RESEARCH ARTICLE

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# Apolipoprotein E genotype impact on memory and attention in older persons: the moderating role of personality phenotype

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**Objectives:** To determine if phenotypic personality traits modify the association of Apolipoprotein E (APOE) genotypes with different domains of cognitive function.

**Design:** Cross-sectional.

**Methods:** 172 non-demented older adults were administered the NEO-Five Factor Inventory (NEO-FFI), a battery of neuropsychological tests assessing memory, attention, executive function, language, and visuospatial ability, and underwent APOE genotyping. Multivariate (multiple-dependent variable) regression models predicting cognitive domains tested APOE interactions with personality traits, adjusting for age, sex, and education.

**Results:** The APOE ε4 allele showed small to modest main effects on memory and executive function (1/3 SD deficits for carriers, $p < .05$), with ε2 status evidencing minimal and non-significant benefit. Neuroticism interacted with both ε2 and ε4 alleles in associations with attention scores ($p = .001$), with ε2 benefits and ε4 deficits being marked at high Neuroticism (Mean [M] covariate-adjusted Z-score = .39 for ε2, −.47 for ε4). The association of ε4 with memory was moderated by Conscientiousness ($p < .001$), such that ε4 memory deficits were apparent at low Conscientiousness ($M = -.56$), but absent at high levels of Conscientiousness. Weaker patterns ($p < .05$) also suggested ε4-related detriments in executive function only at lower Conscientiousness, and ε2 memory benefits only at higher Openness.

**Conclusions:** Conscientiousness and Neuroticism moderate APOE associations with memory and executive function. As such, they may be useful phenotypic markers in refining the prognostic significance of this polymorphism. Effect-modifying personality traits also provide clues about behavioral and psychological factors that influence the cognitive impact of APOE. 

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The ε4 variant of the Apolipoprotein E (*APOE*) polymorphism is an established risk factor for Mild Cognitive Impairment (MCI) and Alzheimer's Disease (AD)(Liu et al., 2013), as well as cognitive decline in normal aging(Small et al., 2004). However, the ε4 variant alone accounts for a relatively small portion

of the variance in cognitive outcomes. The wide heterogeneity in its effects has limited its clinical utility(Goldman et al., 2011) and stimulated interest in potential interacting environmental factors that might distinguish when--or in whom--ε4 is robustly linked to cognitive outcomes(Lahiri et al., 2004). APOE also shows a high degree of inter-individual variability in methylation, suggesting complex but poorly understood epigenetic effects(Zawia et al., 2009). The inverse association between the ε4 allele and cognitive outcomes appears stronger in the presence of cerebrovascular risk factors such as artherosclerosis, peripheral vascular disease, diabetes (Kalmijn et al., 1996; Peila et al., 2002; Haan et al., 1999), smoking(Durazzo et al., 2016), and low physical inactivity(Luck et al., 2014), as well as in the context of low education(Cook & Fletcher, 2015). In the face of so many potential moderating factors, it would be valuable to identify a general phenotype that reliably captures their modulatory effects on APOE.

Personality traits are intriguing candidates for this role because they summarize phenotypic variation in habitual behavioral and psychological tendencies corresponding to a range of possible APOE moderators. Among the so-called "Big 5" personality dimensions, Conscientiousness is robustly linked to a range of vascular risk behaviors and chronic diseases (Bogg & Roberts, 2013). Openness to Experience reflects intellectual and esthetic interests contributing to cognitive reserve(Williams et al., 2013; Hogan et al., 2012). Neuroticism captures an array of habitual negative affects and stress reactivity linked to hypothalamic–pituitary–adrenal (HPA) axis dysregulation, potentially contributing to long-term glucocorticoid and inflammatory-based erosion of cognition(Wilson et al., 2007; Wilson et al., 2003; Wilson et al., 2005). The remaining Big 5 dimensions of Extraversion and Agreeableness reflect interpersonal tendencies toward sociability and warmth/trust, respectively. Because personality phenotype reflects longstanding, stable patterns of protective or risk factors, in older persons it may also capture the cumulative association of such factors across decades. This may be important in AD epigenetics because some have suggested that environmental factors such as health behaviors begin to perturb regulatory activity of relevant genes decades prior to the emergence of symptoms and neural degeneration(Lahiri & Maloney, 2010).

Studies of interaction between the Big 5 and APOE genotype are limited and have occurred only recently. One reported that the negative association of ε4 status with the cognitive scale of the Alzheimer's Disease Assessment (ADAS-Cog) was amplified at higher Neuroticism and possibly higher Openness in the Ginko-Biloba Evaluation of Memory Study(Dar Nimrod et al., 2012). Higher Neuroticism and Extraversion exacerbating the effect of ε4 on ADAS-Cog decline in the same cohort(Dar-Nimrod et al., 2012). An analysis of the Baltimore Longitudinal Study of Aging suggested that ε4 risk was lower at higher Openness, but higher at higher levels of Agreeableness (Terracciano et al., 2014) for AD, albeit AD incidence was somewhat low. The only other report, emanating from the Maricopa County Study, found that persons higher in Agreeableness showed a larger association of ε4 with memory decline, while this genotype's negative association with verbal memory was lower at higher Conscientiousness, and ε4-related impediments on visuospatial tests were lower at higher Openness(Caselli et al., 2014). Other data on distinct domains of cognitive function are absent. It would also be useful to understand putative personality modulatory effects on the ε2 allele's beneficial cognitive assocaitions, which have not been considered. We examined these issues in a non-demented elderly sample with a higher than normal proportion of ε2 and ε4 carriers.

## Methods

### Participants and procedure

Participants were drawn from a cohort study on aging (see(Mapstone et al., 2014) for details), and were community-dwelling older persons from the Rochester, NY area. Recruitment occurred through print and media advertisements, senior organizations, and word of mouth. Inclusion criteria were age 70 or greater, absence of major psychiatric or neurological disorder, English speaking, and not using anticonvulsants, antipsychotics, neuroleptics, highly active antiretroviral therapy, antiemetics, or cholinesterase inhibitors. No attempt was made to screen on the basis of genotype. Written informed consent was obtained from all participants. Participants were assessed with a neuropsychological battery administered by a board certified neuropsychologist (MM) or psychometrician in a geriatric outpatient clinic. Participants received meal vouchers to the local hospital cafeteria as well as feedback on cognitive status in exchange for participation. Procedures were approved by the University of Rochester Institutional Review Board.

Yearly assessments spanned 2007–2014, with most in the 2008–2013 period. During a pilot period in

2012, 61 participants were randomly selected to complete the personality measure at their scheduled assessment. Of the remaining 192 active cohort members, 124 completed surveys by mail in 2013, resulting in an overall personality completion rate of 185 / 253 (73%). A multivariate logit model of non-completers indicated no age, gender, race, or baseline MMSE differences between those with and without personality data, but completers had roughly 1 additional year of education (Mean (M) 16.3, vs. 15.1 years of education). Another 25 participants also completed the personality measure by mail after completing it during the earlier pilot phase, and their most recent scores were used if they were within 1 year of their most recent cognitive testing. No significant differences in scores between administration method were noted. Seven individuals did not have APOE genotype data, and another 6 persons were excluded because they did not have cognitive data within the prior year, resulting in an analysis sample of 172. Table 1 shows sample characteristics; race/ethnicity was 98% white non-Hispanic. Mini-mental status exam (MMSE) scores had a mean / standard deviation (M/SD) of 28.5 / 1.8 (range 25–30).

## Measurements

*Cognitive domains.* The cognitive battery was designed to assess 5 domains (described in detail in (Mapstone et al., 2014)). *Memory* was based on the Rey Auditory Verbal Learning Test (RAVLT)(Rey, 1964) learning over trials (sum of 1st 5 trials – 5 times the initial trial score), delayed recall memory (0–15) and recognition scores. *Executive function* was assessed via the Trail Making Test Part B (TMT-B)(Reitan, 1958) and Wechsler Memory Scales, Third Edition (WMS-3) backward digit span(Wechsler, 1997). *Attention* was based on TMT Part A, and WMS-3 forward digit span. The language domain was assessed with the Boston Naming Test (BNT) (Kaplan et al., 1983) and Category Fluency (CF; using animals) (Borkowski et al., 1967). Finally, visuospatial ability was measured with the Hooper Visual Organization Test (HVOT) (Hooper, 1983). Tests within a given domain were Z-scored, averaged, and the result converted to a robust Z-score using the median and normalized interquartile range, procedures developed for the battery to produce composites for the 5 cognitive domains(Mapstone et al., 2014).

Table 1 Sample Descriptives overall and by genotype

| | Overall | | e2 | | e3 | | e4 | |
|---|---|---|---|---|---|---|---|---|
| | M / % | SD / N | M / % | SD / N | M / % | SD / N | M / % | SD / N |
| Age (years) | 82.4 | 4.1 | 83.4 | 4.8 | 82.5 | 4.2 | 81.2 | 3.1 |
| Female | 52% | 89 | 50% | 12 | 54% | 60 | 47% | 17 |
| Education (years) | 16.3 | 2.4 | 16.4 | 2.4 | 16.3 | 2.4 | 16.4 | 2.5 |
| TMT-A | 38.4 | 18.3 | 35.6 | 14.4 | 38.0 | 15.5 | 41.9 | 26.9 |
| TMT-B | 104.1 | 61.3 | 83.7 | 24.8 | 101.2 | 58.6 | 127.5 | 78.9 |
| WMS-3 FDS | 6.4 | 1.1 | 6.5 | 1.1 | 6.4 | 1.2 | 6.4 | 1.1 |
| WMS-3 BDS | 4.7 | 1.1 | 4.4 | 1.2 | 4.8 | 1.1 | 4.4 | 1.0 |
| RAVLT Learning | 13.1 | 6.4 | 12.3 | 6.8 | 13.5 | 6.6 | 12.6 | 5.4 |
| RAVLT Recall | 8.5 | 3.9 | 8.5 | 3.8 | 9.0 | 3.8 | 6.9 | 4.1 |
| RAVLT Recognition | 13.5 | 2.3 | 14.0 | 1.7 | 13.6 | 2.3 | 13.0 | 2.6 |
| BNT | 55.9 | 5.8 | 56.9 | 4.3 | 55.6 | 6.5 | 56.0 | 4.2 |
| Category Fluency | 25.0 | 7.1 | 26.8 | 7.8 | 25.2 | 6.7 | 23.1 | 7.8 |
| HVOT | 23.6 | 3.3 | 24.6 | 3.4 | 23.3 | 3.5 | 24.0 | 2.5 |
| Neuroticism | 14.7 | 7.6 | 11.2 | 6.0 | 15.6 | 7.9 | 14.4 | 7.0 |
| Extraversion | 27.5 | 5.7 | 29.1 | 5.1 | 26.9 | 5.9 | 28.3 | 5.5 |
| Openness | 26.0 | 5.6 | 26.6 | 6.0 | 26.1 | 5.7 | 25.3 | 5.2 |
| Agreeableness | 35.9 | 4.7 | 37.4 | 4.6 | 35.5 | 4.6 | 36.0 | 5.1 |
| Conscientiousness | 34.0 | 5.7 | 35.9 | 6.1 | 34.1 | 5.6 | 32.8.0 | 5.6 |

Notes: M / % column reflects means for continuous variables, and percentages for categorical variables. SD / N column reflects standard deviations for continuous variables, and category numbers for categorical variables. For genotype groups, N = 24 (14%) for e2, N = 112 (65%) for e3, N = 36 (21% for e4. No significant group differences in age, gender, education, and cognitive comparisons occur on next page. TMT = Trail Making Test, WMS-3 = Wechsler Memory Scale, 3rd edition, FDS = Forward Digit Span, BDS = Backward Digit Span, RAVLT = Rey Auditory Verbal Learning Test, BNT = Benton Naming Test, HVOT = Hooper Visual Organization Test. Personality scores from NEO-Five Factor Inventory. Test scores are raw scores. N = 172 for all except 171 for Trails A and Category Fluency, 177 for Trails B. For genotype groups, e2 reflect either e2/e2 (n = 4) or e2/e3 (n = 20) individuals; the e3 group includes e3/e3 persons (n = 112); the e4 group includes e3/e4 (n = 32), e4/e4 (n = 3), and e2/e4 (n = 1).

*Personality domains.* The NEO-Five Factor Inventory (Costa & MacCrae, 1992) assesses the Big 5 traits of Neuroticism, Extraversion, Openness to Experience, Agreeableness, and Conscientiousness, each with 12 items involving a 0–4 Likert response scale. It is one of the most commonly used personality measures in older adults; internal consistency reliability in the current sample (Cronbach's α) was .89 for Neuroticism, .77 for Extraversion, .70 for Openness, .74 for Agreeableness, and .84 for Conscientiousness.

*APOE genotype.* Genotyping at baseline yielded the following allelic frequencies for the 172 participants: ε2/ ε2, 4; ε2/ ε3, 20; ε3/ ε3, 112; ε3/ ε4, 32; ε4/ ε4, 3; ε2/ ε4, 1. Thus, 21% were ε4 carriers; 65% ε3 homozygotes, and 14% ε2 carriers (excluding the ε2/ ε4 individual). Both ε4 and ε2 carriage were approximately 1.5 times that the ε4 14.5% and ε2 of 8.3% prevalences reported recently among Caucasians in the NIH personalized medicine cohort(Cross et al., 2010).

### Statistical analysis

To control for the correlation between cognitive domains, we employed multivariate (multiple dependent variable [DV]) linear regression analysis with robust standard errors. This procedure models all cognitive domain outcomes at the same time to account for their intercorrelation, similar to a multivariate analysis of variance (MANOVA). Age, education, and an indicator for female gender were included as control variables in all models. APOE was modeled with an indicator for ε2 and an indicator for ε4 groups, against a reference category of ε3 homozygotes. Traits were included as continuous variables, and trait-allele interactions as product terms between trait scores and each of the ε2 and ε4 indicators. Interaction tests involved joint tests of these two product terms. To identify interactions, we first tested the overall significance of each trait-APOE interaction across all 5 cognitive domains, one trait at a time. Significant trait moderators of APOE were then included in a single model with appropriate interaction terms, to control for potential overlap between traits. Traits moderating APOE in this model were then examined specifically for each of the cognitive domains. The False Discovery Rate (FDR) (Benjamini & Hochberg, 1995) was utilized to identify a hard rejection threshold for these specific interactions. We considered conventional significance levels ($p < .05$) indicative of trends. Interactions were described by estimating covariate-adjusted means and 95% confidence intervals (CIs) for the relevant cognitive domain, for ε2 / ε3 / ε4 at high (+1 SD) vs. low (−1 SD) levels of the moderating trait.

## Results

Table 1 provides sample descriptives overall, and stratified by genotype group. Unadjusted associations between genotype and personality revealed an overall difference between APOE genotype groups for Neuroticism ($F(2, 169) = 4.96$, $p = .008$, with e2s scoring significantly lower than e3s in Neuroticism (− .60 SD, $p = .002$ for contrast). We first fit a basic, covariate-adjusted model with no traits or interactions to examine APOE allele main effects on each cognitive outcome. Table 2 shows covariate-adjusted Z-scores across genotype for the cognitive domains. ε4 carriers showed modest deficits (roughly −.3 SD) in the memory and executive function (95% CI's excluding 0, indicating significance at $p < .05$). Smaller ε4 deficits in the other domains (not significantly different than 0) were apparent, with no ε2 allele main effects.

Overall tests of covariate-adjusted trait-APOE interactions across all cognitive domains were significant for Neuroticism ($X^2$ (10 df) = 44.83,

Table 2 Covariate adjusted Z-scores and 95% confidence intervals by APOE genotype group

| Genotype | M (95% CI) |
|---|---|
| | Memory |
| e2 | −.06 (−.26, .14) |
| e3 | −.04 (−.16, .08) |
| e4 | −.32 (−.55, .09) |
| | Executive Function |
| e2 | .05 (−.16, .25) |
| e3 | .05 (−.06, .17) |
| e4 | −.29 (−.53, −.05) |
| | Attention |
| e2 | .06 (−.14, .25) |
| e3 | −.04 (−.14, .06) |
| e4 | −.21 (−.45, .04) |
| | Language |
| e2 | .10 (−.16, .35) |
| e3 | −.11 (−.24, .02) |
| e4 | −.25 (−.46, .04) |
| | Visuospatial |
| e2 | .08 (−.24, .41) |
| e3 | −.30 (−.44–.15) |
| e4 | −.20 (−.41, .01) |

Notes: Genotype group mean Z-scores, adjusted for age, gender, and education. M = Mean, 95% CI = 95% confidence interval. Group means outside of another group's 95% confidence limits indicate significant difference, $p < .05$. Group Ns / % of total = 24 / 14% e2, 112 / 65% e3, 36 / 21% e4.

$p < .001$), Openness ($X^2$ (10) = 31.67, $p < .001$), and Conscientiousness ($X^2$ (10) = 44.83, $p < .001$). When included in the same model to control for possible overlap between traits, these 3 interactions again evidenced overall significance across all cognitive domains (Neuroticism $X^2$ (10) = 32.96, $p < .001$; Openness $X^2$ (10) = 21.96, p = .015; Conscientiousness $X^2$ (10) = 21.64, p = .017).

Examination of the specific trait interactions for each cognitive outcome indicated that by FDR (threshold of $p < .007$), Neuroticism was a robust moderator of APOE effects on attention ($X^2$ (2) = 13.41, p = .001). Individual product terms indicated that ε2 benefits and ε4 impediments both increased as Neuroticism levels rose. Table 3 (top) shows marginal means for APOE alleles at −1 SD and +1 SD Neuroticism. The genotype difference in attention at high Neuroticism was quite pronounced, with ε4 carriers scoring over ½ SD below average and ε2 carriers over .4 SD above average (ε3 carriers falling in the middle). At low Neuroticism, this ε2/ ε3/ ε4 gradient was virtually absent.

Table 3 Cognitive function by APOE Group at High and low Levels of moderating traits

| Genotype | M (95% CI) | M (95% CI) |
|---|---|---|
| | Attention | |
| | *Low Neuroticism* | *High Neuroticism* |
| e2 | −.06 (−.36, .25) | .39 (.15, .62) |
| e3 | .06 (−.09, .21) | −.12 (−.26, .02) |
| e4 | .14 (−.06, .33) | −.47 (−.78, −.15) |
| | Memory | |
| | *Low Conscientiousness* | *High Conscientiousness* |
| e2 | −.03 (−.25, .17) | −.06 (−.33, .20) |
| e3 | −.02 (−.20, .17) | −.05 (−.21, .11) |
| e4 | −.58 (−.85, −.31) | .13 (−.10, .37) |
| | *Low Openness* | *High Openness* |
| e2 | −.41 (−.62, −.19) | .32 (.10, .55) |
| e3 | −.14 (−.29, .02) | .07 (−.12, .25) |
| e4 | −.32 (−.56, −.09) | −.11 (−.42, .20) |
| | Executive Function | |
| | *Low Conscientiousness* | *High Conscientiousness* |
| e2 | .06 (−.23, .35) | .00 (−.38, .37) |
| e3 | .07 (−.09, .23) | .05 (−.12, .23) |
| e4 | −.57 (−.91, −.24) | .19 (−.16, .53) |

Notes: Marginal mean Z-scores for cognitive domains from final multivariate model including Neuroticism, Conscientiousness, and Openness interaction terms with APOE and adjusted for age, gender, and education. Neuroticism-APOE interaction for attention and Conscientiousness-APOE interaction for memory p = .001, Conscientiousness-APOE interaction for executive function p = .029, Openness-APOE interaction for memory p = .012. Low values of trait are −1 SD, high values +1 SD. M = Mean, LCL = lower confidence limit, UCL = upper confidence limit. Marginal means outside 95% confidence limits of others indicate significant difference, $p < .05$.

Conscientiousness also showed a substantial moderating effect of the APOE association with memory performance ($X^2$ (2) = 13.81, p = .001). This interaction primarily involved the ε4 allele. Table 3 shows that at low Conscientiousness (−1 SD), ε4 memory deficits are pronounced (roughly ½ SD below normal), while APOE genotypes are essentially indistinguishable in memory at high Conscientiousness.

Trends were noted for the Openness interaction with APOE for memory ($X^2$ (2) = 8.79, p = .012, primarily driven by ε2). Table 3 shows that for Openness, the expected pattern of e2 > e3 > e4 memory performance is apparent at higher levels of this trait (i.e., + 1 SD). While low Openness degraded memory performance for all genotypes, it did so disproportionately for ε2s. Another weaker APOE interaction occurred for Conscientiousness, with respect to executive function ($X^2$ (2) = 7.08, p = .029, primarily based on the ε4 allele). As seen in Table 3, executive function deficits for the ε4 allele are noticeable at −1 SD of Conscientiousness, but at +1 SD APOE alleles are unassociated with executive function.

## Discussion

These results are the first to document an effect-modifying role for Conscientiousness in the APOE ε4 allele impact on memory function and for Neuroticism on allele differences in attention. Several features of the findings warrant comment. First, Neuroticism interactions with the ε4 allele have previously been detected for multidomain outcomes such as ADAS-Cog scores (Dar Nimrod et al., 2012; Dar-Nimrod et al., 2012). Our findings pinpoint attention as a specific cognitive domain particularly sensitive to the ε4 modulatory role of Neuroticism. Attentional control is often considered a basic element of executive function, and is among outcomes affected by ε4 in non-demented samples(Small et al., 2004). Although ε4 is thought to impact cognition largely via beta amyloid (Aβ) sequestration, neuroinflammation is one of several other candidate mechanisms(Liu et al., 2013). Neuroticism involves a propensity toward stress reactivity and negative emotion, and may promote inflammation (and exert effects on cognition) through chronic dysregulation of the HPA axis(Wilson et al., 2003). While this represents one possible explanation, most studies in that literature focus on peripheral markers of systemic inflammation (i.e., plasma levels of C-reactive protein) and it will be important to probe associations between this trait and neuroinflamation in

particular. The protective associations of the ε2 allele with attention were also more pronounced at higher Neuroticism. While ε2 is also believed to be involved in amyloid clearance, its mechanisms are somewhat less well understood(Liu et al., 2013). It is possible that neuropathology associated with higher Neuroticism, such as global cortical atrophy(Jackson et al., 2011) and neurofibrillary tangles(Terracciano et al., 2013), presents a compromised backdrop in which compensatory ε2 benefits for attention are more noticeable.

Another major finding was that ε4-related memory deficits were modulated by Conscientiousness. Conscientiousness involves self-discipline, reliability, and goal-pursuit, and is a global driver of a wide swath of health behavior including diet, exercise, smoking and alcohol use(Bogg & Roberts, 2013). As a result, Conscientiousness is strongly predictive of BMI, obesity(Sutin & Terracciano, 2016), and chronic disease in old age(Chapman et al., 2007). These factors are consistent with the posited ε4 disruption of CNS cholesterol metabolism and cerebrovascular dysfunction(Liu et al., 2013). Oxidative stress arising from poor health behaviors and obesity also has a powerful impact on brain aging and cognitive function (Stranahan & Mattson, 2012), potentially worsening ε4 effects. The collective and cumulative impact of low Conscientiousness may thus be to amplify or accelerate ε4 memory deficits. Disrupted connectivity in working memory tasks has also been recently reported among younger individuals low in Conscientiousness(Dima et al., 2015), as have greater cortical atrophy (Jackson et al., 2011) and neurofibrillary tangles(Terracciano et al., 2013) in older persons. By contrast, ε4 carriers in this sample who exhibited more Conscientiousness evidenced memory performance comparable to ε2 carriers or ε3 homozygotes.

Two lesser instances of APOE effect modification were also noted, significant at conventional but not FDR levels. First, the benefit of ε3 for memory function was enhanced with increasing Openness, and reversed at low Openness. This is somewhat consistent with a prior cross-sectional finding that a combined ε2/ε3 group evidenced better ADAS-Cog scores than ε4s at higher Openness(Dar Nimrod et al., 2012). Openness reflects intellectual engagement, and is a key dispositional marker of cognitive reserve above and beyond education(Franchow et al., 2013), possibly optimizing ε2 benefits. The second trend was for Conscientiousness to mitigate ε4 links with executive function, and appeared similar in nature to the modulatory role this Big 5 dimension played for memory. Both findings must be regarded as tentative and require further scrutiny in future work. The Big 5 themselves represent the confluence of complex polygenic and environmental influences(De Moor et al., 2012; Terracciano et al., 2010; McCrae et al., 2010). Thus, modification of APOE-cognition linkages may be an indirect function of several gene–gene and gene–environment interactions.

In addition to suggesting possible epigenetic mechanisms, Conscientiousness and Neuroticism may be useful as easily assessed phenotypes that can refine prognoses of APOE genotypes. Sixty-seven percent of people surveyed recently reported that they would be "somewhat" or "very" likely to pursue predictive genetic testing for AD "if such a test became available"(Wikler et al., 2013). Direct-to-Consumer (DTC) genetic test results also exert a powerful impact on beliefs about AD risk(Krieger et al., 2016). Learning APOE status reportedly produces changes within a year in dietary and nutritional supplement practices, induces the purchase of long term care insurance (Goldman et al., 2011), and increases health care utilization within six months(Krieger et al., 2016). Given the salience of this polymorphism for patient beliefs and behaviors, it would appear useful to account for moderating factors that may alter its associations with cognition.

Trials of APOE disclosure methods (Goldman et al., 2011; Green et al., 2015) as well as clinical practice guidelines (Rahman et al., 2012; Goldman, 2012) have often focused on minimizing psychological distress. They utilize broad population-based risk estimates for APOE status while noting its imperfect predictive power. The extent to which these disclosure procedures emphasize genetic risk heterogeneity across different moderating factors is unclear. Such information may be difficult to summarize for laypersons. Nevertheless, precision medicine's goal of ever greater personalization(Montine & Montine, 2015) underscores the importance of understanding and communicating variability in APOE effects. Broad phenotypic traits such as Neuroticism and Conscientiousness may provide an intuitive means of capturing such variability.

Whether underlying traits can be substantially altered in later life is debatable. If epigenetic effects of personality traits have already taken place over decades, even successful change of traits might still not change ε4 risk. It may be more useful to use personality information for outcome improvement in other ways. For instance, ε4 persons who are low in Conscientiousness may benefit from environmental intervention and compensatory strategies that do not, themselves, require Conscientiousness. These

might include strategies such as a readily available calendar maintained by a caregiver, daily medicine caddies arranged and administered by someone else, and opportunities for externally structured (rather than self-motivated) physical activity. Greater surveillance for memory problems, earlier intervention, and/or prevention may be more warranted among ε4 individuals exhibiting low Conscientiousness and/or high Neuroticism.

Study results must be understood within the context of strengths and limitations. First, this is a cross-sectional study. While the direction of effect is clear in the sense that cognition does not alter APOE genotype, the bigger uncertainty is whether these findings generalize to change over time in cognitive domains(Caselli et al., 2016). This cohort was also free from frank dementia. It evidenced both higher than average genetic risk and genetic robustness in the form of both e4 and e2 allele frequencies each roughly 50% higher than the NIH personalized medicine cohort estimates(Cross et al., 2010). Such an allelic distribution presented a strength, in that it enabled a differentiation of personality interactions across ε2/ ε3/ ε4. Nevertheless, cohorts with different allelic frequencies and/or cognitive function ranges may or may not yield similar findings, and power and variation in these factors must always be considered when attempting to compare studies. This sample's mean age is also higher than the typical ages in which symptoms first appear among e4 carriers. Thus, it is possible that the e4 persons in this sample represent a different, more resilient population of e4 carriers. The ethnic heterogeneity, a strength in genetic analysis, also precludes generalization to samples of different ethnic distribution. Other strengths included an examination of multiple domains of cognitive function based on a full neuropsychological battery, as well as a comprehensive measure of personality. Overall, there is a strong need to understand when, how, and why personality dimensions shape genetic associations with cognitive function in later life. This will require longitudinal work, examination of other aspects of personality and more specific biobehavioral mechanisms, and studies of other populations. The present findings suggest that pursuit of these areas is warranted.

## Conflict of interest

None.

### Key Points

- The association of APOE genotype with memory and executive function varies across personality traits in non-demented older adults
- APOE epsilon-4 allele who scored lower on Conscientiousness showed expected memory deficits, but carriers scoring high on Conscientiousness did not.
- Epsilon 4 carriers were also more Neurotic showed attentional impairment, but those who were less neurotic did not.

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