HHS Public Access

Author manuscript

J Alzheimers Dis. Author manuscript; available in PMC 2024 February 06.

Published in final edited form as:

J Alzheimers Dis. 2020 ; 75(2): 417–427. doi:10.3233/JAD-191335.

Interaction between Apolipoprotein E and Butyrylcholinesterase Genes on Risk of Alzheimer's Disease in a Prospective Cohort Study

Yi-Fang Chuang[a,b], **Vijay Varma**[b], **Yang An**[c], **Toshiko Tanaka**[d], **Christos Davatzikos**[e], **Susan M. Resnick**[c], **Madhav Thambisetty**[b,*]

[a]Institute of Public Health, National Yang-Ming University, Taipei, Taiwan

[b]Clinical and Translational Neuroscience Section, Laboratory of Behavioral Neuroscience, National Institute on Aging, Baltimore, MD, USA

[c]Laboratory of Behavioral Neuroscience, National Institute on Aging, Baltimore, MD, USA

[d]Translational Gerontology Branch, National Institute on Aging, National Institute on Aging, Baltimore, MD, USA

[e]Center for Biomedical Image Computing and Analytics, University of Pennsylvania, Philadelphia, PA, USA

Abstract

Background: An epistatic interaction between the ε4 allele of apolipoprotein E (*APOE* ε4) and the K-variant of butyrylcholinesterase (*BCHE-K*) genes has been previously reported to increase risk of Alzheimer's disease (AD). However, these observations were largely from case-control studies with small sample sizes.

Objective: To examine the interaction between *APOE* ε4 and *BCHE-K* on: 1) the risk of incident AD and 2) rates of change in brain volumes and cognitive performance during the preclinical stages of AD in a prospective cohort study.

Methods: The study sample for survival analysis included 691 Caucasian participants (age at baseline, 58.4 ± 9.9 years; follow-up time,16.9 ± 9.7 years) from the Baltimore Longitudinal Study of Aging. The neuroimaging sample included 302 participants with 1,388 brain magnetic resonance imaging (MRI) scans. Cognitive performance was assessed in 703 participants over 4,908 visits.

Results: A total of 122 diagnoses (79 AD, 43 mild cognitive impairment [MCI]) were identified. Participants with both *APOE* ε4 and *BCHE-K* variants had a 3.7-fold greater risk of AD (Hazard ratio [HR] 95%, CI = 1.99–6.89, $p < 0.001$) compared to non-carriers of both genes (APOE ε4

*Correspondence to: Madhav Thambisetty, MD, PhD, Clinical and Translational Neuroscience Section, Laboratory of Behavioral Neuroscience, Room 4B-311, 251 Bayview Blvd, National Institute on Aging (NIA), National Institutes of Health (NIH), Baltimore, MD 21224, USA. Tel.: +1 410 558 8572; Fax: +1 410 558 8674; thambisettym@mail.nih.gov.

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: https://dx.doi.org/10.3233/JAD-191335.

x BCHE-K interaction $p = 0.025$). There was no APOE ε4 BCHE-K interaction effect on rate of cognitive decline and brain atrophy.

Conclusion: The APOE and BCHE genes interact to influence risk of incident AD/MCI but not rates of brain atrophy and decline in cognitive performance before onset of cognitive impairment. This may suggest that the epistatic interaction between APOE ε4 and BCHE-K on AD risk is disease stage-dependent.

Keywords

Alzheimer's disease; Apolipoprotein E4; Butyrylcholinesterase; epistasis; magnetic resonance imaging; mild cognitive impairment

INTRODUCTION

Late-onset Alzheimer's disease (AD) is the most common cause of dementia in older adults and more than 90% of late-onset AD cases appear to be sporadic. Genome-wide association studies have identified several risk genes for late-onset AD. However, the effects of these genes on risk for AD are exceedingly small with allelic odds ratios of 1.15 [1, 2]. The ε4 allele of apolipoprotein E (APOE) gene is the only risk variant that has been consistently found to be associated with sporadic late-onset AD in studies across different ethnic groups [3, 4]. The risk effect is estimated to be three- to fourfold for individuals carrying one ε4 allele and more than 10-fold for ε4 homozygous carriers [5]. In addition, some reports suggest the ε4 allele of APOE may be associated with decline in cognitive performance [6], hippocampal atrophy [7], and *in vivo* brain amyloid deposition [8] in cognitively normal older individuals. APOE is a polymorphic glycoprotein expressed in liver, brain, macrophages, and monocytes, and participates in transport of cholesterol and other lipids. It plays an important role in lipid homeostasis and cholesterol metabolism. Several mechanisms have been proposed to explain the role of APOE ε4 in AD pathogenesis, including roles in Aβ aggregation, tau phosphorylation, neuroinflammation, lipid metabolism, synaptic plasticity, and neurogenesis [9].

Perturbations in the cholinergic system also play an important role in many forms of dementia, including AD [10]. Furthermore, acetylcholine, the principal neurotransmitter in cholinergic neurons, is the main target of currently used drugs to treat AD [11]. The butyrylcholinesterase (BCHE) gene is both involved in regulation of cholinergic tone and has also been associated with AD risk [12]. The BCHE gene is located on chromosome 3 and the BCHE-K variant is one of the most common polymorphisms in the BCHE gene, resulting from substitution of an alanine residue to threonine at codon 539 (A539T). This polymorphism is associated with a 30% reduction in the activity of BCHE enzyme, catalyzing hydrolysis of the neurotransmitter acetylcholine [13]. Many studies have been conducted to evaluate the association between BCHE-K variant and AD risk, and a meta-analysis found that the BCHE-K variant was associated with increased AD risk with a pooled odds ratio of 1.2 [12]. BCHE-K has also been found to have associations with AD-related neuropathology, neurofibrillary tangles, and amyloid-β (Aβ) protein deposition [14].

Late-onset AD is a complex disease where the interactions of many genes and environmental factors likely determine lifetime risk for AD, with each gene independently accounting for only a proportion of risk [15, 16]. Gene-gene interaction, or epistasis, may be an important mechanism underlying complex diseases like late-onset AD. In a previous study, we showed that interaction between the AD risk variant gene CR1 and APOE influences brain amyloid deposition in non-demented older individuals suggesting that this epistatic interaction may modulate early events in AD pathogenesis [17, 18]. Similarly, emerging evidence has shown that APOE ε4 may interact with BCHE-K to increase risk of AD [19–24], hippocampal atrophy, and progression to AD in patients with mild cognitive impairment (MCI) [25, 26], as well as brain Aβ burden [27]. However, these observations are largely from case-control studies with small sample sizes and have not been consistently replicated. Therefore, in this study we examined the interaction between the APOE ε4 and BCHE-K variants on risk of incident AD or MCI prospectively in the Baltimore Longitudinal Study of Aging (BLSA), one of the longest-running prospective cohort studies of aging in the United States. We also investigated the APOE ε4 and BCHE-K interaction effect on longitudinal changes in brain volumes and cognitive performance before the onset of cognitive impairment in this study sample.

METHODS

Overview of study design

The Baltimore Longitudinal Study of Aging (BLSA) is a prospective cohort study of community dwelling volunteer participants, beginning in 1958, and is one of the longest-running longitudinal studies of aging in the United States. The study has been detailed extensively elsewhere [28, 29]. The recruitment of participants is still ongoing and at the time of entry into the study, participants had no physical or cognitive impairment. Detailed examinations, including neuropsychological assessments and neurological, laboratory, and radiological evaluations, were conducted every 2 years. Since 2003, participants older than 80 years received yearly assessments. Written informed consent was obtained at each visit, and the study was approved by the local Institutional Review Board and the National Institute on Aging. The neuroimaging substudy of the BLSA (BLSA-NI) began in 1994 to include a subset of BLSA participants who agreed to annual neuroimaging assessment. From 1994 to 2004, participants had annual imaging assessments and were enrolled according to procedures described elsewhere [30]. Thereafter, participants aged 60–79 years had biennial BLSA and imaging visits, whereas participants aged 80 years and older had annual visits. Individuals with significant health conditions that could affect brain structure or function (i.e. stroke, closed head injury, cranial/brain surgery, metastatic cancer, gliomas, intracranial cysts with brain tissue displacement, seizure, and bipolar disorders) were excluded [31].

Participants

BLSA participants who had data available after age 50 (at risk for developing dementia) and APOE/BCHE genotype information were included in the current study. Participants with diagnosis of dementia other than AD were excluded from the analysis ($N = 28$). The final sample for survival analysis consisted of 691 participants with a mean follow-up time of 16.9 9.7 years. All participants in this study sample were Caucasians (Fig. 1).

For neuroimaging analysis, we used data collected between February 1994 and December 2015. Similar to the study sample in the survival analyses, any visits before age 50 were dropped; additionally for participants who developed MCI or dementia, any visits after the onset of cognitive impairment were also dropped. The final BLSA-NI sample consisted of 302 participants and 1,388 brain MRI scans with mean follow-up visits of 4.6 ± 4.2 (Fig. 1).

We additionally examined the APOE-BCHE interaction on trajectories of cognitive performance before onset of any cognitive impairment. Similar to the study sample in the neuroimaging and survival analyses, any visits before age 50 were dropped; additionally for participants who developed MCI or dementia, any visits after the onset of cognitive impairment were also dropped. The final sample consisted of 703 participants and 4,908 cognitive visits with mean follow-up visits of 7.0 ± 4.5 (Fig. 1).

APOE and BCHE genotyping

APOE genotypes were determined by two methods in the BLSA. Earlier assays were based on polymerase chain reaction (PCR) amplification of leukocyte DNA with HhaI restriction isotyping [32]. More recent assays used the TaqMan method, a PCR-based system using oligonucleotide probes specific for alleles that have been labeled using fluorogenic reporter dyes [33]. We defined two groups based on APOE genotype: APOE $\varepsilon 4$ carriers (APOE $\varepsilon 4+$) (carriers of 1 or 2 $\varepsilon 4$ alleles) and non-carriers (APOE $\varepsilon 4-$). On the other hand, the single nucleotide polymorphism of the BCHE gene (rs1803274) was assessed as a part of genome-wide genotyping in BLSA that used the Illumina Infinium HumanHap550 genotyping chip (Illumina, San Diego, CA), assaying > 555,000 unique SNPs per sample. Standard quality control of genotyping data was conducted including verification of data completeness, Hardy-Weinberg equilibrium, and Mendelian incompatibilities as described previously [34, 35]. Similar to *APOE* genotype, we assumed dominant models and two groups of *BCHE-K* variants were defined: (*BCHE-K*+) (AA or AG) and non-carriers (*BCHE-K*-) (GG).

Diagnosis of Alzheimer's disease and mild cognitive impairment

Cognitive status was ascertained at consensus diagnosis conferences according to established procedures described previously [36], using information from neuropsychological tests and clinical data. Briefly, all BLSA participants were reviewed at a consensus conference if they screened positive on the Blessed Information Memory Concentration score [37] (score ≥ 4), if their Clinical Dementia Rating score [38] was ≥ 0.5 using subject or informant report, or if they screened "abnormal" on the Dementia Questionnaire [36]. Diagnoses of dementia and AD were based on DSM-III-R [39] and the NINCDS-ADRDA criteria [40], respectively. MCI was diagnosed based on the Petersen criteria [41]: 1) cognitive impairment was evident for a single domain or 2) cognitive impairment in multiple domains occurred without any significant functional loss. Onset age for dementia or MCI was also determined in the adjudication consensus conferences. A total of 122 participants were diagnosed as MCI ($n = 43$) or AD ($n = 79$) during follow-up in the current study sample.

Brain MRI

BLSA participants in the neuroimaging study underwent serial brain MRI scans. A detailed description of MRI acquisition and preprocessing procedures has been published previously [42]. Anatomical labels and global and regional brain volumes were obtained using Multi-atlas Region Segmentation Utilizing Ensemble (MUSE) [43]. MUSE generates volumes of interest using an ensemble of labeled atlases in target image space by combining different atlases, registration algorithms, and parameters, and uses a consensus labeling approach to fuse these labels into a final segmentation. The MUSE workflow for anatomical labeling has been extensively validated on the BLSA MRI dataset to achieve a consistent parcellation of brain anatomy and harmonization of longitudinal MRIs with scanner and imaging protocol differences on T1-weighted sequences in the BLSA MRI data [44]. We defined a set of brain regions to explore in longitudinal analyses based on prior work suggesting that these regions are sensitive to age-related changes [31]; the regions included total brain volume, ventricles, total gray matter, frontal gray matter, temporal gray matter, parietal gray matter, occipital gray matter, total white matter, frontal white matter, temporal white matter, parietal white matter, occipital white matter, hippocampus, entorhinal cortex, amygdala, parahippocampal gyrus, fusiform gyrus, and precuneus.

Cognitive performance measures

A comprehensive battery of cognitive tests were administered assessing global cognition, attention, memory, executive function, visuospatial ability, and language. All cognitive tests were transformed to z-scores based on baseline means and standard deviations of each test except for the Mini-Mental State Examination (MMSE). Composite scores for five cognitive domains including attention, verbal memory, executive function, language and visuospatial ability, were calculated from averaging z-scores of the individual measures, The details of individual measures in each cognitive domain have been described elsewhere [45].

Statistical analysis

Demographic comparisons evaluated potential differences in baseline age, sex, education among four groups defined by *APOE ε*4 and *BCHE-K* carrier status: *APOE ε*4/*BCHE-K*, *APOE ε*4/*BCHE-K*+, *APOE ε*4+/*BCHE-K*, and *APOE ε*4+ /*BCHE-K*+.

For continuous variables, normality was tested using Shapiro-Wilk test. For normally distributed variables, analyses of variance was used to examine group differences. For variables that were not normally distributed, non-parametric Kruskal-Wallis test was used. For categorical variables, χ^2 tests were used to test differences between groups. Cox proportional hazards models were used to examine the relationship between time to MCI or AD onset and *APOE ε*4, *BCHE* genotype and their interactions while controlling for potential confounders. Age was used as the time-scale, with age at baseline as the origin. The event time for participants who developed AD or MCI was defined as the estimated age of dementia onset. Participants who survived without dementia or were lost to follow-up were censored at the age of their last visit. We adjusted for potential confounders including sex and years of education, which are established risk factors for AD/MCI. We first examined the associations between *APOE ε*4 carrier status and *BCHE* carrier status and risk of MCI or AD separately and then included both risk genes and their interaction

term (*APOE ε*4 X *BCHE-K*) in the model to test for a potential interaction effect. Results of the final model with the interaction term were presented as hazard ratios (HRs) with 95% confidence intervals (CIs) comparing the three risk groups (i.e., *APOE ε*4−/*BCHE-K*+; *APOE ε*4+ /*BCHE-K*-; *APOE ε*4+ /*BCHE-K*+) to the non-risk group (i.e., *APOE ε*4−/*BCHE-K*-). Kaplan-Meier survival estimates were used to visualize the differences in AD/MCI-free survival between the four *APOE ε*4/*BCHE-K* risk groups without adjusting for any confounders. Finally, a power analysis for the observed results of survival analysis were done using *power cox* command in STATA.

We explored the association between *APOE ε*4 and *BCHE-K* genotype and the interactive effect of the genotypes on rates of brain atrophy and trajectories of cognitive performance using linear mixed effects models with a random intercept and random slope term; covariance structure was defined as unstructured. Time was years between baseline and follow-up visits. The outcome of interest was brain volume or cognitive performance and the predictors of interest were the 3-way interaction of *APOE ε*4, *BCHE-K*, and time, and the expansion of this 3-way interaction including *APOE ε*4, *BCHE-K*, *APOE ε*4 X time, *BCHE-K* X time, and *APOE ε*4 X *BCHE-K*. All models additionally included the following predictors: baseline age, sex, and the two-way interactions of baseline age, sex, *APOE ε*4, *BCHE-K* with time, and *APOE ε*4 X *BCHE-K*. The analyses for rates of brain atrophy was additionally adjusted for intracranial volume at baseline (defined as the first BLSA-NI visit) and scanner-type. The terms were used to calculate the rate of brain volume change in all four risk groups (*APOE ε*4−/*BCHE*-K−; *APOE ε*4−/*BCHE-K*+; *APOE ε*4+ /*BCHE-K*-; *APOE ε*4+ /*BCHE-K*+). We compared the rates of change in brain volumes/cognitive performance between *BCHE-K* carriers and non-carriers in the presence or absence of *APOE ε*4. The significance of 3-way interaction term (*APOE ε*4 X *BCHE-K* X time) indicated whether there is an interaction effect between *APOE ε*4 and *BCHE-K* on rates of change in brain volumes/cognitive performance. Due to multiple brain volumes examined, a false discovery rate (FDR) procedure [46] was applied to correct for multiple comparisons and an FDR adjusted p-value (or q-value) <0.05 would be considered significant. We also performed a sensitivity analysis on brain volume changes among older individuals who remained cognitively normal during follow-up (N = 233; 952 scans). Analyses were performed using STATA version 14 software (StataCorp, College Station, TX, USA).

RESULTS

Demographic characteristics of the study sample used in the survival analyses are shown in Table 1. Among 226 BCHE-K carriers, 29 were homozygous (AA) and 197 were heterozygous (AG). As a result, the minor allele frequency of BCHE-K was 18.5%. Among APOE ε4 carriers, 13 were homozygous and 159 were heterozygous with the E4 allele frequency of 13.4%. There were no differences in demographic characteristics between the four groups of participants based on their APOE ε4 and BCHE-K carrier status.

Table 2 presents results from the Cox proportional hazards model with APOE ε4, BCHE-K, and their interaction term. For the separate associations between APOE ε4 carrier status, BCHE-K carrier status and risk of MCI or AD (model 1 and 2), APOE ε4 was significantly associated with risk of AD/MCI (HR = 1.76, 95%CI:1.18–2.61, p = 0.005) whereas BCHE-

K was not significantly associated with risk of AD/MCI (HR = 1.16, 95%CI: 0.85−1.58, p = 0.350). The interaction between APOE ε4 and BCHE-K, i.e., the synergy factor [47], was 2.67, which was statistically significant (p = 0.021) and indicated a synergistic association between APOE ε4 and BCHE-K on the risk of AD or MCI. In other words, participants with both APOE ε4 and BCHE-K variants had a 3.7-fold greater risk of incident AD or MCI (95%CI = 1.99–6.89, p < 0.001). Figure 2 shows the Kaplan-Meier curves in the four risk groups defined by APOE ε4 and BCHE-K carrier status. The power of this observed interaction effect is 98% (interaction coefficient 0.98, standard error, 0.42, event probability, 0.18, and correlation between variables, 0.2).

Demographic characteristics of the neuroimaging sample are shown in Table 3. There were 155 participants with APOE ε4−/BCHE-K−, 75 APOE ε4−/BCHE-K+, 54 APOE ε4 + /BCHE-K−, and 20 APOE ε4 + /BCHE-K+. Table 4 presents the results of annual rates of change in brain volumes in the four groups, the significance of differences between groups, and the interaction effect of APOE ε4 and BCHE-K. After FDR correction, there was no significant interaction between APOE ε4 and BCHE-K on rates of change in brain volumes. In the presence of APOE ε4, the BCHE-K gene was associated with faster rate of ventricular enlargement (p = 0.01) and faster atrophy in the fusiform gyrus (p = 0.02); neither result was significant after FDR correction. There was a trend of interaction effect between APOE ε4 and BCHE-K on ventricular enlargement (interaction term (APOE ε4 X BCHE-K X time) p = 0.093); this was again not significant after FDR correction. We found that in the absence of APOE ε4, the BCHEK gene was associated with faster atrophy of the parahippocampal gyrus (FDR corrected p = 0.017). For the sensitivity analysis among older individuals who remained cognitively normal during follow-up, the results of APOE ε4−BCHE-K interaction on brain volume changes showed the same direction, but the magnitude of atrophy rate of brain volumes and p value attenuated (Supplementary Table 1).

Demographic characteristics of the sample utilized for analyses of cognitive performance are shown in Table 5. There were 334 participants with APOE ε4−/BCHE-K−, 187 APOE ε4−/BCHE-K+, 134 APOE ε4 + /BCHE-K−, and 48 APOE ε4 + /BCHE-K+. Table 6 presents the results of annual rates of change in cognitive performance in the four groups, the significance of differences between groups, and the interaction effect of APOE _4 and BCHE-K. We found a significantly faster decline in memory among BCHE-K+individuals in the absence of APOE ε4. We did not find any significant interaction effects between APOE ε4 and BCHE-K.

DISCUSSION

In this large, prospective cohort study, we found a significant synergistic association between the APOE ε4 and BCHE-K variants on the risk of incident cognitive impairment, including AD and MCI, in older adults. Compared to APOE ε4 and BCHE-K non-carriers, participants with both APOE ε4 and BCHE-K variants had a 3.7-fold greater risk of incident AD or MCI. Generally, we found minimal evidence of an APOE ε4 and BCHE-K interaction on the rate of brain atrophy or cognitive decline in cognitively normal older individuals.

Our findings are consistent with previous case-control studies indicating an interaction between APOE ε4 and BCHE-K on risk of AD [19–22]. Although the "synergy factor", ranging from 7.1 to 13.4,was larger than that observed in our study (2.67), these case-control studies were smaller in sample size and may have been more susceptible to selection bias. Lane et al. took advantage of a 36–48-month double-blind, placebo-controlled trial of rivastigmine in MCI patients. In a post-hoc analysis in participants in the placebo arm of this trial, they showed a synergistic association between APOE ε4 and BCHE-K on the progression from MCI to AD [25]. In the current study, we confirmed this synergistic effect on the risk of AD or MCI in a population-based prospective cohort study. However, we did not find the APOE ε4 BCHE-K interaction on cognitive performance before onset of impairment. In a study among patients with dementia, a significant interaction between APOE ε4 and BCHE was found on decline in MMSE [24]. This may indicate the APOE ε4 BCHE-K interaction on longitudinal changes in cognitive performance is disease stage-dependent.

Few studies have investigated APOE-BCHE gene-gene interaction on brain atrophy biomarkers of AD. In the post-hoc analysis of the rivastigmine trial in MCI patients described above, the authors reported an APOE-BCHE interaction on left hippocampal volume with an increased atrophy rate in the APOE ε4 + /BCHE-K+ group. Similar to our observation that the APOE ε4 BCHE-K interaction does not affect trajectories of cognitive performance in cognitively normal participants, we did not find an APOE ε4 BCHE-K interaction effect on rates of brain atrophy in older individuals who remain cognitively normal. We suggest that these findings again indicate disease stage-specific effects of these genes that are expressed in later stages of disease progression closer to the onset of cognitive impairment. We identified a counterintuitive finding that in the absence of APOE ε4, BCHE-K gene was associated with greater atrophy of the parahippocampal gyrus. It may be relevant to consider that the BCHE-K variant may exert complex and opposing roles in AD pathogenesis in different stages of the disease [48]. While lower stability of the BCHE-K variant is associated with lower enzyme activity and prolonged acetylcholine maintenance at the synapse, it may also be less efficient in inhibiting formation of Aβ oligomers. Whether such opposing actions are differentially exerted in specific brain regions is a hypothesis that merits consideration in future studies [49].

The APOE ε4 BCHE-K interaction on risk of AD may provide insights about novel mechanisms of AD pathogenesis. Studies in humans and transgenic mice suggest that apolipoprotein E influences Aβ clearance aggregation and deposition in the brain [9]. Although butyrylcholinesterase is a hydrolytic enzyme that regulates acetylcholine in the human brain, its non-enzymatic function involves attenuating amyloid fibril formation by an interaction of the butyrylcholinesterase protein with soluble Aβ [50, 51]. As a result, combined increased Aβ burden in APOE E4 carriers and impaired Aβ aggregating effects of butyrylcholinesterase in BCHE-K+ carriers may accelerate AD pathology, and subsequently increase risk of AD. This proposed mechanism was partly supported by a florbetapir PET genome-wide association study [27], which demonstrated a modulating effect of APOE and BCHE on *in vivo* Aβ deposition in a group of mixed cognitively normal older adults, MCI and AD patients.

The strengths of the current study included a well-characterized prospective cohort, which may reduce selection bias more commonly seen in case-control studies. The major limitation in our study is that all participants were Caucasian, which limits the generalizability of results to other ethnic groups. Furthermore, the rich neuroimaging data in the BLSA enables us to explore the APOE $\varepsilon 4$ and BCHE-K interaction on early brain changes before onset of cognitive impairment. The sample size in the neuroimaging sample was relatively small, especially for the APOE $\varepsilon 4$ + /BCHE+group, which may have limited our power to detect gene-gene interaction effects.

In conclusion, we found a synergistic association between the APOE $\varepsilon 4$ and BCHE-K variants on risk of incident MCI or AD in this prospective cohort study. However, no interaction effect of these two genes on rate of brain volume change and cognitive performance were found. This may suggest the interaction effect between the APOE $\varepsilon 4$ and BCHE-K on AD is disease stage-dependent. The identification of gene-gene interactions on complex diseases like AD may not only help provide insights into disease mechanisms, but also enable more accurate assessment of differential susceptibility to disease risk in drug trials and help target interventions towards high-risk populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

We are grateful to participants in the Baltimore Longitudinal Study of Aging for their invaluable contribution. This research was supported in part by the Intramural Research Program of the NIH, National Institute on Aging.

Authors' disclosures available online (https://www.j-alz.com/manuscript-disclosures/19–1335r2).

REFERENCES

[1]. Bertram L, Tanzi RE (2009) Genome-wide association studies in Alzheimer's disease. Hum Mol Genet 18, R137–R145. [PubMed: 19808789]

[2]. Bertram L, Lill CM, Tanzi RE (2010) The genetics of Alzheimer disease: Back to the future. Neuron 68, 270–281. [PubMed: 20955934]

[3]. Roses AD, Saunders AM, Alberts MA, Strittmatter WJ, Schmechel D, Gorder E, Pericak-Vance MA (1995) Apolipoprotein E E4 allele and risk of dementia. JAMA 273, 374–375; author reply 375–376. [PubMed: 7823377]

[4]. Farrer LA, Cupples LA, Haines JL, Hyman B, Kukull WA, Mayeux R, Myers RH, Pericak-Vance MA, Risch N, van Duijn CM (1997) Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium. JAMA 278, 1349–1356. [PubMed: 9343467]

[5]. Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW, Roses AD, Haines JL, Pericak-Vance MA (1993) Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science 261, 921–923. [PubMed: 8346443]

[6]. Caselli RJ, Dueck AC, Osborne D, Sabbagh MN, Connor DJ, Ahern GL, Baxter LC, Rapcsak SZ, Shi J, Woodruff BK, Locke DE, Snyder CH, Alexander GE, Rademakers R, Reiman EM (2009) Longitudinal modeling of age-related memory decline and the APOE epsilon4 effect. N Engl J Med 361, 255–263. [PubMed: 19605830]

[7]. Reiman EM, Uecker A, Caselli RJ, Lewis S, Bandy D, de Leon MJ, De Santi S, Convit A, Osborne D, Weaver A, Thibodeau SN (1998) Hippocampal volumes in cognitively normal persons at genetic risk for Alzheimer's disease. Ann Neurol 44, 288–291. [PubMed: 9708558]

[8]. Morris JC, Roe CM, Xiong C, Fagan AM, Goate AM, Holtzman DM, Mintun MA (2010) APOE predicts amyloid-beta but not tau Alzheimer pathology in cognitively normal aging. Ann Neurol 67, 122–131. [PubMed: 20186853]

[9]. Liu CC, Liu CC, Kanekiyo T, Xu H, Bu G (2013) Apolipoprotein E and Alzheimer disease: Risk, mechanisms and therapy. Nat Rev Neurol 9, 106–118. [PubMed: 23296339]

[10]. Muir JL (1997) Acetylcholine, aging, and Alzheimer's disease. Pharmacol Biochem Behav 56, 687–696. [PubMed: 9130295]

[11]. Ferreira-Vieira TH, Guimaraes IM, Silva FR, Ribeiro FM (2016) Alzheimer's disease: Targeting the cholinergic system. Curr Neuropharmacol 14, 101–115. [PubMed: 26813123]

[12]. Wang Z, Jiang Y, Wang X, Du Y, Xiao D, Deng Y, Wang J (2015) Butyrylcholinesterase K variant and Alzheimer's disease risk: A meta-analysis. Med Sci Monit 21, 1408–1413. [PubMed: 25978873]

[13]. Bartels CF, Jensen FS, Lockridge O, van der Spek AF, Rubinstein HM, Lubrano T, La Du BN (1992) DNA mutation associated with the human butyrylcholinesterase K-variant and its linkage to the atypical variant mutation and other polymorphic sites. Am J Hum Genet 50, 1086–1103. [PubMed: 1570838]

[14]. Ghebremedhin E, Thal DR, Schultz C, Braak H (2002) Age-dependent association between butyrylcholinesterase K-variant and Alzheimer disease-related neuropathology in human brains. Neurosci Lett 320, 25–28. [PubMed: 11849755]

[15]. Kamboh MI (2004) Molecular genetics of late-onset Alzheimer's disease. Ann Hum Genet 68, 381–404. [PubMed: 15225164]

[16]. Combarros O, Cortina-Borja M, Smith AD, Lehmann DJ (2009) Epistasis in sporadic Alzheimer's disease. Neurobiol Aging 30, 1333–1349. [PubMed: 18206267]

[17]. Thambisetty M, An Y, Nalls M, Sojkova J, Swaminathan S, Zhou Y, Singleton AB, Wong DF, Ferrucci L, Saykin AJ, Resnick SM, Baltimore Longitudinal Study of A, the Alzheimer's Disease Neuroimaging Initiative (2013) Effect of complement CR1 on brain amyloid burden during aging and its modification by APOE genotype. Biol Psychiatry 73, 422–428. [PubMed: 23022416]

[18]. Gandy S, Haroutunian V, DeKosky ST, Sano M, Schadt EE (2013) CR1 and the "vanishing amyloid" hypothesis of Alzheimer's disease. Biol Psychiatry 73, 393–395. [PubMed: 23399469]

[19]. Raygani AV, Zahrai M, Soltanzadeh A, Doosti M, Javadi E, Pourmotabbed T (2004) Analysis of association between butyrylcholinesterase K variant and apolipoprotein E genotypes in Alzheimer's disease. Neurosci Lett 371, 142–146. [PubMed: 15519745]

[20]. Wiebusch H, Poirier J, Sevigny P, Schappert K (1999) Further evidence for a synergistic association between APOE epsilon4 and BCHE-K in confirmed Alzheimer's disease. Hum Genet 104, 158–163. [PubMed: 10190327]

[21]. Lehmann DJ, Johnston C, Smith AD (1997) Synergy between the genes for butyrylcholinesterase K variant and apolipoprotein E4 in late-onset confirmed Alzheimer's disease. Hum Mol Genet 6, 1933–1936. [PubMed: 9302273]

[22]. Tilley L, Morgan K, Grainger J, Marsters P, Morgan L, Lowe J, Xuereb J, Wischik C, Harrington C, Kalsheker N (1999) Evaluation of polymorphisms in the presenilin-1 gene and the butyrylcholinesterase gene as risk factors in sporadic Alzheimer's disease. Eur J Hum Genet 7, 659–663. [PubMed: 10482954]

[23]. Jasiecki J, Limon-Sztencel A, Zuk M, Chmara M, Cysewski D, Limon J, Wasag B (2019) Synergy between the alteration in the N-terminal region of butyrylcholinesterase K variant and apolipoprotein E4 in late-onset Alzheimer's disease. Sci Rep 9, 5223. [PubMed: 30914707]

[24]. Vijayaraghavan S, Darreh-Shori T, Rongve A, Berge G, Sando SB, White LR, Auestad BH, Witoelar A, Andreassen OA, Ulstein ID, Aarsland D (2016) Association of Butyrylcholinesterase-K allele and Apolipoprotein E epsilon4 allele with cognitive decline in dementia with Lewy bodies and Alzheimer's disease. J Alzheimers Dis 50, 567–576. [PubMed: 26757188]

[25]. Lane R, Feldman HH, Meyer J, He Y, Ferris SH, Nordberg A, Darreh-Shori T, Soininen H, Pirttila T, Farlow MR, Sfikas N, Ballard C, Greig NH (2008) Synergistic effect of apolipoprotein E epsilon4 and butyrylcholinesterase K-variant on progression from mild cognitive impairment to Alzheimer's disease. Pharmacogenet Genomics 18, 289–298. [PubMed: 18334913]

[26]. De Beaumont L, Pelleieux S, Lamarre-Theroux L, Dea D, Poirier J, Alzheimer's Disease Cooperative Study (2016) Butyrylcholinesterase K and Apolipoprotein E-epsilon4 reduce the age of onset of Alzheimer's disease, accelerate cognitive decline, and modulate donepezil response in mild cognitively impaired subjects. J Alzheimers Dis 54, 913–922. [PubMed: 27567841]

[27]. Ramanan VK, Risacher SL, Nho K, Kim S, Swaminathan S, Shen L, Foroud TM, Hakonarson H, Huentelman MJ, Aisen PS, Petersen RC, Green RC, Jack CR, Koeppe RA, Jagust WJ, Weiner MW, Saykin AJ, Alzheimer's Disease Neuroimaging Initiative (2014) APOE and BCHE as modulators of cerebral amyloid deposition: A florbetapir PET genome-wide association study. Mol Psychiatry 19, 351–357. [PubMed: 23419831]

[28]. Shock NW, Gruelich R, Andres R, Arenberg D, Costa PT, Lakatta E, Tobin JD (1984) Normal human aging. The Baltimore Longitudinal Study of Aging. US Government Printing Office, Washington, DC.

[29]. Ferrucci L (2008) The Baltimore Longitudinal Study of Aging (BLSA): A 50-year-long journey and plans for the future. J Gerontol A Biol Sci Med Sci 63, 1416–1419. [PubMed: 19126858]

[30]. Resnick SM, Goldszal AF, Davatzikos C, Golski S, Kraut MA, Metter EJ, Bryan RN, Zonderman AB (2000) One-year age changes in MRI brain volumes in older adults. Cereb Cortex 10, 464–472. [PubMed: 10847596]

[31]. Armstrong NM, An Y, Beason-Held L, Doshi J, Erus G, Ferrucci L, Davatzikos C, Resnick SM (2019) Predictors of neurodegeneration differ between cognitively normal and subsequently impaired older adults. Neurobiol Aging 75, 178–186. [PubMed: 30580127]

[32]. Hixson JE, Vernier DT (1990) Restriction isotyping of human apolipoprotein E by gene amplification and cleavage with HhaI. J Lipid Res 31, 545–548. [PubMed: 2341813]

[33]. Koch W, Ehrenhaft A, Griesser K, Pfeufer A, Muller J, Schomig A, Kastrati A (2002) TaqMan systems for genotyping of disease-related polymorphisms present in the gene encoding apolipoprotein E. Clin Chem Lab Med 40, 1123–1131. [PubMed: 12521230]

[34]. Melzer D, Perry JR, Hernandez D, Corsi AM, Stevens K, Rafferty I, Lauretani F, Murray A, Gibbs JR, Paolisso G, Rafiq S, Simon-Sanchez J, Lango H, Scholz S, Weedon MN, Arepalli S, Rice N, Washecka N, Hurst A, Britton A, Henley W, van de Leemput J, Li R, Newman AB, Tranah G, Harris T, Panicker V, Dayan C, Bennett A, McCarthy MI, Ruokonen A, Jarvelin MR, Guralnik J, Bandinelli S, Frayling TM, Singleton A, Ferrucci L (2008) A genome-wide association study identifies protein quantitative trait loci (pQTLs). PLoS Genet 4, e1000072.

[35]. Terracciano A, Balaci L, Thayer J, Scally M, Kokinos S, Ferrucci L, Tanaka T, Zonderman AB, Sanna S, Olla N, Zuncheddu MA, Naitza S, Busonero F, Uda M, Schlessinger D, Abecasis GR, Costa PT Jr. (2009) Variants of the serotonin transporter gene and NEO-PI-R Neuroticism: No association in the BLSA and SardiNIA samples. Am J Med Genet B Neuropsychiatr Genet 150B, 1070–1077. [PubMed: 19199283]

[36]. Kawas C, Gray S, Brookmeyer R, Fozard J, Zonderman A (2000) Age-specific incidence rates of Alzheimer's disease: The Baltimore Longitudinal Study of Aging. Neurology 54, 2072–2077. [PubMed: 10851365]

[37]. Blessed G, Tomlinson BE, Roth M (1968) The association between quantitative measures of dementia and of senile change in the cerebral grey matter of elderly subjects. Br J Psychiatry 114, 797–811. [PubMed: 5662937]

[38]. Morris JC (1997) Clinical dementia rating: A reliable and valid diagnostic and staging measure for dementia of the Alzheimer type. Int Psychogeriatr 9(Suppl 1), 173–176; discussion 177–178. [PubMed: 9447441]

[39]. American Psychiatric Association (1987) Diagnostic and statistical manual of mental disorders: DSM-III-R, American Psychiatric Association, Washington, DC.

[40]. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM (1984) Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 34, 939–944. [PubMed: 6610841]

[41]. Petersen RC (2004) Mild cognitive impairment as a diagnostic entity. J Intern Med 256, 183–194. [PubMed: 15324362]

[42]. Resnick SM, Pham DL, Kraut MA, Zonderman AB, Davatzikos C (2003) Longitudinal magnetic resonance imaging studies of older adults: A shrinking brain. J Neurosci 23, 3295–3301. [PubMed: 12716936]

[43]. Doshi J, Erus G, Ou Y, Resnick SM, Gur RC, Gur RE, Satterthwaite TD, Furth S, Davatzikos C, Alzheimer's Neuroimaging Initiative (2016) MUSE: MUlti-atlas region Segmentation utilizing Ensembles of registration algorithms and parameters, and locally optimal atlas selection. Neuroimage 127, 186–195. [PubMed: 26679328]

[44]. Erus G, Doshi J, An Y, Verganelakis D, Resnick SM, Davatzikos C (2018) Longitudinally and inter-site consistent multi-atlas based parcellation of brain anatomy using harmonized atlases. Neuroimage 166, 71–78. [PubMed: 29107121]

[45]. Williams OA, An Y, Armstrong NM, Shafer AT, Helphrey J, Kitner-Triolo M, Ferrucci L, Resnick SM (2019) Apolipoprotein E epsilon4 allele effects on longitudinal cognitive trajectories are sex and age dependent. Alzheimers Dement 15, 1558–1567. [PubMed: 31561966]

[46]. Benjamini Y, Hochberg Y (1995) Controlling the false discovery rate: A practical and powerful approach to multiple testing. J R Stat Soc Series B Stat Methodol 57, 289–300.

[47]. Cortina-Borja M, Smith AD, Combarros O, Lehmann DJ (2009) The synergy factor: A statistic to measure interactions in complex diseases. BMC Res Notes 2, 105. [PubMed: 19527493]

[48]. Holmes C, Ballard C, Lehmann D, David Smith A, Beaumont H, Day IN, Nadeem Khan M, Lovestone S, McCulley M, Morris CM, Munoz DG, O'Brien K, Russ C, Del Ser T, Warden D (2005) Rate of progression of cognitive decline in Alzheimer's disease: Effect of butyrylcholinesterase K gene variation. J Neurol Neurosurg Psychiatry 76, 640–643. [PubMed: 15834019]

[49]. Podoly E, Shalev DE, Shenhar-Tsarfaty S, Bennett ER, Ben Assayag E, Wilgus H, Livnah O, Soreq H (2009) The butyrylcholinesterase K variant confers structurally derived risks for Alzheimer pathology. J Biol Chem 284, 17170–17179. [PubMed: 19383604]

[50]. Guillozet AL, Smiley JF, Mash DC, Mesulam MM (1997) Butyrylcholinesterase in the life cycle of amyloid plaques. Ann Neurol 42, 909–918. [PubMed: 9403484]

[51]. Diamant S, Podoly E, Friedler A, Ligumsky H, Livnah O, Soreq H (2006) Butyrylcholinesterase attenuates amyloid fibril formation *in vitro*. Proc Natl Acad Sci U S A 103, 8628–8633. [PubMed: 16731619]

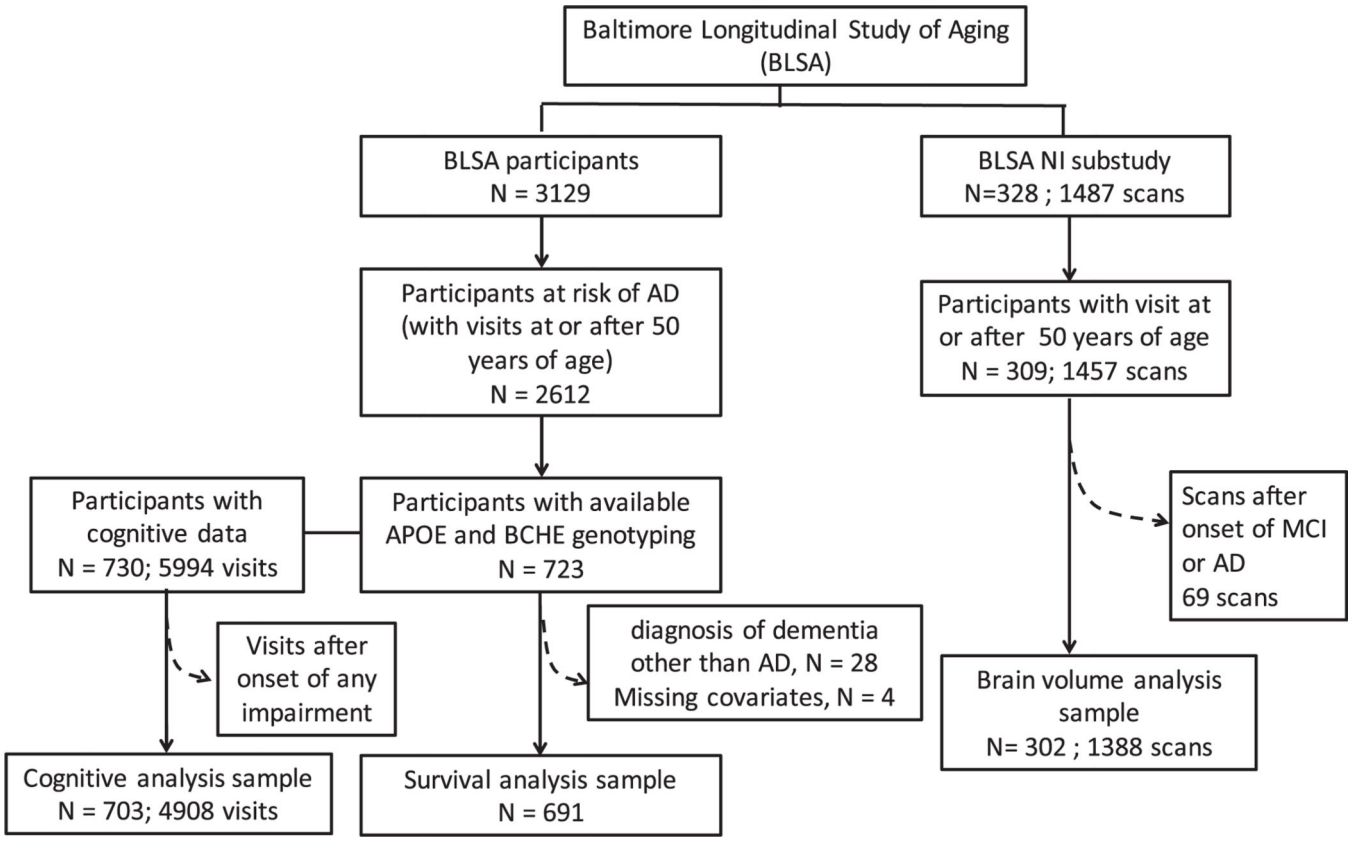

Fig. 1.
Flow chart of study samples from the Baltimore Longitudinal Study of Aging.

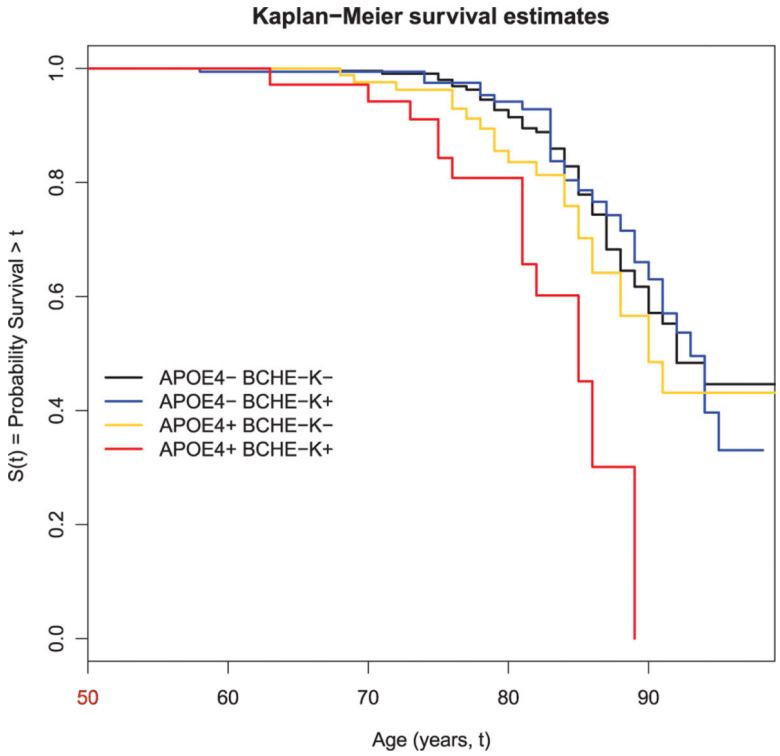

Fig. 2.

Kaplan-Meier survival curves showing differences in AD/MCI-free survival between the 4 *APOE ε4*/*BCHE-K* risk groups.

Table 1

Characteristics of the study sample by *APOE ε*4 and *BCHE-K* carrier status

Characteristics	**Total sample (*N* = 691)**	***APOE ε*4−/ /*BCHE-K*- (*N* = 338)**	***APOE ε*4−/ /*BCHE-K*+ (*N* = 184)**	***APOE ε*4 + / /*BCHE-K*- (*N* = 129)**	***APOE ε*4 + / /*BCHE-K*+ (*N* = 44)**	***p***
Age, mean (SD)	58.4 (10.0)	58.8 (10.4)	59.0 (10.3)	57.9 (9.2)	54.9 (6.6)	0.073
Female, *n* (%)	315 (45.3)	245 (42.9)	83 (45.1)	64 (49.6)	23 (52.3)	0.454
Education, mean (SD)	16.8 (2.4)	16.8 (2.4)	16.8 (2.4)	16.7 (2.5)	16.9 (2.0)	0.975
AD or MCI, *n* (%)	122 (17.6)	57 (16.9)	29 (15.8)	23 (17.8)	13 (29.6)	0.179
Person-years	52341.4	25563.2	13998.1	9495.6	3284.5	

APOE, apolipoprotein E; *BCHE-K*, K variant of butyrylcholinesterase gene; AD, Alzheimer's disease; MCI, mild cognitive impairment.

Table 2

*APOE ε*4 and *BCHE-K* interaction effect on risk of incident AD or MCI by Cox proportional hazards model

Variable	Model 1* Adjusted HR (95% CI)	*p*	Model 2* Adjusted HR (95% CI)	*p*	Model 3* Adjusted HR (95% CI)	*p*
*APOE ε*4	1.76 (1.18, 2.61)	0.005			1.02 (0.65, 1.60)	0.934
BCHE-K			1.16 (0.85, 1.58)	0.35	1.36 (0.83,2.24)	0.219
*APOE ε*4X *BCHE-K*					2.67 (1.16, 6.12)	0.021

APOE, apolipoprotein E; *BCHE-K*, K variant of butyrylcholinesterase gene; AD, Alzheimer's disease; MCI, mild cognitive impairment; HR, hazard ratio.

*Adjusted for sex and years of education.

J Alzheimers Dis. Author manuscript; available in PMC 2024 February 06.

Table 3

Characteristics of the neuroimaging sample by *APOE ε*4 and *BCHE-K* carrier status

	Total	*APOE ε*4−/*BCHE-K*−	*APOE ε*4−/*BCHE-K*+	*APOE ε*4 +/*BCHE-K*−	*APOE ε*4 +/*BCHE-K*+	*p*
N	302	155	73	54	20	
Longitudinal visits, *n*	1388	692	349	250	97	
Follow-up visits, median (IQR)	3 (1–7)	3 (1–6)	3 (1–7)	3 (1–8)	3 (1.5–8)	0.991
Age, median (IQR)	68.2 (63.2–75.7)	69.1 (63.8–77.0)	68.4 (63.5–80.1)	65.7 (61.7–69.2)	68.0 (66.1–73.8)	0.023
Female, *n* (%)	145 (48.0)	65 (41.9)	37 (50.7)	32 (59.3)	11 (55)	0.131

APOE, apolipoprotein E; *BCHE-K*, K variant of butyrylcholinesterase gene; IQR, inter-quartile range (25%–75%).

J Alzheimers Dis. Author manuscript; available in PMC 2024 February 06.

Table 4

Annual rates of change in regional brain volumes (cm^3/year) by *APOE ε4* and *BCHE-K* carrier status (*N* = 302)

Brain structure	*APOE ε4−*					*APOE ε4+*					Interaction	
	BCHE-K−	*BCHE-K+*	Difference*	*p*	*p* (FDR)	*BCHE-K-*	*BCHE-K+*	Difference†	*p*	*p* (FDR)	*p*	*p* (FDR)
Total brain	−5.05 (0.26)	−4.80 (0.37)	0.26 (0.45)	0.571	0.877	−4.92 (0.44)	−5.81 (0.71)	−0.89 (0.83)	0.281	0.406	0.225	0.440
Ventricle	1.18 (0.075)	1.32 (0.11)	0.14 (0.13)	0.286	0.877	**1.37 (0.13)**	**1.98 (0.21)**	**0.61 (0.25)**	**0.013**	0.165	0.093	0.440
Gray matter (GM)	−4.53 (0.20)	−4.59 (0.29)	−0.060 (0.35)	0.864	0.877	−4.49 (0.34)	−5.48 (0.55)	−0.98 (0.64)	0.128	0.366	0.211	0.440
Frontal GM	−1.4 (0.073)	−1.32 (0.10)	0.080 (0.13)	0.524	0.877	−1.42 (0.12)	−1.72 (0.20)	−0.30 (0.23)	0.197	0.406	0.151	0.440
Temporal GM	−0.81 (0.036)	−0.88 (0.051)	−0.068 (0.062)	0.274	0.877	−0.79 (0.06)	−0.97 (0.098)	−0.18 (0.12)	0.117	0.366	0.393	0.568
Parietal GM	−0.64 (0.041)	−0.62 (0.059)	0.019 (0.072)	0.786	0.877	−0.66 (0.069)	−0.82(0.11)	−0.16 (0.13)	0.238	0.406	0.244	0.440
Occipital GM	−0.47 (0.036)	−0.45 (0.051)	0.020 (0.062)	0.743	0.877	−0.42 (0.06)	−0.48 (0.10)	−0.055 (0.11)	0.635	0.635	0.567	0.638
Hippocampus	−0.06 (0.004)	−0.063 (0.005)	−0.003 (0.007)	0.69	0.877	−0.067 (0.006)	−0.085 (0.01)	−0.018 (0.012)	0.141	0.366	0.271	0.440
Amygdala	−0.019 (0.001)	−0.023 (0.002)	−0.004 (0.003)	0.127	0.822	−0.024 (0.002)	−0.027 (0.004)	−0.003 (0.005)	0.551	0.627	0.835	0.835
Entorhinal cortex	−0.042 (0.004)	−0.044 (0.005)	−0.002 (0.006)	0.733	0.877	−0.043 (0.006)	−0.053 (0.01)	−0.010 (0.012)	0.423	0.549	0.589	0.638
Parahippocampal gyrus	**−0.034 (0.003)**	**−0.052 (0.005)**	**−0.018 (0.006)**	**0.001**	**0.017**	−0.044 (0.005)	−0.033 (0.009)	0.011 (0.010)	0.267	0.406	**0.012**	0.156
Fusiform gyrus	−0.10 (0.008)	−0.11 (0.011)	−0.012 (0.013)	0.358	0.877	**−0.09 (0.013)**	**−0.14 (0.021)**	**−0.053 (0.024)**	**0.029**	0.187	0.138	0.440
Precuneus	−0.15 (0.010)	−0.14 (0.014)	0.003 (0.017)	0.877	0.877	−0.16 (0.017)	−0.18 (0.027)	−0.018 (0.032)	0.579	0.627	0.575	0.638

Bold text indicates $p < 0.05$.

*indicates difference in annual rates of change in regional brain volumes (cm^3/year) between *BCHE-K* carriers and non-carriers in the absence of *APOE ε4*.

†indicates difference in annual rates of change in regional brain volumes (cm^3/year) between *BCHE-K* carriers and non-carriers in the presence of *APOE ε4*. Linear mixed-effects models that included age, sex, time, baseline ICV, scan type, *APOE ε4*, *BCHE-K* and two-way interactions of age, sex, *APOE ε4*, *BCHE-K* with time, *APOE ε4*x *BCHE-K*, and three-way interaction of *APOE ε4*x *BCHE-K* x time were used to determine annual rates of change. Continuous variables were mean-centered.

Table 5

Characteristics of the cognitive sample by *APOE ε*4 and *BCHE-K* carrier status

	Total	*APOE ε*4−/*BCHE-K*−	*APOE ε*4−/*BCHE-K*+	*APOE ε*4 +/*BCHE-K*−	*APOE ε*4 +/*BCHE-K*+	*p*
N	703	334	187	134	48	
Longitudinal visits, *n*	4908	2400	1335	851	322	
Follow-up visits, median (IQR)	6 (4–9)	6 (4–10)	6 (1–21)	6 (4–10)	6 (3–8)	0.1845
Age, median (IQR)	63.1 (60.8–71.5)	63.5 (60.7–72.3)	63.1 (61.1–71.7)	62.0 (60.5–70.2)	63.7 (61.3–67.6)	0.278
Female, *n* (%)	309 (44.0)	136 (40.7)	85 (45.5)	64 (47.8)	24 (50)	0.378

APOE, apolipoprotein E; *BCHE-K*, K variant of butyrylcholinesterase gene; IQR, inter-quartile range (25%–75%).

J Alzheimers Dis. Author manuscript; available in PMC 2024 February 06.

Table 6

Annual rates of change in domain-specific cognitive performance (z-scores/year) by *APOE ε*4 and *BCHE-K* carrier status (*N* = 703)

Cognitive domain	*APOE ε*4−			*APOE ε*4+			Interaction *p*
	BCHE-K−	*BCHE-K*+	Difference*	*BCHE-K*−	*BCHE-K*+	Difference†	
Global cognition	−0.039 (0.007)	−0.048 (0.010)	−0.009 (0.012)	−0.047 (0.013)	−0.048 (0.020)	−0.001 (0.023)	0.747
Verbal memory	−0.023 (0.004)	−0.036 (0.005)	**−0.013 (0.006)**	−0.039 (0.006)	−0.050 (0.011)	−0.011 (0.012)	0.92
Attention	−0.022 (0.003)	−0.024 (0.004)	−0.002 (0.005)	−0.029 (0.005)	−0.036 (0.008)	−0.007 (0.009)	0.596
Executive function	−0.029 (0.002)	−0.028 (0.003)	0.001 (0.004)	−0.033 (0.004)	−0.038 (0.007)	−0.005 (0.008)	0.464
Language	−0.033 (0.002)	−0.037 (0.003)	−0.005 (0.004)	−0.037 (0.004)	−0.041 (0.006)	−0.005 (0.007)	0.983
Visuospatial ability	−0.028 (0.003)	−0.026 (0.004)	0.002 (0.005)	−0.025 (0.005)	−0.023 (0.009)	0.002 (0.010)	0.976

Bold text indicates $p < 0.05$.

*Indicates difference in annual rates of change in domain-specific cognitive performance (z-scores/year) between *BCHE-K* carriers and non-carriers in the absence of *APOE ε*4.

†indicates difference in annual rates of change in cognitive domains (z-scores/year) between *BCHE-K* carriers and non-carriers in the presence of *APOE ε*4. Linear mixed-effects models that included age, sex, time, *APOE ε*4, *BCHE-K* and two-way interactions of age, sex, *APOE ε*4, *BCHE-K* with time, *APOE ε*4 x *BCHE-K*, and three-way interaction of *APOE ε*4x *BCHE-K* x time were used to determine annual rates of change. Continuous variables were mean-centered.