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Impact of *APOE-ε4* carriage on the onset and rates of neocortical Aβ-amyloid deposition

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ABSTRACT

Neocortical Aβ-amyloid deposition, one of the hallmark pathologic features of Alzheimer's disease (AD), begins decades prior to the presence of clinical symptoms. As clinical trials move to secondary and even primary prevention, understanding the rates of neocortical Aβ-amyloid deposition and the age at which Aβ-amyloid deposition becomes abnormal is crucial for optimizing the timing of these trials. As *APOE*-ε4 carriage is thought to modulate the age of clinical onset, it is also important to understand the impact of *APOE*-ε4 carriage on the age at which the neocortical Aβ-amyloid deposition becomes abnormal. Here, we show that, for 455 participants with over 3 years of follow-up, abnormal levels of neocortical Aβ-amyloid were reached on average at age 72 (66.5–77.1). The *APOE*-ε4 carriers reached abnormal levels earlier at age 63 (59.6–70.3); however, noncarriers reached the threshold later at age 78 (76.1–84.4). No differences in the rates of deposition were observed between *APOE*-ε4 carriers and noncarriers after abnormal Aβ-amyloid levels had been reached. These results suggest that primary and secondary prevention trials, looking to recruit at the earliest stages of disease, should target *APOE*-ε4 carriers between the ages of 60 and 66 and noncarriers between the ages of 76 and 84.

1. Introduction

Alzheimer's disease (AD), the most common form of dementia, is characterized pathologically by the extracellular accumulation of Aβ-amyloid and intracellular accumulation of tau in the neocortex (Jack et al., 2018). Neocortical accumulation of Aβ-amyloid is a key part of the cascade of pathologic changes leading to the onset of clinical symptoms in AD (Hardy and Selkoe, 2002; Karran et al., 2011) and is a process that initiates decades prior to clinical manifestation of the disease (Jack et al., 2013a; Villemagne et al., 2013). Increased understanding of the onset and rates of neocortical Aβ-amyloid deposition would provide improved disease staging criteria particularly for preclinical AD. This is increasingly important with clinical trials aimed at preventative treatment.

Carriage of an *APOE*-ε4 allele is a well-established risk factor for AD (Harold et al., 2009), reported to impact the levels of neocortical Aβ-amyloid (Liu et al., 2013; Reiman et al., 2009; Rowe et al., 2010; Villemagne et al., 2011); however, the nature of this impact is unclear. The literature appears to agree that *APOE*-ε4 carriage is associated with the deposition of neocortical Aβ-amyloid at an earlier age (Bilgel et al., 2019; Fleisher et al., 2013; Mishra et al., 2018) as well as an earlier onset of disease (Corder et al., 1995). Some contributions report that *APOE*-ε4 carriage is associated with an increased rate of neocortical Aβ-amyloid deposition (Bilgel et al., 2019; Jack et al., 2013a; Mishra et al., 2018; Toledo et al., 2019), others only report a difference in those with low neocortical Aβ-amyloid burden (Lim et al., 2017), while others report no difference in neocortical Aβ-amyloid accumulation rates between carriers and noncarriers (Corder et al., 1995; Resnick et al., 2015; Saunders, 2000). Accounting for the temporal relationship between neocortical Aβ-amyloid deposition and disease stage/progression may provide a clearer understanding of the impact of *APOE*-ε4 carriage on neocortical Aβ-amyloid deposition.

In this study, we evaluate the age at which abnormal levels of neocortical Aβ-amyloid deposition can be detected and test our hypotheses that carriage of an *APOE*-ε4 allele would be associated with a) a younger age of onset and b) faster rates of neocortical Aβ-amyloid deposition. For that purpose, natural history modeling in conjunction with survival analyses is used to jointly consider the onset and rates of neocortical Aβ-amyloid accumulation in reference to disease stage and progression.

2. Materials and methods

2.1. AIBL cohort

The Australian Imaging, Biomarker and Lifestyle (AIBL) cohort study of aging combines data from neuroimaging, biomarkers, lifestyle, clinical, and neuropsychological assessments. Two study centers in Melbourne, VIC, and Perth, WA, Australia recruit mild cognitively impaired (MCI) individuals and individuals with AD from primary-care physicians or tertiary Memory Disorders Clinics. Cognitively healthy normal controls (NCs) were recruited through advertisement or from spouses of participants in the study. Exclusion criteria were a history of non-AD dementia, Parkinson's disease, schizophrenia, bipolar disorder, obstructive sleep apnea, serious head injury, current depression (Geriatric Depression Score >5 out of 15), cancer in the past 2 years (with the exception of basal-cell skin carcinoma), symptomatic stroke, uncontrolled diabetes, or current regular alcohol use. Between November 3, 2006, and October 30, 2008, AIBL recruited 1112 eligible volunteers, who were aged 60 years or older and fluent in English. An enrichment cohort of 86 patients with AD, 124 MCI and 389 NCs were recruited by AIBL between March 30, 2011, and June 29, 2015. At baseline, the AIBL study participants were an average of 72 years of age, consisted of 58% women, and 36% were *APOE*-ε4 carriers. The institutional ethics committees of Austin Health, St Vincent's Health, Hollywood Private Hospital, and Edith Cowan University approved the AIBL study, and all volunteers gave written informed consent before participating.

2.1.1. Positron Emission Tomography Aβ-Amyloid

AIBL Aβ-Amyloid positron emission tomography (PET) studies consisted of a 30-minute acquisition starting 40 minutes after injection of 370 MBq of ^{11}C-Pittsburgh compound-B (^{11}C-PiB). For semiquantitative analysis, PET images were spatially normalized with CapAIBL using an adaptive atlas (Bougeat et al., 2015). The summed and spatially normalized PET images were then scaled to

[1] Alzheimer's Disease Neuroimaging Initiative (ADNI): Data used in preparation of this article were obtained from the ADNI database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

[2] AIBL Research Group: https://aibl.csiro.au/about/aibl-research-team/.

the recommended reference region, cerebellar cortex, to generate a tissue ratio termed SUV ratio (SUVR), and sampled using a preset template of narrow cortical volumes of interest. A global measure of the Aβ-amyloid level was computed using the mean SUVR in the frontal, superior parietal, lateral temporal, lateral occipital, and anterior and posterior cingulate regions. The abnormal threshold for levels of Aβ-amyloid in AIBL participants was set as 1.4 SUVR (Jack et al., 2013b).

2.1.2. Assessment of APOE genotype

APOE genotype was determined through TaqMan genotyping assays (Life Technologies) for rs7412 (Assay ID: C____904973_10) and rs429358 (Assay ID: C___3084793_20). TaqMan genotyping assays were performed on a QuantStudio 12K Flex Real-Time-PCR systems (Applied Biosystems, Foster City, CA) using the TaqMan GTXpress Master Mix (Life Technologies) methodology as per manufacturer instructions. *APOE* carrier status was defined by the presence (1 or 2 copies) or absence (0 copies) of the *APOE*-ε4 allele.

2.2. ADNI cohort

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). 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, PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD participants. Subjects were recruited from 57 sites across the United States and Canada and are followed up annually. ADNI initially (ADNI 1) recruited 200 NC subjects, 400 MCI subjects, and 200 subjects with early AD. In addition, ADNI GO, launched in 2009 included 200 subjects identified as having early mild cognitive impairment (EMCI). In 2011, ADNI 2 [11] recruited 150 NC, 100 EMCI participants, 150 late mild cognitive impairment (LMCI) participants and 150 AD participants. More recently, ADNI 3 was launched (September 2016) to recruit an additional 1200 volunteers.

2.2.1. PET Aβ-Amyloid

ADNI Aβ-amyloid PET studies consisted of an acquisition of 4 × 5-minute frames commencing 50–70 minutes after injection of 10 mCi of ^{18}F Florbetapir (FBP). In the same manner as the AIBL images, the ADNI PET images were spatially normalized with CapAIBL using an adaptive atlas (Bougeat et al., 2015). The summed and spatially normalized PET images were then scaled to a white matter reference region (a composite of the centrum semiovale and corpus callosum) (Chen et al., 2015) to generate a tissue ratio termed SUVR and sampled using the same preset template of narrow cortical volumes of interest as for the AIBL cohort. A global measure of the Aβ-amyloid level was computed using the mean SUVR in the frontal, superior parietal, lateral temporal, lateral occipital, and anterior and posterior cingulate regions. The abnormal threshold for levels of Aβ-amyloid in ADNI participants was set as 0.61 SUVR [equivalent to 1.4 SUVR for ^{11}C-PiB and 1.10 for FBP whole cerebellum correction (Clark et al., 2012)].

2.2.2. Assessment of APOE genotype

A 3-mL aliquot of blood was taken in ethylenediaminetetraacetic acid–containing vacutainer tubes from ADNI participants, and genomic DNA was extracted at Cogenics (now Beckman Coulter Genomics) using the QIAamp DNA Blood Maxi Kit (Qiagen, Inc, Valencia, CA) following the manufacturer's protocol. The two SNPs (rs429358, rs7412) that define the *APOE* epsilon 2, 3, and 4 alleles were evaluated by polymerase chain reaction amplification, followed by HhaI restriction enzyme digestion, resolution on 4% Metaphor Gel, and visualization by ethidium bromide staining (Potkin et al., 2009; Saykin et al., 2010).

2.3. Statistical analysis

AIBL ($n = 209$) and ADNI participants ($n = 246$) with at least 3 years of follow-up evaluations for Aβ-amyloid with ^{11}C-PiB (AIBL) or ^{18}F Florbetapir PET (ADNI), respectively, who were considered to be accumulating Aβ-amyloid [rate of deposition >0.0 SUVR/year(Villemagne et al., 2013)], and had been genotyped for *APOE* were included in this study. The following analyses were produced in parallel for both the AIBL participants and the ADNI participants. Further, all analyses were again replicated for the NC participants (156 AIBL NCs and 106 ADNI NCs) in a sensitivity analysis. For comparison purposes, in ADNI, EMCI, and LMCI participants were both considered as MCI to align with the classifications in AIBL. All analyses were performed in the R environment (R Development Core Team, 2017).

Demographics: Baseline differences between *APOE*-ε4 carriers and noncarriers were assessed with one-way *t*-tests for continuous data (age), $\chi 2$ testing for categorized data (sex, years of education, disease classification), and Kruskal–Wallis testing for nonnormally distributed data (length of follow-up). This was replicated for the individuals excluded from the study as they were not accumulating Aβ-amyloid (46 AIBL and 14 ADNI participants).

The differences in rates of Aβ-amyloid deposition: Each individual's rate of deposition (SUVR/year) was estimated using a linear model regressing their neocortical Aβ-amyloid levels (SUVR) against time since baseline evaluation (years). Differences in these rates between *APOE*-ε4 carriers and noncarriers, as well as between those above or below the neocortical Aβ-amyloid threshold at baseline, were evaluated using one-way *t*-tests, and presented using box and jitter plots. This analysis was also replicated for a combined cohort of those accumulating and not accumulating Aβ-amyloid in a sensitivity analysis.

Natural history of deposition: Individual's rates of Aβ-amyloid deposition, calculated above, were combined to estimate the overall natural history of Aβ-amyloid deposition using the 4-step procedure described previously (Budgeon et al., 2017; Villemagne et al., 2013) and stratified by *APOE*-ε4 carriage. Briefly, the 4-step procedure comprises 1) estimating the mean and slope of each individuals' Aβ-amyloid using linear models, 2) fitting a polynomial to the estimated means and slopes across all individuals, 3) integrating the reciprocal of the fitted polynomial, and 4) inverting the function to obtain the natural history trajectory. Confidence intervals (CI) for the natural history curves were created using the bootstrapping procedure described previously (Budgeon et al., 2017). Note: This analysis was replicated with stratification by sex.

Age of onset: Cox proportional hazards model of survival, corrected for sex, and years of education were used to estimate the age at which the participants reached abnormal levels of neocortical Aβ-amyloid. This analysis was replicated with *APOE*-ε4 carriage stratification, to assess the effect of *APOE*-ε4 carriage on the age at which the participants reached abnormal levels of Aβ-amyloid. Survival was defined as the time between birth and having a PET scan indicating abnormal levels of Aβ-amyloid, withdrawal from the study, or the last completed follow-up examination. The event was classified as having a PET scan indicating abnormal levels of Aβ-amyloid. For some individuals the date at which their amyloid levels would have become abnormal was imputed, further details on the imputation are provided in Supplementary Material. The median age at which the participants reached abnormal levels of Aβ-amyloid, represented by the age at which 50% of the cohort reached abnormal levels of Aβ-amyloid, was reported.

3. Data Availability

All ADNI and a subset of the AIBL data including images are shared through the LONI Image & Data Archive (http://adni.loni.usc.edu), a secure research data repository. Applications for access to the entirety of the AIBL data can be made via application through the AIBL website (https://aibl.csiro.au/).

4. Results

4.1. Demographics

There were a significantly higher proportion of NC participants in the AIBL *APOE*-ε4 noncarriers compared with carriers ($p = 0.001$), for the ADNI participants this relationship held as a trend ($p = 0.057$). Within AIBL, there were significantly more males among the *APOE*-ε4 carriers compared with noncarriers ($p = 0.026$), a finding not observed in the ADNI participants ($p = 0.683$). The ADNI *APOE*-ε4 noncarriers were significantly older than carriers ($p = 0.005$), no differences were observed for age between *APOE*-ε4 carriers and noncarriers in AIBL ($p = 0.196$). No differences were observed between *APOE*-ε4 carriers and noncarriers, in either AIBL or ADNI, for Years of Education, or length of follow-up (Table 1).

There were no significant differences between the *APOE*-ε4 carriers and noncarriers for these demographic measures in the AIBL participants deemed to be nonaccumulators (Supplementary Table 1), caution should be applied to these findings due to the small sample size however. Due to the small sample size, comparisons could not be drawn for the ADNI nonaccumulators (Supplementary Table 1). There appeared to be more males and shorter follow-up in the nonaccumulators compared with the accumulators; again the small sample size of the excluded nonaccumulators should be noted.

4.2. Rates of Aβ-amyloid deposition

A one-way *t*-test comparison suggested that *APOE*-ε4 carriers and noncarriers did not have significantly ($p = 0.60$) different rates of deposition in those above the threshold for Aβ-amyloid at baseline (mean rates of deposition of 0.03 ± 0.02 and 0.03 ± 0.02 SUVR/year, respectively; equivalent to 1.7%/year), (Fig. 1A). However, prior to reaching the abnormal threshold AIBL *APOE*-ε4 carriers appeared to have had significantly ($p = 0.005$) faster rates of Aβ-amyloid deposition (0.02 ± 0.02 SUVR/year; 2.1%/year) in comparison with AIBL *APOE*-ε4 noncarriers (0.01 ± 0.01 SUVR/year; 1.1%/year), (Fig. 1B).

A one-way *t*-test comparison of individual ADNI participants' rate of deposition of Aβ-amyloid suggest that *APOE*-ε4 carriers and noncarriers did not have significantly different rates of deposition either after or prior to reaching the abnormal threshold ($p = 0.99$ and $p = 0.82$, respectively). The mean rates of Aβ-amyloid deposition for ADNI participants beyond the abnormal threshold were 0.02 ± 0.01 SUVR/year (2.2%/year) for both *APOE*-ε4 carriers and noncarriers, (Fig. 1C). Prior to reaching the abnormal threshold, ADNI *APOE*-ε4 carriers and noncarriers both had rates of Aβ-amyloid deposition of 0.01 ± 0.005 SUVR/year (1.3%/year; Fig. 1D).

In a sensitivity analysis considering only the NC participants, the findings were equivalent with the only statistically significant difference ($p = 0.001$) being found in the AIBL participants below the threshold (Supplementary Fig. 1).

Including the nonaccumulators to the full data set resulted in no significant differences between *APOE*-ε4 carriers and noncarriers either above or below the threshold, for AIBL or ADNI participants (Supplementary Fig. 2).

4.3. Natural history of neocortical Aβ-amyloid deposition

Stratifying the natural history of neocortical Aβ-amyloid deposition by *APOE*-ε4 carriage indicated that on average AIBL *APOE*-ε4 carriers reached the abnormal threshold 14.9 (0.3–35.2) years prior to AIBL noncarriers, (Fig. 2A). Similarly, on average ADNI *APOE*-ε4 carriers reached the abnormal threshold 18.9 (CI: 3.5–40.1) years prior to ADNI noncarriers, (Fig. 2B). Plots for individuals' longitudinal data (Step 1 in the method) and slope versus mean plots (Step 2) stratified by *APOE*-ε4 carriage are provided in Supplementary Fig. 3 for AIBL and Supplementary Fig. 4 for ADNI. Note: When stratified by sex, females appeared to reach the abnormal threshold 2 years prior to males, but this was not statistically significant, results not presented.

Replicating this in a sensitivity analysis of the NC, indicated that on average NC AIBL *APOE*-ε4 carriers reached the abnormal threshold 11.1 (-3.9–34.6) years prior to CN AIBL noncarriers, (Supplementary Fig. 5). Please note that due to the small numbers of CN in the ADNI cohort, specifically *APOE*-ε4 carriers (N=37) the models did not converge, and results are not presented.

4.4. Age of onset using survival analysis

Survival analysis indicated that 50% of the AIBL and ADNI participants reached abnormal levels of Aβ-amyloid by ages of 69.3 (66.5–73.5) and 73.6 (CI: 71.2–77.1), respectively, (Fig. 3A and B). Stratifying the participants by *APOE*-ε4 carriage and replicating the survival analysis indicated 50% of *APOE* ε4 carriers reached abnormal levels of Aβ-amyloid by ages 62.0 (CI: 59.6–66.5) and 65.1 (CI: 62.0–70.3) in AIBL and ADNI, respectively. In contrast, 50% of the *APOE*-ε4 noncarriers reached abnormal levels of Aβ-amyloid by ages 77.2 (CI 76.1-NA) and 79.3 (CI 75.9–84.4) in AIBL and ADNI, respectively. These findings suggest that on average *APOE*-ε4 carriers reached abnormal levels of Aβ-amyloid 15.2 years prior to *APOE*-ε4 noncarriers in AIBL and 14.2 (2.5–20.5) years in ADNI (Fig. 3C and D).

In the CN subgroups, 50% of CN *APOE* ε4 carriers reached abnormal levels of Aβ-amyloid by ages 66.2 (CI: 63.6–76.1) and 66.4 (CI: 63.8-NA) in AIBL and ADNI, respectively. In contrast, 50% of the CN *APOE*-ε4 noncarriers reached abnormal levels of Aβ-amyloid by ages 77.6 (CI 71.6-NA) and 79.3 (CI 76.7-NA) in AIBL and ADNI, respectively (Supplementary Fig. 6).

5. Discussion

Survival analyses indicated the average age that AIBL and ADNI participants reached abnormal levels of neocortical Aβ-amyloid was 70 years of age, with CI ranging from 66 to 77 years of age. Stratifying the survival analyses by *APOE*-ε4 carriage suggested that on average *APOE*-ε4 carriers reached the abnormal threshold in their early sixties, 15 (CI: 6–24) years earlier than noncarriers who reached the threshold late in their seventies. Further, evaluation of the natural history of deposition of neocortical Aβ-amyloid also suggested that *APOE*-ε4 carriers reached the abnormal threshold of neocortical Aβ-amyloid deposition approximately 15–19 (CI: 4–40) years prior to noncarriers, in line with previous findings (Bilgel et al., 2019; Fleisher et al., 2013; Mishra et al., 2018).

When restricting the analysis to only consider the cognitively normal participants, cognitively normal *APOE*-ε4 carriers reached the abnormal threshold in their midsixties, 12 (CI: 0–24) years earlier than cognitively normal noncarriers who reached the threshold in their midseventies.

It is noted that while the age of onset and natural history analyses are not independent, there was exceptional consistency in the findings across the methods as well as across the two cohort studies, despite the use of different Aβ-amyloid tracers. The findings are also

Table 1
Demographics table for AIBL and ADNI participants stratified by *APOE*-ε4 carriage

	APOE-ε4 carriage in AIBL		*p*-value	*APOE*-ε4 carriage in ADNI		*p*-value
	No	Yes		No	Yes	
Number of participants (N)	123	86		142	104	
Clinical classification NC/MCI/AD (N)	102/15/6	54/16/16	0.001	69/73/0	37/67/0	0.057
Gender: Males (N [%])	51 (41.46)	50 (58.14)	0.026	62 (43.66)	49 (47.12)	0.683
Age (years) (mean [sd])	72.48 (6.99)	71.18 (7.23)	0.196	72.82 (6.83)	70.33 (6.87)	0.005
Years of education (N [%])						
<9	8 (6.5)	5 (5.81)	0.952	0 (0)	1 (0.96)	0.620
9–12	50 (40.65)	38 (44.19)		20 (14.09)	12 (11.54)	
13–15	24 (19.51)	17 (19.77)		29 (20.42)	20 (19.23)	
>15	41 (33.33)	26 (30.23)		93 (65.49)	71 (68.27)	
Years of follow-up (mean [sd])	6.93 (1.19)	6.68 (1.35)	0.149	5.00 (1.20)	5.09 (1.31)	0.708

consistent with literature looking at the clinical onset of AD which reports *APOE*-ε4 carriage moves the age of clinical onset earlier by 10–20 years in comparison with noncarriers (Bilgel et al., 2016; Corder et al., 1993; Jack et al., 2014; Jansen et al., 2015).

Based on group comparisons, *APOE*-ε4 carriers and noncarriers appeared to have similar rates of neocortical Aβ-amyloid deposition, with the only exception being AIBL participants prior to reaching the threshold for neocortical Aβ-amyloid. In this group, *APOE*-ε4 carriers appeared to have significantly faster rates of deposition than noncarriers.

Overall, the findings presented in this article suggest that the natural history of neocortical Aβ-amyloid deposition in *APOE*-ε4

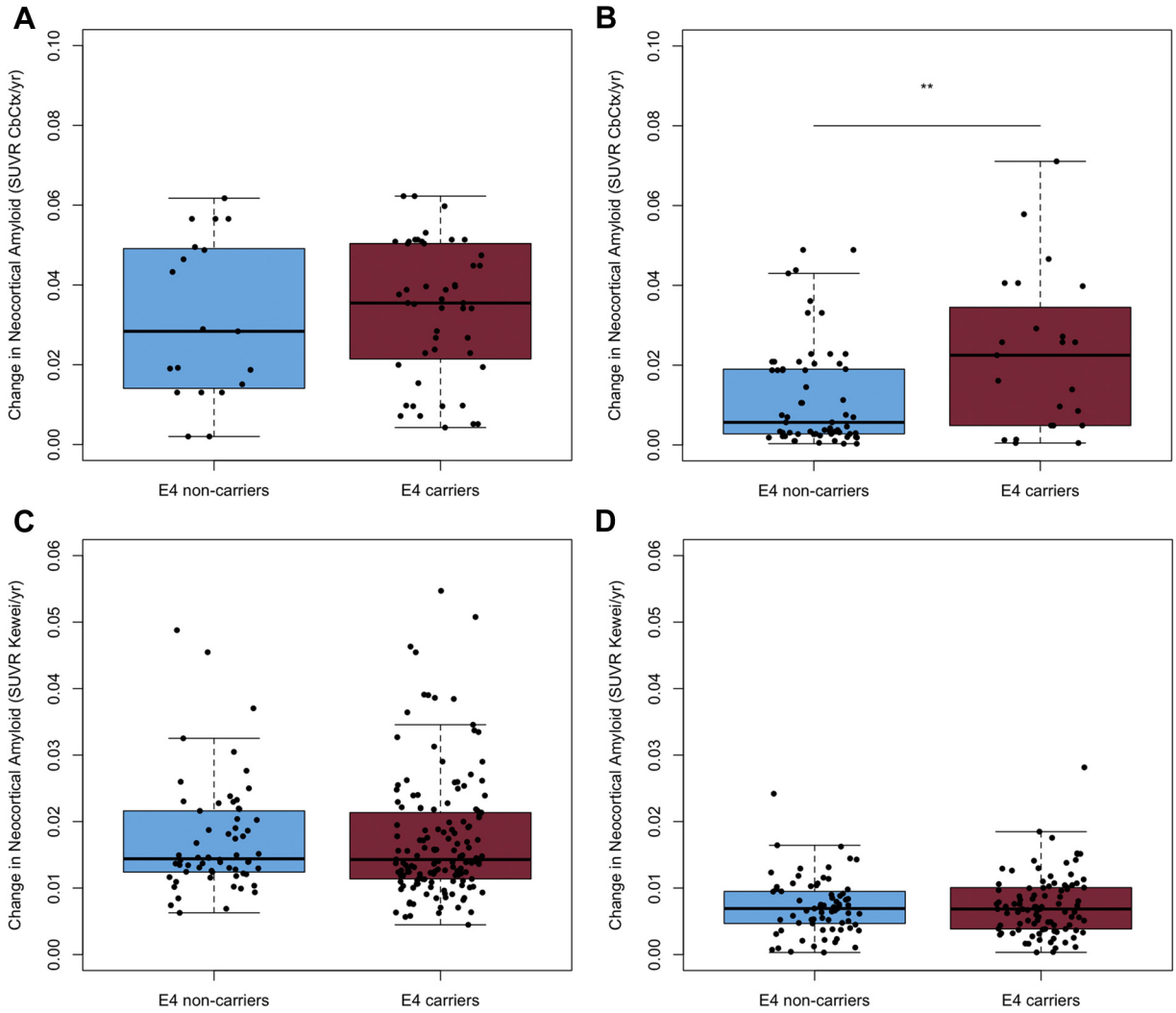

Fig. 1. (A) Boxplots detailing the rates of Aβ-amyloid deposition for AIBL participants above the abnormal threshold for Aβ-amyloid at baseline (^{11}C-PiB PET SUVR≥1.4) stratified by *APOE*-ε4 carriage. (B) Boxplots detailing the rates of Aβ-amyloid deposition for AIBL participants below the abnormal threshold for Aβ-amyloid at baseline (^{11}C-PiB PET SUVR≥1.4) stratified by *APOE*-ε4 carriage. (C) Boxplots detailing the rates of Aβ-amyloid deposition for ADNI participants above the abnormal threshold for Aβ-amyloid at baseline (^{18}F-Florbetapir SUVR≥0.61) stratified by *APOE*-ε4 carriage. (D) Boxplots detailing the rates of Aβ-amyloid deposition for ADNI participants below the abnormal threshold for Aβ-amyloid at baseline (^{18}F- Florbetapir SUVR≥0.61) stratified by *APOE*-ε4 carriage.

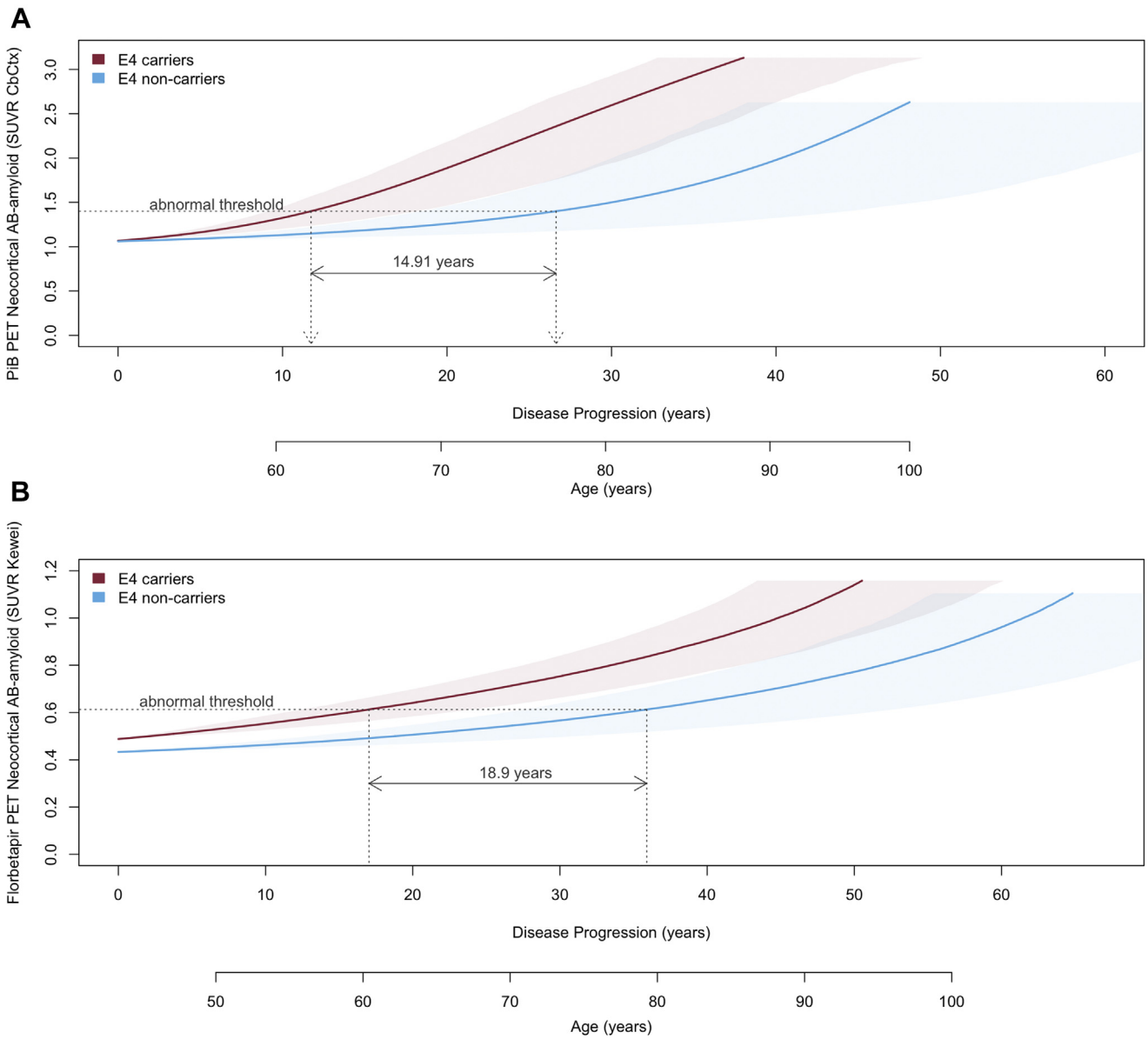

Fig. 2. (A) The natural history of deposition of neocortical Aβ-amyloid in AIBL participants stratified by *APOE*-ε4 carriage. Shaded areas indicate 95% confidence intervals. (B) The natural history of deposition of neocortical Aβ-amyloid in ADNI participants stratified by *APOE*-ε4 carriage. Shaded areas indicate 95% confidence intervals.

carriers starts approximately 15 years earlier but has a similar trajectory to that of *APOE*-ε4 noncarriers. For the same burden of neocortical Aβ-amyloid, the rate of deposition is similar for both *APOE*-ε4 carriers and noncarriers (demonstrated by drawing horizontal lines through Fig. 2A and B). These findings fit with the previous literature that *APOE*-ε4 carriage is not associated with the rate of disease progression, only with earlier onset of disease (Corder et al., 1995; Resnick et al., 2015; Saunders, 2000). Further, they go some way to explaining the conflicting reports that *APOE*-ε4 carriage is also associated with rate of deposition and/or disease progression (Bilgel et al., 2019; Craft et al., 1998; Hoyt et al., 2005; Jack et al., 2013a; Lim et al., 2017; Mishra et al., 2018; Toledo et al., 2019; Villemagne et al., 2011): if an age matched population was considered (or age corrected modeling used) then the rate of deposition would appear to be higher in *APOE*-ε4 carriers versus noncarriers. This would be due to *APOE*-ε4 carriers being 15 years further along in disease progression and having higher neocortical Aβ-amyloid burden as well as potentially higher rates of deposition (demonstrated by drawing vertical lines through Fig. 2A and B). Therefore, the difference in rate of deposition between *APOE*-ε4 carriers and noncarriers previously reported in the literature may be a function of a difference in disease stage opposed to a difference in *APOE*-ε4 carriage. The temporal relationship between onset and rate is an important consideration and previous evaluations considering these as independent factors or not using longitudinal data may have limited their ability to draw valid conclusions.

When stratifying by sex, no significant differences between males and females were observed in the natural history evaluations. As the effect of sex was of a much smaller magnitude at 2 years than that of *APOE*-ε4 at 15 years, it is possible that this study was not powered to observe a statistically significant difference.

This study has a number of other limitations. Firstly, there were not enough *APOE*-ε4 homozygotes to enable evaluations on the dose-effect of *APOE*-ε4 genotype to be undertaken. Secondly, a lack of *APOE*-ε2 carriers prevented further evaluations to understand the implications of *APOE*-ε2 carriage and its interplay with *APOE*-ε4

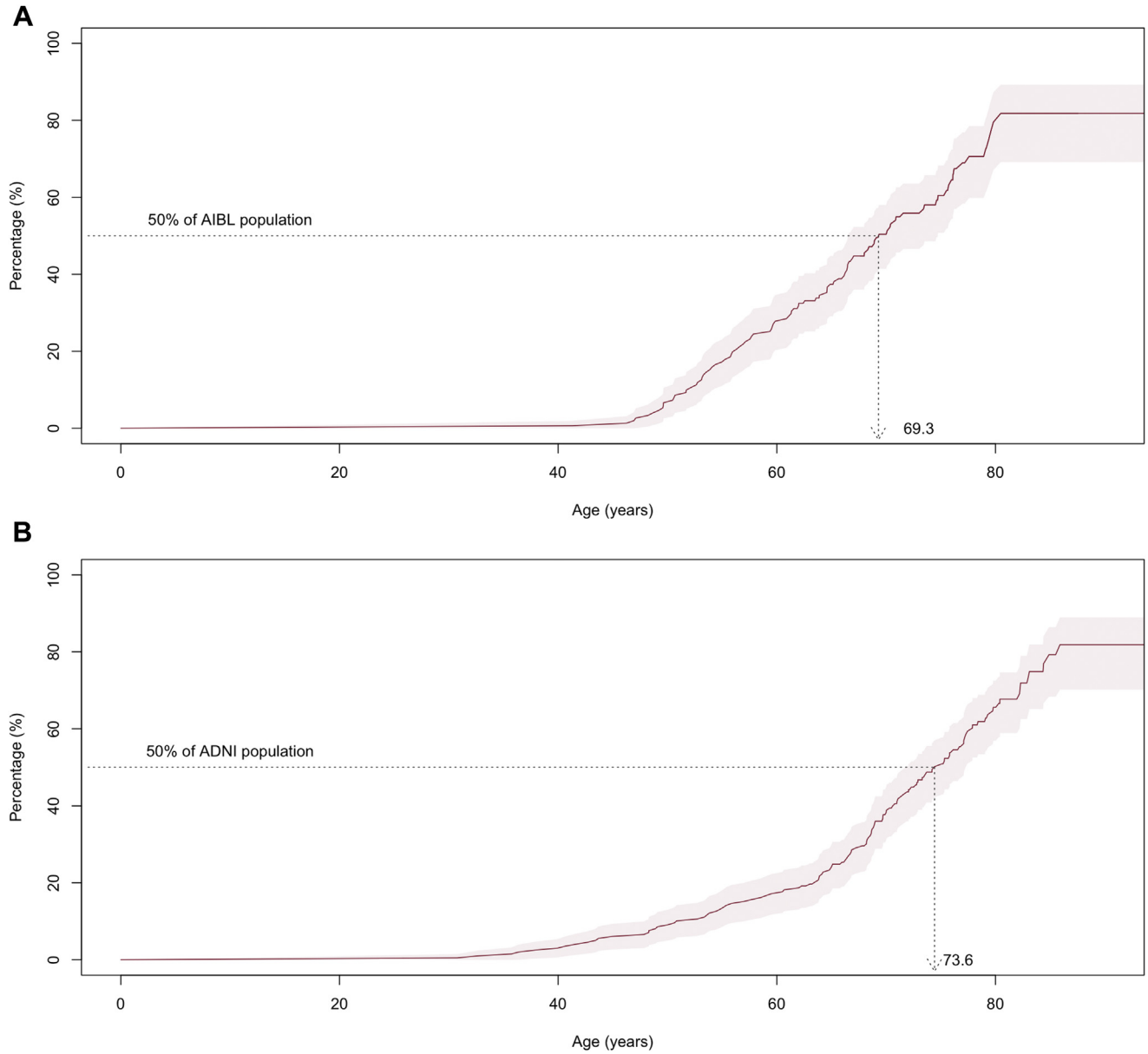

Fig. 3. (A) Kaplan–Meier plot detailing, by age, the prevalence of AIBL participants with high levels of Aβ-amyloid at baseline (^{11}C-PiB PET SUVR≥1.4). Shaded areas indicate 95% confidence intervals. (B) Kaplan-Meier plot detailing, by age, the prevalence of ADNI participants with high levels of Aβ-amyloid at baseline (^{18}F-Florbetapir SUVR≥0.61). Shaded areas indicate 95% confidence intervals. (C) Kaplan-Meier plot detailing, by age, the prevalence of AIBL participants with high levels of Aβ-amyloid at baseline (^{11}C-PiB PET SUVR≥1.4) stratified by *APOE*-ε4 carriage. Shaded areas indicate 95% confidence intervals. (D) Kaplan–Meier plot detailing, by age, the prevalence of ADNI participants with high levels of Aβ-amyloid at baseline (^{18}F-Florbetapir SUVR≥0.61) stratified by *APOE*-ε4 carriage. Shaded areas indicate 95% confidence intervals.

carriage. Thirdly, given the focus on rates of Aβ-amyloid deposition, only accumulators were included in most of this study which may contrast with other reports and might preclude the generalizability of the findings. Analysis of the small number of non-accumulators available resulted in loss of statistical significance of the difference in rates of change between AIBL *APOE*-ε4 carriers and non-carriers prior to reaching the threshold, no other differences were found. Fourthly, the analysis is restricted to the longitudinal evaluation of neocortical Aβ-amyloid, and it will be necessary to extrapolate this analysis to incorporate peripheral Aβ-amyloid and large longitudinal tau studies once they become available. The participants were volunteers who were not randomly selected from the community and were generally well educated; thus, these findings might only be valid in similar cohorts and this limitation precludes the generalization of the findings to the general population. In addition, in view of the stringent selection criteria in both AIBL and ADNI, which excluded individuals with cerebrovascular disease or other dementias, the effect of other comorbidities on the trajectories might be underestimated. Lastly, longitudinal Aβ-amyloid levels were obtained from ^{11}C PiB PET imaging in AIBL and ^{18}F Florbetapir PET imaging in ADNI and while both underwent the same CapAIBL normalization, differences in PET scanner and tracer kinetics may contribute a somewhat larger variance in the results.

It has been established that the rates of neocortical Aβ-amyloid deposition impact disease progression (Villemagne et al., 2013), earlier onset of Aβ-amyloid deposition may therefore lead to earlier disease onset. Therefore, understanding the age-related, temporal, deposition of neocortical Aβ-amyloid as well as the impact of *APOE*-

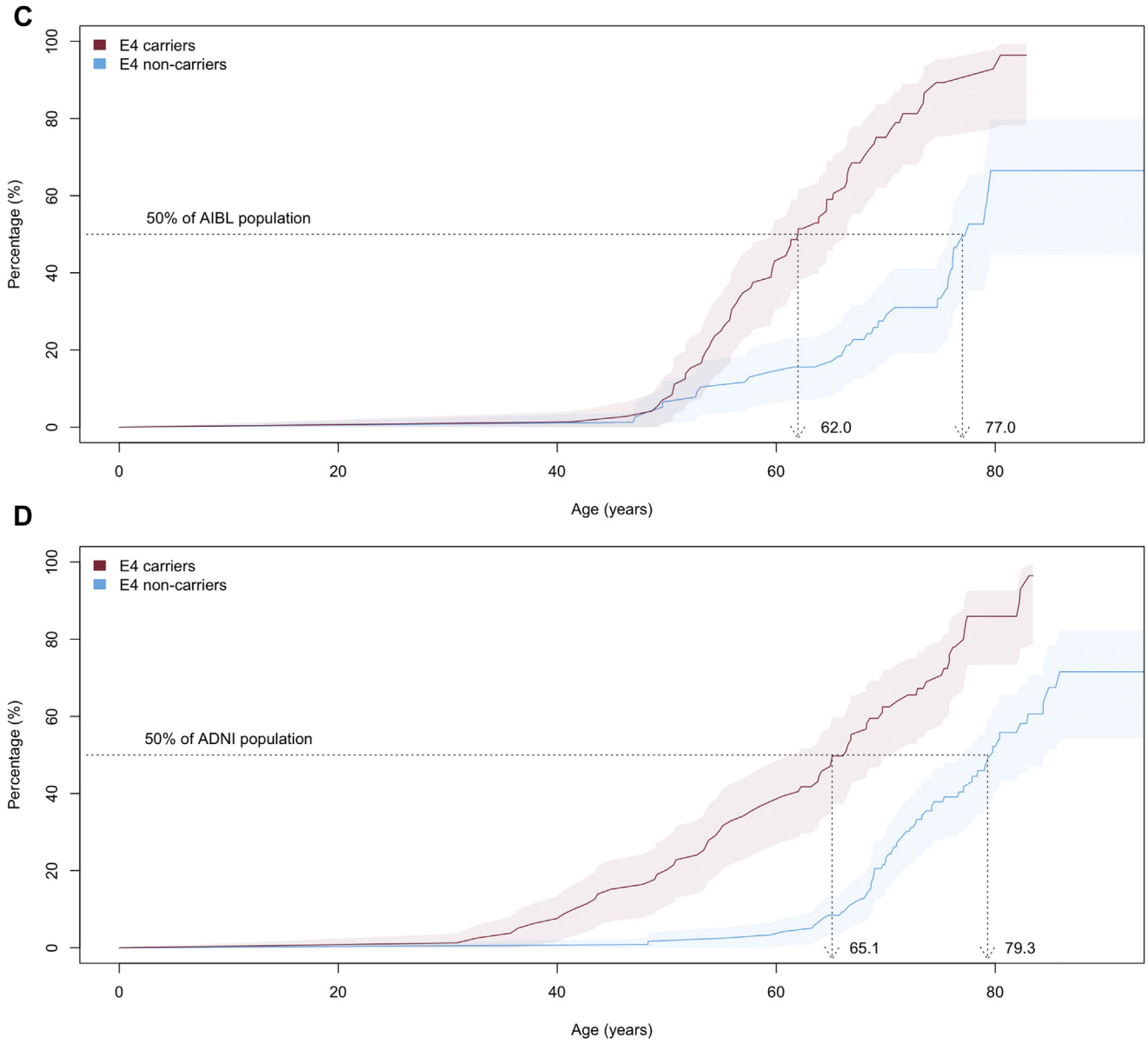

Fig. 3. (*continued*).

ε4 carriage has essential implications for understanding disease mechanisms and informing the timing for therapeutics and diagnostics (Ungar et al., 2014). This is of paramount importance when considering disease staging and/or clinical trial inclusion criteria; for instance, clinical trials will potentially need to consider alternative recruitment criteria such as younger age ranges for *APOE*-ε4 carriers in comparison with non-carriers. The ability to accurately target individuals at appropriate stages of the disease for inclusion in relevant clinical trials could afford such trials a better chance of success in the quest to delay and prevent AD.

CRediT authorship contribution statement

Samantha C. Burnham: Conceptualization, Investigation, Methodology, Data curation, Funding acquisition, Writing - original draft. **Simon M. Laws:** Data curation, Formal analysis. **Charley A. Budgeon:** Methodology, Software. **Vincent Doré:** Data curation, Formal analysis. **Tenielle Porter:** Data curation, Formal analysis. **Pierrick Bourgeat:** Data curation, Formal analysis. **Rachel F. Buckley:** Writing - review & editing. **Kevin Murray:** Methodology, Software. **Kathryn A. Ellis:** Project administration, Data curation. **Berwin A. Turlach:** Methodology, Software. **Olivier Salvado:** Project administration, Data curation. **David Ames:** Project administration, Data curation, Writing - review & editing. **Ralph N. Martins:** Writing - review & editing. **Dorene Rentz:** Writing - review & editing. **Colin L. Masters:** Writing - review & editing. **Christopher C. Rowe:** Writing - review & editing. **Victor L. Villemagne:** Conceptualization, Investigation, Methodology, Writing - original draft.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neurobiolaging.2020.06.001.

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