

## ***APOE* $\epsilon 4$ , rated life experiences, and affect among centenarians**

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**Objectives:** The purpose of this study was to assess the relationship between apolipoprotein E (APOE), life events and engagement, and subjective well-being (as measured by positive and negative affect) among centenarians. Based on the life stress paradigm, we predicted that higher levels of stress would allow *APOE* to influence positive and negative affect.

**Method:** 196 centenarians and near-centenarians (98 years and older) of the Georgia Centenarian Study participated in this research. The *APOE*, positive and negative affect, the number of recent (last 2 years) and lifelong (more than 20 years prior to testing) events, as well as a number of life engagement tasks were assessed.

**Results:** Results suggested that centenarians carrying the *APOE*  $\epsilon 4$  allele rated lower in positive affect, the number of lifelong events, and in engaged lifestyle, when compared to centenarians without the *APOE*  $\epsilon 4$  allele ( $t = 3.43, p < .01$ ;  $t = 3.19, p < .01$ ; and  $t = 2.33, p < .05$ , respectively). Blockwise multiple regressions indicated that the *APOE*  $\epsilon 4$  predicted positive but not negative affect after controlling for demographics. Gene–environment interactions were obtained for the *APOE*  $\epsilon 4$  and lifelong events, suggesting that carriers of the *APOE*  $\epsilon 4$  allele had higher scores of negative affect after having experienced more events, whereas noncarriers had reduced negative affect levels after having experienced more events.

**Conclusion:** *APOE*  $\epsilon 4$  is directly related to positive affect and is related to negative affect in interaction with life events.

**Keywords:** extreme old age; stress; trauma; quality of life/wellbeing; biological markers

### **Introduction**

The  $\epsilon 4$  allele of apolipoprotein E gene (*APOE*) on chromosome 19 has been related to the late age onset of Alzheimer's disease and cognitive decline (Corder, Saunders, & Risch, 1994; Saunders, Schmeider, & Breitner, 1993). The  $\epsilon 4$  allele has also been associated with a number of physical diseases, such as coronary artery disease (Lehtinen, Lehtimäki, & Sisto, 1995), vascular disease in diabetes (Vauhkonen, Niskanen, & Ryyänen, 1997), and stroke (Ferrucci, Gurlanik, & Pahor, 1997). It then comes as no surprise that *APOE* is also related to increased mortality (Corder, Lanfelt, & Vitanen, 1996; Tilvis, Strandberg, & Juva, 1998), even though some centenarian studies did not find significant differences in the frequency of the  $\epsilon 4$  allele between Alzheimer's disease and non-demented centenarians (Asada, Yamagata, & Kinoshita, 1996), whereas others did (Choi et al., 2003).

To date, however, little research has considered the role of *APOE*  $\epsilon 4$  for other psychological outcomes. During the past 15 years, considerable attention has been devoted to genetic associations with human longevity

(Perls & Terry, 2003; Vijg & Campisi, 2008). One approach taken is to assess long-lived individuals, such as centenarians, and compare them to control individuals who did not or who are not likely to achieve such an advanced age (Perls, Kunkel, & Puca, 2002). Even though studying links between genes and longevity in itself is important, it may be even more important to study the relationship between genes and functioning in very late life. The purpose of this study was to assess the relationship between one particular gene, the *APOE*, and affect among centenarians.

Why is it important to study *APOE* in a highly selective group of survivors? Centenarians are obviously long-lived individuals and genetic disadvantages – if they existed – did not compromise the unusual life span of centenarians. The question of genetic and gene–environment interaction effects may inform us whether survivorship comes with a high price (e.g., cognitive, functional, or mental health problems). One of the consequences of extended lives may be to become more susceptible to impairments in very late life. Although a large number of centenarians are quite frail, and functional impairments

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may be quite high (Andersen-Ranberg, Schroll, & Jeune, 2001; Martin, Rott, Hagberg, & Morgan, 2000), there are also individual differences distinguishing relatively well-functioning centenarians from centenarians who may be severely impaired. The question is whether genetic markers, alone or in interaction with stress, can account for these individual differences in very late life.

Explaining individual differences in functioning is our conceptual starting point for this study. Very few studies have examined an association of the  $\epsilon 4$  allele with overall functioning. Blazer, Fillenbaum, and Burchett (2001) assessed whether functional decline was associated with the *APOE*  $\epsilon 4$  allele and noted no direct association. However, a statistically significant interaction of the  $\epsilon 4$  allele with gender and baseline functional status was obtained. Greater functional decline was observed among women with the  $\epsilon 4$  allele who also had poorer baseline functioning. Another interaction effect was reported by Seeman et al. (2005), who noted that the presence of at least one  $\epsilon 4$  allele reduced the protective effects of education resulting in steeper cognitive declines with age.

We propose to extend findings on the relationship between *APOE*  $\epsilon 4$  and physical functioning to mental functioning. A number of studies have investigated the association between *APOE*  $\epsilon 4$  and mental health. Borroni, Costanzi, and Padovani (2010) in reviewing a recent literature linking the *APOE* gene with behavioral and psychological symptoms in dementia reported conflicting results about the effect of *APOE*  $\epsilon 4$  on mental health. Delano-Wood et al. (2008) reported that the frequency of the *APOE*  $\epsilon 4$  allele was significantly higher in depressed vs. non-depressed persons with Alzheimer's disease. In addition, women possessing the *APOE*  $\epsilon 4$  allele were almost four times more likely to be depressed than those without the  $\epsilon 4$  allele. Other studies did not find an overall association between *APOE*  $\epsilon 4$  and depression (Garcia-Pena et al., 2010; Steffens et al., 2003). A significant interaction effect of *APOE*  $\epsilon 4$  and age was reported such that the relationship of late-onset depression with respect to the presence of the  $\epsilon 4$  allele was larger among those 80 years and older compared to those at younger ages. A third study (Gallagher-Thompson, O'Hara, Simmons, Kraemer, & Murphy, 2001) reported that increased stress levels were associated with increased depressive symptoms in caregivers who had the  $\epsilon 4$  allele.

Although there is emerging literature indicating that the *APOE*  $\epsilon 4$  allele has a direct effect on some functional outcomes, several studies point to the importance of gene-environment interactions (Chou, 2010). For example, Dar-Nimrod et al. (2012) reported that *APOE*  $\epsilon 4$  moderated the relationship between neuroticism and cognitive function. Neighborhood environmental factors also appear to attenuate the association of the *APOE*  $\epsilon 4$  allele with depressive symptoms (Yen, Rebok, Yang, & Lung, 2008). Less is known about the interactive relationship between life experiences, the *APOE*  $\epsilon 4$  allele and functioning. We therefore assessed to what extent life experiences can play such a moderating influence on the gene-environment relationship.

A 'molar approach' to study stress, health, and aging places a focus on major life events (Almeida, Piazza, Stawski, & Klein, 2011; Dohrenwend, 2006). Stressful life events can accumulate over time leading to poor health outcomes. The life stress (stress conditioning) hypothesis indicates that the relationship between resources and distress is moderated by stressful experiences (Ensel & Lin, 1991). Stressful events can be distal (i.e., those experienced in the distant past) or proximal (i.e., experiences of more recent nature) (Ensel, Peek, Lin, & Lai, 1996).

Positive and negative affect are important parts of the adaptation process for older adults. Several studies (Gerstorf et al., 2010) have reported that measures of subjective well-being decline across adulthood. Late life appears to be particularly associated with lower levels of positive affect but not with negative affect (Kunzmann, Little, & Smith, 2000; Poon, Martin, & Margrett, 2010). A number of studies (Folkman & Moskowitz, 2000; Mroczek & Almeida, 2004) have provided evidence for the relationship between stress and positive and negative affect. Previous research indicates that stress has a negative effect on mood states (Bolger, DeLongis, Kessler, & Schilling, 1989), and most studies link proximal stress to affective states. However, it is also important to consider lifelong cumulative stressors when assessing the link between stress and well-being. Lifelong stress is particularly important to consider in a sample of very old individuals who may have accumulated many events over their life time. Our previous studies demonstrated that positive and negative events were associated with negative affect, and distal events were associated with positive affect (Martin, da Rosa, & Poon, 2011). This study evaluated both proximal and distal events in its relationship to affective outcomes.

Our research was guided by a life stress hypothesis (Ensel & Lin, 1991) suggesting that the relationship between *APOE*  $\epsilon 4$  and mental health is moderated by stressful experiences. Life stressors can be taxing but can also serve as challenges that keep older adults active and involved. Consistent with the stress paradigm (Ensel & Lin, 1991), there are two pathways, which we tested through which genes and life experiences may influence functional outcomes: (1) genes and experiences may be independent influences or (2) life experiences can serve as a moderator in the relationship between genes and functioning. It is unclear whether the hypothesized effect of *APOE*  $\epsilon 4$  is equally noticeable when predicting positive and negative affect. We hypothesized that *APOE*  $\epsilon 4$  and life stress had independent influences on positive and negative affect. The relationship between *APOE*  $\epsilon 4$  and affect was hypothesized to be moderated by distal and proximal stressors. The direct effect is consistent with the independence model proposed by Ensel and Lin suggesting a direct effect of stressors and biological markers on distress. The moderating hypothesis is consistent with the stress-conditioning model proposed by Ensel and Lin suggesting that stressful events moderate the relationship between biological markers and distress.

## Method

### Participants

The overall study included a total of 234 community-dwelling and institutionalized centenarians and near centenarians from the second Georgia centenarian study (Phase III, Poon et al., 2007). Excluded from this particular analysis were 38 centenarians without genetic data. We therefore included 196 centenarians (mean age = 100.4 years) in this specific study.

Although we have genetic information on all 196 of these participants, a number of them were classified as 'admixed.' Admixture occurs in populations because allele frequencies can vary widely between the ancestral populations of which they are composed (Cardon & Palmer, 2003). The net effect of this admixture depends on patterns of geographical migration, mating practices, reproductive expansions, and stochastic variation that can result in differences in allele frequencies between individuals rather than the association with a particular phenotype of interest (Cardon & Palmer, 2003). Because study populations may be confounded by genetic admixture, we identified 33 participants characterized by admixture, and we conducted our analyses separately for the total population and for the population without these admixed participants.

A large proportion of our participants (85.7%) were women and 75.5% were Caucasian. Most participants (89.2%) were widowed, only 2.6% were married. A sizeable group (37.4%) had no more than eight years of education, whereas 23.7% had a college degree. About a third of the centenarians resided in their private home or apartment (36.7%), whereas 17.9% resided in assisted living facilities and 45.4% in skilled nursing facilities. Only 4.2% were rated by proxies as being in 'poor' health, 20.0% were rated as being in 'fair' health, whereas 48.3% were rated as being in 'good,' and 27.5% in 'excellent' health. The average mini mental state exam (MMSE) (Folstein, Folstein, & McHugh, 1975) score of the participants was  $M = 16.36$ . Therefore, a large number of participants had modest to substantial deficits in cognitive functioning. Demographic characteristics are summarized in Table 1. About 19% of our centenarians were classified with *APOE e4*, which is comparable with the frequencies reported in other population-based studies (Gerdes, Klausen, Sihm, Faergeman, & Vogler, 1992).

Information about affect, life events, and lifetime activities for all centenarians was obtained by proxy informants. Proxies are commonly used in centenarian research because many very old persons are not able to participate in a structured interview and asking proxy informants remains the only option to assess low-functioning centenarians (Gu, 2008). Proxy respondents are particularly useful in research with oldest-old samples to avoid bias in favor of healthy older persons who are able to answer for themselves (Gu, 2008; Rodgers & Herzog, 1992). Several studies have indicated that proxies may in some cases overrate disabilities (Rothman, Hedrick, Bulcroft, Kickam, & Rubenstein, 1991), but they tend to be more knowledgeable about personal, familial,

Table 1. Demographic characteristics.

Variable	<i>N</i>	Percentage	<i>M</i>	<i>SD</i>
Age			100.44	1.967
Gender				
Female	168	85.7		
Male	28	14.3		
Total	196	100.0		
Ethnicity				
White	148	75.5		
African-American	48	24.5		
Total	196	100.0		
Education				
0–8 years	71	37.4		
9–12 years	74	39.0		
13–16 years	37	19.5		
17+	8	4.2		
Total	190	100.1		
Residence				
Private home	72	36.7		
Assisted living	35	17.9		
Skilled nursing	89	45.4		
Total	196	100.0		
<i>e4</i> allele				
No	159	81.1		
Yes	37	18.9		
Total	196	100.0		
MMSE	196		16.36	9.08

and economic situations (Gu, 2008). Our own work suggests that proxy responses and self-ratings in mental health are not significantly different on the mean level (MacDonald, Martin, Margrett, & Poon, 2009).

A proxy-selection decision tree was used to determine proxy participation. Close family, such as spouses or children were first considered as proxies. If more than one child was alive, the centenarian nominated a proxy, or in the case of cognitive impairment, a contacted child made the decision regarding who could provide the most accurate information. Other relatives served as proxies, if no children were alive or available or if nominated by the participant. If no other relatives were alive or available, friends, neighbors, nurses, clergy, or other knowledgeable persons could also serve as proxies. Proxy selection continued until an agreeable participant was found.

Most proxies (61.1%) were adult children. Additional proxies included nieces and nephews (13.9%), granddaughters (9.9%), and additional informants, such as spouses, siblings, or friends (15.1%). Proxy informants received a questionnaire booklet and were asked to fill out all questions and return the information in a self-addressed, stamped envelope. All original scale items were reworded so that they were made in reference to the centenarian. Proxies were specifically instructed to evaluate the centenarians how they were at the time of the assessment.

## Measures

### Positive and negative affect

Proxies assessed affect with the Bradburn Affect Balance Scale (Bradburn, 1969). This scale was used because it had been successfully applied in our earlier centenarian studies. The scale consists of two dimensions 'positive affect' and

'negative affect.' Each scale consists of five items with the categories 'not at all,' 'once,' 'several times,' and 'often.' Internal consistency was  $\alpha = 0.79$  for positive affect, and  $\alpha = 0.74$  for negative affect. Higher scores for positive affect indicated better mental health, whereas higher scores for negative affect were indicative of poorer mental health. The scores could range from 5 to 20.

Although it may be difficult to assess a participant's affect levels by proxy, it is still important to take into account their observations. Proxy informants typically can observe whether centenarians are 'depressed and very unhappy,' 'restless,' 'bored,' or 'lonely.' Of course, these observations may not match those that would be obtained by self-ratings.

#### *Proximal events and distal events*

Proxy informants were also asked to select proximal and distal life events from a commonly used life events list that had been applied in our earlier centenarian studies (Dohrenwend, Krasnoff, Askenasy, Dohrenwend, 1978). These events refer to occurrences such as separation or divorce of parents, marriage, divorce, death of close family members, birth and loss of children, job events (first job, change of jobs, and retirement), a major financial loss, a residential change including institutionalization, a major decrease in activities that one really enjoyed, or worsening relationship with a child. We assessed a total of 23 events and their time of occurrence; events were then classified as to whether they had happened two or fewer years ago (proximal events, two years) or whether these events had happened more than 20 years ago (distal experiences). Time frames were chosen to obtain enough variability in life event occurrence. Consistent with the notion of cumulative advantage and adversity (Ryff, Singer, Love, & Essex, 1998), we assessed the effect of cumulative events rather than discrete events or negative versus positive events.

#### *Engaged lifestyle*

Past engaged lifestyle activities were defined by a series of cognitive engagement tasks participants may have engaged in at any time of their lives (Hultsch, Hertzog, Small, & Dixon, 1999). These past engaged lifestyle activities included eight dichotomous questions such as learning a foreign language, volunteerism, traveling, preparing income taxes, and public speaking. Although it would have been advantageous to use a 'current engaged life style' assessment, it is quite unlikely that centenarians would be still involved in these activities. Cronbach's alpha for this scale was 0.62 for proxies. Higher scores were indicative of greater engagement.

#### *APOE measurement*

*APOE* genotype was determined by resequencing exon 4 of the *APOE* gene. DNA was extracted from blood spotted on FTA cards (Whatman) using the Genra Generation DNA Purification System. Exon 4 sequences

were amplified by the polymerase chain reaction (PCR), using 5'-CTTGGGTCTCTGGCTCATC-3' and 5'-GCAGCCTGCACCTTCTCC-3' as the forward and reverse primers, respectively. The correct size was verified by agarose gel electrophoresis, and the PCR products were cleaned using the Edge Biosystems Performa Ultra 96-well plate cleaning kit. The cleaned DNA was subjected to cycle sequencing using the Applied Biosystems (ABI) Big-Dye Terminator Reagent version 3.1 and the ABI 3130xl DNA sequencing system. Sequencing primers were the same as those used for PCR amplification. Trace files were analyzed with the ABI SeqScape version 2.5 software. Both DNA strands were sequenced twice by two independent investigators, and the sequence calls were validated by comparison between them. For statistical purposes, we classified participants as either *APOE*  $\epsilon 4$  ( $\epsilon 2/\epsilon 4$ ,  $\epsilon 3/\epsilon 4$ ,  $\epsilon 4/\epsilon 4$ ) or non  $\epsilon 4$  ( $\epsilon 2/\epsilon 2$ ,  $\epsilon 2/\epsilon 3$ ,  $\epsilon 3/\epsilon 3$ ).

Population stratification was carried out using the program Structure (Pritchard, Stephens, & Donnelly, 2000). The DNA samples were genotyped at 100 Alu insertion polymorphisms by PCR amplification using locus specific primers followed by gel electrophoresis. These *Alu* sequences served as ethnic affiliation markers that were analyzed using the structure. For this purpose, the same *Alu* genotypes from 715 independent DNA samples from different geographic regions of the world were used. No departure from Hardy-Weinberg proportions was found for the *APOE* variants. The details of these analyses have been published elsewhere (Jazwinski et al., 2010).

#### *Statistical analyses*

Two analysis steps were undertaken. First, mean differences between *APOE*  $\epsilon 4$  carriers and noncarriers were computed with independent group *t*-tests. Second, blocked hierarchical multiple regressions were computed separately for positive affect and negative affect. The first block contained demographic variables age, ethnicity, and gender, as well as the covariates residence (i.e., care facility vs. independent living). We did not control for cognitive status in the statistical analyses given that *APOE*  $\epsilon 4$  is associated with cognitive impairment. Adding cognitive status to the equation would have removed some of the variability that should be attributed to genetic markers. The second block contained the  $\epsilon 4$  variable, the third block contained the life experience variables (i.e., proximal events, distal events, and engaged lifestyle), and the fourth block contained the  $\epsilon 4$  variable by life experience interactions. Analyses were computed with SPSS 19.

#### **Results**

Results are presented in three sections: first, we report differences on life events, engaged lifestyle, and mental health for the two genetic groups: those carrying the *APOE*  $\epsilon 4$  allele as compared to those not carrying the *APOE*  $\epsilon 4$  allele. Next we report on the direct (non-mediated) effects of genes and events on mental health outcome variables. Finally, we will report results of the moderating (gene  $\times$  environment) interaction effects.

Table 2. Mean differences by *APOE*  $\epsilon 4$  allele.

	<i>n</i>	$\epsilon 4$	$\epsilon 4$	<i>t</i>
		No	Yes	
		<i>M</i>	<i>M</i>	
Negative affect	159	8.25	8.32	0.09
Positive affect	157	12.28	9.43	3.43**
Proximal events	176	0.66	0.54	0.60
Distal events <sup>1</sup>	176	4.13	2.60	3.19**
Engaged lifestyle	139	4.14	3.13	2.33*

<sup>1</sup>Equal variance not assumed.

\* $p < 0.05$ , \*\* $p < 0.01$ .

The results comparing the different genetic groups are summarized in Table 2. Carriers of the  $\epsilon 4$  allele had lower positive affect scores,  $t(155) = 3.43$ ,  $p < 0.01$ , and centenarians who were carriers of the  $\epsilon 4$  allele had experienced fewer distal events  $t(175) = 3.19$ ,  $p < 0.001$ , and were lower in engaged lifestyle,  $t(137) = 2.33$ ,  $p < 0.05$ . We repeated the analysis by excluding admixed participants and the same significant differences were obtained.

Tables 3 and 4 summarize the direct effects of the  $\epsilon 4$  allele and events on positive and negative affect. For positive affect, carriers of  $\epsilon 4$  had lower scores in positive affect,  $\beta = -0.21$ ,  $p < 0.05$ . Engaged lifestyle also significantly predicted positive affect,  $\beta = 0.18$ ,  $p < 0.05$ , indicating that those who had higher scores in engaged lifestyle were also perceived as having greater positive affect (Table 3). For negative affect, only distal events were significant predictors,  $\beta = -0.22$ ,  $p < 0.05$ , indicating that centenarians who reportedly had experienced more life events had lower negative affect scores. Table 4 also highlights a significant gene  $\times$  environment interaction for negative affect,  $\beta = 0.25$ ,  $p < 0.05$ . The effect of the  $\epsilon 4$  allele on negative affect was stronger when participants reportedly had more distal (lifetime) experiences (Figure 1). Additional sex  $\times$   $\epsilon 4$  allele interactions on positive and negative affect were also computed but were not significant (data not shown).

Once again, we repeated the regression analyses for the sample that excluded admixed participants. With

regard to positive affect, the  $\epsilon 4$  allele and engaged lifestyle again were significant predictors and no significant interactions were obtained. For negative affect, distal events were again significant but there was only a statistical trend for the gene  $\times$  distal event interaction,  $\beta = 0.21$ ,  $p = 0.086$ .

## Discussion

Although there is quite a bit of research highlighting the relationship between the  $\epsilon 4$  allele and Alzheimer's disease, cardiovascular disease, and mortality, much less is known about the direct and moderating effect of  $\epsilon 4$  on mental health. This research attempted to fill this gap by assessing the relationship between  $\epsilon 4$  and the affect by advancing stressful life events hypotheses of adaptation. We had hypothesized that *APOE*  $\epsilon 4$  and life stress had independent influences on positive and negative affect. The relationship between the *APOE*  $\epsilon 4$  and the affect was hypothesized to be moderated by distal and proximal stressors.

Two primary results emerged from our analyses. First, *APOE*  $\epsilon 4$  allele carriers differed significantly in positive affect, distal events, and engaged lifetime activities. The effect of *APOE*  $\epsilon 4$  was maintained even after adjusting for covariates. Second,  $\epsilon 4$  interacted significantly with distal life events to predict negative affect but not positive affect. Specifically, the effects of distal life experiences more strongly predicted negative affect for carriers of an *APOE*  $\epsilon 4$  allele than for noncarriers.

By following a life stress paradigm (Ensel & Lin, 1991), we evaluated whether *APOE* and stress had an independent effect on late-life functioning or whether the effect of *APOE* on functioning was moderated by stressful life experiences. The carriers of the  $\epsilon 4$  allele were more likely to have lower positive affect, had fewer distal experiences, and lower engaged lifestyle scores. This result is supported by other research indicating that the *APOE*  $\epsilon 4$  allele is directly related to mental health. For example, Delano-Wood et al. (2008) reported that the frequency of *APOE*  $\epsilon 4$  alleles was significantly higher in a depressed

Table 3. Effect of *APOE*  $\epsilon 4$  and life events on positive affect ( $n = 126$ ).

	Model 1			Model 2			Model 3			Model 4			$F_{\Delta}$
	<i>B</i>	SE	$\beta$	<i>B</i>	SE	$\beta$	<i>B</i>	SE	$\beta$	<i>B</i>	SE	$\beta$	
Age	-0.28	0.20	-0.13	-0.30	0.19	-0.14	-0.22	0.19	-0.10	-0.22	0.19	-0.10	
Ethnicity	-0.56	0.86	-0.06	-0.23	0.84	-0.02	-0.25	0.85	0.03	0.26	0.86	0.03	
Gender	1.12	1.04	-0.09	-1.45	1.01	-0.12	-1.58	1.00	-0.13	-1.60	1.02	-0.13	
Residence	-1.04	0.42	-0.22*	-0.95	0.40	-0.20*	-0.81	0.41	-0.17	-0.81	0.41	-0.17	
$\epsilon 4$				-2.84	0.90	-0.26**	-2.31	0.92	-0.21*	-2.27	1.00	-0.21*	9.90**
Proximal events							0.12	0.35	0.03	0.13	0.35	0.03	
Distal events							0.15	0.12	0.11	0.14	0.13	0.11	
Engaged lifestyle							0.40	0.20	0.18*	0.40	0.20	0.18*	
$\epsilon 4 \times$ Proximal events										-0.55	0.94	0.05	0.34
$\epsilon 4 \times$ Distal events										0.04	0.39	0.01	0.01
$\epsilon 4 \times$ Engaged lifestyle										0.78	0.58	0.13	1.83
$R^2$		0.10				0.17			0.21				

Note: Interaction terms were entered separately.

\* $p < 0.05$ , \*\* $p < 0.01$ .

Table 4. Effect of *APOE*  $\epsilon 4$  and life events on negative affect ( $n = 130$ ).

	Model 1			Model 2			Model 3			Model 4			$F_{\Delta}$
	<i>B</i>	SE	$\beta$	<i>B</i>	SE	$\beta$	<i>B</i>	SE	$\beta$	<i>B</i>	SE	$\beta$	
Age	0.26	0.18	0.14	0.26	0.18	0.14	0.24	0.19	0.12	0.26	0.16	0.13	
Ethnicity	-0.73	0.80	-0.08	-0.74	0.81	-0.08	-0.99	0.84	-0.11	-0.75	0.83	-0.08	
Gender	-1.08	0.97	-0.10	-1.07	0.98	-0.10	-1.09	0.98	-0.10	-1.53	0.98	-0.14	
Residence	0.21	0.39	0.05	0.21	0.39	0.05	0.13	0.40	0.03	0.16	0.40	0.04	
$\epsilon 4$				0.05	0.88	0.01	-0.24	0.90	-0.02	0.63	0.96	0.06	
Proximal events							-0.04	0.35	-0.01	-0.01	0.34	0.00	
Distal events							-0.18	0.12	-0.14	-0.27	0.12	-0.22*	
Engaged lifestyle							-0.05	0.19	-0.02	-0.01	0.19	-0.01	
$\epsilon 4 \times$ Proximal events										0.39	0.92	0.04	0.18
$\epsilon 4 \times$ Distal events										0.88	0.37	0.25*	5.60*
$\epsilon 4 \times$ Engaged lifestyle										0.69	0.57	0.13	1.46
$R^2$		0.03				0.03			0.05				

Note: Interaction terms were entered separately.

\* $p < 0.05$ .

group of persons with Alzheimer's disease. Our results extend these findings by indicating that for very old adults, the *APOE*  $\epsilon 4$  appears to relate to reduced positive affect levels but does not appear to be associated with increased negative affect levels. Even after controlling for a number of covariates, our results also suggest that the *APOE*  $\epsilon 4$  allele may be event suppressing and may lessen the frequency with which individuals seek events or engage in activities.

To support the importance of combining the effects of genes and stress, we also found an important gene-environment interaction. The effect of  $\epsilon 4$  on negative affect was enhanced by distal events. Apparently, the  $\epsilon 4$  allele has a stronger effect on negative affect if very old adults have a larger number of distal experiences. It is important to note, however, that no significant interaction was obtained for  $\epsilon 4$  and proximal events or engaged lifestyle. The time frame for proximal events in this study was somewhat arbitrary. We used a two-year time interval to increase variability in the measure, but perhaps a shorter time frame would have been more effective in distinguishing centenarians who were still dealing with acute stressful events from those who had perhaps already overcome them.

*APOE* does not act in isolation to influence longevity and healthy aging. We have described an interaction between *APOE*, *HRAS1* (Harvey Rat Sarcoma Viral

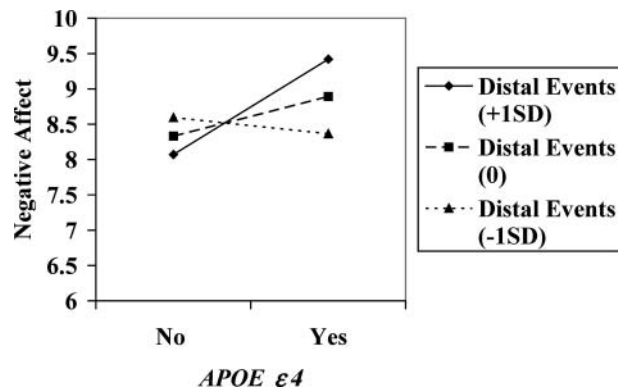


Figure 1. Interaction effect of  $\epsilon 4$  and distal experiences on negative affect (including admixed participants).

Oncogene Homolog 1), and *LASS1* (Longevity Assurance Gene 1 Homolog) that plays a role in determining these phenotypes (Jazwinski et al., 2010). The interaction of these genes supports a model describing a network of molecular and cellular interactions that impact both physical and cognitive function abilities. Favorable genotypes support healthy aging and delay frailty and morbidity. Thus, the role of *APOE* we describe here may emanate from this network and be moderated by interactions with other genes.

This study, like others, has a number of limitations. The results are only generalizable to a very old population in Georgia and would perhaps not be obtained for other age groups or in other regions. In addition, results may be limited to the assessed cohort of centenarians. Other cohorts may not necessarily show the same results. We also recognize that the main results are based on a sample that included admixed participants. Although our findings were essentially the same when excluding admixture participants, the only significant interaction reported barely missed the conventional significance cut-off. This may be because of the loss of power when excluding participants from a relatively small sample, or the results may be confounded because of unique genetic variation unrelated to the phenotype studied here, among admixed participants.

Variables of mental health were obtained from proxy informants, because centenarians who were low in cognitive functioning would not have been able to answer many of our questions. The environmental assessments, therefore, were biased by the views held by close family members of centenarians. Other variables, such as the measure of engaged lifestyle, could be modified to fit an oldest-old population. For example, active engagement in this group may take the form of visiting with others, eating meals in a group room, or taking short walks. Finally, many of our assessments were brief, because they had to be performed together with a long overall assessment battery. The response rate for proxies was very high because we inquired about proxies until we found a suitable person. From our experience, proxy respondents (typically family members) were quite willing to participate in our study.

Future research could consider including different measures of stress. This study only included major

life events (i.e., molar stress, Almeida et al., 2011). ‘Microscopic stressors’ (Almeida et al., 2011) including daily stressors, chronic stressors, and daily hassles may also have a direct impact on negative and positive affect, and these stressors could moderate the relationship between biological markers and emotional affect. Likewise, different genetic markers involved in regulating the stress response system may play an important role in predicting positive and negative affect (Kremen & Lyons, 2011). Finally, different mental health measures, such as depression and depressive symptoms as well as overall life satisfaction may be relevant outcome variables that should be studied.

Our results provide first insight into the relationship between the  $\epsilon 4$  allele of the *APOE* gene and its relationship to functioning and resources for a unique group of survivors. The *APOE* gene appears to be important for predicting positive emotional states directly and negative emotional states in interaction with distal experiences. Taken together, the results suggest that more attention should be paid to resources and emotional states of the oldest members in our society.

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