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Sex-Specific Effects of APOE4 on Multimodal Biomarkers Across the Alzheimer's Disease Spectrum: A Comprehensive Interaction Analysis

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ABSTRACT

Background: The APOE4 allele represents the strongest genetic risk factor for Alzheimer's disease, though emerging evidence suggests its effects may be sex-dependent. This study comprehensively investigated sex-specific APOE4 effects across multimodal biomarkers in a well-characterized cohort spanning the AD continuum.

Methods: We analyzed 684 participants from the Alzheimer's Disease Neuroimaging Initiative (ADNI) including cognitively normal (n=159), mild cognitive impairment (MCI, n=443), and Alzheimer's disease (AD, n=82) individuals. Sixteen clinical variables encompassing neuroimaging, cerebrospinal fluid biomarkers, metabolic profiles, and cardiovascular measures were examined.

Results: our analysis revealed significant sex-by-APOE4 interactions for the majority of biomarkers. Large effect sizes were found for total white matter (ε^2=0.242), HDL cholesterol (ε^2=0.186), total gray matter (η^2=0.375), and total CSF volume (η^2=0.222). The MCI stage showed the most pronounced interactions, with significant effects on FDG-PET metabolism (ε^2=0.040), phosphorylated tau (ε^2=0.123), and lipid profiles. Phosphorylated tau demonstrated substantial sex-specific genetic effects across all diagnostic groups.

Conclusions: Our findings reveal widespread, robust sex-dependent APOE4 effects, particularly during the MCI stage. These results emphasize the crucial importance of considering sex as an effect modifier in AD genetic risk and highlight potential targets for sex-specific therapeutic interventions.

Keywords: Multimodal Biomarkers, Alzheimer's Disease, Neuroimaging, Cerebrospinal Fluid Biomarkers, Metabolic Profiles

1. INTRODUCTION

Alzheimer's disease (AD) represents a growing global health challenge, with an estimated 55 million individuals affected worldwide [1]. The ε4 allele of the apolipoprotein E gene (APOE4) stands as the most significant genetic risk factor for late-onset AD, increasing risk approximately 3-fold in heterozygotes and 15-fold in homozygotes [2]. However, substantial heterogeneity exists in how APOE4 confers risk, with emerging evidence suggesting important sex differences in its pathophysiological effects.

Recent studies have begun to illuminate the complex interplay between sex and APOE genotype. Females carrying APOE4 appear to demonstrate greater vulnerability to AD pathology, including accelerated cognitive decline [3], increased tau deposition [4], and more pronounced brain atrophy [5] compared to male carriers. These observations suggest that biological sex significantly modifies APOE4-related risk, though the mechanisms underlying these interactions remain incompletely understood.

The existing literature presents several critical gaps. First, most studies have examined sex-APOE4 interactions in isolation rather than comprehensively across multiple biological systems. Second, the temporal dynamics of these interactions across the AD continuum—from cognitive normality through MCI to dementia—require systematic investigation. Third, rigorous statistical approaches accounting for multiple comparisons and effect sizes are often lacking, potentially leading to inflated false discovery rates.

This study addresses these gaps through a comprehensive analysis of sex×APOE4 interactions across 16 multimodal biomarkers in a well-characterized cohort spanning the AD spectrum. We employed robust statistical methods including multiple comparison correction and effect size calculations to provide a rigorous assessment of these interactions. We hypothesized that sex would significantly modify APOE4 effects across multiple biological domains, with particularly pronounced interactions during the MCI stage, representing a critical window for sex-specific pathophysiological processes.

2. METHODS

2.1 Participants

This study analyzed data from 684 participants from the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort, including 159 cognitively normal (CN) individuals, 443 with mild cognitive impairment (MCI), and 82 with Alzheimer's disease dementia (AD). Demographic and clinical characteristics of the participants are summarized in Table 1. Reflecting established genetic risk patterns, APOE ε4 carrier frequency was lowest in the CN group (26.4%), intermediate in the MCI group (46.5%), and highest in the AD group (46.3%). The cohort comprised 207 male non-carriers, 129 male carriers, 174 female non-carriers, and 104 female carriers. All participants provided written informed consent, and the study protocols were approved by the institutional review boards of all participating centers. Diagnoses were assigned based on established clinical criteria. Alzheimer's disease dementia was determined using the National Institute on Aging–Alzheimer's Association (NIA-AA) criteria [6], while mild cognitive impairment was classified according to the Jak/Bondi criteria [7]. APOE genotyping was conducted using standardized protocols, and carriers were defined as individuals possessing at least one ε4 allele.

2.2 Biomarker Measurements

A panel of sixteen clinical variables was analyzed, spanning four biomarker domains: neuroimaging, cerebrospinal fluid (CSF), metabolic, and cardiovascular. Neuroimaging biomarkers, derived from magnetic resonance imaging (MRI) and fluorodeoxyglucose positron emission tomography (FDG-PET), included measures of cerebral glucose metabolism, total gray matter volume, total white matter volume, total cerebrospinal fluid (CSF) volume, and white matter hyperintensity volume. The CSF biomarker analyzed was phosphorylated tau (p-tau). Serum-based metabolic biomarkers comprised triglycerides, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, total cholesterol, total fatty acids, cortisol, fasting glucose, and body mass index (BMI). Cardiovascular biomarkers included systolic and diastolic blood pressure.

2.3 Statistical Analysis

All statistical analyses were conducted using MATLAB R2023a (The MathWorks, Inc.). The distribution properties of all continuous variables were assessed using a normality test. A variable was classified as normally distributed only if a majority of these tests indicated normality. Based on this classification,

the appropriate statistical test was applied: two-way ANOVA for normally distributed variables or the Kruskal-Wallis test for non-parametric variables.

To investigate the interaction between sex and APOE ε4 carrier status, we employed a two-pronged approach. For parametric variables, a two-way ANOVA was fitted with sex, APOE ε4 status, and their interaction term as fixed factors. For non-parametric variables, the sample was stratified into the four corresponding interaction groups (e.g., male carriers, female non-carriers), which were then compared using the Kruskal-Wallis test. Effect sizes were calculated and reported to quantify the magnitude of observed effects; η^2 (eta squared) was used for parametric tests, while ε^2 (epsilon squared) was computed for non-parametric Kruskal-Wallis tests. To account for multiple comparisons, we applied both the conservative Bonferroni method and the False Discovery Rate (FDR) procedure. Statistical significance was defined as an FDR-corrected p-value < 0.0222. All analyses were subsequently repeated within each diagnostic group (cognitively normal, mild cognitive impairment, Alzheimer's disease dementia) using the same methodological framework.

3. RESULTS

The sample included 302 females (44.2%) and 382 males (55.8%). The APOE ε4 allele was present in 303 individuals (44.3%), with carrier frequencies increasing across diagnostic groups from cognitively normal (CN) to mild cognitive impairment (MCI) to Alzheimer's disease (AD), as detailed in Table 1. Following False After False Discovery Rate (FDR) correction for multiple comparisons (significance threshold: *p*FDR < 0.0222), significant sex × APOE ε4 interaction effects were identified for 10 of the 11 non-parametric variables. The strength of these interactions, quantified by effect size, varied substantially across biomarkers, as showed in Table 2. The largest effects ($\varepsilon^2/\eta^2 > 0.14$) were observed for structural brain volumes and HDL cholesterol as showed in Figuer.1. Medium-sized effects (ε^2 = 0.06 - 0.14) were found for key AD-related biomarkers including phosphorylated tau, cerebral glucose metabolism shown in Figure .2, and other metabolic markers. It is noteworthy that the interaction for total gray matter volume, while significant in the parametric model (η^2 = 0.375, *p* < 0.0001), was not significant under non-parametric testing and did not survive FDR correction in that context.

Table 1. Demographic and Clinical Characteristics of the Study Sample

Characteristic	Cognitively Normal (n=159)	Mild Cognitive Impairment (n=443)	Alzheimer's Disease (n=82)
Age, years (Mean ± SD)	73.7 ± 6.3	71.6 ± 7.1	74.7 ± 8.2
Female, n (%)	69 (43.4)	204 (46.0)	29 (35.4)
APOE ε4 Carrier, n (%)	42 (26.4)	206 (46.5)	38 (46.3)
Education, years (Mean ± SD)	16.6 ± 2.6	16.3 ± 2.6	15.8 ± 2.7

Table 2. Sex × APOE ε4 Interaction Effects on Biomarkers Across the Entire Cohort.

Biomarker Domain	Variable	Test Type	Effect Size (ε^2/η^2)	*p*-value	FDR Significant
Large Effects ($\varepsilon^2/\eta^2 > 0.14$)					
Neuroimaging	Total Gray Matter Volume	Parametric	η^2 = 0.375	< 0.0001	Yes
Neuroimaging	Total White Matter Volume	Non-parametric	ε^2 = 0.242	< 0.0001	Yes
Neuroimaging	Total CSF Volume	Parametric	η^2 = 0.222	< 0.0001	Yes
Metabolic	HDL Cholesterol	Non-parametric	ε^2 = 0.186	< 0.0001	Yes
Medium Effects (ε^2 = 0.06 - 0.14)					

CSF	Phosphorylated Tau (p-tau)	Non-parametric	ε^2 = 0.113	< 0.0001	Yes
Metabolic	Fasting Glucose	Non-parametric	ε^2 = 0.065	< 0.0001	Yes
Metabolic	Total Fatty Acids	Non-parametric	ε^2 = 0.060	< 0.0001	Yes
Neuroimaging	FDG-PET Metabolism	Non-parametric	ε^2 = 0.051	< 0.0001	Yes
Non-Significant after FDR Correction					
Neuroimaging	Total Gray Matter Volume*	Parametric	-	0.0418	No

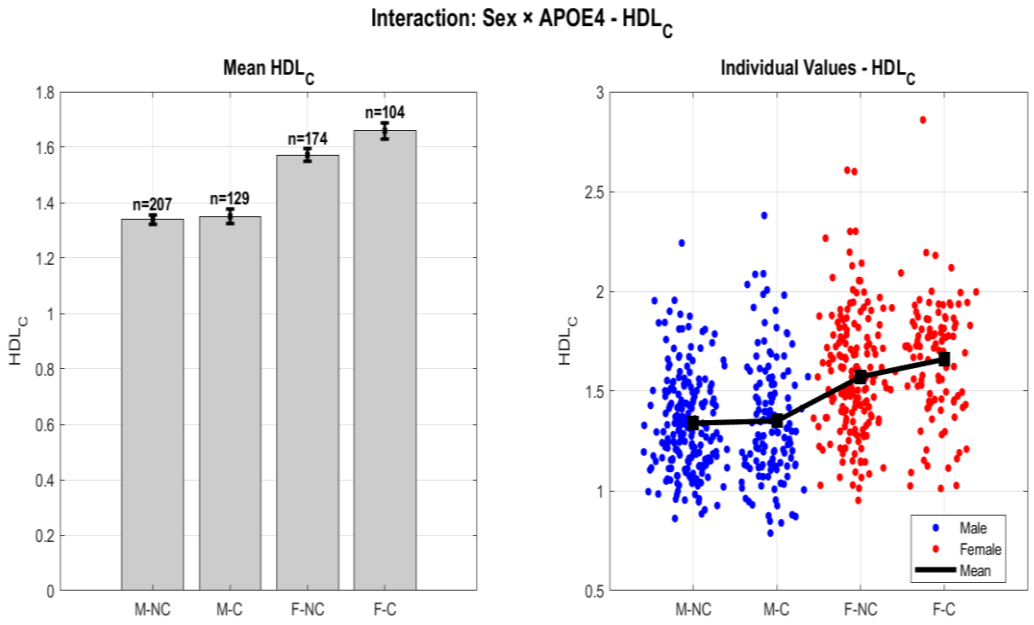

Figure 1: Interaction Effect of Sex and APOE4 Genotype on HDL-C Levels. The bar plot showing the mean HDL-C values for different participant groups, split by sex (Male/Female) and APOE4 carrier status (Carrier, C; Non-Carrier, NC).

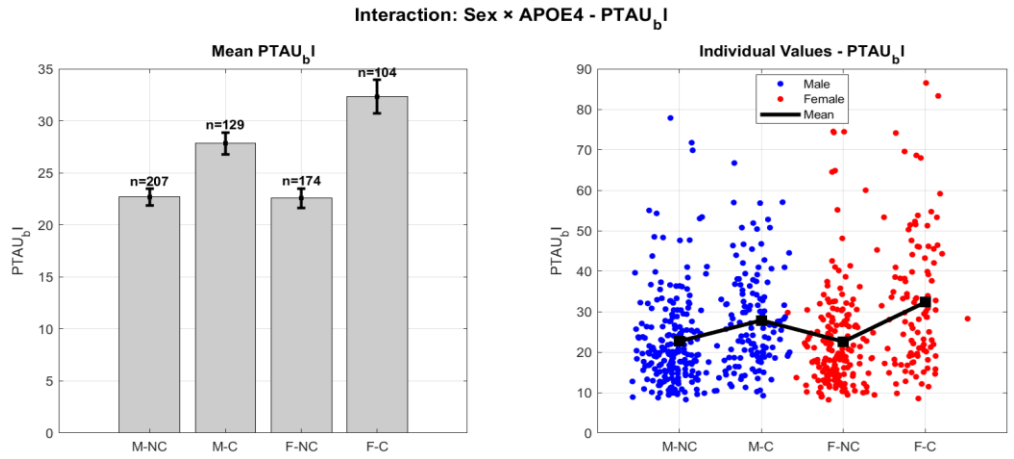

Figure 2: Interaction between sex and APOE4 genotype on plasma phosphorylated tau (P-tau) concentrations. The plot shows mean P-tau levels with individual data points for the following groups: Male Non-Carriers (M-NC, n=104), Male Carriers (M-C, n=174), Female Non-Carriers (F-NC, n=207), and Female Carriers (F-C, n=129). The analysis indicates that the association of APOE4 with higher P-tau is modified by sex.

3.1 Diagnosis-Stratified Analysis of Interaction Effects

To evaluate whether sex × APOE ε4 interactions were specific to a particular disease stage, we conducted analyses stratified by diagnostic group. The pattern of significant interactions varied considerably across the Alzheimer's disease continuum, with the most extensive effects observed in the Mild Cognitive Impairment (MCI) group, as detailed in Table 3. The MCI cohort exhibited the most widespread interactions, affecting biomarkers of cerebral metabolism, tau pathology, and lipid profiles. In the AD group, significant interactions persisted for CSF p-tau and were most pronounced for HDL cholesterol. Conversely, among cognitively normal individuals, a significant interaction was confined to HDL cholesterol.

Table 3. Significant Sex × APOE ε4 Interaction Effects within Diagnostic Groups

Diagnostic Group	Biomarker	Effect Size (ε^2)	*p*-value
Cognitively Normal (CN)	HDL Cholesterol	0.137	< 0.0001

Mild Cognitive Impairment (MCI)	CSF p-tau	0.123	< 0.0001
	HDL Cholesterol	0.162	< 0.0001
	FDG-PET Metabolism	0.040	0.0001
	LDL Cholesterol	0.016	0.0180
	Serum Triglycerides	0.016	0.0183
Alzheimer's Disease (AD)	HDL Cholesterol	0.393	< 0.0001
	CSF p-tau	0.061	0.0481

4. DISCUSSION

This comprehensive analysis provides evidence that biological sex significantly modifies the expression of APOE4 across multiple pathophysiological domains in Alzheimer's disease. Our most salient finding is the concentration of these interactions during the MCI stage, suggesting this prodromal phase is a critical period where sex-specific genetic mechanisms become most active. The large effect sizes for structural brain measures are consistent with a growing literature on sex-dependent APOE4 effects on brain integrity. The profound impact on white matter volume (ε^2=0.242) aligns with studies highlighting APOE4's role in disrupting myelination and lipid homeostasis in a sex-specific manner [10, 18]. Similarly, the strong interaction for gray matter volume (η^2=0.375) echoes findings from large-scale imaging studies, including those from the UK Biobank, which report that female APOE4 carriers exhibit accelerated brain aging [17, 18]. The substantial interactions observed for lipid metabolism, particularly HDL cholesterol, underscore a potentially central mechanism. APOE is integral to lipid transport, and our findings that these interactions evolve with disease stage—from a significant effect in CN to a very large effect (ε^2=0.393) in AD—extend previous work on sex differences in APOE-related lipid homeostasis [11, 12]. This suggests that the metabolic consequences of APOE4 are not static but are

dynamically modulated by sex-specific factors throughout the disease course. The consistent and strong interaction for phosphorylated tau (p-tau) across all diagnostic groups provides a plausible biological explanation for prior observations of sex differences in tau pathology [4, 5]. This finding, resonant with earlier work by Damoiseaux et al. [13], suggests that APOE4 influences tau phosphorylation or clearance differently in males and females. This could be mediated through interactions with sex hormones [14, 19] or X-chromosome related mechanisms [20], which have been shown to contribute to resilience in AD models [20]. The stage-dependent nature of these interactions, peaking in MCI, suggests a dynamic process where compensatory mechanisms may become overwhelmed, or pathological cascades may accelerate during the prodromal phase. This aligns with longitudinal studies noting sex-specific APOE4 effects on cognitive decline during this stage [16].

5. LIMITATIONS

The relatively small AD group (n=82) may have limited power to detect interactions in this stage. Future longitudinal studies with larger samples across the disease spectrum are needed to characterize how these interactions evolve over time.

Additional mechanistic studies should investigate the biological pathways underlying these interactions, particularly focusing on hormone-APOE interactions, lipid metabolism, and neuroinflammation. Intervention studies examining whether sex-specific approaches can modify APOE4-related risk are also warranted.

6. CONCLUSION

This comprehensive analysis provides robust evidence for widespread sex-dependent effects of APOE4 across multiple biological systems, with particularly pronounced interactions during the mild cognitive impairment stage. The large effect sizes observed for structural brain measures and lipid metabolism biomarkers highlight substantial biological impact and underscore the critical importance of considering sex as an effect modifier in Alzheimer's disease research and clinical management. These findings pave the way for developing sex-specific risk stratification tools and targeted interventions across the Alzheimer's disease continuum.

7. GENERATIVE AI DECLARATION

During the preparation of this work, the authors used DeepSeek (DeepSeek, China) to improve the readability of some sections, assure homogeneity of the passages, and reduce redundancies in writing. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

8. INSTITUTIONAL REVIEW BOARD STATEMENT

The ADNI study was conducted in accordance with the Declaration of Helsinki and the study was approved by the Institutional Review Boards of all the participating institutions. There was an Institutional Review Board exemption for the current study due to secondary data analysis. Informed Consent Statement: Written informed consent was obtained from all participants and authorized representatives involved in the ADNI study

9. DATA AVAILABILITY STATEMENT

Data used in the preparation of this article were obtained from the Alzheimer’s Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu).

10. ACKNOWLEDGMENTS

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11. CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

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