Plasma p-tau217 Above and Below Validated Alzheimer Cutoffs in Cardiovascular Disease: Between-Range vs Within-Range Determinants in BROADWAY

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BACKGROUND

- Plasma phosphorylated tau 217 (p-tau217) is increasingly measured in cardiovascular populations, but ALZpath interpretive cutoffs (low <0.40 pg/mL, uncertain 0.40–0.63 pg/mL, high >0.63 pg/mL) were derived in memory-clinic and research cohorts and validated against amyloid positron emission tomography[1-3]
- It is unknown whether the factors that place a patient with atherosclerotic cardiovascular disease (ASCVD) into a higher p-tau217 range are the same factors that explain variation within a range

OBJECTIVE

To compare the determinants of baseline p-tau217 range with the determinants of variation within each range in patients with ASCVD or heterozygous familial hypercholesterolemia (HeFH)

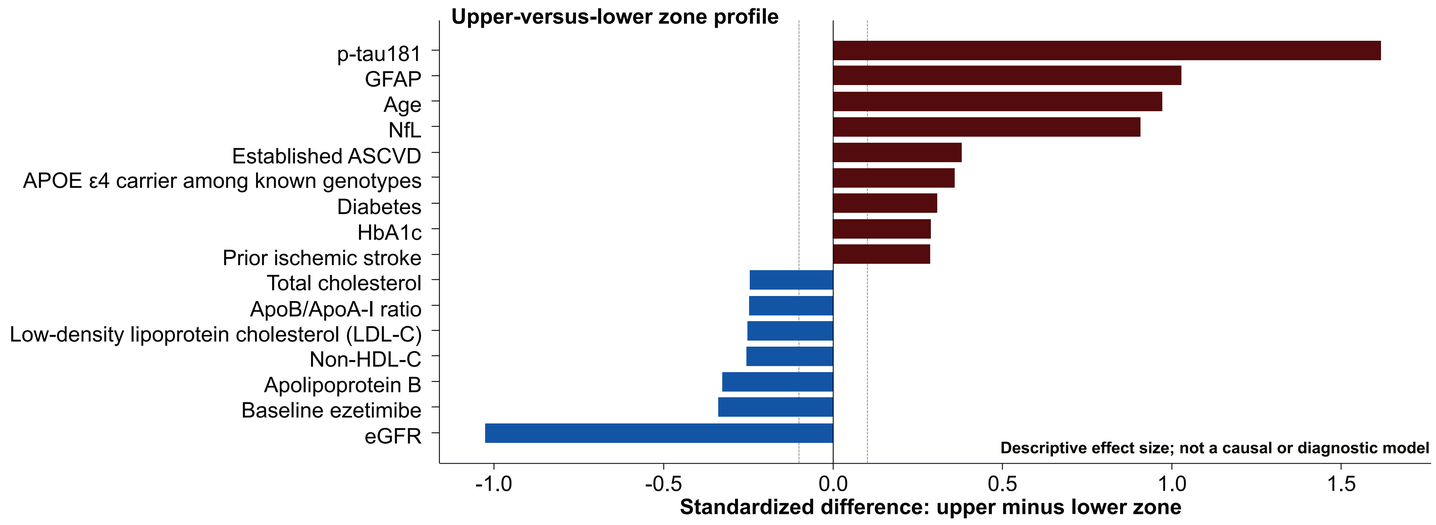
METHODS

- A cross-sectional analysis was conducted in 1,861 participants (73.5% of randomized participants) with a measured baseline p-tau217 in BROADWAY (NCT05142722), a phase 3, randomized, double-blind, placebo-controlled lipid-lowering therapy trial
  - Participants were classified by ALZpath p-tau217 range as low (<0.40 pg/mL), uncertain (0.40-0.63 pg/mL), or high (>0.63 pg/mL); values of exactly 0.40 or 0.63 pg/mL were assigned to the uncertain range
- Ranges were compared descriptively, then log-transformed p-tau217 was modeled within each range by ordinary least squares (OLS) with robust heteroskedasticity-consistent 3 (HC3) standard errors, adjusted for age, sex, apolipoprotein E (APOE) status, and estimated glomerular filtration rate (eGFR)
  - Sixteen factors were tested in each range (48 tests), with Benjamini-Hochberg correction within range and across all 48 tests
  - Each group of factors was added to a model containing age, sex, and APOE, and we measured how much it improved prediction of p-tau217 in participants whose data were not used to fit the model
  - Four Alzheimer's disease (AD)-related biomarkers measured at baseline (p-tau181, glial fibrillary acidic protein [GFAP], neurofilament light [NfL], and amyloid-β 42:40 ratio [Aβ42:40]) were evaluated for their association with p-tau217
  - Because ranges are defined by p-tau217 itself, they are not independent cohorts, and within-range associations are descriptive

RESULTS

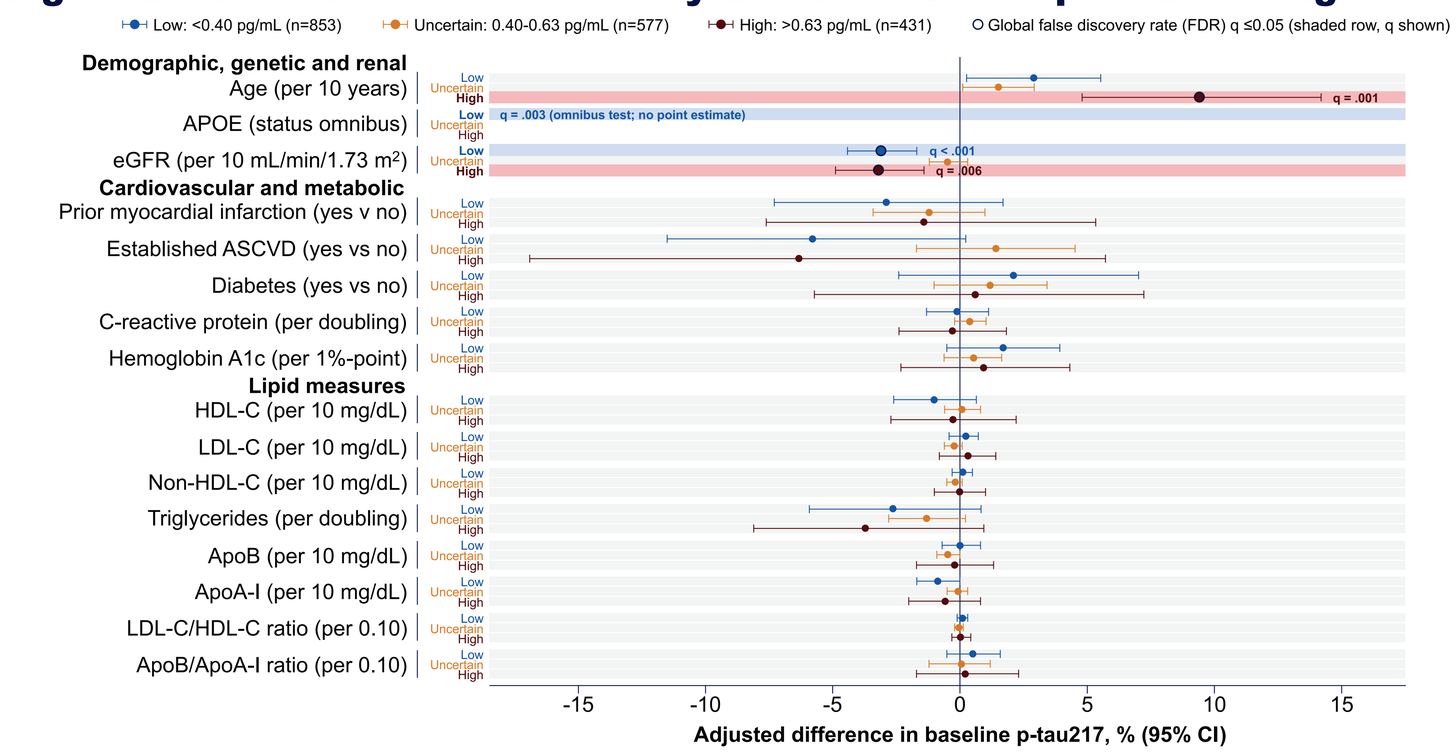
- Of 1,861 participants, 853 (45.8%) were in the low range, 577 (31.0%) in the uncertain range, and 431 (23.2%) in the high range for p-tau217
- Between p-tau217 ranges, kidney function declined stepwise and prior ischemic stroke frequency increased; higher age and APOE ε4 carriage also characterized the high versus low range **(Figure 1)**
- Among the 16 prespecified factors, APOE status in the low range, age in the high range, and eGFR in the low and high ranges were significantly associated with within-range variation in baseline p-tau217 after both within-range and global multiplicity correction **(Figure 2)**
- The companion AD biomarker block provided the greatest incremental predictive value across all p-tau217 ranges **(Figure 3)**
  - Most of this signal came from p-tau181, a closely related p-tau measured in the same sample, so it largely reflects shared analyte biology and assay variance rather than independent confirmation
  - GFAP, NfL, and Aβ42:40 added meaningful predictive value primarily in the high range
- Diabetes, hemoglobin A1c (HbA1c), C-reactive protein (CRP), and all 8 lipid measures showed no independent association with p-tau217 in any range (**Figure 2**)
- Testing 48 factors can produce significant results by chance; after correcting for this, both within each range and across all 48 tests, the age, APOE, and eGFR findings still held

Figure 1: Standardized Differences in Prespecified Factors Across ALZpath Baseline Plasma p-tau217 High vs Low Ranges*



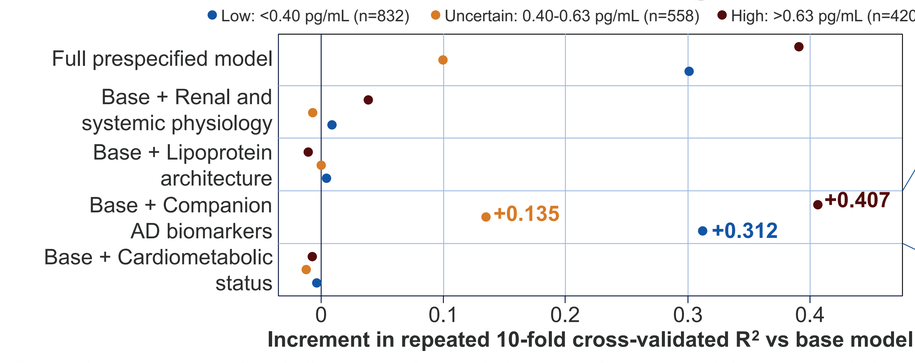
*Unadjusted standardized mean differences. Largest differences: p-tau181 +1.62; GFAP +1.03; eGFR −1.03; age +0.97; NfL +0.91.

Figure 2: Clinical Characteristics by Baseline Plasma p-tau217 Range



Models: HC3 OLS on log baseline p-tau217, adjusted for age, sex, APOE status, and eGFR; the focal factor is omitted from its own adjustment set. APOE is an omnibus test. Ranges are outcome-defined, range-restricted descriptions; BROADWAY has no amyloid truth standard.
Background lipid-lowering therapy was analyzed separately from the 16 prespecified factors. In the low range, no statin versus high-intensity statin was associated with 8.8% higher p-tau217 (q=0.035), a signal not retained on median regression (q=0.140).

Figure 3: How Much Each Group of Factors Improves Prediction of Baseline p-tau217 Within Each Range*



Δ cross-validated R² over a base model of age, sex, and APOE status

Block added	Low	Uncertain	High
Companion AD biomarkers	+0.312	+0.135	+0.407
p-tau181 alone†	+0.318	+0.142	+0.318
GFAP, NfL, Aβ42:40 ratio†	+0.000	−0.003	+0.122

Each point shows how much better p-tau217 was predicted when that group of factors was added to the base model, tested in participants whose data were not used to fit the model. Points further right added more information; points near zero added none.
Base Model: Age, sex, APOE status. Companion AD Biomarkers: p-tau181, GFAP, NfL, Aβ42:40. Renal and Systemic Physiology: eGFR, serum albumin, hemoglobin, urine albumin-to-creatinine ratio, body-mass index. Cardiometabolic Status: Diabetes, HbA1c, CRP. Lipoprotein Architecture: HDL-C, LDL-C, non-HDL-C, triglycerides, ApoB, ApoA-I, LDL-C/HDL-C, ApoB/ApoA-I.
*Figure 3 is restricted to participants with complete data for every variable in all nested models (n=1,810; low 832, uncertain 558, high 420). Comparing the increment in cross-validated R² across nested models requires identical participants and identical cross-validation folds in each model, so 51 participants with incomplete data for one or more model variables are excluded relative to Figure 2.
†Rows 2 and 3 are a breakdown of the companion AD biomarker block in row 1, not additional blocks. They do not sum to row 1 because the components share variance, and adding non-informative predictors can lower cross-validated R².

CONCLUSIONS

- Among patients with ASCVD or HeFH, baseline p-tau217 reflected both AD-related susceptibility and systemic physiology
  - Age, APOE status, renal function, and companion AD blood biomarkers were more informative than cardiovascular history, diabetes, or lipid burden
- These findings support further evaluation of p-tau217–based enrichment while underscoring the need to account for renal function and validate cutpoints against AD pathology

DISCLOSURES
This analysis was funded by NewAmsterdam Pharma. Akash Patel has no financial disclosures. Andrew Hsieh, Adam Johnson, Marc Ditmarsch, John JP Kastelein, and Michael H Davidson are employees of NewAmsterdam Pharma and hold stocks or options. The authors declared no other competing interests.

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1. Davidson MH et al. *J Prev Alzheimers Dis*. 2026;13(1):100394. **2.** French SR et al. *Alzheimers Dement*. 2025;21(8):e70565. **3.** Ashton NJ et al. *JAMA Neurol*. 2024;81(3):255-263.

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