Early Life Conditions and Cause-Specific Mortality In the Cache County Memory and Health Study: Gene-Environment Interactions with APOE Genotypes

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September 2013

We acknowledge the grant support of the National Institute on Aging
(AG02209 Early Life Conditions, Survival, and Health:
A Pedigree-Based Population Study)

Abstract

The purpose of this study is to estimate the effects of the Apolipoprotein E (*APOE*) gene on cause-specific mortality risks in a population-based cohort of elderly subjects. The study relies on 4701 subjects recruited into the Cache County Study on Memory and Aging. There has not been a comprehensive assessment of APOE genotypes on multiple cause-specific risks of mortality associated with aging. Moreover, published estimates of the effects of *APOE* genotypes on all-cause mortality are heterogeneous. Less attention has been given to potential confounders and effect modifiers of the mortality effects of *APOE* alleles. In this paper, we address these shortcomings by estimating the effects of *APOE* genotypes on the risk of death from all-causes and cause-specific mortality. We extend this analysis by estimating whether rates of aging, as measured by familial excess longevity (in this draft) and important early life conditions (in the final version of the paper), moderate the risk of mortality from these same causes of death (i.e., gene x environment interactions). We find adverse effects of APOE4 genotypes on all-cause mortality and mortality due to cardiovascular disease and nervous system disorders but also to respiratory diseases, digestive system disorders, and psychological maladies. We also find a novel result in terms of elevated risk of cancer and respiratory diseases associated with the e22 genotype. The deleterious effects of APOE genotypes occur for several important cause-specific mortality risks but that are attenuated for individuals with a family history of excess longevity.

Introduction

Assessments of mortality risks among the elderly have had a long history in demography. These studies have generally considered nominal biological measures such as gender and age. Recent decades have seen a growing list of risk factors included in such analyses, often termed biomarkers, such as serum cholesterol, blood pressure, and body mass index. With the expansion of molecular biology and its arsenal of techniques for identifying genetic markers for disease and wellness susceptibility, there is now an increasing availability of new genotype information on large population-based samples. This development now affords demographers with an excellent opportunity to integrate these measures into analyses of mortality differentials. In many cases, specific alleles are associated with mortality risks for high risk families that comprise a very small proportion of the population. In less common instances, certain genotypes may affect the health of a substantial portion of the populations. The Apolipoprotein E (*APOE*) is potentially such a gene.

The purpose of this study is to assess the role of the *APOE* gene in affecting not only the risks of all-cause mortality (Ewbank, 2002) and causes known to be associated with genotypes e33 and e44 (cardiovascular disease and Alzheimer's disease) (McDowell, 2001; Roses, 1998; Tilvis, Strandberg, & Juva, 1998) but also for a broad range of other specific causes of death associated with aging (J. Y. Chen et al., 1999; Y. C. Chen et al., 2005; Chowdhury et al., 1998; Economou-Petersen et al., 1998; Eichner et al., 1992; Forsell, Basun, Corder, Lannfelt, & Winblad, 1998; Heijmans et al., 2002; Hough et al., 2000; Inzelberg et al., 1998; Lehrer, 1998; Liestol et al., 2000; McCarron et al., 2003; Slattery et al., 2005; Starinsky et al., 2005; Venanzoni et al., 2003). The study relies on 4700 subjects recruited into the Cache County Study on Memory and Aging.

The association between *APOE* genotypes and all-cause mortality and selected specific causes of death mortality has been examined previously (Eichner et al., 1992; Lee et al., 2001). A recent study based on the Cache County study showed that the risk of all-cause mortality persons doubled for persons with e44 in relation to those with e33 (Hayden et al., 2003). A key feature of this growing literature is the heterogeneity of the mortality (and dementia) risk estimates associated with *APOE* genotypes (Ewbank, 2007; Ferrari et al., 2013; Pardo Silva, Janssens, Hofman, Witteman, & van Duijn, 2008; Rosvall et al., 2009; Tzourio et al., 2008). These discrepant results may be explained by the variety of samples and methods used. Specifically, less attention has been given to potential confounders and effect modifiers of the mortality effects of *APOE* alleles (Beydoun et al., 2013; Ferrari et al., 2013; Ordovas, 2002; Schaefer, 2002). We suggest that much can be learned about the varying mortality effects of *APOE* by focusing on its interactions with measures of rates of aging and indicators of adversity and advantage early in life.

The biodemographic literature on longevity has revitalized interest in the family history of longevity as key concepts in understanding aging and mortality in the later years and individual rates of aging (Kerber, O'Brien, Cawthon, & Smith, 2001; Smith, G.P. Mineau, & Bean, 2003; Vaupel, 1998; Wachter, C.E. Finch, & Population, 1997; Yashin, 1999). An examination of the joint influences of a known genetic factor associated with later life mortality (*APOE*) and measures of aging and early life circumstances is a useful strategy for exploring the heterogeneous effects of *APOE* genotypes on later-life mortality.

In summary, this paper seeks to accomplish the following:

1. Generate estimates of the relative risk of *APOE* e22, e23, e24, e34 and e44 in relation to the *APOE* e33 on the risk of risk of all-causes, cardiovascular disease, cancer, respiratory

diseases, psychoneurotic diseases, external causes, as well as diseases of the digestive, nervous, and genito-urinary systems.

2. Estimate how the association between *APOE* genotype and cause-specific mortality is modified by indicators of rates of aging and early life conditions.

Study Design

This analysis relies on the Cache County Study on Memory and Aging, a longitudinal study of dementia and cognitive health based on a large representative sample of all older adult residents of Cache County, Utah. Briefly, all residents of the county aged 65 or older as of 1 January 1995 were invited to participate. Procedures were approved by the institutional review boards of Utah State University, Johns Hopkins University, and Duke University. Participants were asked to provide buccal DNA for genotyping at the *APOE* locus. They were then asked to complete a two-hour interview on health factors potentially related to dementia, including cardiovascular disorders, and they were evaluated for dementia using a multi-stage assessment procedure (Wave 1). Informed consent was obtained when participants were able to understand the procedure, and proxy consent was obtained from spouses or next of kin for others. Approximately three years after the baseline evaluation, between 1998 and 1999, survivors without dementia at Wave 1 were asked to complete a follow-up interview to assess changes in health factors, and were again evaluated with a similar multi-stage procedure to detect new cases of dementia (Wave 2). Mortality among the participants was monitored continuously through 25 January 2002. Through collaboration with the Utah Population Database at the University of Utah, mortality ascertainment extended through the end of 2002. In the final version of the paper, the death dates will be extended to 2010.

Study Sample

Of 5,956 eligible individuals 5,092 completed the baseline interview. Most (4,969) were also genotyped at the *APOE* locus. Of these, 261 refused to complete the Wave 1 evaluations, often because of medical illness. Of the remaining participants, 4,700 individuals were included in these analyses.

The Cache County Study on Memory and Aging has recently been enriched with the addition of several important variables obtained from the Utah Population Database. These variables include measures of familial excess longevity (FEL as defined below) along with cause of death information obtained from death certificates of Cache County Study decedents.

The Utah Population Database (UPDB) contains over seven million records, including the genealogies of the founders of Utah and their descendants. In the 1970s, approximately 170,000 Utah nuclear families were identified on "Family Group Sheets" from the archives at the Utah Family History Library, each with at least one member having had a vital event (birth, marriage, death) on the Mormon Pioneer Trail or in Utah. These families have been linked across generations; in some instances, the records span seven generations. The UPDB is an active genealogy; new families and their members are continually being added as the UPDB is linked to other sources of data, including birth and death certificates. Additional information on these individuals comes from sources such as drivers' license and the Utah Cancer Registry. The UPDB now holds data from migrants to Utah and their descendants that number more than 1.8 million individuals born from the early 1800's to the mid-1900's and that are linked into multi-generation pedigrees. Through funding from the NIA, nearly all Cache County study subjects have been linked to the UPDB.

We use familial excess longevity (FEL) as a genealogical-based method for measuring slow rates of aging. FEL is a summary measure of excess longevity among all blood relations for a given individual. Calculating FEL first requires that an estimate of the difference between an individual's attained age and the age to which that individual was expected to live according to an accelerated failure time model. This model uses two covariates that are available in the UPDB for all individual records as the basis for expected age at death and that are associated with longevity: gender and birth year.

In the final version of the paper we will also examine the role specific early life conditions including parental age at birth, parental death in childhood, birth order, sibship size, age at first birth, age at marriage, parity, and age at last birth.

The expected age at death is:

$$\hat{y} = \exp(\beta_0 + \beta_1 \, Gender \; + \beta_2 \, Birth \; Year \;),$$

with β_i, i = 0, . . . , 3, regression coefficients. Excess longevity is l = y-ŷ, where y is the age at death or the age at the time last confirmed alive, in years. We focus on only those subjects who reached the age of 65 for this measure. The familial excess longevity for a subject is calculated as the weighted average of individual excess longevity of all blood relatives. The weights are the kinship coefficients, the probability, K_{ij}, that individual i shares a particular allele with individual j. The familial excess longevity for subject i is

$$FEL_{\,i} = \frac{\sum_{j \in J} K_{ij} \, l_j}{\sum_{j \in J} K_{ij}}$$

where J is the set of all blood relatives of subject i living to age 65.

In summary, the merged Cache County-UPDB data set offers an excellent opportunity for

studying aging and risk factors for cause-specific mortality past age 65 with *APOE* genotype information, a genealogically based measure of rates of aging (FEL), cause of death information on all decedents, and a vast set of key covariates measuring known risk factors for mortality among the elderly, including measures depicting early life of these individuals..

Statistical Methods

The outcomes of interest are ages at death (for any cause) and specific causes of death. Given that the analysis is interested in understanding variations in survival, we use Cox proportional hazards regression models and its extensions. Each cause-of-death of interest is estimated using standard competing risk survival techniques. This means that for each Cox regression analysis for a specific cause of death treats the remaining causes of death as uninformative censored cases. Other parametric specifications (Gompertz, Weibull) were also estimated but with little qualitative differences in the results were detected in relation to the results obtained using the Cox proportional hazards model.

The basic model includes covariates that measure *APOE* genotype (dummies, e33 is the reference category), familial excess longevity (FEL), age at baseline interview (centered main effect and its square), marital status (dummies, married is the reference category), and education (dummies, high school graduate is the reference category). Marital status and education are included in the models to adjust for their potential mediating effects. In particular, individuals with more resources (access to informal social support via spouses and better access to and utilization of information attributable to education) may alter the pathways by which *APOE* genotypes affect all-cause and cause-specific mortality. For about 30% of the subjects, FEL was not estimable because study subjects did not link to the UPDB or because the subjects lacked

sufficient information in the UPDB to allow us to confidently estimate FEL. In these instances, the mean value of FEL was substituted for the missing FEL cases and a dummy variable, FELMISS, was included to identify those whose value of FEL was imputed with the sample mean. This procedure allowed us to preserve the full sample while still permitting us to include the FEL measure.

The models incorporate interaction effects between FEL and each of the APOE genotypes. These interaction terms are included to assess whether the potential adverse effects of a specific genetic risk is moderated by familial longevity. In a broad sense, a history of high levels of familial longevity is a proxy for lower risks of mortality across a range of diseases associated with aging. The genetic and environmental factors that contribute to greater longevity in an individual's pedigree may therefore act to offset the negative influences attributed to APOE genotypes.

Results

In Table 1, the descriptive statistics for the key covariates are shown. Note that the distribution of the APOE genotypes parallels the distribution of the US population but with slightly more persons with APOE e4 allele(s) in this cohort.

Table 1 Here

Table 2 provides the distribution of the causes of death for the cohort. Note that death from the circulatory system, cancers, respiratory diseases, and diseases of the nervous system comprise the largest categories of decedents and are therefore the focus of the cause-specific mortality analysis. Those dying from cancer died primarily from (female) breast, prostate, colon, and lung cancer. Respiratory disease deaths were mostly from pneumonia while deaths

from diseases of the nervous system were from Parkinson's disease and Alzheimer's disease.

Table 2 Here

Tables 3 through 10 provide regression coefficient estimates for each of the *APOE* genotypes (in relation to e33) based on Cox proportional hazard models. These first set of models focus on objective 1. In making an assessment of each of the *APOE* genotypes, we find that e22, e34 and e44 significantly increase the risk of all-cause mortality (Table 3). The effects of e44 are significant for several major causes of death including mortality from cardiovascular disease, respiratory disease, and diseases of the nervous and digestive systems (Tables 4-10) while the adverse mortality consequences of e34 did not reach conventional levels of significance.

Tables 3-10 Here

The e22 genotype was also associated with excess mortality in relation to the e33 genotype. Individuals with this genotype have elevated risks of mortality from cancer and respiratory disease. While the relative risks are large (hazard rate ratios >2.7), the number of subjects in the sample with the e22 genotype is very small (n=35), as it is in most populations. Accordingly, this association needs to be interpreted cautiously. At the same, this result is also suggestive of a novel association between APOE genotypes and two major causes of death that is worthy of further investigations.

Associations between FEL and all-cause and cause-specific mortality are also reported in Tables 3-10. Increasing levels of FEL (i.e., greater evidence of a family history of longevity) are found to significantly reduce mortality risks for all-cause and cardiovascular mortality (Tables 3 and 4). For all other causes, no significant associations were detected. (The protective effects of increasing levels of FEL are found to be somewhat more substantial when dummies are

included to reflect extreme levels of FEL (results not shown)). Interestingly, the "missing FEL" dummy variable that signifies whether a case was subject to mean substitution has significant and adverse effects on the risk of several causes of mortality. This association may reflect the fact that individuals for whom there is limited family history information are less likely to be members of the Church of Jesus Christ of Latter-day Saints (LDS Church, or Mormons). Members of the LDS Church generally have fewer mortality risk factors (restrictions on smoking and alcohol consumption; high levels of social integration) and they might be more likely to have sufficient information regarding their family longevity history.

We note that the effect sizes (chi-square statistics) for the variables marital status and education level are generally quite large, especially for the effects of being a college graduate and for being widowed, divorced, or never married. These variables have traditionally had very large effects in studies of adult and older-age mortality. The effects sizes for APOE genotypes often rival or exceed these effects sizes suggesting that demographic models may benefit from the inclusion of genetic markers in their analyses of mortality.

To assess the interactive effects of apo genotypes and FEL, we restrict our attention to all-cause mortality as well as deaths from cardiovascular, cancer, respiratory, and nervous system diseases. This restriction is imposed due to assure adequate numbers of deaths from each of these outcomes. In these models, the APOE and FEL variables are centered so that when we consider a main effect of a variable (involved in the interaction), it can be interpreted as the effect when the other variable is held at its mean value. For Table 11, for example, the effect of each APOE genotype is estimated when FEL is held to its mean value. In this instance, we see that e22, e34, and e44 have adverse effects on all-cause mortality for average levels of FEL (Table 11). However, as FEL increases, the pernicious influence of e34 and e44 significantly

declines suggesting that some of the heterogeneous effects of APOE genotypes may occur because of the actions of other (deleterious or beneficial) genes that may be captured in our FEL variable.

Table 11 Here

The same interactive effect between e44 and FEL is observed for cardiovascular mortality: e44 increases the risk but that risk declines with increasing FEL (Table 12). We now observe that at average levels of FEL, e23 does not have any influence on cardiovascular mortality risk but at higher levels of FEL it is associated with reducing the risk.

Table 12 Here

The genotype e22 was previously found to increase the risk of cancer and respiratory mortality in models without interactions. When interacted with FEL, individuals with the e22 genotype continue to experience the same adverse mortality effects but without effect modification due to FEL (Tables 13 and 14).

Tables 13 and 14 Here

Finally, for nervous system deaths, persons with either the e34 or e44 genotypes continue to have large and significant effects at average levels of FEL. While there are only suggestive interaction effects with FEL, the adverse consequences of e34 and e44 are appreciably altered with changing values of FEL.

Table 15 Here

Discussion

In this analysis, we have confirmed the presence of adverse effects of APOE genotypes, particularly e44, on all-cause mortality and mortality due to cardiovascular disease and nervous

system disorders, primarily Parkinson's and Alzheimer's disease. The influence of e44 extends to additional causes of death, including respiratory diseases, digestive system disorders, and psychological maladies such as psychoses. We also find a novel result in terms of the risk of cancer and respiratory diseases associated with the e22 genotype. In the case of cancer, our analysis is suggestive more than definitive given the sample size of persons with e22. Nonetheless, this e22-cancer association is found largely for the male sub-sample. Some have found that APOE may represent a marker of more aggressive cells in human prostate cancers, an explanation consistent with our results (Venanzoni et al., 2003) while others have found no such association (Zunarelli, Nicoll, Migaldi, & Trentini, 2000).

The effects of our family longevity measure, FEL, were in the predicted direction: individuals with a stronger family history of longevity had lower levels of mortality for all-cause and cardiovascular disease. This inverse association was present in most of the other causes of death considered but did not reach conventional levels of significance. These weaker results may be a function of the fact that a third of the subjects did not have an FEL measure because they did link to the UPDB or had limited family history information in combination with the fact there are fewer deaths from these less common causes of death. (In related analyses using a very large cohort within the UPDB (N=100,000), we find that FEL significantly reduces the risk for all major causes of death except cancer (Kerber, O'Brien, Smith, and Mineau, 2006)). Nonetheless, we showed that the deleterious effects of APOE genotypes occur for several important cause-specific risks of mortality but that their effects are attenuated when they occur to individuals with a family history of excess longevity.

The use of genotype information to explain differences in mortality presents some interesting opportunities. The mortality influences of the APOE genotypes are not deterministic

since social and environmental forces alter the degree to which these genes yield various phenotypes and health outcomes. The combined influences of FEL and APOE genotypes on mortality risk that were examined here are excellent examples of gene-environment interactions and indirectly, gene-gene interactions.

Apart from acquired mutations, individuals inherit their genetic profile at conception and thus genomic information can be considered truly exogenous with no opportunities for change later in life (genetic therapies notwithstanding). In this sense, genetic endowments represent the very earliest life conditions that may have profound effects on later life health and survival. The mortality effects that we reported here therefore represent the cumulative disadvantage of the e22, e34, and e44 genotypes over a lifetime.

Given that our objective is to understand and explain the rich variation in survival during the latter years of the human life span, it is worth noting the strength of the association between a single genotype and mortality risk was found to be comparable to broad social risk factors such aslow educational attainment or marital disruption. Since most health conditions are affected by the influence of many genes and environmental stressors and resources, it is remarkable to see how APOE genotypes generate significant effects on a range of specific causes of death.

The design of this analysis is not free from potential limitations. First, our analysis is based on underlying causes of death as reported on death certificates. This information is extremely valuable but the context in which this information is recorded is subject to measurement error. This may explain why the estimated effects of e44 extend to multiple causes of death beyond cardiovascular disease and nervous system disorders: the cause of death is misclassified and the impact of e44 is therefore found with other causes of death. On the other hand, if measurement error is partly the explanation, it could just as easily (if not more likely)

create weaker rather than stronger associations between APOE genotypes and the risk from a range of causes of death.

Second, the associations presented here are potentially subject to selection biases associated with the APOE genotype. As with any exogenous variable that affects survival, care must be taken in interpreting the effects of APOE genotypes on survival since we do not possess information on the genotypes of those who died prior to age 65. The distribution of genotypes in this sample is naturally affected by the mortality selection imparted by these genes prior to age 65. In an attempt to assess this issue within the sample, we found that mortality selection is relatively weak since the influence of the e34 and e44 are stronger for subjects age 80 or older at baseline (results not shown) in relation to those aged 65 to 79..

Third, our FEL measure was an important addition to this analysis but there was a large minority with missing data. This is being addressed with our database but it is worth noting that those with missing FEL data had unusually high risks of mortality from several specific causes of death. This suggests that those with less available family history data (and hence had missing FEL) had less connection with Utah roots and possibly less social support. This is speculative at this point but is a line of inquiry we are investigating.

In summary, demographers and other population scientists have identified fundamental forces that affect mortality risks among the elderly for all causes and for a wide range of specific types of mortality. Those factors include marital status, education, wealth, disabilities, race/ethnicity, social support, gender and self-reported health status as well as biomarkers such as cholesterol and blood pressure. With developments in molecular biology and genetics over the past decade, it is feasible to collect genomic information on large samples that represent crucial new information on mortality risks that have been heretofore unexamined by

demographers. Genetic data offer demographers a new arsenal of variables with which to expand our understanding of aging and to extend demographic insights into genetic assessments of disease risk and longevity.

Table 1. Descriptive Statistics for Cache County Memory Study Cohort (N=4700)

Variable	Mean	Std Dev	Minimum	Maximum
Age	75.4239524	7.1566078	64.00	105.00
Education (yrs)	13.2127632	2.8963085	0	20.00
<High School	0.1814508	0.3854322	0	1.00
Some College	0.2439906	0.4295328	0	1.00
College Grad	0.2344182	0.4236797	0	1.00
Male	0.4290576	0.4949942	0	1.00
e 22	0.0074452	0.0859731	0	1.00
e 23	0.1297596	0.3360745	0	1.00
e 24	0.0361625	0.1867142	0	1.00
e33	0.5390342	0.4985270	0	1.00
e 34	0.2588811	0.4380668	0	1.00
e 44	0.0287173	0.1670286	0	1.00
FEL	3.3983450	1.7083558	-10.23	16.18
FEL Missing	0.3390768	0.4734463	0	1.00
Married	0.6670921	0.4713040	0	1.00
Widowed	0.2882365	0.4529899	0	1.00
Divorced	0.0319081	0.1757741	0	1.00
Never Married	0.0136141	0.1158949	0	1.00
Duration2002	2029.56	619.6818258	4	2813.00
Censor2002	0.6758137	0.4681198	0	1.00

Table 2. Distribution of Causes of Death

Cause of Death	N	%
Alive by end of 2002	3176	67.57
Infectious	10	0.21
Cancer	231	4.91
Endocrine (Diabetes)	61	1.30
Blood/Blood-forming Organs	4	0.09
Mental/Psychoneurotic (Psychoses)	54	1.15
Nervous System (Parkinson/AD)	101	2.15
Cardiovascular	584	12.43
Respiratory (largely Pneumonia)	175	3.72
Digestive (Chronic liver/Cirrhosis)	55	1.17
Genital-urinary (Renal)	29	0.62
Skin/Subcutaneous Tissue	5	0.11
Bones/Organs of Movement	14	0.30
Congenital Malformations	3	0.06
Symptoms/Senility/Ill-Defined	27	0.57
External Causes	30	0.64
Deceased but no Utah Death Certificate (likely died out of state)	141	3.00

Table 3. Effects of apo E Genotypes on All-Cause Mortality based on Cox Proportional Hazards Models.

Variable	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
Age	0.10232	0.00520	386.6913	<.0001	1.108
Age2**	-0.0002370	0.0003941	0.3618	0.5475	1.000
<Hi School	0.06939	0.07005	0.9812	0.3219	1.072
Some College	-0.07643	0.07150	1.1427	0.2851	0.926
College Grad	-0.19724	0.07504	6.9082	0.0086	0.821
Male	0.45230	0.05791	60.9978	<.0001	1.572
Divorced	0.63345	0.14228	19.8216	<.0001	1.884
Widowed	0.13675	0.06506	4.4185	0.0356	1.147
Never Married	0.60232	0.19390	9.6490	0.0019	1.826
e22	0.58211	0.25381	5.2601	0.0218	1.790
e23	-0.07337	0.08310	0.7795	0.3773	0.929
e24	-0.06484	0.15060	0.1853	0.6668	0.937
e34	0.22658	0.06107	13.7640	0.0002	1.254
e44	0.59788	0.14156	17.8374	<.0001	1.818
FEL	-0.04410	0.01397	9.9618	0.0016	0.957
FEL Missing	0.01024	0.05608	0.0334	0.8551	1.010

Table 4. Effects of apo E Genotypes on Cardiovascular Mortality based on Cox Proportional Hazards Models.

Variable	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
Age	0.09791	0.00743	173.6035	<.0001	1.103
Age2**	0.0002295	0.0005502	0.1739	0.6767	1.000
<Hi School	0.08580	0.09949	0.7438	0.3885	1.090
Some College	-0.21754	0.10622	4.1943	0.0406	0.804
College Grad	-0.24883	0.10882	5.2281	0.0222	0.780
Male	0.37705	0.08386	20.2145	<.0001	1.458
Divorced	0.30153	0.23135	1.6987	0.1925	1.352
Widowed	0.08003	0.09384	0.7273	0.3937	1.083
Never Married	0.35633	0.30784	1.3398	0.2471	1.428
e22	0.48780	0.38308	1.6214	0.2029	1.629
e23	-0.09581	0.11991	0.6385	0.4243	0.909
e24	-0.19852	0.22993	0.7454	0.3879	0.820
e34	0.14098	0.08940	2.4869	0.1148	1.151
e44	0.51486	0.20748	6.1576	0.0131	1.673
FEL	-0.06569	0.02018	10.6012	0.0011	0.936
FEL Missing	0.09238	0.08011	1.3296	0.2489	1.097

Table 5. Effects of apo E Genotypes on Cancer Mortality based on Cox Proportional Hazards Models.

Variable	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
Age	0.07065	0.00965	53.6248	<.0001	1.073
Age2**	-0.00182	0.0009333	3.8238	0.0505	0.998
<Hi School	0.10685	0.14395	0.5509	0.4579	1.113
Some College	-0.05452	0.14053	0.1505	0.6981	0.947
College Grad	-0.32818	0.15220	4.6493	0.0311	0.720
Male	0.42408	0.11568	13.4382	0.0002	1.528
Divorced	0.33186	0.28867	1.3217	0.2503	1.394
Widowed	-0.03974	0.13587	0.0856	0.7699	0.961
Never Married	0.70091	0.34268	4.1836	0.0408	2.016
e22	1.06121	0.38701	7.5191	0.0061	2.890
e23	-0.13868	0.16777	0.6833	0.4085	0.871
e24	-0.47260	0.36092	1.7146	0.1904	0.623
e34	-0.03691	0.12823	0.0829	0.7734	0.964
e44	0.26861	0.29790	0.8130	0.3672	1.308
FEL	0.01739	0.03254	0.2855	0.5931	1.018
FEL Missing	0.53757	0.10588	25.7776	<.0001	1.712

Table 6. Effects of apo E Genotypes on Respiratory (largely Pneumonia) Mortality based on Cox Proportional Hazards Models.

Variable	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
Age	0.10845	0.01159	87.5589	<.0001	1.115
Age2**	0.0002502	0.0008090	0.0957	0.7571	1.000
<Hi School	0.13765	0.14989	0.8434	0.3584	1.148
Some College	-0.12992	0.16014	0.6582	0.4172	0.878
College Grad	-0.26449	0.16879	2.4555	0.1171	0.768
Male	0.44191	0.12750	12.0135	0.0005	1.556
Divorced	0.40577	0.32937	1.5177	0.2180	1.500
Widowed	0.24078	0.14121	2.9074	0.0882	1.272
Never Married	0.17378	0.50886	0.1166	0.7327	1.190
e22	0.99621	0.45697	4.7525	0.0293	2.708
e23	-0.17235	0.18556	0.8627	0.3530	0.842
e24	0.13070	0.29964	0.1903	0.6627	1.140
e34	-0.00145	0.14131	0.0001	0.9918	0.999
e44	0.58577	0.30036	3.8034	0.0511	1.796
FEL	-0.05156	0.03290	2.4570	0.1170	0.950
FEL Missing	0.55943	0.11515	23.6030	<.0001	1.750

Table 7. Effects of apo E Genotypes on Diseases of the Nervous System (largely Parkinson's, Alzheimer's) Mortality based on Cox Proportional Hazards Models.

Variable	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
Age	0.09995	0.01236	65.3695	<.0001	1.105
Age2**	0.0006554	0.0009416	0.4845	0.4864	1.001
<Hi School	0.11880	0.17500	0.4609	0.4972	1.126
Some College	-0.04814	0.17666	0.0742	0.7852	0.953
College Grad	-0.30938	0.19148	2.6107	0.1061	0.734
Male	0.23140	0.14392	2.5852	0.1079	1.260
Divorced	-0.27589	0.45759	0.3635	0.5466	0.759
Widowed	-0.18018	0.16357	1.2134	0.2707	0.835
Never Married	-1.22529	1.00480	1.4870	0.2227	0.294
e22	0.51417	0.71590	0.5158	0.4726	1.672
e23	-0.18511	0.22829	0.6575	0.4174	0.831
e24	0.02907	0.39043	0.0055	0.9407	1.029
e34	0.45541	0.14786	9.4863	0.0021	1.577
e44	1.02291	0.29395	12.1091	0.0005	2.781
FEL	-0.02134	0.04077	0.2739	0.6007	0.979
FEL Missing	0.72244	0.13006	30.8557	<.0001	2.059

Table 8. Effects of apo E Genotypes on Diseases of the Endocrine System (largely Diabetes) Mortality based on Cox Proportional Hazards Models.

Variable	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
Age	0.07068	0.01284	30.3196	<.0001	1.073
Age2**	0.00111	0.00100	1.2319	0.2670	1.001
<Hi School	0.14608	0.18323	0.6356	0.4253	1.157
Some College	-0.36121	0.20417	3.1298	0.0769	0.697
College Grad	-0.50386	0.21217	5.6398	0.0176	0.604
Male	0.31000	0.15812	3.8437	0.0499	1.363
Divorced	0.49467	0.35096	1.9867	0.1587	1.640
Widowed	0.09714	0.17932	0.2935	0.5880	1.102
Never Married	0.20130	0.58759	0.1174	0.7319	1.223
e22	0.88958	0.58879	2.2826	0.1308	2.434
e23	-0.28934	0.24249	1.4237	0.2328	0.749
e24	-0.30715	0.45779	0.4501	0.5023	0.736
e34	-0.08162	0.17614	0.2147	0.6431	0.922
e44	0.46542	0.36699	1.6084	0.2047	1.593
FEL	-0.06419	0.04796	1.7910	0.1808	0.938
FEL Missing	1.07038	0.14491	54.5582	<.0001	2.916

Table 9. Effects of apo E Genotypes on Diseases of the Digestive System Mortality based on Cox Proportional Hazards Models.

Variable	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
Age	0.08697	0.01386	39.3896	<.0001	1.091
Age2**	-0.0001421	0.00109	0.0171	0.8959	1.000
<Hi School	-0.03040	0.18819	0.0261	0.8717	0.970
Some College	-0.32769	0.19977	2.6906	0.1009	0.721
College Grad	-0.56913	0.21818	6.8043	0.0091	0.566
Male	0.33639	0.16201	4.3113	0.0379	1.400
Divorced	0.22944	0.42423	0.2925	0.5886	1.258
Widowed	0.24952	0.17875	1.9485	0.1628	1.283
Never Married	0.30109	0.58856	0.2617	0.6090	1.351
e22	0.45075	0.71667	0.3956	0.5294	1.569
e23	-0.25058	0.23794	1.1091	0.2923	0.778
e24	-0.13876	0.41999	0.1092	0.7411	0.870
e34	-0.12667	0.18124	0.4885	0.4846	0.881
e44	0.66373	0.34793	3.6392	0.0564	1.942
FEL	-0.02293	0.04656	0.2426	0.6223	0.977
FEL Missing	0.84785	0.14471	34.3294	<.0001	2.335

Table 10. Effects of apo E Genotypes on Psychiatric and Mental Disorders (largely Psychoses) Mortality based on Cox Proportional Hazards Models.

Variable	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
Age	0.10002	0.01438	48.3896	<.0001	1.105
Age2**	-0.0007653	0.00111	0.4770	0.4898	0.999
<Hi School	0.11408	0.18835	0.3668	0.5447	1.121
Some College	-0.24679	0.20378	1.4666	0.2259	0.781
College Grad	-0.34564	0.21357	2.6193	0.1056	0.708
Male	0.08542	0.16494	0.2682	0.6045	1.089
Divorced	0.36659	0.39497	0.8614	0.3533	1.443
Widowed	0.18432	0.17752	1.0780	0.2992	1.202
Never Married	-0.20255	0.71639	0.0799	0.7774	0.817
e22	0.55612	0.71739	0.6009	0.4382	1.744
e23	-0.24806	0.25024	0.9826	0.3216	0.780
e24	-0.02108	0.42113	0.0025	0.9601	0.979
e34	0.12490	0.17572	0.5052	0.4772	1.133
e44	1.36474	0.27102	25.3576	<.0001	3.915
FEL	-0.01319	0.04755	0.0769	0.7816	0.987
FEL Missing	0.87958	0.14530	36.6450	<.0001	2.410

Table 11. Main and Interaction Effects of apo E Genotypes and Familial Excess Longevity on All-Cause Mortality based on Cox Proportional Hazards Models.

Variable	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
Age	0.10214	0.00520	385.8542	<.0001	1.108
Age2**	-0.0001735	0.0003959	0.1922	0.6611	1.000
<Hi School	0.06141	0.07024	0.7645	0.3819	1.063
Some College	-0.07292	0.07158	1.0380	0.3083	0.930
College Grad	-0.19902	0.07514	7.0144	0.0081	0.820
Male	0.45640	0.05804	61.8352	<.0001	1.578
Divorced	0.62732	0.14227	19.4422	<.0001	1.873
Widowed	0.13556	0.06519	4.3251	0.0376	1.145
Never Married	0.58938	0.19403	9.2266	0.0024	1.803
e22c	0.60650	0.25410	5.6971	0.0170	1.834
e23c	-0.07120	0.08309	0.7343	0.3915	0.931
e24c	-0.06773	0.15109	0.2009	0.6540	0.935
e34c	0.21710	0.06162	12.4125	0.0004	1.242
e44c	0.54723	0.14764	13.7373	0.0002	1.728
FELc	-0.04262	0.01407	9.1817	0.0024	0.958
FEL Missing	0.01803	0.05621	0.1029	0.7484	1.018
FEL*e22c	-0.12315	0.12695	0.9410	0.3320	0.884
FEL*e23c	-0.06642	0.04532	2.1481	0.1427	0.936
FEL*e24c	-0.06883	0.07206	0.9124	0.3395	0.933
FEL*e34c	-0.08316	0.03384	6.0412	0.0140	0.920
FEL*e44c	-0.13488	0.05777	5.4518	0.0195	0.874

Variables used in interactions have all been centered and are noted with a ‘c’ suffix.

Table 12. Main and Interaction Effects of apo E Genotypes and Familial Excess Longevity on Cardiovascular Mortality based on Cox Proportional Hazards Models.

Variable	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
Age	0.09774	0.00742	173.3960	<.0001	1.103
Age2**	0.0002865	0.0005520	0.2694	0.6037	1.000
<Hi School	0.07821	0.09979	0.6143	0.4332	1.081
Some College	-0.21734	0.10639	4.1731	0.0411	0.805
College Grad	-0.25254	0.10899	5.3689	0.0205	0.777
Male	0.38807	0.08414	21.2731	<.0001	1.474
Divorced	0.29599	0.23135	1.6369	0.2008	1.344
Widowed	0.08041	0.09411	0.7299	0.3929	1.084
Never Married	0.34612	0.30800	1.2628	0.2611	1.414
e22c	0.49658	0.38329	1.6785	0.1951	1.643
e23c	-0.10942	0.12091	0.8189	0.3655	0.896
e24c	-0.19812	0.22992	0.7425	0.3888	0.820
e34c	0.12719	0.09054	1.9732	0.1601	1.136
e44c	0.44739	0.21868	4.1855	0.0408	1.564
FELc	-0.06597	0.02048	10.3743	0.0013	0.936
FEL Missing	0.10021	0.08029	1.5577	0.2120	1.105
FEL*e22c	-0.10147	0.19656	0.2665	0.6057	0.904
FEL*e23c	-0.13390	0.06579	4.1423	0.0418	0.875
FEL*e24c	-0.00872	0.10963	0.0063	0.9366	0.991
FEL*e34c	-0.08141	0.04982	2.6702	0.1022	0.922
FEL*e44c	-0.13863	0.07616	3.3132	0.0687	0.871

Table 13. Main and Interaction Effects of apo E Genotypes and Familial Excess Longevity on Cancer Mortality based on Cox Proportional Hazards Models.

Variable	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
Age	0.07036	0.00965	53.1223	<.0001	1.073
Age2**	-0.00179	0.0009336	3.6798	0.0551	0.998
<Hi School	0.10001	0.14444	0.4794	0.4887	1.105
Some College	-0.04767	0.14053	0.1151	0.7344	0.953
College Grad	-0.32429	0.15228	4.5348	0.0332	0.723
Male	0.41919	0.11597	13.0646	0.0003	1.521
Divorced	0.33457	0.28876	1.3424	0.2466	1.397
Widowed	-0.03079	0.13612	0.0512	0.8211	0.970
Never Married	0.70303	0.34290	4.2036	0.0403	2.020
e22c	1.04331	0.40925	6.4989	0.0108	2.839
e23c	-0.13875	0.16838	0.6790	0.4099	0.870
e24c	-0.48473	0.36468	1.7667	0.1838	0.616
e34c	-0.03833	0.12838	0.0891	0.7653	0.962
e44c	0.27138	0.29840	0.8271	0.3631	1.312
FELc	0.02243	0.03296	0.4628	0.4963	1.023
FEL Missing	0.53806	0.10606	25.7386	<.0001	1.713
FEL*e22c	-0.39036	0.28656	1.8556	0.1731	0.677
FEL*e23c	-0.00495	0.10170	0.0024	0.9612	0.995
FEL*e24c	-0.07263	0.20619	0.1241	0.7246	0.930
FEL*e34c	0.03756	0.07991	0.2210	0.6383	1.038
FEL*e44c	0.02597	0.25263	0.0106	0.9181	1.026

Table 14. Main and Interaction Effects of apo E Genotypes and Familial Excess Longevity on Respiratory Mortality based on Cox Proportional Hazards Models.

Variable	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
Age	0.10831	0.01159	87.3021	<.0001	1.114
Age2**	0.0003023	0.0008123	0.1385	0.7098	1.000
<Hi School	0.12600	0.15020	0.7037	0.4016	1.134
Some College	-0.12591	0.16030	0.6170	0.4322	0.882
College Grad	-0.27013	0.16902	2.5545	0.1100	0.763
Male	0.43804	0.12761	11.7820	0.0006	1.550
Divorced	0.39910	0.32935	1.4684	0.2256	1.490
Widowed	0.23626	0.14123	2.7983	0.0944	1.267
Never Married	0.15819	0.50901	0.0966	0.7560	1.171
e22c	1.00290	0.46897	4.5732	0.0325	2.726
e23c	-0.18200	0.18703	0.9470	0.3305	0.834
e24c	0.10436	0.30661	0.1158	0.7336	1.110
e34c	-0.02919	0.14408	0.0410	0.8395	0.971
e44c	0.56433	0.30860	3.3440	0.0675	1.758
FELc	-0.05353	0.03324	2.5935	0.1073	0.948
FEL Missing	0.57290	0.11589	24.4374	<.0001	1.773
FEL*e22c	-0.05032	0.21978	0.0524	0.8189	0.951
FEL*e23c	0.01044	0.10668	0.0096	0.9220	1.010
FEL*e24c	-0.14268	0.14730	0.9382	0.3327	0.867
FEL*e34c	-0.13867	0.08176	2.8768	0.0899	0.871
FEL*e44c	-0.09168	0.15352	0.3566	0.5504	0.912

Table 15. Main and Interaction Effects of apo E Genotypes and Familial Excess Longevity on Diseases of the Nervous System (largely Parkinson's, Alzheimer's) based on Cox Proportional Hazards Models.

Variable	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
Age	0.09984	0.01238	65.0241	<.0001	1.105
Age2**	0.0005657	0.0009528	0.3525	0.5527	1.001
<Hi School	0.11377	0.17518	0.4218	0.5161	1.120
Some College	-0.05813	0.17743	0.1073	0.7432	0.944
College Grad	-0.30639	0.19167	2.5551	0.1099	0.736
Male	0.24549	0.14431	2.8939	0.0889	1.278
Divorced	-0.27658	0.45759	0.3653	0.5456	0.758
Widowed	-0.17686	0.16424	1.1595	0.2816	0.838
Never Married	-1.22155	1.00486	1.4778	0.2241	0.295
e22c	0.55670	0.71564	0.6051	0.4366	1.745
e23c	-0.18243	0.22875	0.6360	0.4252	0.833
e24c	-0.16054	0.44723	0.1289	0.7196	0.852
e34c	0.45040	0.14835	9.2177	0.0024	1.569
e44c	0.95310	0.30541	9.7391	0.0018	2.594
FELc	-0.01878	0.04153	0.2046	0.6510	0.981
FEL Missing	0.73986	0.13094	31.9286	<.0001	2.096
FEL*e22c	-0.20585	0.44699	0.2121	0.6451	0.814
FEL*e23c	-0.13806	0.14170	0.9492	0.3299	0.871
FEL*e24c	0.24516	0.17163	2.0404	0.1532	1.278
FEL*e34c	-0.07853	0.09650	0.6622	0.4158	0.924
FEL*e44c	-0.20617	0.13182	2.4461	0.1178	0.814

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