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Personality factors moderate the associations between Apolipoprotein genotype and cognitive function as well as late onset Alzheimer's Disease

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Abstract

Objectives—We tested the hypothesis that neuroticism moderates the association between *APOE* (apolipoprotein E) genotype and two major outcomes, cognitive function and Alzheimer's disease (AD). We also explored whether other personality dimensions (extraversion, openness to experience, agreeableness, and conscientiousness) moderate the associations of *APOE* with these outcomes.

Design—Primary analyses of existing randomized clinical trial data.

Sample—Six-hundred and two older adults (mean age of 78 at baseline).

Measurements—*APOE* genotype, the NEO-Five Factor Inventory, the Alzheimer's Disease Assessment Scale- cognitive (ADAS-COG: measured every 6 months for 6.5 years) and relevant covariates.

Results—Fully adjusted multivariate analyses showed that the association between the presence of *APOE* ϵ -4 allele(s) and both outcomes was evident among individuals with high levels of neuroticism and extraversion but not among persons with low levels of these traits.

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Conclusions—Phenotypic personality dimensions, primarily neuroticism and extraversion, moderate the relationship between *APOE* ϵ -4 genotype and cognitive outcomes among older adults. Future research is needed to elucidate the physiological processes involved in these particular phenotype-genotype interactions.

Keywords

G x E interaction; Alzheimer's disease; cognitive function; *APOE* genotype; personality

Late onset Alzheimer Disease (AD) is a progressive neurodegenerative disorder. In the United States, one out of eight individuals aged 65 or older suffers from AD which is the sixth leading cause of death.¹ AD symptoms reflect changes in cognitive function, and gradual cognitive decline often precedes the diagnosis.² At present there is no cure, highlighting the need to identify risk factors.

Genetic studies revealed an association between the apolipoprotein E (*APOE*) ϵ -4 allele on chromosome 19 and AD.³ A combination of 3 common alleles for *APOE* -- ϵ -2, ϵ -3, and ϵ -4 -- form six genotypes out of which the presence of the ϵ -4 allele has been shown to be a genetic risk factor for AD.³ The probabilistic association between *APOE* ϵ -4 (*APOE*4) and AD as well as large variability in its magnitude highlight the likely presence of moderators.⁴ Similarly, evidence for the variability in the association between *APOE*4 genotype and cognitive decline⁵ engenders interest in moderators.⁶ This investigation explores the moderating role of personality phenotypes.

The Five Factor Taxonomy (FFT) has been utilized extensively in research on personality, health, aging, and cognition.⁷⁻⁹ The FFT is a culmination of decades of empirical research to identify the basic underlying dimensions of personality variation.¹⁰ The five primary, continuous domains of personality traits that emerge in a variety of populations, languages and cohorts are neuroticism, openness to experience, extraversion, agreeableness, and conscientiousness.¹¹ These dimensions represent the combined influence of genetics as well as social and physical environments. As powerful predictors of health-relevant behaviors¹² and morbidity,⁸ personality traits are likely to moderate some gene-disease relationships, particularly when the disease is multidetermined. Associations between the FFT and cognitive function^{9, 13,14}, as well as AD^{9, 15} point to a potential moderating role in the relationship between genetic risk factors and cognitive decline in aging populations. Specifically, increased neuroticism, the propensity to experience anxiety and distress, was shown to be predictive of cognitive decline¹⁴ and higher AD risk.^{9, 15} Lower levels of openness to experience, the tendency to experience sensory input in a particular manner and pursue a range of emotional and intellectual stimuli, has also been shown to be associated with cognitive decline¹⁴ and AD.¹⁵ Suggestive findings link higher level of extraversion, an inclination towards sociability and positive affect, with cognitive decline¹⁴ and AD.⁹ Increased conscientiousness was also linked to reduced cognitive decline³¹ and AD.^{9, 15} Lastly, no relevant research has linked agreeableness with cognitive decline and AD.

Cross sectional research has shown that trait anxiety, an aspect of neuroticism, moderated associations between the presence of *APOE*4 and cognitive function.¹⁶ Neuroticism has been linked to elevated Hypothalamic-Pituitary-Adrenal (HPA) axis activity,¹⁷ which in turn

has been suggested as a mechanism for cognitive decline associated with the *APOE* genotype.¹⁸ Thus, to the extent that high Neuroticism is a marker of HPA axis function, it may identify a subset of individuals in whom the presence of *APOE4* is more strongly linked to poorer cognitive function. Given these epidemiological and neuroendocrinological findings we predict a stronger relationship between *APOE4* and cognitive decline/AD among individuals of high neuroticism. Although no prior theory suggests that other personality dimensions may moderate *APOE*-cognitive function outcomes, we examined these interactions in exploratory analyses.

Method

Sample

The sample consisted of older individuals enrolled in the Ginkgo Evaluation of Memory (GEM) study (N = 3069). Details of the full sample¹⁹ and recruitment²⁰ have been published elsewhere. The study was conducted under an investigational new drug application with the Food and Drug Administration under the auspices of the National Center for Complementary and Alternative Medicine and the National Institute on Aging. For the trial, eligible subjects were recruited at 4 sites between 2000 and 2002. Key enrollment criteria in GEM included: age 72 years or older, availability of a proxy respondent, English as usual language, and absence of significant morbidity (including AD). Main exclusion criteria were the use of tricyclic antidepressant, antipsychotic and other psychotropic and cholinesterase medications, as well as electroconvulsive therapy in the last decade or hospitalization for depression in the last year. Additional criteria are specified elsewhere.^{19,20}

A prospective cohort sub-study examining the relationship between personality and AD-related cognitive decline included only subjects enrolled in GEM at the University of California, Davis (UCD) site.¹⁴ These UCD subjects were recruited after consenting to the additional data collection. At UCD, 2234 potential subjects participated in an initial screening telephone interview: 551 (24.7%) were ineligible; 761 (34.1%) refused to participate; and 922 (41.3%) attended the baseline study visit. Of these, 916 (99.3%) were randomized. Subjects at the UCD site had characteristics similar to those at the other sites. Because this sub-study was initiated after the start of the main GEM study, only 771 (84.2%) of the 916 enrolled subjects completed the personality inventory. Finally, *APOE* genotyping was obtained on 80% of subjects, and 602 (78.1%) of those completing the personality inventory. Subjects did not significantly differ statistically on demographic variables (age, minority race, and education) by whether or not they completed the personality inventory or by whether or not *APOE* genotyping was completed. This sample ranged in age from 72 – 91 years. Subjects were examined every 6 months until they met the study outcome (diagnosis of dementia, death, or study conclusion, a maximum of 7.3 years (median 6.1 years). Note that the intervention had no effect on outcomes.¹⁹

Measures

Predictors—The *NEO-Five Factor Inventory* is a 60-item self-report questionnaire with 12 items measuring each factor that comprise the FFT (neuroticism; e.g., “I often feel inferior to others;” openness to experience; e.g., “I have a lot of intellectual curiosity;”

extraversion; e.g., “I like to have a lot of people around me;” agreeableness; e.g., “I try to be courteous to everyone I meet;” and conscientiousness; e.g., “I keep my belongings clean and neat.”).¹⁰ Response options comprise a 5-point Likert scale from Strongly Disagree to Strongly Agree. Item scores ranged from 0 to 4 and were summed to yield a total score for each trait that ranged from 0 to 48, with higher scores indicating more of the trait. The NEO-FFI’s use in research in gerontology and geriatric psychiatry attests to its reliability and applicability to older samples. Internal consistency for the five scales in the current study was adequate (Cronbach’s α ’s .75 - .82).

For *APOE* genotyping DNA was extracted with a Puregene Kit (QUIAGEN; Valencia, CA). *APOE* genotyping was performed utilizing the TaqMan genotyping assays (Applied Biosystems; Foster City, CA) in a method described in detail elsewhere.²¹ *APOE* genotype was dichotomized into ϵ -4 allele present or absent.

The focus of the current article is on the interactions between the *APOE* genotype status and the NEO-FFI. Five interaction terms were calculated as products of individuals’ *APOE4* status and scores on each of the personality factors. Each of these products represents a specific Gene $\times$ Personality interaction term.

Baseline covariates—Covariates were selected to maximize compatibility with prior similar studies^{14,15}, and included age, gender, race (minority vs. white), education (years of schooling), self-rated health (excellent, very good, good, fair, poor) and self-reported diabetes, angina, myocardial infarction, osteoporosis, stroke, transient ischemic attack (TIA), and cancer in the last 5 years. Scores on the 10-item version²² of the Center for Epidemiological Studies Depression scale (CES-D), relevant metabolic phenotypes (BMI [Kg/m²]²³ and waist circumference²⁴) and randomization arm were also covaried.

Outcome Measures—Participants completed the cognitive subscale of the Alzheimer Disease Assessment Scale²⁵ (ADAS-COG) at baseline and each 6-month follow-up visit, yielding 13 possible assessments over the course of the study period. The ADAS-COG is one of the most commonly used cognitive measure in large-scale AD studies and has been shown to be a sensitive and reliable measure for detecting cognitive changes associated with AD.²⁶ The measure is comprised of subtests assessing those clinical features most affected in AD: Temporal and spatial orientation, memory, praxis, and language. It was administered and scored by a trained evaluator. The scale provides a global score of cognitive function with higher scores reflecting increased impairment (possible range 0 – 70; suggested cut-off between control and cognitively-impaired patients 10)²⁶.

Dementia diagnoses were established by an expert panel of clinicians using a previously validated adjudication process, the details of which have been published.²⁰ Briefly, participants were required to complete a neuropsychological battery,¹⁹ a complete neurological exam, and undergo brain magnetic resonance imaging (MRI) or computed tomographic (CT) scan if (a) they fail to pass 2 of 3 neuropsychological tests,²⁰ (b) their proxy reported the onset of a new cognitive problem, or (c) their personal physician diagnosed dementia subsequent to the last research assessment or prescribed a medication for dementia. Diagnosis of dementia was made by an expert panel using criteria from the

DSM-IV (memory impairment, impairment in at least one additional cognitive domain, and decline from a previous level of functioning). Classification of dementia type was made using three set of criteria:¹⁹ National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer Disease and Related Disorder Association (NINCDS-ADRDA),²⁷ the National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN),²⁸ and the Alzheimer's Disease Diagnostic and Treatment Centers (ADDTTC).²⁹ All participants with dementia were assigned to one of the following, possible or probable: (a) AD, (b) AD and vascular dementia, (c) vascular dementia, or (d) dementia, other etiology.

Analyses

The key independent variables were interaction terms of the *APOE* genotype [dummy coded with the value (1) indicating the presence of at least one *APOE4* and the value (0) indicating the absence of such allele] and the FFT personality factors. These factors were calculated using scores on the NEO-FFI, centered to a mean of 0.

Two main analyses examined the interactive effects of genotype and personality phenotype on cognitive function and risk for AD. Initially, binary logistic regression analyses were used to predict missingness of outcome data from the entire set of predictors. No variable significantly accounted for missingness in any of the analyses, using a Bonferroni-corrected criterion for multiple tests. However, a conservative approach led us to use mixed effects models, which yield consistent parameter estimates even when missingness can be predicted from observed factors. One primary analysis was a linear mixed effects regression examining the ADAS-COG score at each visit over the 6.5 years of the study as the dependent variable. The covariates used in the analysis were all measured at baseline, and study wave was included to adjust for possible fluctuations in the interaction over repeated measurements. The second main analysis was conducted using a Cox proportional hazards survival analysis. The end point was time to probable AD, defined from study entry to the midpoint between the last visit with no AD diagnosis to the visit at which the participant received a diagnosis of probable AD. Sensitivity analyses were conducted with a more liberal criterion, possible and probable AD, as well. Participants were censored at study termination, time of death, diagnosis of non-Alzheimer's dementia, or follow-up refusal. A secondary survival analysis was conducted to explore the specificity of the interaction effect to AD by using a diagnosis of non-Alzheimer dementia as the dependent variable. All reported models initially included all two way interactions between the personality factors' scores and the *APOE* genotype and were subsequently trimmed retaining interaction effects with ($p < .10$). Data were analyzed using SPSS (Version 18, IBM, Somers, New-York) for the survival and regression analyses. Linear mixed models analyses were conducted using the *LME4* package (version 0.999375-39)³⁰ and *multcomp* package (version 1.2-6)³¹ for the R software program (Version 2-13). All p-values reported from survival models are based on Wald tests (X^2 statistics), while p-values from mixed models are based on z statistics calculated using the *multcomp* package for R with a critical alpha value of .05 (two-tailed).

Results

Table 1 presents complete baseline data for the participants. Overall, ADAS-COG scores tended to be near the lower end of the scale with median of 5-6. Mean (SD) scores on the ADAS-COG by assessment point were 1: 6.62 (2.87); 2: 6.46 (2.84); 3: 6.01 (2.91); 4: 5.99 (3.07); 5: 5.60 (2.76); 6: 5.77 (2.93); 7: 5.27 (2.34); 8: 5.50 (2.72); 9: 6.01 (2.84); 10: 6.31 (3.06); 11: 6.52 (3.24); 12: 6.15 (2.66); 13: 6.74 (4.34). The average ADAS-COG mean score was 6.65 across waves.

An initial linear mixed effects regression analysis, which included the five personality dimensions and their interactions with APOE4, identified only extraversion and neuroticism as potential moderators of the APOE4-ADAS association (p 's < .10), whereas interactions with the other personality dimensions did not (p 's > .25). Both extraversion and neuroticism moderated the APOE4 -ADAS association over the follow-up period (Table 2). At high levels of Neuroticism (i.e., 1SD above the mean), persons with the APOE4 had ADAS scores that were 1.44 points worse than persons without this allele (7.04 vs. 5.60, or a difference of about $\frac{1}{2}$ of an ADAS SD). However, at low Neuroticism (1 SD below mean), ADAS scores were virtually identical in persons with vs. without APOE4 (5.32 vs. 5.35) - see Fig. 1. At high extraversion, similarly defined, presence of APOE4 was associated with ADAS scores that were roughly 1.20 points worse (6.72 vs. 5.52, a difference of about $\frac{2}{5}$ th of an ADAS SD). At low extraversion, similarly defined, there was no difference in ADAS scores as a function of APOE4 status. Inclusion of three-way interactions, APOE4 $\times$ wave $\times$ personality (neuroticism, extraversion) in the model (not shown) did not affect the estimates. This suggests that the magnitude of these APOE4-personality interactions was consistent across time, neither increasing nor decreasing as the study progressed.

Next, we looked at dementia incidence. Ninety-eight individuals (16.3%) were diagnosed with possible/probable dementia of which 86 were diagnosed with AD (76 probable, 10 possible) and 12 were diagnosed with other types. Twenty-four of the AD diagnosed individuals were also diagnosed with vascular dementia. A Cox proportional hazards survival analysis was conducted predicting the time to a probable diagnosis of AD. Again, all baseline covariates, APOE4, personality scores, and personality by APOE4 interaction terms were entered simultaneously. The analysis was repeated retaining only the gene by personality interaction terms with p values less than (p < .10). The results are presented in Table 3. Among those (+1SD) in neuroticism, APOE4 was associated with a hazard ratio (HR) of 8.68 for AD and its absence was associated with a HR of 0.90. Among those (-1SD) in neuroticism, the HR for APOE4 was 1.80 and for other genotypes the HR was 1.10. Similarly, for (+1SD) in extraversion, the ϵ -4 allele carried a 7.88 hazard ratio for AD and its absence a HR of 0.94, while at (-1SD), the allele carried a 1.98 HR and its absence a HR of 1.07. This analysis revealed that the risk for AD associated with APOE4 was stronger for individuals with increased neuroticism and extraversion tendencies more than for individuals without the allele. Fig. 2 depicts the unadjusted model for APOE4 by neuroticism interaction based on a median split of neuroticism. A model predicting possible + probable AD diagnoses ($n = 86$) showed a similar pattern.

Secondary analyses, which assessed the interaction effects on probable as well as probable or possible diagnosis of non-AD dementias, found no indication for any personality by APOE4 status interactions (all p 's > .5).

Discussion

We tested the hypotheses that neuroticism moderates the association between the presence of APOE4 and two major outcomes, worse cognitive function and incidence of Alzheimer's disease (AD) over a span of 6.5 years. Our results supported these hypotheses, indicating worse cognitive functioning among people with APOE4 with high neuroticism scores but not for individuals with the allele and low neuroticism scores. The incidence of AD in the presence of APOE4 was also higher for individuals high on neuroticism vs. individuals low on neuroticism. This neuroticism effect was not evident in the absence of APOE4.

The analyses identified an additional genetic by personality interaction effect on cognitive function and AD, which was not hypothesized a-priori. Extraversion moderated the association between APOE4 and both cognitive outcomes. Specifically, the risk for worse cognitive function posed by APOE4 was much worse at higher levels of extraversion than at lower levels. As people's age, their social interactions often decline due to loss of a spouse or close friends, physical deterioration which limits mobility, retirement from work, and related processes. An extrapolation of previous research³² suggests that for more extraverted people, cognitive activity is largely derived from social interactions. Thus, diminished social interactions, may reduce cognitive activity more strongly among extraverts, and may "unmask" the effect of APOE4 (which reduces cognitive reserve)³³ more strongly than among those lower in Extraversion, who may turn to internal stimulation for cognitive activity. Future research is needed to test this speculation.

The findings that neuroticism moderated the association between the presence of APOE4 and cognitive outcomes could be viewed through the lens of developmental neuroendocrinology. APOE4 has been shown to increase HPA activity in older adults.³⁴ Elevated levels of glucocorticoids are known to induce hippocampal degeneration.^{35,36} As one of the roles of the hippocampus is to regulate glucocorticoids,³⁶ such degeneration can contribute to a stress-induced repetitive cycle of hippocampal atrophy and HPA dysregulation.³⁶ Perceived stress, due to neuroticism or life events, adversely affects the hippocampus, which has a central role in memory.³⁷ It is possible to view our findings as indicators of allostatic load- the cumulative experience of heightened stress among people with neuroticism-related elevated HPA activity amplifies the pathogenic effects of the APOE4, adversely affecting cognitive function. In other words, neuroticism may be a phenotypic marker of accentuation in the neuro-endocrine mechanisms thought to link *APOE* to cognitive problems in later life.

The present study's results suggest that the neurophysiologic effects of the phenotypic (neuroticism) and genetic (*APOE*) elements are not just additive. Rather, the effects extend beyond the sum of its separate parts, demonstrating the vulnerability of a specific genetically-defined population that is also characterized by a particular personality

phenotype. This compounded risk highlights the appropriateness of more targeted interventions based on phenotypic-genotypic informed perspectives.

Personalized medicine, which could entail a combination of personality and genetic assessments, could potentially mitigate the burdens of AD.⁸ Personality tendencies are more dynamic than was previously thought,³⁸ and interventions which target specific maladaptive manifestations of personality with regard to health may have translational potential. Indeed, neuroticism and its physiological corollaries have been successfully modified in previous interventions.^{39–42} A simple intervention involving worry-reductions skills has been shown to have positive health consequences among students.³⁹ A more extensive approach for neuroticism reduction utilized mindfulness meditation techniques showing stress reduction⁴⁰ and HPA activity modifications,⁴¹ suggesting that persons with a combination of genetic and phenotypic vulnerability to adverse age-related cognitive changes may benefit the most from such programs. Pharmacotherapeutic interventions also showed promising results. Among depressed individuals, selective serotonin reuptake inhibitors (SSRI; e.g., Paroxetine) have been shown to reduce neuroticism⁴² highlighting a potential role for pharmacology in addressing cognitive decline selectively among vulnerable population identified using an interactionist approach. Dispositional proclivity for internal, rather than external, sources of cognitive stimulation can also be enhanced by intervention in older persons.⁴³ An intriguing question arises from these observations. While it is evident that interventions can modify personality traits, what are the implications of these interventions for cognitive outcomes and disorders? Is it possible to enhance cognitive plasticity and prevent cognitive decline by modifying personality?

Before drawing strong conclusions from the study, its strengths and limitations must be considered. The findings highlighted the importance of an interactionist perspective which integrate the scientific consensus that complex cognitive outcomes are best explained by genetic mechanisms and environment processes working interactively- a perspective which often falls by the wayside,^{44,45} engendering some undesirable outcomes.^{45,46} However, it also highlights an important methodological limitation: neither individuals' genotype nor their personality phenotype can be randomized. Despite our rigorous prospective analyses, causal inferences should be made with caution. Second, the effect sizes of the interaction effects were rather small. However, the suboptimal efficiency of interactions' detection in field studies is a known methodological problem⁴⁷ and the weak effects can be indicative of this methodological issue as well. Third, the sample was predominantly White and well educated. We have controlled for these demographics in our analysis but we would advice extreme caution in generalizing these findings to other populations. Fourth, the ADAS-COG measure was scored by a single person potentially decreasing its reliability. The effect of decreased reliability would most likely be an underestimation of the interaction effect in the population.

Lastly, the analyses indicated that higher extraversion may have deleterious effects on cognitive function among elders with specific *APOE* genotypes, but not among the entire population. These findings were not hypothesized in advance. Because of the lack of an a-priori prediction of this relationship and the dearth of putative pathophysiological mechanisms, it is best to consider these findings tentative.

Taking these limitations into account, our findings imply that it is important to consider the moderating effects of *APOE* genotype when evaluating the risk of cognitive decline and AD conferred by neuroticism and extraversion. The genotype-phenotype interactive perspective is supported in this context. It may offer a more cost-effective approach in targeting translational, interventionist research to the appropriate population.

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APPENDIX

GEM Study Personnel

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Table 1

Characteristics of participants at baseline (N = 602).

	M (SD) or %		
	Whole Sample	Low ADAS	High ADAS
<u>Demographics</u>			
Age (72–91 years) ^a	78.6 (3.1)	78.4 (3.0)	78.8 (3.1)
Male %	58.6	55.8	62.2
White, non-Hispanic, %	94.7	96.6	92.4
Education (years of schooling)	14.9 (3.2)	15.2 (3.1)	14.5 (3.2)
<u>Conditions %</u>			
Angina	10.5	8.3	13.2
Myocardial infarction	9.3	7.9	11.1
Diabetes	7.5	5.7	9.8
Cancer	21.4	21.6	20.9
Osteoporosis	12.7	13.4	11.7
Stroke	3.4	1.9	5.1
TIA	7.8	4.7	11.5
Self-rated health %			
Excellent	10.1	12.0	8.0
Very good	43.1	46.4	39.8
Good	42.6	38.2	47.1
Fair	4.0	3.2	5.1
Poor	0.2	0.3	0.0
BMI (Kg./m ²)	27.1 (4.3)	26.9 (4.5)	27.4 (4.1)
Waist circumference (cm)	98 (13)	97 (14)	98 (12)
CES-D (0–19) ^a	4.4 (3.7)	3.9 (3.1)	4.9 (4.3)
<u>Variables of Interest</u>			
APOE ε4 allele present %	22.8	17.9	28.1
<i>Personality Factors</i> [*]			
Neuroticism (0–37) ^a	14.7 (6.3)	14.1 (6.4)	15.6 (6.0)
Conscientiousness (16–48) ^a	32.6 (5.6)	33.2 (5.8)	32.1 (5.2)
Extraversion (9–46) ^a	27.9 (5.4)	28.1 (5.8)	27.7 (4.9)
Openness (11–47) ^a	29.6 (6.9)	30.4 (7.0)	28.8 (6.8)
Agreeableness (16–48) ^a	34.7 (5.0)	35.0 (4.9)	34.2 (5.1)

^a Actual range of scores.

Notes: BMI = body mass index; CES-D = Center for Epidemiologic Studies Depression Scale; APOE = apolipoprotein E genotype, ADAS = Alzheimer's Disease Assessment Scale, cognitive subscale, low/high ADAS indicates stratified descriptives based on a median (= 6) split of the baseline ADAS-COG scores. Mean in category unless otherwise noted. Standard deviations shown in parentheses

* NEO-FFI = NEO Five Factor Inventory's raw scores.

Table 2

Linear Mixed Model Predicting Difference in Cognitive Function (ADAS-COG)

	B	SE	z	p
Intercept	5.47	1.06	5.18	<.001
Wave	0.07	0.01	5.51	<.001
<u>Demographics</u>				
Age	0.18	0.03	5.23	<.001
Gender (female reference)	0.87	0.27	3.27	.001
Education (years)	-0.05	0.04	-1.35	.18
Minority race (White reference)	0.42	0.48	0.88	.38
<u>Physical health conditions</u>				
Angina (no-reference)	0.48	0.39	1.24	.21
Myocardial infarction (no-reference)	-0.07	0.41	-0.16	.87
Osteoporosis (no-reference)	0.62	0.33	1.84	.07
Diabetes (no-reference)	0.02	0.41	0.06	.95
Cancer (no-reference)	-0.13	0.26	-0.52	.60
Stroke (no-reference)	2.09	0.61	3.42	<.001
Tia (no-reference)	0.47	0.41	1.14	.26
<u>Other covariates</u>				
Subjective health evaluation (Excellent-reference)				
Very good	-0.04	0.35	-0.10	.92
Good	0.28	0.37	0.77	.44
Fair	0.80	0.67	1.18	.24
Poor	-1.32	2.36	-0.56	.58
BMI (body mass index)	0.04	0.04	0.93	.35
Waist circumference	-0.01	0.01	-0.73	.47
CES-D	0.04	0.03	1.16	.25
Ginkgo (control group- reference)	-0.16	0.21	-0.79	.43
<u>Variables of interest</u>				
APOE ϵ -4*	0.69	0.25	2.78	.005
Neuroticism	0.02	0.02	1.03	.31

	B	SE	z	p
Openness	−0.03	0.02	−1.69	.09
Extraversion	−0.01	0.02	−0.22	.83
Agreeableness	−0.03	0.02	−0.89	.26
Conscientiousness	0.03	0.02	1.77	.08
Neuroticism×ε-4 interaction	0.12	0.05	2.62	.009
Extraversion×ε-4 interaction	0.10	0.05	1.98	< .05

Notes: ADAS-COG = Alzheimer's Disease Assessment Scale, cognitive subscale, CES-D = Center for Epidemiologic Studies Depression Scale. Personality scores centered (mean = 0). Age centered on sample mean of 78.

* *APOE* (apolipoprotein E genotype) ε-4; absent coded as (0), present coded as 1.

Table 3

Cox Proportional Hazard Model of AD Diagnosis

	B	SE	X ² (df = 1)	p	HR	95% CI for HR	
						Lower	Upper
<u>Demographics</u>							
Age	.207	.040	26.640	<.001	1.230	1.137	1.331
Male	-.624	.362	2.978	.084	.536	.264	1.088
Education (years)	.118	.042	7.756	.005	1.125	1.036	1.222
Minority status	.837	.572	2.143	.143	2.310	.753	7.086
<u>Physical health conditions</u>							
Angina	1.160	.426	7.404	.007	3.191	1.383	7.358
Myocardial infarction	-.108	.503	.046	.830	.897	.335	2.407
Osteoporosis	.172	.419	.169	.681	1.188	.523	2.699
Diabetes	-2.164	1.069	4.096	.043	.115	.014	.934
Cancer	.128	.364	.123	.726	1.136	.557	2.317
Stroke	.896	.616	2.115	.146	2.450	.732	8.200
Tia	.473	.426	1.231	.267	1.604	.696	3.697
<u>Other covariates</u>							
Subjective health evaluation	.281	.226	1.543	.214	1.325	.850	2.065
BMI (body mass index)	-.004	.061	.005	.943	.996	.883	1.123
Waist circumference	-.004	.020	.036	.849	.996	.958	1.036
CES-D	-.024	.041	.343	.558	.976	.901	1.058
Ginkgo treatment	.275	.286	.922	.337	1.316	.751	2.305
<u>Variables of interest</u>							
APOE ε-4 present	1.373	.318	18.626	<.001	3.948	2.116	7.367
Neuroticism	-.017	.037	.219	.640	.983	.915	1.056
Openness	-.012	.022	.274	.600	.988	.946	1.033
Extraversion	-.073	.038	3.600	.058	.930	.862	1.002
Agreeableness	-.040	.032	1.604	.205	.961	.903	1.022
Conscientiousness	-.007	.032	.049	.825	.993	.933	1.057
Neuroticism×ε-4 interaction	.142	.052	7.477	.006	1.153	1.041	1.277

	B	SE	X ² (df = 1)	p	HR	95% CI for HR	
						Lower	Upper
Extraversion×e-4 interaction	.140	.060	5.357	.021	1.150	1.022	1.295

Notes: AD = late onset Alzheimer’s disease, HR = Hazard Ratio, CES-D = Center for Epidemiologic Studies Depression Scale. Personality scores centered (mean = 0). Age centered on sample mean of 78.
* *APOE* = apolipoprotein E genotype.