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Background: The goal was to forecast the global burden of Alzheimer's disease and evaluate the potential impact of interventions that delay disease onset or progression. Methods: A stochastic multi-state model was used in conjunction with U.N. worldwide population forecasts and data from epidemiological studies on risks of Alzheimer's disease.

Findings: In 2006 the worldwide prevalence of Alzheimer's disease was 26.6 million. By 2050, prevalence will quadruple by which time 1 in 85 persons worldwide will be living with the disease. We estimate about 43% of prevalent cases need a high level of care equivalent to that of a nursing home. If interventions could delay both disease onset and progression by a modest 1 year, there would be nearly 9.2 million fewer cases of disease in 2050 with nearly all the decline attributable to decreases in persons needing high level of care.

Interpretation: We face a looming global epidemic of Alzheimer's disease as the world's population ages. Modest advances in therapeutic and preventive strategies that lead to even small delays in Alzheimer's onset and progression can significantly reduce the global burden of the disease.

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INTRODUCTION

As the world population ages, enormous resources will be required to adequately care for persons afflicted with Alzheimer's disease. Research is actively underway to develop interventions to both delay disease onset and slow progression of disease. Effective interventions may significantly reduce the prevalence and incidence of Alzheimer's disease, improve the quality of life both of the patients and their caregivers, and reduce the resources needed to provide adequate institutional and home health care. Several treatments to help slow disease progression, and prevention strategies including lifestyle changes are being investigated (1).

Uncertainty exists in the estimates of the global burden of Alzheimer's disease and the potential impact of interventions. Recently, Alzheimer's Disease International, an international consortium of Alzheimer's associations, produced estimates of the worldwide prevalence of people with dementia (2). These estimates were based on a Delphi consensus study of 12 international experts who systematically reviewed published studies. The consensus method involved a qualitative assessment of evidence by each expert, and then those experts were given an opportunity to revise their estimates of prevalence after reflecting on the input of their colleagues. The resulting Delphi consensus estimates have been considered some of the best currently available estimates of worldwide prevalence. Yet, because the Delphi approach is not based on an underlying quantitative model, the Delphi study cannot be readily used to forecast the potential impact of new interventions on health care needs. Furthermore the study did not take into account the severity of disease. Disease severity is an important consideration for assessing the global burden of Alzheimer's disease because the resources needed to care for patients with advanced disease are very different than for patients early in the disease process. The objective of this article is to forecast the global burden of Alzheimer's disease based on a

mathematical model that incorporates the aging of the world's population. The model is used to forecast the world-wide prevalence of Alzheimer's disease, evaluate the impact of interventions, and incorporate disease severity.

METHODS

The Multi-State Model

Our methodology is based on a multi-state probabilistic model for the incidence and progression of Alzheimer's' disease. The method extends a single stage disease model used for U.S. projections (3) by including early and late stages of disease. According to the model, healthy persons have an annual probability of onset of Alzheimer's disease which begins in an early stage and ultimately progresses to late stage disease. Persons with early stage disease have an annual probability of progressing to late stage disease. The definitions of early and late stage disease including the mean durations are discussed below. Persons are at risk of death during each state. The model is illustrated schematically in figure 1. The transition probabilities between states are the probabilities of moving from one state to the next. We allow some of these transition probabilities to depend not only on age but also calendar year to account both for birth cohort effects (e.g. death rates change over time) and the impact of new interventions that could potentially delay disease onset and progression. The model is implemented as a discrete time stochastic model in which transitions occur only at the beginning of a calendar year, and it is possible that persons may have multiple transitions in a year (e.g. disease onset followed by death could occur in the same year).

We derived formulas for the age-specific prevalence rates of early stage and late stage disease in terms of the model in figure 1. The transition probabilities are inputs into these

formulas. We performed a number of analyses and systematic reviews of published literature, to estimate the transition probabilities (described below.) Then, we forecast disease prevalence by multiplying the formulas for age–specific prevalence rates by demographic population projections. We used the United Nations worldwide population projections (4). Those projections are in terms of 5 year age groups which we interpolated to obtain projections by single year of age. We performed analyses separately by gender, and for each of six regions of the world. Then, we evaluated the potential effects of interventions that delay disease onset, delay disease progression or both by modifying the transition probabilities under different scenarios. We multiplied the transition probabilities by various factors (relative risks) to model the potential effects of the interventions. We translated these relative risks into average delays in disease onset and progression (in the absence of competing causes of death) as an alternative way to express the efficacy of intervention programs. We considered the impact of interventions that begin in the year 2010. The technical details including the formulas for the age specific prevalence rates and computing software are available from the authors at www.biostat.jhsph.edu/project/globalAD/index.htm.

Transition Probabilities

In this section, we discuss inputs for each of the transition probabilities of figure 1.

Incidence rates

We estimated age-specific probabilities of disease onset by performing a systematic review of published Alzheimer's disease incidence rates. Jorm and colleagues (5) reviewed the worldwide literature on Alzheimer's disease incidence rates. We updated the Jorm review to include additional recent studies reporting age-specific incidence rates of Alzheimer's disease.

We fit a linear regression equation to the log of the age-specific incidence rate for each of 27 studies in our review because incidence rates appeared to grow exponentially with age. We then averaged the rates from the fitted regression lines to obtain an equation for the age-specific incidence rate. We found that the annual age-specific incidence of Alzheimer's disease at age *t* expressed in per cent per year (for *t* greater than 60) is given by:

$$\text{Incidence rate (\% per year)} = .132e^{.121(t-60)}. \quad (1)$$

Equation 1 implies that incidence grows exponentially with a doubling time of about 5.7 years. We found no significant geographic differences in the doubling times of Alzheimer's incidence (*p=.3)*, suggesting that any geographic variation may be due to different criteria and thresholds for diagnosis. We used equation 1 for the incidence rates ($r_{t,y}$ in figure 1) in our analyses. We accounted for uncertainty in equation 1 by performing a sensitivity analysis that used a range based on the upper and lower 10th percentiles of the distribution of fitted incidence rates from all the studies. This range spanned from about half to double the incidence estimates from equation 1. For example, the predicted annual incidence at age 80 is 1.48 % per year with range of 0.67% to 3.41%. The ranges we cite in the results section account for this uncertainty in incidence rates. We also performed sensitivity analyses to the assumption that incidence continues to grow exponentially at the oldest ages by holding incidence rates constant after age 90.

Disease Progression

Alzheimer's disease is a progressive disease and persons who have the disease longer often require a higher level of care. Considerable variability exists in the world's literature on the rate of Alzheimer's disease progression which results from differences in definitions of severe disease among studies, and heterogeneity in the disease course among patients. 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 (5). Similarly, a study examining the time for patients needing care equivalent to placement in a health related facility, such as a nursing home, also obtained an estimate of about 6 years (7). We defined late stage disease to refer to the period when patients need such a high level of care. We used an annual transition probability from early to late stage disease of .167 in our model which corresponds to a mean duration of early stage disease of approximately 6 years. The model accounts for variability in the duration of early disease course (the 25^{th}, 50^{th} and 75^{th} percentiles of the distribution of durations of early stage disease are approximately 1.7, 4.2 and 8.3 years respectively). We performed sensitivity analyses to the underlying disease progression rate (γ) We recognize that the rate of disease progression could depend on age or gender; however, we do not believe at this time the epidemiological data is sufficient to more precisely characterize rates of disease progression.

Death rates

We assumed that the effect of Alzheimer's disease was to increase the background mortality rates (d_{ty}). We modeled this excess mortality by an additive model for the death rates whereby the death rates for patients with late stage disease (d^*) are:

$$d^*_{ty} = d_{ty} + k \qquad (2)$$

where d are the background mortality rates, and k is the excess mortality associated with Alzheimer's disease (the subscripts indicate that the model accounts for age (t) and calendar year (y)). Then, we calibrated the parameter k to published studies on Alzheimer's survival using least squares and obtained k =.11. For example, the model predicted that the median survival times for males diagnosed with Alzheimer's at ages 65, 75 and 85 were 7.9, 5.7 and 3.3 years, respectively; the predicted median survival times for females diagnosed at ages 65, 75 and 85

were 9.1, 7.2 and 4.3 years respectively. These model predictions are in good agreement with published studies on Alzheimer's disease (8-10), and in fact were within 6 months of empirical findings (10). The interpretation of this model is that the effect of Alzheimer's disease on mortality is to add 11% per year to the background mortality rates once the disease has progressed to late stage. We also performed sensitivity analyses to evaluate the effect of excess mortality over background during both early and late stage disease.

We assembled U.S. death rates by gender and age from 1959 to the present as a basis for the background death rates (d_{ty}) (11). We recognize that variation is considerable in background mortality rates throughout the world. Accordingly, we performed sensitivity analyses of our results to these background mortality rates. Forecasts of disease prevalence also require assumptions about the background mortality rates into the future. We extrapolated recent past trends in mortality to obtain predictions of future mortality rates. We fit regression models to the mortality rates over a 15 year period (between 1988 and 2002) for each year of age, to obtain estimates of the annual percent change in mortality rates that were then used to predict future background mortality.

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RESULTS

In 2006, there were 26.6 million cases of Alzheimer's disease in the world (range 11.4-59.4). We predict that by the year 2050 the worldwide prevalence of Alzheimer's will grow fourfold to 106.8 million (range 47.2-221.2). Table 1 shows the geographic distribution of the burden of disease. We estimate that 48% of the worldwide cases are in Asia and that percentage will grow to 59% by 2050.

Figure 2 shows the 2006 age-specific prevalence rates of Alzheimer's derived from our model. For example, the prevalence rates at ages 65, 75 and 85 were 0.9%, 4.2% and 14.7% respectively. Figure 2 also shows the age-specific prevalence rate by stage of disease from which one can calculate the percent of cases with late stage disease. For example, the model predicts the percentage of 65 year old cases with late stage disease is 34% and increases to 45% among 85 year old cases. Overall, we estimate about 11.6 (43%) of the 26.6 million worldwide cases living today have late stage disease (table 1). Figure 3 shows the growth in the prevalence of Alzheimer's disease cases through 2050 by stage of disease and by gender. We estimate that about 62% of worldwide cases are female reflecting the lower background mortality rates among women.

We evaluated the potential effects of interventions that could either delay disease onset or disease progression under 6 scenarios. Prevention programs that could delay onset by 1 or 2 years correspond to a relative risk (i.e., the multiplier of the transition probability) of .88 and .77 respectively. Therapeutic treatment interventions that delay disease progression by 1 and 2 years correspond to relative risks of .85 and .75 respectively. Table 2 shows the effects that such interventions could have on the global burden of Alzheimer's disease by the year 2050. Delaying disease onset by an average of 2 years would decrease worldwide prevalence of Alzheimer's by 22.8 million cases (scenario A). Even a modest one year delay in disease onset would result in 11.8 million fewer cases worldwide (scenario B). A therapeutic intervention that delays disease progression by an average of 2 years with no effect on disease onset would actually result in a net increase in global prevalence of 5.2 million cases because of a rise in the number of early stage cases (scenario C). However, under scenario C, there would also be a decrease of nearly 7 million late stage cases. Interventions even modestly delaying both disease

onset and progression can significantly decrease the global burden of disease. For example, if both disease onset and disease progression are delayed by 1 year (scenario F) , there would be nearly 9.2 million fewer cases of disease and nearly all of that decline is attributed to decreases in the numbers of cases with late stage disease.

The sensitivity of our results were evaluated with respect to a number of model assumptions. Equation 1 assumes that the age-specific incidence rate continues to grow exponentially even in the oldest ages. If however, incidence rates plateau and remain constant after age 90 instead of continuing to raise exponentially, then a modest 4% decline is observed for the 2050 estimate of the worldwide prevalence of Alzheimer's disease. We find that estimates of worldwide prevalence are not especially sensitive to the shape of the incidence curve at the oldest ages because the oldest ages represent a relatively small segment of the population.

Sensitivity of our results to the background death rates was also examined. Surprisingly, when the background mortality rates were inflated by 20%, the absolute age-specific prevalence rates in figure 2 decreased very slightly, in fact by at most 3 per 1000. While surprising that the model for the age specific prevalence rates is not sensitive to the background mortality rates, the reason is that the age-specific prevalence rate is the ratio of persons with disease to persons alive, and if the background death rates increase, then *both* the numerator and denominator decrease, and the net effect is that the ratio itself does not change much.

We also considered the sensitivity of our results to our model for Alzheimer's mortality. Initially, we had assumed that excess mortality from Alzheimer's occurred only during late stage disease. If excess mortality also occurs during early stage of disease which was say, half the excess of that in late stage disease (i.e., we added $k/2$ to the background death rates in early

stage) , our estimate of worldwide prevalence in 2006 would decline by about 14%, and the percentage of cases classified as late stage would slightly increase from 43% to 46%.

We considered the sensitivity of our results to the progression rate from early to late stage disease. If the average duration of early stage disease was in fact greater than the 6 years we assumed, then the percentage of prevalent cases that have late stage disease should be smaller than estimated. That phenomenon reflects the epidemiological concept that prevalence increases with duration. For example, if the mean durations of early stage disease were 4, 6, and 8 years, then with all other factors fixed) the estimated worldwide prevalence in 2006 of late stage Alzheimer's disease would be 13.9, 11.6 and 9.8 million cases respectively; and the percentages of prevalent cases that are classified as late stage would be 56%, 43% and 35% respectively.

DISCUSSION

Our model indicates that 26.6 million persons worldwide are currently living with Alzheimer's disease (range 11.4 to 59.4). We project that by the year 2050 worldwide prevalence will quadruple to 106.2 million with 1 in 85 persons living with Alzheimer's disease. The increase is a result of the aging of the world's population. The United Nations Population Division projects that the number of persons at least 80 years of age will increase by a factor of about 3.7 by the year 2050. The Alzheimer's Disease International study concluded there were 24.3 million persons with dementia in the world using a Delphi consensus methodology (2). Wimo and colleagues (12) estimated 25.5 million cases of dementia worldwide in 2000 by multiplying age-specific prevalence rates derived from epidemiological surveys by population estimates. Our estimates, which refer specifically to Alzheimer's disease cases rather than

dementia more generally, are broadly consistent with these estimates which were obtained using different methodologies.

An advantage of the modeling methodology used in this paper is that the effects of interventions may be evaluated. We find that the impact of interventions depend on whether the interventions delay onset of disease, delay progression of disease, or a combination of both. Interventions can differentially affect the stage-specific prevalence depending on which stage of the disease natural history is targeted. We find that interventions that both delay disease onset and delay progression by even a modest amount would result in significant reductions in the global burden of disease. In related work, Sloane and colleagues (13) evaluated the impact of therapeutic advances in the United States. They found, as did we, that therapies that only delayed disease progression would lead to a decrease in advanced disease. But they also found no overall increase in Alzheimer's prevalence which was in contrast to our finding of a net increase (scenario C in table 2). We find that therapeutic advances that delay disease progression would lead to an increase in overall disease prevalence but on average the prevalent cases would have less severe disease.

There are important sources of uncertainty in our results. Main sources of uncertainty are the age-specific Alzheimer's disease incidence rates, which are reflected in the wide ranges of our forecasts. Data was not sufficient to obtain separate incidence rates for each geographic region, and we used equation 1 for all regions. The majority of published studies on age specific incidence rates of Alzheimer's disease are derived from populations in developed countries, and there is a critical need for additional studies in developing countries. We cannot say whether geographic variation in Alzheimer's incidence rates result from real differences in underlying incidence or rather differences in methodology and diagnostic criteria of the epidemiological

studies. Our wide ranges on our estimates account for this uncertainty. However, we did not find any significant geographic differences in the doubling times of the age specific incidence rates. Accordingly, our finding about the *proportionate i*ncrease in Alzheimer's disease, namely a quadrupling in prevalence by 2050, is reasonably precise, even if the absolute number of cases is more uncertain. Indeed, we conclude Alzheimer's disease prevalence will quadruple by 2050 regardless of whether we use the lower or upper limits of our range of disease incidence rates. That conclusion does however depend on the accuracy of the U.N demographic projections of the aging of the world population.

The resources needed to care for an Alzheimer's patient depends on stage of disease. Adult day care programs may be adequate in the early stages, while a high level of care, equivalent to that of nursing homes, will be needed in the late stages. Assessments of the global burden of disease should account for disease stage. We recognize that currently there is no single staging system that is accurate, reproducible and routinely used worldwide. Nevertheless, we believe the two stage model of disease progression used here, produces useful estimates of the numbers of patients requiring a high level of care roughly equivalent to that provided by a health care facility such as a nursing home. Epidemiological surveys of the percentage of cases with severe disease have ranged between 2% to over 50% (14-16). Such wide variation could result either from differences in survey methodology and diagnostic criteria, or sampling enrollment biases. Our modeling approach produces estimates in the upper end of the range. As more information becomes available about disease progression rates the multi-state model can be used with updated input parameters for the transition probabilities. A web site that allows users to input their own transition probabilities and population data, and then implements the multi-state

model to obtain forecasts of the global burden of Alzheimer's disease is available from the authors.

As the world's population ages, we will face a looming epidemic of Alzheimer's disease. Health care systems will be challenged to meet the needs of patients and their caregivers. The worldwide costs will be huge (17). Prevention of Alzheimer's is an ambitious goal (1, 18) that may not be fully achievable in the near term, although delaying disability may be achievable. We find that modest advances in therapeutic and preventive strategies resulting in even small delays in Alzheimer's disease onset and progression can significantly reduce the global burden of the disease.

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Table 1:

Projections of Alzheimer's disease prevalence (in millions) in 2006 and 2050 by regions and stage of disease

	Prevalence (in millions)					
	2006			2050		
	Overall	Early Stage	Late Stage	Overall	Early Stage	Late Stage
Africa	1.33	0.76	0.57	6.33	3.58	2.75
Asia	12.65	7.19	5.56	62.85	34.84	28.01
Europe	7.21	4.04	3.17	16.51	9.04	7.47
Latin Am. / Caribbean	2.03	1.14	0.89	10.85	5.99	4.86
North America	3.10	1.73	1.37	8.85	4.84	4.01
Oceania	0.23	0.13	0.10	0.84	0.46	0.38
Total	26.55	14.99	11.56	106.23	58.75	47.48

Note: Regions defined according to the United Nations Population Division (4):Oceania includes Australia, New Zealand, Melanesia, Micronesia, and Polynesia.

Table 2:

Impact of interventions on world-wide prevalence of Alzheimer's disease. Table shows change in prevalence in 2050 associated with interventions begun in 2010 compared to baseline scenario of no intervention.

Intervention Scenario	Mean Delay (in years)		Change in Worldwide Prevalence (in millions)		
	Onset	Progression	Overall	Early Stage	Late Stage
A	2	0	- 22.76	- 12.28	- 10.48
B	1	0	- 11.76	- 6.32	- 5.44
C	0	2	+ 5.23	+ 12.14	- 6.91
D	0	1	+ 2.84	+ 6.54	- 3.70
E	2	2	- 18.48	- 2.66	- 15.82
F	1	1	- 9.19	- 0.48	- 8.71

Note: These estimates refer to the changes in prevalence compared to the baseline scenario of no intervention. Under the baseline scenario of no intervention, in 2050 there will be 106.23 million cases worldwide of which 58.75 and 47.48 million cases have early and late stage disease respectively (from Table 1).

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References

1. Roberson E, Mucke L. 100 Years and Counting: Prospects for Defeating Alzheimer's Disease. Science 2006: 314:781-784.
2. Ferri CP, Brayne C, Brodaty H, et al. Global Prevalence of Dementia: A Delphi Consensus Study. Lancet 2005: 366:2112-17
3. 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. Am J Pub Health 1998; 88:1337-1342.
4. Population Division of the Department of Economic and Social Affairs of the United Nations Secretariat, World Population Prospects, http://esa.un.org/unpp
5. Jorm AF, Jolley D. The Incidence of Dementia: A Meta-analysis. Neurology.1998:51:728-733.
6. 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
7. Stern Y, Tang MX, Albert M et al. Predicting Time to Nursing Home Care and Death in Individuals with Alzheimer Disease. JAMA 1997; 277:806-812.
8 Guehne U, Riedel-Heller S, Angermeyer M. Mortality in Dementia. Neuroepidemiology 2005; 25:153-162
9. Larson EB, Shadlen MF, Wang L et al. Survival after Initial Diagnosis of Alzheimer Disease. Ann Intern Med 2004; 140:501-509.
10. Brookmeyer R, Corrada M, Curriero F, Kawas C. Survival Following a Diagnosis of Alzheimer Disease. Arch Neurol 2002; 59:1764-1767

11. 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).
12. Wimo A, Winblad B, Aguero-Torres H, Strauss E. The Magnitude of Dementia Occurrence in the World. 2003. Alzheimer Dis Assoc Disord 2003 17:63-67
13. Sloane PD, Zimmerman S, Suchindran C, et al. The Public Health Impact of Alzheimer's Disease, 2000-2050: Potential Implication of Treatment Advances 2002 23:213-31 Annual Rev Pub Health.
14. Hy LX, Keller DM. Prevalence of Alzheimer's Disease Among Whites: A Summary by Level of Severity. Neurology 2000, 55:198-204
15. Pfeffer RI, Afifi AA, Chance JM. Prevalence of Alzheimer's Disease in a Retirement Community. Am J Epidemiol 1987; 125:420-436.
16. Rorsman B, Hagnell O and Lanke J. Prevalence and Incidence of Senile and Multi-Infarct Dementia in the Lunby Study: A Comparison between the Time Periods 1947-1957 and 1957-1972. Neuropsychobiology 1986; 15:122-129.
17. Wimo A, Jonsson L, Winblad B. An Estimate of the Worldwide Prevalence and Direct Costs of Dementia in 2003. Dement Geriatr Cogn Disord 2006; 21:175-181.
18. Pope SK, Shue VM, Beck C. Will a Healthy Lifestyle Prevent Alzheimer's Disease 2003,24:111-132. Annu Rev Pub Health Vol. 24: 11-132.

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