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

Michelle Luciano, PhD, Ana Maria Fernández Pujals, MSc, Riccardo E. Marioni, PhD, Archie Campbell, MA, Caroline Hayward, PhD, Donald J. MacIntyre, MBchB, David J. Porteous, PhD, Andrew M. McIntosh, MD, and Ian J. Deary, PhD, for the Generation Scotland Investigators

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
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 heightening 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
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 18–59-year-old group (14–15 years) compared with the 60–94-year-old group (12–13 years). GS:SFHS ethical approval was granted by the NHS Tayside Committee (14 years) 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 e4e3 as the reference group). Further analyses were performed replacing depression status with continuous scores from the GHQ; these results were expected to mimic those for 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. $\chi^2$ 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 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 e4e3 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).

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 e4e3 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. $\chi^2$ 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
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

| 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 presence | e4 presence | e4 presence | e4 presence | e4 presence | e4 presence | e4 presence |
| $-e4$ | 299 | 10,051 | 1255 | 8796 | 38 | 2845 | 234 | 2611 |
| $+e4$ | 107 | 3922 | 460 | 3462 | 11 | 1050 | 97 | 953 |
| Genotype | Genotype | Genotype | Genotype | Genotype | Genotype | Genotype | 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. | APOE = apolipoprotein E. | APOE = apolipoprotein E. | APOE = apolipoprotein E. | APOE = apolipoprotein E. | APOE = apolipoprotein E. | APOE = apolipoprotein E. | APOE = apolipoprotein E. |
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

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

| Predictor variables         | Adults Aged 18–59 y \((n = 14,379)\) | Adults Aged 60–94 y \((n = 3944)\) |
|----------------------------|--------------------------------------|-----------------------------------|
| **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** | 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/m²**             | 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**| 4970                                | 1897                              |
| 0                          | 2147                                | 461                               |
| 1                          | 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.

\(n = 14,279\) in younger adults; \(n = 3913\) in older adults.

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
### 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

| Depression | APOE e4 | Depression × APOE |
|------------|---------|------------------|
| Current | Lifetime | Current | Lifetime |
| Digit Symbol | −2.76 (0.81) | −1.17 (1.38) | −1.09 (0.42) | −1.17 (1.25) | 0.94 (0.33) | −1.04 (0.12) | −1.04 (0.08) | 0.12 (0.03) | −0.11 (0.15) |
| Verbal Fluency | 0.13 (0.64) | 0.24 (1.45) | 0.14 (0.45) | 0.09 (0.46) | 0.12 (0.08) | 0.18 (0.22) | 0.18 (0.22) | 0.18 (0.22) |
| Vocabulary | −0.29 (0.33) | 0.03 (0.22) | −0.08 (0.27) | 0.08 (0.27) | −0.27 (0.22) | 0.18 (0.22) | 0.18 (0.22) | 0.18 (0.22) |
| Logical Memory | −1.07 (0.43) | −0.03 (0.15) | −1.36 (0.43) | −0.39 (0.33) | 0.73 (0.83) | 0.87 (0.31) | 0.87 (0.31) | 0.87 (0.31) |
| Logical Memory | −1.07 (0.43) | −0.03 (0.15) | −1.76 (1.13) | −0.86 (0.44) | −0.51 (1.72) | −0.27 (0.35) | −0.27 (0.35) | −0.27 (0.35) |
| Logical Memory | −1.07 (0.43) | −0.03 (0.15) | −1.76 (1.13) | −0.86 (0.44) | −0.51 (1.72) | −0.27 (0.35) | −0.27 (0.35) | −0.27 (0.35) |

| APOE e4 Status | APOE e3e4 Interaction |
|----------------|-----------------------|
| Current Depression | −0.08 (0.13) | −0.11 (0.15) |
| Lifetime Depression | 0.03 (0.22) | 0.12 (0.08) |

The exclusion of bipolar cases, whereas for digit symbol, a GHQ × APOE e3e4 interaction effect became significant (p = 0.04) 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,
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

| Gene × Cognitive Function | Current Depression | Lifetime Depression |
|---------------------------|--------------------|---------------------|
| APOE Genotype             | Depression         | APOE Genotype       | Depression | APOE Genotype | Depression |
| e2e2                      | −3.25 (0.89), p < .001 | e2e2 −1.06 (1.53), p = .49 | −1.00 (0.46), p = .029 |
| 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 |
| e2e3                      | −0.08 (0.31), p = .79 | 1.27 (1.73), p = .46 | e2e2 −0.80 (1.32), p = .55 | — |
| 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 | e2e2 −0.43 (0.44), p = .33 | — | **0.38 (0.13), p = .003** |
| 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 |
| e2e3                      | −0.35 (0.21), p = .091 | 1.46 (1.18), p = .22 | e2e2 −0.76 (0.89), p = .40 | — |
| 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 |
| 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 | — |
|                          |          |          |          |          |          |          |
|--------------------------|----------|----------|----------|----------|----------|----------|
|                          | e3e4     | e4e4     | e3e4     | e4e4     | e3e4     | e4e4     |
| Verbal Fluency           | -1.11 (0.54), \(p = .040\) | -3.62 (1.46), \(p = .008\) | -1.01 (0.57), \(p = .076\) | -1.00 (1.86), \(p = .59\) | -3.71 (1.53), \(p = .015\) |
|                          | e3e4     | e4e4     | e3e4     | e4e4     | e3e4     | e4e4     |
|                          | -0.06 (1.72), \(p = .97\) | -1.72 (2.68), \(p = .52\) | 0.95 (0.89), \(p = .29\) | -2.07 (2.99), \(p = .49\) |
|                          | e2e2     | e2e3     | e2e4     | e3e4     | e2e4     | e3e4     |
|                          | 0.06 (1.25), \(p = .96\) | -0.52 (0.60), \(p = .39\) | 0.68 (0.48), \(p = .16\) | 0.62 (0.51), \(p = .22\) | 1.33 (2.40), \(p = .58\) |
|                          | e4e4     | e2e2     | e2e3     | e2e4     | e4e4     | e4e4     |
|                          | 3.35 (1.31), \(p = .015\) | 0.65 (1.01), \(p = .52\) | 0.37 (1.13), \(p = .74\) | 0.86 (1.25), \(p = .60\) | 3.51 (1.36), \(p = .001\) |
| Vocabulary               | -0.36 (0.65), \(p = .58\) | -0.56 (0.23), \(p = .80\) | 0.01 (0.24), \(p = .96\) | 1.04 (0.91), \(p = .25\) | 0.66 (0.34), \(p = .045\) |
|                          | e2e2     | e2e4     | e2e3     | e3e4     | e2e4     | e3e4     |
|                          | 0.66 (1.01), \(p = .52\) | 0.11 (0.50), \(p = .82\) | -0.07 (0.19), \(p = .72\) | 0.20 (0.52), \(p = .69\) |
|                          | e3e4     | e4e4     | e4e4     | e2e4     | e4e4     | e4e4     |
|                          | 0.61 (1.79), \(p = .73\) | 0.62 (0.32), \(p = .051\) | -0.68 (0.34), \(p = .045\) | -1.13 (0.83), \(p = .18\) |
| Logical Memory           | -1.76 (1.15), \(p = .12\) | -0.56 (0.40), \(p = .16\) | -0.63 (0.42), \(p = .13\) | -1.18 (0.87), \(p = .17\) |
|                          | e2e2     | e2e3     | e2e4     | e3e4     | e2e4     | e3e4     |
|                          | 0.50 (2.00), \(p = .80\) | -0.62 (0.32), \(p = .051\) | 0.65 (1.10), \(p = .55\) | 0.87 (0.50), \(p = .96\) |

$\text{APOE} = \text{apolipoprotein E.}$

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: $\beta = 0.66 (0.34), p = .051$. 
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 | GHQ | APOE e4 | GHQ × APOE | APOE Genotype | GHQ | APOE Genotype | GHQ × APOE |
|----------------|-----|---------|------------|---------------|-----|---------------|------------|
| Adults aged 18–59 y |     |         |            |               |     |               |            |
| Digit Symbol      | -0.19 (0.03), p < .001 | 0.14 (0.31), p = .64 | 0.18 (0.06), p = .18 | -0.19 (0.04), p < .001 | e2e2 | 0.12 (1.89), p = .95 | -0.43 (0.40), p = .28 |
| 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 | e2e4 | -0.57 (1.49), p = .70 | -0.14 (0.31), 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 | e2e4 | 0.19 (0.69), p = .78 | 0.05 (0.12), p = .66 |
| Logical Memory    | -0.06 (0.02), p < .001 | 0.14 (0.16), p = .38 | -0.07 (0.03), p = .044 | -0.07 (0.02), p < .001 | e2e2 | -0.39 (1.01), p = .70 | 0.05 (0.21), p = .81 |
| 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 |

Note: Boldface indicates statistical significance.
| Function          | β      | p    | β      | p    | β      | p    | β      | p    |
|-------------------|--------|------|--------|------|--------|------|--------|------|
| **Verbal Fluency**| -0.07  | .32  | 0.97   | .050 | 0.02   | .88  | -0.06  | .43  |
|                   |        |      |        |      |        |      |        |      |
|                   | e2e2   | -3.11| .28    | 2.02 | e2e3   | -0.48| .47    | -0.06|
|                   |        |      |        |      |        |      |        |      |
|                   | e2e4   | -0.72| .61    | 0.65 | e3e4   | 0.83 | .12    | -0.06|
|                   |        |      |        |      |        |      |        |      |
|                   | e3e4   | 0.03 | .13    | 0.49 | e4e4   | 2.48 | .10    | 0.67 |
|                   |        |      |        |      |        |      |        |      |
| **Vocabulary**    | -0.04  | .091 | -0.09  | .64  | 0.02   | .65  | -0.06  | .045 |
|                   |        |      |        |      |        |      |        |      |
|                   | e2e2   | 0.69 | .53    | -0.11| e2e3   | -0.11| .66    | 0.08 |
|                   |        |      |        |      |        |      |        |      |
|                   | e2e4   | -0.16| .77    | -0.09| e3e4   | -0.08| .68    | 0.03 |
|                   |        |      |        |      |        |      |        |      |
|                   | e3e4   | -0.21| .72    | 0.18 | e4e4   | -0.21| .52    | 0.18 |
|                   |        |      |        |      |        |      |        |      |
| **Logical Memory**| -0.08  | .076 | -0.71  | .030 | -0.01  | .93  | -0.07  | .16  |
|                   |        |      |        |      |        |      |        |      |
|                   | e2e2   | 0.51 | .79    | -0.02| e2e3   | -0.49| .27    | -0.05|
|                   |        |      |        |      |        |      |        |      |
|                   | e2e4   | -1.06| .27    | 0.00 | e3e4   | -0.59| .10    | -0.03|
|                   |        |      |        |      |        |      |        |      |
|                   | e4e4   | -2.56| .012   | 0.17 |        |      |        |      |

GHQ = General Health Questionnaire; APOE = apolipoprotein E.

Significant effects appear in bold typeface.

* Excluding bipolar cases: $\beta = -0.14 (0.07), p = .041$.
* Excluding bipolar cases: $\beta = -0.06 (0.03), p = .061$. 
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 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.
We thank all the families who took part, the general practitioners and the Scottish School of Primary Care for their help in recruiting them, and the whole GS:SFHS team, including interviewers, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, receptionists, health care assistants, and nurses.

Source of Funding and Conflicts of Interest: GS:SFHS has received core funding from the Chief Scientist Office of the Scottish Government Health Directorates C2D/16/6 and the Scottish Funding Council HR03006. Genotyping was carried out by the Genetics Core Laboratory at the Wellcome Trust Clinical Research Facility, Edinburgh, Scotland, and was funded by the UK Medical Research Council (MRC). D.J.M. is supported by an NHS Research Scotland Career Fellowship, funded by the Chief Scientist Office. The Quantitative Trait Locus team at the Human Genetics Unit is funded by the MRC. M.L., R.E.M., D.J.P. and I.J.D. undertook the work within The University of Edinburgh Centre for Cognitive Ageing and Cognitive Epidemiology (MR/K026992/1), part of the cross council Lifelong Health and Wellbeing Initiative. Funding from the BBSRC and MRC is gratefully acknowledged. The authors have no conflicts of interest to declare.

REFERENCES

1. McDermott LM, Ebmeier KP. A meta-analysis of depression severity and cognitive function. J Affect Disord 2009;119:1–8.
2. Rabbitt P, Donlan C, Watson P, McInnes L, Bent N. Unique and interactive effects of depression, age, socioeconomic advantage, and gender on cognitive performance of normal healthy older people. Psychol Aging 1995;10:307–13.
3. Wisdom NM, Callahan JL, Hawkins KA. The effects of apolipoprotein E on non-impaired cognitive functioning: a meta-analysis. Neurobiol Aging 2011;32:63–74.
4. Payami H, Grimsli H, Oken B, Camicioli R, Sexton G, Dame A, Howieson D, Kaye J. A prospective study of cognitive health in the elderly (Oregon Brain Aging Study): effects of family history and apolipoprotein E genotype. Am J Hum Genet 1997;60:948–56.
5. Brayne C, Harrington CR, Wischik CM, Huppert FA, Chi LY, Xuereb JH, O’Connor DW, Paykel ES. Apolipoprotein E genotype in the prediction of cognitive decline and dementia in a prospectively studied elderly population. Dementia 1996;7:169–74.
6. Schiepers OJ, Harris SE, Gow AJ, Batty G, Starr JM, Deary IJ. APOE4 status predicts age-related cognitive decline in the ninth decade: longitudinal follow-up of the Lothian Birth Cohort 1921. Mol Psychiatry 2012;17:315–24.
7. Consentino EA, Sawyer K, Sachs-Eliasson N, Blazer DG. Depressive symptoms moderate the influence of the apolipoprotein epsilon4 allele on cognitive decline in a sample of community dwelling older adults. Am J Geriatr Psychiatry 2009;17:155–65.
8. Rajan KB, Wilson RS, Sarupski KA, Mendes de Leon CF, Evans DA. Gene-behavior interaction of depressive symptoms and the apolipoprotein E {epsilon}4 allele on cognitive decline. Psychosom Med 2014;76:101–8.
9. Austin MP, Mitchell P, Goodwin GM. Cognitive deficits in depression: possible implications for functional neuropsychology. Br J Psychiatry 2001;178:200–6.
10. Castaneda AE, Tuulio-Henriksson A, Marttunen M, Suvisaari J, Lonnqvist J. A review on cognitive impairments in depressive and anxiety disorders with a focus on young adults. J Affect Disord 2008;106:1–27.
11. Goodwin GM. Neuropsychological and neuroimaging evidence for the involvement of the frontal lobes in depression. J Psychopharmacol 1997;11:115–22.
12. Pantzar A, Laukka EJ, Atti AR, Fastbom J, Fratiglioni L, Backman L. Cognitive deficits in unipolar old-age depression: a population-based study. Psychol Med 2014;44:937–47.
13. Hasselbalch BJ, Knott U, Kessing LV. Cognitive impairment in the remitted state of unipolar depressive disorder: a systematic review. J Affect Disord 2011;134:20–31.
14. Neu P, Bajbouj M, Schilling A, Godemann F, Berman RM, Schlattmann P. Cognitive function over the treatment course of depression in middle-aged patients: correlation with brain MRI signal hyperintensities. J Psychiatr Res 2005;39:129–35.
15. Reppermund S, Ising M, Lucea S, Zihl J. Cognitive impairment in unipolar depression is persistent and non-specific: further evidence for the final common pathway disorder hypothesis. Psychol Med 2009;39:603–14.
16. Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW, Roses AD, Haines JL, Pericak-Vance MA. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer’s disease in late onset families. Science 1993;261:921–3.
17. Savitz J, Solms M, Ramesar R. Apolipoprotein E variants and cognition in healthy individuals: a critical opinion. Brain Res Rev 2006;51:125–35.
18. Lind J, Larsson A, Persson J, Ingvar M, Nilsson LG, Backman L, Adolfsson R, Cruts M, Sleegers K, Van Broeckhoven C, Nyberg L. Reduced hippocampal volume in non-demented carriers of the apolipoprotein E epsilon4: reflection to chronological age and recognition memory. Neurosci Lett 2006;396:23–7.
19. Steffens DC, McQuoid DR, Payne ME, Potter G. Change in hippocampal volume on magnetic resonance imaging and cognitive decline among older depressed and nondepressed subjects in the neurocognitive outcomes of depression in the elderly study. Am J Geriatr Psychiatry 2011;19:4–12.
20. Shu H, Yuan Y, Xie C, Bai F, You J, Li L, Li SJ, Zhang Z. Imbalanced hippocampal functional networks associated with remitted geriatric depression and apolipoprotein E epsilon4 allele in nondemented elderly: a preliminary study. J Affect Disord 2014;164:5–13.
21. Niti M, Yap KB, Kua EH, Ng TP. APOE-epsilon4, depressive symptoms, and cognitive decline in Chinese older adults: Singapore Longitudinal Aging Studies. J Gerontol A Biol Sci Med Sci 2009;64:306–11.
22. Pedersen CB, Mors O, Bertelsen A, Waltoft BL, Agerbo E, McGrath JJ, Mortensen PB, Eaton WW. A comprehensive nationwide study of the incidence rate and lifetime risk for depression by APOE Interaction on Cognition

Vol. 77 - 480-492

April 2015

Copyright © 2015 by the American Psychosomatic Society. Unauthorized reproduction of this article is prohibited.
25. Kerr SM, Campbell A, Murphy L, Hayward C, Jackson C, Wain LV, Tobin MD, Dominiczak A, Morris A, Smith BH, Porteous DJ. Pedigree and genotyping quality analyses of over 10,000 DNA samples from the Generation Scotland: Scottish Family Health Study. BMC Med Genet 2013;14:38.

26. Goldberg D. General Health Questionnaire. Windsor: NFER Publishing Company; 1978.

27. Wechsler D. WAIS-III Weschler Adult Intelligence Scale. San Antonio, TX: Psychological Corporation; 1997.

28. Wechsler D. WMS-IIIUK Administration and Scoring Manual. London, UK: Psychological Corporation; 1998.

29. Raven JC, Court JH, Raven J. Manual for Raven's Progressive Matrices and Vocabulary Scales. H. K. Lewis: London, UK: H. K. Lewis; 1977.

30. R Development Core Team. R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing; 2008.

31. Butler DG, Cullis BR, Gilmour AR, Gogel BJ. ASReml-R Reference Manual. Brisbane, Australia: Queensland Department of Primary Industries and Fisheries; 2009.

32. Krishnan KR, Tupler LA, Ritchie J Jr, McDonald WM, Knight DL, Nemeroff CB, Carroll BJ. Apolipoprotein E-epsilon 4 frequency in geriatric depression. Biol Psychiatry 1996;40:69–71.

33. Rigaud AS, Traykov L, Caputo L, Coste J, Latour F, Coudere R, Moulin F, Boller F, Forette F. Association of the apolipoprotein E epsilon4 allele with late-onset depression. Neuroepidemiology 2000;20:268–72.

34. Yen YC, Rebok GW, Gallo JJ, Yang MJ, Lung FW, Shih CH. ApoE4 allele is associated with late-life depression: a population-based study. Am J Geriatr Psychiatry 2007;15: 858–68.

35. Cervilla J, Prince M, Joels S, Russ C, Lovestone S. Genes related to vascular disease (APOE, VLDL-R, DCP-1) and other vascular factors in late-life depression. Am J Geriatr Psychiatry 2004;12:202–10.

36. Forsell Y, Corder EH, Basun H, Lammfelt L, Viitanen M, Winblad B. Depression and dementia in relation to apolipoprotein E polymorphism in a population sample age 75+. Biol Psychiatry 1997;42:898–903.

37. Locke DE, Dueck AC, Stonnington CM, Knopman DS, Geda YE, Caselli RJ. Depressive symptoms in healthy apolipoprotein E epsilon4 carriers and noncarriers: a longitudinal study. J Clin Psychiatry 2013;74:1256–61.

38. Parker G. Defining melancholia: the primacy of psychomotor depression. Acta Psychiatr Scand Suppl 2007;21–30.

39. Ballmaier M, Toga AW, Blanton RE, Sowell ER, Lavretskey H, Peterson J, Pham D, Kumar A. Anterior cingulate, gyrus rectus, and orbitofrontal abnormalities in elderly depressed patients: an MRI-based parcellation of the prefrontal cortex. Am J Psychiatry 2004;161:99–108.

40. Shimada H, Park H, Makizako H, Doi T, Lee S, Suzuki T. Depressive symptoms and cognitive performance in older adults. J Psychiatr Res 2014;57:149–56.

41. Ayotte BJ, Potter GG, Williams HT, Steffens DC, Bosworth HB. The moderating role of personality factors in the relationship between depression and neuropsychological functioning among older adults. Int J Geriatr Psychiatry 2009;24:1010–9.

42. Glahnt DC, Almasy L, Barguil M, Hare E, Peralta JM, Kent JW Jr, Dassori A, Contreras J, Pacheco A, Lanzagorta N, Nicolini H, Raventos H, Escamilla MA. Neurocognitive endophenotypes for bipolar disorder identified in multiplex multigenerational families. Arch Gen Psychiatry 2010;67:168–77.

43. Kluger A, Goldberg E. IQ patterns in affective disorder, lateralized and diffuse brain damage. J Clin Exp Neuropsychol 1990;12:182–94.

44. Mason CF. Pre-illness intelligence of mental hospital patients. J Consult Psychol 1956;20:297–300.

45. Robertson G, Taylor PJ. Some cognitive correlates of affective disorders. Psychol Med 1985;15:297–309.

46. Gale CR, Batty GD, McIntosh AM, Porteous DJ, Deary IJ, Rasmussen F. Is bipolar disorder more common in highly intelligent people? A cohort study of a million men. Mol Psychiatry 2013;18:190–4.

47. Fergusson DM, Horwood LJ, Ridder EM. Show me the child at seven II: childhood intelligence and later outcomes in adolescence and young adulthood. J Child Psychol Psychiatry 2005;46:850–8.

48. Gale CR, Deary IJ, Boyle SH, Barefoot J, Mortensen LH, Batty GD. Cognitive ability in early adulthood and risk of 5 specific psychiatric disorders in middle age: the Vietnam experience study. Arch Gen Psychiatry 2008;65:1410–8.

49. Schaie KW. The course of adult intellectual development. Am Psychol 1994;49:304–13.

50. Deary IJ, Whiteman MC, Starr JM, Whalley LJ, Fox HC. The impact of childhood intelligence on later life: following up the Scottish mental surveys of 1932 and 1947. J Pers Soc Psychol 2004;86:130–47.

51. Gow AJ, Johnson W, Pattie A, Whiteman MC, Starr J, Deary IJ. Mental ability in childhood and cognitive aging. Gerontolology 2008;54:177–86.

52. Christiansen P, Larsson HB, Thomsen C, Wieslander SB, Henriksen O. Age dependent white matter lesions and brain volume changes in healthy volunteers. Acta Radiol 1994;35:117–22.

53. Fedden T, Gabrieli JD. Insights into the ageing mind: a view from cognitive neuroscience. Nat Rev Neurosci 2004;5:87–96.

54. Miners JS, Jones R, Love S. Differential changes in Abeta42 and Abeta40 with age. J Alzheimers Dis 2014;40:727–35.

55. Liao C, Forsell Y, Fregni F, Weickert CE, Liao D, Porcellini E, Colonna-Romano G, Franceschi C, Caruso C. Innate immunity and inflammation in ageing: a key for understanding age-related diseases. Immun Ageing 2005;2:8.

56. Diniz BS, Sibille E, Ding Y, Tseng S, Aizenstein HJ, Lotrich FE, Becker JT, Lopez OL, Lotze MT, K lung WE, Reynolds CF, Butters MA. Plasma biosignature and brain pathology related to persistent cognitive impairment in late-life depression. Mol Psychiatry 2014.

57. Holtzman DM, Morris JC, Goate AM. Alzheimer's disease: the challenge of the second century. Sci Transl Med 2011; 3:77sr1.

58. Luciano M. Apolipoprotein E and depressive symptoms: shared or independent routes to age-related cognitive decline? Psychosom Med 2014;76:98–100.