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Sex and *APOE-ε4* carrier effects on atrophy, amyloid PET, and tau PET burden in early-onset Alzheimer's disease

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CONFLICTS

J.L.D. is an inventor on patents or patent applications of Eli Lilly and Company relating to the assays, methods, reagents and / or compositions of matter related to measurement of P-tau217. J.L.D. has served as a consultant for Abbvie, Genotix Biotechnologies Inc, Gates Ventures, Karuna Therapeutics, AlzPath Inc, Cognito Therapeutics, Inc., and received research support from ADx Neurosciences, Fujirebio, AlzPath Inc, Roche Diagnostics and Eli Lilly and Company in the past two years. J.L.D. has received speaker fees from Eli Lilly and Company.

L.I. is currently a full-time employee of Eli Lilly and Company / Avid Radiopharmaceuticals and a minor shareholder of Eli Lilly and Company. His contribution to the work presented in this manuscript was performed while he was affiliated with the University of California San Francisco.

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No other authors associated with this project have reported conflicts of interest that would impact these results.

CONSENT STATEMENT

All authors have read and provided consent to be associated with this manuscript.

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Abstract

INTRODUCTION: We used sex and *apolipoprotein E ε4 (APOE-ε4)* carrier status as predictors of pathologic burden in early-onset Alzheimer's disease (EOAD).

METHODS: We included baseline data from 77 cognitively normal (CN), 230 EOAD and 70 EO non-Alzheimer's disease (EONonAD) participants from the Longitudinal Early-Onset Alzheimer's Disease Study (LEADS). We stratified each diagnostic group by males and females, then further subdivided each sex by *APOE-ε4* carrier status and compared imaging biomarkers in each stratification. Voxel-wise multiple linear regressions yielded statistical brain maps of gray matter density, amyloid and tau PET burden.

RESULTS: EOAD females had greater amyloid and tau PET burden than males. EOAD female *APOE-ε4* non-carriers had greater amyloid PET burden and greater gray matter atrophy than female *ε4* carriers. EONonAD female *ε4* non-carriers also had greater gray matter atrophy than female *ε4* carriers.

DISCUSSION: The effects of sex and *APOE-ε4* must be considered when studying these populations.

Keywords

Sex differences; *APOE-ε4*; Early-onset Alzheimer's disease; Early-onset non-Alzheimer's disease; genetics; neuroimaging; MRI; amyloid PET; tau PET; imaging biomarkers

1 BACKGROUND

Sporadic Alzheimer's disease (AD) is a heterogeneous, multifactorial disorder that presents with a high degree of clinicopathological variability across the AD spectrum. While the morphological hallmarks of extracellular amyloid- β and intraneuronal tau aggregates forming neurofibrillary tangles can be observed across different variants, disease onset, trajectory, and clinical phenotype are highly variable¹.

The early-onset AD (EOAD; onset <65 years) variant is an atypical, insidious, and aggressive form of AD with an accelerated trajectory of cognitive decline and greater pathology burden compared to late-onset AD (LOAD)²⁻⁵. EOAD manifests with more extensive neurodegeneration and tau burden in regions classically correlated with AD. Neuroimaging measures reveal greater global atrophy on magnetic-resonance imaging (MRI), extensive hypometabolism in the bilateral parietal, temporal, and frontal lobes, as

well as insular and cingulate cortices on fluorodeoxyglucose-positron emission tomography (FDG-PET) compared to cognitively normal (CN) controls, with a stronger effect size in EOAD vs. LOAD⁶.

A multitude of factors, including biological sex and certain genes, modulate lifetime AD risk and disease phenotype. When considering sex differences, longitudinal studies examining sex in LOAD and EOAD suggest that female participants are subject to faster disease progression, greater pathology burden and seem to be more susceptible to clinical manifestations of AD than male participants^{7–9}. Female EOAD participants presented with greater global amyloid- β burden and greater tau burden in the frontal, inferior parietal, and temporal lobes, along with more pronounced hippocampal atrophy¹⁰.

While most patients with a clinical diagnosis of AD are positive on amyloid- β scans, 15–35% of clinically diagnosed AD patients are found to be amyloid- β negative^{11–13}. These individuals exhibit evidence of neurodegeneration, but do not meet the biomarker threshold for brain amyloidosis^{14–16}. As a result, they are classified as non-AD or early-onset non-AD (EOnonAD)^{11–13}. EOnonAD dementia is caused by multiple etiologies, presenting as heterogenous clinical trajectories and outcomes¹¹. Chételat et al.¹¹, found EOnonAD populations to be a mix of limbic-predominant pathologies that largely affect the medial temporal lobe, which makes the identification of succinct patterns of atrophy and tau PET deposition difficult⁵.

Among those diagnosed with AD, the prevalence of *apolipoprotein E $\epsilon 4$* (*APOE- $\epsilon 4$*) is upwards of 40%, compared to between 13–23% in non-AD individuals worldwide¹⁷. Compared to other isoforms, the *APOE- $\epsilon 4$* variant is associated with greater amyloid- β deposition in the brain^{18,19}. Tau-mediated neurodegeneration may also be markedly exacerbated by *APOE- $\epsilon 4$* leading to increased tau deposition^{20,21}. *APOE- $\epsilon 4$* is associated with earlier symptom onset in LOAD, and possibly a later symptom onset in EOAD, though it appears the $\epsilon 4$ allele has maximum impact between the onset ages of 60–70 years^{4,22,23}. Further, Polsinelli et al.⁴, found female EOAD *APOE- $\epsilon 4$* non-carriers had significantly younger symptom onset compared to female $\epsilon 4$ carriers and males regardless of their *APOE- $\epsilon 4$* status, suggesting a complex age and sex dependent relationship between *APOE- $\epsilon 4$* and AD²⁴. EOnonAD patients are less likely to be *APOE- $\epsilon 4$* carriers, with a low, 14%, prevalence of the gene^{11,25}.

This study aims to examine the effects of sex on gray matter atrophy, amyloid PET and tau PET burden and further stratify these effects by *APOE- $\epsilon 4$* carrier status in the LEADS cohort. Given the limited literature on sex differences in EOAD and EOnonAD these analyses will fill a valuable gap in the literature. We hypothesized that EOAD females would have greater atrophy, amyloid PET, and tau PET burden than EOAD males. We also suspected that we might observe nonAD-like patterns of pathology in our EOnonAD group due to the multiple etiologies contributing to this disease state. Furthermore, we conducted an exploratory analysis in which we investigated how *APOE- $\epsilon 4$* carrier status within each sex impacted EOAD and EOnonAD pathologic burden.

2 METHODS

2.1 Participants and Data collection

The current study included 230 EOAD, 70 EOnonAD, and 77 CN participants from the Longitudinal Early-Onset Alzheimer's Disease Study (LEADS) with data from their baseline visit. When the study was conducted, 377 participants from LEADS had all necessary baseline imaging data needed for analysis which included T1 structural MRI, Florbetaben PET (FBB PET; amyloid), and Flortaucipir PET (FTP PET; tau) data. Due to batch processing *APOE* genotype data was only available for a subset of participants (204 EOAD, 67 EOnonAD, 74 CN).

LEADS is an ongoing longitudinal multi-site study with the primary goals of advancing knowledge of mechanisms and heterogeneity, and capturing disease progression through collection of clinical, genetic and biomarker data²⁶. The study collects baseline and longitudinal clinical, cognitive, genetic, and neuroimaging and fluid biomarker data. Neuroimaging data collection includes various MRI sequences, FBB PET, FTP PET, and FDG PET (EOnonAD and CN groups only).

The framework, methodology, exclusion and inclusion criteria, and clinical and biomarker assessments of LEADS have been previously published²⁶. Briefly, all participants are between 40–64 years old at the time of consent. Participants are either self-referred or referred from clinic and given the rarity of EOAD, site enrollment is not capped (nor is sex proportion). EOAD and EOnonAD participants meet the NIA-AA criteria for dementia or MCI and have a global Clinical Dementia Rating (CDR)²⁷ score ≥ 1 . CN participants have a global CDR = 0, a Mini-Mental State Examination (MMSE)²⁸ score ≥ 24 , and normal ranges on neuropsychological testing. Impaired individuals with genetic mutations in Amyloid Precursor Protein (APP), Presenilin-1 (PSEN1) or Presenilin-2 (PSEN2), Microtubule Associated Protein Tau (MAPT), Chromosome 9 Open Reading Frame 72 (C9ORF72), or Granulin Precursor aka Progranulin (GRN) were excluded, consistent with LEADS' focus on sporadic early-onset dementia. To assign cognitively impaired participants to the EOAD or EOnonAD group, visual reads and global SUVR quantification of baseline amyloid PET scans were used. Certified physicians first performed visual reads blinded to clinical information and scan quantification. If the visual read and SUVR quantification were both A β -positive or both A β -negative, the participant was assigned to the EOAD or EOnonAD cohort, respectively. If the visual read and quantification were incongruent, a second "tie breaker" visual read was performed by an additional blinded reader for cohort assignment. The quantitative threshold used for amyloid PET positivity is a global SUVR ≥ 1.18 , extracted from a PET-only pipeline. The full details of all PET methods and thresholds are described elsewhere in this special issue²⁹.

Informed consent was obtained from all participants in accordance with U.S. federal and local federations, the Declaration of Helsinki and the Indiana University Institutional Review Board.

2.2 Genotyping

National Alzheimer's Coordinating Center, the Alzheimer's Disease Center Network, National Centralized Repository for Alzheimer's Disease and Related Dementias and Alzheimer's Clinical Trials Consortium collaborate to track phenotypic data, imaging and biologic specimens, including genotypic data from LEADS participants³⁰.

2.3 MRI and PET Data Acquisition and Processing

MRI and PET data acquisition details and any pre-processing steps are fully described in Apostolova et al.²⁶. T1 structural MRI scans and fully pre-processed FBB PET and FTP PET scans were downloaded from LONI IDA³¹ in NifTI format. Fully pre-processed PET scans were already quality controlled, averaged, aligned to standard space, intensity-normalized and smoothed to standard resolution using ADNI procedures^{26,32}. Volumetric measures for MRI and regional and composite standardized uptake value ratio (SUVR) values for amyloid and tau PET were downloaded from LONI, which were extracted using Freesurfer 7.1. Details on the methods to extract these values are described previously and elsewhere in this special issue^{26,29}.

We processed the quality-controlled MRI scans using voxel-based morphometry (VBM) in Statistical Parametric Mapping version 12 (SPM12)³³. The resulting gray matter maps were normalized and smoothed with a 10 mm Gaussian kernel which yielded gray matter density (GMD) images to be used in imaging analysis. The downloaded PET scans were co-registered to the corresponding MRI scan from the same visit, normalized to MNI space using transformation parameters from VBM MRI segmentation, and re-scaled to MRI-defined reference regions^{26,29} (amyloid PET to whole cerebellum and tau PET to inferior cerebellar gray matter) using SPM via MATLAB. Quality control was conducted on all final processed MRI and PET images.

2.4 Statistical analysis and Workflow

Our analyses included the full cohort and the subset of participants with available *APOE* genotype as described in section 2.1. First, we analyzed the effect of sex on imaging biomarkers within each diagnostic group. Next, we analyzed the effect of *APOE-ε4* carrier status within males and females, separately, within each diagnostic group. See Figure 1 for analysis workflow.

2.4.1 Demographic and Imaging Biomarker Comparisons—Full cohort demographics were compared using analysis of variance (ANOVA) for continuous variables and chi-square tests for categorical variables implemented in Statistical Package for Social Sciences (SPSS) version 28. Demographics and imaging biomarkers were compared using independent samples *t* tests for the sex differences and sex stratified by *APOE-ε4* analyses. Box plot representations of means for the imaging biomarkers were produced in R Studio. We used average hippocampal volume as our MRI measure which was corrected for intracranial volume (ICV). For amyloid PET, we used a composite neocortical SUVR value representing global amyloid uptake. For tau PET, we used the MetaROI³⁴ and composite Braak stage³⁵ SUVR values (Braak 1/2, Braak 3/4, Braak 5/6).

2.4.2 3D Comparisons—For analysis in imaging space, voxel-wise multiple linear regression models were employed in SPM 12 to produce whole brain 3D statistical brain maps of GMD, amyloid PET burden, and tau PET burden within each diagnostic group. Part one of our analyses used sex as the predictor (male vs. female). The second part of our analyses used *APOE-ε4* carrier status (*ε4+* vs. *ε4-*) as the predictor within each sex group. All models included age and education as covariates, and GMD models also included ICV as a covariate.

We set our voxel-wise significance threshold at $p < 0.01$ (uncorrected) to visualize results and applied family-wise error (FWE) correction for multiple comparisons at the cluster level. Only clusters surviving a $p_{FWE} < 0.05$ with a minimum cluster size (k) equal to the smallest significant cluster size were visualized. Cluster-corrected statistical maps were saved as NifTI files and rendered in Surf Ice³⁶ producing 3D brain maps.

3 RESULTS

3.1 Sample Characteristics

3.1.1 LEADS Cohort Overview—Demographic and baseline cognitive data for EOAD, EOnonAD, and CN groups are shown in Table 1. The CN group was younger than the EOAD and EOnonAD groups ($p = .006$). The CN group was also the most educated compared to EOAD and EOnonAD ($p < .001$). Predictably, the CN group had the highest MMSE score, followed by EOnonAD and lastly EOAD ($p < .001$).

While all groups were predominantly White non-Latino/a, the racial make-up of our cohort was significantly different across groups ($p < .001$). The CN and EOAD groups had larger proportions of females (68% and 54% respectively) compared to EOnonAD (36% female) ($p < .001$).

As expected, EOAD had the highest proportion of *APOE-ε4* carriers, but the difference was not significant (CN 43%, EOAD 54%, and EOnonAD 42%; $p = .114$).

3.1.2 Demographic Differences by Sex—The results examining demographic differences by sex in each diagnostic group are shown in Table 2. There were no significant differences in age between males and females in either of the CN, EOAD, or EOnonAD groups. CN males had significantly more education than CN females ($p = 0.04$). There were no significant differences in years of education between males and females for EOnonAD or EOAD. Males and females in the CN and EOAD groups showed no significant differences on the MMSE, while EOnonAD males outperformed EOnonAD females on MMSE ($p = .02$). *APOE-ε4* carrier status did not differ between males and females in any diagnostic group. Percentages of *ε4* carriers in males and females in each diagnostic group are shown in Table 2.

3.1.3 Sex Stratified by *APOE-ε4* Carrier Status Demographics—The demographic results examining sex stratified by *APOE-ε4* carrier status in each diagnostic group are shown in Table 3. There were no significant differences in age or education between female *ε4* carriers and female *ε4* non-carriers in the EOAD group. There were also

no significant differences in age, education, or MMSE between male $\epsilon 4$ carriers and male $\epsilon 4$ non-carriers in the EOAD group. EOAD female carriers had a significantly higher MMSE score than EOAD female non-carriers ($p = .01$). Carrier and non-carrier differences by sex were not seen in either CN or EOnonAD for age, education, and MMSE.

3.2 Imaging biomarker and 3D comparisons

3.2.1 Sex Differences

Imaging biomarker comparisons between males and females are shown in Table 2 for all groups and displayed as box plots in Figure 2 for the EOAD group. In the EOAD group, females had significantly greater tau uptake in the metaROI ($p < .001$), as well as Braak 3/4 ($p = .002$) and Braak 5/6 ($p = .006$) and higher mean global amyloid uptake, compared to EOAD males ($p < .001$). Interestingly, EOAD females also had larger mean hippocampal volume than EOAD males ($p = .01$). Sex-based differences were also seen in the CN group (Supplementary Figure 1). CN males had a greater mean tau SUVR in Braak 1/2 ($p = .03$). There were no significant sex-based differences in the EOnonAD group (Supplementary Figure 1).

The FWE cluster-level corrected whole brain maps from the voxel-wise analysis comparing male and female participants within CN, EOAD, and EOnonAD are shown in Figure 3. Overall, EOAD females had greater amyloid and tau burden than EOAD males. For amyloid PET, females showed greater uptake than males in the frontal, inferior parietal, and inferior temporal cortices and the superior frontal, cingulate, and lingual gyri, bilaterally. For tau PET, females showed greater uptake than males primarily in the left temporoparietooccipital and the left middle and inferior temporal cortices. No significant differences between males and females were seen in the CN and EOnonAD groups for amyloid or tau burden. There were also no significant differences between males and females for GMD in CN, EOAD, or EOnonAD.

3.2.2 Sex stratified by APOE- $\epsilon 4$ carrier status—Imaging biomarker comparisons for sex stratified by *APOE- $\epsilon 4$* carrier status are shown in Table 3 for all groups and displayed as box plots in Figure 4 for the EOAD group. In the EOAD group, female $\epsilon 4$ carriers had a higher mean tau SUVR in Braak 1/2 ($p = .004$) than female $\epsilon 4$ non-carriers; however, it was the female $\epsilon 4$ non-carriers with greater global amyloid uptake ($p < .001$). No significant differences were found between male $\epsilon 4$ carriers and male $\epsilon 4$ non-carriers in the EOAD group nor between carriers and non-carriers of any sex in the EOnonAD and CN groups (Supplementary Figures 2 & 3).

The FWE cluster-level corrected whole brain maps from the voxel-wise analysis comparing female $\epsilon 4$ carriers with female $\epsilon 4$ non-carriers within CN, EOAD, and EOnonAD are shown in Figure 5. There were no significant differences between male $\epsilon 4$ carriers and male $\epsilon 4$ non-carriers for GMD, amyloid or tau uptake in any of the diagnostic groups (not shown; all clusters, $p_{FWE} > .05$).

CN female $\epsilon 4$ carriers had greater amyloid uptake than CN female $\epsilon 4$ non-carriers in the superior and medial frontal cortices. In contrast, EOAD female $\epsilon 4$ non-carriers

had greater amyloid uptake compared to EOAD female $\epsilon 4$ carriers in the paracentral, frontal, and occipital cortices and the lingual gyrus and temporal pole. This pattern was present bilaterally but more pronounced on the right. EOAD female $\epsilon 4$ non-carriers also had greater gray matter atrophy than EOAD female $\epsilon 4$ carriers in the lateral temporal, temporoparietooccipital and inferior parietal cortices, bilaterally.

EOnonAD female $\epsilon 4$ non-carriers had greater gray matter atrophy lateralized to the right occipital cortex compared to EOnonAD female $\epsilon 4$ carriers. There were no significant differences between female $\epsilon 4$ carriers and female $\epsilon 4$ non-carriers for GMD in CN, for amyloid uptake in EOnonAD, or for tau uptake in EOAD, EOnonAD or CN.

4 DISCUSSION

Results of our imaging biomarker comparisons demonstrated that both sex and *APOE- $\epsilon 4$* carrier status impact atrophy, amyloid PET, and tau PET burden in EOAD, EOnonAD, and CN individuals.

4.1 Sex Differences

Greater amyloid and tau PET burden have been previously reported in female LOAD patients compared to male patients³⁷. As hypothesized, we found that female patients with EOAD have greater amyloid PET and tau PET burden compared to male patients. Examining the regional distribution of amyloid and tau burden in EOAD females, we observed greater amyloid uptake in frontal, parietal and temporal areas, and greater tau uptake in temporoparietooccipital areas. Consistent with previous findings³⁸, MMSE scores were similar between females and males despite greater pathological burden in females, suggesting that female AD patients may handle greater pathology burden and show some degree of cognitive resiliency. Thus, sex may serve as a moderator of the association between amyloid and tau burden and cognitive function³⁹.

We also found that EOAD females had significantly larger mean hippocampal volume than EOAD males which was seen in MCI and AD patients in prior work⁴⁰, suggesting that females could be less atrophied. However, we did not observe differences in GMD between males and females in our voxel-wise regression, similar to previous cross-sectional results^{41,42}. While no cross-sectional differences were seen, Lee et al.⁴¹, did observe longitudinal changes in cortical thickness between males and females with AD, showing females had more rapid decline than males. This highlights the importance of examining longitudinal changes between sexes within the LEADS cohort in future studies.

The role of sex hormones, such as estrogen, and menopause are important considerations in this age group given their proximity to menopause. Differences in estrogen levels across the lifespan have been linked to risk of dementia. Prevalence of dementia in surgically induced menopause versus natural menopause, and the association between number of pregnancies and rates of AD suggest low estrogen is associated with increased vulnerability to development of AD in female patients^{37,43–50}. Examining the influence of sex hormone fluctuations on cognitive function and neuroimaging biomarkers throughout the lifecycle is an important future direction for understanding sex-linked vulnerabilities to dementia. This

may be particularly fruitful in EO cohorts whose younger age offer a unique and essential perspective by including pre and perimenopausal women.

4.2 Sex stratified by APOE-ε4 carrier status

The most novel aspect of this paper is the further division of sex-split groups to account for *APOE-ε4* carrier status. Novel, exploratory analyses splitting each diagnosis group by sex and then by *APOE-ε4* carrier status showed important effects of *ε4* carrier status. Across all diagnostic groups, *APOE-ε4* carrier status was the most impactful in females.

Our CN group had a 43% *APOE-ε4* carrier rate and while this is not significantly higher than those of the EOAD and EOnonAD groups, it is notably higher compared to the global average proportion of *APOE-ε4* carriers among CN individuals in the population (23.9%)⁵¹. This high carrier rate can be attributed to the CN group being comprised of highly motivated volunteers who may have familial connections to AD.

CN female *APOE-ε4* carriers had more amyloid PET burden in the medial frontal cortices compared to female non-carriers, but no differences were found for tau burden. Amyloid deposition and *APOE* have been shown to interact in cognitively normal individuals, leading to a cascade of decline^{52,53}. Mormino and Papp⁵⁴ have suggested that in older clinically normal individuals, increased amyloid burden may represent a disease precursor and link to expedient decline. These findings and our data in conjunction with evidence that AD disproportionately affects female patients a nearly 2:1 rate over male patients, suggest a sex-driven uptake disparity in amyloid. Mosconi et al.⁵⁵, reported that cognitively normal perimenopausal and postmenopausal women exhibit increased amyloid deposition, hypometabolism, and reduced gray and white matter volume in regions vulnerable to AD when compared with cognitively normal premenopausal women and age-matched men. Further, postmenopausal *APOE-ε4* carriers had greater amyloid deposition relative to the other groups⁵⁵.

Similar to LOAD, EOAD female *APOE-ε4* carriers showed greater tau burden in the medial temporal lobe^{56–58}. The present study found EOAD female *APOE-ε4* carriers to have greater tau uptake in entorhinal and parahippocampal cortices (Braak 1/2) than female non-carriers. These findings reinforce that the *APOE-ε4* genotype facilitates a predisposition to vulnerability in the medial temporal areas^{57–59}.

However, EOAD female *APOE-ε4* non-carriers showed greater amyloid uptake than female carriers in the late Braak regions corresponding to the primary sensorimotor and visual cortices and greater gray matter atrophy, particularly in the lateral temporal, temporoparietooccipital and inferior parietal cortices. These findings suggest that there are yet uncovered risk factors that drive greater amyloid and neurodegenerative pathology burden in female *ε4* non-carriers. Less well-understood risk variants and genetic modifiers in EOAD that may be worth investigating for sex-based differences include *PRNP* *p.MMI29V*, *SORL1*, and *CCL11 p.A23T*, and *MAPT*^{60–62}. Consideration of these and other genetic drivers are essential in illuminating a more comprehensive understanding of AD disease processes and presentations and paving a path for greater sex and gender equity in the research, diagnosis, and precision-medicine-based treatment of EOAD.

Our results also yielded a significant difference between female $\epsilon 4$ carriers and female $\epsilon 4$ non-carriers in the EOnonAD group. EOnonAD female $\epsilon 4$ non-carriers presented with greater gray matter atrophy than $\epsilon 4$ carriers, primarily in the right occipital cortex. Given the heterogeneity of EOnonAD, these results may reinforce or, at least, not contradict, previous assertions that EOnonAD neurodegeneration is not driven by the *APOE* pathway, but rather a unique spectrum of etiologies that differ from AD⁶³.

4.3 Strengths and Limitations

Several strengths and limitations of our study should be noted. We expanded on the first part of our analysis examining sex differences by also exploring the impact of *APOE- $\epsilon 4$* carrier status on gray matter atrophy, amyloid PET, and tau PET burden. By first splitting each diagnostic group by males and females, then further dividing each sex by *APOE- $\epsilon 4$* carrier status, we were able to create a novel sequence of analyses and generate a new set of data.

One of the limitations of our study is the cross-sectional nature of our analyses. Longitudinal analyses are needed to assess atrophy and amyloid and tau uptake overtime; however, LEADS is a longitudinal study and future efforts will be focused on longitudinal changes. Another limitation is that our study focused on the effects of sex and *APOE- $\epsilon 4$* carrier status on neuroimaging biomarkers, so we did not include analysis of cognitive measures beyond MMSE. This limits our interpretation of the cognitive profiles in our cohort but is an opportunity for future research to explore cognitive resiliency and variation between sexes. It is also important to acknowledge that our analyses do not account for menopausal status for female participants. These data are currently being collected to include in future analyses examining the effects of menopause on cognitive function and neuroimaging biomarkers once the full study cohort is enrolled. Additionally, LEADS employs relatively strict inclusion and exclusion criteria which limit the representation of the cohort to all Alzheimer's and dementia patients. Furthermore, insufficient post-mortem data has been collected thus far in LEADS as it is an ongoing study, so pathological verification of AD and non-AD pathologies are lacking. In terms of diversity, equity and inclusion, the LEADS population is largely middle-aged, highly educated, and primarily consists of non-Latino/a White adults. As such, our findings do not generalize well to the AD population at large. Though our current sample lacks diversity, the LEADS study recently added a diversity recruitment supplement to promote community outreach of diverse populations. Replication of our findings in a more diverse group will be essential in ensuring greater inclusivity and applicability of our research.

4.4 Future Directions

These analyses are preliminary, and we plan to continue building on this work. Longitudinal follow-up analyses of atrophy, amyloid PET, and tau PET will provide important insight on outcomes among diagnostic groups. Additionally, we plan to explore cognitive resiliency between sexes by including more neuropsychiatric variables, further dividing groups by amnesic and non-amnesic presentation, and adding fluid biomarkers to our analysis. Other risk factors (such as obesity, hypertension, diabetes, depression etc.) that could be contributing to sex differences in neuroimaging biomarkers should also be included in future work. There is also an opportunity to compare the characteristics of our EOAD population in

LEADS to other AD populations with known genetic risk such as dominantly inherited Alzheimer's disease from the Dominantly Inherited Alzheimer Network Observational Study.

4.5 Conclusion

Despite our limitations, our results show that *APOE-ε4* and sex play a role in AD pathology in EOAD and suggest that the effects may be at least in part different from those observed in LOAD studies. Uncovering the main components of disease heterogeneity by examining the differential effects of sex, age, and genetic risk brings us closer to characterizing these understudied disease states and implementing clinical interventions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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HIGHLIGHTS

- Novel analysis examining the effects of biological sex and *apolipoprotein E e4* (*APOE-e4*) carrier-status on neuroimaging biomarkers among early-onset Alzheimer's disease (EOAD), early-onset non-AD (EOnonAD), and cognitively normal (CN) participants.
- Female sex is associated with greater pathology burden in the EOAD cohort compared to male sex.
- The effect of *APOE-e4* carrier status on pathology burden was the most impactful in females across all cohorts.

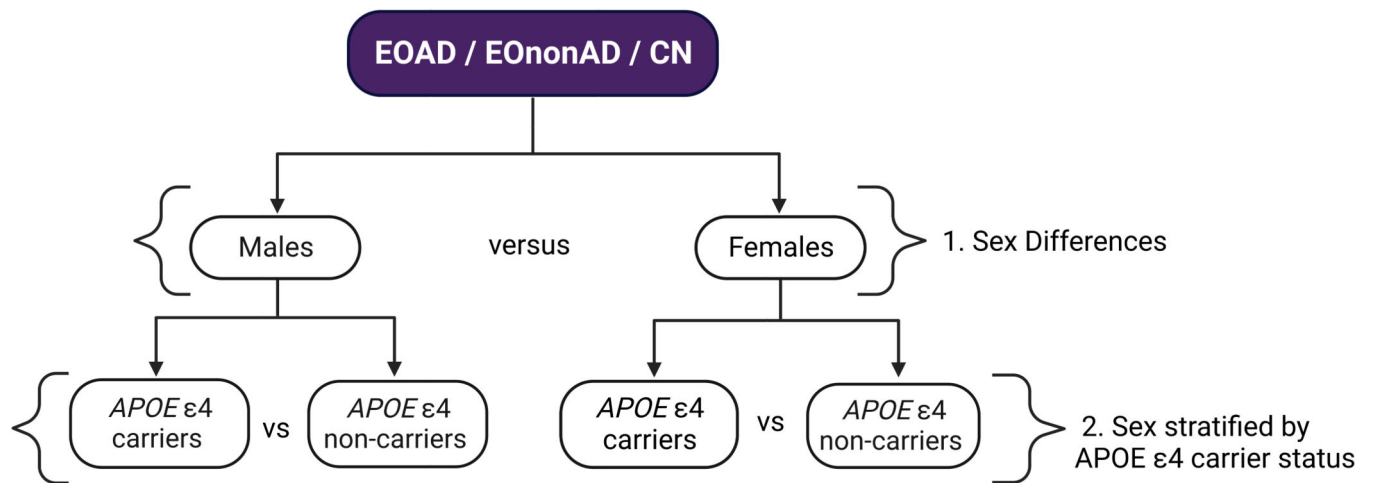
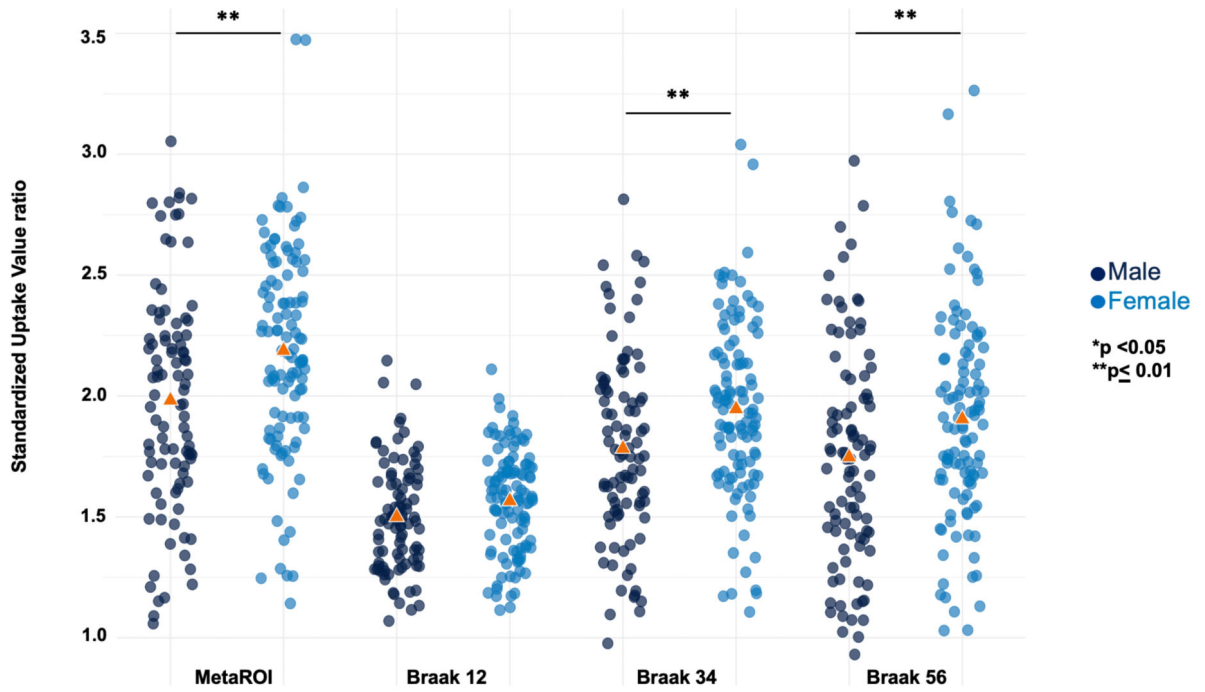


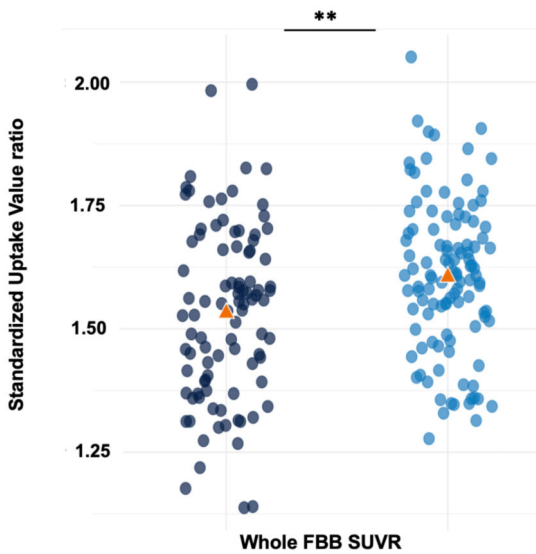
Figure 1. Analysis Workflow.

A visual representation of the groups used for each analysis. 1) Males were compared to females in each diagnostic group for demographic, imaging biomarker and 3D analyses. 2) Male *APOE-ε4* carriers were compared to male *ε4* non-carriers and female *APOE-ε4* carriers were compared to female *ε4* non-carriers in each diagnostic group for demographic, imaging biomarker and 3D analyses.

(A) Tau PET EOAD



(B) Amyloid PET EOAD



(C) MRI EOAD

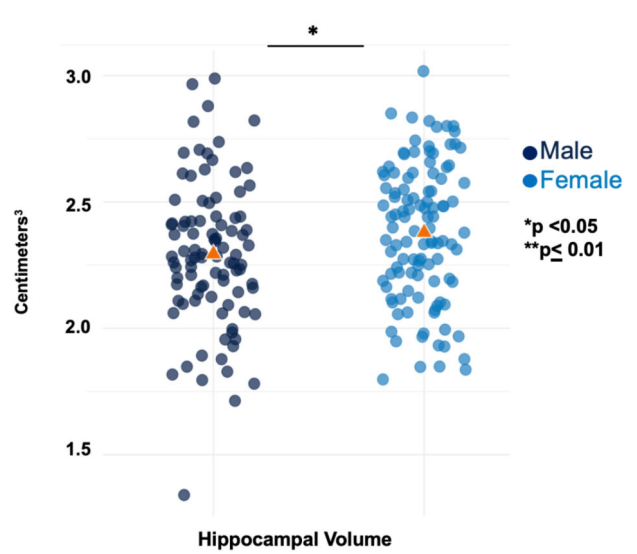


Figure 2. Box plots - Sex differences.

Imaging biomarker measures comparing EOAD males and females: (A) tau uptake measures, (B) global amyloid uptake, (C) hippocampal volume.

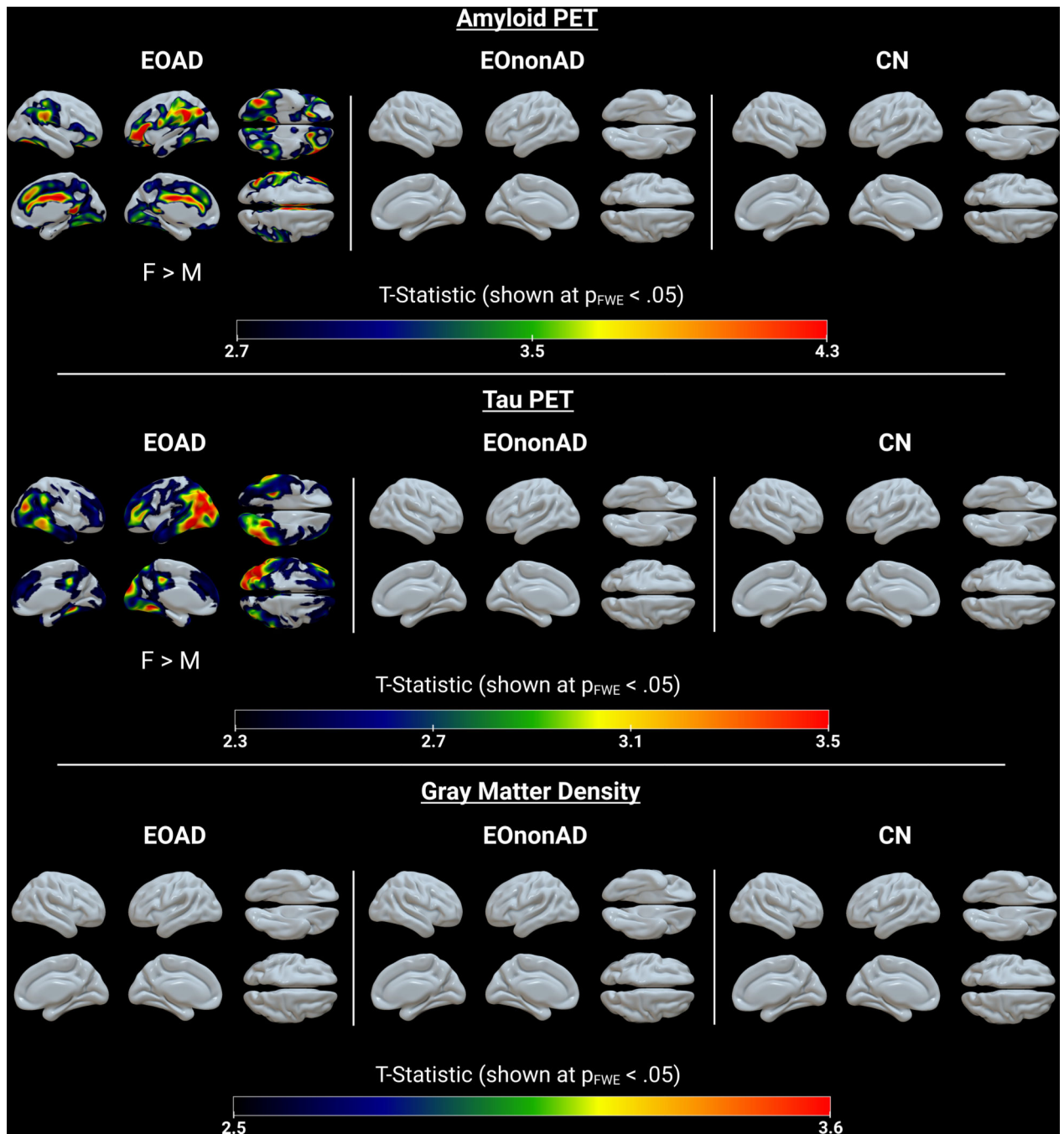
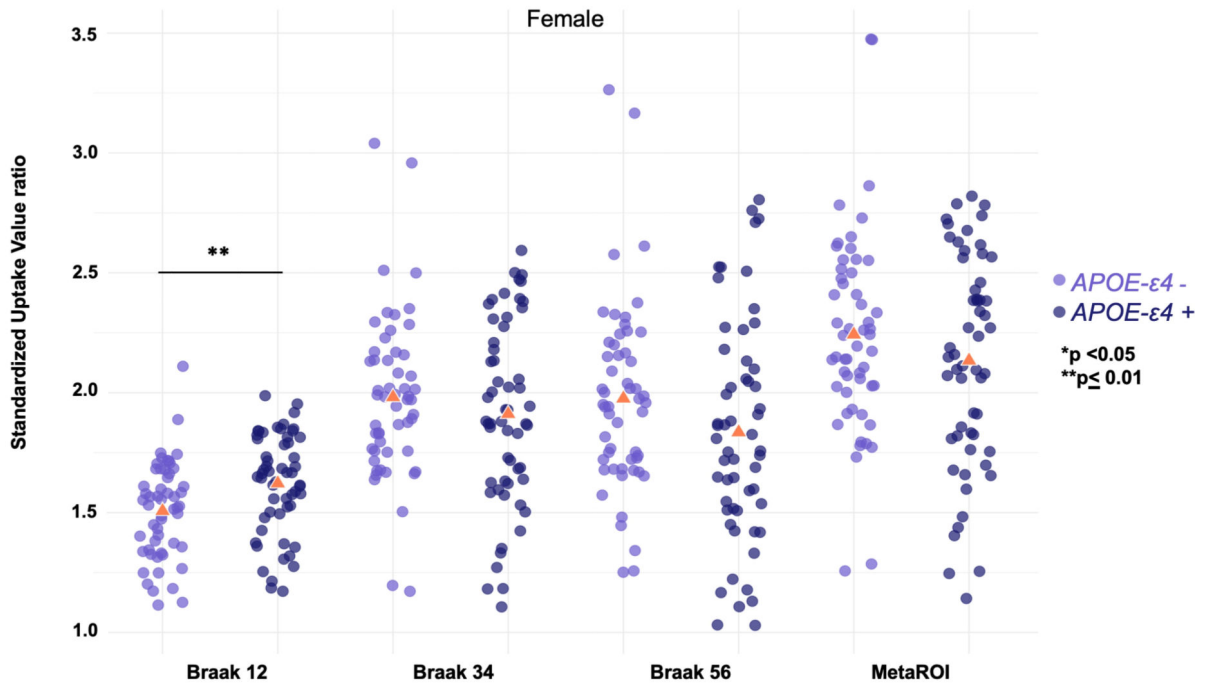


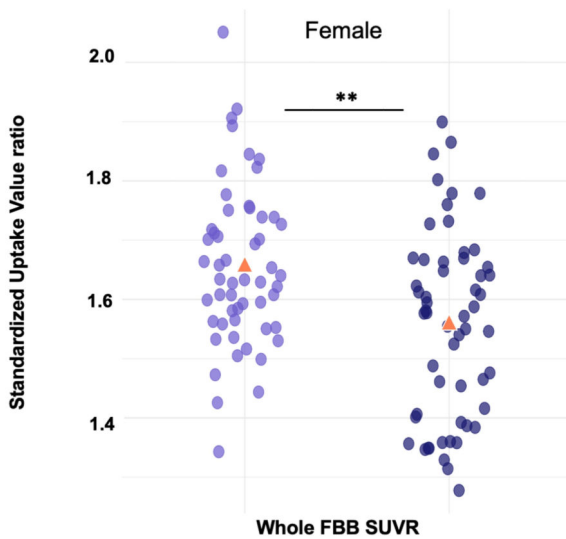
Figure 3. 3D comparisons – Sex Differences.

Voxel-wise multiple linear regression statistical maps showing males vs. females within CN, EOAD, and EOnonAD for amyloid PET, tau PET and GMD. All GMD models were controlled for ICV. *FWE: family-wise error.*

(A) Tau PET EOAD *APOE-ε4*- vs. *APOE-ε4*+



(B) Amyloid PET EOAD *APOE-ε4*- vs. *APOE-ε4*+



(C) MRI EOAD *APOE-ε4*- vs. *APOE-ε4*+

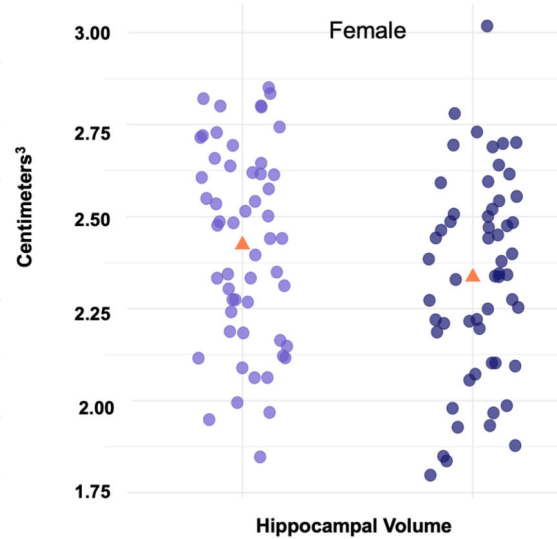


Figure 4. Box plots - Sex stratified by *APOE-ε4* carrier status.

Imaging biomarker measures comparing EOAD female *APOE-ε4* carriers (+) vs. female non-carriers (-): (A) tau uptake measures, (B) global amyloid uptake, (C) hippocampal volume.

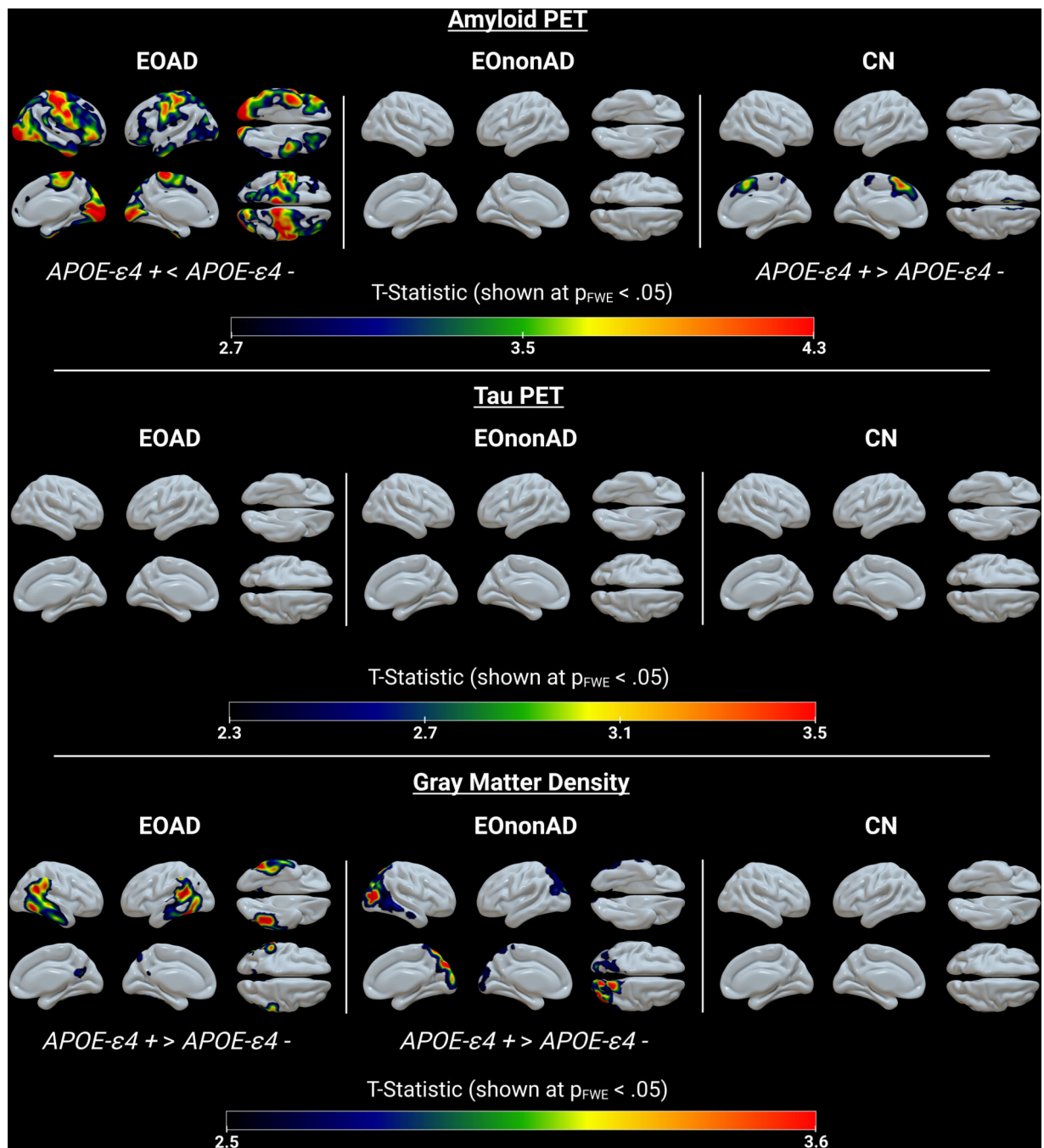


Figure 5. 3D Comparisons – Sex stratified by APOE-ε4 carrier status. Voxel-wise multiple linear regression statistical maps showing female *APOE-ε4* carriers (+) vs female non-carriers (-) within CN, EOAD, and EOnonAD for amyloid PET, tau PET and GMD. All GMD models were controlled for ICV. *FWE*: family-wise error.

Table 1.**Sample Overview.**

Demographic comparisons between EOAD, EOnonAD, and CN cohorts.

	EOAD	EOnonAD	CN	<i>p-value</i>
<i>N</i>	230	70	77	
Age, years, mean (SD)	59.1 (4.2)	58.3 (6.2)	56.5 (6.1)	0.006
Sex, % female	54%	36%	68%	<0.001
Race, % White	94%	89%	75%	<0.001
Years of education, mean (SD)	15.5 (2.4)	15.6 (2.5)	16.7 (2.2)	<0.001
<i>APOE-ε4</i> (%)	54%	42%	43%	0.114
MMSE, mean (SD)	21.6 (5.2)	25.6 (4.2)	29.3 (0.8)	<0.001

Sample Overview. Demographic comparisons between EOAD, EOnonAD, and CN groups.

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Table 2.
Sex Differences.

Demographic and imaging biomarker comparisons between EOAD, EOnonAD, and CN cohorts split by sex. *Whole FBB SUVR = global amyloid uptake; FTP MetaROI SUVR, Braak 12, Braak 34, Braak 56 = tau uptake.*

	EOAD			EOnonAD			CN		
	Males	Females	p-value	Males	Females	p-value	Males	Females	p-value
<i>N</i>	105	125		45	25		25	52	
Age, years, mean (SD)	59.1 (4.3)	59.2 (4.1)	0.9	58.3 (5.8)	58.4 (6.8)	0.9	55.6 (6.6)	56.9 (5.8)	0.4
Education, years, mean (SD)	15.3 (2.2)	15.7 (2.5)	0.2	15.9 (2.7)	15.0 (2.1)	0.1	17.4 (2.3)	16.3 (2.1)	0.04
MMSE (SD)	22.0 (5.4)	21.3 (5.0)	0.3	26.4 (2.4)	24.0 (6.0)	0.02	29.4 (0.7)	29.3 (0.8)	0.6
Race, % White	93%	95%	0.01	84%	96%	0.6	76%	75%	0.4
APOE-ε4+ (%)	57%	51%	0.4	40%	46%	0.6	33%	48%	0.2
Whole FBB SUVR, mean, (SD)	1.53 (0.2)	1.61 (0.1)	<0.001	1.00 (0.06)	1.02 (0.07)	0.3	1.03 (0.1)	1.03 (0.06)	0.8
FTP MetaROI SUVR, mean (SD)	2.00 (0.5)	2.20 (0.4)	<0.001	1.19 (0.2)	1.27 (0.4)	0.3	1.20 (0.2)	1.14 (0.05)	0.1
BRAAK 12 SUVR, mean (SD)	1.51 (0.2)	1.56 (0.2)	0.1	1.17 (0.1)	1.19 (0.2)	0.6	1.20 (0.2)	1.14 (0.08)	0.03
BRAAK 34 SUVR, mean (SD)	1.80 (0.4)	1.95 (0.4)	0.002	1.15 (0.2)	1.21 (0.3)	0.3	1.16 (0.2)	1.11 (0.05)	0.08
BRAAK56 SUVR, mean (SD)	1.75 (0.4)	1.91 (0.4)	0.006	1.07 (0.2)	1.14 (0.3)	0.2	1.08 (0.08)	1.08 (0.05)	0.8
Hippocampal Vol, cm ³ , mean (SD)	2.29 (0.3)	2.39 (0.3)	0.01	2.48 (0.4)	2.64 (0.3)	0.09	2.79 (0.3)	2.77 (0.2)	0.8

Table 3.

Sex stratified by APOE-ε4 carrier status. Demographic and imaging biomarker comparisons in EOAD, EOnonAD, and CN cohorts split by sex and further stratified by *APOE-ε4* carrier status. (A) EOAD male *APOE-ε4* carriers vs. male non-carriers and EOAD female *APOE-ε4* carriers vs. female non-carriers. (B) EOnonAD male *APOE-ε4* carriers vs. male non-carriers and EOnonAD female *APOE-ε4* carriers vs. female non-carriers. (C) CN male *APOE-ε4* carriers vs. male non-carriers and CN female *APOE-ε4* carriers vs. female non-carriers. *Whole FBB SUVR = global amyloid uptake; FTP MetaROI SUVR, Braak 12, Braak 34, Braak 56 = tau uptake.*

	(A)EOAD					
	Female			Male		
	<i>APOE-ε4+</i> Carrier	Non-carrier	<i>p</i> -value	<i>APOE-ε4+</i> Carrier	Non-carrier	<i>p</i> -value
<i>N</i>	56	54		54	40	
Age, years, mean (SD)	62.8 (4.5)	61.8 (3.8)	0.3	62.3 (4.0)	61.5 (4.6)	0.4
Education, years, mean (SD)	15.5 (2.6)	15.6 (2.5)	0.9	15.1 (2.3)	15.5 (2.2)	0.3
MMSE (SD)	22.8 (4.5)	20.4 (5.1)	0.01	22.2 (0.5)	21.5 (5.6)	0.5
<i>APOE-ε4+</i> (%)		51%			57%	
Whole FBB SUVR, mean, (SD)	1.56 (0.2)	1.65 (0.1)	<0.001	1.54 (0.2)	1.53 (0.2)	0.8
FTP MetaROI SUVR, mean (SD)	2.13 (0.4)	2.24 (0.4)	0.2	1.93 (0.5)	2.05 (0.4)	0.2
BRAAK 12 SUVR, mean (SD)	1.62 (0.2)	1.51 (0.2)	0.004	1.51 (0.2)	1.48 (0.2)	0.5
BRAAK 34 SUVR, mean (SD)	1.91 (0.4)	1.98 (0.3)	0.3	1.76 (0.4)	1.82 (0.3)	0.4
BRAAK 56 SUVR, mean (SD)	1.83 (0.5)	1.98 (0.4)	0.09	1.70 (0.5)	1.81 (0.4)	0.2
Hippocampal Vol, cm ³ , mean (SD)	2.34 (0.3)	2.42 (0.3)	0.09	2.26 (0.3)	2.34 (0.2)	0.2
	(B)EOnonAD					
	Female			Male		
	<i>APOE-ε4+</i> Carrier	Non-carrier	<i>p</i> -value	<i>APOE-ε4+</i> Carrier	Non-carrier	<i>p</i> -value
<i>N</i>	11	13		17	26	
Age, years, mean (SD)	61.0 (7.6)	61.0 (5.6)	0.9	62.6 (5.8)	61.0 (6.0)	0.4
Education, years, mean (SD)	14.4 (2.0)	15.4 (2.2)	0.3	16.2 (2.6)	15.7 (2.9)	0.6
MMSE (SD)	24.8 (6.4)	23.4 (6.1)	0.6	26.6 (2.7)	26.6 (2.1)	0.1
<i>APOE-ε4+</i> (%)		46%			40%	
Whole FBB SUVR, mean, (SD)	1.04 (0.09)	1.00 (0.05)	0.2	1.01 (0.08)	1.00 (0.06)	0.3
FTP MetaROI SUVR, mean (SD)	1.27 (0.4)	1.28 (0.4)	0.1	1.24 (0.3)	1.15 (0.07)	0.2
BRAAK 12 SUVR, mean (SD)	1.18 (0.2)	1.19 (0.2)	0.9	1.19 (0.2)	1.15 (0.1)	0.4
BRAAK 34 SUVR, mean (SD)	1.22 (0.4)	1.21 (0.3)	0.1	1.19 (0.3)	1.12 (0.06)	0.2
BRAAK 56 SUVR, mean (SD)	1.15 (0.3)	1.13 (0.2)	0.8	1.11 (0.3)	1.04 (0.05)	0.2
Hippocampal Vol, cm ³ , mean (SD)	2.65 (0.2)	2.64 (0.4)	0.9	2.41 (0.5)	2.52 (0.3)	0.4
	(C)CN					
	Female			Male		
	<i>APOE-ε4+</i> Carrier	Non-carrier	<i>p</i> -value	<i>APOE-ε4+</i> Carrier	Non-carrier	<i>p</i> -value
<i>N</i>	24	26		8	16	
Age, years, mean (SD)	59.7 (5.2)	60.8 (6.1)	0.5	58.0 (6.8)	60.1 (6.2)	0.5
Education, years, mean (SD)	16.3 (1.8)	16.4 (2.5)	0.9	17.3 (3.0)	17.5 (2.0)	0.8

	(A)EOAD					
	Female			Male		
	<i>APOE-ε4</i> Carrier	Non-carrier	<i>p</i> -value	<i>APOE-ε4</i> Carrier	Non-carrier	<i>p</i> -value
MMSE, mean (SD)	29.4 (0.7)	29.2 (0.9)	0.3	29.4 (0.7)	29.3 (0.7)	0.8
<i>APOE-ε4</i> (%)		48%			33%	
Whole FBB SUVR, mean, (SD)	1.04 (0.07)	1.02 (0.06)	0.2	1.08 (0.2)	1.01 (0.1)	0.2
FTP MetaROI SUVR, mean (SD)	1.14 (0.06)	1.15 (0.05)	0.4	1.31 (0.4)	1.15 (0.06)	0.2
BRAAK 12 SUVR, mean (SD)	1.13 (0.1)	1.15 (0.07)	0.4	1.29 (0.2)	1.16 (0.07)	0.06
BRAAK 34 SUVR, mean (SD)	1.11 (0.06)	1.12 (0.04)	0.5	1.24 (0.3)	1.13 (0.06)	0.2
BRAAK 56 SUVR, mean (SD)	1.07 (0.05)	1.08 (0.04)	0.5	1.11 (0.1)	1.06 (0.06)	0.3
Hippocampal Vol, cm ³ , mean (SD)	2.78 (0.2)	2.77 (0.3)	0.8	2.75 (0.3)	2.81 (0.3)	0.6

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