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Gene Behavior Interaction of Depressive Symptoms and the Apolipoprotein E ε4 Allele on Cognitive Decline

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Abstract

Objective—Depressive symptoms and the APOE ε4 allele are independent risk factors for cognitive decline. However, it is not clear whether the presence of both depressive symptoms and the APOE ε4 allele increases cognitive decline.

Methods—A prospective study of a population-based sample of 4,150 (70% African American and 63% women) participants, aged 65 years and older, who were interviewed at 3-year intervals. Depressive symptoms were measured using the 10-item version of the Center for Epidemiologic Studies Depression scale, with each item coded as presence or absence of a symptom. The APOE genotype was ascertained by DNA samples collected during follow-up. Cognitive function was assessed at the initial and follow-up interviews (average follow-up of 9.2 years), using a standardized global cognitive score.

Results—There were 1405 (34%) participants with one or more copies of the APOE ε4 allele. In participants with no depressive symptoms, cognitive function decreased by 0.0412-unit per year among those with no copies and 0.0704-unit per year among those with one or more copies of the APOE ε4 allele. For each additional symptom of depression, cognitive decline increased by 0.0021-unit per year among those with no copies and 0.0051-unit per year among those with one or more copies of the APOE ε4 allele. The three-way interaction of depressive symptoms, APOE ε4 allele, and time was significant (p=0.021).

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Conflicts of Interest
Authors declare no conflict of interest.

Conclusions—The association of depressive symptoms on cognitive decline was increased among participants with one or more copies of the APOE ε4 allele compared to those without the allele.

Keywords

APOE Gene; Depressive Symptoms; Cognitive Decline; Gene Behavior Interaction

Depression is common in older age; in fact, it has been estimated that up to 49% of older adults have clinically-relevant depression (1) and depressive symptoms are also common (2-6), persistent (7), and have been associated with increased co-morbidities (8) and even mortality (9). Depression is a known risk factor for neurodegenerative outcomes, such as Alzheimer's disease (AD) and dementia, cognitive impairment, and cognitive decline (10-13). The causal link of depression and dementia is postulated to occur due to a neurotoxic mechanism, such as cortisol-induced hippocampus atrophy or lower levels of brain-derived neurotrophic factor (14-15). Moreover, there might be genetic links between depressive symptoms and cognitive decline through the Apolipoprotein E (APOE) ε4 allele that is associated with accelerated deposition of beta amyloid consequently leading to a greater risk of AD (16). However, the relationship between the APOE genotype and late-life depressive symptoms is less clear. For example, some studies have found a positive association between the APOE e4 allele and depressive symptoms (17-18), whereas other studies have reported no association (19-20).

Previous studies have investigated the genetic link of the APOE ε4 allele with depressive symptoms and several cognitive outcomes, but the findings have been inconsistent. For example, Niti et al. showed that depressive symptoms were not associated with a decline in the Mini-Mental State Examination (MMSE) scores among participants with no copies of the APOE ε4 allele; however, depressive symptoms were related to increased cognitive decline among participants with one or more copies of the APOE ε4 allele (21). On the contrary, Dean et al. reported that depressive symptoms predicted the time to incident MCI among participants with no copies of the APOE ε4 allele, but the prediction was not significant among participants with one or more copies of the APOE ε4 carriers (22). However, other studies also found a synergistic interaction between depressive symptoms and the APOE genotype on incident MCI (23) and dementia (24). Using a one-wave 6-year follow-up study, Corsentino et al. showed that the association of depressive symptoms with cognitive decline was higher among individuals with the APOE ε4 allele (25). Freiheit et al. (2012) found an increased rate of cognitive decline among patients with both persistent depressive symptoms and the APOE ε4 allele compared to patients with either one or neither (26).

Given the inconsistency in the literature and the fact that some older adults may be genetically susceptible to an increased risk of cognitive decline via presence of the APOE ε4 allele, the scientific hypothesis of interest is to test whether the presence of both depressive symptoms and the APOE ε4 allele increase cognitive decline jointly rather than each individually. Hence, we tested this hypothesis using the Chicago Health and Aging Project (CHAP), a large population-based cohort of 4,150 participants with APOE genotype and at

least two follow-up assessments yielding an average of 9.2 years of follow-up (maximum 18.7 years). In addition to the key genetic and depressive symptoms measures, this study also includes other relevant demographic and health measures that might confound the association of depressive symptoms and the APOE ε4 allele on cognitive decline in older adults.

METHODS

PARTICIPANTS

The Chicago Health and Aging Project (CHAP) is a longitudinal, population-based study of Alzheimer's disease and other common health conditions among adults age 65 years and older conducted from 1993-2012. The CHAP study design has been previously reported in greater detail by Evans et al. (27) and Bienias et al. (28). Beginning in 1993, 78.7% of all residents over 65 years old (defined by a door-to-door census) of a geographically defined, biracial Chicago community were enrolled in CHAP. From 2001, community residents who reached age 65 were also enrolled as successive cohorts. Of the total 10,802 participants enrolled in CHAP, 6,158 were enrolled as members of the original cohort and 4,644 as members of the successive age cohorts.

Population interviews were conducted in participants' homes in approximately three-year cycles. Data were collected for six cycles for the original cohort and two to five cycles for the successive cohorts. At the end of the Cycle 2 population interview, DNA samples were collected from a stratified random sample of the population - about one-sixth of all participants who had a population-interview. At the end of Cycle 5 and for the entirety of Cycle 6, DNA samples were collected from all participants during their population interviews. Thus, the APOE genotype was ascertained via a combination of stratified random sampling and population-based sampling of participants.

Of the total 10,802 participants enrolled in CHAP, we excluded participants for the following reasons: those who died without a follow-up (2,796), participants who declined follow-up participation (171), participants who provided two or more cognitive tests but had no DNA extracted (3,594), participants who did not provide sufficient information for calculating cognitive test results (78), and participants who did not provide either covariate information or data on depressive symptoms (13), resulting in a sample size of 4,150 for this investigation. To understand potential sampling bias, we compared those who died without providing a follow-up interview to those who provided two or more follow-up interviews, and found that those who died had significantly lower cognitive function and higher depressive symptoms at baseline ($p<0.001$ for both the comparisons). We also compared those who provided two or more cognitive function tests without DNA samples to those with two or more cognitive tests with DNA samples and found that those who provided DNA samples had significantly higher cognitive function tests compared to those with no DNA extracted ($p<0.001$). All participants were free of dementia and Alzheimer's disease at the baseline assessment; however, 236 participants whose DNA was extracted were also diagnosed with Alzheimer's disease and dementia during follow-up evaluations, and as such, their cognitive function tests and all data were removed from our analyses after a positive diagnosis.

The Rush University Medical Center Institutional Review Board approved this study. All participants provided informed consent to be eligible to participate in this study.

COGNITIVE FUNCTION

Cognitive function was evaluated using a battery of four tests including two tests of episodic memory (immediate and delayed story recall) derived from the East Boston Test (29, 30); a test of perceptual speed (the Symbol Digits Modalities Test) (31); and a test of general orientation and global cognition (the Mini-Mental State Examination) (32). Because these tests loaded on a single factor that accounted for about 75% of the variance in a factor analysis (33), we constructed a composite measure of global cognitive function based on all four tests. This measure combines variables with different ranges by averaging the four tests together after centering and scaling each to the baseline mean and standard deviation of the original cohort of participants. Thus, a participant whose composite performance matches the average participant from the original cohort has a composite cognitive score of 0. Standardized global cognitive function was assessed during the in-home interviews at baseline and at all subsequent follow-ups and was used as our main outcome of interest.

DEPRESSIVE SYMPTOMS

Depressive symptoms were measured using a 10-item version of the Center for Epidemiological Studies Depression (CES-D) scale developed and tested at the Established Populations for the Epidemiologic Studies of the Elderly in East Boston. Kohout et al. (34) showed that the reliability and factorial validity of the 10-item CES-D scale were similar to the original 20-item CES-D scale. Each item in this scale was scored as the presence or absence of a symptom, and a summary score was derived by adding up the number of items positive for depressive symptoms, yielding a range from 0 to10 (35). In a secondary analysis, we tested whether each domain of depressive symptoms was associated with increased cognitive decline; hence, we considered the four CES-D subscales: positive affect, negative affect, somatic conditions, and interpersonal relationships. The positive affect subscale was reverse coded to signify lower levels of positive affect for higher scores, hence, providing a score for lack of positive affect. Supported by previous factor analyses of the CES-D scale (36,37), we formed sub-scores for lack of positive affect (2 items: I was happy, I enjoyed life; score range: 0-2); negative affect (3 items: I felt sad, I felt lonely, I felt depressed; score range: 0-3); somatic symptoms (3 items: I could not get going, My sleep was restless, I felt like everything I did was an effort; score range: 0-3); and interpersonal problems (2 items: I felt that people disliked me, People were unfriendly; score range:0-2). The discriminant validity of these subscales is supported by evidence that they might be differentially related to dementia (37) and to postmortem measures of the density of dopaminergic neurons in the brainstem (38).

APOLIPOPROTEIN E ALLELE

Apolipoprotein E genotyping was done using the methods described by Hixson and Vernier (39) based on the primers described by Wenham et al. (40) and performed at the Broad Institute. APOEε4 genotypes were determined using two single nucleotide polymorphisms (SNPs): rs7412 and rs429358. These SNPs were genotyped in each participant by using the hME Sequenom MassARRAY® platform. Genotyping success rate was 100% for SNP

rs7412 and 99.8% for SNP rs429358. Both SNPs were in Hardy-Weinberg equilibrium with p-values of 0.0833 and 0.7925 respectively. The three common allelic variants of APOE isoform are the APOE ε2 allele, the APOE ε3 allele, and the APOE ε4 allele, which are derived from rs7412 and rs429358 based on allelic combinations of TT, CT, or CC alleles, respectively. In this sample of 4,150 participants, 1261 (30%) had one copy of the APOE ε4 allele and 144 (4%) had two copies of the APOE ε4 allele. In clinical and population-based studies, participants with one or more copies of the APOE ε4 allele were at higher risk for Alzheimer's disease and cognitive decline (41-43). Because of this evidence and the small sample size for the group with two APOE ε4 alleles, we created an indicator variable for those with one or more copies of the APOE ε4 allele.

COVARIATES

Our analytic models also adjusted for several demographic and health variables. These variables were included to account for known residual association of cognitive decline disease mechanism with depressive symptoms and the APOE ε4 allele. We included four demographic variables: age, sex, ethnicity (African Americans and Caucasians), and education (measured in number of years of schooling completed). As potential confounders, we also adjusted for baseline measures of both body mass index (BMI) (kg/m^2) and number of chronic health conditions (stroke, myocardial infarction, hypertension, diabetes, hip fracture, and cancer), both assessed during the in-home interviews. For our sensitivity analysis, we also included lifestyle variables, such as current and former smoking behavior, current amount of alcohol consumption (in grams), and hours of physical activity per week.

STATISTICAL ANALYSIS

We calculated baseline means and standard deviations for continuous measures and percentages for categorical measures stratified by the number of depressive symptoms and the presence of one or more copies of the APOE ε4 allele. For this descriptive analysis, we classified depressive symptoms into four groups, no depressive symptoms, mild (1-2 depressive symptoms), moderate (3-5 depressive symptoms), and severe (6 or higher depressive symptoms). We compared baseline characteristics using an analysis of variance F-tests for continuous measures and a chi-squared test statistic for categorical measures. However, for our regression analysis, we used a continuous measure of depressive symptoms score as our main predictor of interest (range=0 to 10).

We modeled gene-behavior interaction of depressive symptoms and the APOE ε4 allele using linear mixed-effects regression models with random effects for subjects and slopes with an unstructured correlation structure (44). We used linear contrasts to estimate cognitive decline from coefficients of our regression model that is described below in further detail. The outcome measure for all the analyses were standardized cognitive function at each observation period. We used a time since baseline variable (starting at 0 and measuring number of years to follow-up interview) to model baseline and longitudinal decline in cognitive function. We studied the temporal association of depressive symptoms, the APOE ε4 allele, and cognitive decline using two, two-way interactions of depressive symptoms and time, and the APOE ε4 allele and time, and a three-way interaction of depressive symptoms, the APOE ε4 allele, and time, while adjusting for demographic and health variables in two-

separate analyses. The two-way interaction of depressive symptoms and time can be interpreted as the marginal increase in cognitive decline for each additional depressive symptom among participants with no copies of the APOE ε4 allele. The two-way interaction of the APOE ε4 allele and time can be interpreted as the marginal increase in cognitive decline due to the presence of the APOE ε4 allele among participants with no depressive symptoms. Finally, the three-way interaction can be interpreted as the marginal increase in cognitive decline due to the presence of the APOE ε4 allele and each additional unit of depressive symptoms. Because cognitive decline is higher among participants of older age and may vary by gender, ethnicity, and education, we used two-way interactions of time with age, gender, ethnicity, and education in our models. In a separate analysis, we used two, two-way interactions, and one three-way interaction as described for our main model but substituted each of the subscales of depressive symptoms: (lack of) positive affect, negative affect, somatic symptoms, and interpersonal relationships as the main predictors of interest instead of depressive symptoms score.

Our estimation process was complicated by the mixed sampling scheme of stratified and population samples. Of the 4,150 participants included in the analysis, 2,275 were selected using a stratified random sample from the population and the remaining 1,875 participants were part of the population sample. In order to account for this sampling structure, we computed participant-specific sampling weights for those selected using our stratified random sample, while setting those from the population scheme to be equal to 1. Given that sample weights were design features, the parameter estimates from a weighted linear-mixed effects regression model would be unbiased for this sampling scheme, but the variance estimates may still be biased and inconsistent. To remedy this situation, we estimated bootstrap sampling weights for two-stage sampling scheme (45, 46). We used standard errors from the bootstrapping procedure and weighted parameter estimates from our regression models to estimate the corresponding p-values. All models were fitted using R version 2.15.3 using the *lmer* function in the lme4 package, and bootstrap variances were estimated with a coding program using the *sampling* package (47).

RESULTS

At the baseline assessment, the average age of participants was 71.6 (SD=5.8) years. The study sample consisted of 70% African American participants and 63% women with an average education of 12.6 (SD=3.5) years.

DEPRESSIVE SYMPTOMS AND BASELINE DEMOGRAPHICS

The study sample consisted of 1,795 (43%) participants who reported no depressive symptoms; 1,457 (35%) who reported 1-2 depressive symptoms (mild); 669 (16%) who reported 3-5 depressive symptoms (moderate); and 229 (6%) who reported 6 or more depressive symptoms (severe). Table 1 shows baseline characteristics of participants stratified by the four levels of depressive symptoms. As the number of depressive symptoms increased, a greater proportion of participants were older African American women who were less educated and had higher body mass index. Participants exhibited significantly lower cognitive function with increasing levels of depressive symptoms. We also observed a

higher number of chronic health conditions and higher prevalence of stroke, myocardial infarction, hypertension, and diabetes with increasing levels of depressive symptoms.

APOE AND BASELINE DEMOGRAPHICS

Of the 4,150 participants, 1,405 (34%) had at least one copy of the APOE ε4 allele. Table 2 shows the baseline characteristics of participants stratified by the APOE ε4 allele status. Participants with one or more copies of the APOE ε4 allele were significantly younger, were more likely to be African American, had higher body mass index, lower cognitive function, and a lower prevalence of myocardial infarction. We did not find any significant differences between participants with no copies and one or more copies of the APOE ε4 allele for any of the other demographic and health measures.

Table 3 shows the association of depressive symptoms and the APOE ε4 allele with baseline levels and subsequent cognitive decline after adjusting for main effects of age, gender, ethnicity, education, body mass index, number of chronic health conditions, and two-way interactions of age, gender, ethnicity, and education with time. The main effect of depressive symptoms suggests that each additional symptom of depression was associated with a lower level of baseline cognitive function (coefficient = -0.0215; SE=0.0053; $p < 0.001$). The presence of the APOE ε4 allele was also associated with a lower level of baseline cognitive function (coefficient = -0.1236; SE=0.0424; p=0.007).

Cognitive function declined by 0.0412-unit per year among participants with no depressive symptoms and no copies of the APOE ε4 allele (SE=0.0026; $p<0.001$). For each additional symptom of depression, cognitive decline increased by 0.0021-unit per year among participants with no copies of the APOE ε4 allele (SE=0.0008; p=0.007). For example, cognitive decline increased by 0.0084-unit per year in a person with 4 symptoms of depression (multiply 0.0021 by 4) compared to an asymptomatic person. Therefore, using a linear contrast, cognitive function declined by 0.0496-unit per year (adding 0.0412 and 0.0084) for participants with 4 symptoms of depression and no copies of the APOE ε4 allele.

On the other hand, using a linear contrast, cognitive function declined by 0.0704-unit per year (adding 0.0412 and 0.0292) among participants with no symptoms of depression and one or more copies of the APOE ε4 allele (SE=0.0046; $p<0.001$). For each additional symptom of depression, using a linear contrast, cognitive decline increased by 0.0051-unit per year (adding 0.0021 and 0.0030; SE=0.0011; $p<0.001$) in participants with one or more copies of the APOE ε4 allele. Thus, cognitive decline increased by 1.5-fold for each symptom of depression (dividing 0.0031 by 0.0021) comparing those with one or more copies of the APOE ε4 allele to those with no copies of the APOE ε4 allele (p=0.021). As an example, cognitive decline in this group increased by 0.0204-unit per year for 4 symptoms of depression (multiplying 0.0051 by 4). Using a linear contrast, cognitive decline was 0.0908-unit per year (adding 0.0704 and 0.0204) for participants with 4 symptoms of depression and one or more copies of the APOE ε4 allele.

Figure 1(a) shows the average levels and decline in cognitive function among participants with no copies of the APOE ε4 allele using results from Table 3. From the figure, cognitive decline in participants with no depressive symptoms (solid line) was higher at baseline and

declined slower than participants with 2 depressive symptoms (dashed line), 4 depressive symptoms (dotted line), and 6 depressive symptoms (dotted and dashed line). Figure 1(b) shows the average levels and decline in cognitive function by depressive symptoms among participants with one or more copies of the APOE ε4 allele. The pattern of cognitive decline in this subgroup is similar to participants with no copies of the APOE ε4 allele. However, contrasting Figures 1(a) and 1(b) shows that cognitive decline was faster among participants with one or more copies of the APOE ε4 allele compared to participants with no copies of the APOE ε4 allele as the number of symptoms of depression got larger.

SUBSCALES OF DEPRESSIVE SYMPTOMS

Because depression is multidimensional, we examined the interaction of the APOE ε4 allele with the four depressive symptom subscales to assess whether the interaction was more evident in some symptom domains than others. We found significant interactions between the APOE ε4 allele and the domains of positive affect and negative affect. Specifically, the interaction of the APOE ε4 allele and each positive affect symptom increased cognitive decline by 0.0115-unit per year (SE=0.0058, p=0.047) relative to the APOE ε4 allele or positive affect alone. Similarly, the interaction of the APOE ε4 allele and each negative affect symptom increased cognitive decline by 0.0070 (SE=0.0028; p=0.012) relative to the APOE ε4 allele or negative affect alone. We found no significant interactions between APOE and somatic symptoms or interpersonal problems on cognitive decline.

We also performed a sensitivity analysis by adding lifestyle variables- smoking status, alcohol intake, and physical activity to our main and subscale models, and found that our estimates for interaction of the APOE ε4 allele with depressive symptoms and subscales of depressive symptoms did not change substantively.

DISCUSSION

Our main findings provide evidence for a synergistic interaction of depressive symptoms and the APOE ε4 allele on cognitive decline. We found that the deleterious effect of depressive symptoms on cognitive decline is magnified by the presence of the APOE ε4 allele. Specifically, cognitive decline increased significantly among participants with one or more copies of the APOE ε4 allele and a higher number of depressive symptoms than either one individually. Two subscales—lack of positive affect and negative affect showed significantly increased cognitive decline in the presence of one or more copies of the APOE ε4 allele. Adding lifestyle variables to our regression models did not change our estimates for the interaction of APOE and depressive symptoms.

The joint association of depressive symptoms and the APOE ε4 allele were significantly greater than either one individually. The basis of this finding can be explained using the following mechanisms: (1) Depressive symptoms are related to the causal path leading to cognitive decline, and may also presumably be an early sign of cognitive decline; (2) Depressive symptoms might not be related to the causal path leading to cognitive decline, but still an intermediate variable might lead to both cognitive decline and depressive symptoms; (3) Depressive symptoms might not be related to the casual path leading to cognitive decline, however, the association with cognitive function might be independent of

the casual pathway, thereby resulting in a negative impact of the path; (4) Depressive symptoms result in increased cognitive decline in the presence of a genetic susceptibility factor or another genetic risk factor that may also be related to the APOE mechanism. Our main findings reiterate the notion of interaction depressive symptoms and a genetic susceptibility factor on cognitive decline. However, the four mechanisms outlined above might not be independent of each other, rather, are acting in some combination. From our secondary analysis, depressive symptoms resulted in increased cognitive decline endorsed by a lack of positive affect and negative affect. These two subscales refer to affective symptoms encompassing questions on feeling enjoyment and happiness, and depression and sadness. The two other subscales that focused more heavily on physical or vegetative affect did not show a significant interaction with the APOE ε4 allele on cognitive decline.

Prior studies of depressive symptoms and the APOE genotype on cognitive outcomes have conflicting findings. This can be attributed to several methodological and design issues, specifically, the duration of follow-up, selection of study participants, different measures of cognitive outcomes, and the assessment of cognitive trajectories in APOE ε4 non-carriers and carriers. For example, the two studies that did not find a synergistic interaction had short follow-up and small sample size. Niti et al. created categorical measures of depressive symptoms (Geriatric Depression Scale (GDS) score ≥5) and cognitive decline (at least 1-point drop in MMSE) using a short follow-up of 1-2 years in participants 55 years and older. Even though Dean et al. had a follow-up of 20 years, the findings were based on 126 participants from a clinical sample making the findings of this study less reliable. The three studies that showed a synergistic interaction used different measures of cognitive outcomes. Specifically, Gerda et al. had a sample size of 840 with a median follow-up of 3.5 years investigating the risk of incident MCI. Irie et al. also reported a similar finding in a prospective cohort of 1932 participants after 6-years of follow-up on the risk of dementia. Corsentino et al. reported the interaction of depressive symptoms and cognitive decline in the Short Portable Mental Status Questionnaire (SPMSQ) using a cohort of 1992 participants after one-follow-up 6 years later. Freiheit et al. also reported a significant interaction of depressive symptoms and the APOE ε4 allele in a clinical sample of 350 participants followed for 30 months. In addition to the already existing literature, our study provides further evidence for a synergistic interaction of depressive symptoms and the APOE ε4 allele interaction on cognitive decline using global cognitive scores derived from four brief tests. In addition, our study suggests that the interaction with the APOE ε4 allele may involve some domains of depressive symptoms but not others.

Our study has several strengths. First, CHAP is a longitudinal population-based study of a large cohort of older participants (N=4150) from a geographically defined urban, biracial population. Second, an average follow-up period of 9.1 years enabled us to detect long-term changes in cognitive decline relative to baseline depressive symptoms and the APOE ε4 allele. Third, our study also assessed a large number of demographic and health-related covariates that were adjusted in our models to provide a precise and consistent estimate of the association of depressive symptoms and APOE genotype on cognitive decline. Finally, genotyped data was available on approximately 40% of the population-based sample of European and African Americans using a stratified random sample, and an entire population enumeration during the later part of the study.

Our study also has several limitations. One of the limitations of is that data collection was three years apart making short-term changes in cognitive function less detectable. However, given that the CHAP data was collected for an average of 9.2 years, and that our analysis was restricted to those with two or more interviews, we are confident that estimates of long-term cognitive decline are highly reliable. A second limitation is that the APOE genotype was found in 34% of our population, which is smaller than that reported in a meta-analysis of case-control studies (45). This lower proportion could be due to the higher number of African Americans (70%) in our study with a lower prevalence of the APOE ε4 allele compared to their European counterparts. Finally, our sampling scheme was a mixture of stratified random sampling and population sampling of older adults; however, our statistical models adjusted for design-related complexities using sampling weights and bootstrapping variance estimates.

Given that our study was based on a population-based sample with a fairly large number of participants being genotyped from two different population structures (European and African Americans), we feel confident that these results are generalizable and verifiable by other longitudinal population-based studies of older persons.

In conclusion, depressive symptoms significantly increased cognitive decline in the presence of the APOE ε4 allele. This finding has important implications for older adults, health care practitioners, scientists, and public health experts – further demonstrating the complex interplay of mental health and genetic markers on late-life cognitive health.

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Abbreviations

APOE	Apolipoprotein E
AD	Alzheimer's disease
CHAP	Chicago Health and Aging Project
CES-D	Center for Epidemiologic Studies Depression Scale

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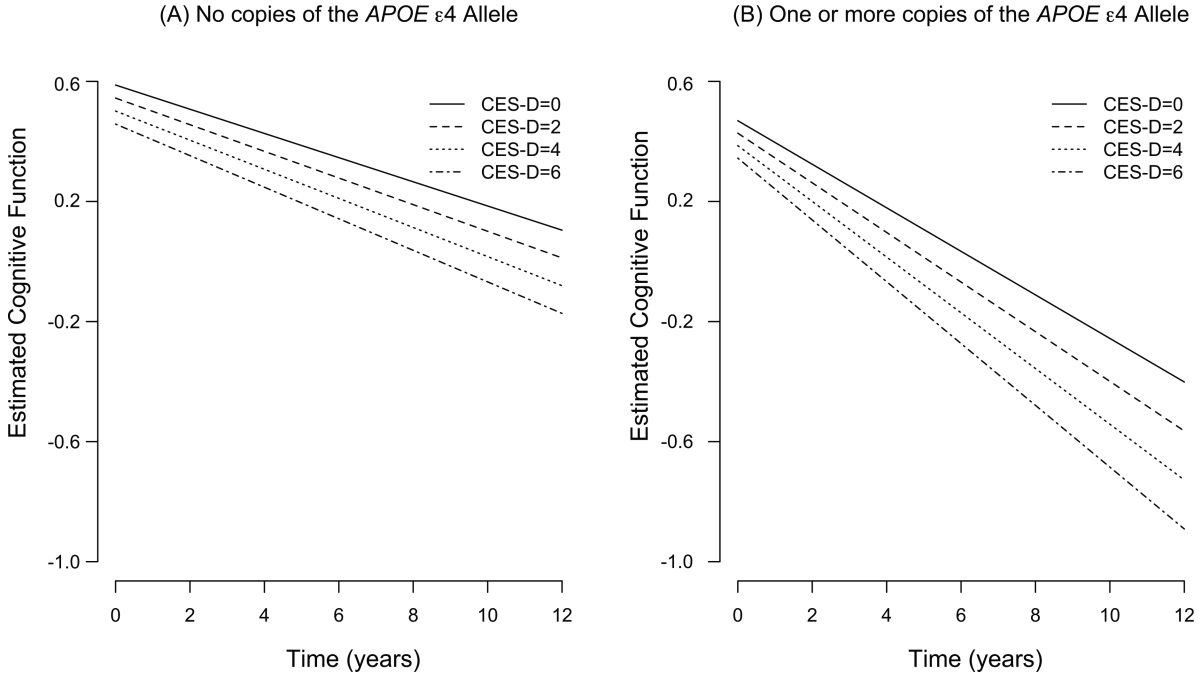

Figure 1. Cognitive decline in participants with no copies and one or more copies of the APOE ε4 allele

Cognitive decline in participants with no copies (A) and one or more copies (B) of the APOE ε4 allele for various levels of shortened Center for Epidemiologic Studies Depression scale are shown by each trend line. The lines are based on parameter estimates from a linear mixed model regression. The estimate of cognitive decline was 0.0412-unit per year (SE=0.0026) that increased by 0.0021-unit per year (SE=0.0008) for each additional symptom of depression among participants with no copies of the APOE ε4 allele (A). The estimate of cognitive decline was 0.0704-unit per year (SE=0.0046) that increased by 0.0051-unit per year (SE=0.0011) for each additional symptom of depression among participants with one or more copies of the APOE ε4 allele (B).

Table 1

Baseline characteristics of study participants by number of depressive symptoms

Characteristics	Depressive Symptoms Mean (SD) or N (%)				p-value[a]
	0 N=1795	1-2 N=1457	3-5 N= 669	≥6 N=229	
Age, years	71.8 (6.1)	72.6 (6.7)	73.3 (7.0)	73.3 (7.0)	<.001
Education, years	13.3 (3.5)	12.4 (3.4)	11.6 (3.2)	11.1 (3.5)	<.001
Women	1,038 (58%)	922 (63%)	473 (71%)	180 (79%)	<.001
African Americans	1,140 (64%)	1,029 (71%)	541 (81%)	187 (82%)	<.001
BMI (kg/m^2)	28.1 (5.4)	28.6 (6.0)	28.9 (6.4)	30.6 (7.8)	<.001
Chronic health conditions	0.87 (.82)	0.98 (.87)	1.07 (.88)	1.30 (.96)	<.001
Stroke	113 (6%)	109 (7%)	31 (9%)	27 (12%)	.006
MI[1]	147 (8%)	170 (12%)	79 (12%)	43 (19%)	<.001
Hypertension	873 (49%)	758 (52%)	375 (56%)	154 (67%)	<.001
Diabetes	98 (5%)	99 (7%)	62 (9%)	26 (11%)	<.001
Cancer	297 (17%)	248 (17%)	122 (18%)	45 (20%)	.56
Hip fracture	34 (2%)	37 (3%)	19 (3%)	4 (2%)	.34
Cognitive function	0.4569 (.6217)	0.3798 (.6155)	0.2332 (.6848)	0.1045 (.6891)	<.001
Symbol digits	34.4 (12.9)	31.9 (12.3)	28.3 (12.5)	25.6 (12.1)	<.001
Delayed recall	8.5 (2.8)	8.3 (2.8)	7.8 (3.1)	7.5 (3.1)	<.001
Immediate recall	9.0 (2.4)	8.9 (2.5)	8.4 (2.7)	8.1 (2.8)	<.001
MMSE[2]	27.4 (3.3)	26.9 (3.7)	26.0 (4.5)	25.3 (5.0)	<.001
APOE ε4 allele	622 (35%)	465 (32%)	225 (34%)	93 (41%)	.057

[1] Myocardial Infarction

[2] Mini-mental state examination

[a] p-value is based on F-test for continuous or chi-square test for categorical measures

Table 2

Baseline characteristics of study participants by number of copies of the APOE ε4 allele

Characteristics	APOE ε4 allele Mean (SD) or N (%)		
	0 N =2745	1-2 N=1405	p-value[a]
Age	71.9 (5.9)	71.0 (5.4)	<.001
Education	12.5 (3.5)	12.6 (3.4)	.45
Women	1747 (64%)	866 (62%)	.20
African Americans	1,820 (66%)	1,077 (76%)	<.001
Body mass index	28.4 (5.9)	28.8 (6.0)	.031
Chronic health conditions	0.96 (.87)	0.97 (.88)	.92
Stroke	192 (7%)	118 (8%)	.10
MI[1]	311 (11%)	128 (9%)	.021
Hypertension	1414 (52%)	746 (53%)	.32
Diabetes	195(7%)	90 (6%)	.40
Cancer	469 (17%)	243 (17%)	.86
Hip fracture	62 (2%)	32 (2%)	.96
Cognitive function	0.3885 (.6332)	0.3467 (.6575)	.047
Symbol digits	32.3 (12.8)	31.6 (13.0)	.12
Delayed recall	8.6 (2.6)	8.5 (2.4)	.083
Immediate recall	9.1 (2.2)	9.0 (2.1)	.11
MMSE[2]	27.3 (3.6)	26.5 (3.7)	.081
Depressive symptoms	1.4 (1.8)	1.5 (1.9)	.67

[1] Myocardial Infarction

[2] Mini-mental state examination

[a] p-value is based on t-test for continuous or chi-square test for discrete measures

Table 3

Linear mixed effects regression model for APOE ε4 allele status and depressive symptoms on cognitive decline

	Coefficient (SE)[a]
Intercept	0.5890 (.0223)[§]
Depressive symptoms	−0.0215 (.0053)[§]
APOE ε4 allele	−0.1236 (.0424)[‡]
Time	−0.0412 (.0026)[§]
Dep. Symp. × Time	−0.0021 (.0008)[§]
APOE ε4 allele × Time	−0.0292 (.0052)[§]
Dep. Symp. × ε4 allele × Time	−0.0030 (.0013)[†]

Note:

All p-values are based on two-tailed tests

[§] p<.001

[‡] p<.01

[†] p<.05

[a] adjusted for main effects of age, sex, ethnicity, education, BMI, number of chronic health conditions, and two-way interactions of time with age, sex, and ethnicity.

Table 4

Interaction of lack of positive affect and negative affect subscales with APOE ε4 allele on cognitive decline

	Coefficient (SE)	
	Positive affect[b] N=4,150	**Negative affect[b] N=4,150**
Intercept	0.5443 (.0187)[§]	0.5522 (.0190)[§]
Pos./Neg. affect	−0.0782 (.0019)[§]	−0.0382 (.0095)[§]
APOE ε4 allele	−0.0250 (.0171)	−0.0264 (.0170)
Time since baseline	−0.0448 (.0022)[§]	−0.0440 (.0023)[§]
APOE ε4 allele × Time	−0.0229 (.0026)[§]	−0.0212 (.0027)[§]
Pos./Neg. affect × Time	−0.0047 (.0034)	−0.0041 (.0017)[†]
APOE ε4 × Pos./Neg. affect × Time	−0.0115 (.0058)[†]	−0.0070 (.0028)[†]

Note:

[‡] p<.01

All p-values are based on two-tailed tests

[§] p<.001

[†] p<.05

[b] adjusted for main effects of age, gender, ethnicity, education, BMI, number of chronic health conditions, and two-way interactions of time with age, ethnicity, and gender.