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Applications of Mixed Effects Modeling in Observational Studies and Clinical Trials for Alzheimer's Disease

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White matter hyperintensity (WMH) is increasingly recognized as a core pathology of Alzheimer's Disease (AD). However, the association between WMH and mutations conferring AD (irrespective of actual AD diagnosis) is less well known. We studied this issue through linear mixed effects modelling, using data from the Dominantly Inherited Alzheimer's Network (n = 456). The model confirmed that mutation carriers have greater WMH than non-carriers after controlling for other predictors ($t = 6.23$, $p < 0.0001$).

We also used three different methods (ANCOVA-like model, unadjusted and fully adjusted linear mixed models) to calculate rate of change (ROC) in WMH. Loess regression was used throughout to qualitatively explore relationships in the data. Using the fully adjusted model, we determined that the ROC in WMH significantly exceeds zero at Baseline EYO of -23.56 years for non-carriers, and at least -25 years for carriers. Percentile bootstrap confidence intervals were also obtained for these EYO points. Our findings suggest that medical intervention is necessary for mutation carriers several decades before symptom onset.

More generally, we also sought to determine an effective linear model for a randomized controlled trial (RCT) with dose escalation at a fixed time point. To do this, we simulated 1,000 clinical trials, used 4 different mixed models for repeated measures (MMRM) to analyze each trial, and then calculated the statistical power of each model. The model which included a continuous dose variable interacting with time was found to have the highest power (0.534).