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Sex differences in cognitive resilience in preclinical autosomal-dominant Alzheimer's disease carriers and non-carriers: Baseline findings from the API ADAD Colombia Trial

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Abstract

INTRODUCTION.—Females may have greater susceptibility to Alzheimer's disease (AD)-pathology. We examined the effect of sex on pathology, neurodegeneration, and memory in cognitively-unimpaired Presenilin-1 (*PSEN1*) E280A mutation carriers and non-carriers.

METHODS.—We analyzed baseline data from 167 mutation carriers and 75 non-carriers (ages 30–53) from the Alzheimer's Prevention Initiative Autosomal Dominant AD Trial, including florbetapir- and fludeoxyglucose-PET, MRI based hippocampal volume and cognitive testing.

RESULTS.—Females exhibited better delayed recall than males, controlling for age, precuneus glucose metabolism and mutation status, although the effect was not significant among *PSEN1* mutation carriers only. *APOE*ε4 did not modify the effect of sex on AD biomarkers and memory.

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DISCUSSION.—Our findings suggest that, among cognitively-unimpaired individuals at genetic risk for autosomal-dominant AD, females may have greater cognitive resilience to AD pathology and neurodegeneration than males. Further investigation of sex-specific differences in autosomal-dominant AD is key to elucidate mechanisms of risk and resilience in AD.

Keywords

Alzheimer's disease; autosomal dominant Alzheimer's disease; sex differences; preclinical; pathology; neurodegeneration; cognition

BACKGROUND

Two thirds of individuals currently living with Alzheimer's disease (AD) in the U.S. are women[1]. Evolving evidence suggests that this discrepancy cannot be attributed solely to differences in life expectancy, whereby more females survive to late life than males[2]. There is evidence suggesting that there may also be a sex-specific risk for AD. Females may have greater pathology burden[3–5] and may be more susceptible to AD pathology than males as evidenced by greater pathophysiological downstream effects and worse clinical and cognitive outcomes[5–8], particularly among apolipoprotein E (*APOE*) ε4 allele carriers[4, 7, 9, 10]. In contrast, females have been shown to perform better in verbal memory measures across the lifespan[11–13] and there may be sex differences in rates of decline in specific cognitive domains[14]. Recent studies show that females continue to exhibit better verbal memory in early stages of AD, despite initial accumulation of pathology and neurodegeneration, including greater postmortem tau pathology[15], hippocampal atrophy,[16] brain glucose hypometabolism.[17]

Further research is needed to investigate sex-specific risk or resilience factors along the AD trajectory. To address this gap in the literature, our approach has focused on investigating sex differences in individuals with autosomal-dominant AD (ADAD) from the world's largest kindred due to a single mutation (E280A) in the Presenilin1 gene (*PSEN1*). *PSEN1* mutation carriers are destined to develop early-onset AD, with mild cognitive impairment (MCI) symptoms emerging at a median age of 44 years and dementia at 49 years[18], and thus have few age-related confounds that confer risk for AD, which are known to vary by sex/gender (e.g., cardiovascular disease[19]). Moreover, this cohort offers a unique opportunity to investigate sex differences with fewer methodological challenges such as survival bias due to differences in mortality or competing risks between males and females[20] than in sporadic/late-onset AD research studies.

Preliminary findings from our group[21] showed that, among cognitively unimpaired *PSEN1* mutation carriers, females exhibited better global cognition than males despite having similar hippocampal volumes, while there were no sex differences when also examining mildly symptomatic carriers. Nonetheless, these findings had important limitations, as the study had a small sample size, larger number of females, and greater number of females with MCI.

Therefore, the current study expands previous findings by using a much larger sample, focusing on preclinical individuals[22], including sensitive neuropsychological measures,

and exploring how *APOE* ε4 genotype modifies the effect of sex on AD biomarkers and memory. To that end, we leveraged baseline data from the Alzheimer's Prevention Initiative (API) Autosomal Dominant AD Colombia Trial, a clinical prevention trial of crenezumab[23], to investigate differences among presymptomatic male and female *PSEN1* carriers and non-carriers in markers of cognition, amyloid burden, and neurodegeneration. We hypothesized that presymptomatic females and males would not differ in markers of AD-pathology or neurodegeneration, while presymptomatic females would exhibit better memory performance than males. Based on previous findings in late-onset AD, we hypothesized that female A*POE*ε4 carriers would exhibit worse AD biomarkers and cognition than male *APOE*ε4 carriers.

METHODS

Participants

A total of 167 *PSEN1* mutation carriers (ages: 30–53, mean age: 37 +/− 5 years; 60% women) and 75 age-matched non-carriers (ages: 30–53, mean age: 42 +/− 6 years; 67% women) from the API Autosomal Dominant AD Colombia Trial were included in the study[24]. Potentially eligible trial candidates from the Colombian API Registry[25] were pre-screened following procedures and included in the study following inclusion and exclusion criteria described in detail elsewhere[23]. In brief, the inclusion criteria were 1) individuals from the *PSEN1* E280 mutation carrier kindred; 2) ages 30 to 60 years old; 3) Mini-Mental State Examination (MMSE)[26] >26 for participants with > 9 years of education and MMSE >24 for participants with <9 years of education; 4) did not meet criteria for MCI or dementia due to AD[27, 28] based on performance on clinical and cognitive measures. Participants in the trial reported their sex assigned at birth (i.e., male/female). For trial blinding and ethical reasons, participants were not provided with their genotype information[23]. Data from 10 participants were excluded from analyses to protect participant confidentiality, genetic status, and trial integrity. Of note, a total of 17 participants enrolled in the current analyses had been included in the previous study reported here[21, 29, 30], although independent data measurements were collected and analyzed for this study.

Procedure

This study leverages baseline data from a prospective, randomized, double-blind, placebo-controlled, parallel-group study of the efficacy of crenezumab versus placebo in preclinical *PSEN1* E280A mutation carriers[23] (Clinicaltrials.gov NCT01998841). Informed consent was obtained from all participants and study partners. All research procedures were conducted in accordance with international and local ethics committee standards[23].

Measures

Clinical and Neuropsychological Tests—Participants completed a battery of clinical and cognitive measures in Spanish, adapted by the Neurosciences Group of Antioquia (GNA) to characterize this Colombian population. These included the MMSE[26], Clinical Dementia Rating Scale (CDR)[31], Geriatric Depression Scale (GDS)[32], Functional Assessment Staging of Alzheimer's Disease (FAST)[33], Word List and Constructional Praxis subtests from the Spanish version of the Consortium to Establish a Registry

for AD (CERAD)[34], the Raven Progressive Matrices[35], the Multilingual Naming Test (MiNT)[36], and the Free and Cued Selective Reminding Test (FCSRT)[37]. Assessments were administered by psychometricians or global raters who did not have access to study data other than those related to the specific assessments that they administered.

Brain Imaging—As previously described[30], fludeoxyglucose (FDG) and florbetapir positron emission tomography (PET) scans were done on a Siemens Biograph 16 HiRez PET/CT scanner. FDG PET scans were performed on a 64-section PET/CT using intravenous administration of 5 mCi (185 million Bq) of FDG after a 30-minute radiotracer uptake period when resting with open eyes in a darkened room, followed by a 30-minute dynamic emission scan (six 5-minute frames). Images were reconstructed with computed tomographic attenuation correction.

Florbetapir PET scans for measuring beta-amyloid were done on a PET/CT scanner after intravenous injection of about 10 mCi of florbetapir, a 50 min radiotracer uptake period, a 20-minute emission scan (four 5-min dynamic frames), and a CT scan for correction of radiation attenuation. Images were reconstructed using an iterative algorithm, measured attenuation–correction, and a 5 mm full-width-at-half-maximum Gaussian filter.

Volumetric MR imaging data were acquired on a 1.5-T imaging system (Avanto; Siemens) with a T1-weighted, magnetization-prepared, rapid-acquisition, gradient-echo pulse sequence (echo time, minimum full; flip angle, 8°; number of excitations, 1; field of view, 22 cm; imaging matrix, 192 × 192 pixels; and section thickness, 1.2 mm).

SPM12, an automated brain mapping algorithm and the automatic anatomical labeling toolbox[16] were used to deform each participant's FDG and florbetapir PET image into the coordinates of a brain atlas based on their T1-weighted MRI. Based on previous findings showing lower precuneus cerebral metabolic rate for glucose in *PSEN1* mutation carriers, 15 years before clinical symptom onset[30], we characterized precuneus to whole-brain cerebral metabolic rate for glucose ratios (FDG Precuneus) from a bilateral region of interest (ROI) in each participant's FDG PET image. Mean cortical florbetapir standard uptake value ratios (SUVRs) were computed in each participant using six cortical grey matter ROIs (frontal, temporal, parietal, anterior cingulate, posterior cingulate, and precuneus) using the pons as a reference region for SUVR calculation, as a previously-validated reference region in *PSEN1* mutation carriers[25]. Hippocampal to total intracranial volume ratios were characterized from bilateral ROIs in each participant's T1-weighted MR image using FreeSurfer 6 (http://surfer.nmr.mgh.harvard.edu)[38, 39]. All images were reviewed for quality and compliance in accord with Alzheimer's Disease Neuroimaging Initiative recommendations[40].

Statistical Analyses

We first compared demographic, clinical, neuroimaging and cognitive data among males and females in both *PSEN1* carrier (with and without controlling for age), and non-carrier groups using T tests and Chi-square tests. Second, we conducted a series of linear regression models to examine how sex modified the relationship between amyloid burden and markers of neurodegeneration while adjusting for age, and *PSEN1* mutation status. Models included amyloid burden as the independent variable and a marker of neurodegeneration

- hippocampal volume and precuneus glucose metabolism, respectively - as the dependent variable. Age, *PSEN1* status (*PSEN1* mutation carriers/non-carriers), and sex were included as covariates of interest. Subsequent models were run adding a sex*amyloid burden interaction term. Third, we examined the association between markers of neurodegeneration and memory performance. Models included markers of neurodegeneration, age, *PSEN1* status, sex, and amyloid burden as the independent variables; and CERAD word list delayed recall as the dependent variable. Again, subsequent models were run adding each of these – sex*precuneus glucose metabolism and sex*hippocampal volume – interaction terms, respectively. Post-hoc analyses examined these models among *PSEN1* mutation carriers only. Lastly, we examined the effect of *APOE*ε4 status on makers of pathology, neurodegeneration and memory performance. *APOE* genotype was coded as positive or negative for the presence of an ε4 allele. These analyses were re-run adding *APOE*ε4 status as an independent variable. Analyses were carried out using R (version 4.0.2, The R Foundation). Analyses used a significance threshold of $p<0.05$. P-values were not adjusted for multiplicity. We tested the assumptions for linear regressions, including normality assumption of the distribution of residuals using Shapiro-Wilk test. When residuals were not normally distributed, we re-fitted the models using transformed variables (i.e., squared delayed recall, $\log_{10}$ amyloid burden). Analyses were performed by a team of biostatisticians who were unblinded to genotype but had no role in study design or data collection.

RESULTS

Cognition, pathology and neurodegeneration in male and female carriers

As previously reported[24], baseline characteristics of *PSEN1* carriers and non-carriers are described in Supplemental Table 1. Demographic, clinical, cognitive, and neuroimaging data among male and female *PSEN1* mutation carriers and non-carriers are described in detail in Table 1. Sex ratio did not differ between *PSEN1* mutation carriers (60% females) and non-carriers (67% females, $p=.36$). Among *PSEN1* mutation carriers, females were younger than males ($p=.04$; see Table 2). Markers of AD pathology and neurodegeneration did not differ between male and female *PSEN1* mutation carriers, although there was a trend towards significance for female *PSEN1* mutation carriers to have lower levels of amyloid burden ($p=.07$) and greater hippocampal volume ($p=. 09$) than male *PSEN1* mutation carriers. Female *PSEN1* mutation carriers exhibited higher word list learning ($p=.03$), word list delayed recall ($p=.02$), and FCSRT Total Recall ($p=.03$) than male *PSEN1* mutation carriers, although these did not remain significant when controlling for age. There were no differences in demographics, clinical variables, markers of pathology and neurodegeneration, or cognition between male and female non-carriers.

Relationship between markers of pathology and neurodegeneration

A regression model controlling for *PSEN1* status and age showed that higher amyloid burden predicted lower glucose metabolism in the precuneus ($\beta=-3.846$, p=<.001; See Table 2). No sex effect was found in the relationship between amyloid burden and glucose metabolism in the precuneus ($\beta=-.234$, $p=.815$; Figure 1A). The interaction effect between

sex and amyloid burden was not significant in predicting glucose metabolism in the precuneus (β=−.063 *p*=.950).

A regression model controlling for *PSEN1* status and age showed that amyloid burden did not predict hippocampal volume (β=−1.101, *p*=.272). Sex and the interaction effect between sex and amyloid burden were not significant in predicting hippocampal volume (Sex: β=1.683, p=.094; Sex*Amyloid burden: β=.854, *p*=.394; Figure 1B).

Post-hoc regression models in *PSEN1* carriers only, controlling for age, showed that there was no sex effect in the relationship between amyloid burden and glucose metabolism (β=−.170, *p*=.865) or hippocampal volume (β=1.222, *p*=.223). The interaction effect between sex and amyloid burden was not significant in predicting glucose metabolism (β=−.145, *p*=.885), or hippocampal volume (β=1.089, *p*=.278).

Relationship between markers of neurodegeneration and memory recall

A model controlling for age, *PSEN1* status and amyloid burden showed that glucose metabolism in the precuneus did not predict delayed recall (β=1.512, *p*=.132; see Table 2). There was a significant effect of sex, wherein for any given level of glucose metabolism in the precuneus, females exhibited better delayed recall than males (β=1.988, *p*=.048; Figure 1C). However, the interaction effect between sex and glucose metabolism in the precuneus was not significant (β=−.607, *p*=.544).

Similarly, a model controlling for age, *PSEN1* status and amyloid burden showed that lower hippocampal volume predicted lower delayed recall (β=2.497, *p*=.013). Sex and the interaction between sex and hippocampal volume were not significant in predicting delayed recall (Sex: β=1.666, *p*=.097; Sex*Hippocampal Volume: β=−1.441, *p*=.151; Figure 1D).

Post-hoc regression models in *PSEN1* carriers only, controlling for age and amyloid burden, showed that greater hippocampal volume predicted higher delayed recall (β=2.127, *p*=.035), while glucose metabolism in the precuneus did not predict delayed recall (β=1.842, *p*=.067). The interaction effects between sex and markers of neurodegeneration were not significant in predicting delayed recall (Sex*Glucose metabolism: β=−1.340, *p*=.182; Sex*Hippocampal volume: β=−1.159, *p*=.248).

Effect of *APOE*ε4 Genotype—Demographic, clinical, neurodegeneration, and cognition data split by *PSEN1* status, sex, and *APOE*ε4 genotype are presented in Table 3. Descriptive data in *APOE* ε4 carriers and non-carriers are shown in Supplemental Table 2. Percentage of *APOE*ε4 carriers did not differ between male and female among *PSEN1* mutation carriers (*p*=.146) and non-carriers (*p* = .845).

Among *PSEN1* mutation carriers, *APOE*ε4 carriers exhibited lower glucose metabolism in the precuneus (*p*=.04), while among *PSEN1* mutation non-carriers, *APOE*ε4 carriers exhibited larger hippocampal volume (*p*=.05) and higher glucose metabolism in the precuneus (*p*=.01).

The presence of one or more *APOE*ε4 alleles did not predict amyloid burden (β=−1.519, *p*=.130), when controlling for age, *PSEN1* status, and sex; and the interaction sex**APOE*ε4

status was not significant (see Table 4). We then examined the effect of *APOE*ε4 on the relationship between amyloid burden and markers of neurodegeneration. We found that the presence of one or more APOEε4 alleles did not predict glucose metabolism in the precuneus (β=−.012, p=.990) or hippocampal volume (β=−.456, p=.649). There was no significant interaction between sex and *APOE*ε4 status in predicting glucose metabolism in the precuneus (β=−.733, p=.464) or hippocampal volume (β=.194, p=.846).

We also examined the effect of *APOE*ε4 status on the relationship between markers of neurodegeneration and memory performance (Figure 2). *APOE*ε4 status did not predict verbal memory delayed recall, when controlling for glucose metabolism in the precuneus (β=.662, p=.509) or hippocampal volume (β=.730, p=.466), as well as other relevant covariates (i.e., age, *PSEN1* status, amyloid burden). Sex did not predict delayed recall when controlling for *APOE*ε4 status and glucose metabolism in the precuneus (β=1.929, p=.055) or hippocampal volume (β=1.600, p=.111). There was no interaction between sex and *APOE*ε4 status in predicting delayed recall when controlling for glucose metabolism in the precuneus (β=−1.338, p=.182) or hippocampal volume (β=−1.465, p=.144).

DISCUSSION

Evidence shows that females may have greater risk for AD, such that they show greater regional tau accumulation[6, 41], faster hippocampal volume loss[8], and greater metabolic dysfunction[42]. In contrast, females have better verbal memory across the lifespan[43] and recent studies showed that, in the early stages of AD, females continue to perform better on verbal memory than males with similar levels of AD pathology,[15, 16, 44] suggesting that females may be more resilient to early AD pathophysiological changes than males by being able to preserve such verbal memory advantage[16, 44, 45]. Yet, as disease progresses, females show faster cognitive decline[7, 46] as well as worse cognitive and clinical outcomes compared with males[5, 7, 41]. Thus, further research is needed to better characterize sex differences in AD biomarker progression. We recently published the first study examining sex differences in carriers of an autosomal-dominant AD mutation (E280A) in Presenilin-1 (*PSEN1*) and showed that cognitively-unimpaired female carriers had better global cognition than male carriers, despite having similar hippocampal volumes[21]. The current study expands and corroborates our previous work by investigating sex differences in markers of pathology, neurodegeneration and cognition among a larger sample of clinically-normal *PSEN1* mutation carriers and non-carriers, as well as exploring the role *APOE*ε4 genotype.

First, we examined whether males and females differed in markers of cognition, pathology, and neurodegeneration. Examining unadjusted, non-confirmatory p values, we found that females were younger, and showed a trend towards lower amyloid burden and greater hippocampal volume among *PSEN1* mutation carriers. These differences, which dissipated when controlling for age, may reflect that females were younger and may have been earlier in the disease course. Subsequently, models adjusted for age, *PSEN1* mutation status, and amyloid burden (when relevant). Female *PSEN1* mutation carriers also showed better verbal memory than male mutation carriers, which is consistent with previous reports where females have been shown to have an advantage in verbal memory[14, 43, 47], however these

effects did not survive when controlling for age. Non-carrier females and males did not differ in amyloid burden, levels of neurodegeneration or cognitive performance.

We then examined the effect of sex on AD pathology and neurodegeneration in *PSEN1* mutation carriers and non-carriers. We found that, as expected, greater amyloid burden predicted lower glucose metabolism in the precuneus (and this effect was also seen when examining *PSEN1* mutation carriers only), while amyloid burden did not predict hippocampal volume. Notably, sex did not modify the effect of amyloid burden on markers of neurodegeneration. These results are somewhat discrepant from previous work showing that as levels of amyloid increase, females show greater hippocampal atrophy across the disease spectrum[8, 48]. However, it is important to note that our study examined cross-sectional data in cognitively unimpaired individuals only, raising the possibility that females' susceptibility to AD-pathology may be secondary to greater downstream effects of amyloid and tau accumulation, and hence, manifest at later stages of the disease (i.e., MCI and early dementia) as previously shown[15]. Supporting this notion, recent findings[42] showed that females displayed greater susceptibility to neurodegeneration than males in the presence of higher tau deposition.

An alternative interpretation of our findings is that females' susceptibility to AD-pathology observed in sporadic, late-onset AD may be mediated by factor(s) that are relatively minimal in our sample (e.g., older age, cardiovascular disease, or menopause). For instance, previous studies showed that reduced levels of estrogen were associated with increased amyloid burden[49, 50], hypometabolism, and greater neurodegeneration[51]. Most females in our study had not presumably undergone menopause, particularly *PSEN1* mutation carriers, and thus sex steroid hormones may have conferred neuroprotective effects. Further research is needed to investigate sex differences in individuals with autosomal-dominant AD across disease stages, using longitudinal designs, and examining potential underlying mechanisms such as sex steroid hormones.

Examining the effect of sex and AD biomarkers on memory in *PSEN1* mutation carriers and non-carriers, our findings showed that, females showed better memory delayed recall than males when adjusting for regional glucose metabolism in the precuneus and other covariates (i.e., age, *PSEN1* status, amyloid burden), although the effect dissipated when controlling for hippocampal volume. However, the interaction effects between sex and markers of neurodegeneration were not significant in predicting verbal memory. These findings are consistent with our hypothesis that presymptomatic females would exhibit better memory performance than males, and suggest that in our cohort, cognitively unimpaired females may be able to preserve memory performance despite having similar levels of pathology and neurodegeneration as males. Importantly, these findings are consistent with our previous study in autosomal-dominant AD[21], and previous work in sporadic AD[16, 44, 45]. Nonetheless, careful interpretation is warranted, as these effects did not survive when examining *PSEN1* mutation carriers only, likely due to power limitations, which may have also reduced our ability to detect interaction effects.

Lastly, we explored whether *APOE*ε4 genotype modified the effect of sex and AD biomarkers on memory performance. *APOE*ε4 allele has been associated with increased risk

of AD[52, 53] and AD biomarker abnormalities[42, 54]. Importantly, few studies have explored the role of *APOE* genotype in autosomal-dominant AD yielding mixed findings, with some studies showing that *APOE*ε4 genotype was associated with an earlier age of disease onset in *PSEN1* E280A mutation carriers[55] and other ADAD-causing mutations[56, 57], whereas other studies found no effect (including a large meta-analysis)[58, 59]. We found that, in our cohort, the presence of one or more *APOE*ε4 alleles was not associated with higher amyloid burden, or lower glucose metabolism in the precuneus or hippocampal volume compared with *APOE*ε4 non-carriers.

When examining the interaction between sex and *APOE*ε4, we found that sex did not moderate the effect between markers of neurodegeneration (i.e., glucose metabolism in the precuneus or hippocampal volume) in predicting verbal memory delayed recall, when controlling for A*POE*ε4 genotype, and the sex by *APOE*ε4 interaction was also not significant. These findings do not support our hypothesis that female A*POE*ε4 carriers would exhibit worse AD biomarkers and cognition than male *APOE*ε4 carriers, and are largely inconsistent with the majority of studies examining the role of *APOE*ε4 and sex in sporadic AD, which showed that female *APOE*ε4 carriers have increased vulnerability to AD pathology compared to male carriers[4, 7, 9, 10, 60–62]. To our knowledge, this is the first study to examine whether sex modifies the effect of *APOE*ε4 on AD-biomarkers and cognition in autosomal-dominant AD. Our findings may be explained by limited power due to small sample sizes, particularly to detect interactive effects between *APOE*ε4 status and sex among cognitively-unimpaired individuals. Therefore, longitudinal studies with larger samples are needed to explore these findings and examine mediating factors of sex-specific effects of *APOE*ε4 in autosomal-dominant AD. Moreover, there may be other genetic modifiers contributing to our findings, beyond *APOE*ε4, and thus it will be important to further examine relevant genetic factors in a larger cohort.

This study has important limitations. First, this is a cross-sectional study. Our sample included more females overall, and more female *PSEN1* mutation carriers. This is possibly a recruitment bias, as previously documented[63], whereby males were more likely to fail pre-screening requirements, particularly due to substance abuse. Moreover, female *PSEN1* mutation carriers were younger (1.8 years) than male *PSEN1* mutation carriers. To account for this difference statistically, we controlled for age in our models. However, this approach has potential limitations as age is commonly used as a proxy for disease progression in this population, and thus, controlling for age may have inadvertently reduced group effects. We also acknowledge that, our sample size, while larger than previous studies of autosomal dominant AD, is smaller relative to studies of sporadic AD, which is generally inherent in autosomal dominant AD research. This may have resulted in power limitations to stratify participants into *PSEN1* carriers/non-carriers, males/females, and APOEe4 status, as well as to address interaction effects, while adjusting for relevant confounds. In order to maximize the power of our analyses, we first investigated sex differences across *PSEN1* mutation carriers and non-carriers (controlling for *PSEN1* mutation status), and then examined post-hoc models in *PSEN1* mutation carriers only. When interpreting our results regarding AD biomarkers among *PSEN1* mutation carriers and non-carriers, we assumed that potential effects are driven by *PSEN1* mutation carriers given that young non-carriers do not have elevated levels of AD-pathology or neurodegeneration, nonetheless, there are limitations to

this approach. Lastly, our sample had a lower percentage of female *APOE*ε4 carriers than male *APOE*ε4 carriers and, while this difference was not statistically significant, careful interpretation of our findings is warranted, particularly with regards to the interactive effects of *APOE*ε4 status and sex.

Notwithstanding, the study has notable methodological strengths, as this is one of the largest studies examining multimodal imaging and genotyping in a homogeneous sample of autosomal-dominant AD due to a single mutation with a robust characterization of pathophysiological and cognitive profiles, which offered a unique opportunity to study sex differences with fewer age-related confounds that are known to vary by sex, such as cardiovascular disease and other comorbidities[19, 64, 65], or survival bias due to differences in mortality or competing risks[20]. Future plans include examining sex differences in longitudinal neuroimaging and cognitive markers at the completion of this clinical trial and as part of the Colombia-Boston Biomarker study of ADAD (COLBOS)[66]. Replication of our results in independent cohorts will also be required to determine generalizability to other at-risk groups for AD and sporadic AD.

Taken together, our findings suggest that, among cognitively unimpaired individuals at genetic risk for autosomal-dominant AD, females may have greater cognitive resilience to AD-pathology and neurodegeneration than males. Further investigation of sex-specific differences in AD biomarkers and cognitive changes in autosomal-dominant AD is key to elucidate mechanisms of risk and resilience in AD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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RESEARCH IN CONTEXT

Systematic Review:

We reviewed the literature on sex differences in pathology, neurodegeneration and cognition in Alzheimer's disease (AD) and autosomal-dominant AD using traditional sources (e.g., PubMed). Our search showed that females may have greater risk for AD, while only one study to date examined sex differences in autosomal-dominant AD.

Interpretation:

We examined sex differences in markers of cognition, pathology and neurodegeneration in preclinical Presenilin-1 E280A mutation carriers and non-carriers, and whether APOE ε4 genotype modified these relationships. Our findings suggest that, among cognitively-unimpaired individuals at genetic risk for autosomal-dominant AD, females may have greater cognitive resilience to AD-pathology and neurodegeneration than males.

Future Directions:

Further research is needed to better characterize sex differences in AD biomarker progression and cognitive trajectories. Investigating sex-specific differences in autosomal-dominant AD is key to elucidate mechanisms of risk and resilience in AD.

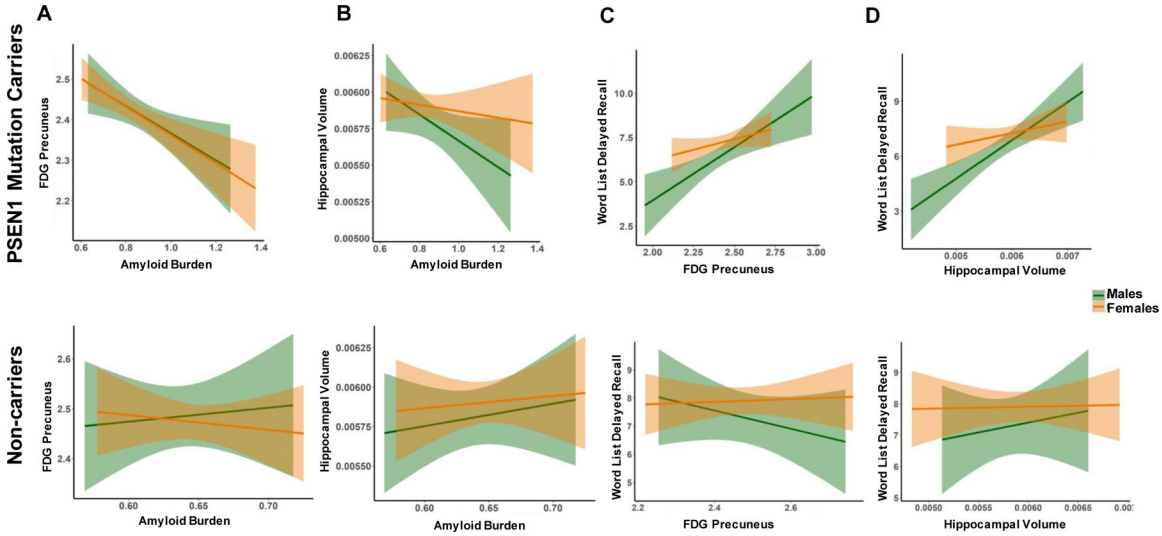

Figure 1. Relations between cortical amyloid burden, markers of neurodegeneration and memory performance in male and female *PSEN1* mutation carriers and non-carriers.

Note. A, FDG precuneus as a function of amyloid burden. **B**, Hippocampal volume as a function of amyloid burden. **C**, Word list delayed recall as a function of FDG precuneus. **D**, Word list delayed recall as a function of hippocampal volume. Orange represents females and green represents males. Top row depicts *PSEN1* mutation carriers, bottom row depicts non-carriers. Abbreviations: Amyloid Burden, mean cortical florbetapir standard uptake value ratios (SUVRs); FDG Precuneus, glucose metabolism in the precuneus relative to the whole brain; Hippocampal Volume, Hippocampal to total intracranial volume ratios.

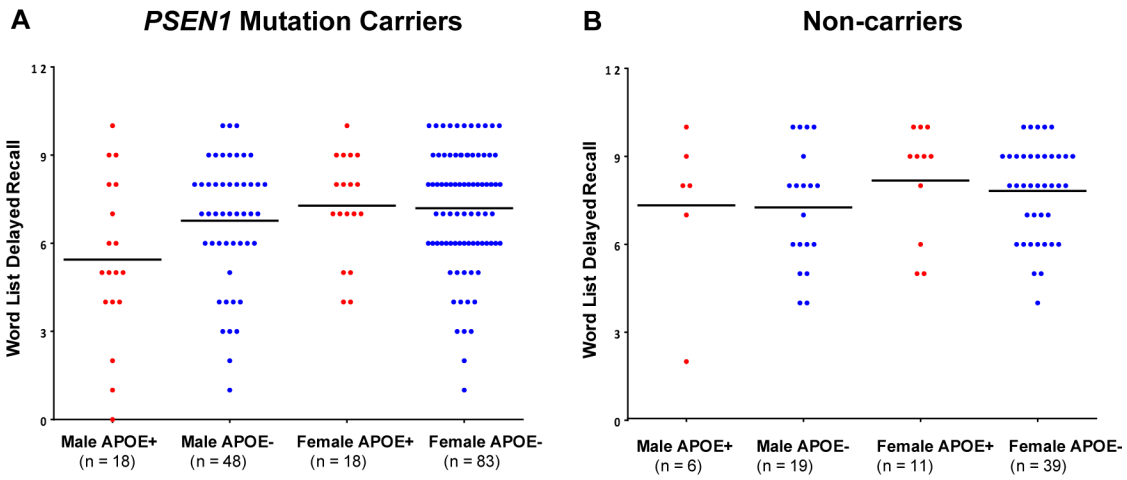

Figure 2. Effect of *APOE* ε4 status on verbal memory

Note. A, Memory delayed recall as a function of sex and APOE ε4 status in *PSEN1* mutation carriers. **B**, Memory delayed recall as a function of sex and APOE ε4 status in *PSEN1* non-carriers. Abbreviations: APOE+, indicates the presence of an ε4 allele; APOE− indicates the absence of an ε4 allele. Red dots represent APOE ε4 carriers and blue dots represent APOE ε4 non-carriers. Horizontal lines represent unadjusted group means.

Table 1.

Demographic, clinical, cognitive, and neuroimaging among male and female PSEN1 mutation carriers and non-carriers

	***PSEN1* Mutation Carriers (n=167)**		**p-value[a]**	**p-value[b]**	**Non-carriers (n=75)**		**p-value[c]**
	Males (n=66)	**Females (n=101)**			**Males (n=25)**	**Females (n=50)**	
Age	37.7±5.8	35.9±5.1	.04		41.5±6.3	42.2±6.1	.62
Education	8.82±4.16	8.73±4.03	.89		8.32±4.75	8.58±4.24	.81
MMSE	28.80±1.15	28.82±1.53	.932	.670	29.28±0.74	29.16±1.06	.61
Amyloid burden	.88± .14	0.84±0.13	.075	.470	0.64±0.04	.65±.03	.30
Hippocampal Volume × 10^3	5.78± .53	5.91±0.41	.087	.219	5.81±0.42	5.90±.46	.39
FDG Precuneus	2.41± .15	2.42±0.14	.634	.992	2.48±0.14	2.47±.12	.72
CERAD Word List Learning	19.20±4.50	20.69±3.97	.026	.173	20.80±3.93	21.30±4.05	.61
CERAD Word List Delayed Recall	6.41±2.40	7.21±2.02	.022	.154	7.28±2.17	7.90±1.66	.17
FCSRT Total Recall	41.0±7.60	43.24±5.46	.029	.145	43.84±3.54	44.92±2.93	.20
FCSRT Delay	13.65±3.20	14.51±2.52	.056	.216	14.88±1.67	15.34±.98	.21
Constructional Praxis	9.83±1.22	9.73±1.44	.632	.488	10.12±0.83	10.12±1.15	1.00
MiNT (Naming)	11.67±3.00	11.68±2.28	.974	.704	11.24±3.92	11.80±2.52	.46
Raven Progressive Matrices	9.20±1.88	9.02±1.89	.556	.231	9.20±2.00	9.00±1.73	.66

Note. Abbreviations: FDG, ^{18}F-fludeoxyglucose (FDG) positron emission tomography; MMSE, Mini-Mental Status Exam; CERAD, Consortium to Establish a Registry for AD; MiNT, Multilingual Naming Test; FCSRT, Free and Cued Selective Reminding Test.

[a] p-value as defined by a t-test for males vs females in *PSEN1* mutation carriers.

[b] p-value as defined by a t-test for males vs females in *PSEN1* mutation carriers controlling for age.

[c] p-value as defined by a t-test for males vs females in non-carriers.

Table 2.

Regression estimates of the effect of sex on markers of neurodegeneration and cognition

		***PSEN1* Mutation Carriers & Non-carriers**		***PSEN1* Mutation Carriers**	
Outcome Variable	**Predictors**	**Standardized β**	***p*-value[a]**	**Standardized β**	***p*-value[b]**
FDG Precuneus	*PSEN1 status*	−.097	.923		
	Amyloid burden	−3.846	**.000**	−3.19	**.002**
	Sex	−.234	.815	−.170	.865
	Age	−.254	.800	−.658	.512
	Sex × Amyloid Burden^	−.063	.950	−.145	.885
Hippocampal Volume	*PSEN1* status	−.222	.824		
	Amyloid burden	−1.101	.272	−.081	.935
	Sex	1.683	.094	1.222	.223
	Age	−1.124	.262	−2.583	**.011**
	Sex × Amyloid burden^	.854	.394	1.089	.278
Word List Delayed Recall	*PSEN1* status	3.336	**.001**		
	FDG Precuneus	1.512	.132	1.842	.067
	Amyloid burden	−.540	.590	−.150	.881
	Sex	1.988	**.048**	1.289	.199
	Age	−6.650	**.000**	−5.284	**.000**
	Sex × FDG Precuneus^	−.607	.544	−1.340	.182
Word List Delayed Recall	*PSEN1* status	3.462	**.001**		
	Hippocampal Volume	2.497	**.013**	2.127	**.035**
	Amyloid burden	−.689	.491	−.508	.612
	Sex	1.666	.097	1.014	.312
	Age	−6.585	**.000**	−4.978	**.000**
	Sex × Hippocampal Volume^	−1.441	.151	−1.159	.248

Note. Abbreviations: FDG Precuneus, ^{18}F-fluodeoxyglucose metabolism in the precuneus; Word List Delayed Recall, squared CERAD Word List – Delayed Recall; *PSEN1* status, *PSEN1* Mutation Carriers/Non-carriers. Bold text represents *p*-value <.05.

[a] p value as defined by models including *PSEN1* mutation carriers and non-carriers.

[b] p value as defined by models including *PSEN1* mutation carriers only.

^ Subsequent model was run adding the interaction term.

Table 3.

Demographic, clinical, cognitive, and neuroimaging characteristics in male and female APOE ε4 carriers and non-carriers

	PSEN1 Mutation Carriers (n=167)						Non-carriers (n=75)					
	Males			Females			Males			Females		
	APOE ε4+ (n=18)	APOE ε4− (n=48)	p	APOE ε4+ (n=18)	APOE ε4− (n=83)	p	APOE ε4+ (n=6)	APOE ε4− (n=19)	p	APOE ε4+ (n=11)	APOE ε4− (n=39)	p
Age	37.2±4.9	37.9±6.2	0.70	35.8±4.4	35.9±5.3	0.91	43.3±6.9	40.9±6.1	0.42	41.6±5.0	42.4±6.4	0.68
Education (years)	8.89±3.16	8.79±4.51	0.93	9.72±3.08	8.52±4.20	0.25	8.67±4.93	8.21±4.83	0.84	9.55±3.67	8.31±4.39	0.40
MMSE	28.83±1.34	28.79±1.09	0.90	29.33±1.09	28.71±1.60	0.12	29.50±0.55	29.21±0.79	0.41	29.64±0.67	29.03±1.11	0.09
FDG Precuneus	2.35±0.11	2.43±0.16	0.83	2.39±0.13	2.43±0.14	0.85	2.59±0.07	2.45±0.15	0.009	2.53±0.11	2.46±0.13	0.95
Hippocampal Volume × 10 ^{3}	5.7±0.6	5.8±0.5	0.67	5.8±0.4	5.9±0.4	0.43	6.1±0.4	5.7±0.4	0.07	6.0±0.5	5.9±0.4	0.25
Amyloid Burden	0.88±0.17	0.87±0.13	0.90	0.88±0.16	0.83±0.13	0.14	0.65±0.04	0.63±0.04	0.32	0.65±0.02	0.65±0.03	0.67
CERAD Word List Learning	18.33±4.41	19.52±4.54	0.34	20.72±4.01	20.43±4.56	0.97	21.67±2.42	20.53±4.31	0.55	22.09±4.23	21.08±4.03	0.47
CERAD Word List Delayed Recall	5.44±2.77	6.77±2.17	0.04	7.28±1.78	7.20±2.08	0.88	7.33±2.81	7.26±2.02	0.95	8.18±1.94	7.82±1.59	0.53

Note. APOE ε4+/−, *APOE* genotype was coded as positive or negative for presence of an ε4 allele. Abbreviations: MMSE, Mental Status Exam; FDG, ^{18}F-fludeoxyglucose (FDG) positron emission tomography; CERAD, Consortium to Establish a Registry for AD.

Table 4.

Regression estimates of the effect of APOE ε4 on markers of pathology, neurodegeneration and cognition

Outcome Variable	Predictors	Standardized β	*p*-value
Amyloid Burden	*PSEN1* status	−17.574	**.000**
	Sex	−.957	.339
	Age	7.157	**.000**
	APOE ε4	−1.519	.130
	Sex × APOE ε4^	−.992	.322
FDG Precuneus	Amyloid burden	−3.820	**.000**
	PSEN1 status	−.097	.923
	Sex	−.232	.816
	Age	−.252	.801
	APOE ε4	−.012	.990
	Sex × APOE ε4^	−.733	.464
Hippocampal Volume	Amyloid burden	−1.140	.255
	PSEN1 status	−.260	.795
	Sex	1.710	.088
	Age	−1.098	.273
	APOE ε4	−.456	0.649
	Sex × APOE ε4^	.194	.846
Word List Delayed Recall	FDG Precuneus	1.513	.132
	Amyloid burden	−.473	.637
	PSEN1 status	3.375	**.001**
	Sex	1.929	.055
	Age	−6.667	**.000**
	APOE ε4	.662	.509
	Sex × APOE ε4^	−1.338	.182
Word List Delayed Recall	Hippocampal Volume	2.514	**.013**
	Amyloid burden	−.612	.541
	PSEN1 status	3.508	**.000**
	Sex	1.600	.111
	Age	−6.606	**.000**
	APOE ε4	.730	.466
	Sex × APOE ε4^	−1.465	.144

Note. Abbreviations: Amyloid burden, Logio mean cortical florbetapir standard uptake value ratios; FDG Precuneus, ^{18}F-fluodeoxyglucose metabolism in the precuneus; Word List Delayed Recall, squared CERAD Word List – Delayed Recall; *PSEN1* status, *PSEN1* Carriers/Non-carriers. Bold text represents *p*-value <.05.

^Subsequent model was run adding the interaction term.