2016

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10.1212/WNL.0000000000002604

This is an Author's Accepted Manuscript of: Lim, Yen Ying, Laws, S.M., Villemagne, V.L., Pietrzak, R.H., Porter, T., Ames, D., ... Maruff, P. (2016). "Aβ-related memory decline in APOE ε4 noncarriers: Implications for Alzheimer disease.". *Neurology*, 86 (17), p. 1635-1642. Article found here

Aβ-related memory decline in *APOE* ε4 non-carriers: Implications for Alzheimer's disease

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Abstract word count: 188
Manuscript word count: 2938

Disclosures

Funding for the study was provided in part by the study partners [Commonwealth Scientific Industrial and research Organization (CSIRO), Edith Cowan University (ECU), Mental Health Research institute (MHRI), National Ageing Research Institute (NARI), Austin Health, CogState Ltd.]. The study also received support from the National Health and Medical Research Council (NHMRC) and the Dementia Collaborative Research Centres program (DCRC2), as well as funding from the Science and Industry Endowment Fund (SIEF) and the Cooperative Research Centre (CRC) for Mental Health, an Australian Government Initiative. Y.Y.L. is currently funded by the Alzheimer's Australia Dementia Research Fellowship and the Yulgilbar Foundation.

Y.Y.L., S.M.L., T.P., C.F., S.R.S., O.S., and P.B. report no disclosures. C.L.M. is an advisor to Prana Biotechnology Ltd and a consultant to Eli Lilly. R.H.P. and P.J.S are scientific consultants to Cogstate Ltd. P.M. is a full-time employee of Cogstate Ltd. D.A. has served on scientific advisory boards for Novartis, Eli Lilly, Janssen, and Pfizer Inc. R.N.M. is a consultant to Alzhyme. C.C.R. has served on scientific advisory boards for Bayer Pharma, Elan Corporation, GE Healthcare and AstraZeneca; has received speaker honoraria from Bayer Pharma and GE Healthcare; and has received research support from Bayer Pharma, GE Healthcare, Piramal Lifesciences and Avid Radiopharmaceuticals. V.L.V. served as a consultant for Bayer Pharma; and received research support from a NEDO grant from Japan.

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Abstract

Objectives: As the absence of Aβ related memory decline in apolipoprotein E (*APOE*) ε4 non-carriers may be due to the relative brevity of previous studies, we aimed to characterize Aβ related cognitive decline over 72-months in *APOE* ε4 carriers and non-carriers who were cognitively normal (CN).

Methods: CN older adults (n=423) underwent Aβ imaging, and *APOE* genotyping. Participants completed comprehensive neuropsychological testing at baseline 18-, 36-, 54- and 72-month assessments.

Results: Relative to Aβ- CN ε4 non-carriers, both Aβ+ CN ε4 carriers and non-carriers showed significantly increased decline in measures of memory, language, and executive function as well as higher rates of progression to a clinical classification of mild cognitive impairment (MCI). Memory decline was greater in Aβ+ CN ε4 carriers than in Aβ+ CN ε4 non-carriers. No cognitive decline was evident in Aβ- CN ε4 carriers.

Conclusions: In CN older adults, Aβ+ is associated with memory decline in ε4 non-carriers; however, the rate of this decline is much slower than that observed in ε4 carriers. These data indicate that the processes by which ε4 carriage increases the rate of Aβ-related cognitive decline occur in the preclinical stage of AD.

Introduction

In cognitively normal (CN) older adults, both high amyloid (Aβ+) and carriage of the apolipoprotein E (*APOE*) ε4 allele increase risk for cognitive decline and dementia of the Alzheimer's type (DAT),[1-3] although the interaction between Aβ+ and ε4 carriage in the preclinical stages of AD is not understood. Clinical studies show substantial cognitive decline over 54 months in Aβ+ CN ε4 carriers, particularly in episodic memory, compared to Aβ- CN ε4 non-carriers. However, cognitive decline has not been observed in Aβ+ CN ε4 non-carriers[4-6] suggesting that in preclinical AD, Aβ related cognitive decline is delayed in the absence of ε4. This hypothesis is consistent with observations from epidemiological studies that in the absence of *APOE* ε4, the average age at which dementia is classified clinically is delayed by approximately 8 years.[7, 8] However, the nature and length of any such delay in preclinical AD is unknown.

This study aimed to characterize the rate of Aβ-related cognitive decline over 72-months in CN older adults who were ε4 carriers and non-carriers. We hypothesized that compared to Aβ- CN ε4 non-carriers and Aβ+ CN ε4 non-carriers, Aβ+ CN ε4 carriers would show greater cognitive decline and higher rates of progression to mild cognitive impairment (MCI) over 72-months.

Methods

Participants

Cognitively normal (CN) older adults (n=767) volunteered to participate in the Australian Imaging, Biomarkers and Lifestyle (AIBL) Study, for which details of the recruitment and classification of cognitive health has been previously detailed.[9, 10] Briefly, participants were excluded from AIBL if they had a previous confirmed

diagnosis of schizophrenia; Parkinson's disease; sleep apnea; depression (e.g., Geriatric Depression Score [GDS] of 6 or greater); cancer (except basal cell skin carcinoma) in the last two years; symptomatic stroke or uncontrolled diabetes, or current alcohol use exceeded four standard drinks per day for men or two per day for women. This study focused on a sub-sample of CN older adults (n=423) who had undergone Aβ neuroimaging with positron emission tomography (PET) and *APOE* genotyping. The demographic and clinical characteristics of the total and PET subsample are shown and compared in Table 1.

All available neuropsychological, psychiatric and medical information for participants on all assessments were reviewed by an expert clinical panel to determine whether individuals' classification remained as CN or whether they met diagnostic classification for MCI,[11, 12] or AD.[13] Clinical classifications were blinded to data obtained from Aβ imaging at all visits.

Standard Protocol Approvals, Registrations, and Patient Consents

The AIBL study was approved by the ethics committees of Austin Health, St. Vincent's Health, Hollywood Private Hospital and Edith Cowan University. These institutions also ensured compliance of all study protocols.[9] Informed consent was provided in writing prior to participation in any study procedure.

Assessments

PET neuroimaging and APOE ε4 genotyping

PET Aβ imaging was conducted using one of three radioligands, that is, Pittsburgh Compound B (PiB), florbetapir or flutemetamol. The acquisition protocol for each radioligand has been detailed previously.[10, 14, 15] Briefly, a 30-minute acquisition

was started 40 minutes after PiB-injection, and 20-minute acquisitions were performed 50 minutes after florbetapir injection and 90 minutes after flutemetamol injection. For PiB acquisition, standardized uptake value (SUV) data for key regions of interest were summed and normalized to the cerebellar cortex SUV. This resulted in a region-to-cerebellar ratio which was termed SUV ratio (SUVR). For florbetapir, SUVR was generated using the whole cerebellum as the reference region,[16] and for flutemetamol, the pons was used as the reference region. Consistent with previous studies, Aβ status was classified as either low (Aβ-) or high (Aβ+). For PiB, an SUVR threshold ≥1.5 was used.[10, 15] For florbetapir and flutemetamol, an SUVR threshold of ≥1.1 and ≥0.62 were employed to discriminate between Aβ- and Aβ+, in accord with results of phase III studies.[16]

An 80ml blood sample was taken from each participant, a sample of which was forwarded for DNA extraction using either QIAamp DNA blood Midi or Maxi kits (Qiagen) in accord with the protocol provided by the manufacturer. *APOE* genotype was determined through TaqMan genotyping assays (Life Technologies) for rs7412 (Assay ID: C___904973_10) and rs429358 (Assay ID: C__3084793_20) on a QuantStudio 12K-Flex real-time PCR system (Applied Biosystems) using the TaqMan GTXpress Master Mix (Life Technologies) methodology per manufacturer's instructions.

Neuropsychological testing

To compute composite cognitive scores, first, each outcome measure on each neuropsychological test was standardized using the baseline mean and SD for the total CN group. Composite scores were then formed by averaging standardized scores for *episodic memory* (California Verbal Learning Test, Second Edition [CVLT-II] delayed recall, Logical Memory delayed recall and Rey Complex Figure Test delayed recall);

executive function (Category Fluency Fruit/Furniture Switching and Letter Fluency); *language* (Boston Naming Test and Category Fluency Animals/Boys' Names total score); and *attention* (Digit Symbol and Digit Span). We have previously detailed the rationale, development and validation for each cognitive composite score.[17, 18]

Procedure

Upon enrolment into AIBL, all participants underwent detailed medical, psychiatric, and neuropsychological assessment. These same assessments were repeated at 18-month intervals. In this study, we report PET neuroimaging and *APOE* ε4 genotyping data obtained at a single assessment, and neuropsychological data obtained at the baseline, 18-, 36-, 54- and 72-month assessments.

Data Analysis

To examine relationships between group (Aβ- CN ε4 non-carrier, Aβ- CN ε4 carrier, Aβ+ CN ε4 non-carrier, Aβ+ CN ε4 carrier) and time (baseline, and 18, 36, 54 and 72 month follow-up) for each composite cognitive score, we conducted a series of analyses using linear mixed effects models (LMM) with an unstructured covariance matrix and maximum likelihood estimation. The linear mixed modelling approach was employed because it is robust to missing data (see Figure 1 for number of participants who withdrew from the study or had deceased), because it can model both fixed and random effects, thus accounting for multiple sources of variability, and because it provides improved estimates of random effects (within-subject coefficients) in prospective studies. For each LMM, the cognitive composite score was the dependent variable. Group, time, and the interaction between group and time were specified as fixed factors; participant was specified as a random factor; and age, and anxiety

symptoms as the only covariates. Group mean slopes were computed for each cognitive composite score to reflect estimates of the rate of cognitive change over time. Where LMMs indicated an interaction between group and time as statistically significant, estimates of slope in the Aβ- CN ε4 carriers, Aβ+ CN ε4 non-carriers, and Aβ+ CN ε4 carriers were compared to that in the Aβ- CN ε4 non-carriers. Differences between slopes were expressed using Cohen's *d*. To provide context for any differences in memory decline observed between study groups, a criterion for clinically-significant memory impairment was defined as performance <1.5 SD below that of Aβ- ε4 non-carriers. The amount of time estimated for memory performance to reach this criterion was computed for each study group based on their LMM-derived linear functions.

Results

Demographic and clinical characteristics

There were no significant differences between the demographic and clinical characteristics of the total CN sample and the PET subsample, as the 95% confidence intervals for each outcome measure overlap (Table 1).

Statistically significant differences between Aβ/ε4 groups were observed for age and anxiety symptoms at baseline (Table 1). Consequently, age and anxiety symptoms were entered as covariates in the LMMs. Groups did not differ significantly on any other demographic or clinical characteristic at baseline.

Effect of Aβ and ε4 on cognitive change

Table 2 provides a summary of the group mean slopes for each cognitive composite for each Aβ/ε4 group. Compared to Aβ- CN ε4 non-carriers, Aβ+ CN ε4 carriers showed a significantly increased decline on all cognitive composites, and the

magnitudes of these differences were moderate-to-large (Figures 2 and 3). However, compared to Aβ+ CN ε4 non-carriers, Aβ+ CN ε4 carriers showed a significantly increased decline only on the measure of episodic memory, and the magnitude of this difference was large.

Compared to Aβ- CN ε4 non-carriers, Aβ+ CN ε4 non-carriers also showed a faster rate of decline for the measures of episodic memory, language and executive function (Figure 3). The rate of decline in episodic memory in Aβ+ CN ε4 carriers indicated that the memory performance of this group would be severe enough to meet criterion for clinically-significant impairment in approximately 10 years (95%CI 6-18 years), as opposed to 27 years (95%CI 10-45 years) in Aβ+ CN ε4 non-carriers. Compared to Aβ+ CN ε4 non-carriers, Aβ+ CN ε4 carriers showed an increased rate of decline only for episodic memory (Figure 3). Group mean slopes of Aβ- CN ε4 non-carriers and Aβ- CN ε4 carriers did not differ significantly on any cognitive composite.

Effect of Aβ and ε4 on rates of disease progression

At the 72-month assessment, the rate of clinical reclassification from CN to MCI/AD was significantly greater for Aβ+ CNs (18%) than for Aβ- CNs (6%), χ^2=9.91, p<.001, Cramér's V=.17 (Figure 1). However, while the rate of clinical reclassification from CN to MCI/AD was greater in Aβ+ CN ε4 carriers (22%) than Aβ+ CN ε4 non-carriers (15%), this difference was not large enough to reach statistical significance, χ^2=0.49, p=.49, Cramér's V=.09.

Discussion

The hypothesis that Aβ+ CN ε4 carriers would show an increased rate of cognitive decline and greater rates of progression to MCI/AD compared to Aβ- CN ε4

non-carriers and Aβ+ CN ε4 non-carriers was supported. Compared to Aβ- CN non-carriers, Aβ+ CN ε4 carriers showed decline in all cognitive domains, although this was greatest for episodic memory (Figures 2-3). Compared to Aβ+ CN ε4 non-carriers, Aβ+ CN ε4 carriers also showed a faster rate of decline in episodic memory, which was, by convention also large in magnitude (Table 2, Figure 2). The exacerbation of Aβ-related memory decline by ε4 is both consistent with, and extends, the results of previous analyses of AIBL data over shorter periods [5, 6] and also from other cohorts,[4] that ε4 carriage increases the rate of Aβ-related memory decline over 18 to 54-months. It is also consistent with animal studies which show that in the presence of Aβ+, the apoE4 isoform causes cognitive impairment. No such impairment is observed in the presence of the apoE3 isoform.[8, 19] The current results also characterize the much slower rate of development of Aβ-related memory decline in CN older adults who do not carry the *APOE* ε4 allele. Previous analyses of data from Aβ+ CN older adults in AIBL conducted over shorter periods (e.g., 36 months) have observed that Aβ-related cognitive decline is restricted to episodic memory.[17] In the current study, cognitive decline in Aβ+ CN older adults extended to executive function, language and attention, albeit with more subtle trajectories (Table 2). We believe that the detection of Aβ-related decline in domains beyond memory, observed in the current study, was due to the larger sample size in this study and that individuals had been assessed over a much longer time interval than previously. In this context, the observation that exacerbation of Aβ-related cognitive decline by *APOE* ε4 was specific to episodic memory confirms the centrality of episodic memory dysfunction to early AD. It is also consistent with previous studies which also observed that Aβ-related cognitive decline in preclinical AD occurs only for *APOE* ε4 carriers and only for episodic memory.[4, 5] We believe that with

a longer study period, Aβ-related decline in cognitive functions other than memory will become evident in Aβ+ CN ε4 non-carriers.

Previously, we have expressed the relevance of Aβ-related memory decline in CN older adults as the time required for a declining memory trajectory to reach a level of clinically-significant memory impairment, that is, memory impairment that would warrant consideration of a diagnosis of MCI.[12] In this study, clinically significant memory impairment was defined as performance that is less than 1.5 standard deviations from matched controls (Figure 2 dashed horizontal line).[5] Extrapolation of the rates of memory decline in this study suggest that the Aβ+ CN ε4 carriers would develop clinically-significant memory impairment approximately 10 years after their first assessment (Figure 2; see Table 1 for baseline demographic characteristics of this group). In contrast, Aβ+ CN ε4 non-carriers would require 27 years to reach the same criterion. Consistent with these estimates of a relatively slow decline in cognition, only 18% of the Aβ+ CN group were classified as having met clinical criteria for MCI or AD over the study period of 72-months, and this proportion was only slightly greater in ε4 carriers (22%) than in non-carriers (15%) (Figure 1). These data reflect the subtlety of Aβ-related cognitive decline observed in current preclinical AD groups and suggest that study over even longer intervals may be required to determine the effect of *APOE* ε4 carriage on clinical progression in Aβ+ CN older adults.

There is increasing evidence from both human and animal studies that the apoE4 isoform affects risk for AD by disrupting Aβ clearance relative to the other apoE isoforms (i.e., apoE3 and apoE2).[7, 8, 20, 21] Further, apoE4 itself has also been implicated directly in neurodegeneration and reduced synaptic integrity,[22] such that even a modest increase in apoE4 levels can increase Aβ accumulation and exacerbate synaptic loss

around plaques. [23] However, it is not clear whether the processes by which apoE4 affects risk for AD are through an increase in neurotoxicity, loss in neuroprotective function, or combination of both.[21] While the processes by which apoE4 increases risk for AD may occur independently of Aβ, it is also likely that Aβ oligomers can further impair the physiological functions of apoE in promoting synaptic and neuronal integrity.[24] Thus, the absence of the *APOE* ε4 allele may afford some level of protection against AD-related neurodegeneration even when the amyloid cascade has begun (i.e., Aβ accumulation). The substantial delay in Aβ-related memory impairment observed in the current CN group suggests that understanding and manipulating the biological processes by which apoE4 exacerbates Aβ toxicity could provide important insight into the pathogenesis of AD and perhaps even a basis for the development of pharmacotherapies to reduce this toxicity and its clinical consequences. The observation in the current study that ε4 carriage accounted for more than 18% of additional variance in Aβ-related cognitive decline suggests strongly that clinical trials of preclinical AD should consider stratification of their Aβ+ samples according to *APOE* ε4 carriage.

While the risk for AD and high levels of Aβ posed by *APOE* ε4 carriage have now been documented consistently,[10, 25] the results of this study suggest that in the absence of Aβ, *APOE* ε4 carriage does not increase risk for cognitive decline. Despite the comparatively large sample, the long period of investigation and the sensitive neuropsychological tasks used, we observed no effect of ε4 carriage on cognitive decline independent of Aβ+. All aspects of cognitive function remained stable in Aβ- CN ε4 carriers, and the rate of change of Aβ- CN ε4 carriers over the 72-month test-retest period was indistinguishable from that of Aβ- CN ε4 non-carriers (Figure 2 and Table 2). The observation that in Aβ-, ε4 carriage is not associated with any cognitive decline has

been reported previously in the AIBL and other cohorts of CN older adults whose Aβ status is known.[4-6] While a series of large and well-designed prospective studies have shown that carriage of the *APOE* ε4 allele is associated with increased decline in cognitive function, a major limitation of these studies has been that the Aβ status of their samples was unknown.[26] It is therefore likely that the decline in cognitive function observed previously in ε4 carriers reflected the effects of both Aβ+ and ε4 carriage, rather than any independent effect of ε4 by itself.

When considering the results of this study, an important caveat is that the AIBL study, like many other natural history early AD cohorts,[27, 28] is not a population-based sample. In AIBL, few CN older adults had existing or untreated medical, neurological or psychiatric illnesses and most participants were highly educated. As such, it will be important for the results of the current study to be replicated in other early AD cohorts, especially in study groups whose ascertainment has been based on epidemiological principles (e.g., the Mayo Clinic Study of Aging).[29] A second caveat is that participants underwent neuroimaging at varying timepoints after their baseline assessment, with the median delay between neuropsychological testing and Aβ neuroimaging 3 years. However, as current empirical models of AD have shown that the rate of Aβ accumulation is very slow, particularly in the preclinical stage of the disease,[3, 30] it is unlikely that individuals classified as Aβ+ at the 36-month assessment were Aβ- at the baseline assessment. To test this assumption, the main statistical models were re-computed with the time lag between baseline neuropsychological assessment and PET scan entered as a covariate. This reanalysis revealed no statistically significant effect for the time lag (Supplementary Table 1). Further, estimates of slopes for each Aβ/ε4 group also did not change substantially. We now await the completion of sequential amyloid scans in the entire AIBL CN cohort so as to appreciate, more accurately, the relationship

between cognitive change and Aβ accumulation in ε4 carriers and non-carriers. Nonetheless, it will be prudent for future studies to determine whether individuals who transition from Aβ- to Aβ+ show a different cognitive profile to those who remain Aβ- or Aβ+ across a study period. However, our current data suggest that the additive effect of Aβ+ and ε4 on cognitive decline in preclinical AD may make an ideal target for pharmaceutical therapies that mitigate Aβ-related neurodegeneration, or from the interaction between Aβ+ and ε4. They further support the hypothesis that reducing the toxic effects of apoE4 or restoring the neuroprotective functions of apoE isoforms in promoting synaptic plasticity and reducing neuroinflammation may be viable therapeutic strategies for the future.[21]

Acknowledgements

Alzheimer's Australia (Victoria and Western Australia) assisted with promotion of the study and the screening of telephone calls from volunteers. The AIBL team wishes to thank the clinicians who referred patients with MCI or AD to the study: Associate Professor Brian Chambers, Professor Edmond Chiu, Dr Roger Clarnette, Associate Professor David Darby, Dr Mary Davison, Dr John Drago, Dr Peter Drysdale, Dr Jacqueline Gilbert, Dr Kwang Lim, Professor Nicola Lautenschlager, Dr Dina LoGiudice, Dr Peter McCardle, Dr Steve McFarlane, Dr Alastair Mander, Dr John Merory, Professor Daniel O'Connor, Dr Ron Scholes, Dr Mathew Samuel, Dr Darshan Trivedi, and Associate Professor Michael Woodward. We thank all those who participated in the study for their commitment and dedication to helping advance research into the early detection and causation of AD.

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Table 1. Demographic and clinical characteristics.

	CN total sample (n=767)	PET subsample (n=423)	CN Aβ- non-ε4 (n=262)	CN Aβ- ε4 (n=64)	CN Aβ+ non-ε4 (n=46)	CN Aβ+ ε4 (n=51)	*p*
% Female	439 (57%)	231 (55%)	142 (54%)	37 (58%)	23 (50%)	29 (57%)	.854
[95% CI]	[52-62%]	[49-61%]					
% *APOE* ε4	207 (27%)	115 (27%)	-	-	-	-	-
[95% CI]	[21-33%]	[19-35%]					
Age Mean (SD)	70.03 (7.00)	69.39 (6.60)	**68.59 (6.03)**	**66.97 (5.47)**	**75.02 (7.37)**	**71.45 (6.82)**	**.000**
[95% CI]	(69.53-70.53)	(68.76-70.02)					
Premorbid IQ Mean (SD)	108.28 (7.27)	108.66 (7.08)	108.44 (6.94)	107.56 (7.59)	110.63 (7.62)	109.37 (6.43)	.118
[95%CI]	[107.77-108.79]	[107.99, 109.33]					
GDS Mean (SD)	0.98 (1.39)	0.87 (1.33)	0.91 (1.38)	0.98 (1.49)	0.61 (1.08)	0.73 (1.08)	.406
[95% CI]	[0.88-1.08]	[0.74, 1.00]					
HADS-D Mean (SD)	2.58 (2.24)	2.62 (2.32)	2.57 (2.24)	2.77 (2.04)	2.02 (1.69)	3.22 (3.24)	.080
[95% CI]	[2.42, 2.74]	[2.40, 2.84]					
HADS-A Mean (SD)	4.30(2.95)	4.28 (2.85)	**4.29 (2.84)**	**4.13 (2.89)**	**3.42 (1.97)**	**5.18 (3.31)**	**.025**
[95% CI]	[4.09, 4.51]	[4.01, 4.55]					
MACQ Mean (SD)	25.19 (4.32)	25.21 (4.41)	24.79 (4.32)	25.98 (3.86)	25.71 (4.87)	26.01 (4.96)	.110
[95% CI]	[24.88, 25.50]	[24.79, 25.63]					
CDR Mean (SD)	0.03 (0.12)	0.03 (0.13)	0.03 (0.11)	0.04 (0.14)	0.07 (0.20)	0.02 (0.10)	.187
[95% CI]	[0.02, 0.04]	[0.02, 0.04]					
CDR sum of boxes Mean (SD)	0.03 (0.15)	0.03 (0.15)	0.03 (0.16)	0.04 (0.14)	0.04 (0.14)	0.02 (0.10)	.852
[95% CI]	[0.02, 0.04]	[0.02, 0.04]					
MMSE Mean (SD)	28.86 (1.19)	28.92 (1.16)	28.97 (1.13)	28.90 (1.21)	28.85 (1.25)	28.75 (1.18)	.627
[95% CI]	[28.78, 28.94]	[28.81, 29.03]					

Note: CN = cognitively normal older adults; APOE = apolipoprotein E; GDS = Geriatric Depression Scale; HADS = Hospital Anxiety and Depression Scale; MACQ = Memory Complaints Questionnaire; CDR = Clinical Dementia Rating scale; MMSE = Mini Mental State Examination

Table 2. Effect of Aβ and ε4 on each cognitive composite score over 72-months in CN older adults

	Episodic Memory		Executive Function		Language		Attention	
	(df) F	*p*	(df) F	*p*	(df) F	*p*	(df) F	*p*
Age	(1,418) 41.75	.000	(1,419) 31.87	.000	(1,423) 25.74	.000	(1,421) 65.49	.000
Anxiety	(1,415) 0.69	.408	(1,412) 0.33	.569	(1,419) 1.64	.201	(1,418) 1.92	.167
Group	(3,421) 0.47	.701	(3,426) 2.52	.057	(3,425) 1.78	.150	(3,427) 4.28	.005
Time	(1,360) 11.78	.000	(1,392) 33.32	.000	(1,331) 30.61	.000	(1,404) 41.67	.000
Group x Time	(3,356) 19.42	.000	(3,386) 3.89	.009	(3,327) 6.45	.000	(3,401) 4.96	.002
	Mean Slope	SD	Mean Slope	SD	Mean Slope	SD	Mean Slope	SD
CN Aβ- ε4- (n=262)	0.024	0.161	-0.048	0.173	-0.022	0.157	-0.045	0.176
CN Aβ- ε4+ (n=64)	0.044	0.131	-0.008	0.141	-0.006	0.128	-0.015	0.143
CN Aβ+ ε4- (n=46)	-0.043	0.129	-0.100	0.139	-0.086	0.126	-0.115	0.139
CN Aβ+ ε4+ (n=51)	-0.173	0.134	-0.112	0.139	-0.120	0.131	-0.123	0.143

*Note: All models have been adjusted for age and the Hospital Anxiety and Depression Scale (HADS) Anxiety subscale score; Group indicates group membership as Aβ- ε4-, Aβ- ε4+, Aβ+ ε4- or Aβ+ ε4+

**Note: CN = Cognitively normal; ε4- = ε4 non-carriers; ε4+ = ε4 carriers

Supplementary Table 1. Effect of Aβ and ε4 on each cognitive composite score over 72-months in CN older adults, after accounting for time lag between baseline neuropsychological assessment and PET scan

	Episodic Memory		Executive Function		Language		Attention	
	(df) F	*p*	(df) F	*p*	(df) F	*p*	(df) F	*p*
Age	(1,417) 38.85	.000	(1,417) 27.52	.000	(1,421) 21.50	.000	(1,420) 58.53	.000
Anxiety	(1,415) 0.68	.409	(1,412) 0.35	.552	(1,419) 1.71	.191	(1,418) 1.95	.163
Scan Time Lag	(1,416) 0.00	.983	(1,410) 0.64	.426	(1,418) 0.91	.342	(1,418) 0.30	.584
Group	(3,422) 0.47	.703	(3,428) 2.40	.067	(3,427) 1.74	.159	(3,429) 4.05	.007
Time	(1,360) 11.78	.001	(1,392) 33.54	.000	(1,331) 30.67	.000	(1,404) 41.74	.000
Group x Time	(3,356) 19.42	.000	(3,386) 3.92	.009	(3,327) 6.47	.000	(3,401) 4.97	.002
	Mean Slope	SD	Mean Slope	SD	Mean Slope	SD	Mean Slope	SD
CN Aβ- ε4- (n=262)	0.024	0.161	-0.049	0.173	-0.022	0.157	-0.046	0.176
CN Aβ- ε4+ (n=64)	0.044	0.131	-0.008	0.141	-0.006	0.128	-0.015	0.143
CN Aβ+ ε4- (n=46)	-0.043	0.129	-0.101	0.139	-0.086	0.126	-0.115	0.139
CN Aβ+ ε4+ (n=51)	-0.173	0.134	-0.112	0.143	-0.120	0.131	-0.123	0.143

*Note: All models have been adjusted for age, amount of time lag between baseline neuropsychological assessment and PET scan, and the Hospital Anxiety and Depression Scale (HADS) Anxiety subscale score; Group indicates group membership as Aβ- ε4-, Aβ- ε4+, Aβ+ ε4- or Aβ+ ε4+

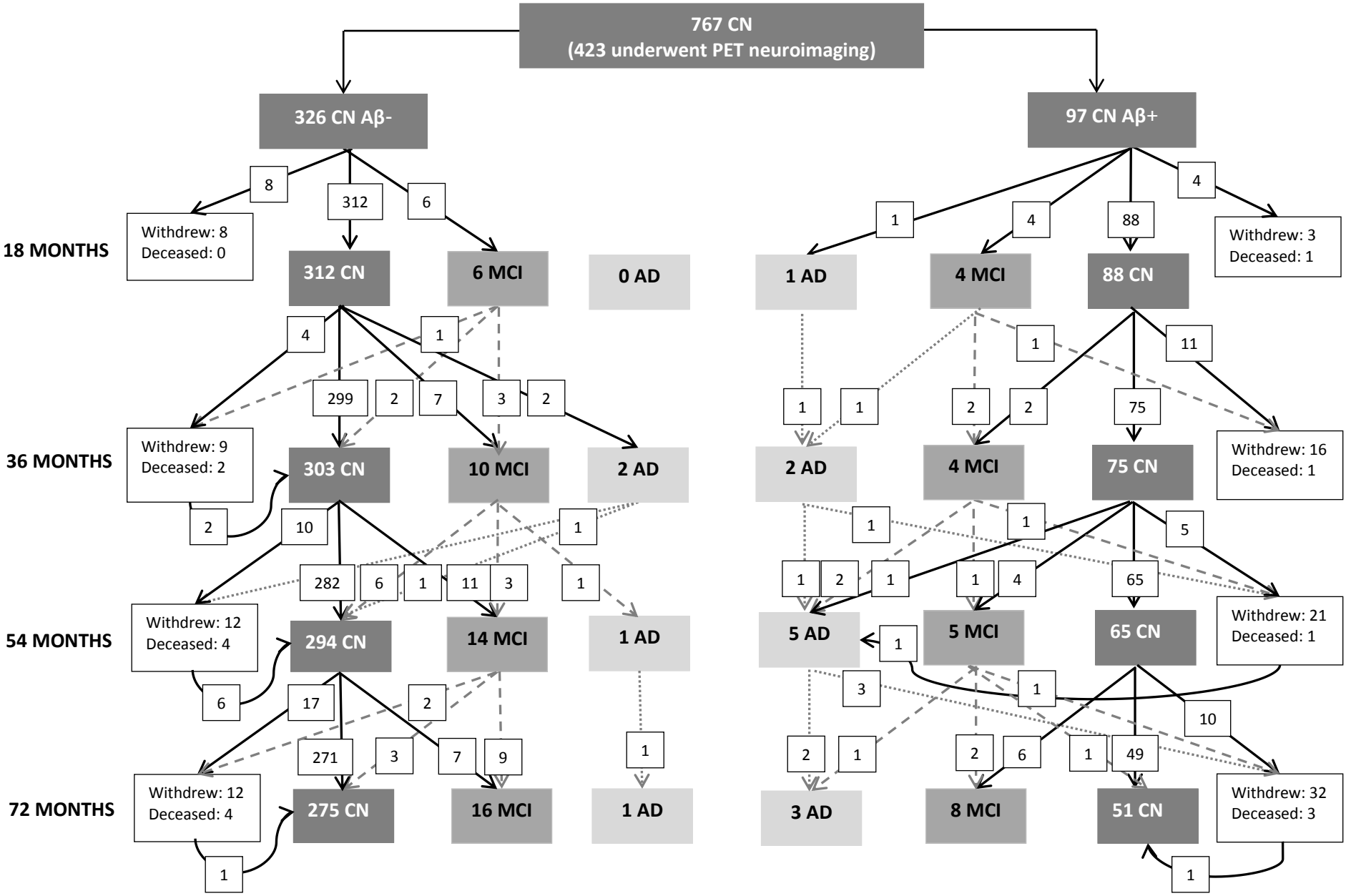
**Note: CN = Cognitively normal; ε4- = ε4 non-carriers; ε4+ = ε4 carriers

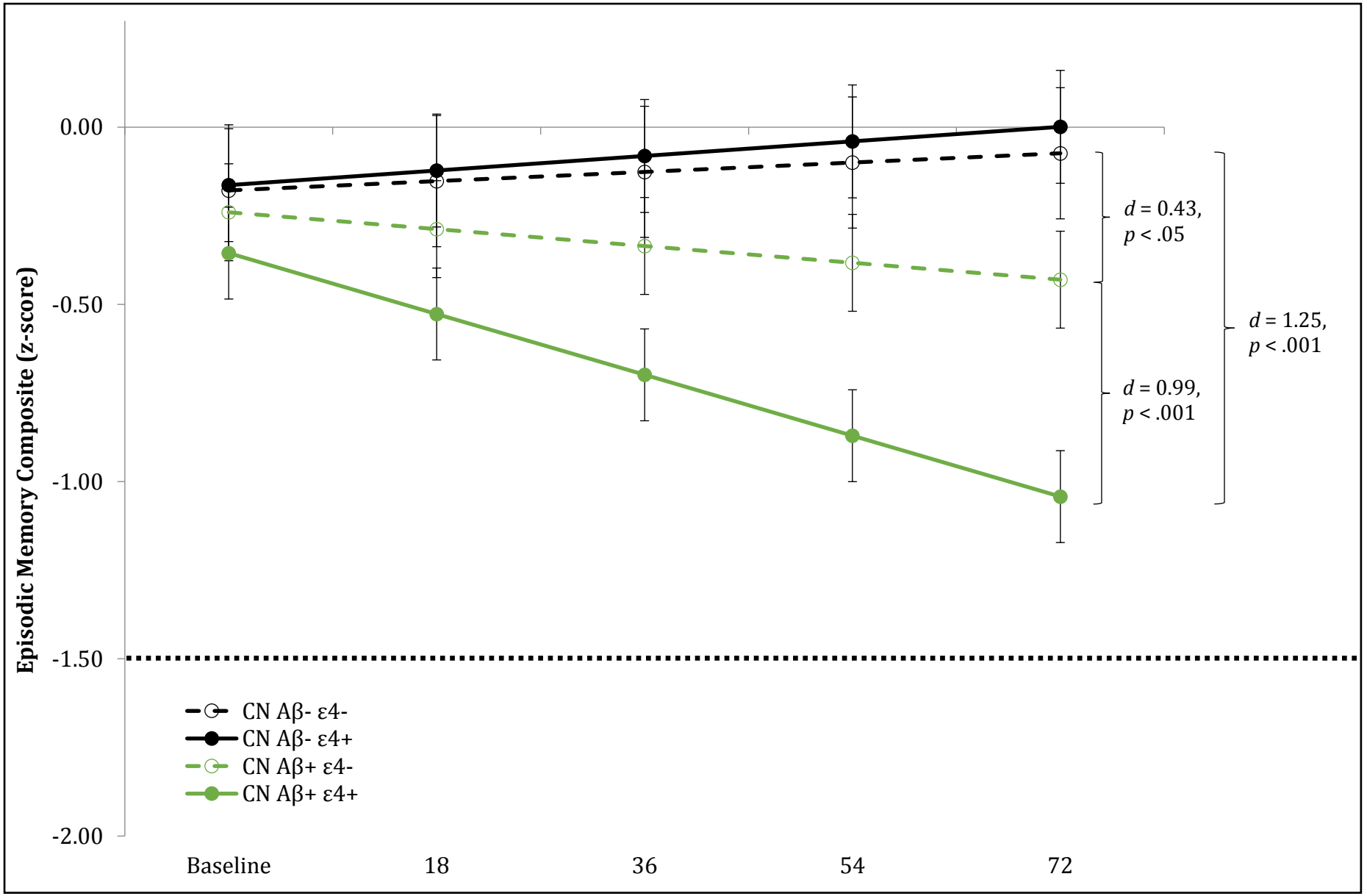
Figure Captions

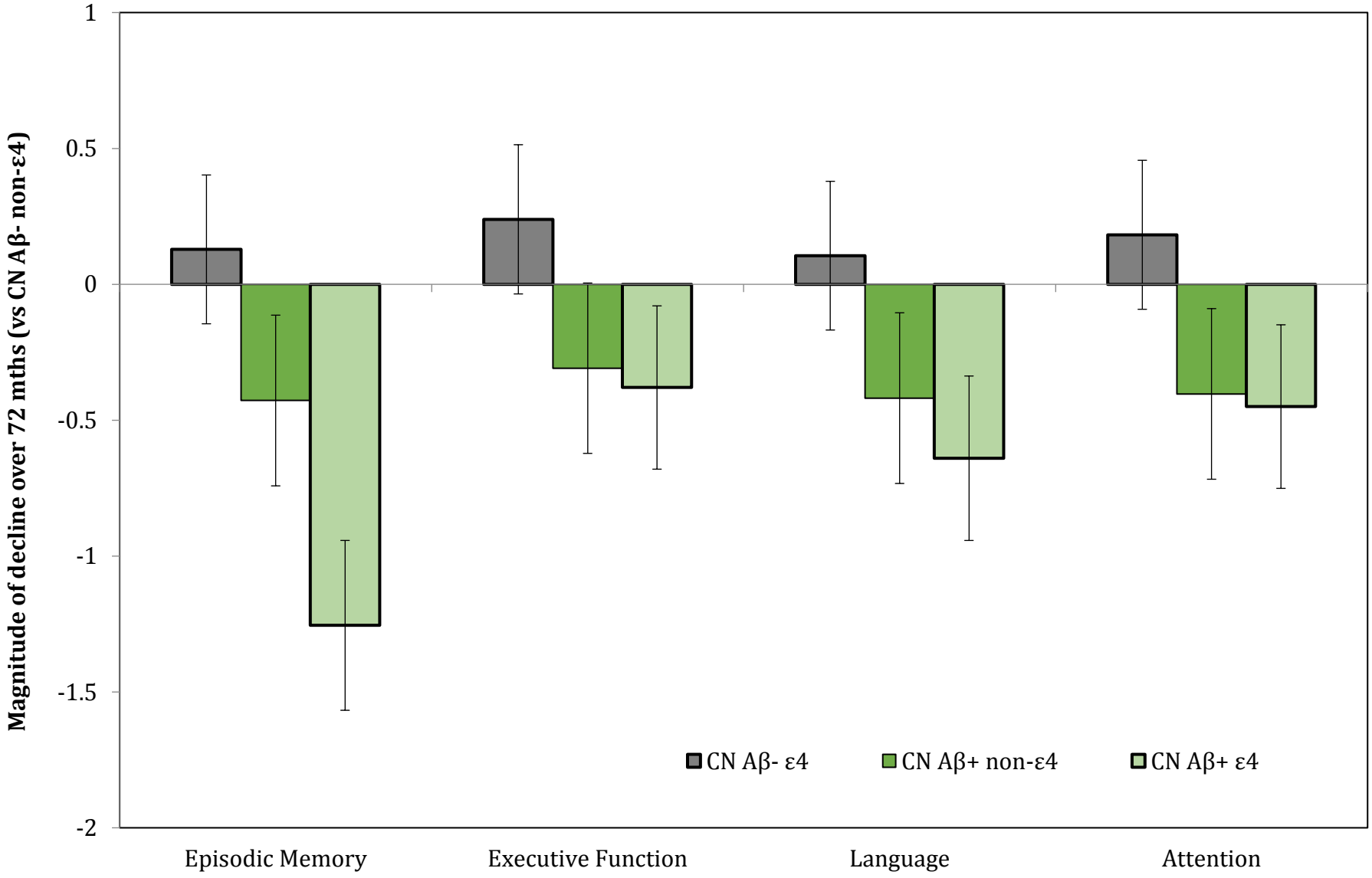
Figure 1. Clinical classification and disease progression of CN Aβ- and CN Aβ+ participants over 72 months.

Figure 2. Trajectories of Episodic Memory change over 72 months.
Dotted line indicates 1.5 SD decline for clinically-significant memory impairment. Error bars represent the 95% confidence intervals of the difference in the rate of cognitive change.

Figure 3. Magnitude of difference (Cohen's *d*) in the rate of cognitive change over 72 months.
Magnitude of difference (Cohen's *d*) in the rate of change in each cognitive composite score between CN Aβ- ε4 carriers, CN Aβ+ ε4 non-carriers, and CN Aβ+ ε4 carriers relative to CN Aβ- ε4 non-carriers (represented by "0" line). Error bars represent the 95% confidence intervals of the difference in the rate of cognitive change.


767 CN
(423 underwent PET neuroimaging)
326 CN Aβ-
97 CN Aβ+
18 MONTHS
36 MONTHS
54 MONTHS
72 MONTHS
Withdrew: 8
Deceased: 0
312 CN
6 MCI
0 AD
1 AD
4 MCI
88 CN
Withdrew: 3
Deceased: 1
Withdrew: 9
Deceased: 2
303 CN
10 MCI
2 AD
2 AD
4 MCI
75 CN
Withdrew: 16
Deceased: 1
Withdrew: 12
Deceased: 4
294 CN
14 MCI
1 AD
5 AD
5 MCI
65 CN
Withdrew: 21
Deceased: 1
Withdrew: 12
Deceased: 4
275 CN
16 MCI
1 AD
3 AD
8 MCI
51 CN
Withdrew: 32
Deceased: 3


Episodic Memory Composite (z-score)
0.00
-0.50
-1.00
-1.50
-2.00
Baseline
18
36
54
72
CN Aβ- ε4-
CN Aβ- ε4+
CN Aβ+ ε4-
CN Aβ+ ε4+
d = 0.43, p < .05
d = 0.99, p < .001
d = 1.25, p < .001


Magnitude of decline over 72 mths (vs CN Aβ- non-ε4)
1
0.5
0
-0.5
-1
-1.5
-2
CN Aβ- ε4
CN Aβ+ non-ε4
CN Aβ+ ε4
Episodic Memory
Executive Function
Language
Attention