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ORIGINAL ARTICLE

Current Versus Lifetime Depression, *APOE* Variation, and Their Interaction on Cognitive Performance in Younger and Older Adults

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ABSTRACT

Objective: An interaction effect of depressive symptoms and *APOE* e4 allele status on cognitive decline has been shown in old age: e4 allele carriers with more depressive symptoms have faster cognitive decline than those with either depression or the e4 allele. We test this interaction effect on four cognitive domains, using a clinical depression measure comparing current versus lifetime depression.

Methods: 14,379 individuals aged 18 to 59 years, and 3944 individuals aged 60 to 94 years from the Generation Scotland: Scottish Family Health Study participated. Linear-mixed models—accounting for participant relatedness and demographic and health indices—tested for effects of depression and *APOE* on cognitive abilities.

Results: There was no interaction between depression and *APOE* on cognition ($p > .05$). Current depression was associated with poorer speed (in both groups) and memory (18- to 59-year-olds); differences ranged from 0.01 to 0.03 standard deviation [SD]. For lifetime depression, cognitive performance was lower for digit symbol in younger adults, but higher for vocabulary in both younger (0.03 SD) and older (0.05 SD) adults. A negative effect of the APOE e4 allele on speed and memory was found in the group 60 years and older (effect sizes of 0.04 SD).

Conclusions: The absence of a depression by *APOE* interaction on cognitive abilities suggests that these synergistic effects only operate at the level of cognitive decline. This implies that it is those biological pathways especially affected by aging that become compromised further by the combined presence of depression and *APOE* e4 in an individual.

Key words: Structured Clinical Interview for DSM-IV depression, general health questionnaire, processing speed, memory, verbal ability, apolipoprotein E.

INTRODUCTION

Depression and variation in the apolipoprotein E (*APOE*) gene are each associated with cognitive ability. The presence of depression/depressive symptoms is related to poorer cognitive function (1,2). Carriers of the *APOE* e4 allele show worse cognitive test performance (3) and increased cognitive decline over time (4–6). There is mounting evidence to suggest that the effects of depressive symptoms and *APOE* combine to accelerate cognitive decline in old age (7,8). However, existing studies have been underpowered to investigate this at the genotype level and have focused on depressive symptoms rather than clinically defined depression. The

AD = Alzheimer's disease, ***APOE*** = apolipoprotein E, **GHQ** = General Health Questionnaire, **GS:SFHS** = Generation Scotland: Scottish Family Health Study

SDC Supplemental Content

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Generation Scotland is a collaboration between the University Medical Schools and National Health Service in Aberdeen, Dundee, Edinburgh, and Glasgow (Scotland).

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present study has a very large sample and measures of clinically derived depression and current psychological distress symptoms. Longitudinal measurements are not available, but the wide age range enables testing of interaction effects in younger and older age groups. The comparison of current versus lifetime depression could provide insight into any enduring effects of depression on cognitive abilities.

Cognitive decrements in a number of different domains have been documented in both young and old people with clinical depression (9–11). A meta-analysis of 14 studies showed that severity of depression was related especially to episodic memory, executive function, and processing speed domains (1). In a population-based study of 2486 people 60 years and older diagnosed as having *International Classification of Diseases, 10th Revision* unipolar depression, moderate/severe depression was related to slower processing speed and poorer attention, executive function, verbal fluency, episodic memory, and vocabulary (12). Effects were not observed for short-term memory, general knowledge, or spatial ability. Observations of cognitive functioning in clinically depressed samples (mostly middle aged or older) in remission (13–15) suggest that cognitive decrements are not simply a state-like feature of the current depressive episode, but rather a more enduring feature.

The *APOE* e4 variant increases risk for late-onset Alzheimer's disease (AD) in a dose-dependent manner (16). A meta-analysis of up to 56 studies has further shown a negative relationship with global cognitive function, episodic memory, executive function, and perceptual speed in nondemented, mostly older (>60 years), adults (3). The effect sizes were small, with the explained variance accounting for, at most, half of a percent. Some argue that such associations reflect incipient AD (e.g., Ref. (17)). A magnetic resonance imaging study (18) comparing AD symptom–free *APOE* e4 carriers and noncarriers showed smaller hippocampal volume in carriers, especially those who were younger than 65 years. A follow-up of this sample could test whether smaller hippocampal volume is associated only with AD progression and inform the debate on whether incipient AD drives the *APOE* findings in normal cognitive aging. Hippocampal atrophy is also a feature of depression in the older people; depressed individuals (≥60 years old) showed larger atrophy in the left hippocampus, accompanied by greater cognitive decline, than did the nondepressed elders (19). In an elderly Chinese population, the presence of depression and the *APOE* e4 allele was related to greater disruption of the hippocampal functional connectivity network projecting to the bilateral dorsal anterior cingulate cortex, and the amount of disruption was associated with poorer cognitive functioning (20). The potential of synergistic effects of depression and *APOE* has also been reported in terms of cognitive decline.

In a prospective longitudinal study of community-dwelling adults 65 years and older (n = 1992), the effects of depressive symptoms (Center for Epidemiological Studies Depression Scale) and *APOE* e4 allele status on global cognitive change over a 6-year period were measured (7). Main effects of depression and *APOE* e4 allele status on cognitive decline were confirmed; moreover, an interaction effect showed that carriers of the e4 allele with more depressive symptoms at baseline had the greatest cognitive decline, and this was consistent across all ages. In older Chinese adults (n = 1487), an interaction of depressive symptoms and *APOE* was found despite an absence of main effects: depressed *APOE* e4 carriers at baseline showed a 40% reduction in their cognitive ability over a 1- to 2-year period compared with a 28.6% reduction in nondepressed *APOE* e4 carriers (21). The largest prospective study (n = 4150) of community-dwelling older adults (≥65 years) followed up to six times every 3 years confirmed an interaction between depressive symptoms (Center for Epidemiological Studies Depression Scale) and *APOE* on cognitive decline over time (8). They evaluated the effect on a general cognitive ability factor. Each extra depressive symptom increased cognitive decline by 0.002 units per year for noncarriers of the e4 allele versus a 0.005-unit increase for e4 carriers. These studies provide strong evidence for a heightened effect of depression and *APOE* e4 status together on cognitive decline in old age, but their small size precluded investigation of genotypic effects. One might, for example, expect more pronounced effects for e4 homozygote carriers, who are at greater risk of AD.

The size of the present study allows for an investigation of a number of genotypic effects. In addition, clinical phenotyping enables dissociation of individuals with depressive illness into those with and without current clinically significant depression at the time of cognitive testing. Current depression might be a direct cause of poorer cognition due to associated reductions in motivation and attention that characterize an episode of depression. However, if such effects remain in people with a history of depression who are not currently depressed, then this could indicate a trait-like causal mechanism (e.g., brain structural differences). In the absence of longitudinal data, the present study compares results for groups of younger (18–59 years) versus older (60–94 years) adults, which captures the bimodal age distribution of incidence rate for mood disorders (22). This age split was based on age ranges reported in previous studies of the elderly (12) and also on the distribution of cognitive data in the Generation Scotland: Scottish Family Health Study (GS:SFHS), which showed changes in mean cognition around 60 years (23). If the depression and *APOE* e4 interaction effect is only related to cognitive decline, then this might be observable (or of larger effect) in the older age group, whose cognitive abilities will reflect increased variation due to aging. The interaction effect will also be considered separately for four cognitive domains (processing speed, executive function, verbal ability, verbal declarative

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memory) given that both depression and *APOE* have shown differential effects across cognitive domains.

METHODS

The sample were from Generation Scotland: the Scottish Family Health Study (GS:SFHS), a large population and family-based study that recruited around 24,000 Scottish participants between the years 2006 and 2011. Further information about sample recruitment and descriptive aspects of this study can be found in Smith et al. (24) (www.generationscotland.org/). Briefly, a sample of probands aged between 35 and 65 years (n = 7953) who were registered with general medical practitioners were invited to participate. No selective sampling for specific medical conditions was undertaken. These probands then asked their relatives to participate in the study resulting in a final GS:SFHS sample with an extended age range of 18 and 99 years. The present study includes those families who had *APOE* genotyping and the relevant complete depression, cognitive ability, and demographic and health data (n = 18,329). Twenty-eight individuals with AD were excluded. Two subgroups were defined: a younger group (18–59 years) including 6057 families, of which 2168 were single individuals, and an older group (60–94 years) comprising 2589 families, 1644 of whom were singletons. The median number of years of education reported by study participants was slightly higher in the 18- to 59-year-old group (14–15 years) compared with the 60- to 94-year-old group (12–13 years). GS:SFHS ethical approval was granted by the NHS Tayside Committee on Medical Research Ethics (REC Reference Number: 05/S1401/89). Research Tissue Bank status was approved by the Tayside Committee on Medical Research Ethics (REC Reference Number: 10/S1402/20), enabling generic ethical approval for medical research purposes.

Genotyping

Two single nucleotide polymorphisms, rs7412 and rs429358, were typed to define *APOE* allele status. Taqman technology (5-μl volume assays) was used for genotyping and performed at the Wellcome Trust Clinical Research Facility Genetics Core, Edinburgh, where the DNA stores from GS:SFHS participants were contained (25).

Measured Traits

Current and lifetime depression was measured by trained researchers by using the Structured Clinical Interview for DSM-IV disorders; those initially screening positive for a history of emotional or psychiatric problems (21.7%) continued the mood disorder–focused interview. Eighty-eight percent completed the interview. Current psychological distress was also measured in the full sample by using the 28-item General Health Questionnaire (GHQ) (26), which measures somatic symptoms, anxiety and insomnia, social dysfunction, and severe depression. Cognitive ability in four domains—perceptual speed, verbal declarative memory, executive function, and vocabulary—was measured by well-validated and reliable psychometric tests. These included the Wechsler Digit Symbol Substitution Test (speed) (27); Wechsler Logical Memory Test (sum of immediate and delayed recall of one paragraph; memory) (28); the phonemic Verbal Fluency Test using the letters C, F, and L, each for 1 minute (executive function) (29); and the Mill Hill Vocabulary Scale combining junior and senior synonyms (vocabulary) (30).

Self-reported information of a medical/health-related nature was collected by questionnaire, and these were data treated as potential confounders in the present study. The variables included smoking status (never, previous, current), alcohol consumption (units in the past week), physical activity (frequency per week of vigorous activity/physical activity of >20-min duration in leisure time), total number of chronic health conditions (heart disease, stroke, high blood pressure, diabetes, Parkinson disease, cancer [breast, bowel, lung, prostate], hip fracture, arthritis [osteomatoid, rheumatoid], asthma). Relevant clinically attained measures included height and weight, used to calculate body mass index.

Statistical Analyses

Linear mixed-effects models including depression and *APOE* and their interaction were fitted to each cognitive measure and included main effects for age, sex, and potential confounding variables (covariates were mean centered). Four sets of mixed models were run so that (1) current depression versus (2) lifetime depression effects could be compared and, similarly (3), *APOE* e4 status (present/absent) versus (4) *APOE* genotype (e2e2, e2e3, e2e4, e3e4, e4e4, and e3e3 as the reference group). Further analyses were performed replacing depression status with continuous scores from the GHQ; these results were expected to mimic those of current depression but with the advantage of having increased statistical power. All analyses were performed separately for younger (<60 years) and older (≥60 years) groups, with the expectation that the depression by *APOE* interaction effect would be stronger in the older group. Relatedness between individuals was based on reported pedigree information and used to fit a random factor that would account for nonindependence between individuals. The "asreml" library within the "R" statistical software package was used for analysis (31,32).

RESULTS

Descriptive

In the 18- to 59-year-old group, the number of Structured Clinical Interview for DSM-IV disorders diagnoses was as follows: 1053 with single-episode depression (7.3%), 1006 with recurrent depression (7%), and 62 instances of bipolar disorder (0.4%). In the 60- to 94-year-old group, there were 181 with single-episode depression (4.6%), 193 with recurrent depression (4.9%), and 6 cases of bipolar disorder (0.1%). Because previous studies of depressive symptoms cannot differentiate between unipolar and bipolar states, bipolar cases were included in the main analysis of depression, but the data were also reanalyzed excluding bipolar cases. The sample size of each of the depression by *APOE* groups by age cohort is shown in Table 1. In the 60- to 94-year-old group, there were too few people with current depression to enable reliable analysis of the depression by *APOE* interaction effect for this trait. Descriptive statistics for the 18- to 59-year-old and 60- to 94-year-old groups are shown in Table 2. χ^2 Tests showed that depression status differed between younger and older groups (current depression: $\chi^2 = 31.92$, $p < .00001$; lifetime depression: $\chi^2 = 20.74$, $p < .00001$), with the 18- to 59-year-old group being more depressed (3% of sample currently depressed versus 1% in the older group, 12.3% of sample with lifetime depression versus 9.6% in the older group). There was no difference in the distribution of *APOE* e4 allele status ($\chi^2 = 1.96$, $p = .16$) between groups and no association between *APOE* e4 status and depression (current or lifetime)/psychological distress symptoms within groups ($p > .05$).

Distributions of the dependent variables were screened for normality, with outlying scores (0 values for verbal fluency [n = 4], digit symbol [n = 7], and logical memory [n = 2], and values <9 for vocabulary [n = 7]) excluded from

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TABLE 1. Sample Size of Differing Depression (Current, Lifetime) by *APOE* (e4 Presence, Genotype) Groups for Adults Aged 18–59 and 60–94 Years

	Adults Aged 18–59 y				Adults Aged 60–94 y			
	Current Depression		Lifetime Depression		Current Depression		Lifetime Depression	
	Yes (n = 406)	No (n = 13,973)	Yes (n = 1715)	No (n = 12,258)	Yes (n = 49)	No (n = 3895)	Yes (n = 331)	No (n = 3564)
e4 presence								
−e4	299	10,051	1255	8796	38	2845	234	2611
+e4	107	3922	460	3462	11	1050	97	953
Genotype								
e2e2	3	89	15	74	1	19	3	16
e2e3	47	1621	196	1425	6	494	31	463
e3e3	249	8341	1044	7297	31	2332	200	2132
e2e4	8	303	38	265	3	98	8	90
e3e4	91	3262	379	2883	7	863	82	781
e4e4	8	357	43	314	1	89	7	82

APOE = apolipoprotein E.

analysis. All cognitive variables were normally distributed. Where significant (see Table S1, Supplemental Digital Content, http://links.lww.com/PSYMED/A213), total chronic diseases, body mass index, and smoking status (scored in the direction of currently smoke) were negatively associated with cognitive performance, whereas physical activity and alcohol intake were positively associated with cognitive performance. Men performed worse than did women on all tests, except vocabulary, in which they scored higher. Younger age was associated with better performance on digit symbol and logical memory. Age effects on verbal fluency were opposite in younger and older groups: age was positively associated in the 18- to 59-year-old group, but negatively in the 60- to 94-year-old group. A positive association between age and vocabulary was also observed in the 18- to 59-year-old group.

Depression and APOE Effects

The results of linear-mixed models which tested the main and interaction effects of depression and *APOE* e4 status on the different cognitive domains are shown in Table 3. No significant interaction effects were present for either cohort. In the 18- to 59-year-old group, current depression main effects were found for digit symbol (0.03 standard deviation [SD] lower) and logical memory (0.02 SD lower), and lifetime depression main effects were found for digit symbol (0.02 SD lower), verbal fluency (0.03 SD higher), and vocabulary (0.03 SD higher). In the 60- to 94-year-old group, a current depression main effect was similarly found for digit symbol (0.01 SD lower), with lifetime depression associated with vocabulary (0.05 SD higher). The direction of these effects was consistent across age groups: depression related to poorer digit symbol and logical memory test performance, but positively to verbal fluency and vocabulary. Main effects of *APOE* e4 presence were observed for verbal fluency in both age groups (e4 allele associated with better performance) and for digit symbol and logical memory in the 60- to 94-year-old group (e4 allele associated with worse performance). Results of modeling *APOE* genotype are shown in Table 4. No interaction effects were observed for those genotype groups in which there was sufficient sample size to test the interaction. Genotypic main effects revealed better performance of *APOE* e3e4 genotype carriers for verbal fluency in the 18- to 59-year-old group. In the 60- to 94-year-old group, *APOE* e3e4 and e4e4 genotype groups showed worse performance in digit symbol and logical memory, whereas the *APOE* e4e4 genotype group demonstrated better performance on verbal fluency. The main effects of depression are more reliable (smaller standard errors) in the *APOE* e4 status analysis, so are not highlighted for the *APOE* genotypic analyses.

Results of the GHQ (Table 5) mimicked those of current depression in the *APOE* genotypic analysis of the adults aged 18 to 59 years and in the *APOE* e4 status analysis of the adults aged 60 to 94 years for all cognitive measures. In the 18- to 59-year-old group analysis of *APOE* e4 status, two measures showed deviation from the current depression results: logical memory showed a GHQ × *APOE* e4 allele interaction effect (p = .04) and there was a (positive) main effect of *APOE* e4 on vocabulary. In *APOE* e4 carriers, the correlation between GHQ and logical memory was −0.07 versus −0.03 in *APOE* e4 noncarriers. In the 60- to 94-year-old group analysis of *APOE* genotypes, an

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TABLE 2. Mean (Standard Deviation) Values/Frequencies for the Predictor and Outcome Variables, Shown Separately for Groups Aged 18–59 and 60–94 Years

	Adults Aged 18–59 y (n = 14,379)	Adults Aged 60–94 y (n = 3944)
Predictor variables		
Age, y	41.57 (11.97)	65.78 (5.74)
Sex, female	8456 (58.8%)	2248 (57%)
Current depression, yes	406 (2.8%)	49 (1.26%)
Lifetime depression, yes	1715 (11.93%)	380 (10.66%)
General Health Questionnaire[a]	2.51 (4.09)	1.71 (3.3)
APOE e4	+e4: 4029 (28.02%)	+e4: 1061 (36.8%)
APOE genotype		
e2e2	92 (0.64%)	20 (0.51%)
e2e3	1668 (11.6%)	500 (12.68%)
e3e3	8590 (59.74%)	2363 (59.91%)
e2e4	311 (2.16%)	101 (2.56%)
e3e4	3353 (23.32%)	870 (22.06%)
e4e4	365 (2.54%)	90 (2.28%)
BMI, kg/m^2	26.40 (5.27)	27.44 (4.88)
Chronic health conditions (range, 0–6)	0.31 (0.61)	0.82 (0.98)
Smoking status		
Current	2757	411
Ex (<12 mo)	497	56
Ex (>12 mo)	3208	1619
Never	7917	1858
Alcohol, units/wk	10.71 (12.98)	18.94 (10.84)
Physical activity, d/wk		
0	4970	1897
1	2147	461
2–3	4236	871
≥4	3026	715
Cognitive outcome measures		
Digit Symbol	76.43 (15.62)	60.62 (15.07)
Verbal Fluency	39.93 (11.45)	40.66 (12.20)
Mill Hill Vocabulary	29.79 (4.45)	31.96 (4.67)
Logical Memory Total	31.81 (7.71)	29.10 (8.19)

APOE = apolipoprotein E; BMI = body mass index.

[a] n = 14,279 in younger adults; n = 3913 in older adults.

interaction effect (not tested for current depression) between GHQ and *APOE* e4e4 was found for digit symbol (p = .04). In *APOE* e4 homozygotes, there was no association between GHQ and digit symbol compared with a significant correlation of −0.18 in the *APOE* e3 homozygote reference group. Given the number of multiple tests performed, albeit on correlated dependent (cognitive) and independent (depression measure, *APOE* status, and genotype) variables in two groups, the interaction effects, all with p values greater than 0.04, are unlikely to represent true effects, especially for the small *APOE* e4e4 genotypic group in the 60- to 94-year-old sample.

For the current and lifetime depression analyses, the exclusion of bipolar cases changed two results in the genotypic analysis (although the direction of the effect did not change), the main effect of current depression became significant for vocabulary (p = .03) in the 18- to 59-year-old group, and the main effect of lifetime depression became nonsignificant for vocabulary (p = .051) in the 60- to 94-year-old group. However, the more reliable *APOE* e4 status analysis did not support a difference between these analyses. For the GHQ analysis, the interaction effect of GHQ and *APOE* e4 status for memory in the 18- to 59-year-old sample became nonsignificant (p = .06) on

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TABLE 3. Main and Interaction Effects (Unstandardized Regression Coefficients and Standard Errors) for Depression and *APOE* e4 Status on Cognitive Test Scores, Separately for Adults Aged 18–59 and 60–94 Years

	Current Depression			Lifetime Depression		
	Depression	*APOE* e4	Depression × *APOE*	Depression	*APOE* e4	Depression × *APOE*
Adult aged 18–59 y						
Digit Symbol	**−2.76 (0.81), $p < .001$**	−0.08 (0.27), $p = .76$	−1.17 (1.58), $p = .46$	**−1.09 (0.42), $p = .009$**	0.03 (0.29), $p = .93$	−0.93 (0.79), $p = .24$
Verbal Fluency	−0.13 (0.64), $p = .84$	**0.54 (0.22), $p = .014$**	−0.24 (1.25), $p = .84$	**1.04 (0.33), $p = .002$**	**0.58 (0.23), $p = .012$**	−0.27 (0.62), $p = .67$
Vocabulary	−0.29 (0.23), $p = .20$	0.14 (0.08), $p = .073$	0.18 (0.45), $p = .68$	**0.39 (0.12), $p < .001$**	0.12 (0.08), $p = .16$	0.18 (0.22), $p = .41$
Logical Memory	**−1.07 (0.43), $p = .014$**	−0.03 (0.15), $p = .85$	0.22 (0.84), $p = .79$	0.03 (0.22), $p = .89$	−0.02 (0.15), $p = .91$	−0.11 (0.43), $p = .80$
Adults aged 60–94 y						
Digit Symbol	**−4.91 (1.94), $p = .009$**	**−1.36 (0.49), $p = .006$**	—	−1.36 (0.93), $p = .14$	**−1.33 (0.52), $p = .010$**	−0.51 (1.71), $p = .76$
Verbal Fluency	−0.11 (1.72), $p = .95$	**0.95 (0.44), $p = .032$**	—	0.73 (0.83), $p = .38$	0.89 (0.46), $p = .055$	0.86 (1.52), $p = .57$
Vocabulary	−0.36 (0.65), $p = .58$	−0.08 (0.17), $p = .65$	—	**0.87 (0.31), $p = .006$**	−0.03 (0.17), $p = .87$	−0.62 (0.58), $p = .29$
Logical Memory	−1.76 (1.15), $p = .12$	**−0.70 (0.29), $p = .017$**	—	−0.92 (0.55), $p = .10$	**−0.77 (0.31), $p = .012$**	0.86 (1.01), $p = .40$

APOE = apolipoprotein E.

Significant effects appear in bold typeface. Dash in cell indicates interactions effect not shown because of insufficient sample size.

the exclusion of bipolar cases, whereas for digit symbol, a GHQ × *APOE* e3e4 interaction effect became significant ($p = .04$) such that the correlation between GHQ and digit symbol was larger in the *APOE* e3e4 group (−0.08) compared with the *APOE* e3 homozygote reference group (−0.05). All other effects were unchanged.

DISCUSSION

The present study found no strong evidence to support a synergistic effect of depression or psychological distress symptoms and *APOE* on four diverse cognitive domains measured in adults aged 18 to 59 years and 60 to 94 years. The comparison of current versus lifetime depression main effects on cognitive performance revealed differences across varying cognitive tasks, with only digit symbol showing a consistent main decrement effect across current and lifetime depression states in the 18- to 59-year-old sample. The main effects of *APOE* are the same as those reported in this sample by Marioni and colleagues (23) despite using a slightly different age group split and set of confounding covariates. Our main findings held on excluding cases with bipolar disorder.

The first important finding to emerge from our analysis was the absence of an association between *APOE* e4 variation and depression. Some previous studies focusing on elderly cohorts have reported a higher frequency of *APOE* e4 alleles in those with depression (33–35). However, these studies have been limited particularly by their small sample size. For example, Rigaud et al. (34) reported an association between *APOE* e4 status and late-life (but not early-life) depression in a late-life depressed sample of only 23 participants. In addition, depression screening questionnaires rather than clinical instruments have been used (e.g., Ref. (35)). Other studies report an absence of an association (e.g., Refs. 36–38), but these, too, have used very small cohorts (e.g., $n = 22$ depressed participants). In the largest previous study, Rajan et al. (8) did not find an association between *APOE* e4 status and depressive symptoms in a sample 65 years and older ($n = 4150$). Our study of adults aged 60 to 94 years uses a comparable sample size and replicates this null association using depression diagnoses rather than symptoms; furthermore, we confirm this null association in the largest sample to date to test this association in younger adults. The most reliable evidence, then, suggests that *APOE* does not directly affect depressive symptoms or clinical states.

Second, we found that digit symbol was the only test affected by both current and lifetime occurrence of depression (in the 18- to 59-year-old group), with performance poorer in depressed adults. Currently depressed older adults also showed worse digit symbol scores than did nondepressed older adults. Psychomotor slowing has been argued to be a defining feature of melancholia (39), so currently,

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TABLE 4. Main and Interaction Effects (Unstandardized Regression Coefficients and Standard Errors) for Associations Between Depression and *APOE* Genotype With Cognitive Function Measures, Separately for Adults Aged 18–59 and 60–94 Years

	Current Depression				Lifetime Depression			
	Depression		*APOE* Genotype	Depression × *APOE* Genotype	Depression		*APOE* Genotype	Depression × *APOE* Genotype
Adults aged 18–59 y								
Digit Symbol	**−3.25 (0.89), $p < .001$**	e2e2	−1.06 (1.53), $p = .49$	—	**−1.00 (0.46), $p = .029$**	e2e2	−0.76 (1.67), $p = .65$	—
		e2e3	0.62 (0.39), $p = .11$	3.14 (2.19), $p = .15$		e2e3	0.68 (0.41), $p = .10$	−0.44 (1.15), $p = .70$
		e2e4	−0.47 (0.82), $p = .57$	—		e2e4	0.06 (0.87), $p = .95$	−3.93 (2.41), $p = .10$
		e3e4	0.14 (0.30), $p = .65$	−1.30 (1.72), $p = .45$		e3e4	0.22 (0.31), $p = .49$	−0.70 (0.87), $p = .42$
		e4e4	−0.85 (0.76), $p = .27$	—		e4e4	−0.70 (0.81), $p = .39$	−1.28 (2.26), $p = .57$
Verbal Fluency	−0.30 (0.70), $p = .67$	e2e2	−0.76 (1.21), $p = .53$	—	**1.05 (0.36), $p = .004$**	e2e2	−0.80 (1.32), $p = .55$	—
		e2e3	−0.08 (0.31), $p = .79$	1.27 (1.73), $p = .46$		e2e3	−0.07 (0.33), $p = .83$	−0.02 (0.90), $p = .98$
		e2e4	−0.96 (0.65), $p = .14$	—		e2e4	−0.74 (0.69), $p = .28$	−1.86 (1.89), $p = .32$
		e3e4	**0.66 (0.23), $p = .005$**	0.08 (1.36), $p = .95$		e3e4	**0.70 (0.25), $p = .005$**	−0.17 (0.69), $p = .80$
		e4e4	0.42 (0.60), $p = .48$	—		e4e4	0.42 (0.64), $p = .51$	0.31 (1.78), $p = .86$
Vocabulary	−0.42 (0.25), $p = .093$[a]	e2e2	−0.43 (0.44), $p = .33$	—	**0.38 (0.13), $p = .003$**	e2e2	−0.72 (0.47), $p = .13$	—
		e2e3	−0.01 (0.11), $p = .90$	0.74 (0.61), $p = .23$		e2e3	0.00 (0.12), $p = .94$	−0.02 (0.32), $p = .95$
		e2e4	0.34 (0.23), $p = .14$	—		e2e4	0.41 (0.25), $p = .093$	−0.48 (0.67), $p = .48$
		e3e4	0.12 (0.08), $p = .16$	0.34 (0.49), $p = .48$		e3e4	0.09 (0.09), $p = .29$	0.16 (0.24), $p = .51$
		e4e4	0.07 (0.22), $p = .74$	—		e4e4	−0.04 (0.23), $p = .86$	1.11 (0.63), $p = .079$
Logical Memory	**−1.37 (0.47), $p = .004$**	e2e2	−0.51 (0.82), $p = .53$	—	−0.01 (0.25), $p = .97$	e2e2	−0.76 (0.89), $p = .40$	—
		e2e3	−0.35 (0.21), $p = .091$	1.46 (1.18), $p = .22$		e2e3	−0.36 (0.22), $p = .11$	0.14 (0.61), $p = .82$
		e2e4	−0.12 (0.44), $p = .79$	—		e2e4	−0.14 (0.47), $p = .77$	0.16 (1.29), $p = .90$
		e3e4	−0.02 (0.16), $p = .88$	0.62 (0.92), $p = .50$		e3e4	−0.03 (0.17), $p = .88$	0.02 (0.47), $p = .97$
		e4e4	−0.72 (0.41), $p = .076$	—		e4e4	−0.61 (0.43), $p = .16$	−0.99 (1.22), $p = .42$
Adults aged 60–94 y								
Digit Symbol	**−4.92 (1.94), $p = .005$**	e2e2	−1.44 (3), $p = .63$	—	−0.82 (1.00), $p = .41$	e2e2	−1.98 (3.36), $p = .56$	—
		e2e3	0.57 (0.67), $p = .39$			e2e3	0.76 (0.70), $p = .28$	−3.84 (2.69), $p = .15$
		e2e4	−0.60 (1.4), $p = .67$			e2e4	−0.72 (1.47), $p = .62$	—

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		e3e4	**−1.11 (0.54), *p* = .040**			e3e4	−1.01 (0.57), *p* = .076	−1.00 (1.86), *p* = .59
		e4e4	**−3.62 (1.46), *p* = .008**			e4e4	**−3.71 (1.53), *p* = .015**	—
Verbal Fluency	−0.06 (1.72), *p* = .97	e2e2	−1.72 (2.68), *p* = .52	—	0.95 (0.89), *p* = .29	e2e2	−2.07 (2.99), *p* = .49	—
		e2e3	−0.52 (0.60), *p* = .39			e2e3	−0.45 (0.63), *p* = .47	−1.33 (2.40), *p* = .58
		e2e4	0.06 (1.25), *p* = .96			e2e4	−0.14 (1.32), *p* = .91	—
		e3e4	.68 (0.48), *p* = .16			e3e4	0.62 (0.51), *p* = .22	0.94 (1.65), *p* = .57
		e4e4	**3.35 (1.31), *p* = .015**			e4e4	**3.51 (1.36), *p* = .010**	—
Vocabulary	−0.36 (0.65), *p* = .58	e2e2	0.65 (1.01), *p* = .52	—	**0.70 (0.34), *p* = .040**[b]	e2e2	0.37 (1.13), *p* = .74	—
		e2e3	0.06 (0.23), *p* = .80			e2e3	0.01 (0.24), *p* = .96	1.04 (0.91), *p* = .25
		e2e4	−0.27 (0.48), *p* = .57			e2e4	.13 (0.50), *p* = .79	—
		e3e4	−0.06 (0.18), *p* = .76			e3e4	−0.07 (0.19), *p* = .72	−0.01 (0.63), *p* = .98
		e4e4	0.11 (0.50), *p* = .82			e4e4	0.20 (0.52), *p* = .69	—
Logical Memory	−1.76 (1.15), *p* = .12	e2e2	0.61 (1.79), *p* = .73	—	−1.09 (0.60), *p* = .067	e2e2	0.50 (2.00), *p* = .80	—
		e2e3	−0.56 (0.40), *p* = .16			e2e3	−0.63 (0.42), *p* = .13	1.10 (1.60), *p* = .49
		e2e4	−1.13 (0.83), *p* = .18			e2e4	−1.18 (0.87), *p* = .17	—
		e3e4	−0.62 (0.32), *p* = .051			e3e4	**−0.68 (0.34), *p* = .045**	0.65 (1.10), *p* = .55
		e4e4	**−2.12 (0.87), *p* = .012**			e4e4	**−2.43 (0.91), *p* = .007**	—

APOE = apolipoprotein E.

Significant effects appear in bold typeface. Dash in cell indicates interactions effect not shown because of insufficient sample size.

[a] Excluding bipolar cases: $\beta = -0.56$ (0.26), $p = .031$.

[b] Excluding bipolar cases: $\beta = 0.66$ (0.34), $p = .051$.

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TABLE 5. Main and Interaction Effects (Unstandardized Regression Coefficients and Standard Errors) for GHQ and *APOE* (e4 Status and Genotype) on Cognitive Test Scores, Separately for Adults Aged 18–59 and 60–94 Years

	APOE e4 Status			APOE Genotype			
	GHQ	*APOE* e4	GHQ × *APOE*	GHQ	*APOE* Genotype		GHQ × *APOE*
Adults aged 18–59 y							
Digit Symbol	**−0.19 (0.03), *p* < .001**	0.14 (0.31), *p* = .64	.18 (0.06), *p* = .18	**−0.19 (0.04), *p* < .001**	e2e2	0.12 (1.89), *p* = .95	−0.43 (0.40), *p* = .28
					e2e3	0.72 (0.45), *p* = .11	−0.01 (0.09), *p* = .94
					e2e4	−0.36 (0.95), *p* = .70	0.07 (0.19), *p* = .70
					e3e4	0.43 (0.34), *p* = .20	−0.12 (0.07), *p* = .067[a]
					e4e4	−0.83 (0.87), *p* = .34	0.08 (0.15), *p* = .60
Verbal Fluency	−0.01 (0.03), *p* = .79	**0.60 (0.25), *p* = .015**	−0.02 (0.05), *p* = .64	−0.02 (0.03), *p* = .53	e2e2	−0.57 (1.49), *p* = .70	−0.14 (0.31), *p* = .66
					e2e3	−0.29 (0.35), *p* = .41	0.08 (0.07), *p* = .29
					e2e4	−0.71 (0.75), *p* = .34	−0.08 (0.15), *p* = .61
					e3e4	**0.70 (0.27), *p* = .008**	−0.01 (0.05), *p* = .80
					e4e4	0.19 (0.69), *p* = .78	0.05 (0.12), *p* = .66
Vocabulary	−0.01 (0.01), *p* = .12	**0.18 (0.09), *p* = .042**	−0.02 (0.05), *p* = .64	−0.02 (0.01), *p* = .090	e2e2	−0.78 (0.54), *p* = .15	0.14 (0.11), *p* = .22
					e2e3	−0.03 (0.13), *p* = .80	0.01 (0.03), *p* = .61
					e2e4	0.47 (0.27), *p* = .080	−0.01 (0.05), *p* = .81
					e3e4	0.15 (0.10), *p* = .11	−0.02 (0.02), *p* = .37
					e4e4	0.07 (0.25), *p* = .78	0.00 (0.04), *p* = .98
Logical Memory	**−0.06 (0.02), *p* < .001**	0.14 (0.16), *p* = .38	**−0.07 (0.03), *p* = .044**[a]	**−0.07 (0.02), *p* < .001**	e2e2	−0.39 (1.01), *p* = .70	0.05 (0.21), *p* = .81
					e2e3	−0.34 (0.24), *p* = .15	0.02 (0.05), *p* = .75
					e2e4	0.27 (0.51), *p* = .59	−0.15 (0.10), *p* = .15
					e3e4	0.11 (0.18), *p* = .55	−0.05 (0.04), *p* = .20
					e4e4	−0.37 (0.46), *p* = .43	−0.11 (0.08), *p* = .17
Adults aged 60–94 y							
Digit Symbol	**−0.44 (0.07), *p* < .001**	**−1.47 (0.55), *p* = .008**	0.10 (0.15), *p* = .50	**−0.45 (0.08), *p* < .001**	e2e2	−2.31 (3.25), *p* = .48	0.68 (1.86), *p* = .71
					e2e3	0.45 (0.75), *p* = .55	0.04 (0.19), *p* = .85
					e2e4	−1.70 (1.59), *p* = .29	0.74 (0.68), *p* = .28
					e3e4	−1.06 (0.61), *p* = .080	0.02 (0.16), *p* = .91
					e4e4	**−5.26 (1.71), *p* = .002**	**1.13 (0.55), *p* = .040**

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Verbal Fluency	−0.07 (0.07), $p = .32$	**0.97 (0.49), $p = .050$**	0.02 (0.13), $p = .88$	−0.06 (0.07), $p = .43$	e2e2	−3.11 (2.90), $p = .28$	2.02 (1.64), $p = .22$
					e2e3	−0.48 (0.66), $p = .47$	−0.06 (0.17), $p = .71$
					e2e4	−0.72 (1.42), $p = .61$	0.65 (0.61), $p = .29$
					e3e4	0.83 (0.54), $p = .12$	−0.06 (0.14), $p = .69$
					e4e4	2.48 (1.53), $p = .10$	0.67 (0.49), $p = .17$
Vocabulary	−0.04 (0.02), $p = .091$	−0.09 (0.19), $p = .64$	0.02 (0.05), $p = .65$	**−0.06 (0.03), $p = .045$**	e2e2	0.69 (1.10), $p = .53$	−0.11 (0.62), $p = .86$
					e2e3	−0.11 (0.25), $p = .66$	0.08 (0.06), $p = .24$
					e2e4	−0.16 (0.55), $p = .77$	−0.09 (0.23), $p = .71$
					e3e4	−0.08 (0.21), $p = .68$	0.03 (0.05), $p = .57$
					e4e4	−0.21 (0.58), $p = .72$	0.18 (0.18), $p = .33$
Logical Memory	−0.08 (0.04), $p = .076$	**−0.71 (0.33), $p = .030$**	−0.01 (0.09), $p = .93$	−0.07 (0.05), $p = .16$	e2e2	0.51 (1.94), $p = .79$	−0.02 (1.11), $p = .98$
					e2e3	−0.49 (0.44), $p = .27$	−0.05 (0.11), $p = .65$
					e2e4	−1.06 (0.96), $p = .27$	0.00 (0.41), $p = .99$
					e3e4	−0.59 (0.36), $p = .10$	−0.03 (0.10), $p = .72$
					e4e4	**−2.56 (1.02), $p = .012$**	0.17 (0.33), $p = .61$

GHQ = General Health Questionnaire; APOE = apolipoprotein E.

Significant effects appear in bold typeface.

[a] Excluding bipolar cases: $\beta = -0.14$ (0.07), $p = .041$.

[b] Excluding bipolar cases: $\beta = -0.06$ (0.03), $p = .061$.

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depressed individuals would be expected to show worse performance on digit symbol. However, the finding in the younger group that those with lifetime depression also show deficits indicates that the biological pathway underlying depression might be constantly impaired. The source of this impairment might stem from differences in brain structure or plasticity of depressed individuals (40,41) or might represent a stable trait, like neuroticism, that is associated with mood states, but does not moderate the relationship between depression and perceptual speed in the elderly (42). The strong genetic correlation between digit symbol performance with both bipolar (43) and major depressive (L. Hall, personal communication) disorders further supports a more enduring biological basis underlying their covariation. The absence of a lifetime occurrence of depression main effect on digit symbol in the 60- to 94-year-old group suggests that this lasting relationship might break down during the aging process. Alternatively, the older aged sample could be underpowered to detect such effects if they are weaker for individuals in a euthymic versus currently depressed phase.

The only other cognitive test negatively associated with depression (current only) was logical memory in the 18- to 59-year-old group. In the 60- to 94-year-old group, this effect was of the same magnitude and, with a larger sample, may have reached significance. Lifetime depression conferred positive effects on verbal fluency and vocabulary (both significant in the younger group and vocabulary significant in the older group). Meta-analysis has shown enhanced verbal compared with performance IQ in people with affective disorders (44), with a small number of studies documenting superior verbal abilities in depressed individuals compared with controls (45,46). More recent and much larger studies show a relationship between very high general intelligence and bipolar disorder (47), although results for unipolar depression are mixed (48,49). Unlike ours, these latter studies did not separate verbal and performance abilities, and this may account for discrepancies in their findings if the general cognitive ability measure is differentially biased toward either verbal or performance subtests. The negative associations between depression and verbal abilities (e.g., Ref. (12)) previously reported are for measures of current depression, which align with our, albeit nonsignificant, results for current depression and GHQ.

With regard to *APOE* main effects, these have been reported previously in this sample (23). Briefly, we confirm Wisdom and colleagues' (3) meta-analysis result that *APOE* e4 allele carriers (particularly e4 homozygotes) have worse performance on episodic memory and perceptual speed tasks, but only in adults aged 60 to 94 years. Vocabulary is a cognitive domain typically spared by the aging process (50), and accordingly, we found no *APOE* effects for this trait. Surprisingly, carriers of the *APOE* e3e4 genotype in the 18- to 59-year-old group and carriers of the e4e4 genotype in the 60- to 94-year-old group demonstrated superior performance on verbal fluency. In the GS:SFHS, verbal fluency scores, like vocabulary scores, are quite resilient to aging effects (23), so it might be that these abilities involve biological pathways that are spared from *APOE*'s negative effects. Moreover, deficits to memory and speed caused by *APOE* might force individuals to compensate by drawing on alternative neural resources that consequently improves their main associated functions.

Depression did not interact with *APOE* to affect cognitive performance, and the interactions identified for current psychological distress (a more powerful analysis which can be considered a proxy for current depression) were likely to represent Type 1 error given their marginal significance level uncorrected for multiple testing. Because such an effect has been demonstrated for cognitive decline (7,8) in studies sufficiently powered to compare *APOE* e4 presence versus absence, one must ask why the interaction exists for cognitive decline but not for stable cognitive ability. Although childhood IQ predicts a large amount of variance in IQ measured later in life (~50%) (51), it explains substantially less in cognitive change as people age. For instance, Gow et al. (52) estimated that age 11 IQ predicted only 1.4% of variance in cognitive change between the years of 79 and 83. A similar estimate was found in a larger cohort for memory and speed decline between the years of 43 and 53 (53). Given the high statistical power of our study, particularly for the lifetime depression and *APOE* e4 status analysis, our results then suggest that this synergistic effect of depression and *APOE* only operates on cognitive decline and not on stable cognition. In seeking an explanation for the cause of this interaction effect, one must focus then on those biological processes that are especially susceptible to change with aging; these might include the development of white matter hyperintensities (54), atrophy of the brain and other neural changes (55), changing levels of soluble and insoluble amyloid-β peptides (56), and changes in immune activity and inflammatory responses (57). These pathways have been implicated in both depression and *APOE*/AD studies (58–60).

In summary, our study of an ethnically homogeneous population (99% of the depressed participants were self-reported white) found a) no association between depression diagnosis and *APOE* variation; b) differences between current depression and lifetime depression effects on cognitive abilities, including positive effects on verbal tests for lifetime depression; and c) no depression by *APOE* interaction effect on cognitive ability, suggesting that this effect is only relevant to cognitive decline (as shown by others) and not the predominantly stable cognitive abilities, which we were limited to measure here. Longitudinal assessments of this cohort are needed to establish this possibility.

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