Sex modifies predictive effects of imaging and CSF biomarkers on Alzheimer's disease cognitive outcomes

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1. Introduction

Previous studies showed sex differences in Alzheimer's Disease (AD) risk potentially attributable to differences in life expectancy, the APOE ε4 genotype, and other factors. To date, no data model or biological paradigm fully explains this disparity, necessitating novel approaches for studying AD-related fluid biomarkers, imaging and cognitive data. Understanding these pathological differences help train fair models for AD that allow for the equally accurate prediction, diagnosis, and treatment of AD in men and women.

2. Materials And Methods

Participants included 1,479 subjects from the ADNI cohort with sixteen AD quantitative measures available over four time points (Figure 1). Chow tests were performed to understand the possible underlying biological mechanisms of sex-modified AD biomarker differences. Results of these tests show whether measures of each of 11 AD imaging and cerebrospinal fluid (CSF) markers predicted one of five AD cognitive outcomes with varying slopes when stratifying upon sex. Effects at each time point were evaluated separately. To determine the direction of the differential effects for each biomarker predictor, additional bootstrapped (n=599) Chow tests were conducted. A Bonferroni correction ($P < 2.94E-4$) was used to correct for multiple comparisons.

3. Results

Multiple imaging and CSF biomarkers predicted AD cognitive scores with differing regression coefficients between men and women over four time points (Figure 1). The strongest signals involved the volumetric measures of the mid-temporal cortex, hippocampus, and fusiform gyrus respectively predicting the ADAS-13 score using baseline and month 24 data. Bootstrapped regression analyses showed effects on the medial-temporal-lobe and hippocampus were uniformly statistically significant, whereas effects in the P-tau biomarker were not (Figures 2-3).

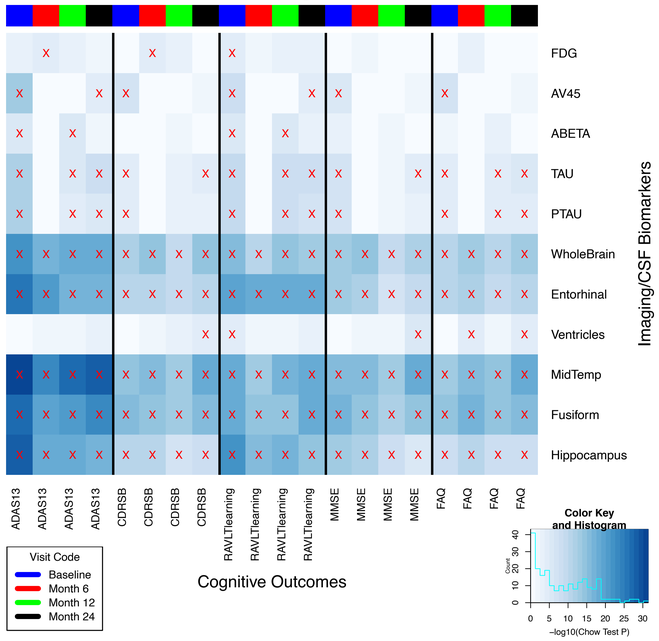

Figure 1 Heat map showing results of Chow test. Regression: predict cognitive outcomes (horizontal axis) using a variety of imaging and CSF biomarkers (vertical axis) when factoring for age and years of education as covariates. Horizontal color bar represents specific QT-PAD visit code data selection is from and shade of cells denotes relative -log(Chow Test P). Significance was determined by a Bonferroni threshold ($P < 2.94E-4$) with significant relationships denoted as X.

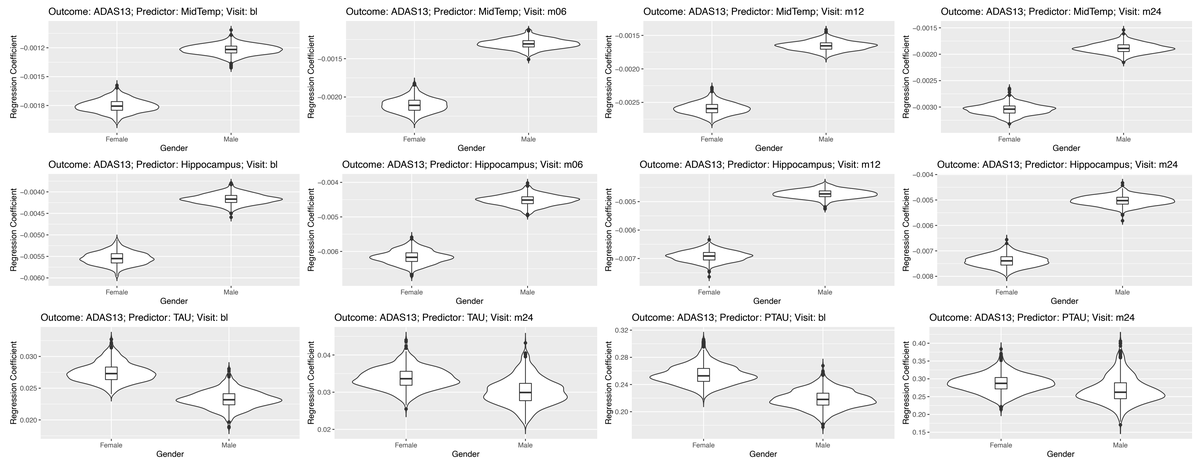

Figure 2 Violin plots showing the results of bootstrapping analysis (*n = 599*; 80/20 split) to evaluate the results of the Chow tests. A select number of extremely significant correlations from the Chow tests (Figure 1) were chosen. The box plot shows the median and IQR of calculated regression coefficients and specific points highlight outliers.

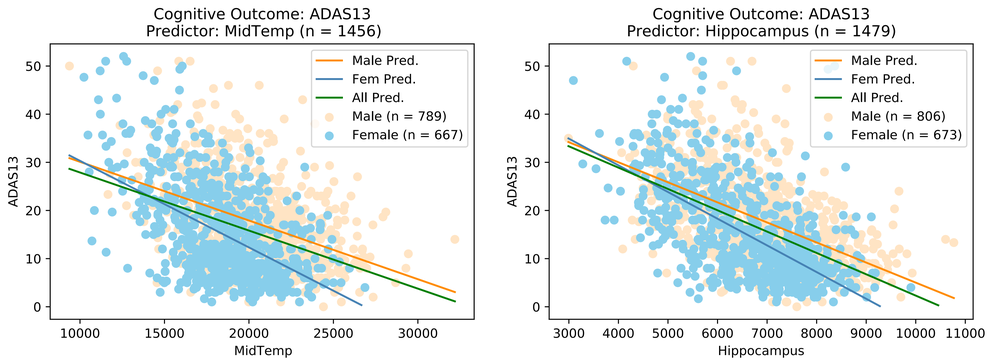

Figure 3 Example linear predictive models learned from male subjects, female subjects, and all subjects, respectively using *baseline* data. The vertical axis represents an adjusted ADAS13 score (after regressing out the effects of two covariates: age and years of education) and the horizontal axis represents the respective imaging predictor.

4. Conclusions

While prior studies mainly investigated sex effects on AD biomarkers, this work examined how sex modified the predictive effects of imaging and CSF biomarkers on AD cognitive outcomes. It warrants further investigation to study if sex modifies multivariate biomarker-based predictive effects on cognitive outcomes. While consistent with prior results showing significant sex differences in brain volumetric and AD tau-based biomarkers, our findings can create fair sex-stratified predictive models to promote precision medicine and help elucidate how biological factors drive the sex-based pathological disparity in AD.

ACKNOWLEDGEMENTS: Supported in part by NIH R01 AG071470, R01 LM013463 , RF1 AG068191and U01 AG068057. Data used in preparation of this abstract were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu), which was funded by NIH U01 AG024904.