

The International Journal of Biostatistics

Volume 3, Issue 1

2007

Article 13

Modeling the Effect of Alzheimer's Disease on Mortality

Elizabeth Johnson*

Ron Brookmeyer[†]

Kathryn Ziegler-Graham[‡]

*Johns Hopkins Bloomberg School of Public Health, ejohnson@jhsph.edu

[†]Johns Hopkins Bloomberg School of Public Health, rbrook@jhsph.edu

[‡]St Olaf College, kziegler@stolaf.edu

Modeling the Effect of Alzheimer's Disease on Mortality*

Elizabeth Johnson, Ron Brookmeyer, and Kathryn Ziegler-Graham

Abstract

Mortality rate ratios and the associated proportional hazards models have been used to summarize the effect of Alzheimer's disease on longevity. However, the mortality rate ratios vary by age and therefore do not provide a simple parsimonious summary of the effect of the disease on lifespan. Instead, we propose a new parameter that is defined by an additive multistate model. The proposed multistate model accounts for different stages of disease progression. The underlying assumption of the model is that the effect of disease on mortality is to add a constant amount to death rates once the disease progresses from an early to late stage. We explored the properties of the proposed model; in particular the behavior of the mortality rate ratio and median survival that is induced by the model. We combined information from several data sources to estimate the parameter in our model. We found that the effect of Alzheimer's disease on longevity is to increase the absolute annual risk of death by about 8% once a person progressed to late stage disease. Most importantly, we find that this additive effect is the same regardless of the patients' age or gender. Thus, the proposed additive multi-state model provides a parsimonious and clinically interpretable description of the effects of Alzheimer's disease on mortality.

KEYWORDS: Alzheimer's, mortality, multi-state, survival

*This work was partially supported by a contract from Elan and Wyeth Pharmaceuticals to Johns Hopkins University. The authors gratefully acknowledge H. Michael Arrighi for helpful comments.

1. Introduction

Alzheimer's disease is a critical global public health problem. Some projections have suggested that the prevalence of Alzheimer's disease will quadruple in the next 50 years (Brookmeyer et al, 2007). These projections depend on models that rely on two critical input factors: the incidence of disease, and mortality from the disease. The focus of this paper is on models that describe the impact of Alzheimer's disease on mortality. An understanding of the effect of Alzheimer's disease on mortality is important for health care planners in assessing the global burden of disease and for caregivers in evaluating the resources that will be needed to care for patients.

The lethality of Alzheimer's disease has been a topic of confusion in the scientific literature. The lethality of the disease has typically been described by the mortality rate ratio, which is the mortality rate among Alzheimer's cases divided by the mortality rate of healthy persons of the same gender and age as the cases. Some studies have suggested that mortality rates for Alzheimer's patients are 1.5 times that of the general population of the same age and gender while other studies have suggested rates over 10 times that of the general population (see Guehne et al, 2005). Furthermore, studies have reported that the mortality rate ratio is not a constant for Alzheimer's disease but decreases with advancing age (Tshanz et al, 2004 and Ostbye et al, 1999).

The variation in the mortality rate ratios for Alzheimer's disease by age would seem to suggest that there is no simple characterization of the lethality of Alzheimer's disease. We wondered if we could identify a model that characterized the lethality of Alzheimer's by a single parameter which was applicable at all ages. If such a parameter could be found it would provide a simple parsimonious description of the lethality of Alzheimer's disease that would be useful for communicating to both the scientific community and the general public. We also wondered if such a parameter could apply equally to both males and females. Studies of the mortality rate ratios do not yield consistent findings with respect to the question of whether Alzheimer's disease is any more or less lethal in men than women (Helmer et al, 2001, Aguero-Torres et al, 1999, Fitzpatrick et al, 2005, Aevarrson et al, 1998).

Several studies have demonstrated the utility of the illness-death model or three-state Markov model for modeling incidence and mortality for dementia and Alzheimer's (Commenges et al, 2004 and Joly et al, 2002). These models allow healthy persons to transition to Alzheimer's disease or death with probabilities that may depend on age and calendar year. Mortality rate ratios arise naturally in these models if proportional hazards are assumed; that is, an Alzheimer's diagnosis acts multiplicatively on the hazard of death among healthy persons or the baseline hazard.

In this paper, we extend the illness-death model to allow for early and late stages of disease and we propose an additive model for the lethality of Alzheimer's. This approach is motivated by the clinical features of the disease. Alzheimer's disease is a progressively debilitating disease. In the earliest stage of disease, patients may need only modest assistance, but in the late stage of disease, patients require very intensive care equivalent to that of a nursing home. Generally, death from Alzheimer's disease occurs only once patients have progressed to the late stage of disease, by which point they are no longer able to feed or dress themselves, and ultimately become bedridden. As Alzheimer's is a disease of the elderly, death from other competing causes (such as cancer) becomes increasingly more significant as patients age, yet Alzheimer's disease itself is not thought to confer higher risks of death from these competing causes.

From these clinical considerations, we propose the following model to describe the lethality of Alzheimer's disease. The disease consists of two stages, the early stage followed by the late stage. Persons in the early stage of disease have mortality rates similar to persons without disease. However, once persons progress to the late stage, the baseline hazard of death is increased by an additive constant representing the incremental effect of Alzheimer's disease on mortality rates. As we will show, this additive constant does not appear to vary either by age or gender for Alzheimer's disease, and thus the model provides a simple way to characterize the effect of the disease on mortality.

Excess hazards models have been considered by a number of authors in the illness-death model, as for example, the work of Sasieni (1996) and Anderson and Vaeth (1989) on continuous time models. However, this appears to be the first attempt to consider an excess additive hazards model in the setting of multiple stages of disease progression. We formally describe the model in section 2. The behavior of the mortality rate ratio induced by the model is considered in section 3. We combine information from several data sources to estimate the additive constant in section 4. The model and its implications are discussed in section 5.

2. Two Stage Additive Mortality Model

2.1 Model Formulation

We consider a progressive disease model in which persons progress from early stage to late stage disease. The underlying model is a multi-state discrete time Markov model. Individuals may transition from the healthy state (state 0), to early stage Alzheimer's disease (state 1) and then to late stage disease (state 2). Persons are at risk of death in each state. The model is illustrated in Figure 1. We use a discrete time model for two reasons. First, there is uncertainty in resolving

the exact age at which persons cross the threshold to meet the criteria for an Alzheimer's diagnosis. Second, as we will discuss, our model incorporates background death rates of the general population obtained from vital statistics which are generally only available on a yearly basis. The unit of time we use for the steps in the discrete time model is year.

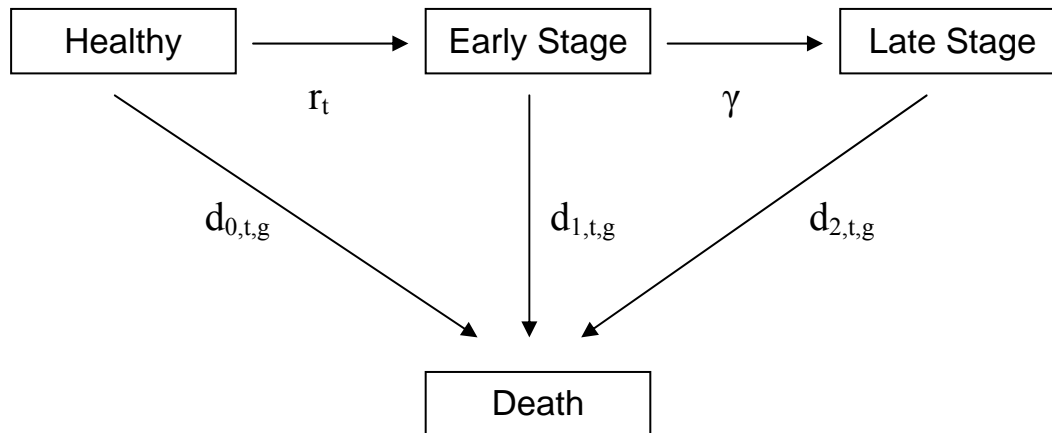


Figure 1: Multi-state model of progression of Alzheimer's disease showing the annual transition probabilities between states.

The transition rates are the conditional probabilities of moving between states in a given year and are shown in Figure 1. We define the death rates to be the conditional probabilities that a person who is age t dies during the year and these depend on the person's current age t , gender g (male or female), stage of disease (early or late), and calendar year. While background death rates of the general population obtained from vital statistics do depend on calendar year, we shall suppress notation for calendar year to simplify notation (although our numerical results in this paper do in fact account for calendar year). The death rates for persons in the healthy state at age t and gender group g are called $d_{0,t,g}$ which we refer to as the background death rates; $d_{1,t,g}$ are the death rates for persons with early stage disease; and $d_{2,t,g}$ are the death rates for persons with late stage disease.

The model that we propose is that the effect of Alzheimer's disease is to increase the background death rates by an additive constant once persons progress to the late stage of disease. Persons with early stage disease are subject only to the background death rates. That is,

$$\begin{aligned}d_{1,t,g} &= d_{0,t,g} \\d_{2,t,g} &= d_{0,t,g} + k_2\end{aligned}\tag{2.1}$$

The parameter k_2 represents the additive effect of Alzheimer's disease on the background death rates for persons with late stage disease. This model assumes that Alzheimer's disease acts to increase background mortality rates only when persons have late stage disease, while persons with early stage disease have mortality rates equivalent to those in the healthy state. As we shall see this relatively simple parsimonious one parameter model (with parameter k_2) explains across all ages and gender, 1) the complex patterns of mortality rate ratios observed in Alzheimer's disease and 2) the observed patterns in the median survival among persons with Alzheimer's .

A more general model can relax the assumption of model 2.1 so that the disease impacts mortality rates during both the early and late stage rather than only during late stage disease. Specifically, in our generalized two stage additive model, the stage specific mortality rates are set to the background death rates plus an additive constant which may be different for the two stages. That is,

$$\begin{aligned}d_{1,t,g} &= d_{0,t,g} + k_1 \\d_{2,t,g} &= d_{0,t,g} + k_2\end{aligned}\tag{2.2}$$

The parameters k_1 and k_2 represent the additive effect of Alzheimer's disease on the background mortality rates for persons with early and late stage disease respectively. However, as we discuss below, the simpler model (2.1) with $k_1=0$ turns out to be an adequate and parsimonious description for Alzheimer's disease.

2.2 Survival Function

In this section, we will explore patterns in median survival by age and gender induced by the two-stage model assuming the additive effect of Alzheimer's disease only in the late stage (equation 2.1). The survival function $S(t; a, g)$ is the probability that an individual with gender g who has disease onset at age a survives to age t . To avoid ambiguity, we assume all transitions occur in the beginning of each year, with transitions to early stage disease occurring first, followed by transitions to late stage disease, and finally death. Thus, an individual could experience multiple transitions in a year. Here, we define the survival function to be the probability of being at risk of death at age t (and it includes the possibility that death occurs at age t .)

The survival function $S(t; a, g)$ is the sum of two components corresponding to the events of being in either the early or late stages at age t . Let $p_{1,t,a,g}$ represent the probability that an individual who had disease onset at age a is at risk of death at age t with early stage disease. Similarly, let $p_{2,t,a,g}$ represent the probability that an individual who had disease onset at age a is at risk of death at age t with late stage disease. The transition probability that a person with early stage disease progresses to late stage disease during a year is γ which is assumed constant and depends neither on age nor gender. Then,

$$S(t; a, g) = p_{1,t,a,g} + p_{2,t,a,g} \quad (2.3)$$

Where

$$p_{1,t,a,g} = \left(\prod_{k=a}^{t-1} (1-\gamma)(1-d_{1,k,g}) \right) (1-\gamma) \quad (2.4)$$

and

$$p_{2,t,a,g} = \sum_{l=a}^t \left\{ \left[\prod_{k=a}^{l-1} (1-\gamma)(1-d_{1,k,g}) \right] [\gamma] \left[\prod_{k=l}^{t-1} (1-d_{2,k,g}) \right] \right\} \quad (2.5)$$

Expression 2.4 is derived by noting that in order for a person to have early stage disease at age t , the patient must not have had disease progression in any year up to and including age t . Expression 2.5 is derived from the following considerations. In order to have late stage disease at age t , an individual must have progressed to late stage disease at an earlier age, say age l (where l varies between a and t). Then, $p_{2,t,a,g}$ is the product of three factors. The first factor (shown in the first set of brackets in equation 2.5) refers to the probability of remaining in early stage disease until age l (we set this term to 1 when $l=a$); the second factor is the probability (γ) of progressing to late stage disease at age l ; and the third factor in brackets refers to the probability of remaining in late stage until age t (we set this term to 1 when $l=t$.)

We explored how the median survival time that is predicted from the model for $S(t;a,g)$ given by equation 2.3 depends on the additive lethality parameter k_2 and the progression rate γ . Figure 2 shows the predicted median survival based on equation 2.3 for different values of k_2 and γ^{-1} (note that γ^{-1} shown in the figure is approximately the mean duration of early stage disease in the absence of competing causes of death). The figure is based on U.S. vital statistics for the background death rates ($d_{0,t,g}$) that were age-gender specific

(Human Mortality Database, 2005); we assumed persons were diagnosed in 2006. The predicted median survival relies on future annual mortality rates by age and gender. To project mortality rates, we fit the following linear model: $\log(\text{mortality rate year } i / \text{mortality rate in 1988}) = \beta (i - 1988)$ for the years $i = 1988$ to 2002. This model was fit for all ages 60 to 100 and separately by gender and used to project future mortality for the years 2003 to 2050.

In figure 2, we observe that the median survival estimates decrease with age and are approximately similar by gender (assuming k_2 does not vary by gender). The figure shows how the predicted median survival decreases as k_2 increases. The median survival also decreases as γ increases because persons enter the late stage more quickly at which point they are exposed to higher death rates. In section 5, we will demonstrate that the two-stage model replicates median survival estimates from a cohort study of Alzheimer's disease completed in Baltimore, Maryland.

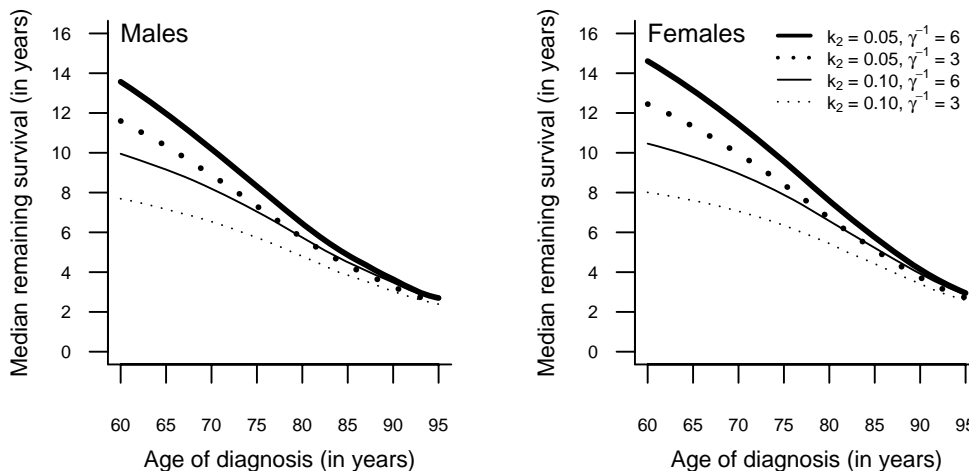


Figure 2: Sensitivity of predicted median survival to the lethality parameter k_2 in the two stage additive model and the disease progression rate γ . Background death rates are based on U.S. vital statistics assuming diagnosis in 2006.

3. Mortality Rate Ratio Function

The mortality rate ratio is an often cited statistic in the literature to describe the lethality of Alzheimer's disease. Here we define the mortality rate ratio at age t , called $m(t)$, as the ratio of the death rates at age t among persons with Alzheimer's disease to that versus persons without disease. Here, age t refers to the current age of the person as opposed to age of disease onset. As we indicated in section 1,

previous studies in the literature have suggested empirical evidence that $m(t)$ declines with age for Alzheimer's disease. We investigated the behavior of $m(t)$ induced by the two stage model (equation 2.1) described in section 2 in order to assess if the model could explain the pattern of mortality rate ratios reported in the literature.

The overall mortality rate at age t for a person with gender g is called $d_{t,g}$ which is a weighted average of the mortality rates for early and late stage disease. Specifically, we have

$$d_{t,g} = \left(\frac{p_{1,t,g}}{p_{1,t,g} + p_{2,t,g}} \right) d_{1,t,g} + \left(\frac{p_{2,t,g}}{p_{1,t,g} + p_{2,t,g}} \right) d_{2,t,g} \quad (3.1)$$

where $p_{1,t,g}$ and $p_{2,t,g}$ are the probabilities that an individual with gender g who was born t years ago is alive at age t with early and late stage disease, respectively. The mortality rate given by equation 3.1, and the probabilities $p_{1,t,g}$ and $p_{2,t,g}$ are marginalized (or averaged) over the ages of onset (a). Thus, we will need to introduce r_t which is the conditional probability that a healthy individual who is age t has onset of disease during the year, that is r_t is the transition probability from the healthy state to early stage disease (see Figure 1). We shall make the simplifying assumption r_t depends on age but not gender (Brookmeyer et al, 1998). Then, we have

$$p_{1,t,g} = \sum_{a=1}^t \left[\prod_{1 \leq j \leq a-1} (1 - r_j)(1 - d_{0,j,g}) \right] [r_a] \quad (3.2)$$

$$x \left[\prod_{k \geq a}^t (1 - \gamma_k)(1 - d_{1,k,g}) \right]$$

Equation 3.2 arises from the following considerations. The first term in brackets refers to the probability of remaining in the healthy state until onset at age a ; the second term in brackets refers to the probability of disease onset at age a ; and the third term refers to the probability of remaining in the early stage of disease from age a through age t . Similarly, $p_{2,t,g}$ is the probability that an individual in gender group g who was born in t years ago is alive at age t and living with late stage disease, and is :

$$p_{2,t,g} = \sum_{a=1}^t \left[\sum_{l=a}^t \left\{ \prod_{1 \leq j \leq a-1} (1-r_j)(1-d_{0,j,g}) \right\} \right] [r_a] \tag{3.3}$$

$$x \left[\prod_{k=a}^{l-1} (1-\gamma)(1-d_{1,k,g}) \right] [\gamma] \left[\prod_{k=l}^t (1-d_{2,k,g}) \right]$$

The mortality rate ratio at age t (for gender group g) is the death rate among persons with Alzheimer’s disease (equation 3.1) divided by the background mortality rate:

$$m(t) = \frac{d_{t,g}}{d_{0,t,g}} \tag{3.4}$$

We studied the behavior of $m(t)$ under different conditions. We used vital statistics for the background mortality rates (Human Mortality Database). We used an exponential growth model for the age specific incidence of disease onset r_t based on a review and analysis of published incidence studies of Alzheimer’s disease (Brookmeyer et al, 2007) given by $r_t = 0.00117 e^{(0.127 (t-60))}$, with $r_t=0$ for $t < 60$.

Figure 3 is a graph of $m(t)$ for males and females observed in calendar year 2006 with $\gamma = 0.167$ and $k_2 = 0.10$. The model predicts that the mortality ratio briefly rises at the youngest ages (60-65), but after about age 65 it declines. This age pattern makes intuitive sense. The small increase in the mortality ratio in the age 60-65 age group reflects the progression of disease in these young patients to late stage disease at which point they are subjected to mortality rates higher than the background rates. But eventually as persons age, death from causes other than Alzheimer’s disease explain an increasing fraction of the total deaths. The mortality rate ratio then declines as the percentage of deaths from causes other than Alzheimer’s increase. The increasing risk of death from causes other than Alzheimer’s explains intuitively why the mortality rate ratio associated with Alzheimer’s disease declines with advancing age.

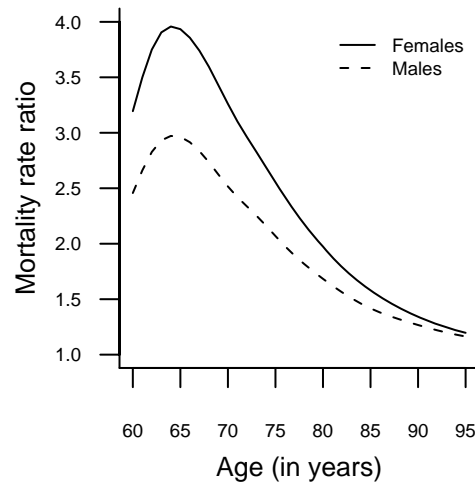


Figure 3: Mortality rate ratio $m(t)$ for males and females versus age, in calendar year 2006. The parameter k_2 was set to 0.10 and γ^{-1} was set to 6 years.

An interesting observation from Figure 3, is that the mortality rate ratios are lower for males than females although k_2 was set to 0.10 for both genders. This behavior may be intuitively explained by the fact that background death rates are higher for males than females and thus Alzheimer's disease explains a smaller fraction of total male deaths than female deaths.

Figure 4 shows the sensitivity of $m(t)$ to different assumptions about the disease progression rate (γ). The figure shows the mortality rate ratio curves for various values of γ^{-1} in calendar year 2006 with $k_2 = 0.10$. We find that as the disease progression rate increases (and the mean duration of early stage disease decreases), the mortality rate ratio increases. Intuitively, the reason for this behavior is that as the disease progression rate increases, disease cases transition more quickly to late stage disease at which point they are exposed to higher death rates. The non-constancy of the mortality rate ratio with age is most pronounced when γ is larger. At the oldest ages, each of the curves converge toward 1, which occurs because of the greatly increasing risks from all other causes of death.

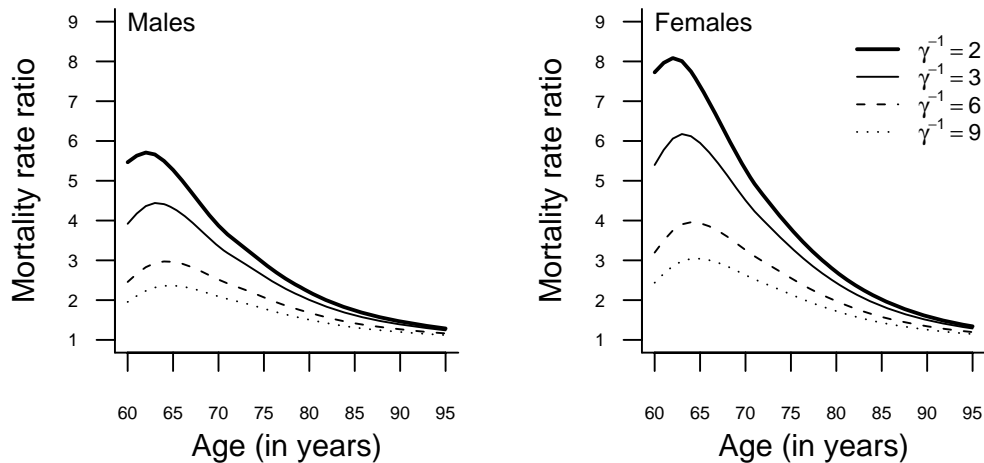


Figure 4: Sensitivity of mortality rate ratio $m(t)$ to the disease progression rate γ in calendar year 2006. The parameter k_2 was set to 0.10.

4. Parameter Estimation

To estimate the additive constant from equation 2.1, we utilized historic mortality data, published literature on the disease progression rate and a study of survival among Alzheimer's cases. Specifically, we applied the model to Alzheimer's cases enrolled in the Baltimore Longitudinal Study of Aging (BLSA) (Kawas et al, 2000, Brookmeyer et al, 2002). The study evaluated participants biennially and identified 108 incident cases of Alzheimer's disease (51 females and 57 males) via consensus diagnostic conferences. These cases were then followed until death or last follow-up. There were 71 deaths (30 females and 41 males) among the 108 incident cases. Stage of disease data was not available. Thus, the available data was the age of disease onset (a), age at last follow-up (t) and a censoring indicator that indicates whether the patient died at age t or was still alive.

Previously published analyses of this data have fit very flexible parametric models to the mortality data with up to 5 parameters (Brookmeyer et al, 2002). The predicted median survival by age of diagnosis and gender from that analysis are shown in column 1 of Table 1 and ranged from about 10 years for a newly diagnosed case at age 60, to about 3 years for a newly diagnosed case at age 90. These results were concordant with nonparametric Kaplan-Meier curves.

We derived the likelihood function for the model described by equation 2.1. The likelihood function for the data is the product of two factors. The factor contributed by persons censored ($\delta = 0$) at age t is the survival function given by equation 2.3. The factor contributed by persons who die ($\delta = 1$) at age t is given by:

$$p_{1,t,a,g} d_{1,t,g} + p_{2,t,a,g} d_{2,t,g} \quad (4.1)$$

Then, the likelihood function for the data is:

$$L = \prod_{i=1}^n [S(t_i; a_i, g_i)]^{1-\delta_i} [p_{1,t_i,a_i,g_i} d_{1,t_i,g_i} + p_{2,t_i,a_i,g_i} d_{2,t_i,g_i}]^{\delta_i} \quad (4.2)$$

We specified the background death rates and disease progression rates in the likelihood. We used U.S. vital statistics for the background death rates ($d_{0,t,g}$) that were age-gender specific that also accounted for the year of diagnosis of each case (Human Mortality Database). The Consortium to Establish a Registry for Alzheimer's disease suggested that 6 years is the mean time from mild to severe disease using the Clinical Dementia Rating scale (Neumann et al, 2002). Accordingly, we used an annual transition probability from early to late stage disease of $\gamma = 0.167$ in our model which corresponds to a mean duration of early stage disease of approximately 6 years. However, we also preformed and report a sensitivity analysis to this parameter.

The likelihood given by equation 4.2 involves one unknown parameter (k_2). Figure 5 displays the log-likelihood function for k_2 . The maximum likelihood estimate was 0.078. We inverted a likelihood ratio test to obtain a 95% confidence interval for k_2 of (0.016, 0.162). The interpretation is that Alzheimer's disease acts to increase background death rates by about 8% per year once patients progress to late stage disease. We also estimated k_2 separately by gender (male vs female) and age of onset (< 75 vs ≥ 75). We estimated that the additive constant was 0.068 (95% confidence interval: -0.013 to 0.192) for males and 0.088 (0.004 to 0.230) for females. Among persons diagnosed under the age of 75 and 75 or older, the additive constant was estimated to be 0.168 (0.034 to 0.358) and 0.038 (-0.032 to 0.134), respectively. We found no significant differences either by age of onset ($p=0.15$) or by gender ($p=.79$).

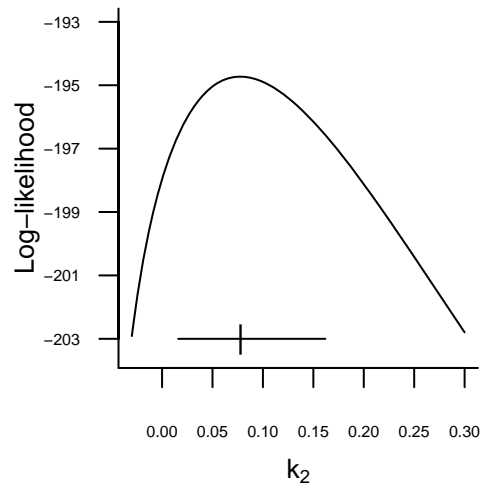


Figure 5: Log-likelihood function for k_2 in the two stage additive model fit to survival times of Alzheimer's disease patients.

Table 1 shows the predicted median survival times by age of onset and gender (from equation 2.4) with $k_2 = 0.078$. The predictions based on our one parameter model (column 2) were in close agreement with the estimates of median survival from the flexible parametric model.

As a point of comparison, we also fit a multiplicative model with a single parameter that assumed that Alzheimer's disease multiplied background death rates by a constant θ . The model, as in the standard proportional hazards model, assumed that there was only a single stage of disease. We obtained a multiplicative constant of $\theta = 2.05$, suggesting that Alzheimer's disease mortality rates were about twice that of the general population. Table 1 (column 3) shows the predicted median survival from the one parameter multiplicative model. The model appears to overestimate the median survival at younger ages of Alzheimer's disease onset. For example, this simple naïve multiplicative model suggests that females who have disease onset at age 60 have a predicted median survival of nearly 20 years. In contrast the analyses given in columns 1 and 2 of Table 1 suggest that the median survival for a female with onset at age 60 is closer to 11 years.

Table 1: Predicted median survival times based on several models of Alzheimer's survival data by age of disease onset and gender

Age of onset	Males			Females		
	Parametric ¹	Two stage additive model ²	One stage multiplicative model ³	Parametric ¹	Two stage additive model ²	One stage multiplicative model ³
60	9.3	10.5	13.8	10.6	11.5	17.9
65	7.8	9.3	10.2	8.9	10.6	13.9
70	6.5	8.0	7.4	7.5	9.4	10.4
75	5.5	6.5	5.1	6.3	8.0	7.4
80	4.6	5.2	3.4	5.2	6.4	5.0
85	3.8	3.7	2.1	4.4	4.8	3.1
90	3.2	2.5	1.3	3.7	3.3	1.8
95	2.7	1.7	0.8	3.1	2.1	1.0

¹ Based on a 5 parameter Weibull regression model to Alzheimer's disease cases that included linear and quadratic terms for age of disease onset, gender, an intercept term and shape parameter (see Brookmeyer et al, 2002)

² Based on two stage disease model with additive effect of Alzheimer's disease on mortality in the late stage of disease. Maximum likelihood estimate of parameter k_2 was .078. Median survivals shown are for persons diagnosed in calendar year 1993 which was the approximate year of diagnosis of the cases.

³ Based on a one stage disease model where Alzheimer's disease acts to multiply background mortality rates by a constant θ estimated to be 2.05.

A key assumption of our model given by equation 2.1 is that persons with early stage Alzheimer's disease have mortality rates equivalent to the general population, while those with late stage disease have elevated rates. It is reasonable to wonder whether mortality rates are also elevated during the early stage of disease. We investigated the validity of the assumption by considering the more general model 2.2. The parameters k_1 and k_2 represent the additive effect of Alzheimer's disease on the background mortality rates for persons with early and late stage disease respectively. We added the parameter constraint that $0 \leq k_1 < k_2$ because of difficulties in obtaining separate estimates for k_1 and k_2 without this constraint. We believe it is very reasonable based on clinical considerations to assume that the increase in mortality rates is greater during late stage than early stage disease. We tested the null hypothesis that $k_1=0$ to assess the validity of our simpler model given by equation 2.1. Our estimates were $k_1 = 0.0$ and $k_2 = 0.078$ and we did not reject H_0 that $k_1 = 0$ ($p \geq 0.50$ based on the MLE test of Self and Liang (1987) when the parameter is on the boundary). Thus, the simplifying assumption of model 2.1 that excess mortality from Alzheimer's disease occurs principally after persons progress to late stage disease appears supported by the data. We investigated the sensitivity of this conclusion to different assumptions

about the underlying disease progression rate γ , and reached similar conclusions. For example, when γ is decreased to 0.11 (corresponding to a mean duration of early stage disease of about 9 years), we obtain $k_1 = 0.0$ and $k_2 = 0.11$, in which case we would still not reject $H_0: k_1 = 0$ ($p \geq .5$).

5. Discussion

Our model suggests that Alzheimer's disease acts to increase background mortality rates by about 8% per year once a patient progresses to the late stage of disease. These conclusions were the same regardless of the age of onset or the gender of the patient. Our model had only one parameter (k_2), yet we were able to obtain predicted median survival times that were in excellent agreement with semi and nonparametric analyses across all ages of disease onset and for both males and females. Our model induces patterns in mortality rate ratios that are consistent with the literature. The advantage of our model is it provides a convenient summary of the lethality of Alzheimer's disease that applies across all ages and gender groups. Software to estimate the survival function induced by the two stage model is available from the authors at www.biostat.jhsph.edu/project/globalAD/index.htm.

As shown in section 3, our model predicts that mortality rate ratios decline with age, as has been empirically reported. That decline may suggest the naïve and incorrect interpretation that the lethality of Alzheimer's disease decreases with age, or that Alzheimer's disease is more aggressive in younger victims than older victims. In fact, our model makes clear that the lethality of Alzheimer's disease does not diminish with age. Regardless of age, late stage Alzheimer's disease adds about 8% to annual background death rates. Why then does the mortality rate ratio decline with age? The explanation lies in the fact that as persons' age they are at increasing risk from many competing causes of death including cancer and cardiovascular disease. Alzheimer's disease represents an increasingly smaller fraction of the all-cause mortality rate.

An underlying assumption of our model is that Alzheimer's disease does not increase mortality risks during the early stage of disease. While the model can be generalized to allow for increased risk during both stages, our analysis indicates that the assumption is supported by the data.

We utilized several sources of data to estimate the effect of mortality on Alzheimer's disease. Death rates among healthy persons and Alzheimer's disease incidence rates were available on a yearly basis; therefore we utilized a discrete time Markov model. Within the Baltimore Longitudinal Study of Aging, diagnosis of Alzheimer's disease was determined by a consensus diagnostic conference where the clinicians assessed subject medical records and information from the biennial follow-up visits. Date of diagnosis was assigned to be the year

during which subjects first met the DSM-III-R criteria for dementia. We acknowledge that there is error in the date of diagnosis based on this diagnostic procedure which is in part why we used a discrete time model.

The data from the Baltimore Longitudinal Study on Aging did not have the transition times from early to late stage disease. We assumed a transition rate of $\gamma = .167$ per year. We performed sensitivity analyses to that parameter. An alternative approach would be to specify a prior distribution on that parameter. Of course, if data was available on the exact transition time to late stage disease that data could be incorporated into the analysis by modifying the likelihood function.

Characterizing the lethality of Alzheimer's disease in elderly populations is challenging because of the very significant risks of competing causes of deaths, and the fact that the disease slowly becomes progressively more debilitating. We have addressed these issues by a two stage model for disease progression together with an additive model for the effect of Alzheimer's disease over and above the background mortality rates. It provides a simple parsimonious description of the lethality of the disease. The approach may also be useful for characterizing the lethality of other diseases in elderly populations.

References

- Aevarsson O, Svanborg A and Skoog I. Seven-year Survival Rate after Age 85 Years: Relation to Alzheimer disease and Vascular Dementia. *Arch Neurol* 1998, 55(9), 1226-1232.
- Aguero-Torres H, Fratiglioni L, Guo Z, Viitanen M, and Winblad B. Mortality from Dementia in Advanced Age: A 5-Year Follow-Up Study of Incident Dementia Cases. *J Clin Epidemiol* 1999, 52(8), 737-743.
- Anderson PK and Vaeth M. Simple Parametric and Nonparametric Models for Excess and Relative Mortality. *Biometrics* 1989, 45, 523-35.
- Brookmeyer R, Gray S, and Kawas C. Projections of Alzheimer's Disease in the United States and the Public Health Impact of Delaying Disease Onset. *American Journal of Public Health* 1998, 88, 1337-1342.
- Brookmeyer R, Corrada M, Curriero F, Kawas C. Survival Following a Diagnosis of Alzheimer's Disease. *Archives of Neurology* 2002, 59, 1764-1767.

- Brookmeyer R, Johnson E, Ziegler-Graham K, Arrighi M. Forecasting the Global Burden of Alzheimer's disease. *Alzheimer's & Dementia* 2007, 3, 186-191.
- Commenges D, Joly P, Letenneur L and Dartigues, JF. Incidence and mortality of Alzheimer's disease or dementia using an illness-death model. *Statistics in Medicine* 2004, 23, 199-210.
- Fitzpatrick AL, Kuller LH, Lopez OL, Kawas CH and Jagust W. Survival Following Dementia Onset: Alzheimer's Disease and Vascular Dementia. *Journal of the Neurological Sciences* 2005, 229-230, 43-49.
- Guehne U, Riedel-Heller S, Angermeyer M. Mortality in Dementia. *Neuroepidemiology* 2005, 25, 153-162.
- Helmer C, Joly P, Letenneur L, Commenges D and Dartigues J-F. Mortality with Dementia: Results from a French Prospective Community-based Cohort. *Am J Epidemiol* 2001, 154(7), 642-648.
- Human Mortality Database. University of California, Berkeley(USA) and Max Planck Institute for Demographic Research (Germany). Available at www.mortality.org or www.humanmortality.de (data downloaded on 12/06/2005).
- Joly P, Commenges D, Helmer C, Letenneur L. A Penalized Likelihood Approach for an Illness-Death Model with Interval-Censored Data: Application to Age-Specific Incidence of Dementia. *Biostatistics* 2002, 3, 433-443.
- Kawas C, Gray S, Brookmeyer R, Fozard J, and Zonderman A. Age-specific incidence rates of Alzheimer's disease: The Baltimore Longitudinal Study of Aging. *Neurology* 2000, 54, 2072 – 2077.
- Neumann PJ, Araki SS, and Arcelus SM et al. Measuring Alzheimer's Disease Progression with Transition Probabilities: Estimates from CERAD. *Neurology* 2001, 57, 957-964
- Ostbye T, Hill G, Steenhuis R. Mortality in Elderly Canadians with and without Dementia: A 5 Year Follow-up. *Neurology* 1999, 53, 521-526.
- Sasieni P. Proportional Excess Hazards. *Biometrika* 1996, 83, 121-141.

Self SG and Liang KY. Asymptotic Properties of Maximum Likelihood Estimators and Likelihood Ratio Tests Under Nonstandard Conditions. *Journal of the American Statistical Association* 1987, 82, 605-610.

Tschanz, JT, Corcoran C, Skoog I, Khanchaturian AS, Herrick J, Hayden KM, Welsh-Bohmer KA, Calvert T, Norton MC, Zandi P and Breitner JCS. Dementia: The Leading Predictor of Death in a Defined Elderly Population: The Cache County Study. *Neurology* 2004, 62, 1156-1162.