

Substituting blood-based biomarkers for imaging measures in Alzheimer’s disease studies

Implications for sample size and bias

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KEY TAKEAWAY Blood biomarkers improve scale and access, but substituting p-tau for amyloid-PET can require 1.5–6.5x larger samples and can attenuate exposure associations.

BACKGROUND & OBJECTIVE

- Blood-based biomarkers (BBMs) for Alzheimer's disease (AD) pathology are attractive due to their low cost, minimal invasiveness, and ease of collection in non-clinical settings.
- However, BBMs have lower test-retest reliability compared to neuroimaging measures like amyloid-PET Centiloids.
- The trade-offs in statistical power and potential bias when using BBMs in place of neuroimaging measures are not well-explored.

RESEARCH QUESTION

What happens to power, sample size required for 80% power, and bias when plasma p-tau 181 or p-tau 217 is used in place of amyloid-PET Centiloids?

DATA & SIMULATION DESIGN

- Empirical data came from ADNI and A4, which both included amyloid-PET and blood-based measures.
- Key measures were Centiloids, plasma p-tau 181/217, age, and harmonized memory z-scores.
- Simulations varied sample size and random measurement error across 165 scenarios.
- Each scenario used 5,000 simulated datasets to estimate power and bias.

ANALYTIC ROLES COMPARED

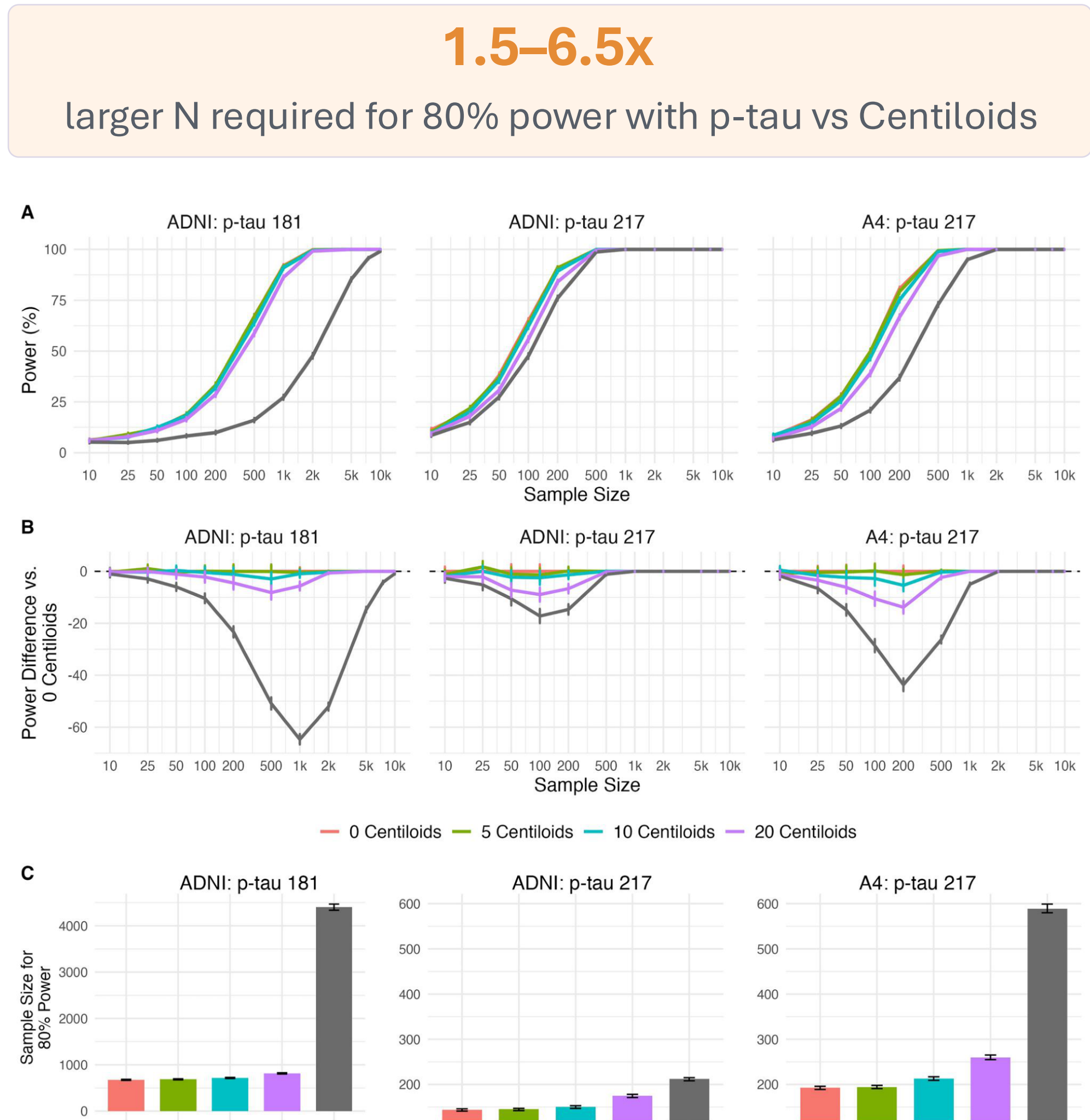
Biomarker as outcome: age → biomarker

Biomarker as exposure: biomarker → memory

- Measurement error in an outcome mainly reduces precision.
- Measurement error in an exposure can also bias estimates toward the null.

BIOMARKER AS OUTCOME: SAMPLE SIZE

When the biomarker was the outcome, replacing Centiloids with plasma p-tau reduced power — especially for p-tau 181.



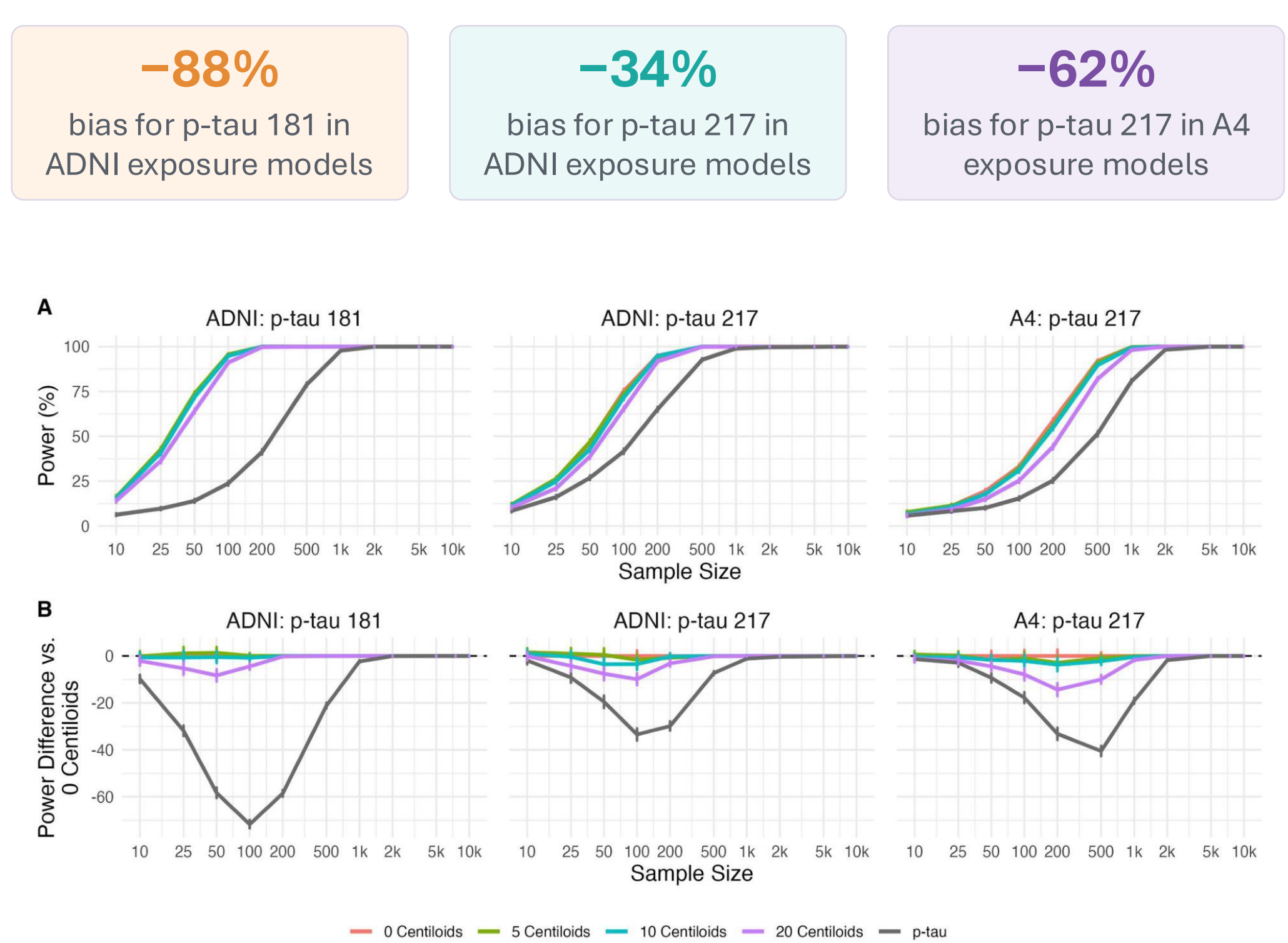
Biomarker-outcome models. (A) Power to detect age-biomarker associations by sample size. Added Centiloid error had little effect, whereas p-tau reduced power, especially p-tau 181. (B) Power difference versus true Centiloids; reductions were larger for p-tau 181 than p-tau 217. (C) Sample size for 80% power: p-tau required 1.5-6.5x more participants than true Centiloids.

INTERPRETATION

- Blood collection may enable larger studies, but that advantage must offset lower biomarker precision.
- Study planning should estimate power for the specific assay, cohort, and analytic question.
- A cheaper biomarker is not necessarily a cheaper study if many more participants are required.

BIOMARKER AS EXPOSURE: BIAS

When the biomarker was the exposure, measurement error produced regression dilution bias and reduced power.



Biomarker-as-exposure models. (A) Power to detect biomarker-memory associations, adjusted for age, by sample size. Plasma p-tau substantially reduced power. (B) Power difference versus true Centiloids; losses were greatest for p-tau 181 in ADNI, with p-tau 217 showing smaller but still meaningful reductions.

INTERPRETATION

- Sample-size requirements and bias depend on isoform and biomarker analytic role.
- p-tau 217 generally outperformed p-tau 181.
- BBMs are valuable for scalable AD research but are not one-to-one substitutes for imaging.
- Researchers should consider quantitative bias analysis and PET imaging in a validation subset.

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