

Featured Articles

## Forecasting the global burden of Alzheimer's disease

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### Abstract

**Background:** Our 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, multistate model was used in conjunction with United Nations worldwide population forecasts and data from epidemiological studies of the risks of Alzheimer's disease.

**Results:** In 2006, the worldwide prevalence of Alzheimer's disease was 26.6 million. By 2050, the 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 the disease in 2050, with nearly the entire decline attributable to decreases in persons needing a high level of care.

**Conclusions:** 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 the onset and progression of Alzheimer's disease can significantly reduce the global burden of this disease.

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### Keywords:

Alzheimer's; Forecast; Prediction; Statistics

### 1. Introduction

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

Uncertainty exists in the estimates of the global burden of Alzheimer's disease and the potential impact of interven-

tions. 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 are considered some of the best currently available estimates of worldwide prevalence. However, because the Delphi approach is not based on an underlying quantitative model, the Delphi study cannot readily be used to forecast the potential impact of new interventions on healthcare needs. Furthermore, the study did not take into account the severity of disease. Disease severity is an important consideration when assessing the global burden of Alzheimer's disease, because the resources needed to care for patients with advanced disease are very different from those for

Conflict of interest: H.M.A. is Director of Epidemiology at Elan Pharmaceuticals, a sponsor of the study.

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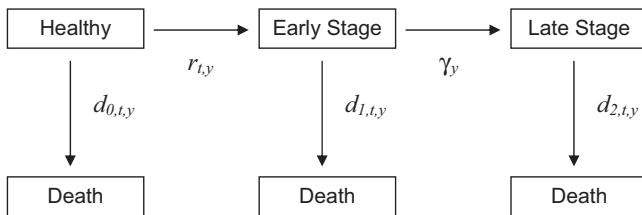


Fig. 1. Multistate model of progression of Alzheimer's disease. Transition probabilities include disease incidence rates ( $r$ ), disease progression rates ( $\gamma$ ), and death rates ( $d$ ), which can depend on age ( $t$ ) and calendar year ( $y$ ).

patients early in the disease process. The objective of this study 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 worldwide prevalence of Alzheimer's disease, evaluate the impact of interventions, and incorporate disease severity.

## 2. Methods

### 2.1. The multistate model

Our methodology is based on a multistate probabilistic model for the incidence and progression of Alzheimer's disease. The method extends a single-stage disease model used for United States projections [3] by including early and late stages of the 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-stage and late-stage disease, including mean durations, are discussed below. Persons are at risk of death during each state. The model is illustrated schematically in Fig. 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 for 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 Fig. 1. The transition probabilities are inputs into these formulas. We performed a number of analyses and systematic reviews of the 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 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 age-specific prevalence rates and the computing software, are available from the authors at <http://www.biostat.jhsph.edu/project/globalAD/index.htm>.

### 2.2. Transition probabilities

Here, we discuss inputs for each of the transition probabilities of Fig. 1.

#### 2.2.1. Incidence rates

We estimated age-specific probabilities of disease onset by performing a systematic review of published incidence rates of Alzheimer's disease. Jorm and Jolley [5] reviewed the worldwide literature on incidence rates of Alzheimer's disease. We updated the review of Jorm and Jolley [5] to include 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 percentage per year (for  $t > 60$ ) is given by:

$$\text{Incidence rate (\% per year)} = 0.117e^{.127(t-60)}. \quad (1)$$

Equation 1 implies that incidence grows exponentially with a doubling time of about 5.5 years. We found no significant geographic differences in the doubling times of Alzheimer's incidence ( $P = 0.3$ ), 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 Fig. 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 studies. This range spanned from about half to double the incidence estimates from Equation 1. For example, the predicted annual incidence at age 80 years is 1.48% per year, with a range of 0.67–3.41%. The ranges we cite in Results

account for this uncertainty in incidence rates. We also performed sensitivity analyses of the assumption that incidence continues to grow exponentially at the oldest ages by holding incidence rates constant after age 90 years.

### 2.2.2. Disease progression

Alzheimer's 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 progression of Alzheimer's disease, which results from differences in definitions of severe disease among studies, and heterogeneity in 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 [6]. Similarly, a study examining the time by which 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 as referring to the period when patients need such a high level of care. We used an annual transition probability from early-stage to late-stage disease of 0.167 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 25th, 50th, and 75th 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 of the underlying disease progression rate ( $\gamma$ ). We recognize that the rate of disease progression could depend on age or gender. However, we do not believe at this time that the epidemiological data are sufficient to more precisely characterize rates of disease progression.

### 2.2.3. Death rates

We assumed that the effect of Alzheimer's disease was to increase the background mortality rates ( $d_{t,y}$ ). 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:

$$d_{t,y}^* = d_{t,y} + k \quad (2)$$

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  $k = 0.11$ . For example, the model predicted that the median survival times for males diagnosed with Alzheimer's disease at ages 65, 75, and 85 years were 7.9, 5.7, and 3.3 years, respectively. The predicted median survival times for females diagnosed at ages 65, 75, and 85 years 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 inter-

pretation 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-stage and late-stage disease.

We assembled United States death rates by gender and age from 1959 to the present as a basis for the background death rates ( $d_{t,y}$ ) [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 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 1988–2002) 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.

## 3. Results

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

Fig. 2 shows the 2006 age-specific prevalence rates of Alzheimer's disease derived from our model. For example, the prevalence rates at ages 65, 75, and 85 years were 0.9%, 4.2%, and 14.7%, respectively. Fig. 2 also shows the age-specific prevalence rates by stage of disease, from which one can calculate the percentage of cases with late-stage disease. For example, the model predicts that the percentage of 65-year-old cases with late-stage disease is 34%, with an increase to 45% among 85-year-old cases. Overall, we estimate that about 11.6 million (43%) of the 26.6 million worldwide cases living today have late-stage disease (Table 1). Fig. 3 shows the growth in 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 in six scenarios. Prevention programs that could delay onset by 1 or 2 years correspond to relative risks (i.e., the multipliers of the transition probability) of 0.88 and 0.77, respectively. Therapeutic treatment interventions that delay disease progression by 1 and 2 years correspond to relative risks of 0.85 and 0.75, respectively. Table 2 shows the effects that such

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 America and 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

\* Regions defined according to the United Nations Population Division [4]. Oceania includes Australia, New Zealand, Melanesia, Micronesia, and Polynesia.

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 the worldwide prevalence of Alzheimer's disease by 22.8 million cases (scenario A). Even a modest 1-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, in 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 the disease, and nearly all of that decline is attributable to decreases in the number of cases with late-stage disease.

The sensitivity of our results was evaluated with respect

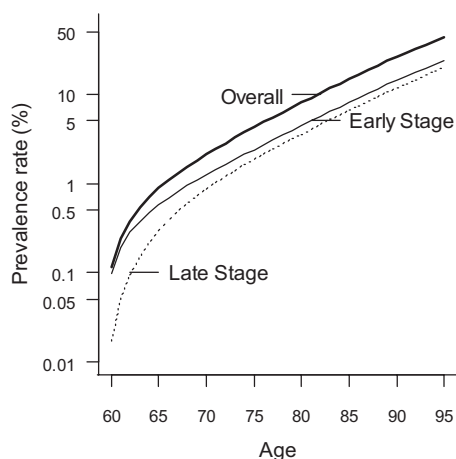


Fig. 2. Age-specific prevalence rates for Alzheimer's disease derived from multistate model.

to a number of model assumptions. Equation 1 assumes that the age-specific incidence rate continues to grow exponentially, even at the oldest ages. However, if incidence rates plateau and remain constant after age 90 years instead of continuing to rise 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.

The sensitivity of our results to background death rates was also examined. Surprisingly, when background mortality rates were inflated by 20%, the absolute age-specific prevalence rates in Fig. 2 decreased very slightly, at most by 3 per 1,000. Surprisingly, the model for age-specific prevalence rates is not sensitive to background mortality rates. This is because 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 the 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

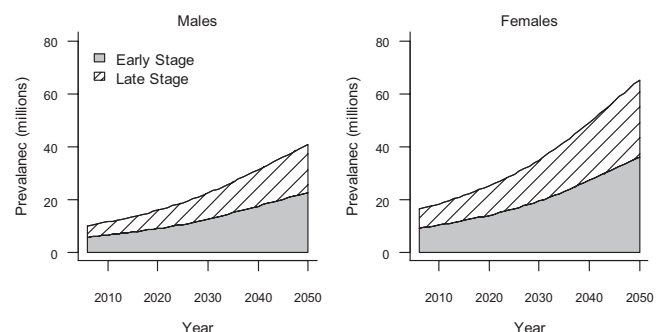


Fig. 3. Worldwide projections of Alzheimer's prevalence (in millions) for the years 2006–2050, by stage of disease: (a) males and (b) females.

Table 2  
Impact of interventions on worldwide prevalence of Alzheimer's disease\*

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

\* Change in prevalence in 2050 is associated with interventions begun in 2010, compared with baseline scenario of no intervention. These estimates refer to changes in prevalence compared with the baseline scenario of no intervention. In the baseline scenario of no intervention, in 2050 there will be 106.23 million cases worldwide, of which 58.75 million and 47.48 million will have early-stage and late-stage disease.

that excess mortality from Alzheimer's disease occurred only during late-stage disease. If excess mortality also occurs during early-stage disease, expressed here, for the sake of argument, as half the excess of that in late-stage disease (i.e., we added  $k/2$  to the background death rates in early-stage disease), 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-stage to late-stage disease. If the average duration of early-stage disease was in fact longer than the 6 years we assumed, then the percentage of prevalent cases with 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 prevalences 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.

#### 4. Discussion

Our model indicates that 26.6 million persons worldwide are currently living with Alzheimer's disease (range, 11.4–59.4 million). 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 that there were 24.3 million persons with dementia in the world, using a Delphi consensus

methodology [2]. Wimo et al. [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 refer specifically to Alzheimer's disease rather than all dementias. Thus, our estimates of the global prevalence of Alzheimer's disease are higher than those suggested by either the Alzheimer's Disease International Study [2] or Wimo et al. [12]. On the other hand, our results are lower than those suggested by a recent report that 5.1 million Americans are living with Alzheimer's disease [13]. That estimate [13] was based principally on a single study of Alzheimer's incidence in one community, while our results are based on a systematic review of published Alzheimer's disease incidence rates throughout the world.

There are important sources of uncertainty in our results, and the ranges of uncertainty are wide. The main sources of uncertainty are the age-specific incidence rates of Alzheimer's disease, which are reflected in the wide ranges of our forecasts. The data were insufficient to obtain separate incidence rates for each geographic region; 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 variations in Alzheimer's incidence rates result from real differences in underlying incidence or from differences in methodology and diagnostic criteria of the epidemiological studies. The wide ranges of 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* increase in Alzheimer's disease, i.e., a quadrupling in prevalence by 2050, is reasonably precise, even if the absolute number of cases is more uncertain. Indeed, we conclude that the prevalence of Alzheimer's disease 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 United Nations demographic projections of the aging of the world population. An advantage of the modeling methodology used here is that the effects of interventions may be evaluated. We find that the impact of interventions depends on whether the interventions delay the onset of disease, or delay the progression of disease, or a combination of both. Interventions can differentially affect stage-specific prevalence, depending on which stage of the disease's 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 reduction of the global burden of disease. In related work, Sloane et al. [14] 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.

The resources needed to care for an Alzheimer's patient depend on stage of disease. Adult daycare programs may be adequate in the early stages, while a high level of care, equivalent to that in nursing homes, will be needed in the late stages. Assessments of the global burden of disease should account for disease stage. We recognize that there is no single staging system that is accurate, reproducible, and routinely used worldwide. Nevertheless, we believe that the two-stage model of disease progression, as used here, produces useful estimates of the numbers of patients requiring a high level of care roughly equivalent to that provided by a healthcare facility such as a nursing home. In epidemiological surveys, the percentage of cases with severe disease ranged from 2% to >50% [15–17]. Such wide variation could result either from differences in survey methodology and diagnostic criteria, or from sampling enrollment biases. Our modeling approach produces estimates at the upper end of the range. As more information becomes available about disease progression rates, the multistate model could be used with updated input parameters for the transition probabilities. Ultimately, the model could be extended to allow for three states, using the Clinical Dementia Rating Scale to define the states.

A website that allows users to input their own transition probabilities and population data, and then implements the multistate model to obtain forecasts of the global burden of Alzheimer's disease, is available from the authors [18].

As the world's population ages, we will face a looming epidemic of Alzheimer's disease. Healthcare systems will be challenged to meet the needs of patients and their caregivers. The worldwide costs will be huge [19]. The prevention of Alzheimer's disease is an ambition [1,20] 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 the onset and progression of Alzheimer's disease, can significantly reduce the global burden of the disease.

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