Sex differences of *APOE neuropathology-based scores* in brain aging

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There is slowed brain aging (at the group median level) when *APOE npscore* <0 suggesting protective effects of APOE ε2 on brain aging (more so for males compared to females). Conversely, there is slightly accelerated brain aging for both the sexes (at group median level) when *APOE npscore* ≥0.

INTRODUCTION

The apolipoprotein E gene (APOE) is the predominant genetic risk factor for late-onset Alzheimer disease (AD), with three alleles contributing to disease risk and strongly associated with many AD endophenotypes: ε2 (reduced risk), ε3 (reference), and ε4 (increased risk).

Researchers often include APOE ε4 carrier status (ε4+/ε4-) in analyses to account for the genetic effect; however, this does not adequately account for the protective effects of APOE ε2 or the heterogeneous effect of different APOE genotypes (ε2ε2, ε2ε3, ε2ε4, ε3ε3, ε3ε4, and ε4ε4).

By reinterpreting the difference between a model prediction and calendar age, machine learning algorithms allow for estimation of "brain age" using MRI. Brain age provides an estimate of the "neuro clock" which can differentiate accelerated or slowed aging of the brain due to disease processes underlying AD. There is growing evidence for sex differences in the influence of APOE genotype on AD endophenotypes at various stages of disease.

The **purpose of this study** is to examine the influence of an APOE neuropathology-based score (*APOE npscore*), on the brain aging estimated from a pre-trained deep learning model. *APOE npscore* accounts for the effect of the full APOE genotype would effectively recapitulate the influence of APOE than just APOE ε4 status.

METHODS

T_1w MRI data were minimally transformed to (1) strip the non-brain tissue using ANTSPyNet[1], (2) reduce B1 field bias using N4 algorithm in ANTS[2], and (3) linearly and non-linearly registered to standard MNI T_1w template using FSL[3].

Brain age from 274 participants in the Wisconsin-Alzheimer's Disease Research Center (W-ADRC) was estimated from T1w MRI using a publicly available deep learning model called two-stage-age-network (TSAN)[4] that was pre-trained on over four thousand scans from Open Access Series of Imaging Studies (OASIS), Alzheimer's Disease Neuroimaging Initiative (ADNI)-I and Prediction Accuracy Challenge (PAC)-2019.

TSAN uses a novel rank-based loss along with mean squared loss and makes predictions in two steps which does not require a posteriori bias correction. This is a significant improvement from prior deep learning models in reducing the "regression-to-mean bias" typically present in brain age clock models.

APOE genotypes (ε2ε2, ε2ε3, ε3ε3, ε2ε4, ε3ε4, ε4ε4) were weighted by the log(odds-ratio) from a large study of autopsy-confirmed AD cases/controls, providing a variable representing the relative amount of risk across APOE genotypes. Mood's median test was used to examine the sex differences between the excess brain aging as a function of the *APOE npscore*.

RESULTS

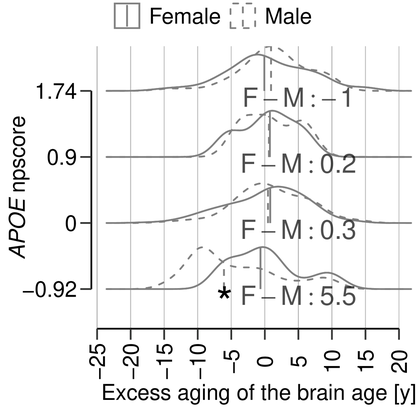

Figure 1. Sex differences in densities of excess brain aging (brain age – calendar age) as a function of the *APOE npscore*. The density estimates (using a bandwidth of 2 years) of the excess brain age along with the medians are shown. *p ≤ 0.05 according to Mood's median test. The median values for females (F) and males (M) for each of the APOE npscore are shown by the vertical lines. The median difference values (F–M) are also shown on the left for each *APOE npscore*.

Code availability: Minimal image transformations and post-prediction analysis code available at https://github.com/nadluru/aaic2022. The brain age prediction itself was based on publicly available code from the TSAN GitHub repository[4].

CONCLUSIONS

We report sex differences in the influence of APOE genotype on brain aging. There is heterogeneity in the differences within the ε4+ (*APOE npscore* > 0) and ε4- (*APOE npscore* ≤ 0) groups. These sex differences may not be observed when using just ε4 carrier status instead of the *APOE npscore*. This provides evidence for a shift in paradigm for the way we analyze APOE genotype because of latent nuances of the ε4-status influence on AD outcomes.

Our findings are the first report of sex differences in the influence of APOE genotype on brain aging outcome and are consistent with the prior findings on other AD outcomes. For example, women who were APOE ε4 carriers had higher CSF pTau than men in early disease for both subjective cognitive decline (SCD) and mild cognitive impairment (MCI), but not AD dementia, and in non-ε4 carriers, women had higher CSF pTau than men in MCI and dementia AD, but not the earliest SCD stages. Another group suggested that sex differences observed in the APOE effect on pTau may be due to sex hormones like testosterone. It is interesting to note that these sex differences may not be observed when using just APOE ε4 carrier status instead of the *APOE npscore*, and that there is heterogeneity in the sex differences within the ε4+ (*APOE npscore* > 0).

Future work involves looking at the interaction effects of *APOE npscores* with vascular risk scores on brain aging. 0) and ε4- (*APOE npscore* ≤ 0) groups.

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