[The public health impact of Alzheimer's disease, 2000-2050: Potential implication of treatment advances](#)

By: Philip D. Sloane, Sheryl Zimmerman, Chirayath Suchindran, Peter Reed, Lily Wang, Malaz Boustani, and [S. Sudha](#)

Abstract:

Recent developments in basic research suggest that therapeutic breakthroughs may occur in Alzheimer's disease treatment over the coming decades. To model the potential magnitude and nature of the effect of these advances, historical data from congestive heart failure and Parkinson's disease were used. Projections indicate that therapies which delay disease onset will markedly reduce overall disease prevalence, whereas therapies to treat existing disease will alter the proportion of cases that are mild as opposed to moderate/severe. The public health impact of such changes would likely involve both the amount and type of health services needed. Particularly likely to arise are new forms of outpatient services, such as disease-specific clinics and centers. None of our models predicts less than a threefold rise in the total number of persons with Alzheimer's disease between 2000 and 2050. Therefore, Alzheimer's care is likely to remain a major public health problem during the coming decades.

Keywords: public health impact | Alzheimer's disease | Alzheimer's care

Article:

INTRODUCTION

Alzheimer's disease (AD) is a chronic neurodegenerative disease characterized by progressive deterioration of cognitive function. It begins insidiously, with early signs including patchy memory loss and subtle behavioral changes. The illness gradually progresses until, often after a decade or more, the individual is unable to speak or comprehend language, no longer controls his or her bowels, and requires assistance with all aspects of personal care. Persons in the later stages of the illness are often placed in nursing homes, which have become increasingly populated by older persons with cognitive impairment. Since AD predominantly affects older persons, one

outcome of the graying of America during the coming decades is likely to be a tidal wave of persons with AD.

What will be the effect on public health of AD during the coming decades? How many people will have the disease in the future, and what will be their service needs? This paper addresses these questions empirically by presenting and discussing several future scenarios of AD prevalence in the United States between 2000 and 2050. Two of these scenarios have already been published—resulting in high (12) and low (46) estimates of prevalence derived by applying current disease patterns to future population projections. Such projections are likely to be inaccurate, however, because recent developments in AD research suggest that one or more therapeutic breakthroughs is likely in the coming decades (26, 32, 38). Therefore, to project the impact of potential advances in therapy, this paper applies estimates based on historical data from two chronic diseases for which management has changed markedly during the past five decades: congestive heart failure and Parkinson's disease. In this manner, we discuss a fuller range of possibilities facing the public health system, toward the goal of better informing public debate on the needs and priorities of health care for the elderly over the coming decades.

ALZHEIMER'S DISEASE TODAY

Etiology and Clinical Course

The specific cause of AD is unknown, and it may well be a multifactorial syndrome rather than a single disease (41). Age and family history of the disease in a first-degree relative are the strongest epidemiological risk factors for AD. Persons age 85 and older have 14 times the incidence of AD compared with persons age 65 to 69 (16A), and the relative risk of AD for those with at least one first-degree relative with dementia is 3.5 (95% CI 2.6 to 4.6) (46A). Other putative risk factors include head trauma, education level, number of siblings, non-suburban residence, maternal age at birth, hypothyroidism, and apolipoprotein E4 genotype (27A, 46A). In addition, between one and two percent of cases demonstrate an autosomal dominant genetic pattern with nearly complete penetrance (7). During the past decade a number of advances have been made in understanding the biochemical nature of the disease. Current thinking is that several biochemical mechanisms may contribute to neuronal degeneration, with final pathways involving both the cleavage of β amyloid precurser protein to form β amyloid (a major component of senile plaques), and abnormal processing and accumulation of tau protein (a major component of neurofibrillary tangles) (38, 41). In addition, small and large vessel cerebrovascular disease can cause dementia syndromes that often are difficult to distinguish from, and can occur concurrently with, AD (7).

The disease can be characterized by three phases: a prolonged preclinical phase, in which subtle signs are detectable but the diagnosis cannot be established; a mild symptomatic period, where patients suffer memory loss, impaired judgment, and decreasing ability to carry out everyday activities such as shopping, cooking, and grooming [stage 1 on the Clinical Dementia Rating Scale (CDR) (22)]; and a moderate/severe period, in which patients require 24-hour supervision and are increasingly impaired in basic functional areas such as locomotion, speech, ability to maintain continence, feeding, and hydration (23, 33). Figure 1 provides a schematic overview of the course of AD; this schema can be applied to most chronic diseases. The rate of progression of

untreated cases of AD varies among individuals. On average, about one quarter of people progress each year from mild (CDR stage 1) to moderate disease (CDR stage 2) (9, 25). In addition, multiple longitudinal studies have identified an average annual decline of 3.5 points on Mini-Mental State Examination (a 30-point scale) and 7–9 points on the Alzheimer's Disease Assessment Scale (a 70-point scale) (43).

preclinical -[a]-> mild disease -[b]-> advanced disease -[c]-> death

[a]Incidence rate, [b]rate of progression from early disease to advanced disease, [c]mortality rate

Figure 1. General model of the course of Alzheimer's disease and other chronic diseases.

Current and Projected Prevalence

Obtaining accurate assessment of the current and projected prevalence of AD is a challenge because there is no definitive diagnostic test and because many of its signs and symptoms are shared by several other forms of cognitive decline and dementia. Other factors that contribute to the difficulty of determining the prevalence of AD include the absence of a formal reporting system for diagnosed cases and misrepresentation of disease prevalence due to unrecognized cases. Therefore, existing prevalence rates vary widely.

A conservative (low) estimate for the current and future prevalence of AD was provided by the U.S. General Accounting Office (GAO) (46). Based on a meta-analysis integrating estimates from 18 studies of Alzheimer's disease prevalence, the GAO published age-specific, five-year prevalence rates for all cases and moderate/severe AD. A more liberal (high) estimate of the current and future prevalence of AD was provided by Evans et al. (12). They estimated prevalence by age, in ten-year intervals, based on a community study of 3623 adults over age 65 in East Boston, MA. While the study provided age-specific rates for Alzheimer's disease, stage-specific rates were provided only for cognitive impairment. Therefore, we estimated stage-specific rates by applying the cognitive impairment staging ratios to the number of estimated cases of AD. This calculation was based on an assumption that, although there are more cases of cognitive impairment than AD, the relative proportions of cases at various disease stages would be equivalent.

These methods estimated that there were between 2.17 and 4.78 million cases of AD in the United States in 2000, of which between 44 (12) and 57 (46) percent had moderate or severe disease. To calculate the possible range of the total number of AD cases over the next 50 years, assuming no significant change in disease epidemiology, we applied both the liberal and conservative rates to the middle series Census estimates for age-specific populations (45). Table 1 displays these projections. They indicate that, if no scientific advances alter the incidence and progression of AD, between 7.98 and 12.95 million people in the United States will be suffering from the illness by the year 2050, a fourfold increase from the current prevalence.

TABLE 1. Three estimates of the prevalence of Alzheimer's disease, by stage, United States, 2000–2050*

	Stage	2000	2005	2010	2015	2020	2025	2030	2035	2040	2045	2050
GAO[a]	Mild	0.93	1.03	1.13	1.26	1.41	1.63	1.93	2.28	2.66	2.99	3.26
	Moderate/severe	1.24	1.38	1.53	1.71	1.94	2.23	2.63	3.13	3.69	4.25	4.72
	All	2.17	2.41	2.67	2.97	3.35	3.86	4.55	5.41	6.35	7.24	7.98
UNC[b]	Mild	0.93	1.21	1.14	1.53	1.55	1.87	2.10	2.56	3.00	3.45	3.75
	Moderate/severe	1.24	1.49	2.00	2.05	2.54	2.83	3.44	4.07	4.88	5.68	6.46
	All	2.17	2.70	3.14	3.58	4.09	4.70	5.54	6.63	7.88	9.12	10.21
Evans[c]	Mild	2.69	2.83	3.10	3.58	4.16	4.83	5.44	5.85	6.13	6.37	6.65
	Moderate/severe	2.08	2.25	2.51	2.86	3.23	3.70	4.24	4.81	5.33	5.85	6.29
	All	4.78	5.07	5.61	6.43	7.39	8.53	9.68	10.66	11.46	12.22	12.95

*Millions of cases.
[a] Source: Reference (46).
[b] Based on applying estimated rates of transition across stages of the disease to U.S. Census projections. See text for details.
[c] Source: Reference (12, pp. 283–399).

Current Public Health Impact

The clinical symptoms of AD are not limited to memory loss and other cognitive deficits but extend to a wide spectrum of noncognitive secondary features, such as impaired activities of daily living, depression, and challenging behavioral disturbances. Assessment of overall disease impact on quality of life is challenging, but over the last few years several self-report, proxy-report and observational tools have been developed and linked to health outcomes. For example, one proxy-based rating system that assesses behavioral engagement (participation in activities) and subjective states (affective expression) shows increasing decline with dementia severity (1). Another instrument, which evaluates physical condition, mood, interpersonal relationships, ability to participate in meaningful activities, and financial situation, has been associated with depressive symptoms and functional dependence (24A). Given the impact of the disease on function and quality of life, it is not surprising that persons with AD utilize health services at higher rates and experience more accidents and falls than age-matched controls. As their independence continues to decrease, persons with the disease place an increasing physical, psychological, and financial burden on family caregivers. As a result, they are frequently placed in residential care/assisted living facilities, nursing homes, and geropsychiatric hospitals.

There are as many different estimates of the total cost of AD care as there are estimates of disease prevalence. One mid-range estimate, excluding costs of morbidity, premature death, and lost employment income, is $38,000 per patient per year, amounting to $65 billion nationally (1995 dollars), although estimates as much as 50 percent lower and 50 percent higher have been proposed (11). Over time, these costs will increase proportionate to the increase in the total size of the AD population and the proportionate distribution of mild and moderate/severe cases.

Regardless of disease severity, most of the burden of caring for individuals with AD is shouldered by informal caregivers, with unpaid caregiver time constituting one half to two thirds of the total cost of care (11). The average family caregiver spends 16.1 hours per week providing care, with increasing burden as the disease progresses. Thus, the average time spent providing care is 5.9 hours per week for individuals with no impairments in activities in daily living and rises to as much as 35.2 hours per week for those with severe limitations (28).

The largest increase in the cost of care occurs when individuals are institutionalized (11, 17). Nursing home placement is a notable milestone in the progression of AD because it proxies for severe disability and imposes a huge financial burden on our health system. In 1994, the cost to Medicaid of nursing home care for persons with AD is estimated to have exceeded $8 billion. Largely due to the costs of care in nursing homes and other residential long-term care settings, the total cost of caring for persons with severe AD is 2.25 times higher than for patients with mild or moderate disease (21).

Effectiveness of Current Treatment

Until recently, treatment of AD has been entirely supportive. Management has consisted of provision of a safe, "prosthetic" environment, education and support of family caregivers, assistance with daily activities and personal care, and management of behavioral problems using nonpharmacological strategies and psychoactive drugs. Although these treatment strategies remain the mainstay of AD management today (1A), drugs are increasingly being used not just for problem behaviors but also to retard the disease progression. Current pharmacological treatment involves one of four strategies:

- enhancing levels of the brain transmitter acetylcholine by administering cholinesterase inhibitors,
- reducing inflammatory responses that accompany brain injury through the use of nonsteroidal agents such as aspirin or ibuprofen,
- enhancing putative protective factors through strategies such as vitamin E supplementation, and
- treating concomitant cardiovascular risk factors, especially hypertension.

Recent pharmacological advances have been largely limited to the development of cholinesterase inhibitors. Four drugs of this type having been approved by the U.S. Food and Drug Administration during the past decade: tacrine, donepezil, rivastigmine, and galantamine. Numerous randomized clinical trials with thousands of patients have demonstrated small to moderate effects of these agents on cognitive, global, and physical functioning among patients who respond favorably and do not have intolerable side effects (2, 3, 4, 35, 37, 44, 47). As many as two thirds of patients fail to respond, however (26). Furthermore, it is unclear whether cholinesterase inhibitors exert only temporary effects on the course of AD, causing patients to improve at best to levels observed six to nine months earlier, or slow long-range progression as well (24).

Other agents for which randomized controlled trials have indicated a possible effect on the course of AD include gingko biloba (31) and vitamin E (38). In addition, the treatment of hypertension has been demonstrated to reduce the incidence of dementia in placebo-controlled trials (13). Although this finding may be largely due to an effect on vascular dementia, AD and vascular dementia coexist often enough to lead to significant treatment interaction effects.

In summary, the current treatment options for AD offer modest but significant benefits for those who already suffer from the disease. Use of cholinesterase inhibitors and vitamin E, treatment of

hypertension, and possibly the use of non-steroidal antiinflammatory agents and gingko biloba may have a stabilizing effect on cognitive and global function of patients with mild to moderate disease and may delay their transition from the community to an institutional setting. Unfortunately, effects are modest, and therefore the public health impact of these treatment advances has been minimal. Recent breakthroughs in basic research suggest, however, that new medications may be introduced during the coming decades that will have an extensive effect on the prevalence and course of AD, which will then result in significant changes in the public health needs of this patient population.

THE LIKELIHOOD OF THERAPEUTIC ADVANCES

The past decade has seen impressive advances in basic research on the etiology of AD, and these advances are likely to lead to more effective treatments in the future. Perhaps the most promising breakthrough has been the elucidation of the biochemical pathways that lead to β-amyloid deposition. Increasingly, amyloid appears to be a central factor in the events leading to neuronal damage in AD. Four autosomal dominant forms of early-onset AD disease have been characterized, each of which involves a defect in some aspect of amyloid metabolism. One is on chromosome 21, where the locus for β-amyloid precurser protein (APP) is located (42). Two are on chromosomes 14 and 1; they involve mutations of presenilin 1 and 2—genes that appear to normally inhibit amyloid formation. The other is on chromosome 12 and involves a mutation on the gene for an α2-macroglobulin that mediates clearance and degradation of β-amyloid (5). Furthermore, the only genetic locus universally accepted to be an important risk factor for late-onset AD, apolipoprotein E on chromosome 19, also appears to be involved in the amyloid pathway, although the mechanism is not yet clear (38). In the late 1990s, two research teams began to zero in on the structure of β-secretase, the enzyme that controls the final step in amyloid production (cleavage of APP to form β-amyloid), and drug companies are already developing compounds that block its activity (32). Similar, less well-developed lines of research involve the tau protein, the key component of neurofibrillary tangles; the tau protein has recently been linked to multiple loci on chromosome 17 that are associated with hereditary frontotemporal dementias (14, 16, 20).

A final area of recent progress is in the development of vaccines. Using a transgenetic mouse model that overexpresses mutant human APP, investigators have demonstrated that immunization with a peptide found in amyloid plaques leads to an effective antibody response. In young mice, immunization prevented the development of β-amyloid formation; in older animals, treatment markedly reduced the progression of neuropathology (29, 40). Another promising line of research involves the use of oral vaccines to generate autoantibodies against the N-methyl-D-aspartate receptor, thereby blocking a key pathway leading to neuronal injury in neurodegenerative diseases (10).

These and other recent discoveries make it increasingly likely that useful treatments will be generated in the years to come (38). In the subsequent sections we provide projections, based on historical data from other treatments for chronic diseases, of the effect that drug development may have on the prevalence and public health needs of persons with AD over the next half-century.

HOW THERAPEUTIC ADVANCES MAY ALTER DISEASE PREVALENCE THROUGH 2050

To model the potential impact of therapeutic advances on the demography of AD during the next 50 years, we applied data based on the observed results of new, effective treatments on the natural history of congestive heart failure (CHF) and Parkinson's disease (PD) over the past half-century. These diseases were chosen as models because they are chronic diseases that commonly affect older persons and lead to gradual, progressive functional decline, and they have both seen significant advances in treatment during the past decades.

Congestive heart failure provides a model of effective delay in the onset of disease. In the 1950s, the mean age of disease onset was 57.3 years; by the 1980s, it was 76.4 years (19). Preventive strategies that have contributed to this change include treatment of hypertension, lower dietary fat intake, and prevention of rheumatic fever. In addition, medications have been developed that slowed the progression of CHF in randomized trials; however, because these new therapies have been associated with adverse effects, comorbid conditions, poor diffusion into common medical practice, noncompliance, and high costs, the prognosis of CHF in the general population has not been altered by these new therapies (8).

Parkinson's disease provides a model of new therapies that slow disease progression. The disease is described in five stages, which had a mean duration ranging from 2 to 5 years in 1949–1954 (18). Subsequently, the introduction of levodopa and other agents, such as selegiline and bromocriptine, has doubled the length of time that patients spend in each stage (34).

Methods

DEVELOPMENT OF UNC ESTIMATES OF DISEASE PREVALENCE, 2000–2050

We estimated the number of individuals in the United States with mild or moderate/severe AD over the next 50 years by using a multistage projection model (30). This method requires the knowledge of a base year population in various stages of AD and age-specific rates of (*a*) disease incidence, (*b*) transition from mild to moderate/severe disease, (*c*) mortality rates for the general population, and (*d*) stage-specific mortality rates for persons with the disease. Our projections considered the U. S. Bureau of Census's middle series estimate of the 2000 U.S. population as the baseline population. We used the prevalence rates of the disease estimated by the GAO (46) to allocate the year 2000 population into various stages of the disease (none, mild, or moderate/severe). Staging by the GAO, and therefore in these analyses as well, was based on the CDR scale, with mild dementia corresponding to CDR stage 1 and moderate/severe dementia corresponding to CDR stages 2 and 3 (22).

Following Brookmeyer et al. (6), we assumed that the age-specific rate of onset of AD increases exponentially with age. Our analyses further assumed that the number of people under age 60 with the disease was negligible, and therefore we modeled disease incidence starting at that age. Specifically, the incidence rate at age greater than 60 is

$$\text{onset incidence rate} = 0.001278 e^{.142(age-60)} \qquad\qquad 1.$$

We assumed the incidence rate at age 60 is 0.001278, which is slightly higher than that of Brookmeyer et al. (6); this change was made so that our number of new cases would be more consistent with the GAO estimates. The age-specific incidence rate of onset was set as constant after age 95, and the incidence rate for transition from mild to moderate/severe was set at a constant of 0.28 for all ages; this value is reasonable under the expectation that on average a person will remain in a mild state for four years (9, 25). The age-specific mortality rates from a disease-free stage were assumed to be the same as for the middle series population projection by the Bureau of Census. Finally, mortality rates were considered to be 10 and 20 percent higher than that of a disease-free state for those who have mild or moderate/severe disease, respectively.

To make the task of projection simple the baseline population was grouped into five-year age groups, with the highest age at 110. These age groupings permitted projections in steps of five years (i.e., 2005, 2010, 2015, … 2050). The age-specific incidence rates and mortality rates were assumed to be constant within a five-year age group. The first step in the projection was to convert the single-year incidence rates into a five-year transition matrix. The elements of the five-year transition matrix provided the probability that an individual in a specified state (e.g., normal) at the beginning of the period would be in a specified state (normal, mild, moderate/severe, or dead) at the end of five years. A simple matrix conversion formula was used to convert the incidence matrix into a five-year transition matrix (30). These transition matrices were applied to the population in various stages of the disease at the beginning of a year to obtain the population in the next five-year age class five years later. Repeated applications of the age specific transition rates were used to carry the projection further into the future.
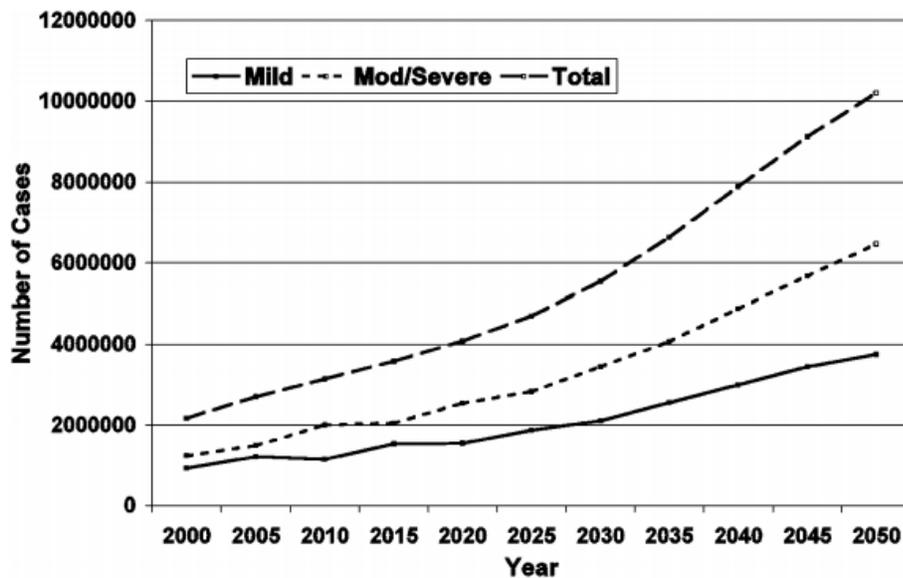

Figure 2. UNC projections of the prevalence of mild, moderate/severe, and total cases of Alzheimer's disease, United States, 2005–2050, assuming no significant change in treatment effectiveness over the next 50 years. Note that the projected total number of cases is projected to more than quadruple between 2000 and 2050, and that the majority of cases will be in the moderate or severe stages throughout that period.

Baseline projections provided estimates of the prevalence of disease, in five-year intervals, by stage and overall. These estimates are provided in Table 1 and displayed graphically in Figure 2 (as the UNC projections); the table compares these results with the GAO report and with the projections of Evans et al. (12). In this baseline projection, the age-specific incidence rates of onset based on the modified Brookmeyer formula remained the same for the years 2000 to 2050. The transition rate from mild to moderate/severe was set at 0.28 for all ages throughout the projection. The age-specific mortality rates were also assumed to be the same as described above.

PROJECTING THE IMPACT OF DRUG DEVELOPMENT ON DISEASE PREVALENCE AND STAGING

We developed modified projections based on three scenarios: delayed disease onset (CHF model), reduced rate of progression (PD model), and combined delayed onset/reduced progression (CHF/PD). Each represented projections based on one or more breakthroughs in therapy being introduced into the general population in 2010.

- The delayed disease onset model projects the impact of effective preventive strategies to delay the age of onset of Alzheimer's disease. Data from the Framingham study indicated that the age of onset of CHF was delayed by 19 years between the 1950s and the 1980s; some of this delay represents aging of the population and some represents true treatment effects (19). Because of the older average age of onset of AD and the incorporation of population aging into our initial projections (Table 1), we assumed that a corresponding breakthrough would be one that increased the median age at disease onset by 6.7 years. This assumption was implemented by altering the rate of increase in the incidence rates in Equation 1 from 0.142 to 0.109, beginning in 2010. All other incidence rates remained the same as in the baseline projections.
- The delayed disease progression model projects the impact of effective treatment strategies that reduce the rate of disease progression. PD patients are severely disabled by stage 3 of the disease, which roughly corresponds in functional status to moderate/severe AD (18); the introduction of levadopa and other agents halved the rate of progression across each of the earlier stages (34). Correspondingly, we modeled a decrease in the rate of transition from mild to moderate/severe AD from 0.28 to 0.10. All other incidence rates remained the same as in the baseline projection.
- The combined model simultaneously applies both delayed onset and reduced progression.

For each model, estimates were generated by a five-year interval of the number of persons aged 65 and older in the U.S. population with mild and moderate/severe AD.

Results

Table 2 displays the projected prevalence of AD based on the three models of treatment advances introduced in 2010. Figures 3, 4, 5 and 6 provide graphic representation of these results.

TABLE 2. Prevalence of Alzheimer's disease, 2005–2050: projections based on three models of the effects of significant treatment advances introduced in 2010

	Delayed disease onset model			Slowed disease progression model			Combined model		
	Number of cases (millions)			Number of cases (millions)			Number of cases (millions)		
Year	Total	Mild	Moderate/ severe	Total	Mild	Moderate/ severe	Total	Mild	Moderate/ severe
2005	2.70	1.21	1.49	2.70	1.21	1.49	2.70	1.21	1.49
2010	3.14	1.14	2.00	3.14	1.14	2.00	3.14	1.14	2.00
2015	2.76	0.56	2.20	3.59	2.05	1.54	2.76	1.26	1.49
2020	2.78	1.09	1.68	4.11	2.49	1.62	2.81	1.50	1.31
2025	3.11	0.96	2.15	4.75	2.89	1.86	3.13	1.78	1.35
2030	3.62	1.34	2.27	5.60	3.39	2.21	3.66	2.11	1.55
2035	4.29	1.44	2.85	6.70	4.04	2.66	4.33	2.49	1.84
2040	5.01	1.75	3.27	7.97	4.78	3.19	5.07	2.89	2.18
2045	5.71	1.91	3.79	9.23	5.49	3.74	5.77	3.27	2.51
2050	6.31	2.10	4.21	10.33	6.08	4.25	6.39	3.58	2.81

Compared with the UNC baseline predictions (Figure 2), the delayed disease onset model projects 35.6 percent fewer cases of Alzheimer's disease by 2050. In this model, a reduction in disease incidence after 2010 leads to a temporary drop in new cases, but within less than two decades the total number of cases is again rising rapidly, owing largely to increases in the numbers of persons over age 85. Of cases projected in this model to be present in 2050, the vast majority (66.7%) are in the moderate or late stages. These trends are graphically displayed in Figure 3.
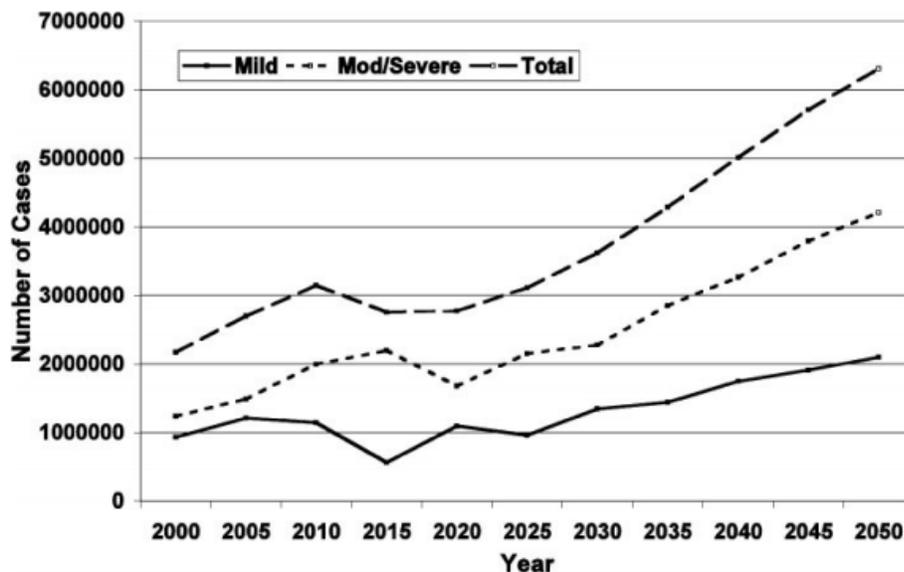

Figure 3. Projected prevalence of mild, moderate/severe, and total cases of Alzheimer's disease, United States, 2005–2050, assuming that a significant breakthrough is introduced into the general population in 2010 that delays disease onset by an average of 6.7 years. An example of such a breakthrough would be the introduction of a vaccine that reduces the rate of accumulation of amyloid in the brain. Note that the overall number of cases would be temporarily reduced but would begin rising by 2025 owing to increases in the elderly population, so that the projected number of cases in 2050 is approximately three times the current number. Also note that moderate/severe disease would constitute the majority of cases.

In contrast, the slowed disease progression model projects a slight increase (1.2%) in the number of cases in 2050, when compared with our baseline predictions. This lack of effect on overall prevalence arises because medications that slow disease progression would not reduce disease incidence; instead, they would result in a higher proportion of patients (58.9%) having mild disease, where the mortality rate is lower. This is displayed graphically in Figure 4.
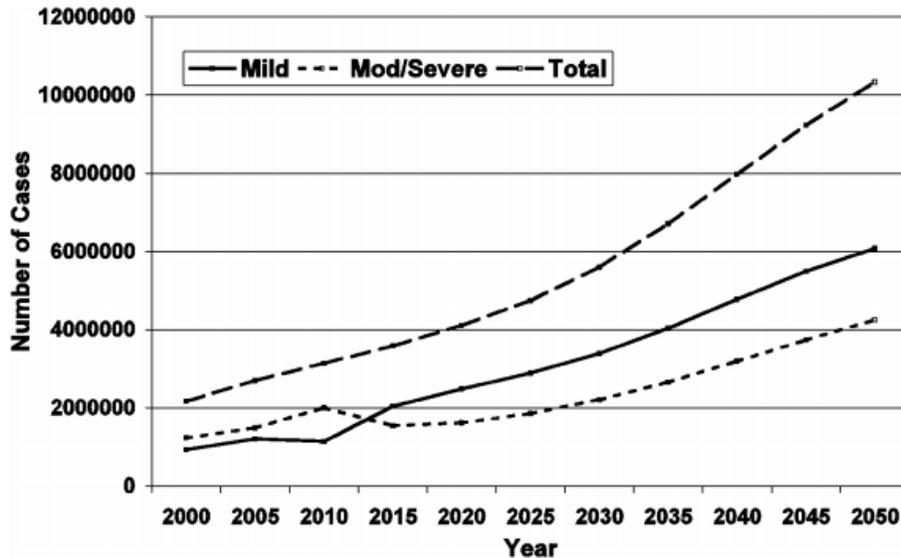

Figure 4. Projected prevalence of mild, moderate/severe, and total cases of Alzheimer's disease, United States, 2005–2050, assuming that a significant breakthrough in treatment is introduced into the general population in 2010 that reduces the rate of progression of mild (CDR 1) to moderate/severe (CDR 2 or 3) disease from 28% to 10% per year. An example of such a breakthrough would be introduction of one or more drugs that blocked the activity of the enzyme β-secretase, thereby reducing the rate of accumulation of amyloid in the brain. Note that such treatment would increase the proportion of mild cases and decrease the proportion of moderate/severe cases while not altering the overall number of cases of the disease.

The combined model projects a similar reduction to the delayed onset model (37.4%), since a similar magnitude reduction in incidence rates has been projected. However, because disease progression is also slowed, mild cases predominate (56%). The projected number and distribution of cases in this model are graphically represented in Figure 5.

Figure 6 displays the baseline model and the three projections on a single scale, allowing for comparison of the projected total number of AD patients and the relative proportions of mild and moderate/severe cases across the four models.
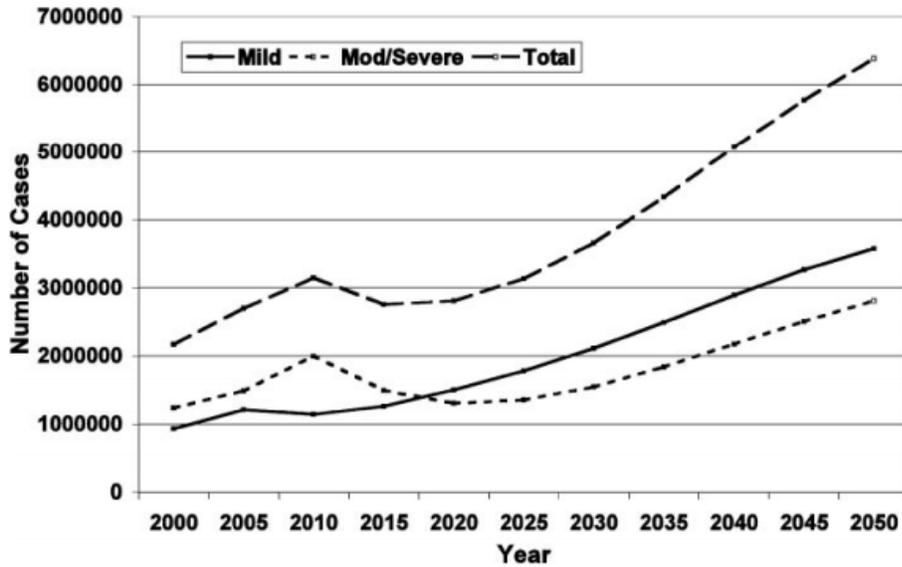
Figure 5. Projected prevalence of mild, moderate/severe, and total cases of Alzheimer's disease, 2005–2050, assuming that in 2010 significant breakthroughs are introduced to delay both disease onset and disease progression. Note that the total number of cases is reduced (as in Figure 2) and that mild cases begin to predominate (as in Figure 3). However, due to growth of the elderly population, the total number of cases is projected to triple during the time period.
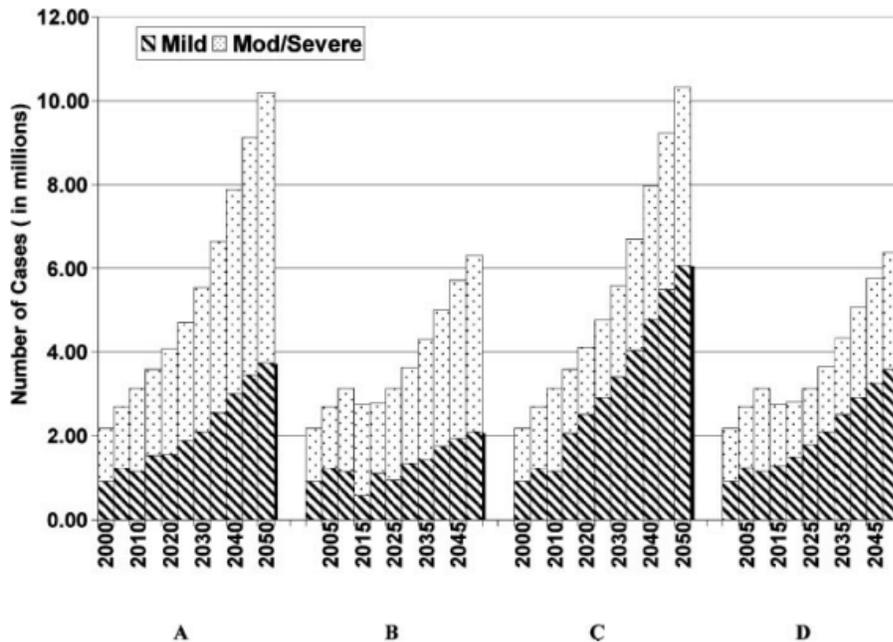

Figure 6. Bar graph comparing the prevalence of mild, moderate/severe, and total cases of Alzheimer's disease in the United States, 2000–2050, based on four projections: no therapeutic advances (A), delayed disease onset (B), delayed disease progression (C), and both delayed disease onset and delayed disease progression (D).

IMPLICATIONS ON FUTURE HEALTH SERVICE NEEDS AND COSTS

The estimated number of persons in the U.S. who will have AD in 2050 varies widely. This paper developed estimates that are mid-range between the GAO report (46) and the projections of Evans et al. (12). Our model projects that, if no major therapeutic advances occur, 10.2 million persons will have the disease in 2050, of which 3.8 million (37%) will have mild disease and 6.5 million (63%) will have moderate/severe disease. This is a projected increase of 8 million persons with AD over the next half-century, and it represents a more than fourfold increase in the burden of care. The public health impact of this increase would be immense, because of both the absolute increase in numbers and the fact that most cases would have moderate/severe disease and therefore be candidates for institutionalization. At present, the public sector finances only a small proportion of Alzheimer's care (12.5% for community care and 34% for institutional care); however, the roles and responsibilities of the public and private sectors would need to be reassessed in light of this explosive increase in the need for care (36).

It is unlikely, however, that no scientific advances will occur. Already, cholinesterase inhibitors can delay disease progression by six to nine months, and greater advances in treatment are highly probable. For this reason, we developed three alternative scenarios (Table 2 and Figures 3, 4, 5 and 6), in which we used historical data from treatment for other chronic diseases to model the potential impact of treatment innovations over the next half-century.

If a successful method of delaying the onset of AD were introduced in 2010 (Figure 3), and if treatment compliance and effectiveness were similar to that witnessed for congestive heart failure, the overall projected number of people with AD will be reduced by 38 percent by 2050, becoming 6.31 million, of which 2.10 million (33%) will be mild and 4.21 million (67%) will have moderate/severe disease (Figure 6). The overall burden on the private and public health system would still increase threefold over current estimates; however, the reduction in numbers of persons with the disease would be significant. To put this in an economic perspective, using an estimated cost of $47,000/patient/year (1990 dollars), Brookmeyer et al. estimated that a mere six-month delay in disease onset would save nearly $18 billion annually after 50 years (6). Care systems would not be likely to change under this scenario, however, because the majority of care would remain directed at persons with moderate and advanced disease. Thus, the long-term care industry would require major expansion, and long-term care quality and financing would be major public health issues. Current innovations, such as certain models in assisted living (48) and the activities of the Pioneer Network to transform institutional culture (27), suggest directions that the long-term care industry may take to better serve this growing population of persons with moderate and severe Alzheimer's disease.

Alternately, if successful treatments to slow disease progression became readily available by 2010 (Figure 4), and assuming that compliance, toxicity, and effectiveness were similar to those of levodopa for Parkinson's disease, then 10.33 million elderly will have AD by 2050 (virtually the same as if there was no change in treatment), but the preponderance of persons with the disease will be mild cases (59%) (Figure 6). This would result in a shift away from institutional care, as has already been modestly demonstrated among patients treated with cholinesterase inhibitors (24). The net effect would be to increase the burden on families by requiring additional years of caregiving. Although many families may want to prolong the time that their relative is able to live at home and, therefore, willingly sacrifice time and energy toward this end, additional outpatient support services would likely be needed. Furthermore, these new treatments

would be costly and require medical monitoring. As a result, this scenario would give rise to whole new service modalities, such as outpatient clinics devoted to Alzheimer's care, expanded dementia day programs and respite care services, and perhaps multipurpose Alzheimer's centers or malls.

The most promising model is one that involves both delayed onset and retarded disease progression (Figure 5). In this model the total number of cases is similar to that for prevention (6.39 compared to 6.31 million), but the majority of cases (56%) are mild. Although the proportionate distribution is skewed toward mild cases, the absolute number of mild cases projected in 2050 is similar to the number had there been no treatment (3.58 compared to 3.75 million with no treatment), whereas the number of moderate/severe cases is markedly less (2.81 compared to 6.46 million). This model would result in continued growth in our systems of care, but that growth would be largely in outpatient services. Long-term care would grow only modestly, as the number of persons with moderate/severe dementia in 2050 would only be twice the current number—not the nearly fourfold rise projected by the no treatment model. Nonetheless, these reductions would allow these same individuals more time to become ill and/or disabled by other costly conditions, such as osteoporosis, osteoarthritis, macular degeneration, heart disease, cancer, and stroke. It is plausible, therefore, that savings in the care required for AD may be less than the costs required to care for other conditions, and that treatment may actually result in societal dissavings (11). On the other hand, the emotional costs of AD may far outweigh the suffering caused by these other conditions, resulting in an overall reduction in the human costs associated with chronic illness.

As the nation enters the twenty-first century, the projected increase in AD will need to be paralleled by efforts to assure the availability and quality of care for persons with the disease. As this chapter outlines, new treatments are likely to occur, altering the epidemiology of the disease and resulting in altered service needs. Such changes in disease patterns could occur over relatively few years (Figures 3, 4 and 5), so health system responses would need to be rapid in order to meet changing demand. To prepare for these changes, research and planning should address such issues as surveillance and monitoring for the disease, dissemination of new therapies into common practice, the impact of the illness on quality of life, and new models of home, office-based, community-based, and institutional care. Quality-of-life measures developed specifically for AD, in consort with established measures of caregiver burden, will help track the personal impact of the disease and provide direction for future public health efforts.

In conclusion, even if major treatment breakthroughs occur, the management of AD will undoubtedly be a major and growing public health issue during the first half of the twenty-first century. However, the absolute number and the pattern of service needs will vary markedly depending on the timing and the type of treatments that evolve. Also noteworthy is the fact that new treatments would alter disease patterns within a few years after their introduction (Figures 4, 5 and 6). Thus, our health care system will need to be prepared to rapidly develop new service delivery models. Currently, the focus is on reforming long-term care; as shown here, it is likely that major innovations in outpatient services will be needed as well.

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