APOE ε4, rated life experiences, and affect among centenarians

Peter Martin, S. Michal Jazwinski, Adam Davey, Robert C. Green, Maurice MacDonald, Jennifer A. Margrett, Ilene C. Siegler, Jonathan Arnold, John L. Woodard, Mary Ann Johnson, Sangkyu Kim, Jianliang Dai, Li Li, Mark A. Batzer, Leonard W. Poon.

How to cite this manuscript

Published Version Information

Running Head: *APOE ε4* AND AFFECT

APOE ε4, Life Experiences, and Affect among Centenarians

Peter Martin[1]

S. Michal Jazwinski[2]

Adam Davey[3]

Robert Green[4]

Maurice MacDonald[5]

Jennifer A. Margrett[1]

Ilene C. Siegler[6]

Jonathan Arnold[7]

John Woodard[8]

Mary Ann Johnson[7]

Sangkyu Kim[2]

Jianliang Dai[2]

Li Li[9]

Mark A. Batzer[10]

Leonard W. Poon[7]

for the Georgia Centenarian Study[11]

[1]Iowa State University, [2]Tulane University, [3]Temple University, [4]Brigham and Women's Hospital and Harvard Medical School, [5]Kansas State University [6]Duke University, [7]University of Georgia, [8]Wayne State University, [9]Louisiana State University Health Sciences Center, and [10]Louisiana State University

Abstract

The purpose of this study was to assess the relationship between *APOE*, life events and engagement, and positive and negative affect among centenarians. One hundred and ninety six centenarians and near centenarians (98 years and older) of the Georgia Centenarians Study participated in this research. Next to *APOE* assessment, positive and negative affect, proximal (last two years) and distal (more than 20 years prior to testing) events, as well as a number of life engagement tasks were assessed. Results suggested that centenarians carrying the *APOE ε4* allele rated lower in positive affect, distal events, and in engaged lifestyle when compared to centenarians without the *APOE ε4* allele ($t = 3.43$, $p < .01$, $t = 3.19$, $p < .01$, and $t = 2.33$, $p < .05$, respectively). Blockwise multiple regressions indicated that *APOE ε4* predicted positive but not negative affect after controlling for demographics. Gene-environment interactions were obtained for *APOE ε4* and distal life events suggesting that carriers of the *APOE ε4* allele had higher scores of negative affect after having experienced more distal events, whereas non-carriers had reduced negative affect levels after having experienced more distal events.

APOE ε4, Life Experiences, and Affect among Centenarians

During the past 15 years, quite a bit of attention has been given to genetic effects on longevity (e.g., 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 (e.g., 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, *APOE*, and affect balance among centenarians.

The *ε4* allele of apolipoprotein E (*APOE*) on chromosome 19 has been related to late age onset of Alzheimer's disease and cognitive decline (Corder, Saunders, & Risch, 1994; Saunders, Schmader, & Breitner, 1993). The *ε4* allele has also been associated with a number of physical diseases, such as coronary artery disease (Lehtinin, Lehtimaki, & Sisto, 1995), vascular disease in diabetes (Vauhkonen, Niskanen, & Ryynanen, 1997), and stroke (Ferrucci, Gurlanik, & Pahor, 1997). It then comes as no surprise that *APOE* is also related to increased mortality (Corder, Lannfelt, & Vitanen, 1996; Tilvis, Strandberg, & Juva, 1998), even though some centenarian studies did not find significant differences in the frequency of the *ε4* allele between Alzheimer's disease and nondemented centenarians (Asada et al., 1996), whereas others did (Choi et al., 2003).

Why is it important to study APOE in a highly select 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 at 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 may be quite high (Andersen-Ranberg,

Schroll, & Jeune, B., 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 *ε4* allele with overall functioning.

Blazer, Fillenbaum, and Burchett (2001) assessed whether functional decline was associated with

the *APOE ε4* allele and noted no direct association. However, a statistically significant

interaction of the *ε4* allele with gender and baseline functional status was obtained. Greater

functional decline was observed among women with the *ε4* allele who also had poorer baseline

functioning. Another interaction effect was reported by Seeman, Huang, Bretsky, Crimmins,

Launer, and Guralnik (2005) who noted that the presence of at least one *ε4* allele reduced the

protective effects of education resulting in steeper cognitive declines with age.

More specifically, we propose to extend findings on the relationship between *APOE ε4*

and physical functioning to mental functioning. A number of studies have investigated the

association between *APOE ε4* and mental health. Borroni, Costanzi, and Padovani (2010) in

reviewing recent literature linking the APOE gene with behavioral and psychological symptoms

in dementia reported conflicting results about the effect of *APOE ε4* on mental health. Delano-

Wood et al. (2008) reported that the frequency of the *APOE ε4* allele was significantly higher in

depressed vs. non-depressed Alzheimer's disease patients. In addition, women possessing the

APOE ε4 allele were almost four times more likely to be depressed than those without the *ε4* allele. Other studies did not find an overall association between *APOE ε4* and depression (Garcia-Pena et al., 2010; Steffens, Norton, Hart, Skoog, Corgoran, & Breitner, 2003). A significant interaction effect of *APOE ε4* and age was reported such that the relationship of late-onset depression with respect to presence of the *ε4* allele was larger among those 80 years and older compared to those at younger ages. A third study (Gallagher-Thomson, O'Hara, Simmons, Kraemer, & Murphy, 2001) reported that increased stress levels were associated with increased depressive symptoms in caregivers who had the *ε4* allele.

Although there is emerging literature indicating that the *APOE e4* allele has a direct effect on some functional outcomes, several studies point to importance of gene-environment interactions (e.g., Chou, 2010). For example, Dar-Nimrod, Chapman, Robbins, Porsteinsson, Mapstone, and Duberstein (2012) reported that *APOE ε4* moderated the relationship between neuroticism and cognitive function. Neighborhood environmental factors also appear to attenuate the association of the *APOE ε4* allele with depressive symptoms (Yen, Rebok, Yang, & Lung, 2008). Less is known about the interactive relationship between life experiences, the *APOE ε4* allele and functioning. We therefore assessed to what extent life experiences can play such a moderating influence on the gene-environment relationship.

A number of studies have provided evidence for the relationship between stress and positive and negative affect (e.g., Folkman & Moskowitz, 2000; Mroczek & Almeida, 2004). Previous research indicates that stress has a negative effect on mood states (e.g., Bolger, DeLongis, Kessler, & Schilling, 1989) and most studies link proximal stress to affective states. However, it is also important to consider life-long cumulative stressors when assessing the link between stress and well-being. Life-long 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 stress in its relationship to affective outcomes.

Our research was guided by a life stress hypothesis (Ensel & Lin, 1991) suggesting that

the relationship between *APOE ε4* 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: (a)

genes and experiences may be independent influences or (b) life experiences can serve as a

moderator in the relationship between genes and functioning. It is unclear whether the

hypothesized effect of *APOE e4* is equally noticeable when predicting positive and negative

affect. We hypothesized that *APOE e4* and life stress had independent influences on positive and

negative affect. The relationship between *APOE e4* and affect was hypothesized to be moderated

by distal and proximal stressors.

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 who had no 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 percent) were women and 75.5 percent were Caucasian. Most participants (89.2%) were widowed, only 2.6 percent were married. A sizeable group (37.4%) had no more than eight years of education, whereas 23.7 percent had a college degree. About a third of the centenarians resided in their private home or apartment (36.7 %), whereas 17.9 percent resided in assisted living facilities and 45.4 percent in skilled nursing facilities. Only 4.2 percent were rated by proxies as being in "poor" health, 20.0 percent were rated as being in "fair" health, whereas 48. 3 percent were rated as being in "good" and 27.5% in "excellent" health. The average MMSE score of the participants was $M = 16.36$. Demographic characteristics are summarized in Table 1.

Information about affect balance, life events, and lifetime activities 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, & Rubinstein, 1991) but they tend to be more knowledgeable about personal, familial, 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).

Proxies were nominated by the centenarians, and most of them (61.1%) were adult children. Additional proxies included nieces and nephews (13.9%), granddaughters (9.9%), and miscellaneous 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 visit.

Measures

Positive and negative affect. Proxies assessed affect with the Bradburn Affect Balance Scale (Bradurn, 1969). The scale consists of the 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 $\alpha = .79$ for positive affect and $\alpha = .74$ 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 (Dohrenwend, Askenasy, Krasnoff, & 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"). 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, working, 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 .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 Gentra Generation DNA Purification System. Exon 4 sequences were amplified by the polymerase

chain reaction (PCR), using 5'-CTTGGGTCTCTCTGGCTCATC-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 amplicaton. 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 ε4 (ε2/ε4, ε3/ε4, ε4/ε4)* or non-*ε4 (ε2/ε2, ε2/ε3, ε3/ε3)*.

Population stratification was carried out using the program Structure (Pritchard et al., 2000). 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 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 ε4* carriers and non-carriers 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). The second block contained the *ε4* variable,

the third block contained the life experience variables (i.e., proximal events, distal events, and engaged lifestyle), and the fourth block contained the *ε4* 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 ε4* allele as compared to those not carrying the *APOE ε4* 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 x environment) interaction effects.

The results comparing the different genetic groups are summarized in Table 2. Carriers of the *ε4* allele had lower positive affect scores and centenarians who were carriers of the *ε4* allele had experienced fewer distal events and were lower in engaged lifestyle. We repeated the analysis by excluding admixed participants, and the same significant differences were obtained.

Table 3 and 4 summarize the direct effects of the *ε4* allele and events on positive and negative affect. For positive affect, carriers of *ε4* had lower scores in positive affect. Engaged lifestyle also significantly predicted positive affect indicating that those who had high scores in engaged lifestyle also reported higher scores in positive affect (Table 3). For negative affect, only distal events were significant predictors, indicating that centenarians who reportedly had experienced more life events had lower negative affect scores. Table 4 also highlights a significant gene x environment interaction for negative affect. The effect of the *ε4* allele on negative affect was stronger when participants reportedly had more distal (lifetime) experiences (Figure 1). Additional sex by *ε4* 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 *ε4* allele and engaged lifestyle again were significant predictors and no significant interactions were obtained. For negative affect, distal events was again significant but there was only a statistical trend for the gene X distal event interaction, $\beta = .21$, $t = 1.73$, $p = .086$.

Discussion

Although there is quite a bit of research highlighting the relationship between the *ε4* allele and Alzheimer's disease, cardiovascular disease, and mortality, much less is known about the direct and moderating effect of *ε4* on mental health. This research attempted to fill this gap by assessing the relationship between *ε4* and affect by advancing a stressful life events hypotheses of adaptation. We had hypothesized that *APOE ε4* and life stress had independent influences on positive and negative affect. The relationship between *APOE ε4* and affect was hypothesized to be moderated by distal and proximal stressors.

Two primary results emerged from our analyses. First, *APOE ε4* allele carriers differed significantly in positive affect, distal events, and lifetime activities. The effect of *APOE ε4* was maintained even after controlling for covariates. Second, *ε4* interacted significantly with distal life experiences to impact negative affect but not positive affect.

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. Carriers of the *ε4* 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 ε4* allele is directly related to mental health. For example, Delano-Wood et al. (2008) recently reported that the

frequency of *APOE e4* alleles was significantly higher in a depressed group of Alzheimer's diseases patients. Our results extend these findings by indicating that for very old adults the *APOE ε4* appears to reduce positive affect levels but does not appear to increase negative affect levels. Even after controlling for a number of covariates, our results also suggest that the *APOE ε4* 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 interactions. The effect of *ε4* on negative affect was enhanced by distal events. Apparently, the *ε4* 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 *ε4* and proximal events or engaged lifestyle.

APOE does not act in isolation to influence longevity and healthy aging. We have described an interaction between *APOE*, *HRAS1*, and *LASS1* 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 ability. 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 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. Finally, many of our assessments were brief, because they had to be performed together with a long overall assessment battery. Nonetheless, our results provide us with first insights about the relationship between the *ε4* allele of the *APOE* gene and its relationship to functioning and resources for a unique group of survivors. Distal experiences amplify the effect of *ε4* on negative affect.

Acknowledgements

References

Andersen-Ranberg, K., Schroll, M., & Jeune, B. (2001). Healthy centenarians do not exist, but autonomous do: A population-based study of morbidity among Danish centenarians. *Journal of the American Geriatrics Society, 49*, 900-908.

Asada, T., Yamagata, Z., Kinoshita, T. et al. (1996). Prevalence of dementia and distribution of ApoE alleles in Japanese centenarians: an almost-complete survey in Yamanashi prefecture, Japan. *Journal of the American Geriatrics Society, 44,* 151-155.

Borroni, B., Costanzi, C., & Padovani, A. (2010). Genetic syseptibility to beavhioral and psychological symptoms in Alzheimer disease. *Current Alzheimer Research, 7*, 158-164.

Blazer, D. G., Fillenbaum, G., & Burchett, B. (2001). The APOE-E4 allele and the risk of functional decline in a community sample of African American and White older adults. *Journal of Gerontology: Biological and Medical Sciences, 56,* M785-M789.

Bolger, N., DeLongis, A., Kessler, R. C., & Schilling, E. A. (1989). Effects of daily stress on negative mood. *Journal of Personality and Social Psychology, 57*, 808-818.

Bradburn, N. M. (1969). *The structure of psychological well-being.* Chicago: Aldine.

Cardon, L. R., & Palmer, L. J. (2003). Population stratification and spurious allelic association. *The Lancet, 361*, 598-604.

Choi, Y.-H. Kim, J.-H., Kwan Kim, D., Kim, J.-W., Kim, D-K., Lee, M. S., Kim, C. H., & Park, S. C. (2003). Distributions of ACE and APOE polymorphisms and their relations with dementia status in Korean centenarians. *Journal of Gerontology: Medical Sciences, 58A,* 227-231.

Chou, K.-L. (2010). Moderating effect of Apolipoprotein genotype on loneliness leading to depressive symptoms in Chinese older adults. *American Journal of Geriatric Psychiatry, 18,* 313-322.

Corder, E., Lanfelt, L., & Vitanen, M. (1996). Apolipoprotein E genotype determines survival in the oldst old (85 years or older) who have good cognition. *Arch Neurol, 53,* 418-422.

Corder, E., Saunders, A., & Risch, N. (1994). Protective effect of apolipoprotein E type 2 allele for late onset Alzheimer's disease. *Nat. Genet., 7,* 180-184.

Dar-Nimrod, I., Chapman, B. P., Robbins, J. A., Porsteinsson, A., Mapstone, M., & Duberstein, P. R. (2012). Gene by neuroticism interaction and cognitive function among older adults. *International Journal of Geriatric Psychiatry, 27,* 1147-1154.

Delano-Wood, L., Houston, W. S., Emond, J. A., Marchant, N. L., Salmon, D. P., Jeste, D. V., Thal, L. J., & Bondi, M. W. 2008) APOE genotype predicts depression in women with Alzheimer's disease: A retrospective study. *International Journal of Geriatric Psychiatry, 23,* 632-666.

Dohrenwend, B. S., Krasnoff, L., Askenasy, A. R., & Dohrenwend, B. P. (1978). Exemplification of a method for scaling life events: The PERI Life Events Scale. *Journal of Health and Social Behavior, 19,* 205-229.

Ensel, W.M., & Lin, N, (1991). The life stress paradigm and psychological distress. *Journal of Health and Social Behavior, 32,* 321-341.

Ferrucci, L., Gurlanik, J., & Pahor, M. (1997). Apolipoprotein E epsilon 2 allele and risk of stroke in the older population. *Stroke, 28,* 2410-2416.

Folkman, S., & Moskowitz, J. T. (2000). Positive affect and the other side of coping. American Psychologist, 55, 647-654. doi: 10.1037/0003-066X.55.6.647

Gallagher-Thompson, D., O'Hara, R., Simmons, A., Kraemer, H. C., & Murphy, G. M., Jr. (2001). Apolipoprotein E ε4 allele affects the relationship between stress and depression in caregivers of patients with Alzheimer's disease. *Journal of Geriatric Psychiatry and Neurology, 14,* 115-119.

Garcia-Pena, C., Juarez-Cedillo, T., Cruz-Robles, D., Fragoso, J. M., Sanchez-Garcia, S., Rodriguez-Perez, J. M…Vargas-Alarcon, G. (2010). Depressive symptoms and APOE polymorphisms in an elderly population-based sample. *Psychiatric Genetics, 20,* 215-220. Doi: 10.1097/YPG.0b013e32833a211a.

Gu, D. (2008). General data quality assessment of the CLHLS. In Z. Yi, D. L. Poston, Jr., D. A. Vlosky, & D. Gu (Eds.), *Healthy longevity in China: Demographic, socioeconomic, and psychological dimensions* (pp. 39-59). New York: Springer.

Hultsch, D. F., Hertzog, C., Small, B. J., & Dixon, R. A. (1999). Use it or lose it: Engaged lifestyle as a buffer of cognitive decline in aging? *Psychology and Aging, 14,* 245-263.

Jazwinski, S.M., Kim, S., Dai, J., Li, L., Bi, X., Jiang, J.C., Arnold, J., Batzer, M.A., Walker, J.A., Welsh, D.A., Lefante, C.M., Volaufova, J., Myers, L., Su, L.J., Hausman, D.B., Miceli, M.V., Ravussin, E., Poon, L.W., Cherry, K.E., Welsch, M.A., Georgia Centenarian Study, & Louisiana Healthy Aging Study. (2010). *HRAS1* and *LASS1* with *APOE* are associated with human longevity and healthy aging. *Aging Cell, 9,* 698-708.

Lehtinin, S., Lehtimaki, T., & Sisto, T. (1995). Apolipoprotein E polymorphism, serum lipids, myocardial infarction and severity of angiographically verified coronary artery disease in men and women. *Artherosclerosis, 114,* 83-91.

MacDonald, M., Martin, P., Margrett, J., & Poon, L. W. (2009). Correspondence of perceptions about centenarians' mental health. *Aging and Mental Health, 13, 827-837.*

Martin, P., Rott, C., Hagberg, B., & Morgan, K. (2000). *Centenarians - Autonomy vs. dependence in the oldest old*: New York: Springer.

Martin, P., da Rosa, G., & Poon, L. W. (2011). The impact of life events on the oldest old. In L. W. Poon & J. Cohen-Mansfield (Eds.), *Understanding the well-being of the oldest old* (pp. 96-110).. Cambridge: Cambridge University Press.

Mroczek, D. K., Almeida, D. M. (2004). The effect of daily stress, personality, and age on daily negative affect. *Journal of Personality, 72,* 355–378.

Perls, T., Kunkel, L. M., & Puca, A. A. (2002). The genetics of exceptional human longevity. *Journal of the American Geriatrics Society, 50,* 359-368.

Perls, T., & Terry, D. (2003). Genetics of exceptional longevity. *Experimental Gerontology, 38,* 725-730.

Poon, L. W., Jazwinski, S.M., Green, R. C., Woodard, J. L., Martin, P., Rodgers, W. L., Johnson, M. A., Hausman, D., Arnold, J., Davey, A., Batzer, M. A., Markesbery, W. R., Gearing, M., Siegler, I. C., Reynolds, S., & Dai, J. (2007). Methodological considerations in studying centenarians: Lessons learned from the Georgia Centenarian Studies. In L. W. Poon & T. T. Perls (Eds.), *Annual Review of Gerontology and Geriatrics: Vol. 27. Biopsychosocial approaches to longevity* (pp. 231-264). New York: Springer.

Pritchard, J.K., Stephens, M., & Donnelly, P. (2000). Inference of population structure using multilocus genotype data. *Genetics, 155,* 945-959.

Rodgers, W. L., & Herzog, A. R. (1992). Collecting data about the oldest: Problems and procedures. In R. M. Suzman, D. P. Willis, & K. G. Manton (Eds.), *The oldest old* (pp. 135-156). New York: Oxford University Press.

Rothman, M. L., Hedrick, K. A., Bulcroft, K. A., Kickam, D. H., & Rubenstein, L.Z. (1991). The

validity of proxy-generated scores as measures of patient health status. *Medical Care, 29,*

115-124.

Ryff, C.D., Singer, B., Love, G.D., & Essex, M.J. (1998). Resilience in adulthood and later life:

Defining features and dynamic processes. In J. Lomranz (Ed.), *Handbook of aging and*

mental health (pp. 69-96). New York: Plenum.

Saunders, A., Schmader, K., & Breitner, J. (1993). Apolipoprotein E epsilon 4 allele distributions

in late onset Alzheimer's disease and in other amyloid forming diseases. *Lancet, 342,*

710-711.

Seeman, T. E., Huang, M.-H., Bretsky, P., Crimmins, E., Launer, L., & Guralnik, J. M. (2005).

Education and APOE-e4 in longitudinal cognitive decline: MacArthur Studies of

Successful Aging. *Journal of Gerontology: Psychological Sciences, 60B,* P74-P83.

Steffens, D. C., Norton, M. C., Hart, A. D., Skoog, I., Corcoran, C., & Breitner, J. C. S. (2003).

Apolipoprotein E genotype and major depression in a community of older adults. The

Cache County Study. *Psychological Medicine, 33,* 541-547.

Tilvis R. S., Strandberg T. E., & Juva K. (1998). Apolipoprotein E phenotypes, dementia and

mortality in a prospective population sample. *Journal of the American Geriatrics Society*

46, 712-715.

Vauhkonen, I., Niskanen, L., & Ryynanen, M. (1997). Divergent association of apolipoprotein E

polymorphism with vascular disease in patients with NIDDM and control subjects.

Diabetes Med., 14, 748-756.

Vijg, J., & Campisi, J. (2008). Puzzles, promises, and a cure for ageing. *Nature, 454,* 1065-1071.

Yen, Y.-C., Rebok, G. W., Yang, M.-J., & Lung, F.-W. (2008). A multilevel analysis of the

influence of Apolipoprotein E genotypes on depressive symptoms in late-life moderated

by the environment. *Progress in Neuro-Psychopharmacology & Biological Psychiatry,

32,* 479-486.

Table 1

Demographic Characteristics

Variable	N	Percentage	M	SD
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		

(table continues)

Table 1 *continued*

Variable	N	Percentage	M	SD
Residence				
Private Home	72	36.7		
Assisted Living	35	17.9		
Skilled Nursing	89	45.4		
Total	196	100.0		
ε4 allele				
No	159	81.1		
Yes	37	18.9		
Total	196	100.0		
MMSE	196		16.36	9.08

Table 2

Mean Differences by APOE ε4 Allele

	n	ε4 No M	ε4 Yes M	t
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[1]	176	4.13	2.60	3.19**
Engaged Lifestyle	139	4.14	3.13	2.33*

Note. [1]Equal variance not assumed.

*p < .05. **p < .01.

Table 3

Effect of APOE ε4 and Life Events on Positive Affect (n = 126)

	Model 1			Model 2			Model 3			Model 4			F_Δ
	B	SE	β	B	SE	β	B	SE	β	B	SE	β	
Age	-.28	.20	-.13	-.30	.19	-.14	-.22	.19	-.10	-.22	.19	-.10	
Ethnicity	-56	.86	-.06	-.23	.84	-.02	-.25	.85	.03	.26	.86	.03	
Gender	1.12	1.04	-.09	-1.45	1.01	-.12	-1.58	1.00	-.13	-1.60	1.02	-.13	
Residence	-1.04	.42	-.22*	-.95	.40	-.20*	-.81	.41	-.17	-.81	.41	-.17	
ε4				-2.84	.90	-.26**	-2.31	.92	-.21*	-2.27	1.00	-.21*	9.90**
Proximal Events							.12	.35	.03	.13	.35	.03	
Distal Events							.15	.12	.11	.14	.13	.11	
Engaged Lifestyle							.40	.20	. 18*	.40	.20	.18*	
ε4*Proximal Events										-.55	.94	.05	0.34
ε4*Distal Events										.04	.39	.01	0.01
ε4*Engaged Lifestyle										.78	.58	.13	1.83
R^2		.10			.17			.21						

Note. Interaction terms were entered separately.

p < .05. **p* < .01.

Table 4

Effect of APOE ε4 and Life Events on Negative Affect (n = 130)

	Model 1			Model 2			Model 3			Model 4			F_Δ
	B	SE	β	B	SE	β	B	SE	β	B	SE	β	
Age	.26	.18	.14	.26	.18	.14	.24	.19	.12	.26	.16	.13	
Ethnicity	-.73	.80	-.08	-.74	.81	-.08	-.99	.84	-.11	-.75	.83	-.08	
Gender	-1.08	.97	-.10	-1.07	.98	-.10	-1.09	.98	-.10	-1.53	.98	-.14	
Residence	.21	.39	.05	.21	.39	.05	.13	.40	.03	.16	.40	.04	
ε4				.05	.88	.01	-.24	.90	-.02	.63	.96	.06	
Proximal Events							-.04	.35	-.01	-.01	.34	.00	
Distal Events							-.18	.12	-.14	-.27	.12	-.22*	
Engaged Lifestyle							-.05	.19	-.02	-.01	.19	-.01	
ε4*Proximal Events										.39	.92	.04	.18
ε4*Distal Events										.88	.37	.25*	5.60*
ε4*Engaged Lifestyle										.69	.57	.13	1.46
R^2		.03			.03			.05						

Note. Interaction terms were entered separately.

*p < .05.

Figure Caption

Figure 1. Interaction Effect of *ε4* and Distal Experiences on Negative Affect (Including Admixed Participants)