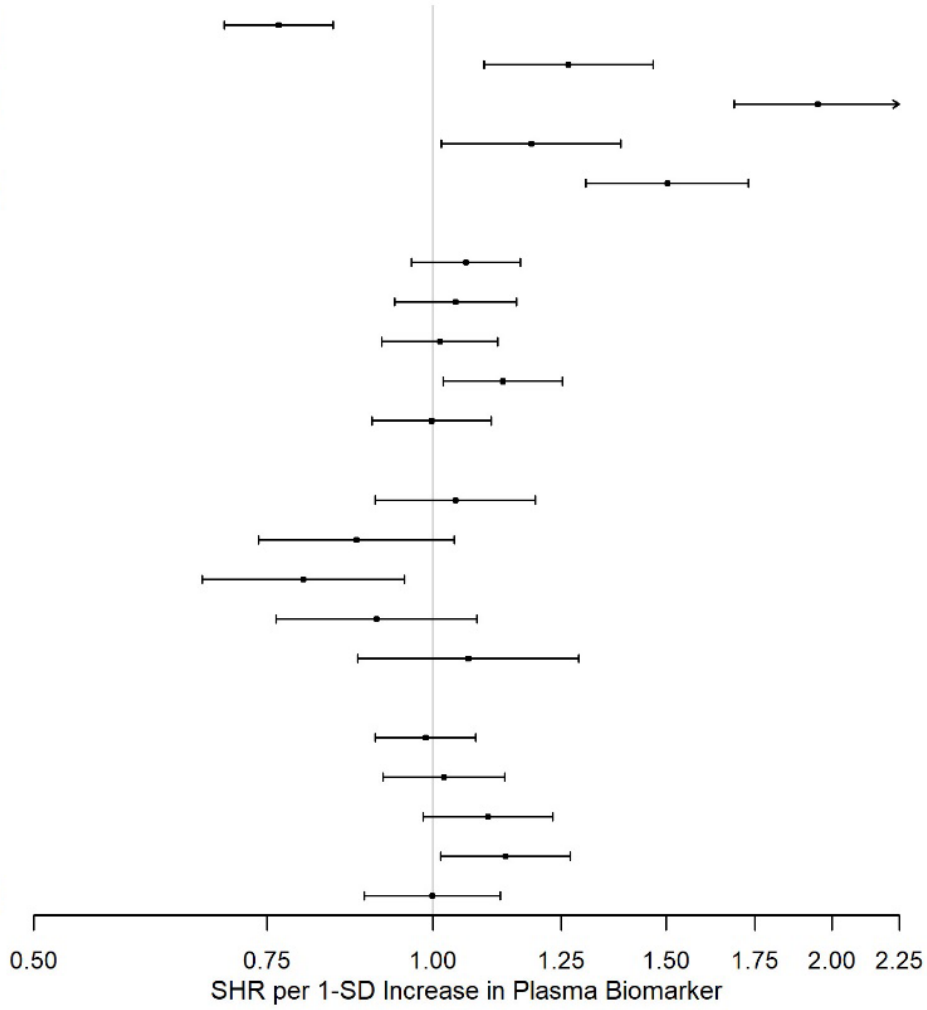
Contrast	HR (95% CI)	P-Interaction
Aβ42:Aβ40		
White	0.96 (0.89, 1.05)	.99
Black	0.96 (0.88, 1.06)	
p-tau181		
White	1.10 (1.01, 1.21)	.18
Black	1.00 (0.89, 1.13)	
p-tau217		
White	1.34 (1.22, 1.48)	.08
Black	1.16 (1.02, 1.32)	
NfL		
White	1.19 (1.08, 1.31)	.04
Black	1.37 (1.18, 1.59)	
GFAP		
White	1.17 (1.07, 1.28)	.66
Black	1.13 (0.98, 1.31)	



Associations of Plasma Biomarkers with Cause-Specific Mortality

- Subdistribution hazard ratios and 95% confidence intervals from Fine-Gray subdistribution hazard.
- Models were adjusted for age, race, ethnicity, hormone therapy trial group, education, BMI, and eGFR.
- Models were weighted to account for biomarker sample selection.
- The analytic sample included 2700 women after removing those with missing race or ethnicity.

Plasma Biomarker	SHR (95% CI)	P-value
Dementia Death		
Aβ42:Aβ40	0.77 (0.70, 0.84)	<.001
p-tau181	1.27 (1.09, 1.47)	.002
p-tau217	1.95 (1.69, 2.25)	<.001
NfL	1.19 (1.02, 1.39)	.03
GFAP	1.50 (1.30, 1.73)	<.001
CVD Death		
Aβ42:Aβ40	1.06 (0.96, 1.16)	.24
p-tau181	1.04 (0.94, 1.16)	.47
p-tau217	1.01 (0.92, 1.12)	.81
NfL	1.13 (1.02, 1.25)	.02
GFAP	1.00 (0.90, 1.11)	.96
Cancer Death		
Aβ42:Aβ40	1.04 (0.90, 1.19)	.58
p-tau181	0.88 (0.74, 1.04)	.13
p-tau217	0.80 (0.67, 0.95)	.01
NfL	0.91 (0.76, 1.08)	.27
GFAP	1.06 (0.88, 1.29)	.53
Other Death		
Aβ42:Aβ40	0.99 (0.91, 1.08)	.78
p-tau181	1.02 (0.92, 1.13)	.72
p-tau217	1.10 (0.98, 1.23)	.10
NfL	1.13 (1.01, 1.27)	.03
GFAP	1.00 (0.89, 1.12)	>.99



Summary & Conclusions

- Elevated levels of p-tau181, p-tau217, NfL and GFAP at baseline were associated with increased risk of all cause mortality.
- Largest associations were observed for p-tau217; particularly among APOE e4 carriers.
- Differences in NfL associations with all cause mortality between White and Black women may reflect differences in cause of death.

Summary & Conclusions

- All biomarkers were associated with risk of dementia death.
- Elevated NfL was associated with increased risk of CVD mortality and with other causes of death besides CVD, cancer, and dementia; no other biomarker was associated with CVD mortality or mortality from other causes.
- Higher levels of p-tau217 were associated with *decreased* risk of cancer mortality.

Plasma biomarkers are informative not only of dementia risk, but also of mortality risk.

Thank You

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