

Measurement error in blood-based Alzheimer's disease biomarkers leads to underestimation of mediation effects



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Background and Objective

- Amyloid and tau burden may mediate effects of genetic and lifestyle factors on cognition.
- Most studies have not evaluated how blood-based biomarker measurement error (e.g., batch effects, assay differences, health conditions like kidney function that affect biomarker levels) may bias estimated mediation effects.
- Given potential magnitude of error in blood-based AD biomarkers, quantifying potential bias is important for planning and interpreting mechanistic studies.
- We aimed to simulate the impact of mediator measurement error on estimates of the true proportion mediated in causal mediation models.

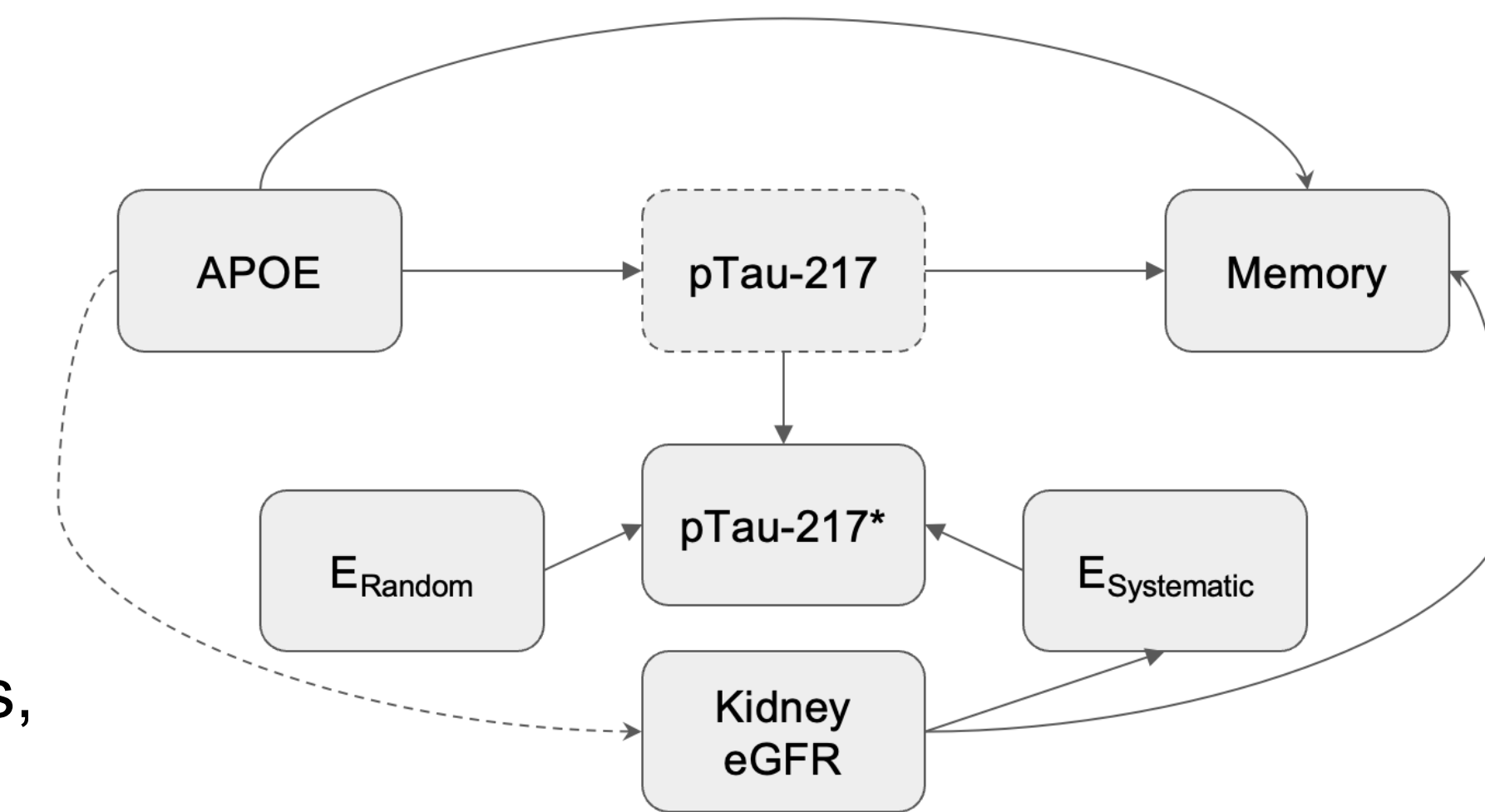
Methods

Empirical data to parameterize simulation models: Alzheimer's Disease Neuroimaging Initiative (ADNI)

- *Exposure:* APOE ϵ 4 allele carriership
- *Outcome:* composite episodic memory score (z-scored)
- *Mediator:* plasma ptau-217

Simulation methods:

- Simulated total, direct, and indirect effects of APOE ϵ 4 carriership on cognition to match ADNI cohort estimates
- Simulated measurement error in biomarker measure and re-estimated effects in observed data (with error)
- Evaluated bias across 5000 simulation runs in 4 different scenarios,
 1. non-differential (random) error only;
 2. heteroskedastic random error with larger errors at higher true p-tau217 levels;
 3. differential (systematic) error dependent on kidney function combined with random error;
 4. differential (systematic) error dependent on kidney function combined with heteroskedastic random error.



Results

- Simulated total effect of APOE ϵ 4 carriership on episodic memory z-score was 0.7; true proportion mediated by ptau-217 was 0.59 (59%).
- **Across all scenarios, measurement error in ptau-217 attenuated (biased toward null) estimates of the proportion mediated.**
 - With random error only, bias scaled approximately linearly with the fraction of ptau-217 variance due to measurement error (Figure 1).
 - Heteroskedastic random error (Scenario 2) produced less attenuation, likely due to smaller overall error (Figure 2).
 - Differential error (Scenarios 3–4) contributed little extra bias, but kidney function was only weakly associated with p-tau217 in ADNI.

Figure 1. Change in estimated proportion mediated based on standard deviations of added error (Scenario 1, random error only)

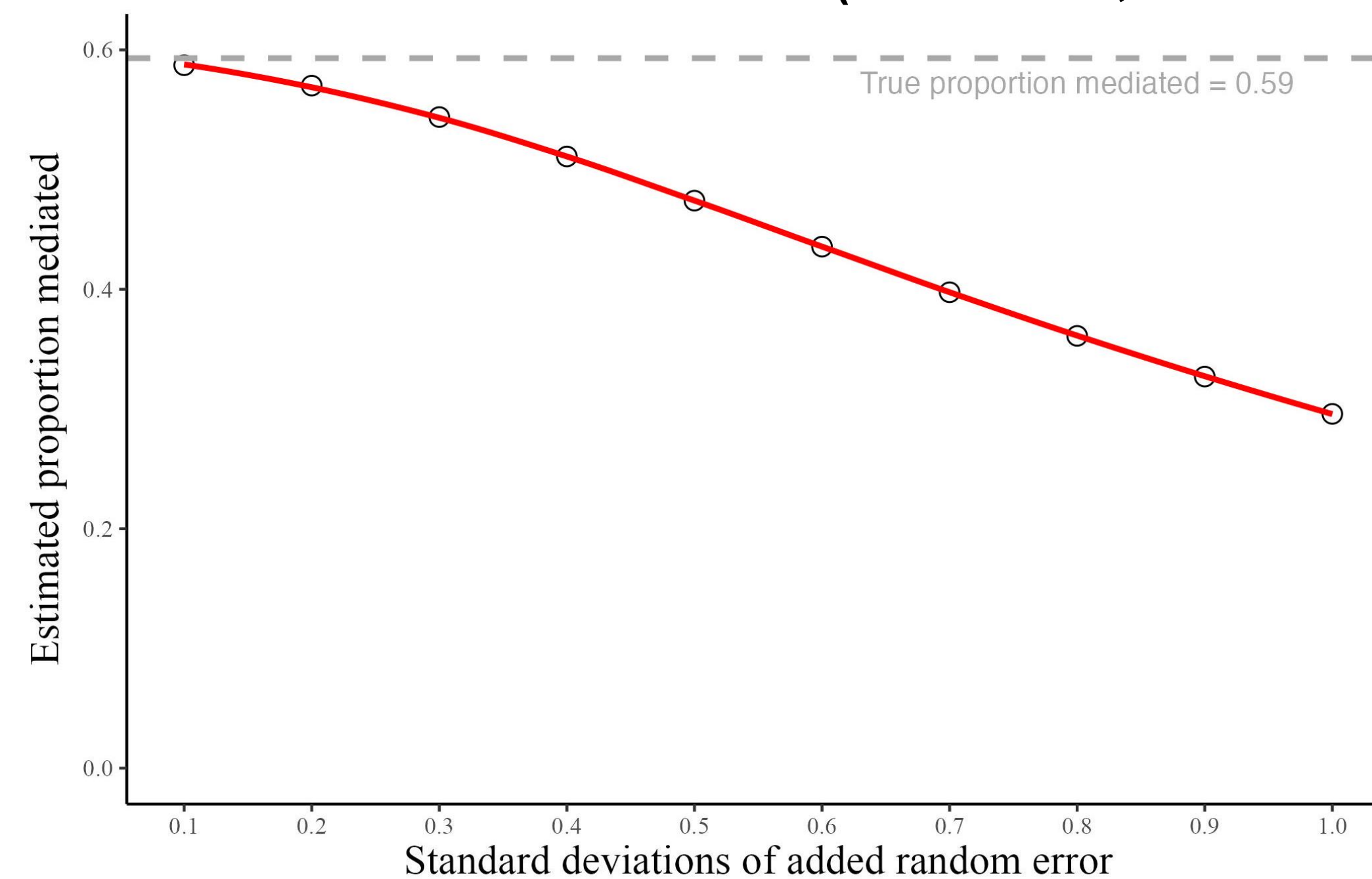
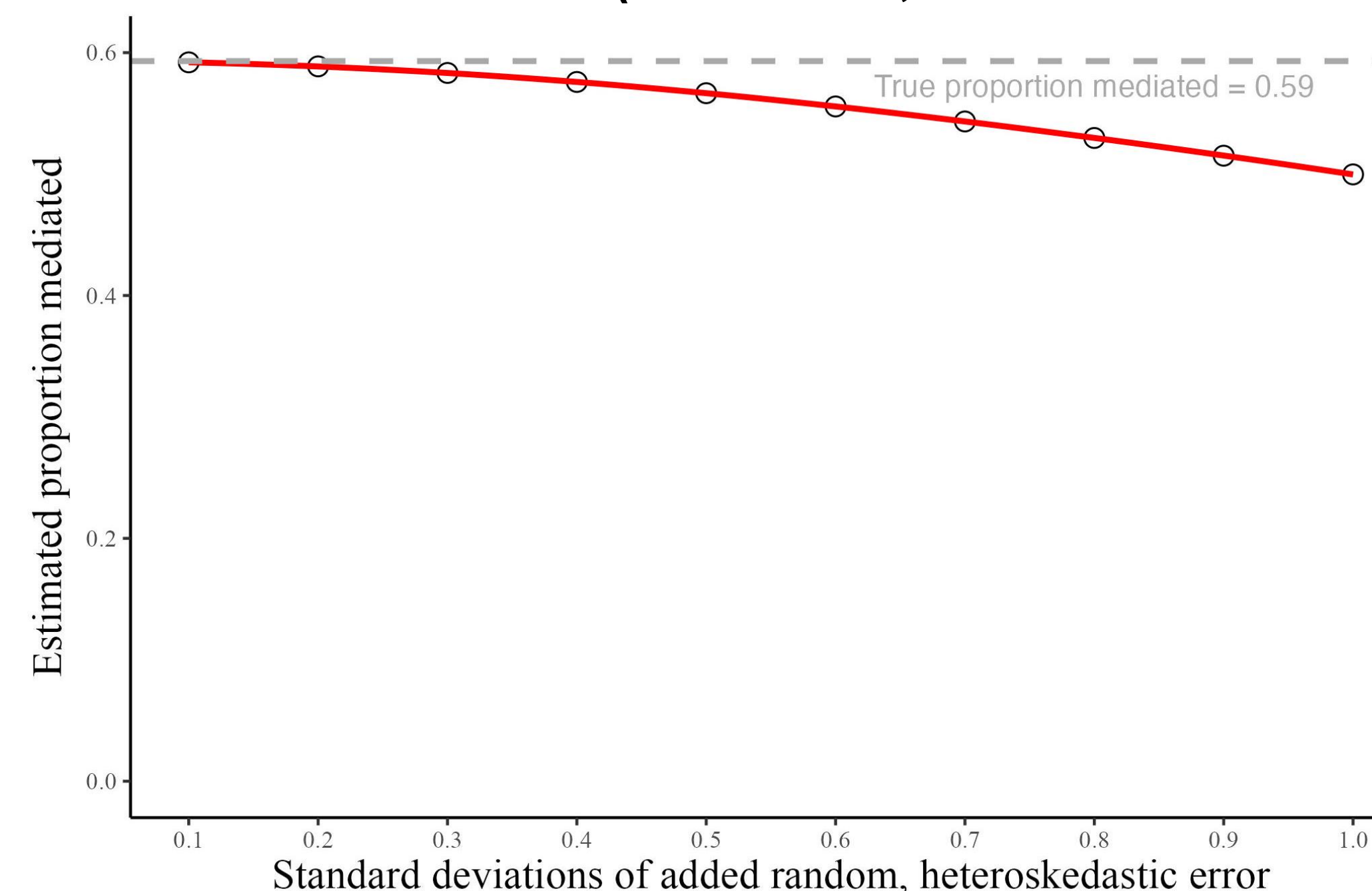


Figure 2. Change in estimated proportion mediated based on standard deviations of added error (Scenario 2, heteroskedastic random error)



Conclusions

- Non-differential (random) measurement error in mediators like plasma p-tau217 can substantially attenuate estimated mediation effects.
- This attenuation may lead to incorrect conclusions regarding the absence or strength of biological mechanisms linking risk factors to cognition.
- Systematic (differential) measurement error related to kidney function had limited impact in this analysis, but these findings may not generalize to populations or biomarkers where kidney function is more influential.
- **Researchers using blood-based AD biomarkers should consider quantitative bias analysis for mediation analyses.**