



Metabolic Modifiers of Blood-Based Neurodegeneration, Tau Biomarkers and Cognitive Performance

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Introduction:

- Low-density lipoprotein (LDL-C), total cholesterol (TC), and triglycerides (TG) are modifiable lipid markers that may influence the relationship between blood-based biomarkers of neurodegeneration (neurofilament light [NfL]) and tau pathology (phosphorylated tau-181 [pTau₁₈₁]) and cognitive performance.
- Although these biomarkers are increasingly used to characterize early neurodegeneration, heterogeneity in their cognitive associations persists. Lipid measures are rarely considered when interpreting plasma biomarker–cognition relationships.
- We therefore investigated whether these lipids modify NfL and pTau₁₈₁ associations with cognitive performance.

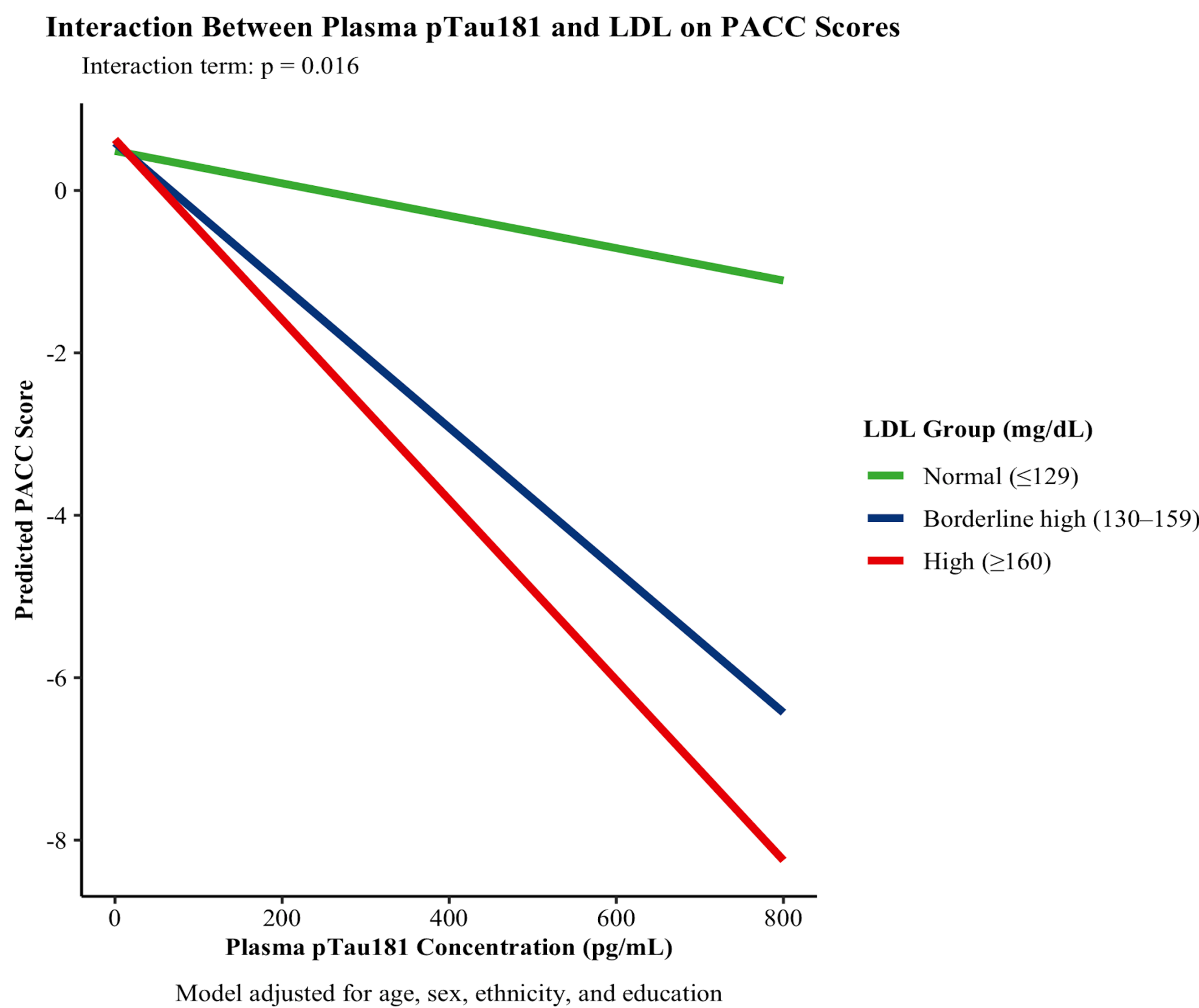
Methods:

- We analyzed cross-sectional baseline data from 2,855 adults aged ≥50 years enrolled in the Health and Aging Brain Study–Health Disparities (HABS-HD).
- Cognitive performance was assessed using the Preclinical Alzheimer Cognitive Composite (PACC). Plasma NfL, pTau₁₈₁, and Aβ₄₂/Aβ₄₀ were quantified on the Quanterix Simoa HD-X platform.
- Lipids were categorized per 2018 ACC/AHA guidelines for LDL-C, TC, and TG; continuous lipid models were examined in sensitivity analyses.
- Generalized linear models evaluated biomarker–cognition associations and biomarker–lipid interactions, adjusted for age, sex, ethnoracial group, and education.
- Additional sensitivity models included HbA1c, creatinine, statin use, and APOE ε4 status.

Results:

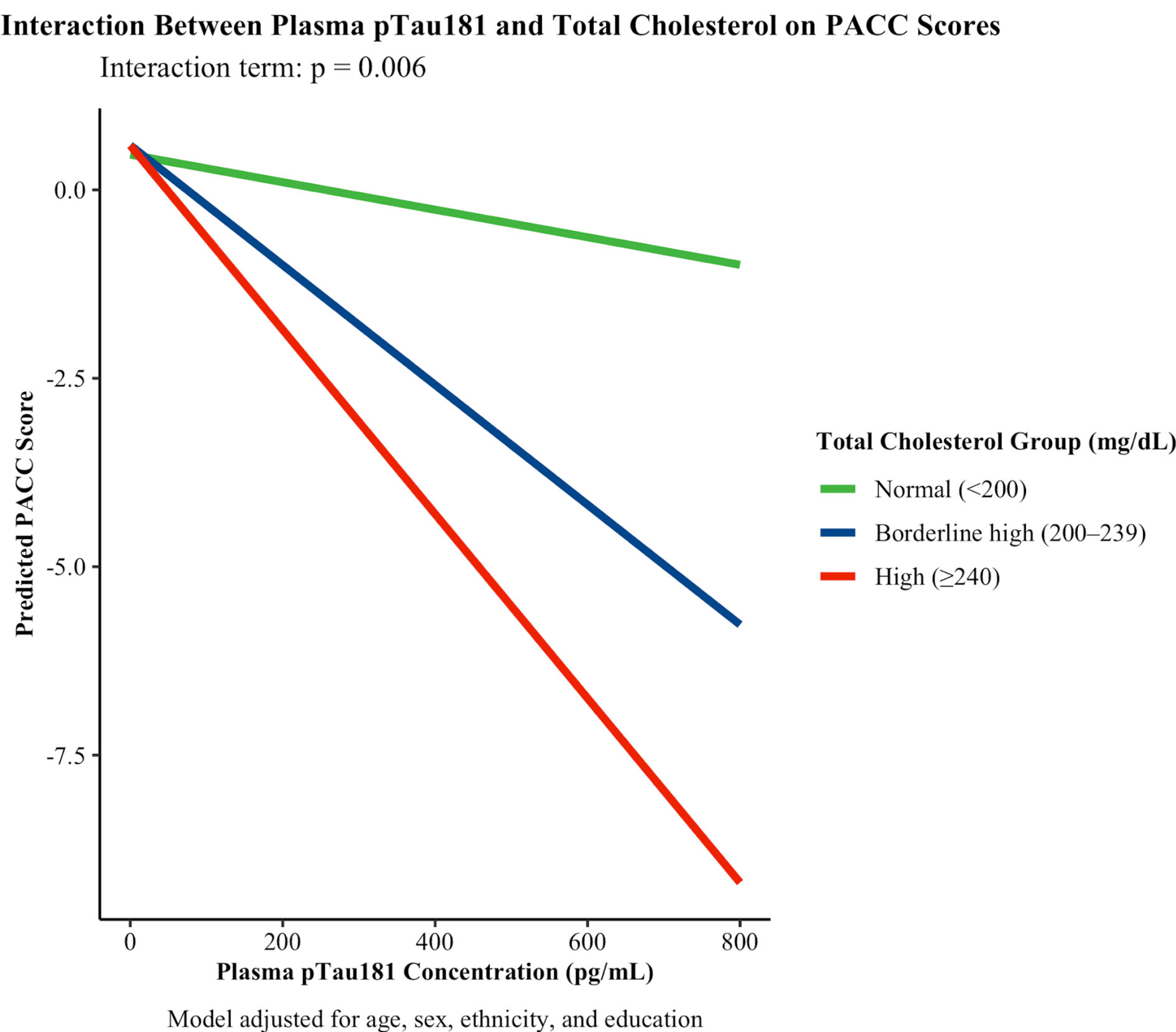
- Among participants (mean age 65.7 years [standard deviation 8.7]; 38.0% men), higher plasma NfL (β −0.005 [SE 0.001]; $p < 0.0001$) and pTau₁₈₁ (β −0.002 [0.001]; $p = 0.004$) were associated with lower PACC scores. Elevated LDL-C strengthened these inverse associations.
- For NfL, a significant interaction was observed at borderline-high LDL-C levels (130–159 mg/dL; β −0.009 [0.003]; $p = 0.004$). For pTau₁₈₁, borderline-high and high LDL-C (≥160 mg/dL) categories significantly strengthened the negative association with PACC.
- TC showed smaller interactions with pTau₁₈₁, whereas TG interactions were not significant. No modifying effects were observed for plasma Aβ₄₂/Aβ₄₀.

Figure 1. Interaction Between Plasma pTau₁₈₁ and LDL-C on PACC Scores



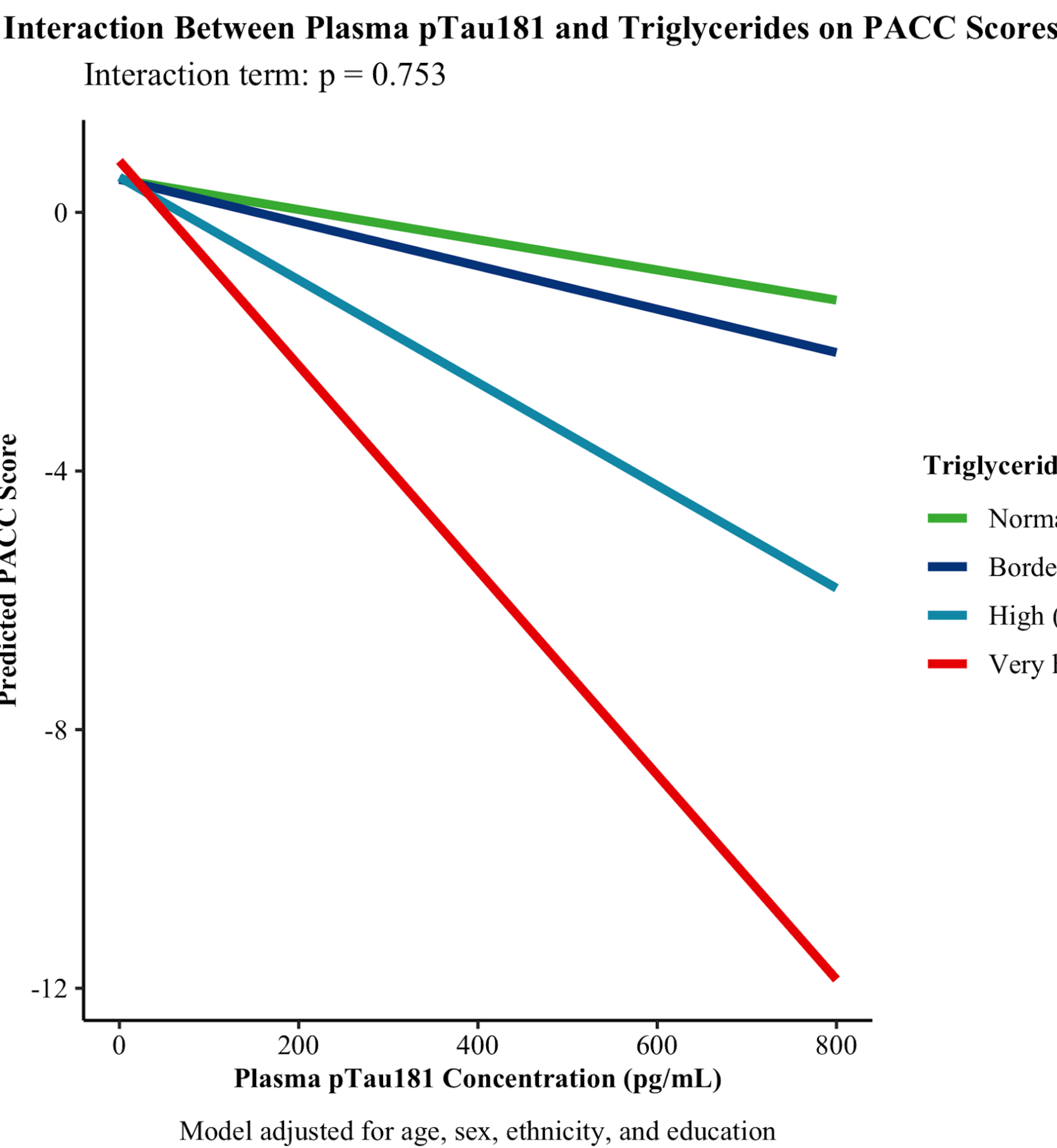
Solid lines show adjusted marginal predictions of PACC from a Gaussian generalized linear model including plasma pTau₁₈₁ (pg/mL), LDL-C, and their interaction (p for interaction = 0.016), adjusted for age, sex, ethnicity, and education. Abbreviations: PACC, Preclinical Alzheimer Cognitive Composite; pTau₁₈₁, phosphorylated tau-181; LDL-C, low-density lipoprotein cholesterol.

Figure 2: Interaction Between Plasma pTau181 and Total Cholesterol on PACC Scores



Solid lines show the adjusted marginal predictions of PACC from a Gaussian generalized linear model that includes plasma pTau₁₈₁ (pg/mL), total cholesterol category, and their interaction (p for interaction = 0.006), adjusted for age, sex, ethnicity, and education. Abbreviations: PACC, Preclinical Alzheimer Cognitive Composite; pTau₁₈₁, phosphorylated tau-181.

Figure 3: Interaction Between Plasma pTau181 and Triglycerides on PACC Scores



Solid lines display the adjusted marginal predictions of PACC from a Gaussian generalized linear model that includes plasma pTau₁₈₁ (pg/mL), triglyceride category, and their interaction (p for interaction = 0.753), with adjustments for age, sex, ethnicity, and education. Abbreviations: PACC, Preclinical Alzheimer Cognitive Composite; pTau₁₈₁, phosphorylated tau-181.

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Conclusions:

- Higher NfL and pTau₁₈₁ were associated with worse cognitive performance, while LDL-C strengthened these associations. Synthesizing NfL, pTau₁₈₁, and LDL-C values can support clinicians to identify individuals at higher risk of cognitive decline and target follow-ups and personalized lipid management.
- This approach also lays the groundwork for clinical decision-making that combines biomarker and lipid data to optimize prevention strategies where risk is greatest.

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