

Association of Plasma Biomarkers of Alzheimer’s Disease with All-Cause and Cause-Specific Mortality

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Introduction

- Plasma biomarkers of Alzheimer’s disease and related dementias (ADRD) are associated with increased risk of dementia. Less is known about how they relate to all-cause and cause-specific mortality.
- We examined the association of plasma biomarkers with all-cause and cause-specific mortality, examining biomarkers of AD pathology (ratio of amyloid- β 42 to amyloid- β 40 [A β 42: A β 40] phosphorylated tau at threonine 181,[p-tau181], and at 217, [p-tau217], as well as a non-specific biomarker of neural injury, neurofilament light chain protein (NfL), and of inflammation, glial fibrillary acidic protein (GFAP).

Methods

- Biomarkers were measured in plasma samples obtained at baseline (1996-1999) from 2,784 participants of the Women’s Health Initiative Memory Study (WHIMS).
- Deaths were ascertained through 02/17/2024. Cause of death was determined by centralized review of medical records and death certificates at each WHI clinical center.
- Primary analyses focused on all-cause mortality (2104 deaths), secondary analyses examined cause-specific mortality including mortality due to:
 - Dementia:** deaths attributed to any form of dementia (n=422)
 - CVD:** deaths from possible or definite coronary heart disease, cerebrovascular disease, other cardiovascular conditions, or unknown cardiovascular causes (n=755)
 - Cancer:** deaths due to any type of cancer (n=249)
 - Other-causes:** deaths not classified as dementia, cancer, or CVD (n=678)
- Separate cox proportional hazards models were used to estimate association of each biomarker with all-cause mortality.
- Fine-Gray subdistribution hazard models were used to estimate associations of each biomarker with cause-specific mortality, treating other causes of death as competing events.
- All models adjusted for race, ethnicity, hormone therapy trial arm, education, BMI, and eGFR.

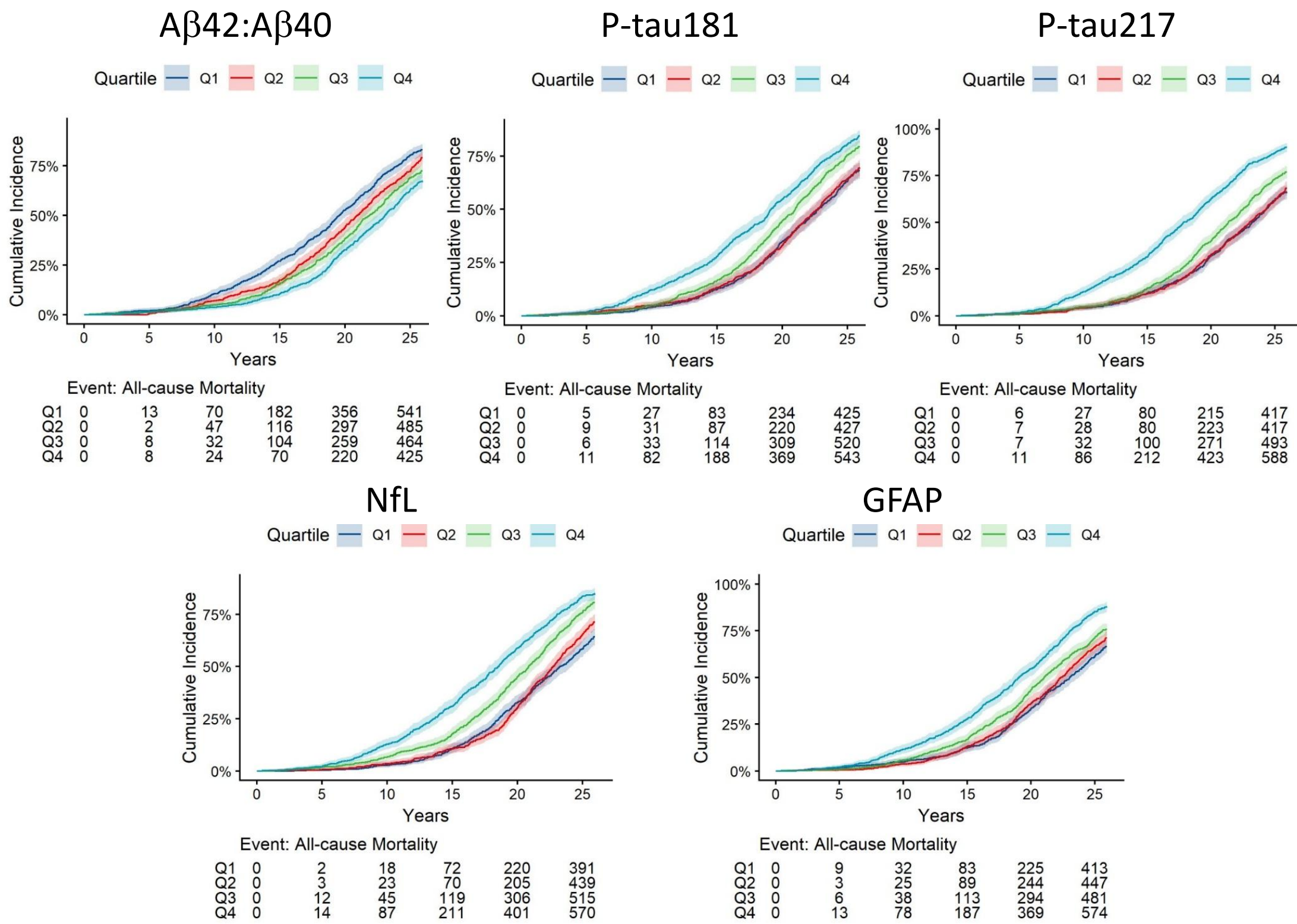
Characteristics of 2784 WHIMS Participants at Baseline

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)
Hypertension	1874 (7%)
Diabetes	196 (7%)
Cardiovascular Disease	134 (5%)
APOE ϵ 4 Carrier	486 (27%)

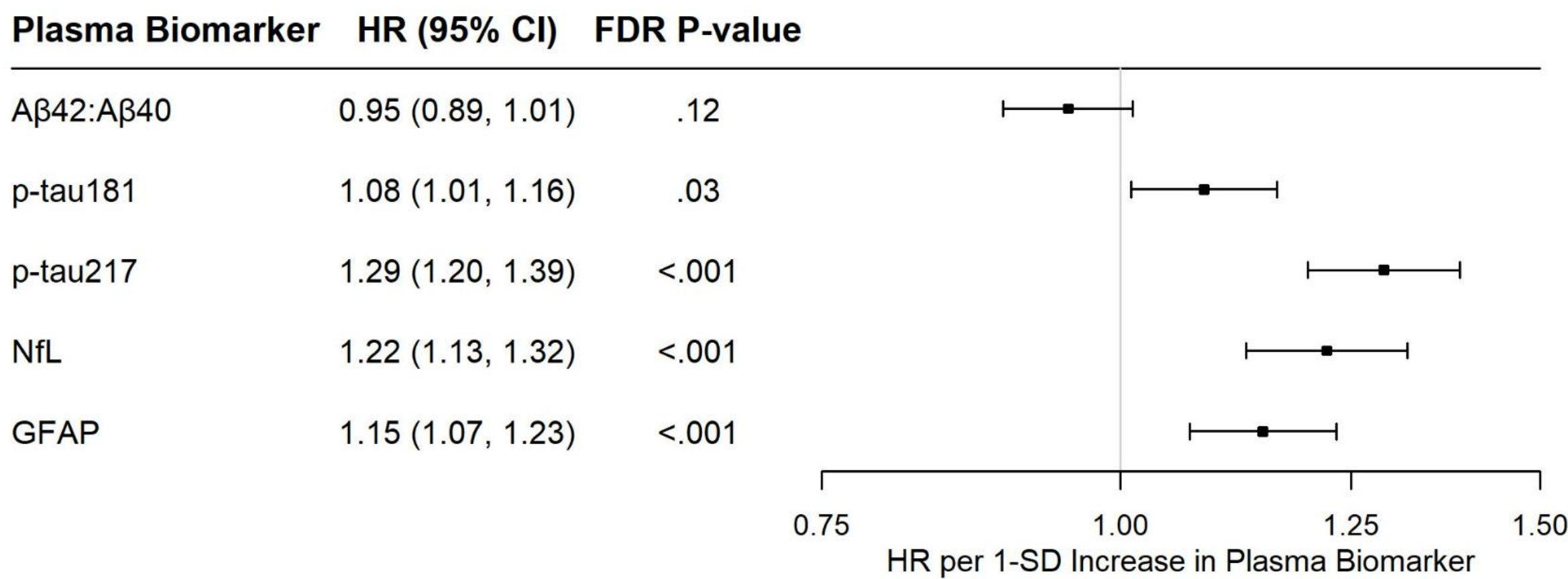
Results

Biomarker Associations with All-Cause Mortality

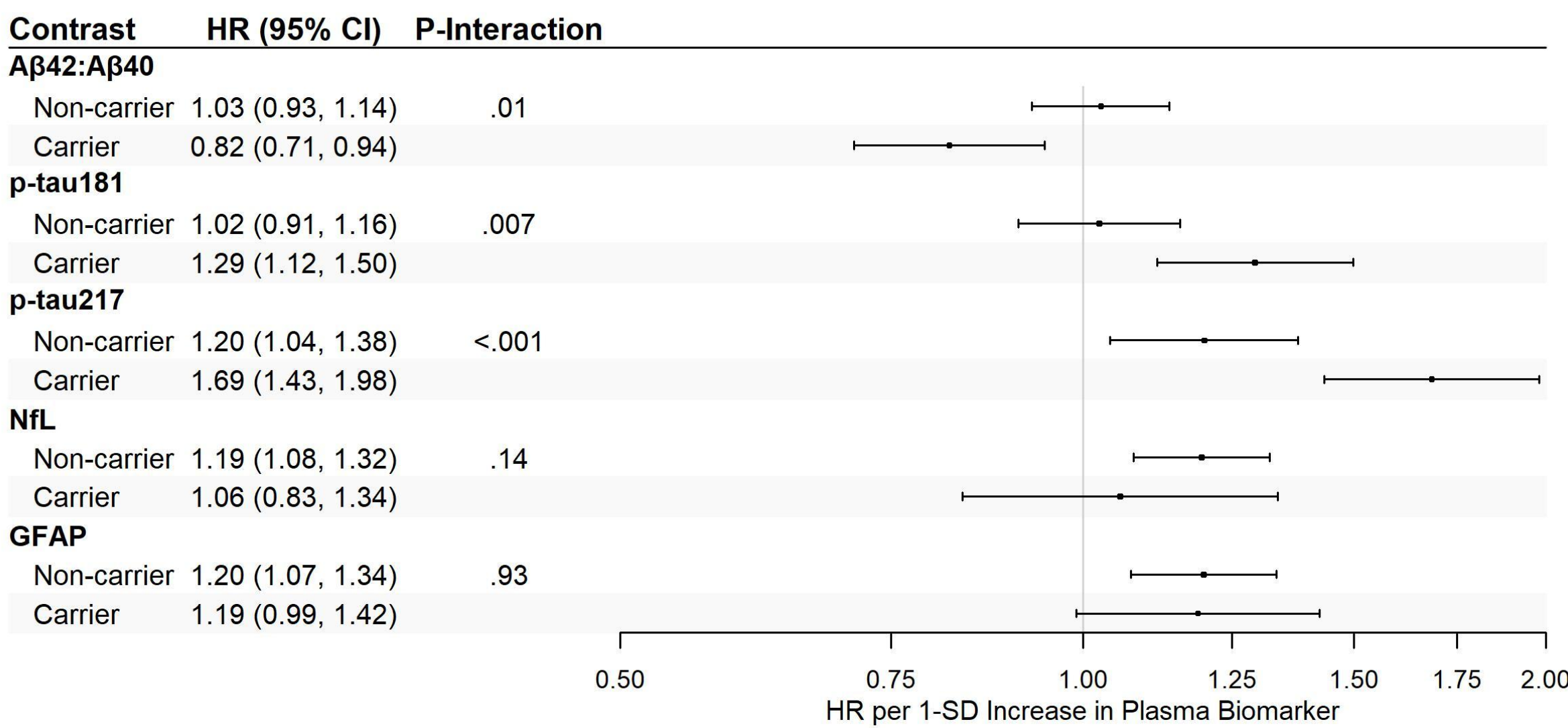
Kaplan Meier Cumulative Incidence of All-Cause Mortality by Biomarker Quartiles



Cox Proportional Hazard Models of Biomarker Association with All-Cause Mortality



Biomarker Associations with All-Cause Mortality Stratified by APOE ϵ 4 Carrier Status

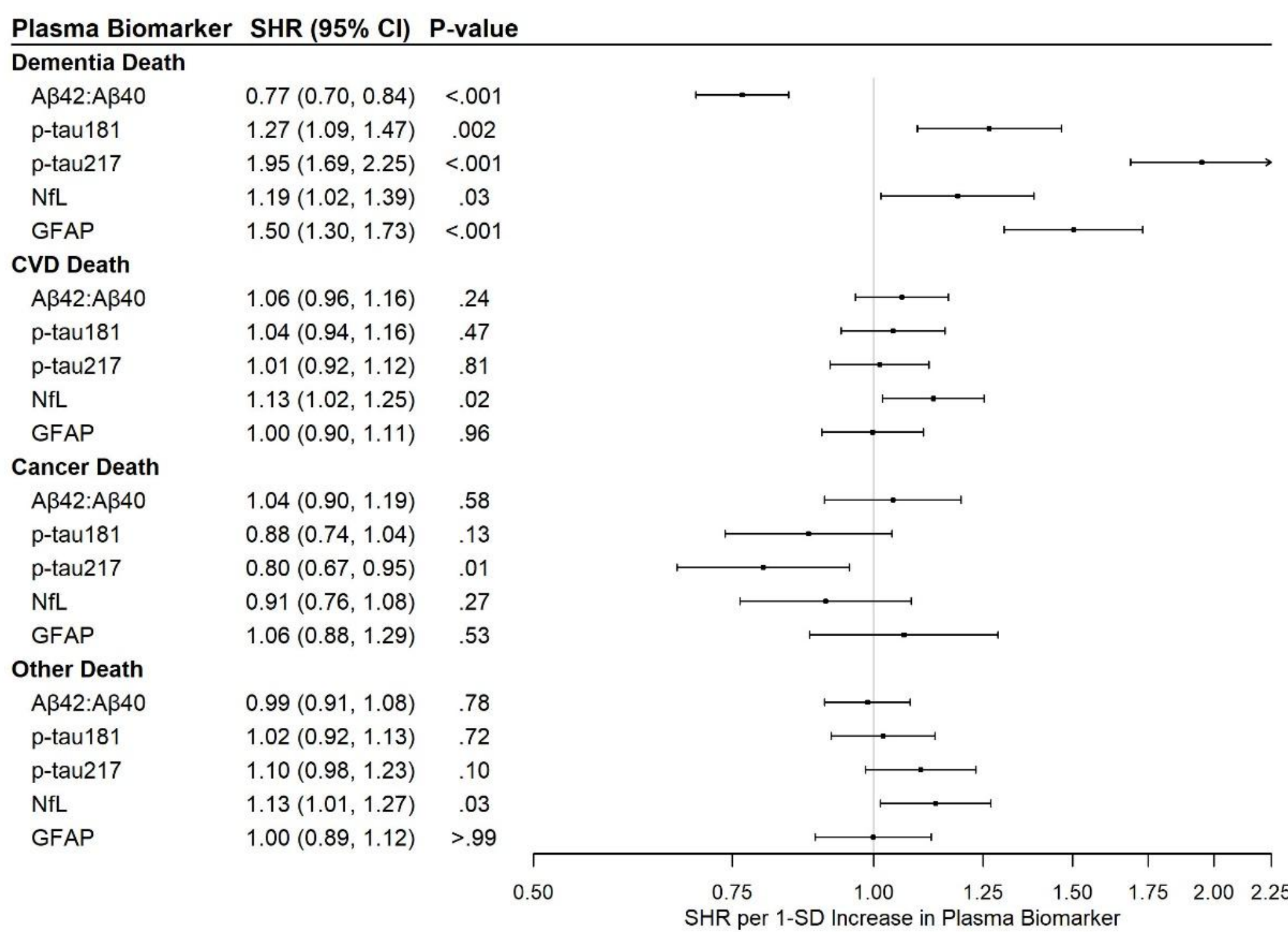


Higher levels of pathology at baseline were associated with increased risk for all-cause mortality, with the largest association for p-tau217. Associations were stronger among APOE ϵ 4 carriers than non-carriers for A β 42:A β 40, p-tau181 and p-tau217.

Results

Biomarker Associations with Cause-Specific Mortality

Subdistribution Hazard Ratios of Association of Each Biomarker with Cause-Specific Mortality



All biomarkers were associated with dementia mortality. NfL was also associated with CVD mortality and mortality due to other causes. P-tau217 was inversely associated with cancer mortality.

Summary and Conclusions

ADRD biomarker levels reflective of higher pathology at baseline were associated with increased risk of all cause mortality. Largest associations were observed for p-tau217.

Associations of AD-specific biomarkers with all-cause mortality were larger among APOE ϵ 4 carriers than non-carriers; APOE ϵ 4 status did not modify associations of NfL or GFAP with all-cause mortality.

All biomarkers were associated with risk of dementia mortality.

Elevated NfL was associated with increased risk of CVD mortality and with causes of death other than 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, consistent with prior findings of inverse associations between risk of Alzheimer’s disease and of cancer.

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

Please see our companion poster P#3437: Associations of plasma biomarkers of Alzheimer’s pathology with cognitively healthy longevity. (Tuesday, July 14).

Supported by National Institutes of Health (NIH), National Institute on Aging R01AG074345; content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH