ORIGINAL ARTICLE

Apolipoprotein E ε4 Count Affects Age at Onset of Alzheimer Disease, but Not Lifetime Susceptibility

The Cache County Study

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Background: The incidence of Alzheimer disease (AD) increases strongly with age, but little is known about the cumulative incidence of AD over a lifetime of 100 years, or its relationship to the polymorphic *APOE* locus that encodes apolipoprotein E. *APOE* is a strong genetic risk factor for AD.

Objectives: To estimate the occurrence of AD as a function of age and number of *APOE* ε4 alleles; and to explore evidence for heterogeneity of AD risk related to *APOE* genotype and to other sources.

Design: Nonparametric and parametric survival analyses of AD incidence in prospective longitudinal study.

Setting and Participants: A total of 3308 elderly residents of Cache County, Utah.

Main Outcome Measures: Cumulative incidence of AD; in mixture models assuming susceptible and nonsusceptible individuals, the proportion of individuals not susceptible to AD at any age.

Results: Models that assumed a proportion of invulnerable individuals provided strongly improved fit to the data. These models estimated the 100-year lifetime incidence of AD at 72%, implying that 28% of individuals would not develop AD over any reasonable life expectancy. We confirmed the acceleration of AD onset in individuals with 1 or, especially, 2 *APOE* ε4 alleles, but observed no meaningful difference in 100-year lifetime incidence related to number of ε4 alleles.

Conclusions: The *APOE* ε4 allele acts as a potent risk factor for AD by accelerating onset. However, the risk of AD appears heterogeneous in ways independent of *APOE*. Some individuals seem destined to escape AD, even over an extended lifespan. Their relative invulnerability may reflect other genes or environmental factors that can be investigated.

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THE INCIDENCE OF ALZHEIMER disease (AD) doubles with each 5 years of age through 90 years,[1,2] so that the prevalence of AD may reach 45% or higher after age 85 years.[3] Less is known about the proportion who will develop AD over a theoretical life expectancy of 100 years or more. The Framingham study estimated the unadjusted cumulative incidence of AD at 43.0% (men) and 48.3% (women) by age 99 years,[4] while similar analyses from East Boston, Mass, suggested 49.6% by age 90 years.[5] Neither of these studies included many observations after age 90 years, however, nor were they able to examine the lifetime incidence of AD in relation to genotype at *APOE*, the polymorphic genetic locus for apolipoprotein E.[6,7]

The Cache County, Utah, population affords an unusual opportunity to examine these questions. With 5092 initial respondents, the Cache County Study is among the largest single-population investigations of the occurrence of AD. The population is one of the longest lived in the United States[8] and includes some 719 individuals older than 85 years and 249 individuals 90 years and older. Low rates of chronic diseases associated with tobacco and alcohol use facilitate the detection and differential diagnosis of dementia among its oldest members.[9] Response rates are high,[10] and 97% of the population has donated buccal DNA for analysis of *APOE* genotype. These attributes enabled us to analyze the lifetime incidence of AD and other dementias in relation to *APOE* genotype by fitting both nonparametric and parametric survival models to the onset of AD.

METHODS

STUDY POPULATION AND DATA GATHERING METHODS

Between 1995 and 1997, the Cache County Study invited participation of all elderly county residents 65 years and older, enrolling 5092 individuals (90%). *APOE* genotype was determined by restriction isotyping of buccal DNA.[10] A multistage screening and assessment protocol for dementia ("wave I")[10,11] began with the modified Mini-Mental State Examination[12] or, for those unable to participate, a brief informant questionnaire to identify those with apparent cognitive difficulty.[13] We then administered the informant-based Dementia Questionnaire[14] to collateral informants for these impaired participants, and for all members of a stratified subsample of 960 individuals (19% of all participants) weighted to include the oldest elements of the population and those with 1 or 2 copies of the *APOE* ϵ4 allele. Clinical assessment (CA) of this 19% subsample (regardless of their results on the modified Mini-Mental State Examination and the Dementia Questionnaire) and of screen-positive individuals included the following: (1) a brief medical history and examination; (2) a chronologic history of cognitive symptoms; (3) a structured neurologic examination (all administered by trained nurses); and (4) a 1-hour battery of neuropsychological tests. After review of these data, 86% of living individuals who received working diagnoses of dementia were examined by a geriatric psychiatrist or neurologist and referred for laboratory studies including neuroimaging. Eighteen months later, we reexamined surviving participants whose initial evaluation had suggested dementia or any substantial cognitive impairment. A consensus conference of experts in neurology, neuropsychology, and geriatric psychiatry then assigned final diagnoses. These experts also reevaluated previous estimates for age at onset, defined as the year when participants unambiguously met *DSM-III-R* criteria for dementia.[15] These methods identified 340 individuals with dementia prevalent at their initial interview.

Between 1998 and 2000 we applied similar screening procedures and an identical CA protocol among 3396 (83%) of the 4104 living Cache County Study participants who had not received wave I diagnoses of dementia ("wave II"). These procedures identified 152 instances of incident dementia, and another 15 individuals with dementia prevalent at wave I who had escaped detection by our earlier screening procedures. Adding 33 individuals with incident dementia discovered in the later stages of wave I yielded a total of 185 individuals with incident dementia. Of these, 123 (122 with known genotype at *APOE*) received diagnoses of definite, probable or possible AD.[16] A remaining 3123 participants completed the wave II study procedures per protocol and were judged to be free of dementia. As in wave I, we administered all screening and assessment procedures as well as a CA to the 441 surviving members of the 19% subsample (excluding those with dementia at wave I). Comparing these screening results with CA findings, we estimated the sensitivity of the wave II dementia screening procedures at 86%.[17]

ANALYTIC APPROACH

Nonparametric Models of Disease-Free Survival

We used the Kaplan-Meier product-limit method[18] to estimate the probability of disease-free survival by age in the 3-year interval between waves I and II. This method considers each participant's person-year contribution during the follow-up interval, and then combines these contributions to yield estimates of cumulative disease-free survival through any specified year of age. Because the outcome of interest was onset of AD, we censored observations on individuals who developed other types of dementia from their year of onset onward. The crude cumulative survival $S(t)$ from age 65 years to age t (conditioned on disease-free survival to the beginning of the observation period) may be estimated as

$$S(t) = \prod_{j=65}^{t} \frac{y_j - e_j}{y_j},$$

where y_j is the number of person-years of observation at age j, and e_j is the number of individuals who developed AD at age t.

We adjusted the foregoing formula to account for the refusal of 10% of wave II subjects to participate in a requested CA, and also to account for the estimated sensitivity of our screening procedures (86%) in identifying individuals appropriate for referral to CA. This adjustment considered separately onsets that occurred within subsample (e'_j) and others (e''_j) whose referral for CA was prompted by screening. The adjusted estimate for the total number of onsets at age j divided e'_j by 0.90, the response rate at CA, and e''_j by 0.77 (the product of the 90% CA response rate and the 86% sensitivity estimate), as follows:

$$S(t) = \prod_{j=65}^{t} 1 - \left[\frac{e'_j}{0.90y_j} + \frac{e''_j}{0.77y_j}\right]. \quad (1)$$

We considered the problem of response bias (disproportionate occurrence of dementia among nonrespondents) by recalculating survival estimates from equation 1 modified to reflect an extreme assumption of doubled occurrence of dementia among nonresponders as compared with responders. An extension of the adjusted Kaplan-Meier approach was then used to calculate empirical survival curves for strata of the population bearing 0, 1, or 2 ϵ4 alleles at *APOE*.

Parametric Models of Disease-Free Survival

The foregoing, nonparametric approach does not consider whether the population may be heterogeneous with regard to susceptibility of developing AD, ie, whether there are definable subpopulations with substantially different risk profiles. Standard parametric survival analyses also assume homogeneity of risk, allowing only for random differences in age-specific risk of AD. Thus, they model the onset of AD under the assumption that its probability is represented by a single distribution so that the hazard of AD onset increases without bound as age increases. Equivalently, the entire population must develop AD if its members live long enough, and the probability of disease-free survival approaches zero by some (perhaps very) late age.

An extension of this approach permits testing of the assumption of homogeneity by embedding the above single-distribution model in a more complex framework that posits heterogeneity in susceptibility. In its simplest form, such a revised framework postulates the existence of 2 subpopulations, one with a proportion ρ of individuals susceptible to AD and the other with a complementary proportion $1 - \rho$ of people who will never fall ill no matter how long they live. The probability distribution for disease onset by age in the corresponding mixtures distribution is the sum of the distributions for the 2 subpopulations, the standard onset distribution applying only to the susceptible subpopulation. Conventional modeling techniques are then used to estimate ρ as well the parameters that characterize the age distribution of onsets in the susceptible subpopulation (if $\rho = 1$, then the mixture distribution reduces to the more familiar single-distribution model). One may also define additional subpopulations by their number of *APOE* ϵ4 alleles, estimating the distribution of onsets for the mixture dis-

tribution that combines these subpopulations. Still more complex formulations are also possible, but their drawbacks are substantial (see the "Comment" section).

Following this approach, we used the Weibull distribution to model the probability of AD onset as a function of time *t*, here as years of participant age. This distribution is used widely in epidemiologic and other types of time-to-event analyses, to model the onset of disease.[19] Its probability density function $f(t)$ is written as $f(t)=\lambda t^{(\lambda-1)}exp[(-t)^{\lambda}]$.

Being more flexible than the exponential distribution (a special case of the Weibull where $\lambda=1$), the Weibull model allows for hazards that monotonically increase with age when $\lambda>1$ or decrease when $\lambda<1$. As with other standard distributions, when $\lambda>1$ the Weibull hazard increases ceaselessly with increasing *t*, implying that the hazard (incidence) of AD increases without bound. In other words, if an individual lives long enough, he or she will inevitably develop AD.

A useful generalization of the Weibull function adds a second parameter *a* that introduces scale but does not otherwise alter the shape of the onset probability density. Our analyses used this form, which may be written as follows:

$$(2) \qquad f(t)=(\lambda/\alpha)(t/\alpha)^{(\lambda-1)}exp[(-t/\alpha)^{\lambda}].$$

Our first analyses compared the fit to the Cache County incidence data of the above 2-parameter Weibull model vs a 3-parameter model that considered the population as comprising a proportion ρ susceptible to AD and a complementary proportion of nonsusceptible individuals. We fitted these parametric models by means of maximum likelihood estimation, which is fully efficient (it achieves maximum inference theoretically available from the data) and generates asymptotically unbiased minimum variance estimators of the distribution's underlying parameters. Maximum likelihood estimation requires a "likelihood equation," which yields the likelihood (probability after the fact) of each observation under the specified set of parameters. Because there are many such independent observations, the likelihood over the entire data set with a given set of parameters is the product of the individual likelihoods. Varying the likelihood equation's parameters iteratively yields a unique set of parameters with the highest (maximum) likelihood value for the data set. This operation is typically simplified by calculating the natural logarithm of the individual likelihoods and summing the individual log-likelihoods to search for the unique set of parameters that yields the maximum log-likelihood. Using log-likelihoods affords the further advantage of allowing the use of a likelihood ratio χ^2 test for nonchance improvement in the fit of more complex models with larger numbers of parameters (this derives from the fact that −2 times the difference in the log likelihoods under the less complex vs the more complex model is asymptotically distributed as a χ^2 distribution with degrees of freedom equal to the difference in the number of parameters in the 2 models).

We used PROC NLIN in SAS (version 8; SAS Institute Inc, Cary, NC) to calculate maximum likelihood estimation parameters in models of increasing complexity, using a number of assumptions and procedures that we note here: (1) Although the likelihood equations were written as if they were continuous, we did not have continuous data. Instead, we had onsets dated to the nearest year of chronologic age. Therefore, we calculated likelihoods as if they were step functions with integer intervals, ie, we dealt with annualized discrete-time probabilities. (2) For each individual year of observation, the likelihood function was conditioned on the participant having survived free of disease until the specified age. This conditioning is needed to account for the existence of other individuals born in the same year who might have experienced earlier disease onsets. We would have no knowledge of such events, so the available data are "left-truncated." (3) Each person-year of observation up to and including a year containing an onset was regarded as independent of each other year of observation. Therefore, the likelihood calculations considered each such year individually. Specifically, individuals who entered the 3-year observation window and remained free of disease for the entire time contributed 3 independent annual observations; other individuals with disease onset in the third year of the window also contributed 3 observations (2 disease free and 1 with an onset), but those who developed AD in the second year contributed only 2 years of observation, etc. In this sense, the available data were also "right-censored." (4) The likelihood expressions differed for observation years that included an onset vs those that did not. For years with an onset, the likelihoods were written as the (annualized) probability density of onset within the participant's year of age, conditioned on disease-free survival up to the age of observation. This is equivalent to the discrete annualized hazard of onset in the stated year, and may be written as follows:

$$(3) \qquad H(t)=f(t)/[1-F(t-1)],$$

where $f(t)$ is the probability density function at age *t* as described by equation 2, and $F(t-1)$ is the cumulative probability of onset (using the same distribution) through all ages before *t*. For those who survived an observation year free of disease, the likelihood was written as the complement of the prior expression. (5) In mixture models that included a parameter ρ describing the proportion of susceptible individuals, we assumed that all individuals with an AD onset were susceptible. By contrast, those with no onset might have been members of the nonsusceptible subpopulation, or they might have been susceptible but have escaped disease onset in the year of observation (ie, they were "destined" to develop AD at a later age). Therefore, the likelihood expression for affected individuals was written as $\rho \cdot H(t)$ and the likelihood for nonsusceptible individuals was $(1-\rho)+\{\rho \cdot [1-H(t)]\}$, which reduces to $1-\rho \cdot H(t)$, the complement of the prior expression. (6) As is exemplified in the last point, the value of the likelihood expressions for disease onset or escape at age *t* must sum to 1; this satisfies the logical requirement that a specified individual either did or did not experience an onset in his or her *t*th year.

Following a similar approach, we also constructed and evaluated more complex formulations that estimated different Weibull parameters λ and scale parameters α for individuals with 0, 1, or 2 ϵ4 alleles at *APOE*, and still more elaborate models that estimated separate Weibull parameters along with separate estimates of ρ in those with different numbers of ϵ4 alleles.

RESULTS

Table 1 presents *APOE* genotypes and demographic characteristics of the analysis pool of 3308 individuals who contributed 10 541 person-years of risk. **Figure 1**A displays the product-limit estimates with and without adjustment for incomplete ascertainment. Figure 1B displays the (unadjusted) product-limit graphs for participants with 0, 1, and 2 ϵ4 alleles at *APOE*, showing the familiar acceleration of AD onsets in those with 1 or, particularly, 2 ϵ4 alleles. The pooled plots of Figure 1A corroborate our prior analysis[1] suggesting a decline in AD risk as measured by the hazard after the mid-90s; they suggest a relaxation in the rate of new disease in 122 person-years of observation after age 93 years and an absence of incident AD cases in 16 person-years after age 97 years. Figure 1A also shows that adjustment for incomplete ascertainment produced a relatively modest change in the estimate of 100-year disease-free survival: 0.19, with 95% confidence interval of 0.05

Table 1. Demographic Characteristics of Individuals by Number of *APOE* ε4 Alleles in the Cache County, Utah, Study, 1995-1998

Characteristics	No. of *APOE* ε4 Alleles				
	0	1	2	Missing	Total
No. of individuals	2262	938	83	25	**3308**
No. of person-years	7223	2980	261	77	**10 541**
Sex, No. (%) F	1318 (58.3)	549 (58.5)	41 (49.4)	16 (64.0)	**1924** (58.2)
Age at wave I, y, No. (%)					
65-69	651 (28.8)	302 (32.2)	33 (39.8)	1 (4.0)	**987** (29.8)
70-74	614 (27.1)	286 (30.5)	24 (28.9)	6 (24.0)	**930** (28.1)
75-79	504 (22.3)	202 (21.5)	13 (15.7)	7 (28.0)	**726** (21.9)
80-84	294 (13.0)	101 (10.8)	10 (12.0)	7 (28.0)	**412** (12.5)
85-89	146 (6.5)	33 (3.5)	2 (2.4)	3 (12.0)	**184** (5.6)
≥90	53 (2.3)	14 (1.5)	1 (1.2)	1 (4.0)	**69** (2.1)
Level of education					
Mean No. of years	13.3	13.5	13.8	12.2	13.3
No. (%) with ≥8 y	2164 (95.7)*	916 (97.7)	81 (98.8)*	24 (96.0)	**3185** (96.3)
AD, No. (%)	69 (3.1)	41 (4.4)	12 (14.5)	1 (4.0)	**123** (3.7)
Dementia, No. (%)	104 (4.6)	65 (6.9)	15 (18.1)	1 (4.0)	**185** (5.6)

Abbreviation: AD, Alzheimer disease.
*One individual was missing education data.

to 0.33 vs 0.25 (95% confidence interval, 0.06-0.44). Although not shown, the assumption of double rates of dementia among nonresponders yielded a cumulative survival of 0.10 (95% confidence interval, 0.03-0.18).

Table 2 shows the maximum likelihood estimation parameter estimates (with standard errors) for the 4 different parametric models as suggested in the "Analytic Approach" subsection of the "Methods" section. Model 1 assumes homogeneity, ie, the entire population is susceptible or, equivalently, $\rho = 1$, with onset age distributed according to a 2-parameter Weibull formulation. Model 2 assumes that the population includes 2 subpopulations, one of susceptible persons in proportion ρ, and the balance of nonsusceptible individuals. For the former subpopulation, onset age has a Weibull distribution with scale and location parameters as indicated. The table shows that this 3-parameter model with a mixture parameter ρ yields a considerably improved log likelihood ($P<.001$). **Figure 2** depicts models 1 and 2, along with the empirical Kaplan-Meier survival estimates. Model 2 estimates ρ at 0.74; ie, about three fourths of the population appear to be susceptible.

Model 3 (Table 2) includes a mixture parameter ρ but also estimates separate shape parameters λ and scale parameters α for each *APOE* stratum. The log likelihood of this 7-parameter model is thereby improved substantially over the previous 3-parameter formulation ($\chi^2_4 = 124.2$, $P<.001$). **Figure 3** shows this expanded model, along with empirical Kaplan-Meier survival graphs for the 3 *APOE* strata. The 3 shape parameter estimates are similar, but the scale parameters vary distinctly, reflecting acceleration in rate of onset for the groups with 1 or, especially, 2 *APOE* ϵ4 alleles. This model estimates the mixture parameter ρ at 0.72, essentially unchanged from model 2's value of 0.74.

Finally, model 4 estimates separate mixture parameters for each of the 3 *APOE* groups. This model therefore estimates 9 unique parameters, including not only distinct Weibull parameters λ and α for the 3 groups but also 3 corresponding mixture parameters ρ. Predictably, the added parameters in the model improve the likelihood value (ie, the fit to the data), but the improvement is modest, and the likelihood ratio χ^2 test suggests that this improvement is well within the range expected by chance ($\chi^2_2 = 2.4$, $P = .32$). Under the principle of parsimony, model 3 thus appears to provide the best description of disease onsets in the data. Even the large Cache County sample is therefore unable to provide evidence that *APOE* affects the proportions of susceptible and nonsusceptible individuals in the population. Instead, its influence appears to reside primarily in its influence on timing of AD onset.

COMMENT

These analyses support our previous observation[1,20] that *APOE* genotype primarily influences *when*, and not *whether*, individuals will develop AD. They also provide evidence that the Cache County population is heterogeneous in its vulnerability to AD, and that the onset of dementia is not an inevitable consequence of aging. Instead, the population appears heterogeneous in its susceptibility to AD, and some of this heterogeneity is unrelated to the count of *APOE* ϵ4 alleles. A sizable proportion of the population appears relatively nonsusceptible to AD regardless of *APOE* genotype.

Our findings do *not* dispute the importance of *APOE* as a risk factor for AD. They do, however, suggest a different role for *APOE* than is sometimes discussed. Through its effects on the timing of disease expression, the gene appears to influence the age-specific risk of AD onset. In typical (age-adjusted) epidemiologic analyses, the acceleration of onset with 1 or, especially, 2 ϵ4 alleles translates to a strongly increased age-specific risk of AD, especially in early old age. We note, however, that the inclusion in the population of relatively nonsusceptible individuals predicts a complementary finding in late old age, when most susceptible individuals with 1 or, especially, 2 ϵ4 alleles will have developed dementia. Then the relative risks with these

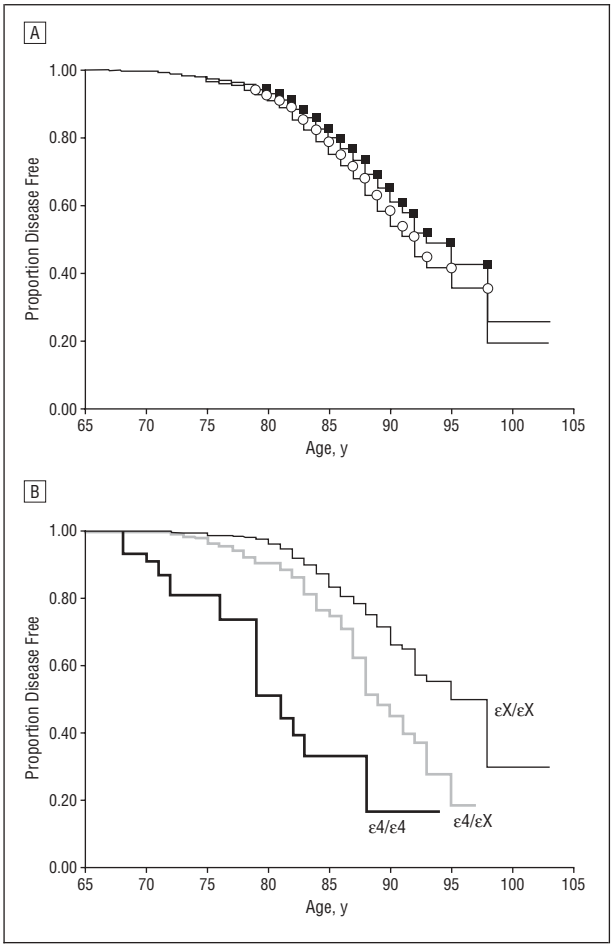

Figure 1. A, Disease-free survival by age among 3308 residents of Cache County, Utah, 1995 to 1997 and 1998 to 2000. Altogether, 9 participants survived a combined total of 16 person-years with no further onsets of Alzheimer disease after age 98 years. The heavy line with closed squares represents the unadjusted product-limit estimates. The light line with open circles shows the product-limit estimates after adjustment for incomplete case ascertainment. B, Unadjusted disease-free survival by age, stratified by 0, 1, and 2 apolipoprotein E (*APOE*) ϵ4 alleles, among 3308 residents of Cache County, Utah, 1995 to 1997 and 1998 to 2000. The graph shows 3 unadjusted product-limit estimates for the 3 strata of 0 (hashed line), 1 (gray line), and 2 (black line) *APOE* ϵ4 alleles.

genotypes is predicted to decline below 1 because individuals in the reference group with no ϵ4 alleles will continue to accumulate new AD onsets,[21] while the portion with ϵ4 will be largely depleted of susceptible persons. Indeed, our group previously observed such an inversion of the prevalence odds ratios among Cache County's elderly population[10] and also reported[1] that the incidence of AD in Cache County declines after age 97 years. The present analyses suggest that this decline reflects a depletion of susceptible individuals at extreme old ages, while substantial numbers of relatively nonsusceptible individuals remain in the person-year denominators of the incidence calculations.

The present analyses yield conclusions similar to those previously obtained using prevalence data.[20] Our parametric models assigned equal weights to all person-year observations and are therefore unlikely (as product-limit estimates might be) to have been influenced unduly by a relatively small number of observations at late ages. The study was aided in this respect by the relatively good physical health and the longevity of the Cache County population, which surpasses US norms by nearly 10 years[22] and afforded 230 person-years of observations after age 90 years.

We note several limitations of our analyses, however. First, survival estimates can easily be distorted in analyses that preferentially exclude some categories of individuals. For example, residents with incident dementia may have disproportionately refused the study's wave II procedures (response bias), or they may have suffered excess mortality in the wave I–wave II interval (informative censoring). Both possibilities could yield an underestimate of true incidence (ie, an overestimate of cumulative survival). The threat of response bias is diminished somewhat in Cache County by the population's unusually high response rates. Beyond this, a hypothetical analysis that assumed double enrichment for dementia among nonresponders did not alter our finding that a proportion of individuals will not develop AD within their lifespan. The threat of informative censoring was also somewhat attenuated by a relatively brief follow-up interval of 3 years. Participants who developed incident AD in this interval would have been ill only about an average of 1.5 years or (probably) less—a duration not likely to incur a many-fold excess in mortality. Further assurance on this point came from analyses of postmortem Dementia Questionnaire interviews administered to collateral informants of 433 participants who had died in the wave I–wave II interval. Comparison of these interview results with those among the fully examined subsample suggested that 42 cases of incident dementia (9.7%) went undetected among the decedents, as contrasted with an age-adjusted figure of 11.7% in the responding sample.

Another potential problem is sensitivity bias, or underascertainment of cases by screening measures with imperfect sensitivity. With its subsample strategy, the Cache County Study design afforded estimates of screening sensitivity for all-cause dementia,[17] and we applied these estimates when calculating adjusted product-limit estimates (equation 1). Unfortunately, we know of no convenient method to adjust for sensitivity bias in parametric models. However, the adjusted empirical analyses and the study's overall screening sensitivity of 89% suggest that this bias alone is unlikely to explain the appreciable numbers who survived disease free into late old age.

A different source of error relates to the diagnostic process itself. Especially when dealing with very old people, one might easily "explain away" dementia as a simple consequence of age or physical illness. We specifically tried to avoid this error. In other analyses, we compared conventional clinical dementia diagnoses with algorithmic diagnoses based purely on objective psychometric methods.[23] Reanalyzing these comparisons by age group, we found no age-related differences in agreement between the 2 diagnostic approaches.

Similarly, our diagnoses of AD among those with dementia might have been either excessively stringent or overly inclusive. Comparison of our differential diagnoses with neuropathological findings showed sensitivity of AD diagnoses (85%) comparable to findings from university clinics. Even so, we evaluated the potential con-

sequences of errors in AD diagnosis first by considering as cases only individuals with a diagnosis of AD and no other dementing disorder. At the opposite extreme, we reran the analyses including as an AD "case" any individual with dementia. In both instances our major conclusions were unchanged. We emphasize that all of these diagnoses required the initial finding of *clinical dementia*; we do not have sufficient autopsies from elderly participants without dementia to know whether they have substantial AD pathologic changes, or whether their measure of such pathologic changes varies with *APOE* genotype.

Another question is the aptness of our analytical assumptions[24] and, in particular, our choice of the Weibull distribution.[25] Not surprisingly, the 2-parameter Weibull distribution fit the Cache County data much better than a single-parameter exponential model. However, there are other distributions with variable hazards. Thus, we also attempted to fit a survival model with a gamma distribution to these data[26] but, probably owing to the mathematical complexity of the gamma function, we were unable to obtain convergence within our algorithms to produce maximum likelihood estimates for the 2 gamma parameters.

We know of no previous empirical investigation of the heterogeneity of susceptibility in a population survey of AD. Our method of dichotomizing the population into a proportion ρ of susceptible individuals and a complementary proportion who are nonsusceptible is therefore of interest. This method is almost certainly an oversimplification, however, and a more realistic model might postulate degrees of *relative* instead of absolute susceptibility or nonsusceptibility. Unfortunately, estimation of such a model would require the specification not only of one or more parameters analogous to ρ but also of other parameters describing the relative susceptibility of the various corresponding population subsets. Without prior knowledge of its structure, such a model would seem too complex to estimate from the available data. One can readily speculate, nonetheless, on several sources of relative susceptibility, including genes other than *APOE* (several such are under investigation), and a variety of environmental risk factors (eg, head injury or homocysteinemia) or postulated protective factors (eg, exposure to nonsteroidal anti-inflammatory drugs or antioxidant vitamins).

Finally, although the unusual sociocultural attributes of the Cache County sample facilitate the study of AD, these same attributes may suggest lack of generalizability of our results. In particular, we caution that the present estimates ρ of the proportion susceptible could differ substantially from estimates in other populations.

As noted elsewhere,[1] heterogeneity in susceptibility to AD predicts an eventual decline in the incidence of dementia in late old age.[2] In keeping with the known influence of *APOE* on AD onset, this decline becomes apparent at different ages for individuals with 0, 1, or 2 ε4 alleles. Independent of *APOE*, however, there is heterogeneity in the risk of AD. This heterogeneity suggests other genetic or environmental factors that can influence AD pathogenesis. To the extent that one could identify nonsusceptible individuals, as suggested by the present work, analyses that contrasted these with other individuals should provide important new opportunities for research into the causes and prevention of AD.

Table 2. Parameter Estimates and Corresponding Standard Errors for Parametric Survival Models Using the Weibull and Mixed-Weibull Distributions From the Cache County Study

	Model			
	1	2	3	4
λ	11.9 (0.63)	13.6 (1.10)		
$\lambda_{\varepsilon 4=0}$			14.6 (1.32)	14.9 (1.42)
$\lambda_{\varepsilon 4=1}$			14.5 (2.09)	14.3 (2.46)
$\lambda_{\varepsilon 4=2}$			12.2 (3.33)	12.2 (3.62)
α	94.9 (0.49)	90.9 (1.03)		
$\alpha_{\varepsilon 4=0}$			91.7 (1.01)	91.1 (1.20)
$\alpha_{\varepsilon 4=1}$			88.4 (0.96)	89.2 (2.29)
$\alpha_{\varepsilon 4=2}$			82.0 (1.68)	82.0 (2.69)
ρ		0.74 (0.06)	0.72 (0.05)	
$\rho_{\varepsilon 4=0}$				0.68 (0.07)
$\rho_{\varepsilon 4=1}$				0.78 (0.12)
$\rho_{\varepsilon 4=2}$				0.72 (0.12)
Log likelihood	−1536.1	−1501.6	−1439.5	−1438.3

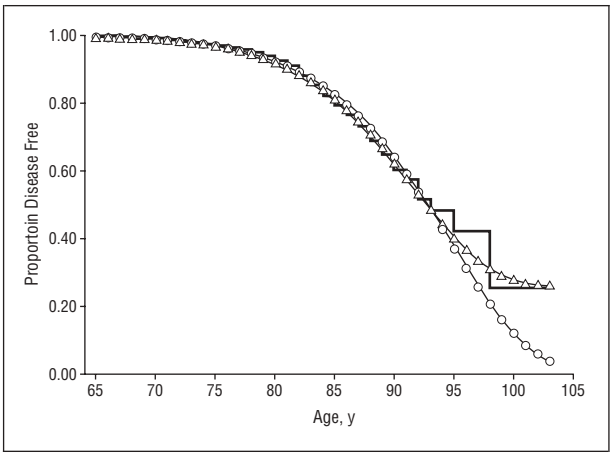

Figure 2. Disease-free survival predicted from a 2-parameter Weibull model (open triangles) and a 3-parameter mixed-Weibull model (open circles) among 3308 residents of Cache County, Utah. For reference, the heavy line shows the unadjusted product-limit estimate of survival probability.

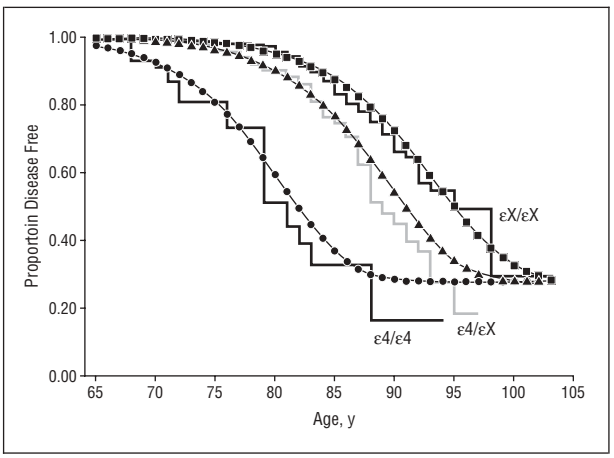

Figure 3. Disease-free survival predicted from a 7-parameter mixed-Weibull model among 3283 residents of Cache County, Utah. The graph shows 3 parametric curves for the 3 strata of 0 (closed circles), 1 (closed triangles), and 2 (closed squares) apolipoprotein E (*APOE*) ε4 alleles. The corresponding unadjusted product-limit estimates are also shown for reference.

Cache County Study Investigators

Cache County Study Investigators involved in the project in addition to the authors are as follows: James Burke, MD; Michelle Carlson, PhD; Marion David, PhD; Robert Green, MD; Andrea Hart, MS; Kathleen M. Hayden, PhD; Michael Helms, MS; Carole Leslie, MS; Constantine Lyketsos, MD; Maria Norton, PhD; Brenda Plassman, PhD; Russell Ray; Christine Reagan; Ingmar Skoog, MD; David C. Steffens, MD; Martin Steinberg, MD; Jeannette J. Townsend, MD; JoAnn T. Tschanz, PhD; Kathleen A. Welsh-Bohmer, PhD; Nancy West, MS; Michael Williams, MD; and Bonita W. Wyse, PhD.

Neuropsychological testing procedures were developed by Drs Tschanz and Welsh-Bohmer. Dr Tschanz reviewed all individual test results. The board-certified or board-eligible geriatric psychiatrists or neurologists who examined the study members included Drs Steinberg, Breitner, Steffens, Lyketsos, and Green. Dr Williams also examined several subjects and provided expert neurologic consultation. Autopsy examinations were conducted by Dr Townsend. Ms Leslie coordinated the autopsy enrollment program. Diagnosticians at the expert consensus conferences included Drs Breitner, Burke, Lyketsos, Plassman, Steffens, Steinberg, Tschanz, Welsh-Bohmer, and Williams.

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