United States General Accounting Office

GAO

Report to the Secretary of Health and Human Services

January 1998

ALZHEIMER'S DISEASE

Estimates of Prevalence in the United States

GAO/HEHS-98-16

GAO

United States
General Accounting Office
Washington, D.C. 20548

Health, Education, and
Human Services Division

B-277607

January 28, 1998

The Honorable Donna Shalala
Secretary of Health and Human Services

Dear Madame Secretary:

Alzheimer's disease (AD) is a neurological disease, devastating to patients and their families and friends. It is expected to cost this country billions of dollars annually, with severe consequences to patients and informal caregivers as well as to the health care system.[1] Valid estimates of disease prevalence—that is, how many people have a disease at a given time—as well as projections of prevalence in the future, can play an important role in setting health research priorities and in identifying the need for services. A number of published studies have cited AD prevalence rates that range from 2 percent to 12 percent of the population older than 64.

Meta-analysis is an analytic method that can be used, as we do in this report, to (1) estimate the number of people with AD, (2) project the numbers of people with AD in the near future, and (3) determine the prevalence rates of AD for both men and women of specific ages. Meta-analysis uses existing studies to quantitatively integrate prevalence data. This approach uses data from all relevant studies to derive prevalence estimates that are not likely to be affected by the biases of any individual studies. Because of limitations associated with the estimates presented in this report, we also identify ongoing efforts by the National Institute on Aging (NIA) to develop more accurate prevalence estimates, including ones applicable to racial and ethnic minorities.

Our analysis was developed from 18 studies (see app. I) that (1) estimate prevalence rates for populations that are considered relevant to the United States and (2) use widely accepted diagnostic criteria for finding cases of AD (see app. II for a list of the criteria). Many of the studies we relied on are of European populations. The major limitation of the studies is that they include mainly whites and few members of the other racial groups that are part of the U.S. population, such as African-Americans and Asian-Americans. However, since whites currently represent a majority (about 83 percent of the population in 1997), we would not expect our results to change substantially if others were represented in proportion to their numbers.

[1]J. W. Hay and R. L. Ernst, "The Economic Costs of Alzheimer's Disease," American Journal of Public Health, Vol. 77 (1987), pp. 1169-75.

Using meta-analysis, we integrated the prevalence estimates in order to provide age- and gender-specific estimates of AD prevalence rates. We used the prevalence rates, in combination with population estimates and projections from the Bureau of the Census, to estimate (1) the number of Americans in 1995 with AD at any level of severity and those with moderate or severe AD and (2) the number of Americans likely to have the disease in the near future.

We also adjusted the overall AD prevalence estimates to account for two limitations of the age- and gender-specific rates presented in the literature. Specifically, we estimated the AD prevalence rates, over all ages and both genders, that would be obtained if all studies (1) counted cases of mixed dementia—persons with both AD and another kind of dementia—as cases of AD and (2) corrected the estimates, when necessary, for the expected number of cases missed by insufficiently sensitive screens.

At all stages of our work, we consulted with experts in the fields of AD, disease measurement, and the quantitative integration of research results, including experts at the National Institutes of Health (NIH). Details of our methods for (1) defining and locating the most relevant studies, (2) extracting prevalence rates from them, and (3) integrating these rates quantitatively are provided in appendixes III, IV, and V, respectively. Our evaluation of some of the strengths and limitations of the studies integrated is presented in appendix VI. Our adjustments to the data are described in appendix VII.

We conducted our study from May 1995 to December 1997 in accordance with generally accepted government auditing standards.

Results in Brief

Recognizing the limitations associated with such estimates, our meta-analysis shows that at least 1.9 million Americans 65 years of age or older suffered from any level of AD—mild, moderate, or severe—in 1995. This number would be closer to 2.1 million if we adjusted for the omissions, in many of these studies, of cases with mixed dementia and cases missed by the screening instruments used. Most of the estimated 1.9 million cases—58 percent, or 1.1 million—are among those in the 75-89 age group. When we calculated comparable projections of the number of cases in this age group based on the data from individual studies, the values ranged from about 700,000 to 3.2 million, with most studies yielding values of 1.4 million or less.

When only people likely to need at least some active assistance with personal care are considered (those with moderate or severe AD), the results of our meta-analysis show slightly more than 1 million people with AD over the age of 64. Here, too, the result would be higher—closer to 1.4 million people with AD—if all mixed cases and missed cases were included in all studies. Consistent with all earlier research, the results for both any AD and moderate or severe AD demonstrate that the prevalence rates increase sharply with age, doubling about every 5 years, at least until the age of 85, when the increase begins to slow. Also consistent with some earlier research, the estimated rates for women are higher than for men.

Projecting the number of people with AD into the future gives some indication of the long-term care and research challenges that will face this nation as people grow older. Our meta-analysis, when combined with Bureau of the Census projections, shows that more than 2.9 million people would have at least a mild case of AD in 2015; of these, more than 1.7 million would need active assistance in personal care. These figures jump to 3.2 million and 2.1 million, respectively, when mixed cases and missed cases are included.

Given the uncertainty surrounding existing estimates of AD, a number of studies are now underway, supported by NIA, that should yield better prevalence estimates of African-Americans, Hispanics, and other nonwhite subpopulations. The results of these studies, expected to be published over the next several years, should improve our picture of AD prevalence for the United States as a whole, as well as for the specific population segments studied.

Background

AD is a kind of dementia, with the essential feature the development of multiple cognitive deficits, including memory impairment, and at least one other deficit, such as impaired language functioning (aphasia). The definition of dementia also requires that the condition be severe enough to cause a significant impairment in social or occupational functioning that represents a decline from a previous level of functioning. Common clinical signs of dementia include emotional and behavioral disturbances.

AD is a dementia of gradual onset and progressive decline. It may be difficult to distinguish clinically between mild—that is, early—AD and normal aging, but severe AD is characterized by a need for much help with personal care as the result of incontinence and almost total lack of comprehension of the environment. AD is said to be differentiated from

other dementias on the basis of its cause, but that cause is not, in fact, well understood. That AD is accepted as a distinct disease entity is because AD patients manifest specific kinds of abnormalities in the brain—observable only in those who are autopsied or undergo a brain biopsy, a rare procedure—differing from the abnormalities found in other dementias with better understood causes.

Measuring the Extent of AD

The prevalence of AD is defined as the number of people in a specific population who suffer from the disease at some specified time. It is often expressed as a rate, the number of cases of that disease existing at a given point in time divided by the total population at that same time. When the number of cases in the target population is too costly to count, prevalence may be estimated by testing, in a prevalence survey, a representative sample of the population. An alternative is to develop a register of people seeking services, but this does not work well for AD because many cases are not treated.

The restriction of AD prevalence surveys to the elderly population, 65 years of age or older, makes sense because the majority of cases of AD are elderly. In addition, because AD prevalence tends to increase sharply with age, doubling about every 5 years, at least over the age range of 65 to 85 years, it is common to estimate age-specific prevalence rates of AD.[2] Thus, the population studied is divided into age groups—for example, 65 to 69 years, 70 to 74 years, 75 to 79 years—and a prevalence rate is estimated for each group. This is especially important when comparing AD rates across groups so that differences in prevalence stemming from differences in age distribution can be separated from those stemming from real health differences.

Although the dependence of AD rates on gender is not as well established in the scientific literature as dependence on age, there is some tendency for prevalence to be greater for women than for men; therefore, rates that are specific to both age and gender are of interest. The reasons for this tendency are not known. It may be that (1) women are more likely than men to contract the disease or (2) women live longer once they get AD and are therefore more likely to be counted when a prevalence survey is conducted or (3) both of these factors operate.

[2]R. Katzman and C. Kawas, "The Epidemiology of Dementia and Alzheimer Disease," in Alzheimer Disease, edited by R. D. Terry, R. Katzman, and K. L. Bick (New York: Raven, 1994).

Measuring the Severity of AD

When severity is measured, people with AD are categorized into degrees or levels of illness; thus, for every specific prevalence rate, several categories are used to describe the different levels of severity. For the dementias (including AD), descriptive categories like mild, moderate, and severe are commonly used to indicate how severe a person's AD is. Sometimes a borderline category, "questionable," is used for those whose impairment is not great enough to qualify as even mild AD. Today, there are standardized systems for rating severity, often using such descriptive categories. According to one system, the Clinical Dementia Rating (CDR), a person with mild AD needs only prompting in personal care activities, a person with moderate AD needs some assistance, and a person with severe AD needs much assistance and is frequently incontinent.[3]

Estimated Number of People With AD

The results of our meta-analysis, based on the pooling of the data of individuals from each of the studies, were used to project the numbers of Americans, in 1995, with (1) AD of any level of severity (mild, moderate, or severe) and (2) moderate or severe AD (see table 1). The AD prevalence estimates are generated by multiplying prevalence rates (discussed in the section below called "Estimated Prevalence Rates") by the corresponding age- and gender-specific 1995 estimates from the Bureau of the Census.[4] When these results are summed over the several age intervals and both genders, the overall estimate for Americans 65 years of age or older with any AD is 1.9 million. Of these 1.9 million cases, an estimated 1.1 million have moderate or severe AD.

[3]See, for example, L. Berg, "Mild Senile Dementia of the Alzheimer Type: Diagnostic Criteria and Natural History," The Mount Sinai Journal of Medicine, Vol. 55 (Jan. 1988), pp. 87-96.

[4]U.S. Bureau of the Census, Statistical Abstract of the United States: 1996, 116th ed. (Washington, D.C.: 1996).

Table 1: Estimates of Any AD and Moderate or Severe AD for Americans 65 Years of Age or Older in 1995

	Any AD		Moderate or severe AD	
Age	**Number**	**Percent**	**Number**	**Percent**
65-69	104,785	1.1	61,815	0.6
70-74	194,716	2.2	111,111	1.3
75-79	304,399	4.6	169,549	2.5
80-84	411,363	9.2	227,757	5.1
85-89	412,764	17.8	232,726	10.0
90-94	312,509	31.5	185,516	18.7
95+	166,287	52.5	110,595	34.9
Total	**1,906,822**	**5.7**	**1,099,069**	**3.3**

Source: Our integration of prevalence rates from 18 studies in the literature and the U.S. Bureau of the Census population estimates in Statistical Abstract of the United States: 1996 (Washington, D.C.: 1996).

To see how this overall prevalence estimate compares with the projections that would be derived from individual studies, we calculated comparable estimates when it was possible to do so. Most of the people with AD—58 percent, or 1.1 million—fall between the ages of 75 and 89. Within this age group, it was possible to project from 9 of the 15 studies dealing with any AD and provide age- and gender-specific estimates for the population based on each study. Two of the studies yield estimates below 1 million. Six fall between 1.1 million and 1.4 million; one (the East Boston study) provides the basis for an estimate of 3.2 million. (For further detail, see app. VIII.)

These numbers correspond to overall percentages for Americans 65 years of age or older of 5.7 and 3.3 with any AD and with moderate or severe AD, respectively. When adjusted for the cases of mixed dementia and missed cases not included in some of the studies, these percentages become 6.3 and 4.1, respectively. As noted, individual studies of the AD prevalence rate have produced varied estimates of the percentage of elderly with any AD, ranging from less than 2 percent to 12 percent.

Projections for Numbers of People With AD

We also developed projections into the next century of the number of AD cases and the number of AD cases requiring assistance. We derived these results from the prevalence rates, which we used in conjunction with age- and gender-specific population projections from the Bureau of the Census. These projections, which take the aging of the U.S. population into

account, are presented in 5-year intervals until 2015.[5] As shown in table 2, based on the Bureau's middle series of population projections, the numbers of cases of AD are expected to increase approximately 12 percent every 5 years.[6] When adjusted to include all mixed cases and missed cases, the numbers in this table increase by 10 percent and 24 percent for any AD and moderate or severe AD, respectively. These adjustments yield, for example, in 2015, 3.2 million cases for any AD and 2.1 million cases for moderate or severe AD.

Table 2: Projected Estimates of Any AD and Moderate or Severe AD for Americans 65 Years of Age or Older, 1995-2015

	Any AD		Moderate or severe AD	
Year	Number	% change[a]	Number	% change[a]
1995	1,906,822	[b]	1,099,069	[b]
2000	2,141,772	+12	1,233,932	+12
2005	2,370,615	+24	1,365,085	+24
2010	2,605,231	+37	1,500,727	+37
2015	2,872,420	+51	1,656,046	+51

[a]All percentage changes are relative to the baseline number for 1995.

[b]Zero by definition.

Source: The figures for 1995 are estimates based on the integration of the literature (taken from table 1). The figures for the other years are projections based on the estimates and the Bureau of the Census middle series of population projections (P-25, No. 1130).

Because prevalence is partially determined by the length of time people with AD survive, improvements in AD care will tend to increase future prevalence, just as any general improvements in human longevity will.[7] Thus, significant unanticipated improvements in the longevity of either the elderly in general or people with AD in particular may lead to even greater numbers of people with AD in the future.

[5]See, for example, D. A. Evans and others, "The Impact of Alzheimer's Disease in the United States Population," in The Oldest Old, edited by R. M. Suzman, D. P. Willis, and K. G. Manton (New York: Oxford University Press, 1992), pp. 283-99.

[6]This series is defined by the assumptions of (1) a continuation of present fertility trends, (2) a gradual increase in life expectancy to 82.0 years in 2050, and (3) a constant net immigration of 820,000 persons per year.

[7]A. B. Graves and W. A. Kukull, "The Epidemiology of Dementia," in Handbook of Dementing Illnesses, edited by J. C. Morris (New York: Dekker, 1994), pp. 23-69.

Estimated Prevalence Rates

We developed age- and gender-specific prevalence rates based on our meta-analysis, stopping at the age of 95, when the data become sparse for both any AD and moderate or severe AD (see tables 3 and 4).[8] Our first step in generating these estimates was to take severity of disease into account by excluding any data presented in the 18 published studies that included persons with questionable AD. Even with this exclusion, the estimates of AD prevalence for a given combination of age and gender that we obtained from the 18 studies varied greatly. (See app. II for a list of the studies.) For example, the estimated prevalence for men in the age interval from 85 to 95 ranged from 12 percent to 54 percent (see app. IV). Before attempting to integrate these data, we took severity of disease further into account by dealing separately with the three studies—numbers 1, 5, and 18 (see table IV.1)—that excluded mild cases.

Table 3: AD Prevalence Rates for Men and Women Ages 65-95, All Severity Levels

	Men		Women	
Age	Rate[a]	95-percent confidence interval[b]	Rate	95-percent confidence interval[b]
65	0.6%	0.6, 0.7	0.8%	0.7, 0.9
70	1.3	1.2, 1.5	1.7	1.5, 1.9
75	2.7	2.5, 3.0	3.5	3.2, 3.8
80	5.6	5.2, 6.0	7.1	6.7, 7.5
85	11.1	10.3, 11.9	13.8	13.2, 14.5
90	20.8	19.2, 22.4	25.2	24.0, 26.5
95	35.6	32.9, 38.3	41.5	39.3, 43.8

[a]The rates were estimated by logistic regression model.

[b]The 95-percent confidence interval is a pair of values between which the true rate is likely to fall 95 percent of the time.

[8]These estimates were needed to generate the estimated numbers and projections discussed in the two previous sections.

Table 4: AD Prevalence Rates for Men and Women Ages 65-95, Moderate or Severe Cases

	Men		Women	
Age	Rate[a]	95-percent confidence interval[b]	Rate[a]	95-percent confidence interval[b]
65	0.3%	0.2, 0.4	0.6%	0.4, 0.8
70	0.6	0.4, 0.8	1.1	0.9, 1.5
75	1.1	0.8, 1.5	2.3	1.8, 2.8
80	2.3	1.7, 3.0	4.4	3.8, 5.3
85	4.4	3.3, 5.9	8.6	7.2, 10.2
90	8.5	6.3, 11.5	15.8	12.8, 19.5
95	15.8	11.2, 21.8	27.4	21.4, 34.5

[a]The rates were estimated by logistic regression model.

[b]The 95-percent confidence interval is a pair of values between which the true rate is likely to fall 95 percent of the time.

In our first integration of these data, the results of our meta-analysis show prevalence rates for any AD in the 15 studies that do not exclude mild cases. (See table 3.) These results tend to differ only slightly from estimates presented in previous articles reviewing AD prevalence. These rates are each increased by 10 percent when all mixed cases and missed cases are included.

These results demonstrate that the AD prevalence rate increases sharply with age, doubling about every 5 years at least until about the age of 85, as expected from previous reports of this relationship. In addition, the rate is greater for women than for men.

In our second integration of these data, we included only studies that provided number of cases with moderate or severe AD. These studies either excluded mild cases (the three studies mentioned earlier) or enabled us to exclude mild cases by presenting the data for these cases separately (numbers 6 and 13). When only cases with moderate or severe AD are counted, the rates are lower. But the increase in prevalence with age and the higher rates for women are observed at the moderate and severe levels too. These rates are each increased by 24 percent when all cases of mixed dementia and missed cases are included.

Two of the studies allow for the counting of only the cases with severe AD. When this is done, the resulting rates are still lower, as logic would dictate,

but the margins of error are so large that we do not present these results for severe AD.

NIA's Ongoing Studies

NIA is currently supporting a number of studies of AD prevalence in the United States. Many of these studies include minority groups in addition to whites. For example, one such study looks at prevalence among African-Americans, Hispanics, and whites in a neighborhood of New York City. The results of these studies are expected to be published within the next several years. When they are, our knowledge about the extent of AD in the United States will be enhanced. Not only will our ability to estimate AD prevalence for the whole country improve but so will our ability to make such estimates for specific racial and ethnic populations. Projections for future numbers with AD will then be able to take into account the changing demographics of the country.

The implications of these findings lie in the specific results and projections presented. The number of people with AD is at least 1.9 million now and can, with relatively conservative assumptions about population growth, be expected to grow to at least 2.9 million by 2015. Depending on severity, these cases will need some kind of long-term care. Such care will also be required by people with other disabling diseases, both dementias and nondementias. However, the kinds of care needed by people with AD and other dementias differ, for both patients and their caregivers, from the kinds needed by the disabled without any dementia.

Agency Comments and Our Evaluation

Noting that the results of our meta-analysis of AD prevalence (about 2 million) are lower than those NIA uses (about 4 million), NIA found three methodological limitations in our study that it believes call into question its validity. First, NIA noted that only 3 of the 18 studies are of U.S. populations and questions whether our combining of U.S. and non-U.S. populations is warranted, given that the U.S. data tend to yield higher prevalence rates than do the non-U.S. data.

Second, NIA was concerned about variation in how some of the studies we reviewed applied diagnostic criteria. The agency was concerned that most of the questionable cases in the studies reviewed, which we did not include in our estimates, were actually mild cases of dementia. Further, NIA believes that many of the studies we relied on had insufficiently sensitive initial screens that led to their missing many mild cases of dementia. NIA was also concerned that in many of the studies reviewed,

only persons with pure AD were coded as cases of AD but not those persons with a mixed dementia, including AD as a component. Third, NIA commented that the meta-analytic method we used cannot compensate for the large differences in rates observed across studies.

Although we have made some adjustments to account for NIA's criticisms, we believe our methodology remains useful for estimating AD prevalence. First, with regard to the use of non-U.S. studies, we note that when severity is taken into account, the results of U.S. and non-U.S. studies are comparable when one of the U.S. studies is excluded. This study, the East Boston study, yields prevalence estimates that are far higher than any of the other studies, suggesting a disparity in methodology rather than in population characteristics.

As for NIA's criticisms related to diagnostic criteria, we recognize the utility of including cases of mixed dementia and of adjusting for insensitive screens; we have, therefore, included in this report estimates to reflect these adjustments. We disagree, however, with the idea that questionable cases should be included. Although such people may become demented, they do not at the time of the prevalence survey satisfy the accepted diagnostic criteria for dementia or AD.

Finally, we disagree with NIA's conclusion that meta-analysis is an inappropriate method because of the heterogeneity of the prevalence rates in the studies we reviewed. With severity accounted for, 17 of the 18 studies we reviewed reported relatively homogeneous rates, with one outlying study.

We also received a letter from the Alzheimer's Association expressing similar concerns about our methodology. The Alzheimer's Association is especially concerned about how forthcoming data from studies currently underway may change the picture of AD prevalence we present. Again, we acknowledge that NIA is supporting new and hopefully better studies of the extent of AD in the U.S. and that these should improve our understanding of how the disease is distributed in all the major subpopulations.

The full text of NIA's comments, along with our response, is included in appendix IX.

We will send copies of this report to the directors of the National Institutes of Health, the National Institute on Aging, and the Administration on

Aging. In addition, we will make copies available upon request to others who are interested.

If you or your staff have any questions about this report, please call me at (202) 512-7119 or Donald M. Keller, Evaluator-in-Charge, at (202) 512-2932. GAO staff acknowledgments are listed in appendix X.

Sincerely yours,

Bernice Steinhardt
Director of Health Services
Quality and Public Health

Contents

Tables

Abbreviations

AD	Alzheimer's disease
ADRDA	Alzheimer's Disease and Related Disorders Association
CDR	Clinical Dementia Rating
CT	computerized tomography
NIA	National Institute on Aging
NIH	National Institutes of Health
NINCDS	National Institute of Neurological and Communicative Disorders and Stroke

18 Studies We Reviewed

The following 18 studies are the AD prevalence studies we reviewed for this report; 3 other studies are supplementary sources, providing data and other information about one or more of the studies reviewed, as indicated. The studies reviewed are numbered for reference in table IV.1.

Sources for Studies Reviewed

1. Bachman, D.L., and others. "Prevalence of Dementia and Probable Senile Dementia of the Alzheimer Type in the Framingham Study." Neurology, Vol. 42 (1992), pp. 115-19.

2. Brayne, C., and P. Calloway. "An Epidemiological Study of Dementia in a Rural Population of Elderly Women." British Journal of Psychiatry, Vol. 155 (1989), pp. 214-19.

3. Canadian Study of Health and Aging Working Group. "Canadian Study of Health and Aging: Study Methods and Prevalence of Dementia." Canadian Medical Association Journal, Vol. 150 (1994), pp. 899-913.

4. Coria, F., and others. "Prevalence of Age-Associated Memory Impairment and Dementia in a Rural Community." Journal of Neurology, Neurosurgery, and Psychiatry, Vol. 56 (1993), pp. 973-76.

5. Corso, E.A., and others. "Prevalence of Moderate and Severe Alzheimer Dementia and Multi-Infarct Dementia in the Population of Southeastern Sicily." Italian Journal of Neurological Sciences, Vol. 13 (1992), pp. 215-19.

6. D'Alessandro, R., and others. "Dementia in Subjects Over 65 Years of Age in the Republic of San Marino." British Journal of Psychiatry, Vol. 153 (1988), pp. 182-86.

7. Evans, D.A., and others. "Prevalence of Alzheimer's Disease in a Community Population of Older Persons: Higher Than Previously Reported." Journal of the American Medical Association, Vol. 262 (1989), pp. 2551-56.

8. Fratiglioni, L., and others. "Prevalence of Alzheimer's Disease and Other Dementias in an Elderly Urban Population: Relationship with Age, Sex, and Education." Neurology, Vol. 41 (1991), pp. 1886-92.

9. Lobo, A., and others. "The Epidemiological Study of Dementia in Zaragoza, Spain." In Psychiatry: A World Perspective. Proceedings of the

VIII World Congress of Psychiatry, edited by C.N. Stefaniss, C.R. Soldators, and A.D. Rabavilas. Amsterdam: Elsevier, 1990, pp. 133-37.

10. Manubens, J.M., and others. "Prevalence of Alzheimer's Disease and Other Dementing Disorders in Pamplona, Spain." Neuroepidemiology, Vol. 14 (1995), pp. 155-64.

11. O'Connor, D.W., and others. "The Prevalence of Dementia as Measured by the Cambridge Mental Disorders of the Elderly Examination." Acta Psychiatrica Scandinavica, Vol. 79 (1989), pp. 190-98.

12. Ott, A., and others. "Prevalence of Alzheimer's Disease and Vascular Dementia: Association with Education. The Rotterdam Study." British Medical Journal, Vol. 310 (1995), pp. 970-73.

13. Pfeffer, R.I., A.A. Afifi, and J.M. Chance. "Prevalence of Alzheimer's Disease in a Retirement Community." American Journal of Epidemiology, Vol. 125 (1987), pp. 420-36.

14. Rocca, W.A., and others. "Prevalence of Clinically Diagnosed Alzheimer's Disease and Other Dementing Disorders: A Door-to-Door Survey in Appignano, Macerata Province, Italy." Neurology, Vol. 40 (1990), pp. 626-31.

15. Roelands, M., and others. "The Prevalence of Dementia in Belgium: A Population-Based Door-to-Door Survey in a Rural Community." Neuroepidemiology, Vol. 13 (1994), pp. 155-61.

16. Rorsman, B., O. Hagnell, and J. Lanke. "Prevalence and Incidence of Senile and Multi-Infarct Dementia in the Lundby Study: A Comparison Between the Time Periods 1947-1957 and 1957-1972." Neuropsychobiology, Vol. 15 (1986), pp. 122-29.

17. Skoog, I., and others. "A Population-Based Study of Dementia in 85-Year-Olds." New England Journal of Medicine, Vol. 328 (1993), pp. 153-58.

18. Sulkava, R., and others. "Prevalence of Severe Dementia in Finland." Neurology, Vol. 35 (1985), pp. 1025-29.

Supplementary Sources

Beckett, L.A., P.A. Scherr, and D.A. Evans. "Population Prevalence Estimates From Complex Samples." Journal of Clinical Epidemiology, Vol. 45 (1992), pp. 393-402. (Relevant to study 7.)

Ebly, E.M., and others. "Prevalence and Types of Dementia in the Very Old: Results from the Canadian Study of Health and Aging." Neurology, Vol. 44 (1994), pp. 1593-1600. (Relevant to study 3.)

Rocca, W.A., and others. "Frequency and Distribution of Alzheimer's Disease in Europe: A Collaborative Study of 1980-1990 Prevalence Findings." Annals of Neurology, Vol. 30 (1991), pp. 381-90. (Relevant to studies 2, 9, 11, 14, 16, and 18.)

Diagnostic Criteria for Probable and Possible Alzheimer's Disease

The source of the diagnostic criteria is G. McKhann and others, "Clinical Diagnosis of Alzheimer's Disease: Report of the NINCDS [National Institute of Neurological and Communicative Disorders and Stroke]—ADRDA [Alzheimer's Disease and Related Disorders Association] Work Group Under the Auspices of the Department of Health and Human Services Task Force on Alzheimer's Disease."[9]

Criteria for Diagnosis of Probable AD

The criteria for the clinical diagnosis of probable Alzheimer's disease (AD) include

- dementia established by clinical examination and documented by the Mini-Mental Test, Blessed Dementia Scale, or some similar examination and confirmed by neuropsychological tests;
- deficits in two or more areas of cognition;
- progressive worsening of memory and other cognitive functions;
- no disturbance of consciousness;
- onset between the ages of 40 and 90, most often after the age of 65; and
- absence of systemic disorders or other brain diseases that in and of themselves could account for the progressive deficits in memory and cognition.

The diagnosis of probable AD is supported by

- progressive deterioration of specific cognitive functions such as language (aphasia), motor skills (apraxia), and perception (agnosia);
- impaired activities of daily living and altered patterns of behavior;
- family history of similar disorders, particularly if confirmed neuropathologically; and
- laboratory results of normal lumbar puncture as evaluated by standard techniques; normal pattern of nonspecific changes in the electroencephalogram, such as increased slow-wave activity; and evidence of cerebral atrophy on computerized tomography (CT), with progression documented by serial observation.

Other clinical features consistent with the diagnosis of probable Alzheimer's disease, after exclusion of causes of dementia other than Alzheimer's disease, include

- plateaus in the course of progression of the illness;

[9]See Neurology, Vol. 34 (1984), pp. 939-44.

- associated symptoms of depression; insomnia; incontinence; delusion; illusions; hallucinations; catastrophic verbal, emotional, or physical outbursts; sexual disorders; and weight loss;
- other neurological abnormalities in some patients, especially with more advanced disease, and including motor signs such as increased muscle tone, myoclonus, or gait disorder;
- seizures in advanced disease; and
- CT normal for age.

Criteria that make the diagnosis of probable Alzheimer's disease uncertain or unlikely include

- sudden, apoplectic onset;
- focal neurological findings such as hemiparesis, sensory loss, visual field deficits, and lack of coordination early in the course of the illness; and
- seizures or walking disturbances at the onset or early in the course of the illness.

Criteria for Diagnosis of Possible AD

Clinical diagnosis of possible Alzheimer's disease

- may be made on the basis of the dementia syndrome, in the absence of other neurologic, psychiatric, or systemic disorders sufficient to cause dementia, and in the presence of variations in the onset, in the presentation, or in the clinical course;
- may be made in the presence of a second systemic or brain disorder sufficient to produce dementia, which is not considered to be the cause of the dementia; and
- should be used in research studies when a single, gradually progressive severe cognitive deficit is identified in the absence of other identifiable cause.

Defining and Locating the Most Relevant Studies

Defining Relevant Studies

We defined relevant studies as published studies of original research satisfying each of three inclusion criteria. The studies had to (1) include age- and gender-specific prevalence rates of AD (2) diagnosed by NINCDS-ADRDA (or equivalent) criteria (see app. II), along with the corresponding sample sizes, (3) from white (that is, European-American or European) populations.

Because the AD prevalence rate is known to vary by age and may vary by gender, overall rates for elderly people are likely to be sensitive to differences among populations in age and gender.[10] One way in which the AD prevalence rates from different populations can be validly compared is if the rates are specific to a particular combination of age and gender (for example, the rate for women between the ages of 70 and 74). Thus, we include only studies that present age- and gender-specific AD prevalence rates, along with the sample sizes needed to weight them in a quantitative integration.

The published studies presenting these rates include populations from North America, Europe, and Asia. These populations are typically small, often a neighborhood within a city or a small town, and none of them individually or in any combination can be assumed to be representative of the U.S. population. The white (that is, European-American and European) populations studied contain few participants not of European background. The best that can be done until a sufficiently large population representative of the United States is studied is to integrate the results from available studies, excluding those with AD prevalence rates that are likely to differ systematically from those of the majority white population of the United States.

Prevalence rates for AD from Asian countries tend to be lower than those observed in Europe and North America, although Asian-American rates are closer to those of the white population.[11] The reason for this difference is not known, but we decided that to be cautious in extracting prevalence rates, we would exclude the numerous studies of Asian and Asian-American populations. This leaves us with only studies of

[10]A. F. Jorm, The Epidemiology of Alzheimer's Disease and Related Disorders (London: Chapman and Hall, 1990), pp. 69-72.

[11]A. B. Graves and others, "Prevalence of Dementia and Its Subtypes in the Japanese American Population of King County, Washington State: The Kame Project," American Journal of Epidemiology, Vol. 144 (1996), pp. 760-71. Also see L. White and others, "Prevalence of Dementia in Older Japanese-American Men in Hawaii," Journal of the American Medical Association, Vol. 276 (1996), pp. 955-60.

populations not known to differ systematically from European-Americans with respect to AD prevalence.

If different diagnostic criteria are used to ascertain cases in various studies, then observed differences in AD prevalence may reflect the different criteria rather than true population differences in AD prevalence. Integrating only prevalence estimates with the same diagnostic criteria can reduce the effects of criteria as a source of differences among estimates. In order to minimize the possible role of differences in diagnostic criteria, we include only studies using the NINCDS-ADRDA criteria for probable AD (or for probable and possible AD—see app. II) or equivalent diagnostic criteria.[12]

Locating Studies

We used a systematic computer-assisted search of the medical and social science literature, supplemented by expert advice and references found in the literature, in order to locate published studies on AD prevalence that meet the inclusion criteria listed above. We found 18 studies meeting these criteria (see app. I).

[12]Given the difficulty of obtaining direct pathological evidence of AD in living patients, a clinical diagnosis can be made only when other potential causes of dementia have been ruled out. Even then it is called "probable"—not "definite"—AD. (A diagnosis of definite AD requires both evidence of AD pathology and satisfaction of the clinical criteria for probable AD.) When other potential causes have not been ruled out but appear unlikely to be the main cause of the dementia, it is called "possible" AD.

Extracting Prevalence Rates From Reviewed Studies

Using published results (in tables or graphs) from each of the studies, we recorded the age- and gender-specific AD prevalence rates for all reported age intervals with lower limits of 60 years or older. In most of the studies, the AD rates excluded all other kinds of dementia, but in four of them a number of cases of mixed dementia (cases diagnosed with AD and another dementia) were included. For each age interval reported, we recorded the midpoint. If the open-ended age interval "85 and older" was used, we considered it as extending to 95 and recorded the midpoint (90.5). We considered "90 and older" and "95 and older" as extending to 99. When prevalence rates were not given explicitly, we computed them from available data or read them from graphs. When differing estimates of the same rate were presented in different articles about the same study, we consulted an expert to determine the correct values.

The rates for analysis are listed in table IV.1, with each of the 18 studies numbered, as identified in appendix I. We refer to cases of mild, moderate, or severe AD as cases of "any AD." Some rating systems include other categories of severity. For example, "questionable dementia"—a category intermediate between "normal" and mild dementia—is used in the Clinical Dementia Rating (CDR) for people who are only slightly impaired and do not satisfy the NINCDS-ADRDA criteria for dementia. People in this intermediate category may or may not be counted as cases of dementia in different studies. We do not consider them to be cases of dementia, however.

Table IV.1: AD Prevalence Rates According to Age and Gender in 18 Studies We Reviewed

Study number, place, ethnicity of participants	Severity	Age	Men		Women	
			Sample	Rate	Sample	Rate
1. Framingham (U.S.A.), Italian-American	Moderate+	61-64	129	0.000	156	0.000
		65-69	284	0.352%	384	0.781%
		70-74	190	1.053	314	0.000
		75-79	128	0.781	207	2.899
		80-84	81	3.704	147	8.844
		85-93	41	7.317	119	15.126
2. East Cambridgeshire (U.K.), English	Mild+	70-74	0	[a]	185	1.622
		75-79	0	[a]	180	6.667
3. Canada, Canadian	Mild+	65-74	3,800	0.500	2,857	1.400
		75-84	1,691	5.500	2,654	7.800
		85-89	387	11.886	941	18.810

(continued)

Study number, place, ethnicity of participants	Severity	Age	Men		Women	
			Sample	Rate	Sample	Rate
		90-94	91	27.473	280	33.929
		95-99	16	56.250	88	39.773
4. Turegano (Spain), Spanish	Mild+	55-64	72	0.000	69	1.449
		65-74	51	0.000	55	3.636
		75-84	32	0.000	46	8.696
		85-94	10	10.000	14	7.143
		95-99	1	0.000	1	0.000
5. Ragusa (Italy), Italian	Moderate+	60-64	197	0.000	241	0.415
		65-69	219	0.457	259	1.158
		70-74	181	1.105	209	2.392
		75-95	225	2.222	269	6.320
6. San Marino, Italian	Mild, moderate, and severe	67	82	2.439	81	0.000
		72	72	0.000	64	3.125
		77	48	4.167	63	6.349
		82	21	0.000	29	10.345
		87	14	7.143	14	35.714
7. East Boston (U.S.A.), Italian-American	Mild+	65-69	506	1.433	747	3.232
		70-74	399	1.146	653	3.938
		75-79	243	22.210	417	7.533
		80-84	130	32.839	246	27.448
		85-95	104	40.502	178	46.545
8. Stockholm (Sweden), Swedish	Mild+	75-79	193	2.073	522	3.831
		80-84	153	4.575	463	4.536
		85-89	59	10.169	264	12.121
		90-99	27	3.704	129	19.380
9. Zaragoza (Spain), Spanish	Mild+	65-69	36	0.000	49	0.000
		70-79	79	2.532	99	3.030
		80-89	29	17.241	37	8.108
		90-99	1	0.000	3	33.333
10. Pamplona (Spain), Spanish	Mild+	72-74	71	1.408	75	0.000
		75-79	152	3.289	159	11.321
		80-84	152	5.921	150	13.333
		85-89	142	11.972	137	20.438

(continued)

Study number, place, ethnicity of participants	Severity	Age	Men		Women	
			Sample	Rate	Sample	Rate
		90-91	45	20.000	44	27.273
11. Cambridge (U.K.), English	Mild+	75-79	382	1.309	655	2.901
		80-84	290	8.276	496	8.065
		85-89	115	15.652	241	15.768
		90-94	22	40.909	85	24.706
12. Rotterdam (Holland), Dutch	Mild+	55-64	1,118	0.179	1,495	0.134
		65-74	1,116	0.806	1,447	1.037
		75-84	569	5.448	1,074	8.380
		85-95	136	25.000	573	27.225
13. Southern California (U.S.A.), European-American	Questionable, mild, moderate, and severe	65-69	64	3.125	58	0.000
		70-74	83	1.205	91	4.396
		75-79	102	15.686	88	9.091
		80-84	93	35.484	90	22.222
		85-95	80	53.750	68	51.471
14. Appignano (Italy), Italian	Mild+	60-69	173	0.578	186	0.538
		70-79	126	0.794	178	2.809
		80-89	43	6.977	65	12.308
		90-94	1	0.000	6	16.667
15. Heist-op-den-Berg, (Belgium), Belgian	Mild+	65-69	166	0.000	170	0.000
		70-74	192	1.563	164	2.439
		75-79	154	2.597	148	6.081
		80-84	118	9.322	123	9.756
		85-95	76	11.842	76	19.737
16. Lund (Sweden), Swedish	Mild+	60-69	191	0.000	177	0.565
		70-79	87	3.448	115	1.739
		80-89	21	9.524	43	11.628
17. Gothenburg (Sweden), Swedish	Mild+	85-85	143	11.888	351	13.390
18. Finland, Finnish	Moderate+	60-69	583	0.343	764	0.262
		70-74	208	2.404	346	2.601
		75-79	108	3.704	246	5.691
		80-89	83	7.229	[b]	[b]
		80-84	[b]	[b]	136	11.765
		85-89	[b]	[b]	41	21.951

(Table notes on next page)

Note: The study numbers are keyed to the list in appendix I.

[a]Rate undefined.

[b]In the presentation of these data, different age categories were used for men and women.

By our definition of AD, one of the 18 sets of prevalence rates—the set from the Southern California study (study 13)—does not qualify because it includes cases of questionable dementia. Therefore, we omitted these rates from further analysis. However, using the published reports of this study, it is possible to isolate the cases of AD at each of the severity levels—mild, moderate, or severe—for further analysis. We did this, and the resulting data are included in the analyses that follow.

We extracted not just the overall AD prevalence rates as indicated above but also, wherever possible, the rates according to each of three cumulative severity levels: (1) cases of mild or greater severity (any AD), (2) cases of moderate or severe AD, and (3) cases of severe AD. The mild or greater severity level would include all cases. The moderate or severe level would include only cases of moderate or severe dementia, and the severe level would include only the cases of severe dementia. For many of the studies, the data were presented in such a way that a breakdown of this kind was not possible.

For 13 of the 18 studies (2-4, 7-12, and 14-17), the only information available about severity for the age- and gender-specific AD prevalence rates is that all cases of mild or greater severity are included. Their prevalence rates correspond exactly to their overall rates, as listed in table IV.1. For three more of the studies (1, 5, and 18), the cases include only moderate or severe AD. Their prevalence rates also correspond exactly to their overall rates in table IV.1, but the prevalence rates represent the level of moderate or severe AD.

In the remaining two studies (6 and 13), age- and gender-specific AD prevalence rates are presented for different levels of severity. It is therefore possible to compute from these two studies, by the process of summation, the rates of each cumulative severity level: any AD, moderate or severe AD, and severe AD.

Integrating Prevalence Rates Quantitatively

To obtain relatively precise estimates, based on all the data for each level of severity, we quantitatively integrated the estimates. To integrate the data for a given level to arrive at estimates of age- and gender-specific prevalence, we used a method previously employed by Maria Corrada and her associates at Johns Hopkins University.[13] This method, which pools the data of individuals from each of the studies, involves fitting a logistic regression model to the data—age interval midpoints, gender, numbers of participants, numbers of cases, and levels of severity—from a series of relevant prevalence studies so as to estimate the age- and gender-specific prevalence rates for each level of severity.[14] Such a model implies that (1) AD prevalence at a given level is determined by age and gender and (2) the quantitative nature of the relationship is of the kind known to statisticians as logistic.

Logistic regression models are similar to the more commonly encountered linear regression models, but they are especially designed to analyze variables that take on only two values (variables that may be called binary or dichotomous). An example of such a variable is the presence or absence of disease in a person. The status of all people in a population with respect to this binary variable determines the prevalence rate for that population. Thus, logistic regression is an appropriate method for analyzing data for prevalence rate.

We applied the approach of Corrada and her colleagues. Our work differs from theirs both in that we were able to include some more recent studies than they were and in the way in which we took severity into account. The approach was applied to three sets of data. One set was composed of the age- and gender-specific AD prevalence rates from the 15 studies that include such rates for cases with any AD. The second set was composed of the rates from the five studies that include these rates for cases with moderate or severe AD. The third set was composed of the rates from the two studies that include these rates for cases with severe AD. The results of this application are presented in tables 3 and 4, which correspond to the first two sets of data. The results of the application to the third set are not presented because these results included relatively imprecise prevalence estimates. We did not extend our estimates beyond the age of 95 because of the few people in the study older than 95.

[13]M. Corrada, R. Brookmeyer, and C. Kawas, "Sources of Variability in Prevalence Rates of Alzheimer's Disease," International Journal of Epidemiology, Vol. 24 (1995), pp. 1000-5.

[14]For four of the studies, the number of cases had to be computed from the prevalence rates and the number of people in the sample, and for one study the number of people in the study had to be computed from the prevalence rates and the number of people with AD.

These results can be compared with other reviews of the AD literature. Most published reviews of the literature on AD prevalence rates are qualitative. These reviews have not been designed so as to obtain prevalence estimates through a systematic quantitative integration of the study data, such as that provided by meta-analysis. One representative qualitative review notes that rates are typically estimated at about 0.5 percent, 3 percent, and 10 percent for the ages of 65, 75, and 85, respectively, both genders combined.[15] The percentages from one of the few quantitative reviews—based on combining data from individual studies—were similar to those from the qualitative reviews.[16]

[15]M. M. B. Breteler and others, "Epidemiology of Alzheimer's Disease," Epidemiologic Reviews, Vol. 14 (1992), p. 76.

[16]K. Ritchie and others, "The Relationship Between Age and the Prevalence of Senile Dementia: A Meta-Analysis of Recent Data," International Journal of Epidemiology, Vol. 21 (1992), pp. 763-69.

Some Strengths and Limitations of the Studies We Reviewed

The strengths of the studies reviewed are that they include representative samples of well-defined populations we believed to be similar to the population of the United States with respect to AD prevalence and diagnosed by accepted diagnostic criteria for AD.

There are some limitations concerning how well the study populations can represent the population of interest, the residents of the United States. Although each sample represents a well-defined population and each population provides estimates of AD, the samples, taken individually or combined, are not representative of the U.S. population with respect to all likely determinants of the AD prevalence rate. Two of the possibly significant ways the study populations differ from the U.S. population are discussed here. In addition, the geographic difference must be acknowledged: most of the studies included in our analysis are based on European populations. We know of no argument, however, that the prevalence of AD for white Americans differs from that of Europeans.

None of the studies include significant amounts of data from major U.S. subpopulations, such as blacks (that is, African-Americans). It is not known whether blacks or other minorities (for example, Native Americans) have different prevalence rates than do whites and Europeans.[17] As indicated in appendix III, there is some evidence that Asian-American rates differ little from the rates of white populations, in spite of the racial similarity between Asian-Americans and Asians; Asian rates tend to be systematically lower than those for whites. If minorities do have different rates, it is desirable to know their rates for at least two reasons: (1) these rates affect the overall U.S. estimates and (2) the kinds of care these minorities require may differ, for cultural reasons, from the kinds required by other Americans. NIH supports research designed to compare the AD prevalence rates of different racial and ethnic groups.

Most of the studies include institutionalized people in the populations they survey, but two of the three U.S. studies do not. Logically, one might expect that since AD rates for the institutionalized are most likely higher than those for the noninstitutionalized (that is, community dwellers), omitting the institutionalized would lower prevalence estimates. There is little evidence from a previous analysis, however, that such omission has

[17]No conclusive information is available pertaining to this issue. One study does suggest that blacks have a higher prevalence of severe AD than whites. See B. S. Schoenberg, D. W. Anderson, and A. F. Haerer, "Severe Dementia: Prevalence and Clinical Features in a Biracial U.S. Population," Archives of Neurology, Vol. 42 (1985), pp. 740-43. Another, however, indicates that the AD rate for blacks differs little from typical rates from white populations. See H. C. Hendrie and others, "Prevalence of Alzheimer's Disease and Dementia in Two Communities: Nigerian Africans and African Americans," American Journal of Psychiatry, Vol. 152 (1995), pp. 1485-92.

any effect.[18] Further, the two U.S. studies that omit the institutionalized present prevalence estimates that are high relative to those from most of the other studies. It may be that too small a proportion of the elderly population is institutionalized for the assumed higher AD prevalence rate to have mattered much in these studies. Nevertheless, prevalence studies of AD should ideally include all elderly people, whether institutionalized or noninstitutionalized. We have no reason to conclude, however, that variation across studies in the handling of institutional status compromises the validity of the estimates to any significant extent.

[18]See Corrada, Brookmeyer, and Kawas, "Sources of Variability in Prevalence Rates of Alzheimer's Disease," pp. 1000-5.

Adjustments Based on Alternative Conventions

All prevalence studies are based on conventions that may be questioned. When a convention is judged to be inappropriate for a given purpose, it may lead to biased prevalence estimates. Our use of quantitative integration to generate estimates and projections is, in part, an attempt to get around some of the inappropriate conventions in individual studies by diluting them, if not by canceling them out.

Two common conventions, in particular, seem inappropriate for our purposes, although they were reasonable to those who adopted them in the 1980s and early 1990s, when most of the reviewed work was done. One is that people with mixed dementia (AD and another kind of dementia) should not be counted as AD cases. Most of the studies we reviewed have counted as cases of AD only people with "pure" AD, AD in the absence of other dementia. Although this convention was useful for isolating those with no known cause of dementia—those with AD only—it is illogical if one wants to know how many people have AD. A person with both AD and another dementia is logically a person with AD. If we drop the usual convention and instead treat all cases of AD the same, regardless of other dementias, we can then infer that the estimates presented are too low. This is because only four of the studies include mixed cases in the age- and gender-specific AD rates; therefore, our estimates, based on an integration of the published rates, underestimate the true rates of all AD cases.

Given the available data, it is not possible to derive, on the basis of our revised convention, age- and gender-specific estimates of the true rates of all AD. We can provide rough overall ones, however. Ten of the studies enable us to estimate the overall percentage increase in the number of AD cases that would be obtained if mixed cases are added. These estimates vary, with a median (middlemost) value of 20 percent. If none of the studies reviewed included mixed cases, then it would be reasonable to assume that this 20 percent is the adjustment factor needed to increase our estimates by taking into account the mixed cases. However, the 11 studies of mild or more severe dementia that do not include mixed cases in their AD counts also include only 29 percent of the participants in the studies of any AD; in addition, these 11 studies happen to use, on the average, relatively small samples. Thus, the value of 20 percent greater prevalence with mixed cases can only be applied to this 29 percent of the participants in the studies of any AD, yielding an overall percentage bias of 5.8 percent (20 percent times 29 percent).

The 20-percent adjustment for mixed cases can also be applied to 90 percent of the participants in studies of moderate or severe AD since this is the percentage of participants in studies of similar populations that exclude mixed cases from their AD counts. The resulting adjustment factor is 18 percent (20 percent times 90 percent). When this factor is applied to the estimates given above, the findings for 1995 are 2 million people with AD of any kind and 1.3 million cases of moderate or severe AD, rather than the 1.9 million and 1.1 million, respectively, that were originally reported.

The other common convention that now seems inappropriate is that prevalence counts are not corrected for the likely number of people with AD missed by initial screening tests (and therefore not given workups for dementia). In some of the studies we reviewed, we found a potential problem: Some AD cases were missed as a result of the use of insufficiently sensitive screens for which no corrections in the age- and gender-specific rates were made. When such a problem is likely, it is illogical to present prevalence rates without correcting the prevalence estimates for the expected number of people with AD missed by the screen. Because studies that do not avoid the problem of missed cases generate rates that are too low, our estimates, to the extent they are based on such studies, are underestimates of the true rates.

As with the adjustment for mixed cases, it is not possible to derive age- and gender-specific rates adjusted for missed cases, but a rough overall adjustment factor can be derived. Of the 15 studies we reviewed that investigated mild dementia, 5 can be identified as having a known or possible problem with missed cases.[19] Of these five studies, two present their overall percentage increases as a result of missed cases (although they do not correct the age- and gender-specific rates for these); the higher of these two increases is 7.2 percent. The correction rate undoubtedly varies with the specific screen used, but we adopted this 7.2 percent as a representative value. If all the studies we reviewed had a possible problem with missed cases, then it would be reasonable to assume that this 7.2 percent is the adjustment factor needed to increase our estimates so as to take into account the expected missed cases. The five studies known to have a possible problem with missed cases, however, use relatively large samples, including 50 percent of all participants in the studies of any AD. Thus, the value of 7.2 percent greater prevalence with missed cases can be applied only to the 50 percent of the participants in the studies of any AD,

[19]The others (1) are one-phase studies, including all elderly in the population without use of an initial screen, (2) use a sensitive screen so that no cases are missed at the prediagnostic phase, or (3) statistically correct for the expected rate of missed cases.

yielding an overall percentage bias of 3.6 percent (7.2 percent times 50 percent).

The 7.2-percent adjustment for missed cases can also be applied to 71 percent of the participants in studies of moderate or severe AD. This is because 71 percent is the percentage of the participants in studies of severe AD without correction to all or part of the data for missed cases. The resulting adjustment factor is 5.1 percent (7.2 percent times 71 percent). These adjustments for missed cases, when made in addition to the adjustment for mixed dementia that was already made, yield an increase of 10 percent in 1995, for an adjusted estimate of 2.1 million cases for any AD. The corresponding adjustment for moderate or severe AD is 24 percent, for a 1995 total of 1.4 million cases at these levels of severity.

Number of AD Cases for Persons 75 to 89 Years Old Based on Individual Studies and on the Meta-Analysis

Table VIII.1 facilitates the comparison of the individual studies reviewed in the meta-analysis of the prevalence of any AD. The basis of comparison is the age- and gender-specific numbers of cases of any AD projected for the U.S. population of 1995 aged 75 to 89 years. As explained in the report, only nine of the studies we reviewed provide the appropriate data; the meta-analysis is based on these 9 plus an additional 6, for a total of 15.

Table VIII.1: Millions of U.S. AD Cases as Projected From Individual Studies and From Meta-Analytic Results

	Study number									Meta-analytic
Group	**3**	**6**	**7**	**8**	**10**	**11**	**12**	**13**	**15**	**results**
Men 75-79	0.15	0.11	0.60	0.06	0.09	0.04	0.15	0.13	0.07	0.11
Men 80-84	0.09	0.00	0.53	0.07	0.09	0.13	0.09	0.14	0.15	0.13
Men 85-89	0.08	0.05	0.29	0.07	0.08	0.11	0.18	0.25	0.08	0.11
Women 75-79	0.31	0.25	0.30	0.15	0.45	0.11	0.33	0.09	0.24	0.20
Women 80-84	0.22	0.29	0.78	0.13	0.38	0.23	0.24	0.22	0.28	0.28
Women 85-89	0.30	0.58	0.75	0.20	0.33	0.26	0.44	0.45	0.32	0.30
Total	**1.16**	**1.28**	**3.25**	**0.68**	**1.43**	**0.88**	**1.42**	**1.28**	**1.14**	**1.13**

Note: The study numbers are keyed to the list in appendix I. Summations may not equal totals because of rounding.

Comments From the National Institute on Aging

Note: GAO comments supplementing those in the report text appear at the end of this appendix.

DEPARTMENT OF HEALTH & HUMAN SERVICES — Public Health Service

National Institutes of Health
Bethesda, Maryland 20892

JUN - 4 1997

Ms. Bernice Steinhardt
Director of Health Services Quality
and Public Health
U.S. General Accounting Office
Washington, DC 20548

Dear Ms. Steinhardt:

The National Institute on Aging (NIA) appreciates the opportunity to comment on the draft GAO report entitled *Alzheimer's Disease: Estimates of Prevalence in the United States* (Code 108317). The report addresses the important scientific and health policy issue of estimating the number of persons with Alzheimer's Disease (AD) in the United States. It also provides estimates and projections of AD that are substantially lower than those used by NIA and others. The GAO developed its estimates by integrating 18 selected studies (three involving U.S. populations and 15 with European populations). In contrast, the prevalence estimate used by NIA is based on United States data only.

Due to the important policy implications inherent in the GAO estimates and projections, we obtained input from other components of the National Institutes of Health and Department of Health and Human Services, and—with your permission—several reviewers outside of the Federal Government. It is the view of these parties, and of the NIA, that fundamental limitations of the methods used in the GAO report call into question the validity of these estimates of AD for the United States and reduce the report's usefulness for public policy.

We believe that the limitations of the GAO report fall into three categories: the selection of studies included in the analysis; the variations in diagnostic criteria and definitions of cases across the studies; and concerns with the appropriateness of using meta-analysis for data of this type. Each of these categories is described in greater detail in the enclosed comments.

Certainly, an accurate estimate of AD prevalence in the U.S. is important, but it is even more important that policy makers and public health officials improve their understanding of the differences in prevalence among populations in U.S. communities and in other countries. Over the past five years, NIA and other components of NIH have launched large studies in several communities, involving a variety of racial and ethnic populations, to develop improved estimates of AD prevalence, better understanding of differences among populations to provide clues as to risks for the disease, and to suggest protective factors. Data from these studies will begin to be reported over the next several months. The NIA will continue to support research targeted to these goals as well as to find the cause of AD, develop effective treatments to halt progression of the disease, and to prevent AD in future generations.

Sincerely,

Richard J. Hodes

Richard J. Hodes, M.D.
Director
National Institute on Aging

Enclosures

Now on p. 1.

Comments on the GAO Report:

ALZHEIMER'S DISEASE: Estimates of Prevalence in the United States

National Institute on Aging

Summary: This GAO report addresses the important scientific and health policy issue of estimating the number of persons with Alzheimer's disease (AD) in the United States. The report attempts to obtain a prevalence estimate "reflecting all the available data" and suggests that this estimate and related projections of future prevalence "can play important roles in setting health research priorities as well as in identifying the need for services" (page 2). The National Institute on Aging (NIA), in consultation with outside experts, has identified serious limitations in the methods used for the study and considers the findings to significantly underestimate the actual prevalence of Alzheimer's disease in the U.S. The NIA cautions against the uncritical use of the estimates provided in the GAO report for the purposes of health policy and research planning.

The estimates of AD prevalence in the GAO report are substantially lower than those used by the NIA and others. The estimate of 4 million persons with AD used by NIA is based on available U.S. data, and has provided a useful guide to set research priorities to better understand the causes of this devastating disease, and to identify effective ways to treat or prevent AD and related disorders. Several fundamental limitations of the methods used by the GAO call into question the validity of these GAO prevalence estimates of AD in the United States and reduce their usefulness as a guide for public policy.

Limitations of the Methods Used in this Report: The limitations of the GAO report fall into three categories: the selection of studies included in the analysis; the variations in diagnostic criteria and definitions of cases among studies; and concerns with the appropriateness of using a meta-analysis for data of this type. Each of these limitations poses major concerns, and taken together, call into serious question the findings of the GAO study. Several external reviewers were asked, with GAO permission, to review the draft report. A summary of their concerns is included in the following sections, and their comments are provided in their entirety as attachments.

See comment 1.

Selection of studies included in the GAO analysis: All but three of the 18 studies upon which this report is based are on populations outside of the United States. The appendices to the report describe the methods used to survey published studies, to apply various criteria, and to select the 18 studies used for this analysis. Although the report does not describe all studies surveyed or those rejected, it does state that it excludes U.S. studies focused on minority populations, such as Japanese Americans, because AD prevalence rates "are likely to differ systematically from those of the majority, European-American, populations of the United States." In contrast, the GAO analysis itself is comprised primarily of foreign studies, with the stated rationale that the populations in European studies are "not known to differ systematically from European Americans" with respect to AD prevalence. This conclusion is inconsistent with differences in reported prevalence across the studies. Moreover, the assumption of homogeneity among populations is further challenged by noting that, when the methods of the GAO study are used to calculate AD prevalence, using only the three U.S. studies (East Boston, Southern California, and Framingham, Massachusetts), the estimate of Alzheimer's cases in the U.S. is about 3,700,000 or 10.9 percent of those 65 years of age and older. This estimate is considerably higher than the 2 million persons calculated by the GAO report by averaging in 15 non-U.S. sites, including Ragusa and Appignano, Italy; Zaragoza and Pamplona, Spain; and Lund and Gothenburg, Sweden. It is quite likely that the differences in estimated prevalence resulted from differences in how AD diagnostic criteria are applied across studies in various countries (see appended reviews). It is also possible that prevalence rates differ in various countries. In either event, the difference between the AD prevalence rates reported in the three U.S. studies included in the GAO report and the prevalence rates of the 15 non-U.S. studies raises serious question about the GAO assumption that these 18 studies are appropriately used to draw conclusions about U.S. prevalence.

Variations in applying diagnostic criteria: One of the most serious problems with the estimates in this report is a failure to acknowledge fully the importance of identifying patients in all stages of the disease. The primary challenge in accurately estimating the prevalence of AD stems from the characteristics of the disease itself. AD develops gradually over an extended period, rather

See comment 2.

See comment 3.

See comment 4.

than occurring as an abrupt event. There is no single test to accurately diagnose the disease. The ability to identify mild or early cases is critical as we begin to identify interventions that slow or stop progression of the disease. Underestimation of mild or early cases of AD constitutes a public health concern, both for the accuracy of future projections, but more importantly for missed opportunities for early intervention to stop or slow disease progression. Several of the studies used in the GAO report used cut-off scores in initial screening tests that severely limited identification of mild cases. Moreover, persons scoring above these cutoffs were assumed not to be demented and were not tested further, despite evidence from other studies that a proportion of such persons would be determined to have dementia if they had received more detailed evaluation. These methodologies therefore increased the numbers of false negative cases. As research knowledge progresses, and screening and diagnostic strategies have become more sophisticated, the ability to identify mild cases accurately has improved. The GAO report explicitly excludes cases categorized as "questionable." It is now widely recognized that most of what were once called questionable cases are actually mild cases that will progress to moderate and severe dementia. The GAO report does not account for advances in diagnosis and resulting differences across studies, and thereby seriously underestimates the number of mild cases, which may represent up to 50 percent of cases in persons who are 65-84 years old.

Additionally, there are differences across studies in how coexisting medical conditions influence the diagnosis of AD. In many of these studies, only "pure" AD dementia was scored as AD, thus eliminating from the analysis cases in which AD occurred concurrently with other medical conditions contributing to dementia. However, recent studies of brain infarcts and AD indicate that the concomitant presence of infarcts in patients with the brain pathology of AD is a major contributor to the dementia symptoms experienced by these patients. Recent research has shown that failure to include patients with mixed causes of dementia in prevalence calculations results in underestimates of the prevalence of the disease, and a missed potential for prevention, where successful interventions are available.

See comment 5.

Limitations of meta-analysis for this purpose: There are fundamental limitations in the analytic method used by the GAO in deriving the estimates in this report. A statistical overview, or meta-analysis, is most useful in summarizing results from very similar studies, each of which is too small to provide a statistically precise answer by itself. Great caution is required in attempting to summarize the results of non-randomized, observational studies in such an analysis. It is difficult, if not impossible, for a meta-analysis to compensate for large differences across the studies it combines. For example, in the GAO analysis, a logistic method promoted by Corrada et al. was used. There are serious concerns as to the appropriateness of this model for combining data across heterogeneous studies. This approach considers neither the variability in the methods used to evaluate patients for a diagnosis of dementia nor the obvious variability in the populations under investigation. Several of the studies, for example, used in the GAO analysis excluded nursing home residents from the populations examined. The exclusion of nursing home residents from the study population would result in serious underestimation of prevalence because of the greater likelihood that nursing home residents have AD, especially in the older age categories.

Conclusion: Alzheimer's disease is devastating and costly, destroys the lives of those who have it, and disrupts the lives of those who care for them. The GAO report concurs with other studies that the prevalence of the disease doubles each five years over the age of 65. Accurate estimates of prevalence in the United States are important, but even more important is an improved understanding of the differences in prevalence among populations in United States communities and in other countries. The NIA continues to support research addressing these questions. Over the past five years, the NIA and other components of the National Institutes of Health have launched large studies in several communities, involving a variety of racial and ethnic populations. These studies are designed to develop improved U.S. estimates of AD prevalence, and to better understand differences among populations. These studies also will provide important clues to genetic and environmental risk factors for the disease, as well as to suggest potentially protective factors. This research draws upon improved screening and diagnostic strategies, and reporting of data from these studies will begin over the next several months. The

ultimate success of these approaches does not diminish, however, the very real concerns of patients who have Alzheimer's disease and their families, who urge us to find the cause of AD, to develop effective treatments to halt progression of the disease, and to prevent the disease in future generations. Both NIA and other components of the National Institutes of Health are committed to research that will continue to address both the human and scientific challenges of Alzheimer's disease.

The following are GAO's comments on NIA's June 4, 1997, letter.

GAO Comments

1. We disagree with NIA's comment about the countries in which the prevalence studies were conducted. Studies of European and other countries with predominantly white populations are legitimately used to arrive at prevalence rates characteristic of the white population in the United States. None of the populations studied, including those from the United States, is representative of the white U.S. population with respect to ethnic, linguistic, and socioeconomic variables, but these have not been shown to determine AD prevalence rates. The relatively high rates of the combined U.S. studies are driven by the contributions of a single study that focused on the population of East Boston. This study, the one that NIA bases its estimates on, yields rates that are higher than those of all other studies, including the other U.S. studies. The difference between the U.S. and non-U.S. studies reduces to a difference between East Boston and all other studies.

2. The report has been changed to reflect the likely limiting role of screen cut-off scores.

3. We disagree with NIA's point about "questionable" dementia. In accordance with the conventions of the field, we defined people with AD as those rated as having mild or more severe dementia. While it is true that a certain proportion of those with questionable dementia will develop AD, prevalence estimates are traditionally given for persons who have a disease and do not include those who may get the disease at a later time.

4. The report has been changed to reflect the likely role of excluding mixed dementia.

5. To examine the role of heterogeneity among studies in our meta-analysis, we took the following steps: We analyzed the data for any AD, focusing on each study as a possible source of variation. Then we dropped the one study (East Boston) found to be a statistically significant source of variation relative to the set of studies as a whole, and we reanalyzed the remaining ones. No other study was a statistically significant source of variation, and thus the heterogeneity among studies was eliminated with the elimination of that single outlier. If the remaining studies are used to generate prevalence estimates, these are somewhat lower than the original ones, for example, by 5 percentage points for men at the age of 95. One can debate about which estimates are better.

However, although the heterogeneity of the data can be eliminated by dropping the one outlier, we are reluctant to exclude the data from a major American study of prevalence.

GAO Contact and Staff Acknowledgments

GAO Contact

Donald M. Keller, Evaluator-in-Charge, (202) 512-2932

Staff Acknowledgments

This report was prepared under the direction of George Silberman. Sushil K. Sharma, Assistant Director, and Lê X. Hy were responsible for much of the research and analysis.

Ordering Information

The first copy of each GAO report and testimony is free. Additional copies are $2 each. Orders should be sent to the following address, accompanied by a check or money order made out to the Superintendent of Documents, when necessary. VISA and MasterCard credit cards are accepted, also. Orders for 100 or more copies to be mailed to a single address are discounted 25 percent.

Orders by mail:

U.S. General Accounting Office
P.O. Box 37050
Washington, DC 20013

or visit:

Room 1100
700 4th St. NW (corner of 4th and G Sts. NW)
U.S. General Accounting Office
Washington, DC

Orders may also be placed by calling (202) 512-6000 or by using fax number (202) 512-6061, or TDD (202) 512-2537.

Each day, GAO issues a list of newly available reports and testimony. To receive facsimile copies of the daily list or any list from the past 30 days, please call (202) 512-6000 using a touchtone phone. A recorded menu will provide information on how to obtain these lists.

For information on how to access GAO reports on the INTERNET, send an e-mail message with "info" in the body to:

info@www.gao.gov

or visit GAO's World Wide Web Home Page at:

http://www.gao.gov

United States
General Accounting Office
Washington, D.C. 20548-0001

Bulk Rate
Postage & Fees Paid
GAO
Permit No. G100

Official Business
Penalty for Private Use $300

Address Correction Requested