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# Age, sex and APOE ε4 effects on memory, brain structure and β-amyloid across the adult lifespan

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## Abstract

**Importance—**Typical cognitive aging may be defined as age associated changes in cognitive performance in individuals who remain free of dementia. Ideally the full adult age spectrum should be included to assess brain imaging findings associated with typical aging.

**Objective—**To compare age, sex and Apolipoprotein E (*APOE ε4*) effects on memory, brain structure (adjusted hippocampal volume, HVa) and amyloid PET in cognitively normal individuals aged 30 to 95 years old.

**Design, Setting, and Participants—**Cross sectional observational study (Marc 2006 to October 2014) at an academic medical center. We studied 1246 cognitively normal subjects; 1209 participants aged 50–95 years old enrolled in a population-based study of cognitive aging and 37 self-selected volunteers aged 30–49.

**Main Outcomes and Measures—**Memory, HVa, and amyloid PET

**Results—**Overall, memory worsened from age 30 years through the 90s. HVa worsened gradually from 30 years to the mid-60s and more steeply beyond that age. The median amyloid PET was low until age 70 years and increased thereafter. Memory was worse in men than women overall ($p<0.001$) and more specifically beyond age 40 years. HVa was lower in men than women overall ($p<0.001$) and more specifically beyond age 60 years. There was no sex difference in amyloid PET at any age. Within each sex, memory performance and HVa were not different by *APOE ε4* at any age. From age 70 years onward *APOE ε4* carriers had significantly greater median amyloid PET load than noncarriers. However the ages at which 10% of the population were amyloid PET positive were 57 years for *APOE ε4* carriers and 64 years for non-carriers.

**Conclusions and Relevance—**Male sex is associated with worse memory and HVa among cognitively normal individuals while *APOE ε4* is not. In contrast, *APOE ε4* is associated with greater amyloid PET values (from age 70 years onward) while sex is not. Worsening memory and HVa occur at earlier ages than abnormal amyloid PET. Therefore, neuropathological processes other than β-amyloidosis must underlie declines in brain structure and memory function in middle age. Our findings are consistent with a model of late-onset Alzheimer's disease in which β-amyloidosis arises in later life on a background of preexisting structural and cognitive decline that is associated with aging and not with β-amyloid deposits.

### Keywords

Cognitive Aging; Amyloid Imaging; Alzheimer Disease; Memory Performance; Brain Atrophy

## Introduction

Typical cognitive aging may be defined as age-associated changes in cognitive performance in individuals who remain free of dementia. Interrelationships among biomarkers of β-amyloid, neurodegeneration, and cognitive performance have been the focus of much recent literature. However studies that include all of these variables have focused predominantly on elderly individuals, typically included few, if any, individuals younger than 60 years, and tended to be composed of selected volunteers rather than population-based samples[1–3]. We measured memory performance, hippocampal volume, and β-amyloidosis as a function of age using cross-sectional data from a large sample of cognitively normal individuals 30–95 years old. Individuals were grouped by sex and Apolipoprotein E (*APOE ε4)* status. The present study differs from a recent publication[4] in which our group examined neither memory performance, nor individuals younger than 50 years and in which our independent variables were not continuous measures. Differentiating features of the present study compared with other multimodality imaging studies in aging are (1) inclusion of the full adult age spectrum, 30–90 years, (2) the population-based nature of 97.0% of our participants, (3), our transformation of the imaging and cognitive measures to a common scale to facilitate comparison across different modalities, and (4) the large sample size. Our objectives were to compare age, sex and *APOE ε4* effects on memory performance, hippocampal volume, and amyloid positron emission tomography (PET) across the adult life span.

## Methods

### Standard Protocol Approvals, Registrations, and Patient Consents

This study was approved by the Mayo Clinic and Olmsted Medical Center (Rochester, Minnesota) institutional review boards. Written informed consent was obtained from all participants.

### Subject methods

We studied 1246 cognitively normal individuals from two different cohorts. The largest group (n=1209) was 50 to 95 years old and comprised participants enrolled in the Mayo Clinic Study of Aging (MCSA). The MCSA is a population-based study of cognitive aging among Olmsted County, MN, residents [5]. The Olmsted County population is enumerated in the eligible age strata. From this enumeration, we select individuals for recruitment using an age- and sex-stratified random sampling strategy. These individuals were then invited to participate. The second group (n=37) was 30 to 49 years old, equally stratified by 5-year age-groups and sex (referred to as young normal). These individuals were self-selected volunteers and were not population-based. The study dates were March 2006 to October 2014.

All subjects in this study were judged to have no cognitive impairment according to published criteria [5]. All 1246 individuals (MCSA and young normals) underwent identical PET, MRI and memory testing protocols which included the Auditory Verbal Learning Test (AVLT). The sum of trials 1 through 5 plus the immediate and delayed recall trials (possible total score of 105) was the learning and memory performance measure (referred to as memory) used in our analyses.

## Imaging Methods

Amyloid PET imaging was performed with $^{11}$C Pittsburgh Compound B (PIB).[6] Standardized uptake value ratios (SUVR) were formed from the prefrontal, orbitofrontal, parietal, temporal, anterior cingulate, posterior cingulate, and precuneus regions-of-interest normalized to the whole cerebellum.[7, 8] MRI was performed at 3T and hippocampal volume was measured with available software (FreeSurfer, version 5.3.0; https://surfer.nmr.mgh.havard.edu/). Total intracranial volume (TIV) was measured using an in-house method.[4]

## Statistical Methods

Some subjects were enrolled in the MCSA prior to availability of amyloid PET and received prior cognitive testing. To eliminate confounding due to the well-established learning effect on serial AVLT performance in cognitively normal individuals, we created a partial residual that adjusted for education and the number of times a subject had taken the AVLT prior to baseline which for this study was the date of the imaging studies. This adjusted AVLT measure can be interpreted as the difference, in number of words correctly recalled, from the expected number for a person given his or her education and number of previous exposures to the test. To adjust hippocampal volume for total intracranial volume (TIV), we fit a regression model among the 133 individuals aged 30 to 59 years old of hippocampal volume versus TIV. The adjusted hippocampal volume (HVa) was defined as the residual from this model [8] and can be interpreted as the difference (in cubic centimeters) compared to the expected hippocampal volume given a person's head size.

Memory performance, HVa, and amyloid PET levels are reported in modality-specific native units and also in "centiloid-like" units (scale 0 to 100).[9] This process is similar to scaling biomarkers from normal to maximum abnormal levels (as described by Jack et al[10]). To create reference points for scaling, we defined 0 (normal) for the scaled units as the 95th percentile for memory and HVa and the 5th percentile for amyloid PET among the young normal study participants aged 30 to 49 years old. We defined 100 (abnormal) for the scaled units as the 5th percentile for HVa and the 95th percentile for amyloid PET among a group of 42 individuals with moderately demented Alzheimer's disease (AD) (Clinical Dementia Rating, 1–3). We defined 100 (abnormal) for memory based on the 5$^{th}$ percentile among a larger group of 382 individuals with moderately demented AD (Clinical Dementia Rating, 1–3) who underwent memory testing but not necessarily MRI and PET. These individuals with AD were participants in the MCSA or Mayo Alzheimer's Disease Research Center and had undergone the same battery of evaluations as our study participants. An individual's memory, HVa, or amyloid PET in native units was scaled linearly to centiloid-like units (Figure 1S).

We used quantile regression to estimate median (rather than mean) memory, HVa, and amyloid PET versus age by sex and *APOE ε4* status. Quantile regression is particularly appropriate for modeling amyloid PET because its distribution is highly skewed and not conditionally normal even after log or other parametric transformations. For each response variable, we fit a single model that included age, sex, and *APOE ε4* status along with all two-way interactions. To allow for nonlinear associations with age, we modeled age with restricted cubic splines using knots at ages 50, 75, and 80 years[11]. As recommended by Harrel,[11] we prespecified the knot locations based on the distribution of ages in our data set and to serve as reference points to support a broad class of flexible nonlinear curves.

We used the percentile bootstrap based on 5000 replicates to report 95% CIs for the median memory, HVa, or amyloid PET as a function of age and to report 95% CIs for differences in medians between two measures or between two groups. We base inferences on whether 95% CIs for differences include the null value of zero.

We also report the p-values for a general sex effect for each outcome from a four degree of freedom Wald test which tests the additive and interaction terms involving sex. Similarly, we report the p-values for a general *APOE ε4* effect for each outcome.

We assessed the influence of individuals younger than 50 years on model fit and our conclusions. This assessment was performed with a sensitivity analysis limited to individuals aged 50 years or older.

In a secondary analysis, we fit a logistic regression model with age and *APOE ε4* genotype to predict the probability of abnormal amyloid PET and used the estimates from this model to identify the age at which the probability reached 10% for both *APOE ε4* carriers and noncarriers. To be consistent with our group's recent publications[4, 12, 13], we defined abnormal as a SUVR of 1.4 or greater. Sex was not included in the model because it was not significantly associated with the probability of abnormal amyloid PET.

## Results

Demographic features, imaging and memory performance data by age group are found in the Table. There was no significant difference in age by sex but *APOE ε4* carriers were on average one year younger than noncarriers (median, 71 vs 72 years; p=0.04). The proportion of *APOE ε4* carriers did not differ by sex. Educational level was not different by *APOE ε4* status, but men were slightly more educated than women (median, 16 vs 14 years of education; $p < 0.001$). We show the young normal volunteers separately from the MCSA participants, who are grouped into 15-year age strata to illustrate the effects of advancing age (Table and Fig 1S).

Associations of memory, HVa and amyloid PET versus age by sex and *APOE ε4* are illustrated in Figs 1, 2 and 2S and are interpreted descriptively. Plots comparing differences in outcomes among *APOE ε4* carriers versus noncarriers within men and within women isolate the effect of *APOE ε4* within sex (Fig 3). Plots comparing differences in outcomes among men versus women within carriers and within noncarriers isolate the effect of sex within *APOE ε4* genotype (Fig 3).

These difference plots (Fig 3) illustrate approximate ages at which significant differences were present in the outcomes by sex and *APOE ε4* status. That is, when the 95% bootstrap confidence interval (CI) around the median is above 0, we interpret this result as a significant difference in the outcomes by the group of interest at those ages. Therefore, plots in Figs 1, 2 and 2S are interpreted qualitatively while plots in Fig 3 are interpreted statistically.

### Age, sex and APOE ε4 group effects on memory

In all four groups, median memory performance worsened from age 30 through the 90s (Figs 1, 2 and 2S) with a steeper decline after age 70 years in male *APOE ε4* carriers and in women. Memory was worse in men than women overall ($p<0.001$) and more specifically beyond age 40 years (Fig 3). There was no difference in memory by *APOE ε4* status ($p=0.24$, Fig 3); however, carriers trended toward worse memory beyond age 80 years (Fig 3). Individual values within each group follow a Gaussian distribution around the median for age (Figs 1 and 2S).

### Age, sex and APOE ε4 group effects on HVa

In all four groups, HVa worsened gradually from age 30 years to the mid-60s and more steeply beyond that age (Figs 1, 2 and 2S). HVa was lower in men than in women overall ($p<0.001$) and more specifically beyond age 60 years (Fig 3). Within each sex, HVa was not different by *APOE ε4* status ($p=0.15$, Fig 3). Individual values within each group follow a Gaussian distribution around the median for age (Figs 1 and 2S).

### Age sex and APOE ε4 group effects on amyloid PET

Unlike memory or HVa, the distribution of amyloid SUVR by age is highly skewed above age 65 years (Figs 1 and 2S). Amyloid PET was different by *APOE ε4* status ($p<0.001$). The median amyloid PET value has a slight upward trend from age 30 years through the 90s among *APOE ε4* noncarriers. In *APOE ε4* carriers there is a slight upward trend until age 70 years and then a steeper increase in the median after that (Figs 1, 2 and 2S). While the median amyloid PET was greater in *APOE ε4* carriers compared to noncarriers over age 70 years (Fig 3), the ages at which 10% of the population were classified as amyloid PET positive were 57 (95% CI, 53–59 years) for *APOE* ε4 carriers and 64 years (95% CI, 62–66 years) for noncarriers (Fig 4). Sex differences in amyloid PET were not significant ($p=0.25$); however, women trended toward greater β-amyloid beyond age 70 years (Fig 3).

### Comparisons between memory, HVa and amyloid PET versus age within group

Both memory and HVa were more abnormal than amyloid PET beyond age 30 to 40 years in all four groups (Figs 3S and 4S).

## Discussion

Our major findings are that the median amyloid PET is greater in cognitively normal *APOE ε4* carriers compared to noncarriers older than age 70 years and the age at which 10% of the carriers are classified as amyloid PET positive is 7 years year younger compared with noncarriers. Male sex is associated with worse memory and HVa among cognitively normal

individuals, while *APOE ε4* is not. Declining memory performance and HVa occur at earlier ages than abnormal amyloid PET.

The estimated age at which 10% of our *APOE ε4* carriers were amyloid PET positive was 57 years compared with 64 years for noncarriers. These ages depend on the cut-point used for amyloid PET positivity as well as the threshold chosen for the proportion who are positive.

However, we wanted to make a concrete statement about the age at which abnormal amyloid PET first appears in the population and operationalized this finding as the age when the frequency of abnormality in the population reaches 10%. This is more robust than reporting the age when an abnormal scan first occurs in a single individual, which is very sensitive to outliers. In addition, our data show that from the age of 70 years onward, *APOE ε4* carriers had significantly greater median amyloid PET than noncarriers. These results are consistent with the well-established link between *APOE ε4* and increased risk of β-amyloidosis.[2, 3, 14, 15, 16, 17] In turn, β-amyloidosis increases the risk of cognitive impairment and dementia [1, 18–24].

Overall age-dependent trends in our data are largely consistent with prior studies that show progressive declines in memory [25, 26] and brain volumes [27, 28] with age. Recognition that AD pathology, particularly amyloid plaques, can exist in situ for over a decade or longer without producing overt cognitive symptoms [1, 29–31] has raised the idea that subclinical declines in brain structure and cognitive function in middle age are often due to underlying β-amyloid deposition. However, we found that memory and HVa worsen continuously from age 30 years onward and that these trends are established before obviously abnormal amyloid PET values appear in the population (Figs 1, 2 and 2S). Memory and HVa values are symmetrically distributed around the population age median which implies that declines in bran structure and memory are a fundamental characteristic of typical aging. In contrast amyloid PET values are skewed above age 65 years (Figs 1 and 2S) such that some individuals accumulate high amyloid loads, while many survive to old age without developing significant β-amyloidosis. The differing distributions of memory and HVa vs amyloid PET around population medians with age imply that declining memory and HVa must have some mechanistic independence from β-amyloid accumulation. Also, direct comparisons of memory, HVa and amyloid PET within each group (Figs 3S and 4S) show that memory and HVa were consistently more abnormal than amyloid PET beyond age 30 to 40 years. We acknowledge that amyloid PET measures only fibrillar amyloid deposits and therefore potential effects of soluble β-amyloid cannot be assessed. Given this caveat, our data are nonetheless consistent with the concept that age-related degenerative processes affecting brain structure and cognitive function that are unrelated to fibrillar β-amyloid deposition [8, 13, 32–37] exist from at least age 30 years onward and are characteristic of typical aging. Reasonable candidates for non-AD processes associated with structural and functional decline in middle age are cerebro-vascular disease and its risk factors, including primary age-related tauopathy, [38, 39] brain aging in the absence of any specific pathophysiological process,[36, 40] or combinations of these. Our data are consistent with models of late-onset AD in which β-amyloidosis, which defines preclinical AD,[41] typically arises in later life on a background of pre-existing age-related cognitive and structural decline [12, 13, 34, 38, 42–46].

With regard to sex effects, we found that men perform worse than women on memory beginning in their 40s, as has been shown previously.[47] We also found that HVa was smaller in men than women beyond age 60 years. This sex effect on memory and HVa was likely not due to sex differences in age or *APOE ε4* because differences in age by sex or by *APOE ε4* were small (median, approximately 1 year different) and because there were no differences in *APOE ε4* prevalence by sex. Men were slightly more educated than women (median, 16 vs 14 years of education). However, if anything, this factor would tend to enhance memory performance in men compared with women, which is opposite from what we found. Moreover, we adjusted memory for educational level and practice effects. This detrimental effect of male sex on memory and HVa must also be independent from β-amyloid deposition because (1) we found no sex differences in amyloid PET at any age (Fig 3) and (2) sex differences were present in memory (beginning at age 40 years) well before abnormal amyloid PET first appeared in the population (Figs 1, 3, 4 and 2S). These sex differences in memory and HVa could be developmental,[48] a hormonal protective effect,[49] or attributable to a greater prevalence of adverse life style related exposures (eg, vascular risk factors) in men.[27]

Perhaps the most controversial findings from this study come from comparing the associations between sex vs *APOE ε4* on age-dependent trends in memory and HVa. Some prior studies are consistent with our finding of no association between *APOE ε4* and hippocampal volume in cognitively normal individuals.[50, 51] However, other studies have indicated that, among cognitively normal individuals without β-amyloid deposition, *APOE ε4* carriers have hypo-metabolism in AD-like regions,[52] abnormal functional connectivity,[53, 54] worse cognitive performance,[55] and smaller regional brain volumes.[56, 57] Such findings have been taken as evidence that *APOE ε4* exerts harmful effects throughout life on brain structure and function that are independent from its role in promoting β-amyloid deposition.[58, 59] In contrast, we found that, while male sex was associated with smaller hippocampal volume and worse memory, *APOE ε4* carriers within each sex did not have worse memory or HVa than noncarriers at any age.[60] Had we examined other imaging measures (eg, fluorodeoxyglucose F18 PET or functional MRI) or perhaps other cognitive indexes, the findings might have been different. Nonetheless, our results paint a different picture than is presented in much of the recent imaging literature, which has focused great attention on the effects of *APOE ε4* but little on the effect of sex on brain structure and function.

Our study has limitations. While all individuals 50 years or older in our sample were derived from an epidemiologically defined cohort, the non-population based nature of those 30 to 49 years old and the small sample size in this age range are acknowledged limitations. However, when obvious inflection points exist in the plots of memory, HVa, and amyloid PET vs age, they occur well within the age range of 50 years to the 90s of the MCSA cohort (Figs 1, 2, 2S and 3S), and not at the age junction of the young normal group and the MCSA cohort. In addition, a sensitivity analysis indicated that plots (among those 50 years or older) of memory, HVa, and amyloid PET vs age did not change when individuals younger than 50 years were excluded. This finding indicates that the imbalance in numbers of individuals aged 50 years or older vs younger than 50 years did not unduly influence conclusions.

Another limitation is that cross-sectional studies tend to confound age effects with birth cohort effects.[61] However, cohort effects are unavoidable when examining age-dependent trends covering a range of 60 years. Within-individual longitudinal data typically found in studies with intensive multimodality imaging (1–5 years) will not ameliorate birth cohort effects when the research questions of interest are age trends spanning 60 years. A final methodological point concerns interpretation of results given that all participants were cognitively normal. Individuals who remain cognitively normal into old age represent a subset of those who were members of their birth cohort at younger ages.

Despite these limitations, we believe that this study of typical aging reveals interesting sex and *APOE ε4* effects on age-related trends in brain structure, function and β-amyloidosis. To date, these effects have not been widely appreciated. Our findings are consistent with a model of late-onset AD in with β-amyloidosis arises in later life on a background of preexisting structural and cognitive decline that is associated with aging and not with β-amyloid deposits.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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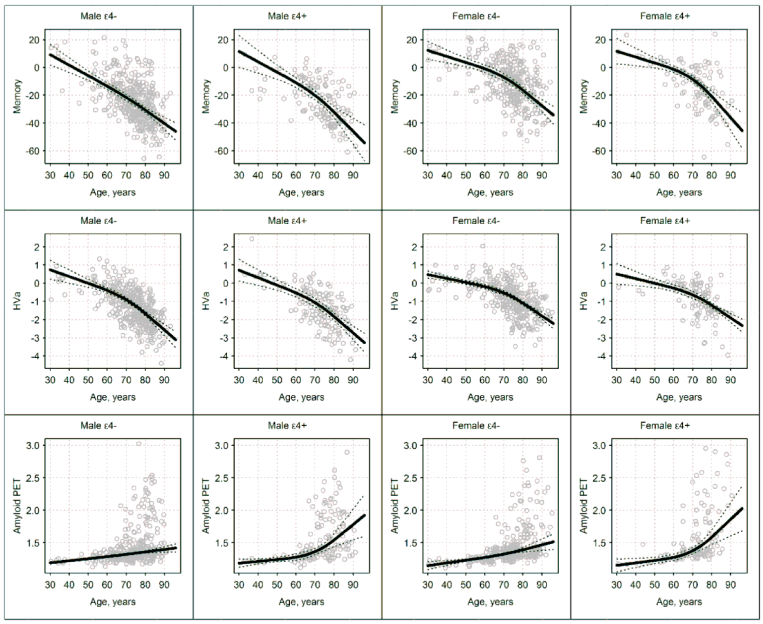


**Figure 1.**

Memory, Adjusted Hippocampal Volume (HVa), and Amyloid Positron Emisison Tomography (PET) in Modality-Specific Units by Age, With Participants Categorized Into 4 Groups by Sex and *APOE ε4* Genotype (Carriers vs Noncarriers). Solid lines represent estimated median regression lines, while dotted lines represent 95% bootstrap CIs. Knots were placed at ages 50, 75, and 80 years.

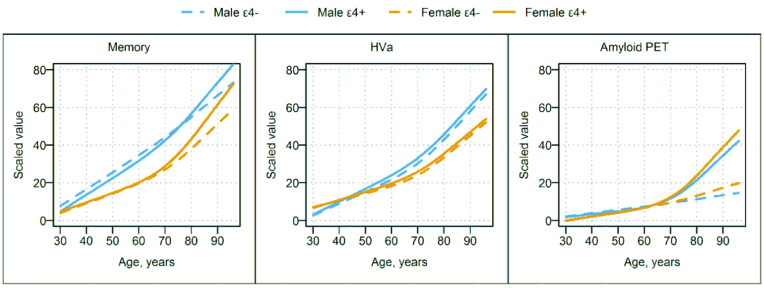


**Figure 2.**

Estimated Median Regression Lines in Scaled Units vs Age for All 4 Demographic Groups, With Separate Panels for Memory, Adjusted Hippocampal Volume (HVa), and Amyloid Positron Emission Tomography (PET). Knots were placed at ages 50, 75, and 80 years. Blue lines represent relationships in men, and orange represent relationships in women. Solid lines represent *APOE ε4* carriers, and dashed lines *APOE ε4* noncarriers.

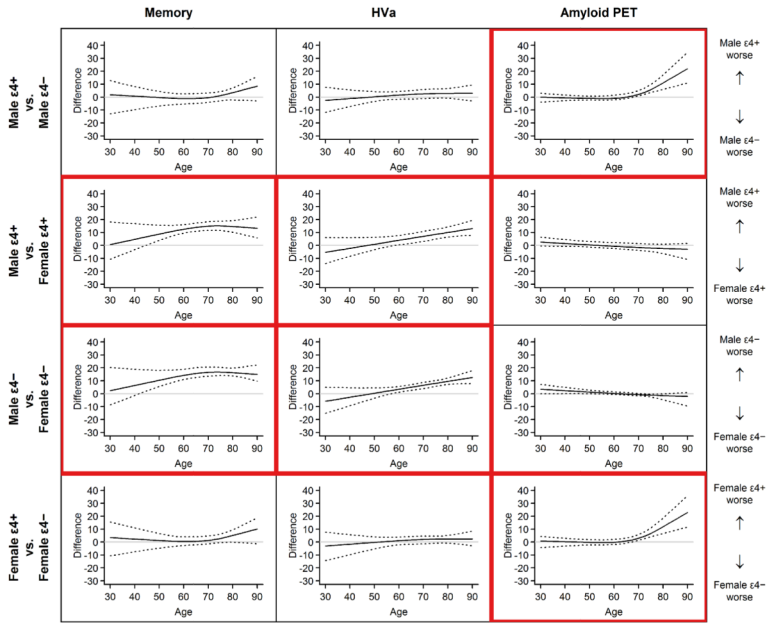


**Figure 3.**

Plots of Groupwise Differences in Scaled Units for Memory, Adjusted Hippocampal Volume (HVa), and Amyloid Positron Emission Tomography (PET). Comparisons are shown for differences among *APOE ε4* carriers vss noncarriers within sex and for male vs female within *APOE ε4* genotype. The solid line in each plot represents the estimated difference in medians, while the dotted lines represent 95% bootstrap CIs for this difference. A horizontal line at 0 (ie, no difference) is shown for reference. Plots in which significant groupwise differences were found are outlined in red. This red outlining illustrates a pattern showing differences in memory and HVa were due to sex not *APOE ε4*, while differences in amyloid PET were due to *APOE ε4* and not sex.

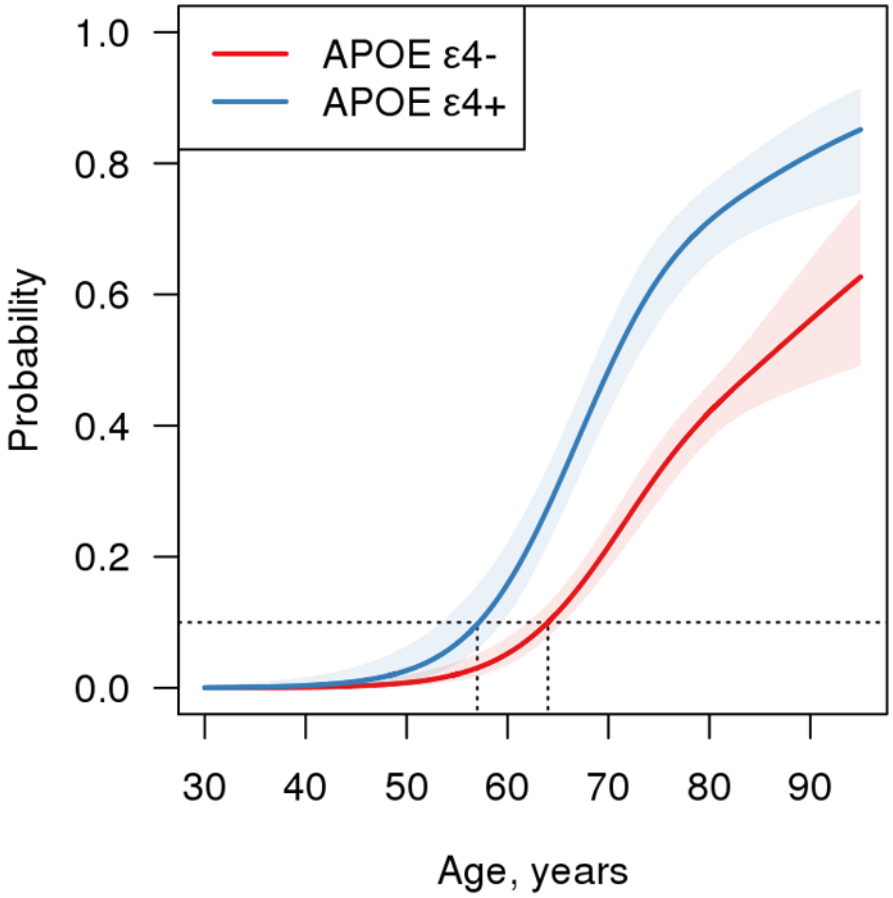


**Figure 4.**

Probability of Amyloid Positron Emission Tomography (PET) Positivity vs Age by *APOE ε4* Genotype. The data are estimated from a logistic model. Amyloid PET positivity was defined as a SUVR of 1.4 or greater. The estimated age at which 10% (the dashed horizontal line) of the population is positive is 57 years (95% CI, 53–59 years) for *APOE ε4* carriers and 64 years (95% CI, 62–66 years) for *APOE ε4* noncarriers.

## Table

Characteristics of All Participants[a]

| | | Young Normal | MCSA | | |
|---|---|---|---|---|---|
| **Characteristic** | **Overall (n = 1246)** | **30–49 y (n = 37)** | **50–64 y (n = 320)** | **65–79 y (n = 628)** | **80–95 y (n = 261)** |
| Age, y | 72 (63 to 78) [30 to 95] | 39 (34 to 44) [30 to 49] | 60 (55 to 62) [50 to 64] | 73 (69 to 76) [65 to 79] | 83 (82 to 86) [80 to 95] |
| Male sex, No. (%) | 655 (52.6) | 18 (48.6) | 155 (48.4) | 327 (52.1) | 155 (59.4) |
| *APOE ε4*+, No. (%) | 340 (27.3) | 15 (40.5) | 91 (28.4) | 176 (28.0) | 58 (22.2) |
| Educational level, y | 14 (12 to 16) [8 to 20] | 16 (14 to 16) [12 to 20] | 16 (13 to 16) [9 to 20] | 14 (12 to 16) [8 to 20] | 14 (12 to 16) [8 to 20] |
| AVLT sum of trials | 61 (50 to 73) [20 to 105] | 78 (65 to 86) [50 to 99] | 69 (59 to 78) [34 to 100] | 60 (49 to 71) [24 to 105] | 51 (41 to 63) [20 to 103] |
| Adjusted AVLT sum of trials | −16 (−28 to −4) [−66 to 25] | 5 (−9 to 10) [−26 to 23] | −6 (−17 to 3) [−40 to 22] | −17 (−27 to −6) [−66 to 25] | −30 (−39 to −19) [−65 to 24] |
| Amyloid PET SUVR | 1.33 (1.27 to 1.44) [1.10 to 3.03] | 1.21 (1.19 to 1.23) [1.11 to 1.48] | 1.27 (1.23 to 1.31) [1.10 to 2.24] | 1.35 (1.30 to 1.45) [1.13 to 3.03] | 1.44 (1.33 to 1.86) [1.18 to 2.96] |
| HV, $cm^3$ | 7.5 (6.9 to 8.2) [3.9 to 11.6] | 8.6 (7.9 to 9.2) [6.8 to 11.6] | 8.2 (7.6 to 8.8) [5.8 to 10.5] | 7.5 (6.9 to 8.1) [3.9 to 10.1] | 6.8 (6.2 to 7.2) [3.9 to 8.7] |
| HVa, $cm^3$ | −0.90 (−1.61 to −0.22) [−4.41 to 2.44] | 0.18 (−0.33 to 0.41) [−0.91 to 2.44] | −0.15 (−0.59 to 0.30) [−3.02 to 2.04] | −0.99 (−1.60 to −0.47) [−3.80 to 1.23] | −1.76 (−2.41 to −1.32) [−4.41 to 0.48] |
| Range of study dates | Mar 2006 to Oct 2014 | Jun 2012 to Jan 2013 | Mar 2012 to Oct 2014 | Mar 2006 to Oct 2014 | May 2006 to Apr 2014 |

Abbreviations: AVLT, Auditory Verbal Learning Test; HV, hippocampal volume; HVa, adjusted HV; MCSA, Mayo Clinic Study of Aging; PET, positron emission tomography; SUVR, standardized uptake value ratio.

[a] Unless otherwise indicated, data are given as the median (interquartile range) [range].