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SHORT REPORT

APOE ε4 is associated with earlier symptom onset in LOAD but later symptom onset in EOAD

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Abstract

Background: We studied the effect of apolipoprotein E (*APOE*) ε4 status and sex on age of symptom onset (AO) in early- (EO) and late- (LO) onset Alzheimer's disease (AD).

Method: A total of 998 EOAD and 2562 LOAD participants from the National Alzheimer's Coordinating Center (NACC) were included. We used analysis of variance to examine AO differences between sexes and *APOE* genotypes and the effect of *APOE* ε4, sex, and their interaction on AO in EOAD and LOAD, separately.

Results: *APOE* ε4 carriers in LOAD had younger AO and in EOAD had older AO. Female EOAD *APOE* ε4 carriers had older AO compared to non-carriers ($P < 0.0001$). There was no difference for males. Both male and female LOAD *APOE* ε4 carriers had younger AO relative to non-carriers ($P < 0.0001$).

Conclusion: The observed earlier AO in EOAD *APOE* ε4 non-carriers relative to carriers, particularly in females, suggests the presence of additional AD risk variants.

KEYWORDS
age of onset, apolipoprotein E ε4, early-onset Alzheimer's disease, late-onset Alzheimer's disease, sex

1 | INTRODUCTION

Apolipoprotein E (*APOE*) ε4 is the strongest genetic risk factor for sporadic late-onset Alzheimer's disease (LOAD). It causes an earlier age of symptom onset compared to other *APOE* genotypes.[1,2] However, it has been suggested that in early-onset Alzheimer's disease (EOAD), *APOE* ε4 might be counterintuitively associated with later disease onset.[3]

Female sex is also a risk factor for developing AD.[4] A recent meta-analysis including individuals 55 to 85 years of age showed that sex has a maximal AD risk effect between the ages 65 and 75.[5] However, whether sex and *APOE* ε4 status interact to impact age of onset is less clear,[6,7] particularly in EOAD.

Here we examined the association of *APOE* genotype and sex with age of symptom onset in a large sample of LOAD and EOAD participants from the National Alzheimer's Coordinating Center (NACC).

2 | METHOD

2.1 | Participants

Our analyses used data from 36 past and present Alzheimer's Disease Centers (ADC) that are part of NACC. Data were collected between September 2005 and January 2021 following informed consent as mandated by the respective institutional review boards at each ADC institution.

This study included all eligible EOAD and LOAD participants (onset age < or ≥65) who had *APOE* genotyping, full Uniform Data Set (UDS) testing, and primary diagnosis of mild cognitive impairment (MCI) or dementia due to probable AD for at least three consecutive visits from the NACC database (n = 4693 participants, 22,734 visits). All participants had an MCI or dementia diagnosis from first observation.

Participants with autosomal dominant AD or frontotemporal dementia (FTD) mutations; significant comorbid conditions, including severe white matter hyperintensities (Cardiovascular Health Study score 5–8+); psychiatric disorders (except depression); and cognitive disorder due to other neurological, neurodegenerative, or systemic illness, were excluded (n = 1113). Another 20 participants were excluded because their age of onset could not be determined. Our final sample consisted of 3560 (75.9%) participants: 998 EOAD and 2562 LOAD.

2.2 | Genotyping

NACC, its partners, and the ADCs work together to track phenotypic data, biologic specimens, and genotypic data from ADC participants (https://naccdata.org/nacc-collaborations/partnerships). Participants in the present study were selected based on the availability of *APOE* allele data.

2.3 | Age of onset

Age of onset was collected during the initial clinical evaluation by a clinician. NACC states that determination of age of onset is "Based on the clinician's assessment, at what age did the cognitive decline begin? (The clinician must use his/her best judgment to estimate an age of onset)." Therefore, clinical judgment plays a large role in determining age of onset when there is no objective data (e.g., a previously normal cognitive exam), which is the large majority of cases. This clinical judgment relies heavily on patient and informant report of onset of symptoms via thorough clinical interview.

2.4 | Statistical analysis

All analyses were run in SAS version 9.4. *T* tests and Fisher's exact tests as appropriate were used to compare baseline characteristics between EOAD and LOAD subjects. Analysis of variance (ANOVA) models were used to determine the association of *APOE* ε4 status, sex, and their interaction with age of onset in EOAD and LOAD, separately.

3 | RESULTS

3.1 | Sample characteristics

Demographic data are shown in the Table 1A. Compared to the EOAD group, the LOAD group was less educated ($P < 0.0001$) and had a lower rate of the *APOE* ε4 allele ($P < 0.0082$). The EOAD group had higher rates of dementia diagnosis and lower rates of MCI than did the LOAD group ($P < 0.0001$). There were no significant sex differences between groups ($P = 0.97$). Both groups were near 90% White, non-Hispanic/Latino/a. The LOAD group outperformed the EOAD group on Clinical Dementia Rating Scale–Sum of Boxes ($P = 0.0084$) and Montreal Cognitive Assessment (MoCA; $P = 0.0006$) at their initial visit. Of note, some MoCA scores were Mini-Mental State Examination scores converted using crosswalk analysis ($n = 2992$; see Polsinelli et al.[8] for a description of crosswalk data used in these analyses and Powell et al.[7] for a description of crosswalk procedures). The LOAD group was more likely to have a positive family history among first-degree relatives ($P = 0.02$).

RESEARCH IN CONTEXT

1. **Systematic Review**: We used defined search terms in traditional search engines (e.g., PubMed) and reference sections from prior related works to identify relevant papers. We reviewed the literature broadly as there are few studies examining the impact of apolipoprotein E (*APOE*) ε4 and particularly sex, on the age of onset in early-onset Alzheimer's disease (EOAD).
2. **Interpretation**: In a large sample of syndromically diverse patients with sporadic probable Alzheimer's disease (AD), our findings highlight the clinical importance of *APOE* ε4 and sex in predicting age of onset in AD, particularly in EOAD. Additionally, we provide further evidence of disease variance in the patterns of symptom presentation in EOAD and late-onset Alzheimer's disease.
3. **Future Directions**: Investigation in other large research consortia such as the Longitudinal Early-Onset Alzheimer's Disease Study (LEADS) can help further characterize influences of *APOE* ε4 and sex on age of onset in EOAD.

3.2 | Main analyses

LOAD *APOE* ε4 carriers had a significantly younger age of onset compared to non-carriers (73.0 ± 5.5 vs. 76.1 ± 6.1, $P = 0.0001$). *APOE* ε4/ε4 were the youngest, followed by *APOE* ε3/ε4, *APOE* ε2/ε4, *APOE* ε3/ε3, *APOE* ε3/ε2, and *APOE* ε2/ε2 (Table 1B and Figure 1A).

EOAD *APOE* ε4 carriers had a significantly older age of onset compared to non-carriers (57.9 ± 5.0 vs. 56.7 ± 5.3, $P = 0.0003$). In EOAD, *APOE* ε3/ε3 were the youngest, followed by *APOE* ε3/ε4, *APOE* ε2/ε4, *APOE* ε3/ε2, *APOE* ε4/ε4, and *APOE* ε2/ε2 (Table 1B and Figure 1B).

ANOVAs showed significant interactions between sex and *APOE* ε4 carrier status for both EOAD, $P = 0.005$, and LOAD, $P = 0.0004$ (Figure 1C and Table S1 in supporting information). In EOAD, female *APOE* ε4 carriers were significantly older compared to non-carriers (58.1 ± 4.9 vs. 56.0 ± 5.5, $P < 0.0001$) but male *APOE* ε4 carriers and non-carriers did not differ by age of onset (57.6 ± 5.1 vs. 57.5 ± 4.9, $P = 0.700$). In LOAD, both male and female *APOE* ε4 carriers had younger age of onset relative to non-carriers (males: 73.0 ± 5.3 vs. 75.3 ± 5.9; females 72.9 ± 5.6 vs. 76.8 ± 6.2, $Ps < 0.0001$). However, female *APOE* ε4 carriers were significantly younger than male *APOE* ε4 carriers ($P < 0.001$). Of note, adjusting for race in the models did not result in any differences in the significant interactions between *APOE*

TABLE 1 (A) Demographics and (B) *APOE ε4* comparisons between EOAD and LOAD

A. Demographics	EOAD (*n* = 998)	LOAD (*n* = 2562)	*P*-value
Current age, years, mean + SD	62.5 ± 5.9	78.3 ± 5.9	**<0.0001**
Age of onset, mean + SD	(*n* = 994) 57.5 (5.1)	(*n* = 2518) 74.1 (5.9)	**<0.0001**
Female	549 (55%)	1411 (55%)	0.9724
Hispanic/Latino/a	(*n* = 993) 75 (7.6%)	(*n* = 2554) 196 (7.7%)	0.9028
Race, *N* (%)	(*n* = 981)	(*n* = 2524)	**0.0066**
Black or African American	56 (5.7%)	223 (8.8%)	
White	873 (89.0%)	2187 (86.6%)	
Other	52 (5.3%)	114 (4.5%)	
Years of education, mean + SD	(*n* = 995) 15.2 ± 3.1	(*n* = 2555) 14.7 ± 3.6	**<0.0001**
Diagnostic group, *N* (%)			**<0.0001**
Dementia	810 (81.2%)	1912 (74.6%)	
MCI	188 (18.8%)	650 (25.4%)	
First degree relative with dementia	(*n* = 936) 577 (61.6%)	(*n* = 2319) 1529 (65.9%)	**0.0205**
CDR-SB	5.0 ± 3.6	4.7 ± 3.5	**0.0084**
MoCA	(*n* = 950) 15.8 ± 5.5	(*n* = 2513) 16.5 ± 4.8	**0.0006**
B. *APOE ε4*			
APOE ε4 carriers, *N* (%)	655 (65.6%)	1559 (60.9%)	**0.0082**
Female *APOE ε4* carriers	364/549 (36.4%)	872/1411 (34.0%)	
Male *APOE ε4* carriers	291/449 (29.2%)	687/1151 (26.8%)	
APOE genotype, *N* (%)			**<0.0001**
APOE ε4/ε4	225 (22.5%)	285 (11.1%)	
APOE ε3/ε4	413 (41.4%)	1193 (46.6%)	
APOE ε2/ε4	17 (1.7%)	81 (3.2%)	
APOE ε3/ε3	317 (31.8%)	892 (34.8%)	
APOE ε3/ε2	24 (2.4%)	107 (4.2%)	
APOE ε2/ε2	2 (0.2%)	4 (0.2%)	
Age of onset x *APOE*, Mean + SD			**<0.0001**
APOE ε4/ε4	58.4 (4.5)	71.1 (4.6)	
APOE ε3/ε4	57.6 (5.3)	73.3 (5.5)	
APOE ε2/ε4	57.9 (4.7)	74.4 (6.0)	
APOE ε3/ε3	56.6 (5.3)	75.9 (6.0)	
APOE ε3/ε2	58.0 (4.7)	77.5 (6.7)	
APOE ε2/ε2	59.0 (2.8)	78.8 (7.6)	

Note: *N* is noted where data are missing.
Abbreviations: *APOE*, apolipoprotein E; CDR-SB, Clinical Dementia Rating Scale–Sum of Boxes; EOAD, early-onset Alzheimer's disease; LOAD, late-onset Alzheimer's disease; MoCA, Montreal Cognitive Assessment (of note, some MoCA scores were Mini-Mental State Examination scores converted using crosswalk analysis [*n* = 2992; see Powell et al.[7] for description of crosswalk data]); SD, standard deviation.
Bolded values are statistically significant.

ε4 and sex on age of onset. As such, we report only the race-unadjusted models.

4 | DISCUSSION

As hypothesized, LOAD *APOE ε4* carriers had younger age of onset than non-carriers and the opposite was observed in EOAD—*APOE ε4* carriers were older than non-carriers. However, this latter finding was driven largely by females, suggesting sex also plays an important role in age of symptom onset in EOAD.

Our findings are consistent with the dose-dependent risk effect of the *APOE ε4* allele and the dose-dependent protective effect of the *APOE ε2* allele on age of onset in LOAD.[9,10] Those at highest risk of AD, *APOE ε3/ε4*, also had the youngest age of onset while those with lowest risk *APOE ε2/ε2* had the oldest age of onset (although there were

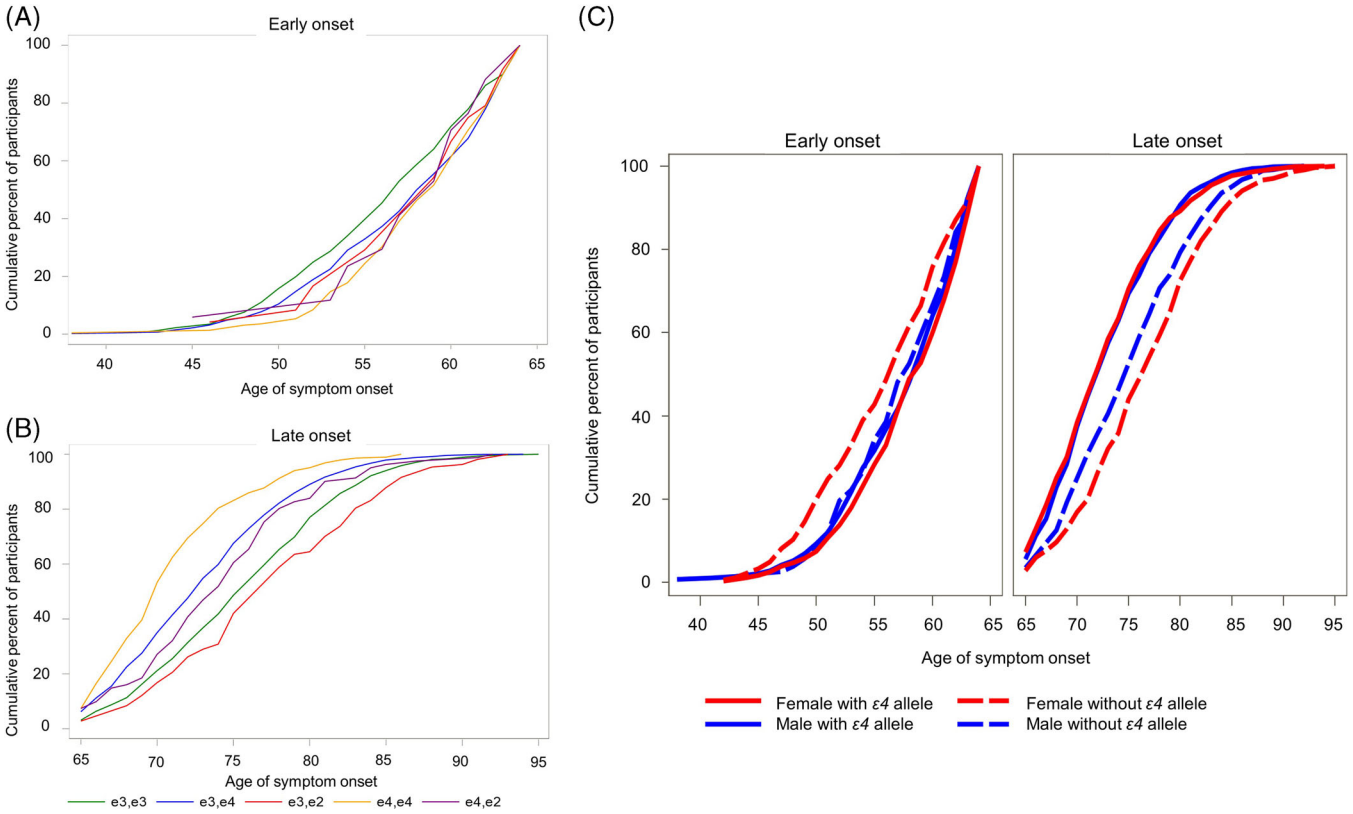

FIGURE 1 A, Cumulative percentage of age of symptom onset in early-onset Alzheimer's disease by apolipoprotein E (*APOE*) status. B, Cumulative percentage of age of symptom onset in late-onset Alzheimer's disease by *APOE* status. C, Cumulative percentage of age of symptom onset in early- and late-onset Alzheimer's disease as a function of sex and *APOE* status

only four participants in the latter group). These findings were similar between females and males, suggesting sex does not alter the risk of effect of *APOE* ε4 on age of onset in LOAD.

In contrast, a dose-dependent risk effect of *APOE* ε4 was not found in EOAD. Instead, the pattern among all genotypes was more mixed than in LOAD and ε4 non-carriers were at overall higher risk for earlier onset. While there appears to be an age window of maximal effects for ε4 carriers, with peak onset for this group between early 60s to 70s, non-ε4 variants show a bimodal distribution.[10] Age of onset in non-ε4 carriers peaks around 57, then drops off and peaks again around 77 years of age. However, this genotype effect in the age range of EOAD appears primarily driven by female sex.

Previous work has shown *APOE* genotype interacts with sex to impact risk of AD,[6] but this appears to be the case only in younger individuals (ages 55–70).[5] We found sex also impacts age of symptom onset but only in a younger group (i.e., EOAD). Female but not male ε4 carriers showed a significantly older age of onset than non-carriers. This interaction effect has not been previously studied in EOAD to our knowledge. Younger females, particularly those who are amyloid-positive, accumulate tau at faster rates than others.[11] Exploring genetic markers of abnormal tau accumulation could help explain some of these age of onset differences in EOAD. It is also possible that hormonal and metabolic alterations associated with menopause and perimenopause may be interacting with *APOE* genotype to create differences in symptom onset between ε4 carriers and non-carriers[12] but these studies have yet to be conducted. With respect to our LOAD group, our results are consistent with prior work showing no sex differences in age of onset for *APOE* ε4 carriers versus non-carriers.[7]

4.1 | Limitations and strengths

We addressed prior limitations in the field by using a large well-characterized sample (n = 3560) and by excluding individuals with significant comorbid pathologies that could contribute independently to cognitive decline and affect disease onset. We further excluded individuals with genetic mutations associated with AD and FTD who have disease onset at young age by virtue of their autosomal dominant mutations.

However, the current study was not without limitations. Age of onset was determined by retrospective self- or informant report, which is less reliable than an objective evaluation. Participants did not have pathologically confirmed AD and as such misdiagnoses might have occurred.[13] Disease severity was distributed differently between EOAD (dementia > MCI) and LOAD (MCI > dementia). This difference is potentially meaningful if disease stage plays a role in associations with *APOE* ε4. Our sample contained only individuals from North America who were mostly White, non-Hispanic/Latino/a/x and well

educated, limiting the generalizability of our results. While re-running our analyses adjusting for race did not change the findings, this may have been influenced by the very low sample sizes of other groups compared to the non-White, non-Hispanic/Latino/a group. This is an important limitation as race-based differences in *APOE* genotype have consistently been shown.[3,6,7,14]

5 | CONCLUSIONS

Female *APOE ε4* non-carriers are at greatest risk for younger age of onset of symptoms in EOAD. This suggests the role of still unknown genetic risk factors in the development of AD, particularly at younger ages. Investigation in other large research consortia such as the Longitudinal Early-Onset Alzheimer's Disease (LEADS[15]) Study are ongoing and can further characterize genetic and other risk factors in EOAD.

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CONFLICTS OF INTEREST

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