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Alzheimer's Disease as a Cause of Death in the U.S.: Estimates and Projections

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ALZHEIMER'S DISEASE AS A CAUSE OF DEATH IN THE U.S.:

ESTIMATES AND PROJECTIONS

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The phrase "the demography of Alzheimer's disease" may be the best litmus test to distinguish demographers from epidemiologists. A typical reaction to this phrase from a demographer is "why Alzheimer's disease?" A typical reaction from an epidemiologist is "why demography?" It is always tricky to describe the exact boundaries that separate two similar disciplines and this is especially true of the difference between demographic and epidemiologic approaches to mortality and health. What made Preston's work on smoking and mortality demography rather than epidemiology? What differentiates a demographer's or a sociologist's work on factors affecting residence in nursing homes from an epidemiologist's work on the same topic?

The demographer's question, "why Alzheimer's disease," is relatively simple to answer. If Alzheimer’s disease (AD) is as important a cause of death and institutionalization as is often claimed, we cannot forecast mortality or residence patterns without considering the possible effects of new treatments or therapies for AD. It is often claimed that Alzheimer's disease is the fourth leading cause of death in the U.S. If there is any truth to this statement, we should be as interested in Alzheimer's disease as we are in cancer, heart disease, AIDS or violence. We should also be as interested in the potential impact of slowing or stopping the progression of Alzheimer's disease as we are in following trends in smoking or in the sexual practices that spread AIDS in the U.S. or in Africa. Similarly, there is research that suggests that as much as 40% of persons entering nursing homes have Alzheimer's disease (Rovner, 1993). If we are interested in understanding and projecting residence patterns of the elderly, we would ignore developments in the treatment or management of Alzheimer's disease at our peril.

The epidemiologist's question, "why demography," is not as

easy to answer in a few sentences. I think that asking questions that demographers are apt to ask leads to different models for studying and describing the progression of Alzheimer's disease. In particular, demographers' interest in projecting population size, mortality rates, and residence patterns leads to different ways of conceptualizing the role of AD and different methods for studying it.

Predicting future advances against disease is a perilous business. For example, there are wildly varying projections of the likelihood breakthroughs in preventing or treating cancer or AIDS. Often disease processes turn out to be more complicated than expected, optimistic claims for new discoveries turn out to be unwarranted, and progress with rare forms of the disease don't prove to be effective against more common forms. On the other hand, breakthroughs often come from unexpected directions and are hard to foresee.

Although it is difficult to predict when new therapies for AD will be available, how effective they will be and what proportion of the population will actually benefit, several things are clear. First, there is a great deal of money being spent to find treatments for AD and a number of different avenues of research are proceeding simultaneously. Second, one drug (Cognex) currently provides short term improvement for some patients. It is very likely that better drugs will be discovered to slow the progress of the disease or at least slow its effects on cognitive functioning. It is less likely that there will soon be drugs to prevent the disease, and very little likelihood that a cure will be discovered that can substantially reverse the effects of the disease. Third, it is still not clear whether AD is the result of a single causal mechanism or whether there are really several disease processes that can lead to the same

symptoms. For example, AD may be caused by an increase in the particular forms of amyloid produced by the body or it could be caused by a failure of the body to break down unwanted forms. Either could lead to accumulations that cause the plaques and tangles that are the defining characteristic of AD. Alternatively, the accumulation of plaques and tangles could result from rather than cause cell death. Since there may be several mechanisms causing the disease, it is not clear that one drug would be equally effective against all forms of the disease.

Given these facts, demographic projections with 10 to 20 year time horizons should at least include considerations of what will happen if the rate of progression of AD is slowed in a sizeable proportion of cases. Optimistic expectations for the next 10 years seem to involve reducing the rate of progression by half, at least during the early and middle stages of the disease.

The first section below reviews studies of the prevalence of Alzheimer's disease. This is not meant to be a thorough literature review of these topics. Instead it is meant as a summary of the findings of the most prominent studies and the conclusions from previous literature reviews. A simulation of incidence and prevalence is used to test the importance of timing of diagnosis (or minimal severity for diagnosis) on prevalence. This is a preliminary model with ignores heterogeneity in the disease and relies on data collected from several different populations. The next part of the paper explores the claim that Alzheimer's disease is the fourth leading cause of death in the U.S. This widely quoted claim is based on one paragraph in a editorial published in 1976 (Katzman). The second section uses results from two community studies to test this claim. The third section uses the preliminary simulation derived previously to test this claim. The evidence on these topics is not as strong as

we would like. However, it is clear that Alzheimer's disease is very common among the elderly and is at least an important underlying cause of death and institutionalization. The fourth section carries out a simple simulation to illustrate what might happen to mortality if the rate of progression of AD were slowed substantially.

The Prevalence and Incidence of Alzheimer's Disease

Many surveys have estimated the prevalence of senility, dementia or Alzheimer's disease (AD) in communities. These surveys have used different screening tests and varying criteria for clinical diagnoses. The variation in the methods used in these surveys reflect changes over the past four decades in our understanding of dementia. Forty years ago, Alzheimer's disease was considered to be a minor cause of dementia. Today, it is estimated to be responsible for about 60 to 65% of all dementia. During the last ten years there have been many changes in the diagnostic criteria, particularly in the criteria used to rule out small strokes (i.e., multi-infarct or vascular dementias) as the cause of dementia.

The best surveys are based on active surveillance. This involves canvasing the population (preferably both the community-dwelling and institutionalized populations) with a relatively simple screening test for dementia then performing clinical evaluations of those with a low score on the screening test. In addition, it is necessary to have clinical evaluations of a sample of those who did well on the screening test to estimate the sensitivity of the screen. However, many of the surveys published in the past 15 years have relied on cases identified through routine medical examinations (i.e., on passive surveillance). The results of the two types of studies are often

very different. For example, some long term studies based on passive surveillance suggest that the prevalence of AD has increased over the past fifteen years. Since it is most likely that passive surveillance studies might be biased by under diagnosis of AD, it is preferable to limit reviews of prevalence to studies based on active surveillance.

Figure I presents age-specific prevalence rates from several major surveys or reviews of surveys. One of the best reviews of the prevalence of dementia is that by Jorm, et al. (1987). They reviewed studies of the prevalence of dementia published between 1945 and 1985. Eighteen studies provided separate figures for Alzheimer's disease. They found a consistent exponential increase in the prevalence of dementia by age with the rate doubling between 5-year age groups. Specifically, they estimate that the prevalence of dementia increases from 1.4% at ages 65-69 to 38.6% at ages 90-95. They found that the prevalence of AD doubles with every 4.5 year increase in age, but they do not present age-specific estimates for AD.

A review of prevalence studies in Europe was carried out as part of the European Community Concerted Action Epidemiology and Prevention of Dementia (EURODEM) project (Rocca, 1991). The average prevalence rates for six European studies shows AD increasing from a prevalence of 0.3% at ages 60-69 to 10.8% at ages 80-89.

The most frequently quoted study of the prevalence of AD in the U.S. was carried out in East Boston, Massachusetts. This study covered all noninstitutionalized individuals living in a defined community. This study produced very high prevalence rates for AD. They estimated the prevalence rate over age 65 at 10.3% compared to only 3.1% in the European studies. Although a few other studies have found similar high estimates (e.g.,

Pfeffer, 1987, for individuals living in owner-occupied houses in a retirement community in southern California), it is quite possible that the East Boston results overstate the prevalence of AD in the U.S. as a whole.

The Canadian Study of Health and Aging (CSHA) is a more recent study designed to estimate the prevalence of dementia and Alzheimer's disease in community and institutional-dwelling Canadians (CSHA, 1994, Ebly, 1994). The large sample (9,008 community-dwelling and 1,255 institution-dwelling) was selected using computerized records of the provincial health insurance plan (or other records in Ontario). The population over age 85 was oversampled to improve the reliability of the estimates at the oldest ages. Because of its size, the quality of the sampling frame, the coverage of both community and institutionalized population, and the similarity of Canadian demography to that of the U.S., the Canadian survey may provide the best estimates of the proportion of the U.S. white population that meet the most recent criteria for clinically diagnosed Alzheimer's disease. The CSHA produced estimates of the prevalence of AD that are similar to the results of a number of European studies. However, the CSHA estimates are much lower than those produced for East Boston. The estimate for those over age 65 is 5.1% which falls between the estimates from the European (3.1) and the East Boston (10.3%) studies. Over age 85, the CSHA gives a prevalence of 21.5% (95% C.I: 19.5-23.8) compared to 47.8 (37.0-63.2) for East Boston.

There are numerous potential sources of differences between various estimates of prevalence. These include real differences among populations, differences in the accuracy of disease histories given by informants, and differences in the sensitivity and specificity of screening tests in different populations.

The simulations of the incidence and prevalence of AD are useful for investigating the potential importance of another sources of differences between studies: the use of different levels of severity as the cut-point for diagnosing cases. At present, we do not diagnose Alzheimer's disease until the effects of cognitive impairment are apparent in daily life (although rarely used biopsy methods are available). However, many researchers are examining potential early markers for the disease. A recent example is research suggesting that hypersensitivity of the eye to tropicamide might serve this purpose (Scinto, 1994). With different clinical criteria used in various surveys and with the potential for a predictive test, the measured prevalence of Alzheimer's might change substantially over time as the definition of diagnosable AD changes. This could cause confusion of the sort caused by changes in the definition of AIDS and the development of serum tests for HIV positivity. It is therefore useful to examine the extent to which estimates of prevalence might be affected by changes in the duration at which diagnoses can be made.

To examine these issues, we need a model that simulates the relationship between hypothesized age-specific incidence rates, duration-specific mortality rates for cases and non-cases, the timing of diagnosis and observed prevalence. Figure II presents the results of a simple model to fit the observed prevalence by age reported by the CSHA. The model uses mortality rates for U.S. whites from the life table for 1985 (the most recent life table for which I had mortality rates for five-year age groups over age 85). The incidence rate is assumed to increase at a constant rate by age. This assumption reflects the observation that prevalence increases exponentially across age (Jorm, 1987).

Modeling the relationship between the observed prevalence

rates and the generally unobserved incidence rates requires survival rates for cases and non-cases. It is clear that the relative survival rate of AD patients relative to controls declines with increasing severity or duration of disease. However, there are few studies that provide estimates of the survival of patients with AD by duration of disease. Most studies start with the assumption that survival is a function of age and then ask whether some measure of severity or duration has an additional effect. Although most studies find a clear effect of severity or duration (as we would expect in a disease characterized by persistent deterioration), few studies provide enough detail on the effects of age or duration to be useful for modeling.

An exception is the study by Mölsä, et al (1986), which provides six-year survival rates for patients identified in a survey of community-dwelling individuals in Finland. They provide survival rates for three levels of initial severity (moderately demented, markedly demented, and severely demented). Unfortunately, the data are only presented graphically and relative to the survival of non-demented individuals. Table Ia presents estimates read off of their graphs. Table Ib presents estimates of the one-year survival rates relative to nondemented individuals. The values for the three groups are matched with durations of disease which lead to maximum agreement among the three groups for the same durations. Since the actual onset of disease cannot be observed (and its definition is not clear at this time), I have set the diagnosis of the moderately demented at duration 3 years. When aligned as they are in Table Ib, the survival rates for the three groups are very consistent. This allows us to estimate the schedule of survival relative to nondemented individuals by duration of disease shown in the last

column of Table Ib.

The simulation model starts with estimated incidence rates. Non-cases are projected using age-specific mortality rates for non-cases estimated by the model (see below). Cases are projected forward by age and duration using the age-specific mortality rates for non-cases combined with duration-specific relative survival rates for AD cases relative to non-cases. Since the relative risk data compare cases and non-cases and we only have overall mortality rates (for the U.S. in 1985), we need to calculate the mortality rate for non-cases. The formula for this includes the prevalence rate. Therefore, the computer program needs to iterate a few times so that the prevalence rates and the mortality rates for cases and non-cases are consistent with the assumed overall mortality rates and relative risks. At each iteration the relative risk associated with AD at each age is calculated from the distribution of cases by duration (derived from the incidence rates and survival rates) and the duration-specific relative mortality rates.

This leads to a model of the prevalence of AD which involves two parameters: the proportionate increase in incidence over age, and the incidence rate at one given age (arbitrarily chosen as age 87). I have identified the values of these two parameters which minimize the mean squared error fit to the data from the CSHA. This model fits the CSHA data extremely well (Figure II). The root mean squared error for the five age-specific prevalence estimates (measured in percent) is only 1.21 which is well within the standard errors for the estimates from the CSHA. The parameters suggest that the incidence rate increases by about 13.2 percent per year of age (equivalent to a continuous rate of change of 12.4%) which implies that the incidence rate doubles every 5.6 years. The estimated incidence rates at ages 77 and 82

(1.7% and 3.2%) are similar to the incidence rates for dementia observed in the Bronx Aging Study (Aronson, 1991), 1.3% at 75-79 and 3.5% at ages 80-84.

Figure II also shows estimates from the simulation of the proportion of the population that is at various stages of Alzheimer's disease. I have rather artificially set at three years the point at which a patient could clearly be diagnosed with AD using the NINCDS/ADRDA criteria used in the CSHA. If we could diagnoses AD three years earlier (through predictive changes in cognitive tests, or biological markers), the estimated prevalence rates (labeled "earlier dx." in Figure II) would be substantially higher. On the other hand, studies that applied more severe symptoms for diagnosis might not diagnose cases for an additional three years (on average). This would lead to the prevalence of what might be termed "moderate and severe" AD. Moderate cases (those at 3-5 years after early diagnosis) would generally require substantial assistance with everyday functioning. Even more stringent criteria might include only patients about 6 years after they because diagnosable according to the NINCDS/ADRDA criteria (9 years after incidence). This would approximate the prevalence of "severe" cases. These patients would require extensive care. It is at this stage of the disease that many families decide to place a patient in a nursing home.

The simulation suggests that if we could diagnose AD on average three years earlier than the CSHA study, the prevalence at age 85 would increase from 13.6% to 23.9%. If we used a more strict criteria and diagnosed AD on average three years later than the CSHA, prevalence would drop to 6.8 at age 85. At age 99, the three criteria would lead to estimates of 80%, 58% and 35%. Clearly, the estimated prevalence of AD is very sensitive

to the diagnosis criteria or the stage of the disease that is relevant for a given purpose. Despite the wide range of estimates, the estimates from the study in East Boston are still about 35% higher than the estimates from the simulation based on diagnosis three years earlier than in the CSHA. Therefore, the high rates in East Boston are probably not merely a result of including more mild cases of AD.

It is interesting to note that the CSHA and the simulation model show the prevalence rate continuing to increase up to (and beyond) age 100. The CSHA shows the prevalence of all dementias increasing to 85% at ages 100-106. If the proportion due to AD is the same as at ages 95-99, this leads to an estimated 64% with AD over age 100. This is in contrast to estimates for the oldest old in Berlin. Wernicke and Reischies (1994) found that the estimated prevalence for ages 90-94 and 95-99 were both 42.3%. Debates over whether the incidence of AD continues to increase at the very oldest ages may have relevance to whether or not dementia is a “normal” part of the aging process.

The estimated incidence rates provide an interesting opportunity to look ahead twenty to thirty years and ask what the demand would be for a drug that would stop the progression of AD indefinitely. The drug model here might be insulin for diabetics or annual vaccinations against pneumonia or influenza. This projection would be important to estimating the costs of preventing AD. If we could diagnose AD three years earlier than is now possible and prevent any progression of the disease in all patients (and therefore eliminate their excess mortality), the proportion of the population that would have to be using that drug would be given by the cumulative incidence rates. The estimated incidence rates suggest that at age 75 about 11% would require treatment. This would increase to 33% at age 85 and 77%

at age 95.

The simulation can also be used to examine what might happen to mortality if the rate of progression of AD were slowed substantially. Since changing mortality rates will change future age distributions, we have to switch from a population perspective to a life cycle approach to examine this issue. Figure III shows the survival rates used in the simulation for AD cases relative to the rest of the population (labeled “current”). It also shows a curve with appreciably slower progression. This involves taking the relative survival rates during the first 10 years and spreads them out over the first 20 years. This is an optimistic scenario of what might be possible in the next 10 to 15 years. If this change in survival rates were applied to a cohort, the prevalence of “diagnosable” AD would decline slightly (Figure IV). The average person-years lived with mild, moderate or severe AD (now at 6 years after onset instead of 3) would drop from about 1.09 years to 1.04 years. The average person-years lived with moderate to severe AD (now 12 years after onset instead of 6+) would drop from 0.55 years to 0.35 years. The largest change is seen in the prevalence of severe AD (Figure IV). The average person-years lived with severe AD (now 18 years after onset instead of 6) would drop from 0.12 years to 0.08. The decline in the person-years lived with severe AD might be reflected in reduced demand for nursing home care and intensive in-home care for severely impaired patients.

It is important to note, however, that these results are probably very sensitive to the changes assumed in the survival rates at various durations and the definitions of severity. Therefore, they would depend on the effectiveness of likely treatments at different stages of the disease as well as the actual proportion of cases receiving the treatment at each stage.

In addition, slowing the progression of AD for large numbers of patients would delay the date at which services would be required. With a high discount rate applied to future costs, this in itself would lower the current value of future expected costs of AD care. *However, the only conclusion that can be drawn from these preliminary simulations is that changes in the rate of progression of AD might have significant effects on future demand for nursing home placement and intensive home care services*.

Alzheimer's Disease as a Cause of Death

The claim that Alzheimer's disease is the fourth leading cause of death in the U.S. plays a central role in much of the literature produced by the Alzheimer's Disease and Related Disorders Association and is prominently mentioned in many scientific articles on AD. The original claim that AD played such an important role in mortality appeared in an editorial in the *Archives of Neurology* by Katzman (1976). He based this statement on survival rates observed among patients seen at research centers. Fox credits this claim with playing a major role in “altering the biomedical conceptualization of Alzheimer’s disease”(1989:71). He also states that along with estimates of the long-term care costs for the elderly this claim was “one of the primary justifications for increasing federal support for Alzheimer’s disease research” (1989:71).

Demographers are generally very skeptical about these claims. Alzheimer's disease is not listed among the 72 causes of death selected for detailed tables in the U.S. vital statistics (Kochanek, 1994). Instead it is lumped into the "All other Diseases" category which includes only 8% of deaths. AD is more likely to be listed as a associated cause. A study by the Centers for Disease Control (1991) found that Alzheimer's disease

was listed as an associated cause for 26,325 deaths in 1987. Since the classification of dementias was changing rapidly during the 1970s and 1980s, many dementias that would now be classified as Alzheimer's disease might have been coded as "presenile dementia" or "senile dementia." In fact the ICD-9 codes for dementias do not reflect current diagnostic categories very well. However, even if we ascribe to AD all of the deaths with "senile and presenile dementias" listed as an associated cause, the total is only 32,624 which would push Alzheimer's up to about eighth on the list for 1987. Although this at least gets AD onto the top ten list, this is only about one-third of the number of deaths required to push it up to number four or five.

Although vital statistics data for other low mortality countries show similar rates for Alzheimer’s disease, it is likely that the true significance of AD is much greater. It is very likely that AD is underreported on death certificates in all countries. This is not surprising given that AD is also grossly underreported in patient records in nursing homes and in health surveys. Even death certificates for patients followed for years in research studies are just as likely to ignore AD as to report it.

Mortality in Community Studies An alternative approach is to examine data for community-based studies designed to measure the prevalence and incidence of Alzheimer's disease. There are two major studies based on community screening that provide comparisons of mortality rates by cognitive status: the East Boston study (Evans, 1989; data for five-year age groups are available in Beckett, 1992) and a study in Iceland (Magnusson, 1989). The two studies provide a good contrast because they produce very different estimates of prevalence and mortality. As noted above, the East Boston study produced estimates of the

proportions with Probable AD that are higher than the rates found in the majority of studies. At age 80-84, the estimated prevalence in East Boston was 25%. In contrast, the Icelandic study estimated that at age 81.5 only 2.8% had severe Primary degenerative dementia. Part of the difference between the two rates is that the East Boston study included moderate, mild and borderline cases whereas the Iceland study provides detailed data only on severe cases.

The difference in the severity of cases reported in East Boston and Iceland is reflected in differences in the reported relative risks of mortality in the two studies. In the East Boston study, the relative risk of death for AD cases was 1.44 compared to that of others in the population. The comparable figure for the study in Iceland was 2.37 for severe AD cases. If we apply the prevalence estimates from the two studies and their respective relative risks to age distribution and mortality rates for the U.S. in 1991, the results provide a reasonable range of estimates for the proportion of deaths in U.S. that are attributable to AD. The East Boston estimates suggest that excess deaths among AD cases in the U.S. in 1991 amounted to about 8.2% of deaths over age 60. The estimates for Iceland suggest that excess AD deaths amounted to 4.6% of deaths over age 60. These correspond to 6.4% and 3.6% of deaths at all ages. This would place AD somewhere between Cerebrovascular deaths and Chronic Obstructive Pulmonary disease, the third and fourth leading causes, which are responsible for 6.6% and 4.2% of all deaths (Figure V).

It is useful to consider possible sources of bias in these estimates. The diagnosis of AD is not considered definite until the presence of the plaques and tangles that cause AD has been confirmed pathologically. Definite diagnosis is possible through

biopsy, but this procedure is quite rare. Even confirmation at autopsy is not common because autopsies are performed infrequently. Diagnoses based on clinical examinations of the type performed in the CSHA are about 90% accurate. Although the remaining 10% may often be dementias caused by strokes, and, therefore, falsely include some cases at high risk of death, it is not likely that misdiagnosis could explain much of the mortality attributed to AD.

The estimates of the significance of AD in mortality are estimates of "attributable risk," that is, estimates of the excess mortality among cases of AD. Estimates of attributable risk rarely provide good estimates of how much mortality would decline if a disease or risk factor were eliminated from the population. For example, since smokers are statistically more likely to have other risk factors for mortality (e.g., higher alcohol consumption, lower exercise rates), some of the excess mortality among smokers can be attributed to other risk factors. However, in the case of AD, the attributable risk estimates may closely approximate the proportion of deaths attributable to AD as an underlying cause. The reason for this is that there are few important other risk factors for mortality that have been associated with increased risk of AD. Those risk factors that have been identified (or suggested) by previous research are quite varied in their likely effect on mortality to other causes. For example, although head trauma is a risk factor for AD, its contribution is probably small enough that it would have little affect on the mortality rate among AD cases. In addition, it is not likely that head trauma sustained many years earlier will have a direct effect of risk of death. A recent study suggests that daily aspirin use (often recommended for reducing the risk of heart attack) may reduce the risk of AD. On the other hand,

other studies suggest that smoking (which increases the risk of heart attach) may also protect against AD. The most common genotype associated with increased risk of AD (the apolipoprotein ε-4) is actually a low risk gene for problems associated with cholesterol. Overall, there is no reason to suspect that the estimates of attributable risk associated with AD are seriously biased upward by associations between AD and other risk factors for mortality.

Simulation of the Role of AD in Mortality. We can use the simulation of the CSHA to produce another estimate of the proportion of deaths attributable to AD. Given the age distribution and mortality rates for U.S. whites in 1985, the simulation suggests that 9.6% of deaths over age 60 or 7.8% of all deaths are excess deaths attributable to (diagnosable) AD. If we limit the deaths attributable to AD to deaths among moderate and severe cases (arbitrarily defined as 6 years after incidence and 3 years after diagnosis), we estimated that 5.0% of all deaths are attributable to AD. This range between total excess deaths among AD patients to excess deaths among severe cases (5.0% to 7.8%) is slightly higher than the range between the East Boston estimates based on mild, moderate and severe cases and the Iceland estimates based only on severe cases (3.6% to 6.5%). Therefore is possible that AD could rank as high as the third leading cause of death if we ascribed all excess deaths among AD patients to AD as a cause of death; however, it is much more likely AD would rank as the fourth leading cause.

The simulation also offers us the chance to examine the potential impact of likely new treatments for AD on mortality rates. We can examine the effect of the changes in the relative survival rates of AD patients shown in Figure IV and described

above. These changes would increase the life expectancy at age 65 by 0.31 years. However, because of the increased severity of cases surviving to older ages, life expectancy at age 85 would drop by about 0.16 years. This difference between the effect on life expectancy at ages 65 and 85 is surprising. It probably results from the sharp change in the relative survival rates assumed to occur at about 20 years of duration. If excess mortality associated with AD were eliminated completely, life expectancy at age 65 would increase by about 0.95 years. Life expectancy at age 85 would increase by almost as much, about 0.73 years.

Summary and Conclusions

Alzheimer's disease is so prevalent among the oldest old that demographers should be interested in it simply as a characteristic of the population. However, its likely role in mortality and nursing home placement make AD an important disease for demographic projections of population, mortality and residence patterns.

The evidence presented here substantiates the claim that Alzheimer's disease is an important element in U.S. mortality. It appears that about 4% to 7% of all deaths are attributable to AD. This is large enough to rank AD as the third or fourth largest cause of death in the U.S. today. A simulation of the effects of slowing the progression of AD suggests that the life expectancy at age 65 would increase by almost one-third of a year if the rate of progression of AD were cut in half during the first ten years after diagnosis. Changing the rate of progression might also change the prevalence of the disease as well as the average person-years lived at various levels of severity. Cutting in half the rate of progression during the

twenty years following onset could reduce the average person-years lived with severe AD by about one-third. These changes could have a substantial impact on the demand for nursing home placement and home care services.

The simulation presented here is very crude and will need to be refined. In particular, it ignores heterogeneity in the progression of Alzheimer's disease. Differences in rate of progression complicate the simple relationship between severity and duration and will require more complex modeling. The simulation of the possible impact of slowing progression is simply a first attempt to begin examining what is actually a very difficult question. It will be important to examine in detail the mechanisms that will underlie likely new treatments and how they might affect mortality and cognitive functioning. However, the simulation presented here probably provides a good indication of the types of conclusions that are apt to emerge from more elaborate models.

The modeling of nursing home placement will be a much more complex project. One reason for this is that the timing of institutionalization is dependent on much more than just the severity of the impairment of cognitive function. A minimal model might include the effect of behavioral disturbances, the availability of a caregiver, and some modeling of how "caregiver burden" might be affected by slowing the rate of progression. In addition, slowing the rate of progression might affect the length of stay in a nursing home (generally the time until death) as well as the time of entry. Another complication is that increased availability of alternative sources of care, in particular expanded home care services, will alter the relationship between severity of disease and nursing home placement. However, the simple simulations presented here

suggest that changes in the rate of progression might have significant effects on the age pattern of institutionalization.

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Table Ia: Survival Rates in Alzheimer's Disease

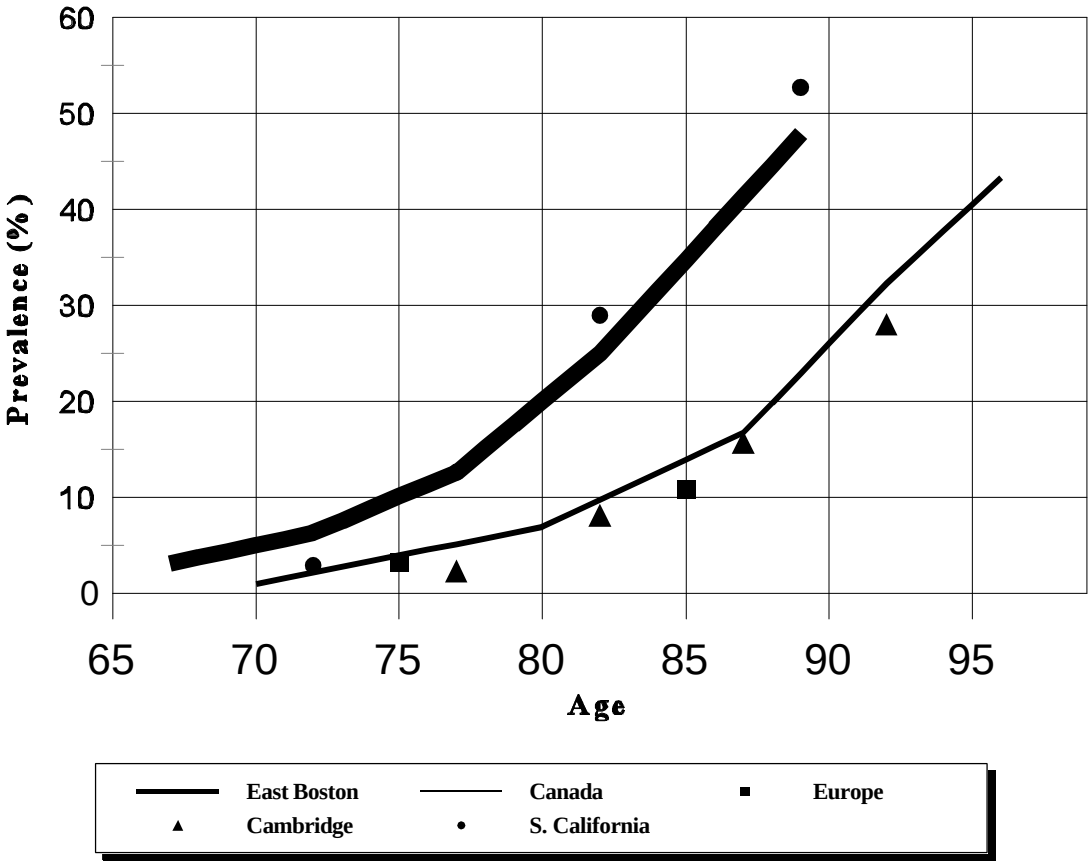
Relative to Nondemented Individuals

	Mild	Moderate	Severe
0	1.000	1.000	1.000
1	0.930	0.910	0.890
2	0.860	0.820	0.780
3	0.790	0.730	0.670
4	0.720	0.640	0.560
5	0.650	0.550	0.450
6	0.580	0.460	0.340

Table Ib: One-Year Relative Survival Rates, by Severity and Estimated Overall Rates by Duration

	Relative $_1P_x$				Relative
	Mild	Moderate	Severe	Combined	l_x
0				1.000	1.0000
1				1.000	1.0000
2				0.970	1.0000
3				0.959	0.9700
4	0.930			0.930	0.9300
5	0.925			0.925	0.8649
6	0.919			0.919	0.7998
7	0.911	0.910		0.911	0.7347
8	0.903	0.901		0.902	0.6691
9	0.892	0.890	0.890	0.891	0.6035
10		0.877	0.876	0.877	0.5376
11		0.859	0.859	0.859	0.4712
12		0.836	0.836	0.836	0.4049
13			0.804	0.804	0.3385
14			0.756	0.756	0.2720
15				0.600	0.2055
16				0.500	0.1233
17				0.300	0.0617
18				0.200	0.0185

Figure I: Estimated Prevalence of Alzheimer's Disease, by Age



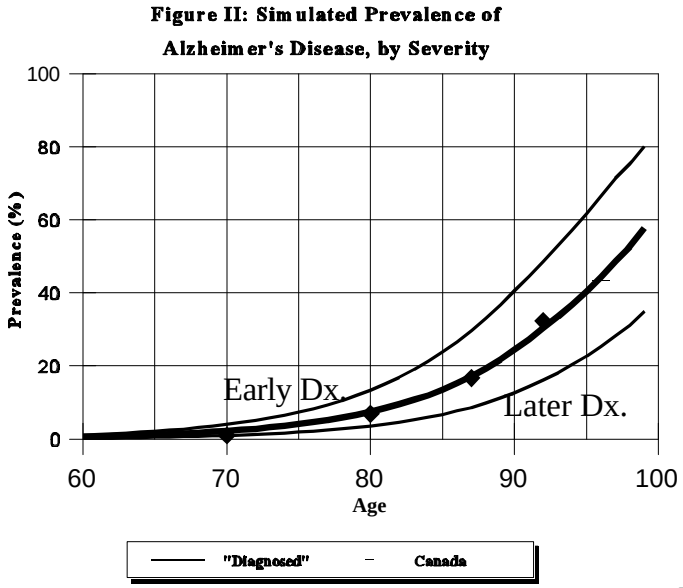


Figure II: Simulated Prevalence of
Alzheimer's Disease, by Severity
100
80
60
40
20
0
Prevalence (%)
Early Dx.
Later Dx.
60
70
80
90
100
Age
"Diagnosed"
Canada

Later Dx.

Figure III: Survival with Alzheimer's Disease Current and Slowed Progression

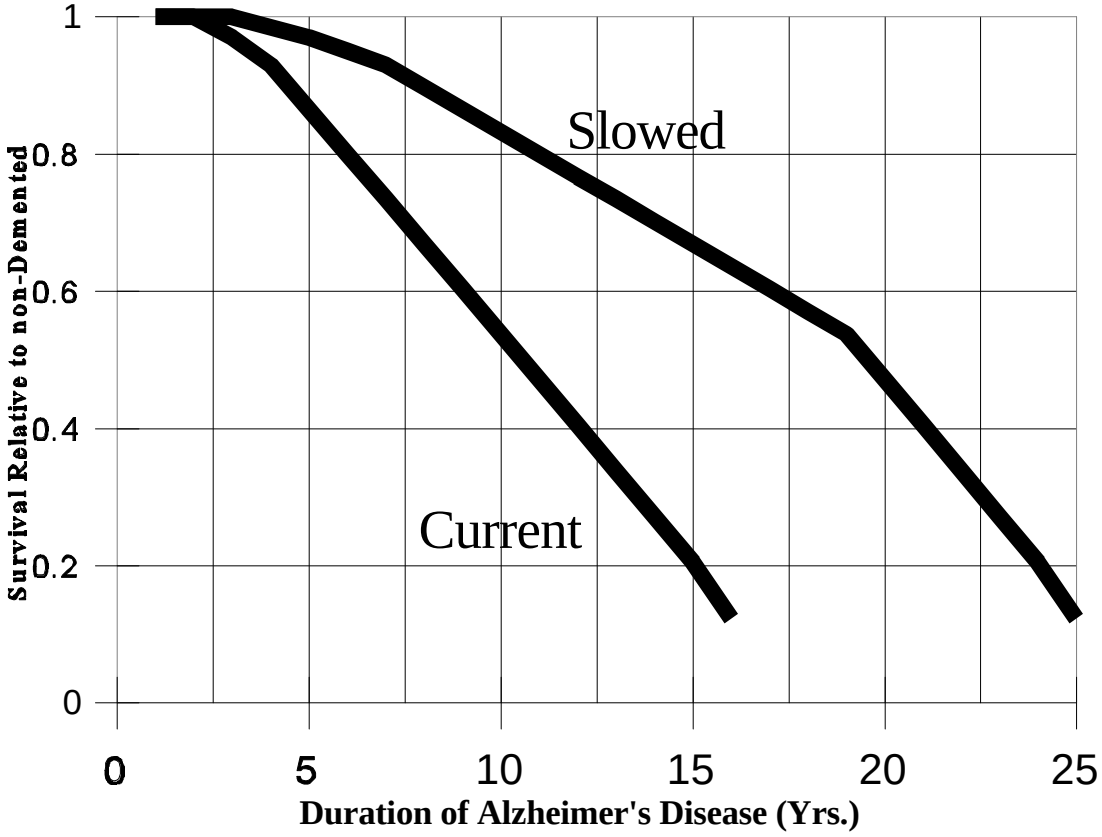


Figure IV: Prevalence of Alzheimer's Disease with Slower Progression

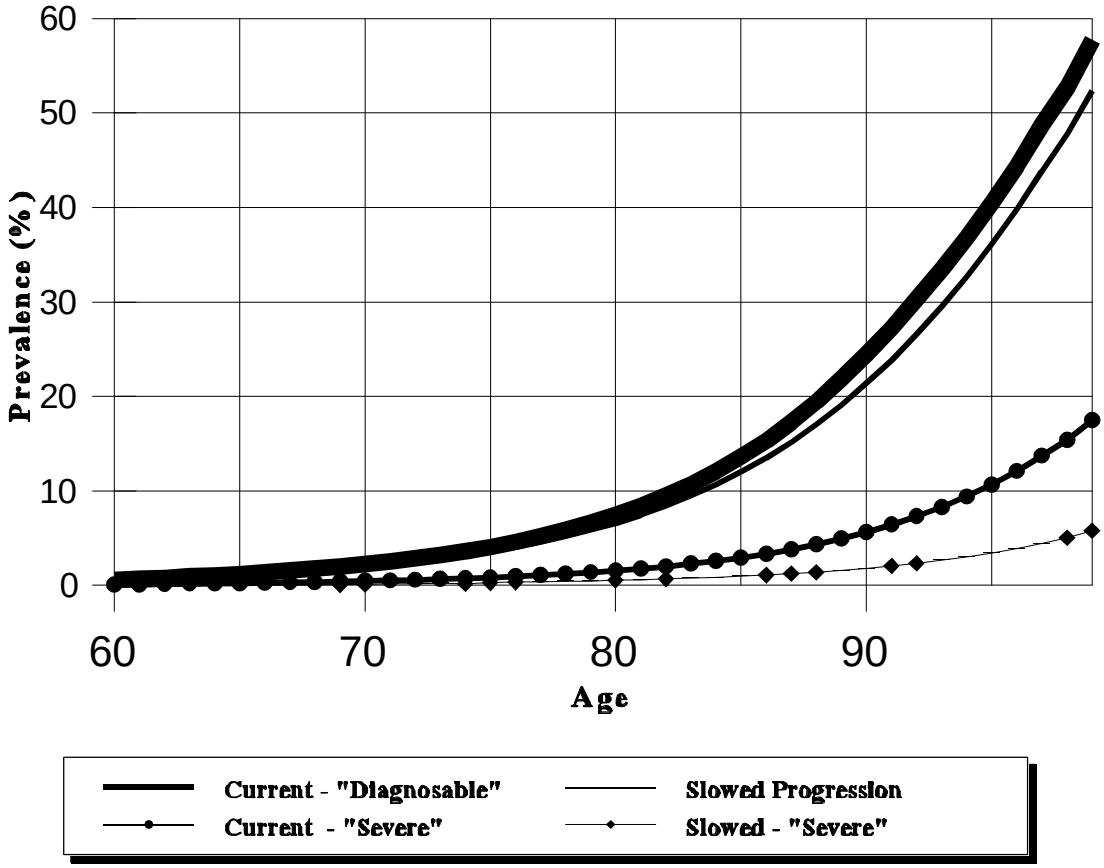
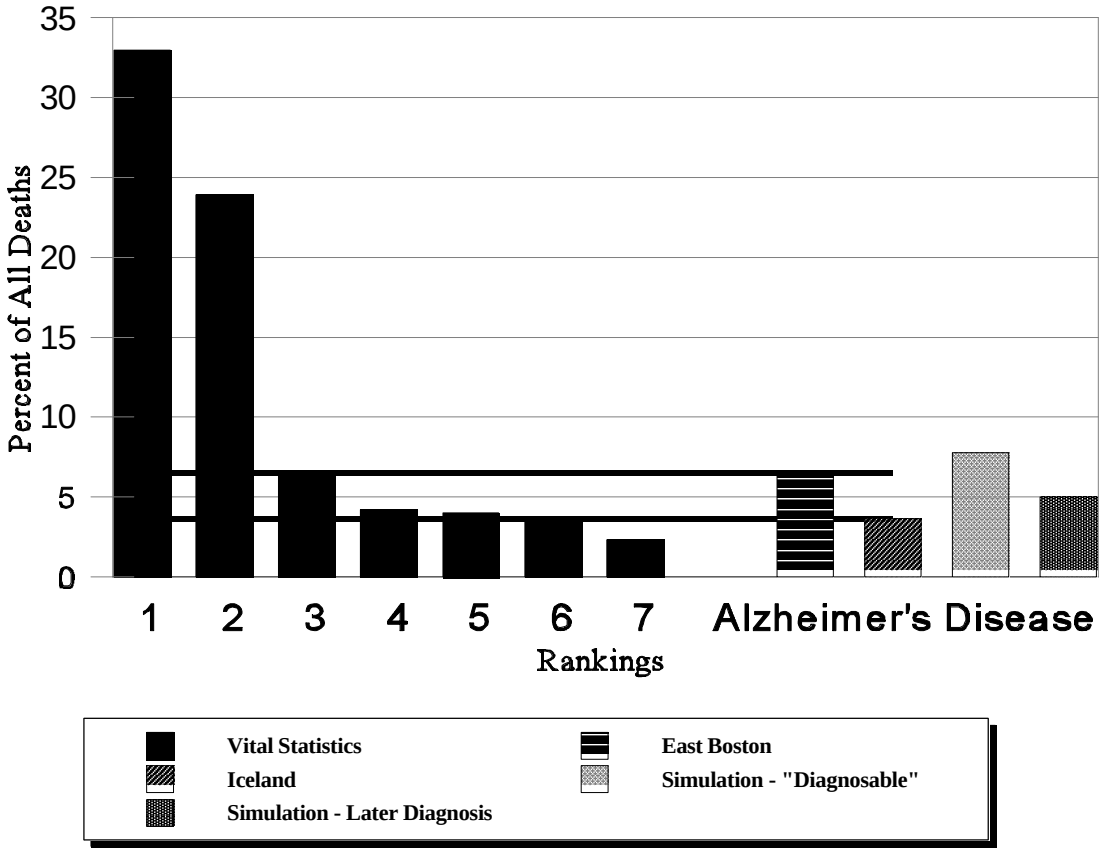


Figure V: Causes of Death, U.S. 1991
with Estimates for Alzheimer's Disease



Key for Top Ranked Causes of Death from U.S. Vital Statistics, 1992:

1) Diseases of the Heart
2) Malignant Neoplasms
3) Cerebrovascular Diseases
4) Chronic Obstructive Pulmonary Diseases and Allied Conditions
5) Accidents and Adverse Effects
6) Pneumonia and Influenza
7) Diabetes Mellitus