

Associations of plasma biomarkers of Alzheimer’s pathology with cognitively healthy longevity

Bowei Zhang, MS¹; Andrea Z. LaCroix, PhD¹; Susan M. Resnick, PhD²; Steve Nguyen, PhD¹; Towia A. Libermann, PhD³; Long Ngo, PhD³; Ramon Casanova, PhD⁴; Alexander P. Reiner, MD, MS⁵; Danni Li, PhD⁶; Caroline M. Nievergelt, PhD¹; Adam X. Maihofer, PhD¹; Linda K. McEvoy, PhD⁷; Aladdin H. Shadyab, PhD¹

¹ University of California San Diego, La Jolla, CA, USA; ² University of Pennsylvania, Philadelphia, PA, USA; ³ Harvard University, Boston, MA, USA; ⁴ Wake Forest University, Winston-Salem, NC, USA; ⁵ University of Washington, Seattle, WA, USA; ⁶ University of Minnesota, Minneapolis, MN, USA; ⁷ Kaiser Permanente Washington Health Research Institute, Seattle, WA, USA



Introduction

- The aging of the population has been accompanied by an increase in the prevalence of Alzheimer’s disease (AD).
- Plasma biomarkers of Alzheimer’s disease and related dementias (ADRD) have previously been investigated in relation to cognitive decline and dementia risk; however, their associations with cognitively healthy longevity remain unclear.

Objective

To evaluate whether plasma ADRD biomarkers were associated with:

- Survival to age 90 vs. death before age 90
- Survival to age 90 without cognitive impairment vs survival to age 90 with cognitive impairment

Methods

- 2760 cognitively unimpaired women, born on or before February 28, 1934, enrolled into the Women’s Health Initiative Memory Study (WHIMS) in 1996-1999 and followed through 2024.
- P-tau217, p-tau181, GFAP, NfL, and Aβ42:Aβ40 measured using Simoa assays
- Outcomes included: 1) exceptional longevity (survival to age 90 vs death before age 90); 2) cognitively healthy longevity (survival to age 90 without cognitive impairment vs survival to age 90 with cognitive impairment)
- We used cognitive assessments within 3 years of the 90th birth year to identify cognitive status at age 90
- We used logistic regression models to examine associations of plasma ADRD biomarkers with the outcomes
- Models were adjusted for age, race, ethnicity, education, hormone trial arm, smoking, physical activity, BMI, diabetes, cardiovascular disease, non-melanoma cancer, eGFR, total cholesterol, HDL cholesterol, and hypertension.

Please see our companion poster, #3273: Associations of ADRD plasma biomarkers with all-cause and cause-specific mortality.

Results

Table 1. Baseline characteristics (N = 2,760)

Characteristic	Mean (SD) or No. (%)
Age	69.9 (3.8)
White	1,976 (73.2%)
Hispanic or Latino	199 (7.3%)
Physical activity (MET-hours/week)	11.5 (13.6)
BMI	28.6 (5.6)
Current smoker	150 (5.5%)
College graduate or higher	852 (31.0%)
Diabetes	196 (7.1%)
Cardiovascular disease	135 (4.9%)
Non-melanoma cancer	239 (8.7%)
Hypertension	1,957 (71.2%)
eGFR (ml/min/1.73 m²)	83.6 (13.6)
Total cholesterol (mg/dL)	233.6 (39.5)
HDL cholesterol (mg/dL)	54.0 (13.0)
APOE ε2 carrier	226 (14.8%)
APOE ε4 carrier	400 (26.2%)

Abbreviations: APOE ε2, apolipoprotein E epsilon 2 allele; APOE ε4, apolipoprotein E epsilon 4 allele; BMI, body mass index; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; MET-hour, metabolic equivalent of task hour.

- A total of 986 women died before reaching age 90. Of the 1,774 women who survived to age 90, 1,261 women had cognitive assessments within 3 years of the 90th birth year: 683 survived to age 90 with cognitive impairment, and 588 survived to age 90 without cognitive impairment.

Elevated levels of baseline plasma p-tau181, p-tau217, NfL, and GFAP were associated with lower odds of survival to age 90 vs death before age 90 (Figure 1).

Among women who survived to age 90, higher levels of pathology measured by Aβ42:Aβ40, p-tau181, p-tau217, and GFAP were associated with reduced odds of surviving to age 90 without cognitive impairment vs. survival to age 90 with cognitive impairment.

Figure 1. Odds Ratios Relating Plasma ADRD Biomarkers to Survival to Age 90

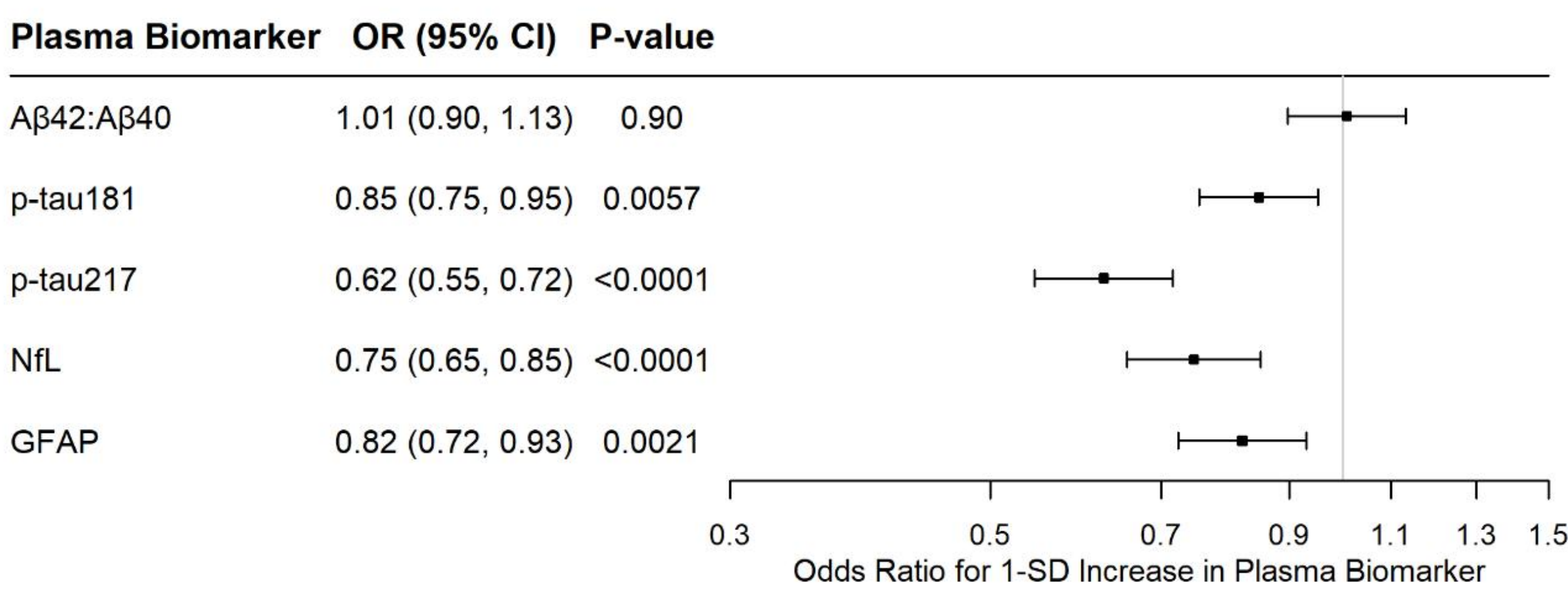
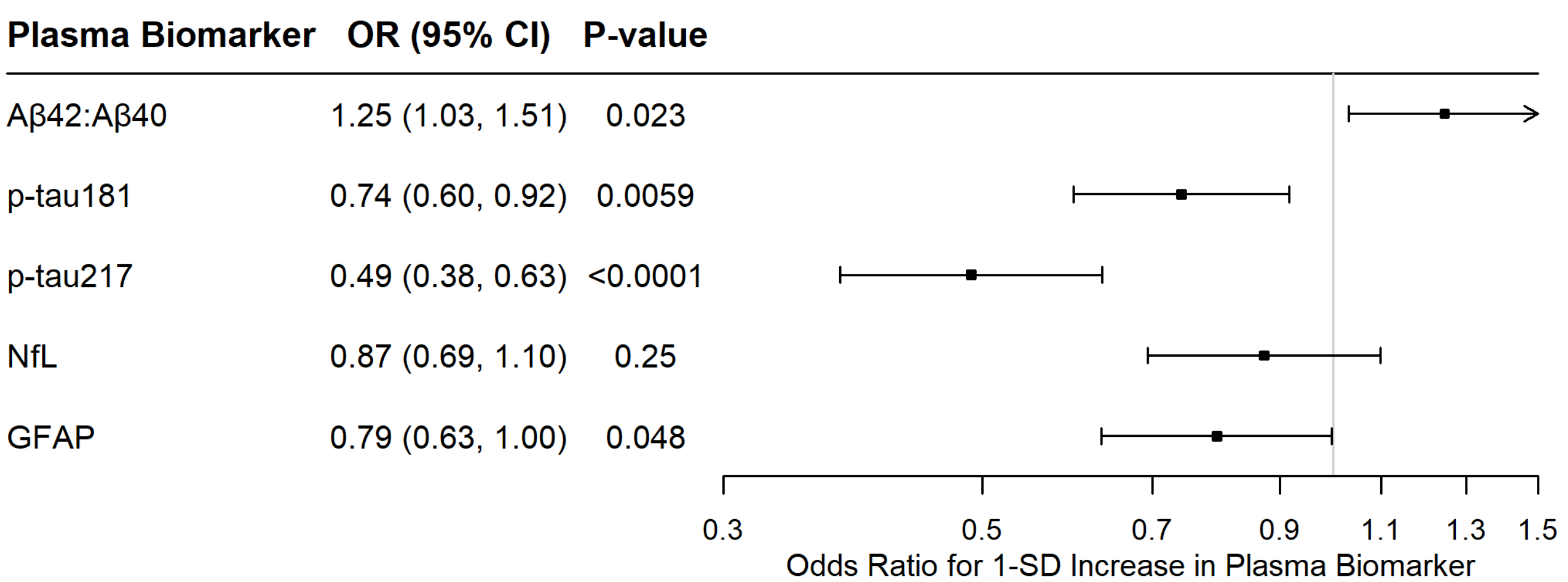


Figure 2. Odds Ratios Relating Plasma ADRD Biomarkers to Survival to Age 90 without Cognitive Impairment



Odds ratios (OR) are reported per 1-SD increase in log₂ of plasma biomarker: Aβ42:Aβ40 (SD 0.32), p-tau181 (SD 0.55), p-tau217 (SD 0.81), NfL (SD 0.58), and GFAP (SD 0.63).

Conclusions

Higher pathology as measured by plasma ADRD biomarkers at around age 70 was associated with lower odds of living to age 90 and of remaining cognitively healthy at age 90. Associations were largest for elevated p-tau217. P-tau217 may be useful for predicting exceptional longevity and cognitively healthy longevity.