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Cognitive resilience among *APOE* ε4 carriers in the oldest old

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The authors have no conflicts to declare.

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The data that support the findings of this study are available upon request from the Women's Health Initiative and the Women's Health Initiative Memory Study subject to study policies as well as privacy and ethical restrictions.

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Abstract

Objective: Relatively few *APOE* ε4+ carriers survive to old age (age 80+) without cognitive impairment (CI), thus little is known about distinguishing characteristics of resilient *APOE* ε4+ carriers. Herein we describe the sociodemographic characteristics of a large sample of resilient *APOE* ε4+ women from the Women's Health Initiative Memory Study (WHIMS) and compare them to non-carriers and *APOE* ε4+ women who developed CI before age 80.

Methods: Women were recruited for clinical trials evaluating post-menopausal hormone therapy and incidence of dementia. During post-trial follow-up, cognitive status was adjudicated annually. Among 5,716 women, we compared groups by *APOE* ε4 status using logistic regression, co-varying for treatment, demographics, lifestyle, cardiovascular and physical function, well-being, and self-rated general health.

Results: Among 557 *APOE* ε4+ women, those who survived to age 80+ without CI had higher baseline self-rated general health (odds ratio [OR] 1.02, 95% confidence interval [CI] 1.01-1.04) and cognitive scores (OR 1.18, 95% CI 1.12-1.25) than those who did not reach age 80 without CI. Baseline high total cholesterol and LDL levels were similar across *APOE* ε4+ groups but were higher compared with *APOE* ε4− women. Among women who survived to 80+ without CI, more *APOE* ε4+ women had a history of high total cholesterol (p=0.003) and LDL cholesterol (OR 1.01, 95% CI 1.00-1.01). There were no differences in hypertension, diabetes, or other vascular risk factors in *APOE* ε4+ women compared with non-carriers.

Conclusions: Results highlight the importance of baseline cognitive function, and general health for late-life cognition among ε4+ women.

Keywords

cognitive resilience; *APOE* ε; oldest old; mild cognitive impairment; probable dementia

1. Introduction:

Resilience has been defined as the ability to avoid negative outcomes in the presence of significant risk factors.[1] Older adults who survive to late old age without physical or cognitive deficits, or those who recover function following aversive exposures, can be considered resilient. The primary genetic risk factor for Alzheimer's disease (AD) is the Apolipoprotein E (*APOE*) ε4 allele; those who carry one or more *APOE* ε4 allele(s) are at significantly increased risk of AD.[2,3] When ε4 carriers survive to late old age without impairment in the form of mild cognitive impairment (MCI) or dementia, including AD,

they stand out as “survivors” of the primary genetic risk factor for late-onset AD. Although several studies have evaluated the association between *APOE* ε4 carriage and normal cognitive function in late old age specifically among *APOE* ε4 carriers, they have had relatively small samples.[4-6] A large and well-characterized cohort of aged women ε4 carriers can be found in the Women’s Health Initiative Memory Study (WHIMS).

Carriage of one or more *APOE* ε4 allele(s) is not only an established risk factor for AD,[2,3] it is also a risk factor for cardiovascular disease (CVD),[7] and early mortality.[8,9] Yet, little is known about the characteristics of cognitively resilient *APOE* ε4 carriers. Higher literacy and levels of education,[4,6] actively participating in cognitively stimulating leisure activities,[6] and maintaining vascular health[6] have been previously associated with cognitive resilience in *APOE* ε4 carriers. For the purposes of this study, we define cognitive resilience as surviving to age ≥80 without CI (adjudicated MCI or probable dementia). Comparing resilient ε4 carriers to non-resilient ε4 carriers and to resilient non-carriers may suggest modifiable protective factors. Currently, there are limited data on characteristics that distinguish cognitively healthy (or resilient) *APOE* ε4 carriers who survive to old age from ε4 carriers who become impaired. Nor do we know whether such characteristics are unique to ε4 carriers, or if they are common characteristics of survivors across genotypes. Among the other common *APOE* isoforms, the ε3 allele is considered neutral with respect to AD risk,[10] while the ε2 allele is thought to offer protection from AD[10,11] and has been associated with increased longevity.[12] The *APOE*-ε alleles are distinguished by two missense SNPs, rs429358 and rs7412, that result in a cysteine to arginine change in the case of rs429358 (T > C), and arginine to cysteine in the case of rs7412 (C > T). The combination of these two SNPs define the common *APOE-ε3* allele (rs429358:T; rs7412:C) and the less common *APOE-ε4* (rs429358:C; rs7412:C) and *APOE-ε2* (rs429358:T; rs7412:T) alleles.[13] The most common genotype is ε3/ε3 (~55%) followed by ε3/ε4 (~25%), and ε2/ε3 (~15%); the ε4/ε4, ε2/ε2, ε2/ε4, and other rarer genotypes comprise the remaining ~5%.[13]

Goveas et al,[14] evaluated independent predictors of preserved global cognitive function in WHIMS women aged 80 years and older, noting that the absence of the *APOE* ε4 allele was associated with maintenance of cognitive function. More recently, Driscoll et al,[15] showed increased risk of probable dementia associated with *APOE* and *TOMM40* in WHIMS in a detailed study of SNPs from candidate genes associated with cognitive impairment or AD. In the current study, we focus specifically on *APOE* genotypes and use age and cognitive outcomes (cognitively normal, MCI, or probable dementia) to define resilience spanning ~20 years of follow-up across WHIMS and its extension studies. We compare older (≥ 80 years) cognitively resilient *APOE* ε4 carriers (cognitively normal) to non-resilient *APOE* ε4 carriers (adjudicated MCI or probable dementia) and to other *APOE* genotypes on demographic and health status characteristics including common risk factors for AD. Age 80 was selected as an appropriate cutoff to define resilience among *APOE* ε4 carriers as these individuals account for ~90% of incident AD cases prior to age 80, [16] after which the risk of AD in ε4 carriers declines. The specific objectives of this study were to: a) characterize cognitively resilient *APOE* ε4 carriers who survived to age 80 or older without MCI or probable dementia, b) compare these women to non-resilient *APOE* ε4 carriers (who have MCI or dementia), and c) identify independent factors that distinguish resilient *APOE* ε4 carriers from others.

2. Methods:

2.1 Participants

The Women's Health Initiative Memory Study, an ancillary study to the Women's Health Initiative (WHI) Hormone Trials, enrolled women between the ages of 65 to 79 years from 1995 to 1999. Written informed consent was obtained from all participants, and the Institutional Review Board at each clinic site approved the consent form. The study design has been published previously.[17-20] WHIMS was designed to study the effects of post-menopausal hormone therapy on the incidence of MCI or probable dementia in parallel clinical trials. The trials compared conjugated equine estrogen alone (CEE-alone in women with hysterectomy), or CEE combined with medroxyprogesterone acetate (progestin, [E + P]), with respective placebo groups. Annual cognitive screening, comprehensive clinical and neurocognitive exams for participants screening positive and other information collected from participants and knowledgeable friends or family members, were used in central adjudication (described below) by specialists who classified women as having no cognitive impairment, MCI, or probable dementia. Participants were followed after the trials were ended in 2002 (E + P)[17,19] and 2004 (E-alone)[18,21] with annual in-person cognitive assessments until 2007-2008 at which time the study transitioned to telephone cognitive assessments (currently ongoing). Participants included in this analysis were limited to 5,714 white women with *APOE* genotype data.

2.2 *APOE* Genotypes:

APOE genotypes were based on two SNPs, rs429358 and rs7412. Genetic data were imputed and harmonized across WHI genome wide association studies. Imputation used the 1000 Genomes Project reference panel and MaCH algorithms implemented in Minimac.[22] Both SNPs had high imputation quality (R^2 >0.97 for rs429358 and R^2 > 0.97 for rs7412). The genotypes were grouped as follows: ε2/ε2 and ε2/ε3 (generally accepted as protective); ε2/ε4 (protective *and* high risk alleles); ε3/ε3 (neutral); ε3/ε4 and ε4/ε4 (increased risk for AD). Because the ε2/ε4 carriers have both the high risk and "protective" alleles, and because they have a very low population frequency, they were excluded from the primary analyses.

2.3 Cognitive Assessment:

WHIMS had two phases, one during the active intervention period (1996-2006) and the second, a follow-up observational period which continues through today. During the active intervention period (in the first ~10 years of the study), participants were administered the Modified Mini-Mental State Exam (3MS) annually.[23] Women scoring below pre-determined age- and education-adjusted cut points were referred for a clinical evaluation by a board certified physician and neuropsychological testing, including portions of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) battery,[24] the Mini Mental State Exam (MMSE),[25] the Trail Making Test Parts A and B,[26] a structured psychiatric interview,[27] and the Geriatric Depression Scale 15-item short form (GDS).[28] A knowledgeable informant completed the Acquired Cognitive and Behavior Changes (ACBD)[20] interview. A central panel of dementia experts then adjudicated cases, classifying participants as cognitively normal, MCI, or probable dementia, according to standard criteria.[29,30] In the

WHIMS observational extension period (2007-present), a validated telephone cognitive battery[31] was administered annually to all participants comprising a modified version of the Telephone Interview for Cognitive Status (TICS-m),[32] the Oral Trail Making Tests Part A and B,[33] the East Boston Memory Test,[34] Digit Span,[35]and Verbal fluency/Animals.[36] When participants scored below 31 points on the TICS-m, the Dementia Questionnaire[37] was administered to an informant to evaluate functional status. Cognitive status was then adjudicated as MCI, probable dementia, or no impairment, as described above.

2.4 Predictors:

At baseline, participants reported their age, race/ethnicity, education level, marital status, family income, hysterectomy status, alcohol consumption, and cigarette smoking. Health history included history of stroke, coronary heart disease, hypertension, diabetes, and high cholesterol treated with medication. Two measures of seated blood pressure were taken, and the average of the two recorded. Hormone therapy (HT) study arm and the region of the US where the participant was recruited were included as covariates. Participants provided responses to the validated WHI Insomnia Rating Scale (WHIIRS)[38,39] to quantify their sleep quality.

We used several constructs derived from the RAND 36-item Health Survey including physical function, emotional wellbeing, quality of life, and general health.[40-42] A physical function construct was derived from 10 questions about a typical day's activities with rankings from no limitation to quite a lot of limitation, with higher scores indicating better function [range 0-100]. Items included: vigorous activities, moderate activities, lifting, climbing, bending, walking (>1 mile, several blocks, one block), and bathing or dressing oneself. Ratings of emotional well-being were derived [range 0-100; higher scores being more favorable] and a rating of quality of life was scored on a scale from 0 (dissatisfied) to 10 (satisfied). A general health construct was derived from a series of health questions ranked from 1-5. These questions focused on whether one gets sick easier than others, is as healthy as others, their expectations of health, and two questions on overall rating of health [range 0-100; higher scores reflect better health]. Scores on the Burnam depression screener, which includes a short version of the Center for Epidemiologic Studies-Depression Scale,[43] were used to quantify depressive symptoms. Baseline 3MS scores were also included.

2.5 Statistical Analysis:

2.5.1 Descriptive Statistics: The women's baseline characteristics were evaluated in descriptive analyses by *APOE* genotype with analysis of variance for continuous variables and χ^2 tests for categorical variables. Participants were classified by adjudicated cognitive status (normal, MCI, probable dementia) and status at age 80: MCI or probable dementia onset at <80 years; normal cognition at 80 or older. Women who did not have a diagnosis and did not survive to age 80 or older were excluded.

2.5.2 Prediction of Survival to 80+ without Cognitive Impairment Among ε4 Carriers: Logistic regression models were used to identify independent predictors of survival to age ≥80 without a diagnosis of CI. We controlled for time from baseline to diagnosis of MCI or probable dementia or age 80, whichever came first, and compared

APOE ε3/4 and ε4/4 carriers who survived to age 80 without CI to those who received a diagnosis prior to age 80.

2.5.3 Comparison of Survivors to 80+ without Cognitive Impairment Across all Genotypes: A second set of models compared *APOE* ε3/4 and ε4/4 "survivors" to women with other genotypes who also survived to age 80 without CI. Model building included a series of models: 1) demographic, cognitive and health variables, 2) adding well-being and lifestyle variables measured at baseline, 3) reduced models retaining only key variables (time to age 80, education, and randomization arm) and significant variables, and 4) reduced models including women who developed impairment after age 80 in the "survivors" group.

3. Results:

3.1 Descriptive Statistics:

A total of 5,714 white women had data on *APOE* genotypes and were eligible for inclusion in the study. Table 1 provides a description of the women's demographic, health, and well-being characteristics by genotype. More women with one or two *APOE* ε4 alleles (ε3/4 and ε4/4; n=1,298) reported having a history of high cholesterol requiring pills (p<.0001), higher LDL cholesterol levels (p<.0001), and significantly more of the women in this group were classified as having probable dementia (p<.0001) compared to the other groups.

3.2 Prediction of Survival to 80+ without Cognitive Impairment Among ε4 Carriers:

Table 2 portrays the results of logistic regression models comparing *APOE* ε3/4 and ε4/4 carriers who survived to age ≥80 without a diagnosis of CI (*i.e.*, MCI or probable dementia), to ε4 carriers who received a diagnosis of CI prior to age 80. Model 1 shows a significantly increased odds of escaping CI among those without a history of diabetes (p=0.03). In the reduced model (Model 3a), the only remaining significant predictors besides time to age 80, were indicators of better general health (odds ratio (OR) 1.02, 95% confidence interval (CI) 1.01, 1.04) and higher baseline 3MS score (OR 1.18, 95% CI 1.12, 1.25). When 172 additional women in the resilient group who developed impairment after the age of 80 were included (Model 3b), there was no appreciable change in results.

3.3 Comparison of Survivors to 80+ without Cognitive Impairment Across all Genotypes:

Table 3 presents comparisons between *APOE* ε3/4 and ε4/4 carriers who survived to age ≥80 without a diagnosis of CI and those of other genotypes who similarly survived to age ≥80 without a diagnosis of CI. The reduced model (Model 3a) shows that the only item significantly differentiating *APOE* ε3/4 and ε4/4 from other genotypes was a history of high cholesterol among *APOE* ε3/4 and ε4/4 carriers compared to non-carriers (OR 0.68, 95% CI 0.53, 0.88) and greater chance of survival without impairment per unit increase in LDL cholesterol (OR 1.01, 95% CI 1.00, 1.01). As in Table 2, Model 3b includes 172 women who developed impairment after the age of 80 and results did not change significantly.

3.4 Sensitivity Analyses:

As noted above, inclusion of women who developed CI after the age of 80 did not materially change our results in either the comparison among *APOE* ε3/4 and ε4/4 carriers or between *APOE* ε3/4 and ε4/4 carriers and non-carriers. Comparisons of *APOE* ε3/4 and ε4/4 carriers to *APOE* ε3/3 women yielded results very similar to the comparisons that also included ε2/2 and ε2/3 carriers (Supplemental Table 1). Inclusion of n=135 ε2/4s with the other ε4 carriers did not change the within ε4 comparison (Supplemental Table 2) but it did change results in comparisons of ε4 carriers to non-carriers (Supplemental Table 3). History of high cholesterol (yes/no) was no longer significant, likely because fewer ε2/4 carriers had a history of high cholesterol at baseline (9%) compared to ε3/4 and ε4/4 carriers (22.4%). LDL remained marginally significant (OR 1.01, 05% CI 1.00, 1.01) and HDL per unit increase in cholesterol became marginally significant (OR 0.99, 95% CI 0.98, 1.00) as ε2/4 carriers had slightly lower levels of HDL similar to ε3/4 and ε4/4 carriers (Table 1). A comparison between all ε4 carriers and ε3/3s (Supplemental Table 4), showed that women without a history of hypertension had better odds of survival to age 80 without CI (OR 1.25, 95% CI 1.02, 1.54).

4. Discussion:

In this analysis, we explored the associations between various health, lifestyle, and potentially modifiable risk factors for CI across subgroups defined by *APOE* ε4 carrier status to determine what characterizes *APOE* ε4 carriers who survive to age 80+ without CI. Carriers who survived to ≥80 years of age without CI had a better self-rating of general health and higher level of baseline global cognitive functioning. Compared to women of other *APOE* genotypes who survived to age ≥80 without CI, cognitively resilient *APOE* ε3/4 and ε4/4 carriers were more likely to have a history of high cholesterol. Yet there was no significant difference in cholesterol (history of high cholesterol, LDL levels, or HDL levels) across *APOE* ε4 carrier groups as a whole. This is not unexpected as ε4 carriage is associated with cholesterol metabolism.[7] There were no significant differences between groups in other measures of cardiovascular health or lifestyle factors that are typically associated with increased risk for CI such as diabetes. However, a *post-hoc* examination among *APOE* ε4 carriers revealed that a significantly greater number of ε4 carriers who developed impairment had diabetes while few of the ε4 carriers who escaped impairment had diabetes.

The *APOE* gene codes for apolipoprotein E, which is a transport protein that plays a role in cholesterol transport and maintenance of lipid homeostasis in both the periphery and central nervous system. The *APOE* ε4 allele is a risk factor for both CVD and high cholesterol levels.[44] In the brain, *APOE* is implicated in beta-amyloid clearance, and this dual role, in the periphery and in brain, may explain the pleiotropic effect of the *APOE* ε4 as a risk variant for both CVD and Alzheimer's disease.

Observational studies have reported conflicting results with regard to serum cholesterol levels and dementia risk. High cholesterol in mid-life has been shown to increase risk of dementia,[45] while high cholesterol in *later* life has been previously associated with decreased dementia risk in the Gŏteborg Study[46] and the Longitudinal Aging Study

Amsterdam.[47] Moreover, declines in cholesterol levels from mid-life to late life have been associated with increased dementia risk.[48] In the Honolulu Asia Aging Study (HAAS), older Japanese-American men demonstrated declines in cholesterol levels up to 15 years prior to dementia onset.[48] A longitudinal evaluation of cholesterol levels across the life span in the Framingham Heart Study (original cohort) showed that those who lived past age 90 had lower mid-life levels of cholesterol and in late life they had higher levels of total cholesterol than those who did not survive to late old age.[50] It is possible that pathological processes associated with dementia facilitate a decline in total cholesterol levels from mid-life to late life, correlating with the development of AD pathology.[49] Or perhaps changes in cholesterol levels are associated with other disease processes as the pool of serum cholesterol is separate from cholesterol metabolism in the brain.[51] Among those who have cholesterol levels that increase from mid-life to late life, potential explanations for the increase in cholesterol include dietary changes associated with age and an aging-associated decrease in the ability to eliminate excess serum cholesterol. Our finding of higher cholesterol levels in *APOE* ε4 carriers is in line with other studies showing that ε4 carriers are prone to higher levels of cholesterol.[44]

The fact that fewer *APOE* ε4 carriers who survived to age ≥80 without impairment had diabetes is intriguing even though the association was no longer significant in fully adjusted models. The converse association, *i.e.*, potential interactions between *APOE* ε4 carriage and diabetes resulting in increased risk for cognitive dysfunction,[5253] and increased AD pathology[54,55] have been found in several, but not all [56] studies. Therefore, it remains unclear whether diabetes is associated with AD pathology or vascular pathology. *APOE* ε4 carriers also have demonstrated reduced cerebral metabolic rates of glucose metabolism in the brain compared to non-carriers.[57] Further studies in WHIMS will target these *APOE* ε4 carrier women to investigate the mechanisms supporting their resilience.

Our study has both strengths and limitations. This is one of the largest studies of older *APOE* ε4 carriers and the WHI (and WHIMS) cohort has been extensively phenotyped, allowing us to explore in great detail the characteristics that might be associated with avoiding CI in late old age. However, our study is limited by the fact that it is focused on women only. Our ascertainment of CI was based on standardized cognitive testing with central adjudication. One limitation is the lack of dementia subtype classification and confirmatory neuropathology or imaging data to be able to identify AD. Finally, our definition of resilience was similarly not based on pathological evidence but on the observation that these women passed through the age range of greatest risk of AD for *APOE* ε4 carriers without developing CI.

Conclusion

We have explored modifiable and situational risk factors that may serve to protect individuals at an elevated risk for AD from CI in a relatively large sample of *APOE* ε4 carriers who survived to age ≥ 80 without impairment. In this analysis, we found that among *APOE* ε4 carriers, better general health at baseline and higher baseline 3MS scores were associated with survival to age 80 without CI. Compared to non-carriers, the only distinguishing feature of ε4+ women who survived to late old age was high cholesterol.

Future planned studies in this cohort will consider mechanistic pathways including lipid and glucose metabolism.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key Points:

1. Among women who carry the *APOE* ε4 allele, those with better baseline self-rated general health and higher baseline scores on the Modified Mini Mental State Exam were more likely to survive to late old age (age 80+) without cognitive impairment.
2. Compared to non-carriers, women who carry the *APOE* ε4 allele and survive to late old age without cognitive impairment have high cholesterol.
3. There were no common characteristics across all genotypes that predicted survival to late old age without cognitive impairment.

Table 1.

Demographic and physiologic characteristics (n=5,716)

Baseline Characteristics	ε2/2 or ε2/3 (n=775)	ε2/4 (n=135)	ε3/3 (n=3508)	ε3/4 or ε4/4 (n=1298)	Total (n=5716)	*p*-value
Age at baseline (SD)	70.70 (4.04)	70.61 (4.19)	70.55 (3.83)	70.33 (3.68)	70.52 (3.84)	0.153
Education (%)						0.95
< High school	40 (5.17)	10 (7.41)	208 (5.94)	68 (5.26)	326 (5.72)	
High school/GED	182 (23.5)	29 (21.5)	761 (21.7)	290 (22.4)	1262 (22.1)	
Some college	312 (40.4)	55 (40.7)	1413 (40.4)	531 (41.1)	2311 (40.5)	
College grad	239 (30.9)	41 (30.4)	1117 (31.9)	404 (31.2)	1801 (31.6)	
Prior HT use (%)						0.365
Never used hormones	437 (56.4)	79 (58.5)	1873 (53.4)	719 (55.4)	3108 (54.4)	
Past hormone user	297 (38.3)	45 (33.3)	1400 (39.9)	501 (38.6)	2243 (39.3)	
Current hormone user	41 (5.29)	11 (8.15)	233 (6.65)	78 (6.01)	363 (6.35)	
Trial Variables						
Prior Hysterectomy (%)	271 (35.0)	53 (39.3)	1311 (37.4)	488 (37.6)	2123 (37.1)	0.568
HT Randomization assignment (%)	384 (49.5)	67 (49.6)	1725 (49.2)	645 (49.7)	2821 (49.4)	0.989
Lifestyle Factors						
Sleep Disturbance Construct (SD)	7.31 (4.31)	7.04 (4.61)	6.95 (4.56)	6.85 (4.34)	6.98 (4.48)	0.154
Cardiovascular Risk Factors						
Body-mass Index (BMI), kg/m^2 (SD)	28.44 (5.65)	28.46 (6.11)	28.43 (5.47)	28.25 (6.05)	28.39 (5.64)	0.810
Systolic BP (SD)	131.5 (18.16)	131.7 (17.82)	131.8 (17.54)	132.9 (17.26)	132.0 (17.57)	0.202
Diastolic BP (SD)	74.87 (9.19)	74.83 (8.93)	74.56 (9.16)	74.91 (9.39)	74.69 (9.21)	0.637
Stroke (%)	10 (1.29)	2 (1.48)	54 (1.54)	17 (1.31)	83 (1.45)	0.916
Hypertension (%)	365 (47.1)	63 (46.7)	1643 (46.8)	649 (50.0)	2720 (47.6)	0.268
Diabetes (%)	62 (8.00)	10 (7.41)	269 (7.67)	72 (5.55)	413 (7.23)	0.066
High cholesterol (%)	74 (9.70)	12 (9.02)	657 (19.0)	288 (22.4)	1031 (18.3)	<.001
LDL Cholesterol (SD)	132.4 (32.50)	142.5 (40.55)	152.6 (34.83)	157.8 (35.73)	150.8 (35.72)	<.001
HDL Cholesterol (SD)	55.67 (13.28)	52.90 (12.78)	53.97 (12.65)	52.72 (12.84)	53.89 (12.81)	<.001
Physical function						
Physical Functioning Construct (SD)	78.63 (19.93)	76.31 (19.48)	78.40 (20.18)	77.89 (20.55)	78.26 (20.21)	0.551
MET-hours per week from walking (SD)	4.32 (5.66)	3.83 (5.57)	4.20 (5.63)	4.24 (5.45)	4.22 (5.59)	0.806
Episodes moderate to strenuous phys activity per week (SD)	2.52 (3.24)	1.95 (2.80)	2.47 (3.13)	2.37 (3.05)	2.44 (3.12)	0.194
Episodes moderate to strenuous activity ≥ 20 min/week (SD)	1.91 (2.92)	1.53 (2.68)	1.91 (2.91)	1.84 (2.79)	1.89 (2.88)	0.435
Energy/Fatigue (SD)	64.54 (18.28)	61.15 (20.09)	64.06 (18.74)	65.10 (17.34)	64.29 (18.41)	0.072
Well-being						
Emotional Well-being (SD)	81.04 (13.08)	81.08 (12.97)	81.19 (13.23)	81.25 (12.64)	81.18 (13.07)	0.988
Satisfied with quality of life (SD)	8.16 (1.86)	8.30 (1.69)	8.23 (1.79)	8.24 (1.75)	8.22 (1.79)	0.688
Rate quality of life (SD)	8.26 (1.43)	8.41 (1.36)	8.31 (1.42)	8.31 (1.34)	8.31 (1.40)	0.670

Baseline Characteristics	ε2/2 or ε2/3 (n=775)	ε2/4 (n=135)	ε3/3 (n=3508)	ε3/4 or ε4/4 (n=1298)	Total (n=5716)	*p*-value
General Health Construct (SD)	75.67 (16.21)	73.14 (17.96)	75.40 (15.90)	75.67 (15.66)	75.45 (15.94)	0.362
Pain Construct (SD)	75.00 (22.13)	73.61 (23.44)	75.46 (21.91)	74.76 (22.44)	75.19 (22.10)	0.627
Shortened CES-D/DIS Screening Instrument (SD)	0.03 (0.09)	0.04 (0.10)	0.03 (0.10)	0.03 (0.10)	0.03 (0.10)	0.591
Stressors						
Currently helping a sick, limited, or frail family member on a regular basis (%)	285 (37.2)	51 (37.8)	1437 (41.3)	553 (42.8)	2326 (41.0)	0.066
Number of times per week currently helps a friend or family member (SD)	0.87 (1.32)	1.01 (1.44)	0.99 (1.37)	1.04 (1.40)	0.99 (1.37)	0.063
Life Event Construct #2 (0-3 scoring) (SD)	3.02 (2.90)	3.36 (3.17)	2.84 (2.82)	2.98 (2.95)	2.91 (2.87)	0.072
Life Event Construct #1 (0,1 scoring) (SD)	1.56 (1.33)	1.76 (1.46)	1.47 (1.30)	1.53 (1.35)	1.51 (1.32)	0.031
Cognitive function						
Baseline 3MS score (SD)	96.06 (3.51)	95.63 (4.16)	95.81 (3.67)	95.68 (3.98)	95.81 (3.73)	0.139
Most severe adjudicated cognitive status (%)						<.001
Normal	667 (86.1)	114 (84.4)	2989 (85.2)	984 (75.8)	4754 (83.2)	
MCI	53 (6.84)	8 (5.93)	220 (6.27)	109 (8.40)	390 (6.82)	
Probable Dementia	55 (7.10)	13 (9.63)	299 (8.52)	205 (15.8)	572 (10.0)	

Abbreviations: 3MS= Modified Mini Mental State Exam; BP=blood pressure; CES-D=Center for Epidemiologic Studies Depression Scale; DIS=Diagnostic Interview Schedule; GED=general equivalency diploma; HDL=high density lipoprotein; HT=hormone therapy; LDL=low density lipoprotein; MCI=mild cognitive impairment; MET=metabolic equivalent of task; SD=Standard Deviation.

Table 2.

Logistic Regression Models modeling Survivorship among ε3/4 and ε4/4 participants (n=451 versus 106)

	Model 1		Model 2		Model 3a		Model 3b	
Variable	**OR (95% CI)**	***p*-value**	**OR (95% CI)**	***p*-value**	**OR (95% CI)**	***p*-value**	**OR (95% CI)**	***p*-value**
APOE		0.025		0.105				
ε3/4	2.41 (1.12, 5.19)		2.14 (0.85, 5.35)					
ε4/4	1.0		1.0					
Time to Impairment or Age 80	1.21 (1.13, 1.29)	<.001	1.10 (1.02, 1.19)	0.016	1.12 (1.05, 1.20)	0.001	1.12 (1.05, 1.19)	0.001
Education		0.259		0.686		0.592		0.767
< High school	1.06 (0.33, 3.42)		1.71 (0.42, 7.00)		1.66 (0.52, 5.26)		1.49 (0.50, 4.49)	
High school/GED	0.61 (0.32, 1.15)		0.82 (0.38, 1.78)		0.84 (0.44, 1.62)		0.90 (0.48, 1.66)	
Some college	1.11 (0.62, 1.98)		1.13 (0.58, 2.23)		1.17 (0.65, 2.09)		1.12 (0.64, 1.96)	
College grad	1.00		1.00		1.00		1.00	
Randomization assignment		0.38		0.474		0.522		0.611
HT	0.81 (0.50, 1.30)		0.82 (0.47, 1.42)		0.85 (0.53, 1.38)		0.89 (0.56, 1.40)	
Placebo	1.00		1.00		1.00		1.00	
Region		0.122		0.131				
Northeast	0.55 (0.27, 1.11)		0.58 (0.26, 1.27)					
South	0.63 (0.32, 1.26)		0.77 (0.35, 1.67)					
Midwest	0.42 (0.20, 0.86)		0.38 (0.16, 0.88)					
West	1.00		1.00					
Hysterectomy status		0.463		0.755				
No	0.83 (0.50, 1.38)		0.91 (0.51, 1.63)					
Yes	1.00		1.00					
Prior HT use		0.284		0.358				
Curr. HT user	0.57 (0.17, 1.84)		0.75 (0.19, 2.90)					
Never used HT	0.68 (0.40, 1.14)		0.64 (0.35, 1.18)					
Past HT user	1.00		1.00					
Cardiovascular Risk Factors for Dementia								
Body-mass Index (BMI), kg/m^2	1.00 (0.96, 1.05)	0.914	0.99 (0.94, 1.03)	0.546				

	Model 1		Model 2		Model 3a		Model 3b	
Variable	**OR (95% CI)**	***p*-value**	**OR (95% CI)**	***p*-value**	**OR (95% CI)**	***p*-value**	**OR (95% CI)**	***p*-value**
Systolic BP	1.01 (0.99, 1.03)	0.421	1.01 (0.99, 1.04)	0.254				
Diastolic BP	0.99 (0.96, 1.02)	0.633	0.99 (0.95, 1.02)	0.437				
History of hypertension		0.410		0.544				
No	1.30 (0.70, 2.41)		1.25 (0.61, 2.56)					
Yes	1.00		1.00					
History of diabetes		0.031		0.073				
No	2.65 (1.09, 6.42)		2.53 (0.92, 6.96)					
Yes	1.00		1.00					
History of high cholesterol		0.931		0.354				
No	0.97 (0.54, 1.75)		0.72 (0.36, 1.45)					
Yes	1.00		1.00					
LDL Cholesterol	1.00 (1.00, 1.01)	0.446	1.00 (0.99, 1.01)	0.928				
HDL Cholesterol	1.00 (0.98, 1.02)	0.956	1.00 (0.98, 1.02)	0.982				
History of stroke		0.094		0.382				
No	3.71 (0.80, 17.19)		2.29 (0.36, 14.57)					
Yes	1.00		1.00					
Lifestyle Factors				0.994				
Alcohol use			0.86 (0.25, 2.88)					
Non			0.97 (0.33, 2.86)					
Past			0.93 (0.37, 2.32)					
Up to <7 drinks			0.86 (0.25, 2.88)					
7+ drinks			1.00					
Cigarette smoking				0.463				
Current Smoker			0.58 (0.17, 2.05)					
Never Smoked			0.71 (0.39, 1.30)					
Past Smoker			1.00					
Physical Function								
MET-hours per week from walking			0.96 (0.92, 1.01)	0.087				

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	Model 1		Model 2		Model 3a		Model 3b	
Variable	**OR (95% CI)**	***p*-value**	**OR (95% CI)**	***p*-value**	**OR (95% CI)**	***p*-value**	**OR (95% CI)**	***p*-value**
Well-being								
Emotional Well-being			1.02 (0.99, 1.05)	0.150				
Rate quality of life			0.97 (0.74, 1.26)	0.798				
General Health Construct			1.02 (1.00, 1.04)	0.057	1.02 (1.01, 1.04)	0.004	1.03 (1.01, 1.04)	0.001
Shortened CES-D/DIS Screening Instrument			1.74 (0.95, 3.19)	0.072				
Cognitive Function								
Baseline 3MS score			1.20 (1.13, 1.27)	<.001	1.18 (1.12, 1.25)	<.001	1.16 (1.11, 1.22)	<.001

Model 1: *APOE* and Time to Impairment or Age 80, treatment arm, education, region, hysterectomy, prior HT, BMI, hx of stroke, systolic BP, diastolic BP, hx of hypertension, hx of diabetes, hx of high cholesterol, HDL, LDL

Model 2: Includes Model 1 plus physical function including MET-hours per week from walking and lifestyle factors including emotional well-being, rated quality of life, smoking, drinking (4 groups: non, past, up to <7 drinks (group all), and 7+ drinks), general health, CESD (0.1 unit increase), 3MS

Model 3a: Reduced model, retaining only significant and key factors (including Time to Impairment or Age 80, edu, trt status)

Model 3b: Includes women who developed impairment after age 80, n=623 versus 106.

Abbreviations: 3MS= Modified Mini Mental State Exam; BP=blood pressure; CES-D=Center for Epidemiologic Studies Depression Scale; DIS=Diagnostic Interview Schedule; edu=education; GED=general equivalency diploma; HDL=high density lipoprotein; HT=hormone therapy; hx=history; LDL=low density lipoprotein; MCI=mild cognitive impairment; MET=metabolic equivalent of task; trt=treatment.

Table 3.

Logistic Regression Models modeling ε3/4 and ε4/4 survivorship versus other *APOE* group survivorship (n=451 versus 2057)

	Model 1		Model 2		Model 3a		Model 3b	
Variable	**OR (95% CI)**	***p*-value**	**OR (95% CI)**	***p*-value**	**OR (95% CI)**	***p*-value**	**OR (95% CI)**	***p*-value**
Time to Impairment or Age 80	1.02 (1.00, 1.05)	0.093	1.03 (1.00, 1.06)	0.099	1.01 (0.99, 1.04)	0.306	1.00 (0.98, 1.02)	0.868
Education		0.934		0.836		0.839		0.938
< High school	1.11 (0.65, 1.90)		1.03 (0.57, 1.85)		1.16 (0.69, 1.97)		1.03 (0.65, 1.64)	
High school/GED	0.96 (0.71, 1.30)		0.88 (0.64, 1.21)		0.97 (0.72, 1.30)		1.04 (0.81, 1.33)	
Some college	1.04 (0.81, 1.33)		1.00 (0.77, 1.29)		1.07 (0.84, 1.36)		1.07 (0.87, 1.32)	
College grad	1.00		1.00		1.00		1.00	
Randomization assignment		0.577		0.757		0.622		0.456
HT	1.06 (0.86, 1.31)		1.03 (0.83, 1.29)		1.05 (0.86, 1.30)		1.07 (0.89, 1.28)	
Placebo	1.00		1.00		1.00		1.00	
Region		0.294		0.426				
Northeast	0.79 (0.58, 1.06)		0.82 (0.60, 1.11)					
South	0.78 (0.58, 1.04)		0.82 (0.61, 1.10)					
Midwest	0.80 (0.58, 1.10)		0.78 (0.56, 1.10)					
West	1.00		1.00					
Hysterectomy status		0.153		0.210				
No	0.85 (0.67, 1.06)		0.86 (0.68, 1.09)					
Yes	1.00		1.00					
Prior HT use		0.259		0.357				
Current HT user	0.82 (0.51, 1.31)		0.84 (0.51, 1.36)					
Never used HT	1.15 (0.91, 1.44)		1.13 (0.89, 1.43)					
Past HT user	1.00		1.00					
Cardiovascular Risk Factors for Dementia								
Body-mass Index (BMI), kg/m^2	0.98 (0.96, 1.00)	0.131	0.98 (0.96, 1.01)	0.130				
Systolic BP	1.00 (0.99, 1.01)	0.457	1.00 (1.00, 1.01)	0.305				
Diastolic BP	1.00 (0.98, 1.01)	0.489	0.99 (0.98, 1.01)	0.447				
History of hypertension		0.413		0.585				

	Model 1		Model 2		Model 3a		Model 3b	
Variable	**OR (95% CI)**	***p*-value**	**OR (95% CI)**	***p*-value**	**OR (95% CI)**	***p*-value**	**OR (95% CI)**	***p*-value**
No	0.89 (0.67, 1.18)		0.92 (0.69, 1.23)					
Yes	1.00		1.00					
History of diabetes		0.518		0.666				
No	1.18 (0.72, 1.93)		1.12 (0.67, 1.86)					
Yes	1.00		1.00					
History of high cholesterol		0.012		0.005		0.003		0.031
No	0.71 (0.55, 0.93)		0.68 (0.52, 0.89)		0.68 (0.53, 0.88)		0.78 (0.62, 0.98)	
Yes	1.00		1.00		1.00		1.00	
LDL Cholesterol	1.01 (1.00, 1.01)	<.001	1.01 (1.00, 1.01)	<.001	1.01 (1.00, 1.01)	<.001	1.01 (1.00, 1.01)	<.001
HDL Cholesterol	0.99 (0.98, 1.00)	0.024	0.99 (0.98, 1.00)	0.039				
History of stroke		0.808		0.488				
No	1.13 (0.42, 3.05)		1.47 (0.49, 4.40)					
Yes	1.00		1.00					
Lifestyle Factors								
Alcohol use				0.928				
Non			0.96 (0.60, 1.55)					
Past			1.08 (0.72, 1.63)					
Up to <7 drinks			0.98 (0.70, 1.36)					
7+ drinks			1.00					
Cigarette smoking				0.841				
Current Smoker			0.98 (0.58, 1.67)					
Never Smoked			0.93 (0.74, 1.18)					
Past Smoker			1.00					
Physical Function								
MET-hours per week from walking			1.00 (0.98, 1.02)	0.730				
Well-being								
Emotional Well-being			1.00 (0.99, 1.01)	0.854				
Rate quality of life			0.96 (0.87, 1.06)	0.461				

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	Model 1		Model 2		Model 3a		Model 3b	
Variable	**OR (95% CI)**	***p*-value**	**OR (95% CI)**	***p*-value**	**OR (95% CI)**	***p*-value**	**OR (95% CI)**	***p*-value**
General Health Construct			1.00 (0.99, 1.01)	0.896				
Shortened CES-D/DIS Screening Instrument			1.01 (0.89, 1.14)	0.923				
Cognitive Function								
Baseline 3MS score			0.99 (0.96, 1.03)	0.718				

Model 1: Time to Impairment or Age 80, treatment arm, education, region, hysterectomy, prior HT, BMI, hx of stroke, systolic BP, diastolic BP, hx of hypertension, hx of diabetes, hx of high cholesterol, HDL, LDL

Model 2: Model 2 plus physical function including MET-hours per week from walking and lifestyle factors including emotional well-being, rated quality of life, smoking, drinking (4 groups: non, past, up to <7 drinks (group all), and 7+ drinks), general health, CESD (0.1 unit increase), 3MSE

Model 3a: Reduced model, retaining only significant and key factors (including Time to Impairment or Age 80, edu, trt status)

Model 3b: Includes women who developed impairment after age 80, n=623 versus 2510

Abbreviations: 3MS= Modified Mini Mental State Exam; BP=blood pressure; CES-D=Center for Epidemiologic Studies Depression Scale; DIS=Diagnostic Interview Schedule; edu=education; GED=general equivalency diploma; HDL=high density lipoprotein; HT=hormone therapy; hx=history; LDL=low density lipoprotein; MCI=mild cognitive impairment; MET=metabolic equivalent of task; trt=treatment.