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Relationship of *APOE*, age at onset, amyloid and clinical phenotype in Alzheimer disease

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ABSTRACT

The apolipoprotein E (*APOE*) ε4 allele is the most well-established risk factor for Alzheimer's disease (AD), although its relationship to age at onset and clinical phenotype is unclear. We aimed to assess relationships between *APOE* genotype and age at onset, amyloid-beta (Aβ) deposition and typical versus atypical clinical presentations in AD. Frequency of *APOE* ε4 carriers by age at onset was assessed in 447 AD patients, 138 atypical AD patients recruited by the Neurodegenerative Research Group at Mayo Clinic, and 309 with typical AD from ADNI. *APOE* ε4 frequency increased with age at onset in atypical AD but showed a bell-shaped curve in typical AD where highest frequencies were observed between 65 and 70 years. Typical AD showed higher *APOE* ε4 frequencies than atypical AD only between the ages of 57 and 69 years. Global Aβ standard uptake value ratios did not differ according to *APOE* e4 status in either group. *APOE* genotype varies by both age at onset and clinical phenotype in AD, highlighting the heterogeneous nature of AD.

1. Introduction

The apolipoprotein E (*APOE*) ε4 allele is the most common and well established risk factor for typical late-onset amnestic Alzheimer's dementia (Corder *et al.*, 1993; Strittmatter *et al.*, 1993a; Strittmatter *et al.*, 1993b). The presence of one ε4 allele increases the risk of developing Alzheimer's dementia by 2–4 fold and the presence of two ε4 alleles increases the risk by 8–10 fold (Farrer *et al.*, 1997). The presence of the ε4 allele has also been associated with an earlier age of onset in Alzheimer's dementia (Meyer *et al.*, 1998). In contrast, presence of the *APOE* ε2 allele has been shown to reduce the risk for developing Alzheimer's dementia and delay the age at onset (Corder *et al.*, 1994).

Thirty-eight percent of patients with AD pathology under the age of 60 (Balasa *et al.*, 2011), and 25% of all AD patients (Whitwell *et al.*, 2012), do not complain of early memory loss, but instead present with other cognitive complaints and can be referred to as atypical presentations of AD. Two of the most common variants of atypical AD are logopenic progressive aphasia (LPA) (Gorno-Tempini *et al.*, 2011) which is characterized by language abnormalities and posterior cortical atrophy (PCA) (Crutch *et al.*, 2017) which is characterized by visuospatial and perceptual abnormalities. These atypical AD variants often have a relatively young age at onset, although age at onset can vary widely. Less is known about the role of the *APOE* genotype in patients with atypical AD. It does appear as though *APOE* ε4 greatly increases the odds of PCA (OR = 4.7, 95% CI 3.4–6.7; $p < 0.0001$) (Carrasquillo *et al.*, 2016;

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Carrasquillo *et al.*, 2014), although studies have found varying results concerning the *APOE* ε4 allele frequency in atypical AD. Some investigators have found that the frequency of the *APOE* ε4 allele is lower in LPA and PCA compared to typical AD (Josephs *et al.*, 2014; Mesulam *et al.*, 1997; Phillips *et al.*, 2019; Rogalski *et al.*, 2011; Schott *et al.*, 2006; van der Flier *et al.*, 2006), although others have observed similar frequencies, particularly between PCA and typical Alzheimer's dementia (Carrasquillo *et al.*, 2014; Lehmann *et al.*, 2013; Tang-Wai *et al.*, 2004). Given that age is related to *APOE* ε4 risk in typical Alzheimer's dementia, it is possible that discrepancies across these atypical AD studies may be related to differences in age at onset.

APOE has been associated with beta-amyloid (Aβ) mechanistic pathways (Castellano *et al.*, 2011; Zerbinatti *et al.*, 2004), and studies have shown that both age and *APOE* ε4 carriers are associated with higher Aβ PET burden and lower CSF Aβ1-42 in cognitively normal and undemented populations (Jack *et al.*, 2015; Lim *et al.*, 2017; Morris *et al.*, 2010; Reiman *et al.*, 2009; Rowe *et al.*, 2010; Vemuri *et al.*, 2010). However, findings relating *APOE* genotype to Aβ in cohorts of patients with Alzheimer's dementia have given mixed results (Baek *et al.*, 2020; Drzezga *et al.*, 2009; Fleisher *et al.*, 2013; Ge *et al.*, 2018; Lehmann *et al.*, 2014; Mattsson *et al.*, 2018; Murphy *et al.*, 2013; Nitsch *et al.*, 1995; Ossenkoppele *et al.*, 2013; Prince *et al.*, 2004; Rowe *et al.*, 2010; Tapiola *et al.*, 2000; Vemuri *et al.*, 2010), possibly due to clinical heterogeneity across cohorts and differences in age at onset. The relationship between *APOE* genotype and Aβ PET in patients with atypical clinical presentations of AD, and whether this relationship differs from typical AD, is unclear.

The primary aim of this study was to assess the relationship between *APOE* genotype frequency and onset age in a large cohort of atypical AD patients, and determine how frequencies in atypical AD across the age spectrum compare to those observed in a cohort of typical Alzheimer's dementia patients from the Alzheimer's disease Neuroimaging Initiative (ADNI). A secondary aim was to assess the relationship between *APOE* genotype and Aβ PET in atypical and typical AD to determine whether *APOE* plays a role in determining the degree of Aβ deposition in AD when accounting for age and clinical phenotype. We hypothesize that any relationship between *APOE* and Aβ PET would be similar in typical and atypical AD given that it likely reflects a fundamental disease mechanism in AD.

2. Methods

2.1. Patients

The atypical AD cohort consisted of 138 patients that fulfilled clinical diagnostic criteria for either LPA (Gorno-Tempini *et al.*, 2011) (n = 81) or PCA (Crutch *et al.*, 2017) (n = 57) that had been recruited by the Neurodegenerative Research Group (NRG) from the Department of Neurology, Mayo Clinic, Rochester, MN, between November 30, 2010 and November 10, 2018. Patients were enrolled regardless of age. All patients underwent a detailed neurological evaluation by one of two behavioral neurologists (KAJ/JGR), detailed neuropsychological testing, a 3T volumetric MRI and provided a blood sample for *APOE* testing. All but one patient also underwent Aβ-PET using Pittsburgh Compound B (PiB) PET. The study was approved by the Mayo Clinic IRB and all patients gave written informed consent to participate in the study.

The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging, positron emission tomography, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment and early AD. From ADNI, we selected typical AD patients who had an *APOE* genotype and a known age at onset (n = 309). These patients were identified from ADNI 1, 2, 3 and ADNI-GO. The inclusion criteria for AD patients in ADNI have been previously published (www.adni.loni.usc.edu). Briefly, patients must have had abnormal memory function on the Logical Memory II subscale from the Wechsler Memory Scale-Revised, a Mini-Mental State Examination (MMSE) score between 20 and 26, a Clinical Dementia Rating (CDR) score of 0.5 or 1.0, with a Memory Box score of 1.0, and meet NINCDS/ADRDA criteria for probable AD (McKhann *et al.*, 1984; McKhann *et al.*, 2011; Petersen *et al.*, 2010). Patients enrolled in ADNI were between 55 and 90 years old. One-hundred and twenty-one patients in the ADNI cohort had undergone (^{18}F)florbetapir PET to assess Aβ deposition. Florbetapir was included in ADNI 2, 3 and ADNI-GO.

APOE genotyping for the atypical AD cohort was performed as previously described (Crook *et al.*, 1994). ADNI methods are provided at www.adni-info.org.

2.2. Aβ PET analysis

The atypical AD patients were all scanned on a PET/CT scanner (GE Healthcare) while operating in 3D mode. Patients were injected with PiB of approximately 628 MBq (range, 385-723 MBq) and after a 40–60-minute uptake period a 20-minute PiB scan was obtained. Emission data was reconstructed into a 256 × 256 matrix with a 30-cm FOV. All patients also underwent a 3T volumetric head MRI within two days of the PiB-PET scan, which included a 3D magnetization prepared rapid acquisition gradient echo sequence (MPRAGE). All MPRAGE scans underwent corrections for intensity inhomogeneity and gradient unwarping before analysis. The Aβ-PET scans were registered to the corresponding MPRAGE scan using a 6 degrees-of-freedom registration in SPM12. The Mayo Clinic Adult Lifespan Template (MCALT) (https://www.nitrc.org/projects/mcalt/) was then transformed into the native space of each MPRAGE using ANTs software. Median Aβ uptake was calculated for the following regions-of-interest defined using MCALT: inferior parietal, superior parietal, supramarginal gyrus, angular gyrus, cingulate [anterior, mid, posterior and retrosplenial], precuneus, superior frontal, middle frontal, orbitofrontal, inferior frontal [operculum+triangularis], medial frontal, fusiform, lateral temporal [inferior, middle and superior temporal gyri + Heschl], and temporal pole. Uptake was calculated from the grey and white matter in each region and divided by uptake in the cerebellar crus grey matter to calculate standard uptake value ratios (SUVRs). A global Aβ SUVR was calculated as the weighted average from the regions-of-interest and a cut-point of 1.48 was used to determine positivity (Jack *et al.*, 2017).

The ADNI patients were injected with 370 MBg (10 mCi) of florbetapir with a 20 minute acquisition performed 50–70 minutes post injection. Images were collected as a series of 4 × 5 min frames, and attenuation corrected with either CT or PET transmission. The global Aβ SUVR that is calculated by the ADNI group was utilized in this study (Jagust *et al.*, 2015). Briefly, florbetapir analyses used coregistered MRI images obtained concurrently with PET which are segmented and parcellated using FreeSurfer 5.3.0 (https://surfer.nmr.mgh.harvard.edu/). A composite cortical target reference ROI was created using a weighted average of the frontal, lateral temporal, lateral parietal, and anterior/posterior cingulate regions, and the whole cerebellum was used as a reference region to generate a global Aβ SUVR. The ADNI cut-point of 1.11 was utilized to determine positivity (Landau *et al.*, 2013).

2.3. Statistical analysis

We used logistic regression to estimate the proportion of *APOE* $\varepsilon4$ carriers by onset age and clinical group. Rather than assume a linear relationship on the logit scale, we modelled onset age using a restricted cubic spline with knots at 60, 70, and 80 years and allowed the age effect to vary by clinical group (Harrell, 2001). We tested for group-wise differences across age at onset using a likelihood ratio test comparing nested models. The reduced model had only a non-linear age effect in the model (3 degrees of freedom [d.f.]). The full model had the non-linear age effect, group, and the interaction between age and group (6 d.f.). Using the inverse logit transformation, $p = \exp(x^T\beta) / (1 + \exp(x^T\beta))$, we report estimates and 95% confidence intervals on the probability scale. We also performed hypothesis testing for the difference in *APOE* $\varepsilon4$ frequency between atypical AD and typical AD at onset ages 50–80 using linear contrasts from the logistic model. The results of these hypothesis tests, along with point and interval estimates of the difference in $\varepsilon4$ frequency, are summarized graphically. The relationship between confidence intervals and *p*-values enables us to interpret significance from the graph since a 95% CI that does not include zero indicates the difference is significant at $p < 0.05$. Further details and age-specific estimates are provided in the Supplementary Materials. These logistic regression models were performed using all atypical and typical AD patients (N = 138 and N = 309) to increase statistical power, and then repeated in the sub-sample that had a positive Aβ PET (N = 133 and N = 108). We used linear regression to estimate mean Aβ burden by age at PET and *APOE* $\varepsilon4$ status within each clinical group. These analyses were limited to patients who were Aβ PET positive to ensure that we were assessing relationships in patients with underlying AD (only four atypical AD and 13 typical AD patients were Aβ-negative and removed from this analysis). Separate regression models were fit for atypical AD and typical AD. The full model included age, *APOE* genotype, and the interaction. We used the main effects model to compare age-adjusted difference between *APOE* $\varepsilon4$ carriers and non-carriers by diagnosis group as follows. The log-transformed dependent variable allows us to interpret the difference between *APOE* $\varepsilon4$ carriers and non-carriers in terms of percentage difference in SUVR. This interpretation is approximate and applies to small difference as reported here. Since these two estimated differences were on a comparable percentage scale and from two independent samples, we used the regression estimates and their standard errors to perform a z test comparing the two estimates (Clogg *et al.*, 1995).

3. Results

3.1. Demographic comparisons

The demographic features of the cohorts are shown in Table 1. Compared to typical AD, the atypical AD cohort had a higher frequency of women, a decade younger age at onset, and less impaired performance on the CDR sum of boxes and MMSE. The frequency of *APOE* $\varepsilon4$ carriers was lower in atypical AD (52%) compared to typical AD (66%), particularly for $\varepsilon4\varepsilon4$ homozygotes (9% vs. 20%).

3.2. APOE $\varepsilon4$ frequency by age at onset

Based on a likelihood ratio test, *APOE* $\varepsilon4$ frequency differed significantly by age between atypical and typical AD ($p = 0.023$). Specifically, the frequency of *APOE* $\varepsilon4$ carriers steadily increased with age at onset in atypical AD but showed a bell-shaped curve in typical AD where highest frequencies were observed between the onset ages of 65 and 70 years (Fig. 1, Supplementary Material). Typical AD showed significantly higher frequencies of *APOE* $\varepsilon4$ carriers compared to atypical AD between the onset ages of 57 and 69 years. No significant differences in *APOE* $\varepsilon4$ frequency were observed between the cohorts in patients younger than 57 or in patients older than 69 years (Fig. 1, Supplementary Material). These age at onset relationships remained the same when the analysis was limited to only patients with positive Aβ-PET.

3.3. Aβ burden by age and APOE $\varepsilon4$

Fig. 2 shows plots illustrating the relationship between Aβ PET SUVR and age at scan for atypical AD and typical AD, split by *APOE* $\varepsilon4$ status. In atypical AD, Aβ SUVR stays relatively flat with increasing age with no differences observed according to *APOE* $\varepsilon4$ status. In typical AD, Aβ SUVR declines with increasing age with again no difference in burden observed according to *APOE* $\varepsilon4$ status. Age was significantly associated with Aβ SUVR in typical AD in the regression analyses (Table 2). There was no difference in the effect of *APOE* $\varepsilon4$ on Aβ SUVR between the atypical and typical AD models ($p = 0.55$).

3.4. Influence of atypical AD clinical phenotype

LPA and PCA did not differ in *APOE* $\varepsilon4$ frequency and Aβ SUVR, although the PCA patients were about five years younger at onset and at PET (Table 3). We did not find any evidence that the relationship between age at onset and *APOE* $\varepsilon4$ frequency differed in atypical AD when including clinical phenotype ($p = 0.26$) (Fig. 3). Furthermore, we found no evidence for differences between PCA and LPA in the relationship between Aβ SUVR and age at scan, with neither group showing an effect of *APOE* $\varepsilon4$ status on these relationships (Fig. 3).

4. Discussion

This study demonstrated that frequency of the *APOE* $\varepsilon4$ genotype differs across atypical and typical clinical presentations of AD, although *APOE* $\varepsilon4$ frequency was highly dependent on age of onset with significant differences concentrated in patients between the ages of 57 and 69 years old. There was no evidence that *APOE* $\varepsilon4$ status was associated with higher Aβ PET uptake in either group.

Our findings using the ADNI cohort showed that the frequency of *APOE* $\varepsilon4$ carriers in typical AD increases with increasing age of onset up until approximately 70 years but then declines with increasing age at onset after that. Previous studies have found a similar bell-shaped relationship between age at onset and *APOE* $\varepsilon4$ frequency in typical Alzheimer's dementia, with *APOE* $\varepsilon4$ carriers most common in patients with an onset in the 60–69 age decade and less common after age 70 years in one study (Davidson *et al.*, 2007) and most common in the 60–79 onset age range in another study (Bickeboller *et al.*, 1997). The effects of the *APOE* $\varepsilon4$ allele on AD risk has also been shown to reduce after age 70 years in one study (Farrer *et al.*, 1997), and after age 75 in another (Liu and Caselli, 2018). It has also been shown that the effects of *APOE* genotype on progression from normal cognition to MCI or AD peak between age 70 and 75 years (Bonham *et al.*, 2016). This bell-shaped relationship suggests an increase in the frequency of Alzheimer's dementia not associated with the *APOE* $\varepsilon4$ allele in older patients. Interestingly, we did not observe the same bell-shaped curve in atypical AD; instead, the frequency of *APOE* $\varepsilon4$ carriers continued to increase with increasing age at onset, suggesting that *APOE* risk may increase with increasing onset age in atypical AD. There was perhaps a slight flattening of the slope over age 70 but frequencies continued to rise until age 80 years. However,

Table 1
Patient characteristics

	All patients (n = 447)			Patients with positive Aβ PET scans (n = 241)		
	Atypical AD (n = 138)	Typical AD (n = 309)	*p*-value	Atypical AD (n = 133)	Typical AD (n = 108)	*p*-value
Female, n (%)	82 (59%)	135 (44%)	0.003	79 (59%)	49 (45%)	0.038
APOE carrier, n (%)	72 (52%)	205 (66%)	0.006	70 (53%)	80 (74%)	0.001
ε2/ε2	0 (0%)	0 (0%)		0 (0%)	0 (0%)	
ε2/ε3	7 (5%)	7 (2%)		7 (5%)	0 (0%)	
ε2/ε4	6 (4%)	7 (2%)		5 (4%)	2 (2%)	
ε3/ε3	59 (43%)	97 (31%)		56 (42%)	28 (26%)	
ε3/ε4	53 (38%)	135 (44%)		52 (39%)	52 (48%)	
ε4/ε4	13 (9%)	63 (20%)		13 (10%)	26 (24%)	
Age at onset, yr	62 (42, 80)	72 (52, 88)	<0.001	61 (42, 80)	72 (52, 88)	<0.001
Age at PET, yr	65 (48, 85)	75 (56, 96)	<0.001	65 (48, 85)	74 (56, 96)	<0.001
MMSE	24 (6, 30)	23 (16, 29)	0.043	24 (7, 30)	23 (16, 26)	0.06
CDR sum of boxes	3.0 (0.0, 18.0)	4.5 (1.5, 10.0)	<0.001	3.0 (0.0, 18.0)	4.5 (1.5, 10.0)	<0.001
Aβ SUVRs						
PiB	2.38 (1.29, 3.53)			2.40 (1.50, 3.53)		
Florbetapir		1.44 (0.84, 1.80)			1.45 (1.11, 1.80)	

Data shown are n (%) or median (range).
Key: APOE, apolipoprotein E; CDR, clinical dementia rating scale; MMSE, mini-mental state examination; PiB, pittsburgh compound B; SUVR, standard uptake value ratio.

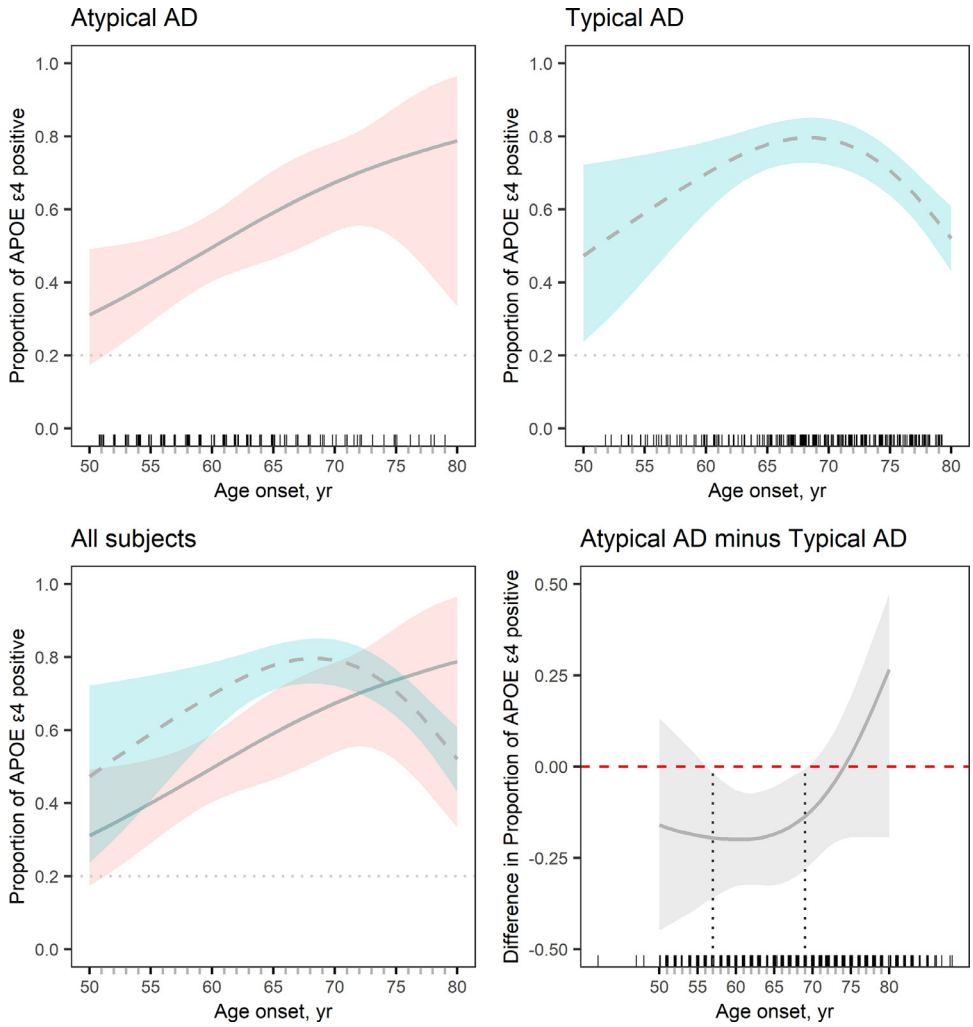

Fig. 1. *Plots of APOE ε4 carrier frequency by age at onset in atypical AD and typical AD.* The estimated proportion of *APOE ε*4 carriers is plotted with 95% percentile confidence intervals. Plots are shown for atypical AD (top left) and typical AD (top right) and then these plots are overlaid in the bottom left panel. The bottom right plot shows the difference in proportion of *APOE ε*4 carriers between atypical AD and typical AD by age at onset. Proportions differ significantly between groups at an alpha level of 0.05 when the 95% confidence interval does not cross the 0 line, i.e., between the ages of 57 and 69 y. Small tick marks above the x-axis reflect individual patient points to demonstrate the density of data across the age at onset spectrum. The grey dotted line in the top plots and bottom left plot represents the *APOE ε*4 frequency (20%) in a control population. This frequency was calculated from 241 ADNI participants that were cognitively unimpaired at their last visit and all visits prior to that visit, had an available *APOE* genotype, and had a normal amyloid-PET scan.

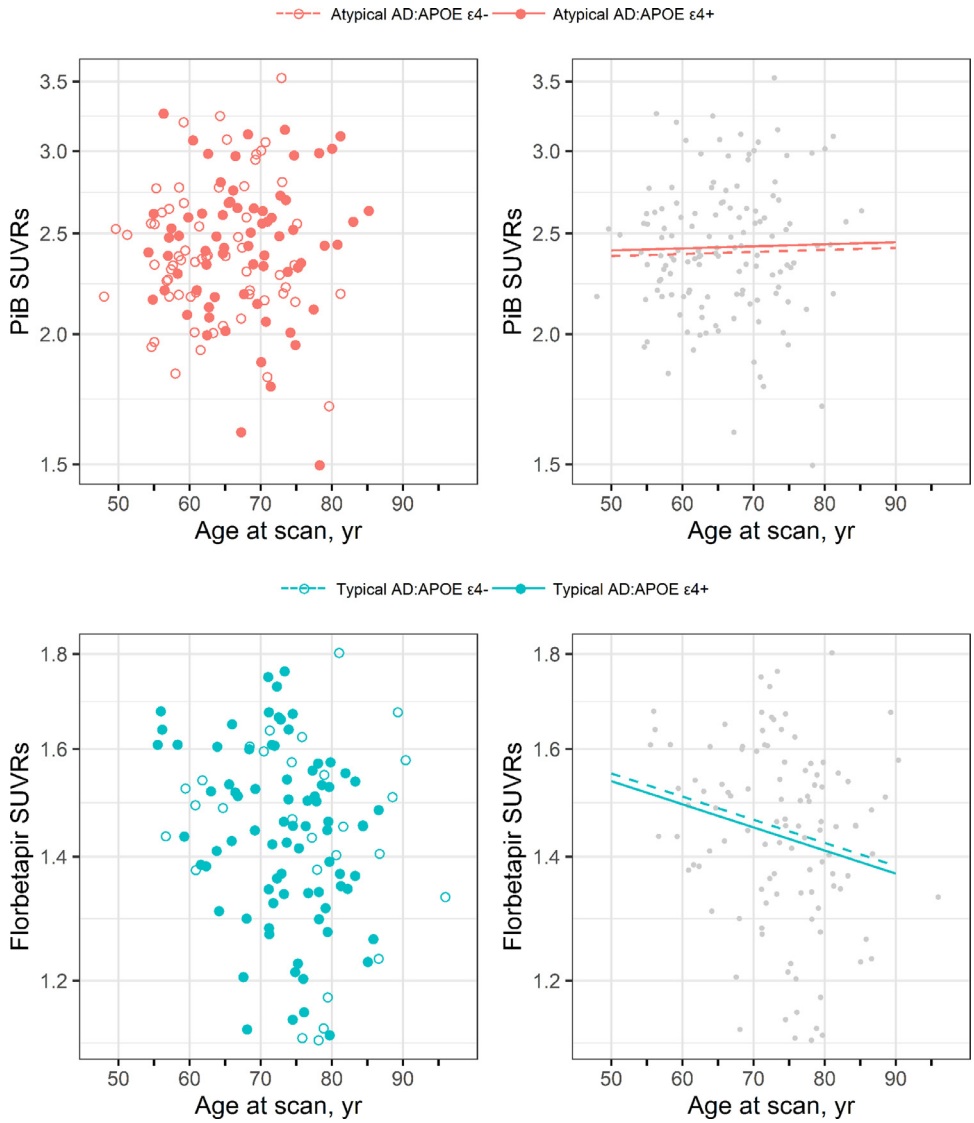

Fig. 2. *Plots of Aβ SUVR versus age for atypical AD and typical AD by APOE ε4 status.* The top row shows the results for atypical AD using Pittsburgh Compound B (PiB) PET while the bottom row shows the results for typical AD using florbetapir PET. The scatter-plots on the left show log-transformed Aβ SUVR versus age at scan separately by *APOE ε4* status. The plots on the right show the estimated mean in the *APOE ε4* carriers and non-carriers based on a model without an interaction between age at scan and *APOE*.

Table 2
Regression analysis predicting log-transformed Aβ SUVRs

	PiB SUVRs in atypical AD					
	2-way interaction			No interaction		
	Est (95% CIs)	Standard Error	*p*	Est (95% CIs)	Standard Error	*p*
Intercepts	0.875 (0.825, 0.926)	0.0256	<0.001	0.875 (0.831, 0.920)	0.0223	<0.001
Age at scan	0.000 (-0.005, 0.006)	0.0026	0.87	0.000 (-0.003, 0.004)	0.0018	0.80
APOE ε4 carrier	0.012 (-0.051, 0.075)	0.0319	0.70	0.012 (-0.042, 0.067)	0.0274	0.65
Age x *APOE ε4*	0.000 (-0.007, 0.007)	0.0035	>0.99			
	Florbetapir SUVRs in typical AD					
	2-way interaction			No interaction		
	Est (95% CIs)	Standard Error	*p*	Est (95% CIs)	Standard Error	*p*
Intercepts	0.375 (0.326, 0.423)	0.0245	<0.001	0.382 (0.338, 0.427)	0.0225	<0.001
Age at scan	-0.002 (-0.006, 0.003)	0.0021	0.45	-0.003 (-0.006, -0.000)	0.0013	0.034
APOE ε4 carrier	0.001 (-0.055, 0.056)	0.0280	0.98	-0.010 (-0.058, 0.040)	0.0247	0.70
Age x *APOE ε4*	-0.002 (-0.008, 0.003)	0.0027	0.43			

Key: *APOE*, apolipoprotein E; SUVR, standard uptake value ratio

Table 3
Atypical AD patient characteristics

	LPA (n = 81)	PCA (n = 57)	*p*-value
Female, n (%)	45 (56%)	37 (65%)	0.30
APOE ε4 carrier, n (%)	41 (51%)	31 (54%)	0.73
ε2/ε2	0 (0%)	0 (0%)	
ε2/ε3	4 (5%)	3 (5%)	
ε2/ε4	3 (4%)	3 (5%)	
ε3/ε3	36 (44%)	23 (40%)	
ε3/ε4	31 (38%)	22 (39%)	
ε4/ε4	7 (9%)	6 (11%)	
Age at onset, year	64 (42, 80)	59 (48, 74)	<0.001
Age at PET, year	68 (48, 85)	63 (54, 75)	0.007
MMSE	24 (6, 30)	24 (7, 30)	0.18
CDR sum of boxes	3.0 (0.0, 13.0)	3.0 (0.0, 18.0)	0.35
Aβ SUVRs	2.34 (1.29, 3.20)	2.42 (1.42, 3.53)	0.15

Data shown are n (%) or median (range).
Key: APOE, apolipoprotein E; CDR, clinical dementia rating scale; MMSE, mini-mental state examination; SUVR, standard uptake value ratio

data on atypical AD patients with age at onset over 70 years was relatively sparse so some caution is needed in interpreting trends in these older ages. We only observed a significant difference in *APOE* ε4 genotype between clinical groups, with a higher *APOE* ε4 frequency in typical AD, in patients with an age at onset between 57 and 69 years. There was a tendency for atypical AD to have a lower frequency in patients with onset age under age 57 and a higher frequency in patients with an onset age over 75, although no significant differences were observed; possibly due to a lack of power at the age extremes. Data in the typical AD group was sparse at these low onset ages. Nevertheless, differences in age at onset likely contributed to discrepancies across previous studies in reported *APOE* ε4 frequencies in atypical AD cohorts, and in studies that compared typical and atypical AD.

Previous studies have associated the *APOE* ε4 genotype with greater medial temporal and less cortical atrophy and tau deposition on PET in AD (La Joie et al., 2021; Mattsson *et al.*, 2018; Therriault *et al.*, 2020), which fits with findings of lower *APOE* ε4 frequencies in atypical AD patients who show more cortical atrophy and tau uptake and a relative sparing of the medial temporal lobe compared to typical AD. However, our findings suggest that the relationship between *APOE* and clinical phenotype may be more complicated than this and depend highly on age at onset. Age at onset also strongly influences the neuroimaging outcomes in AD. Typical AD patients in the 60–70 age range show the expected imaging characteristics of AD, including hippocampal atrophy and tau deposition measured on PET, while those older than 70 years show hippocampal atrophy but less tau deposition on PET suggesting contributions from other pathologies, such as TDP-43, to medial temporal atrophy in older patients (Josephs *et al.*, 2020). It is possible that other pathologies may contribute somewhat to the lower *APOE* ε4 frequency in the older patients, that is that older-onset Alzheimer's dementia is less driven by *APOE* ε4 and more driven by the presence of other age-associated pathologies that target the medial temporal lobe, and may help explain the differences observed between typical and atypical AD. This fits with the fact that amyloid PET burden decreases with age in typical AD. The story is, however, likely more complicated than this given that the risk of age-associated pathologies such as TDP-43 and Lewy bodies have both been shown to be related to *APOE* (Dickson *et al.*, 2018; Wennberg *et al.*, 2018). While TDP-43 is uncommon in atypical AD (Sahoo *et al.*, 2018), Lewy bodies are a relatively common co-pathology (Buciuc *et al.*, 2020). Younger age at onset is associated with greater cortical atrophy and tau uptake in both atypical and typical AD (Josephs *et al.*, 2020; Whitwell *et al.*, 2019), which concurs with the lower *APOE* ε4 frequencies in young onset age in both groups. Future studies will be needed to determine the contributions of other pathologies and to determine the relationship between *APOE* ε4 genotype, neuroimaging signatures and age at onset across clinical phenotypes in AD.

There was no evidence that *APOE* ε4 status influenced the degree of Aβ deposition in either cohort across the age spectrum. Some previous studies have similarly found no relationship between *APOE* ε4 status and burden of Aβ PET or CSF Aβ1-42 in Alzheimer's dementia cohorts (Fleisher *et al.*, 2013; Nitsch *et al.*, 1995; Rowe *et al.*, 2010). Other studies have identified relationships, although the direction of the relationship in PET studies has varied with some studies finding greater Aβ PET burden in *APOE* ε4 positive patients (Drzezga *et al.*, 2009; Murphy *et al.*, 2013; Vemuri *et al.*, 2010) and others finding greater burden in *APOE* ε4 negative patients (Baek *et al.*, 2020; Lehmann *et al.*, 2014; Ossenkoppele *et al.*, 2013). The explanation for these discrepancies in the literature is unclear. Cohorts in previous studies may have been heterogeneous in terms of AD clinical phenotype and vary in age and disease severity, although our data does not suggest different relationships in these clinical phenotypes. Some of the previous studies included Aβ-negative individuals which could have influenced the findings and helped drive the associations (Fleisher *et al.*, 2013). In contrast to the heterogeneous results in Alzheimer's dementia populations, studies concur that *APOE* ε4 genotype is associated with Aβ in undemented populations (Jack *et al.*, 2015; Lim *et al.*, 2017; Morris *et al.*, 2010; Reiman *et al.*, 2009; Rowe *et al.*, 2010). It is possible that *APOE* has an effect early in the disease, increasing the risk of developing AD and hence Aβ deposition, but does not determine the burden of Aβ in later stages of the disease. Alternatively, Aβ-PET burden may have already plateaued in these advanced disease stages (Jack *et al.*, 2013).

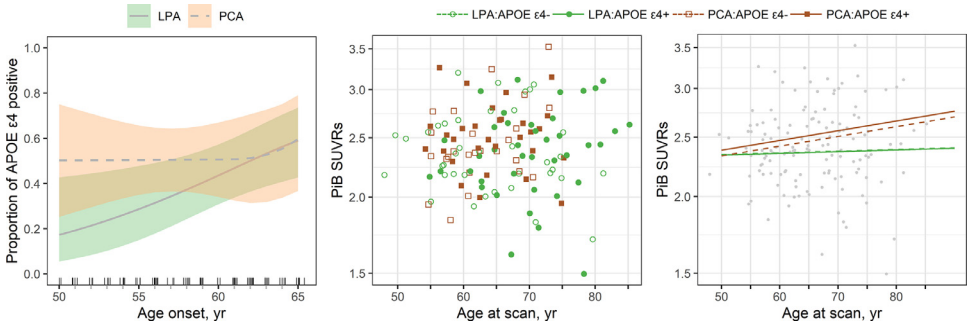

Fig. 3. *Plots showing the relationships between APOE ε4 status, age at onset and Aβ SUVR in LPA and PCA.* The first panel shows the estimated proportion of *APOE* ε4 carriers by age at onset for LPA and PCA with shaded regions indicating 95% CIs. The second panel shows a scatter plot of log-transformed Pittsburgh Compound B (PiB) Aβ SUVR versus age at scan with colors and symbols differentiating phenotype and *APOE* ε4 status. The third panel shows the estimated mean Aβ SUVR for the four subgroups.

We found that the relationships of *APOE* ε4 were similar in the two different clinical phenotypes of atypical AD. We did not find evidence for any differences in the relationship between *APOE* ε4 frequency and age at onset between LPA and PCA, although PCA seemed to have a flat slope while the frequency in LPA appeared to trend up. We also did not find any evidence that Aβ SUVR differed between PCA and LPA at any age. The only clear difference observed between the groups was that the LPA patients were about five years older at onset and PET than the PCA patients. In fact, none of our PCA patients were older than 75 years at the time of PET. Hence, the LPA patients would have contributed more to our understanding of *APOE* genotype and Aβ SUVR in atypical AD at the older onset ages. Both groups were, however, much younger at onset than the typical AD group, as one would expect.

This study utilized a large cohort of both atypical and typical AD patients allowing us to model the relationships between *APOE* genotype, age at onset and phenotype. The atypical AD cohort was also well characterized clinically and all patients had undergone standardized neurological batteries by one of two behavioral neurologists. Limitations of the study include the fact that the ADNI cohort did not have the same clinical variables available for comparison to the atypical AD cohort as the data comes from multiple different sites. The distributions of age at onset of the two cohorts also differed which limited power to compare the cohorts at very young and very old onset ages. Given that both cohorts had a clinical diagnosis of dementia we lacked enough *APOE* ε2 carriers to assess potential differences in frequency of this protective allele.

5. Conclusion

The findings highlight the importance of age at onset and clinical phenotype in understanding the effects of *APOE* genotype in AD, and contribute to knowledge concerning the heterogeneity present in AD. A better understanding of this heterogeneity will be important to help better target patients for inclusion in clinical treatment trials, and to allow improved interpretation of neuroimaging, clinical and genetic findings across the age spectrum in AD.

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Verification

This work has not been published previously, is not under consideration for publication elsewhere, that its publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out. If accepted, it will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright-holder.

Disclosure statement

The authors have no actual or potential conflicts of interest.

Author contributions

Jennifer L. Whitwell: Conceptualization; Funding acquisition; Investigation; Methodology; Project administration; Writing - original draft. **Nirubol Tosakulwong:** Formal analysis; Visualization; Writing - review & editing. **Stephen D. Weigand:** Formal analysis; Writing - review & editing. **Jonathan Graff-Radford:** Data curation; Writing - review & editing. **Nilufer Ertekin-Taner:** Data curation; Writing - review & editing. **Mary M. Machulda:** Data curation; Writing - review & editing. **Joseph R. Duffy:** Data curation; Writing - review & editing. **Christopher G. Schwarz:** Data curation; Software; Writing - review & editing. **Matthew L. Senjem:** Data curation; Software; Writing - review & editing. **Clifford R. Jack:** Resources; Software; Writing - review & editing. **Val J. Lowe:** Resources; Writing - review & editing. **Keith A. Josephs:** Data curation; Investigation; Methodology; Writing - review & editing.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.neurobiolaging.2021.08.012.

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