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# National estimates of the prevalence of Alzheimer's disease in the United States

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**Abstract** Several methods of estimating prevalence of dementia are presented in this article. For both Brookmeyer and the Chicago Health and Aging project (CHAP), the estimates of prevalence are derived statistically, forward calculating from incidence and survival figures. The choice of incidence rates on which to build the estimates may be critical. Brookmeyer used incidence rates from several published studies, whereas the CHAP investigators applied the incidence rates observed in their own cohort. The Aging, Demographics, and Memory Study (ADAMS) and the East Boston Senior Health Project (EBSHP) were sample surveys designed to ascertain the prevalence of Alzheimer's disease and dementia. ADAMS obtained direct estimates by relying on probability sampling nationwide. EBSHP relied on projection of localized prevalence estimates to the national population. The sampling techniques of ADAMS and EBSHP were rather similar, whereas their disease definitions were not. By contrast, EBSPH and CHAP have similar disease definitions internally, but use different calculation techniques, and yet arrive at similar prevalence estimates, which are considerably greater than those obtained by either Brookmeyer or ADAMS. Choice of disease definition may play the larger role in explaining differences in observed prevalence between these studies.


*Keywords:* Alzheimer's disease; Dementia; Cognitive impairment; Prevalence; Population-based; Projection; Probability sampling

## 1. Introduction

Prevalence is a straightforward concept: it is simply the count or proportion of persons who have disease at a single point in time, in a defined population. As a proportion, prevalence does not imply the risk or probability of a person becoming affected by the disease in question. Instead, prevalence portrays the potential burden—for care, services, and other things—that the disease places on the population. The specific quality of the healthcare burden is also dictated by the duration, disability, and family resources (public and private) required to treat the disease or to cope with it. Because dementias are relatively common, have relatively long duration, and lead to marked impairment in social and occupational functioning, their burden level is high. Epidemiologists have routinely observed that persons who live longer with the disease are also more likely to be the ones to be included in a cross-sectional survey and counted as "prevalent" cases.

Since 1980, most but not all the prevalence figures for Alzheimer's disease (AD) that have been generated in the United

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States have come from community-based, cohort studies where the primary purpose was to investigate risk factors and protective factors based on incident cases. The prevalence figures were a by-product of the baseline effort to identify a disease-free cohort. Although these figures could be published as prevalence estimates for a specific community, many were not intended to represent the full-range of disease from very mild to severe cases [1]. More recently, the research field has taken a keen interest in mild cases of AD and in other forms of age-related, mild cognitive impairment.

The U.S. national prevalence estimates of AD have been produced using projection methodology [2–4], and they have also been obtained directly from a national cross-sectional survey known as the Aging, Demographics, and Memory Study (ADAMS) [5]. ADAMS produced prevalence figures, not only for AD and other dementia, but also for cognitive impairment not dementia (CIND) [6,7]. The current article focuses on some major prevalence estimates and how they were obtained. Brookmeyer provides an overview of forward calculation projection methodology and uses that approach to generate various national prevalence estimates for comparison purposes on the basis of the data obtained from different populations—to note similarities and differences. Evans and Hebert, who always had an interest in including mild AD in addition to moderate and severe AD, describe their use of projection methodology, including the forward calculation method, and present national prevalence projections on the basis of data from the East Boston Senior Health Project (EBSHP) and the Chicago Health and Aging Project (CHAP). Langa, Heeringa, and Plassman describe the ADAMS sampling methodology and provide prevalence figures for AD, other dementia, and CIND that were produced in ADAMS. In the Discussion, Kukull provides a synthesis of this material and gives some perspective.

## 2. Approaches for estimating AD prevalence in the U.S. population

National estimates of AD prevalence in the U.S. population have differed by a factor of more than two. It is important to understand the sources of uncertainty underlying the various methodologies for prevalence estimation. There are two main approaches for estimating the national prevalence of AD. The first approach is essentially a forward calculation method that relies on AD incidence rates [3]. The second approach relies on representative cross-sectional prevalence surveys of AD [2,6]. Both approaches have important sources of uncertainty. One of the most significant sources of uncertainty with the forward calculation approach concerns the critical assumptions about the age-specific incidence of AD. One of the most significant sources of uncertainty with the prevalence survey approach concerns the representativeness of the survey sample.

In this section, the forward calculation approach is discussed and various comparisons are made of national prevalence estimates of AD. Specifically, there is an attempt to reconcile differences in the prevalence estimates produced using the forward calculation approach. In addition, forward calculation prevalence estimates are compared with corresponding ones derived from a national prevalence survey.

The forward calculation method requires several critical inputs. One input is the age-specific incidence rates of AD. Another input is the survival rates among persons with AD. These two inputs are then used in a competing risks model. The competing risks model is a multi-state model which includes a healthy state, AD, and death. The AD state may be further subdivided into an early stage and advanced stage of disease. Figure 1 illustrates the multi-state model and the transition rates from one state to the next. The prevalence estimates can be expressed in terms of the transition rates (e.g., see equation 5 in [8]). Once the prevalence estimates have been calculated (i.e., the percent of people with AD), the numbers of persons in a population living with AD are obtained by multiplying those prevalence estimates by population sizes.

To implement forward calculation, the transition rates in Fig. 1 must be specified. Brookmeyer et al performed a forward calculation to estimate the global prevalence of AD [9]. Their calculation was based on systematic reviews of 27 published studies to determine the transition rates in Fig. 1 [10]. In the present study, the transition rates used in those calculations are briefly reviewed. The age-specific incidence rate per 100 person-years versus age was found to increase linearly on a log scale, doubling after approximately every 5 years (Fig. 2). Advanced-stage disease was defined as a state which takes on average 6 years to reach after diagnosis, which corresponds to an annual disease progression rate of about 16% per year. National vital statistics were used to determine background mortality rates (the transition rates from healthy state to death). The mortality among persons with advanced-stage AD was determined by adding 11% per year to the background mortality rates [9]. That determination was based on an additive model for death rates in which the parameters were calibrated from a published study on AD survival [11]. The results were consistent with several other published studies on AD survival. With these inputs placed into the competing risks model, the Brookmeyer calculations estimated that there were approximately 2.8 million Americans living with AD in 2008.

An alternative to forward calculation for determining national prevalence is based on nationally representative cross-sectional prevalence surveys. ADAMS, with its nationally probability-based representative sample [5,6], estimated that in 2002 the U.S. prevalence of dementia among persons aged >70 years was 3.4 million. With the ADAMS results, there is the opportunity to compare forward calculation estimates with survey estimates. However, the ADAMS figures are not directly comparable with the Brookmeyer figures because the ADAMS figures cited earlier in the text refer to all dementia in 2002 among

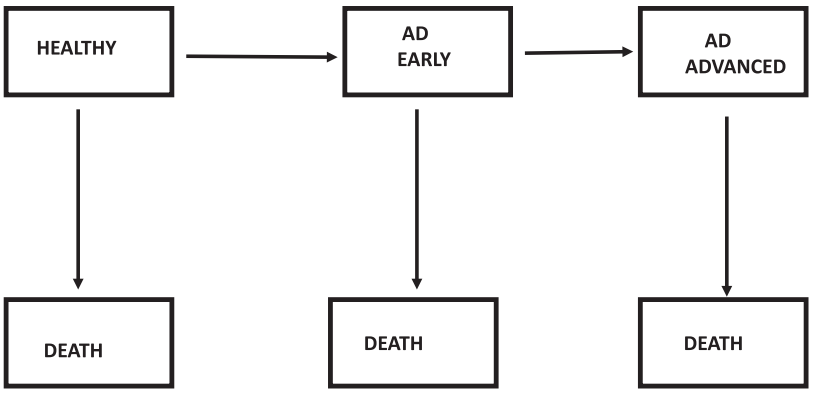


Fig. 1. Multi-state model of progression of Alzheimer's disease (AD). Transition rates from one state to the next may depend on age, gender, and calendar year.

persons aged >70 years, whereas the Brookmeyer figure refers to AD cases in 2008. An update of the ADAM's study suggested that the U.S. prevalence of AD in 2008 among persons aged >70 years was 2.6 million (see Appendix 5, p 131, in [12]). When the Brookmeyer analysis is restricted to persons aged >70 years, a prevalence of 2.65 million is obtained. Thus, the two approaches (the Brookmeyer forward calculation and ADAMS survey approach) give fairly consistent prevalence estimates (2.65 vs 2.60 million).

Another forward calculation by Hebert et al yielded somewhat different results [4]. That calculation was based on AD incidence from CHAP, which was conducted in biracial neighborhoods in Chicago. Hebert calculated that in 2000 there were 4.5 million Americans living with AD who were aged >65 years. When those numbers were updated to 2008 and also included cases of individuals aged <65 years, it produced AD prevalence of 5.2 million in 2008 (see page 130 in [12]). That number is about two times larger than suggested either by the Brookmeyer forward calculation or the ADAMS prevalence survey.

If the Brookmeyer and Hebert estimates both use forward calculation methods, then why do they give such different estimates? The main reason is that different assumptions about AD incidence were used. Figure 2 illustrates the incidence estimates from the systematic review [10] and the CHAP estimates [13]. The CHAP incidence rates were provided in 10-year age intervals [13], and here they have been plotted at the midpoint of the intervals. The CHAP incidence rates used in the Hebert calculation are considerably higher than those used in the Brookmeyer calculation. For example, at age 80 years, the rates were 4.73% per year for CHAP versus 1.48% per year from the systematic review. The differences are even more extreme at the younger ages (at age 70 years the rates were 1.45% per year from CHAP vs 0.13% per year from the review).

There were other differences with how the Hebert and Brookmeyer forward calculation estimates were produced, including different assumptions about survival of AD patients, and differences in the computing software used to perform the calculations. To determine the main reasons for the discrepancy between the two forward calculation estimates, the CHAP AD incidence was inserted into the Brookmeyer forward calculation software (keeping everything else the same), and it was found that the AD prevalence estimate increased by about a factor of 2.5. The conclusion from this sensitivity analysis is that the difference between the two forward calculation (Brookmeyer and Hebert) estimates is driven mainly by differences in the AD incidence rates that are input into the calculations.

One advantage of forward calculation is that it can be used to forecast future prevalence by disease severity, and evaluate the potential effect of preventive and therapeutics advances. Different scenarios can be investigated by modifying the transition rates. For example, forward calculation indicates that the number of people currently living with AD is 26.6 million and that number would grow to 106 million by 2050 [9]. Worldwide, about 62% of persons with AD are

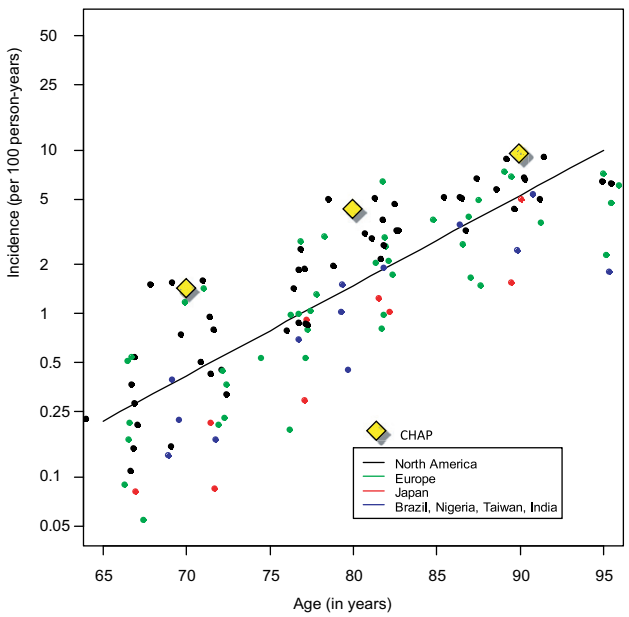


Fig. 2. AD incidence rates from a systematic review [10] and the Chicago Health and Aging Project (CHAP) [13]. For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.

women. About 43% have "advanced disease," where "advanced disease" is defined as a state that takes on average 6 years to reach after the initial diagnosis of AD. If disease onset could be delayed at an average of 2 years, then the worldwide prevalence in 2050 of AD would decrease by 22 million, with the decrease approximately evenly divided between early and advanced stage disease. If the onset of disease is not delayed but the progression of disease to advanced stage is delayed, then prevalence actually increases. If disease progression and disease onset are both delayed by 1 year, then there is a decrease of >9 million in worldwide prevalence, with almost all of that decrease being among persons with advanced disease. The take-home message from these calculations is that even small delays in disease onset and progression can significantly reduce the global burden of disease. A Web-based software application that implements the forward calculation methodology is available, which enables researchers to project the burden of AD, to investigate the sensitivity to input assumptions, and to evaluate the effect of potential interventions [14].

In closing, there are two main approaches for estimating prevalence, cross-sectional prevalence surveys and forward calculation. Both approaches have uncertainties. An important issue with cross-sectional prevalence surveys concerns their representativeness. Important sources of uncertainty with forward calculation concern the transition rates including the incidence rates of AD and also mortality rates. Both methodologies rely critically on the diagnostic criteria for AD case definition. Different thresholds for case definition will lead to different prevalence estimates. Having said that, it is noteworthy that although the absolute prevalence number is sensitive to the threshold used for case definition, relative changes are not. Worldwide AD prevalence will quadruple in the next 50 years because of the aging of the world population and the quadrupling conclusion is relatively insensitive to the diagnostic threshold of case definition.

## 3. AD projections from EBSHP and CHAP data

Projections of AD prevalence in the U.S. population were made from two similar source studies. The first [2] used estimates of AD prevalence from the EBSHP and was published in 1990. The second [4] used estimates of AD incidence from CHAP and was published in 2003. The most basic design elements were similar to those of previous approaches: estimates of current AD prevalence or incidence were taken from one or more studies. Estimates of the future growth of the U.S. population were taken from the U.S. Census. As in previous estimates, multiple other variables were considered as follows: age, gender, education, race, and survival.

The source studies [13,15] for the two estimates used similar methods. Both were large population-based studies of people aged >65 years. Both achieved strong participation, 85% of all age eligible residents of a geographically defined community for the EBSHP and 78% of all age eligible residents for CHAP. Both were of clinically rather than pathologically diagnosed AD. Ascertainment of AD in both studies was by direct evaluation and independent of receipt of healthcare. Both studies used the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS)-Alzheimer's Disease and Related Disorders Association (ADRDA) diagnostic criteria except that individuals meeting criteria for probable AD and also having another condition potentially impairing cognition were retained [1,16]. As will be discussed subsequently, both used two-stage designs—that is, a first stage of population interviewing followed by a second stage of detailed clinical evaluation. In both studies, the second-stage sample was not restricted to the subjects who scored poorly on the first-stage cognitive testing. Rather, those evaluated at the second stage were a stratified random sample of all first-stage participants. This sample was from all levels of performance on the first stage tests, that is first-stage cognitive performance was used as a tool for stratifying the random sample for clinical evaluation rather than a screening test. In both studies, second-stage examiners were masked to first-stage cognitive performance. Uniform, completely specified criteria and procedures were used by examiners in both studies. In both studies, the criteria and procedures used detected mild as well as moderate and severe AD. Both studies considered age (by single year), education, and gender in forming estimates.

There were also differences both in the methods used in these two source studies and in the methods used to apply these source-study estimates to the U.S. population. The source-study differences included the obvious differences in location and dates of the studies. The relevant portion of the EBSHP was conducted in East Boston, an almost exclusively white community of Boston, Massachusetts in 1982, and 1980 U.S. Census figures were used for the estimates of the U.S. population. CHAP was conducted in a biracial (African American and non-Hispanic white) community of the southwest side of the city of Chicago. The relevant portion of the study was conducted between 1996 and 2000, and the 2000 U.S. Census was used for U.S. population estimates. In the 1990 estimates from the EBSHP, the prevalence of AD in the U.S. population was estimated directly from the prevalence of AD observed in the source study.

In the 2003 estimates from CHAP, the prevalence of AD in the U.S. population was estimated from the incidence of AD observed in the source study using methods similar to those of Brookmeyer et al [3]. Use of incidence estimates from the source study with conversion to prevalence in population allows better consideration of changes in survival over the projection period. Such changes in survival among people both with and without AD, and the aging of the population during the projection period affect projected prevalence. These estimates assume that the general increase in survival will affect both people with and without AD, but the excess mortality associated with the disease will continue to be elevated to the same degree as it is at present. The estimates were not sensitive to excluding a term for African American race/ethnicity (not significant) from the

2003 estimates or to including a term for gender in either estimate. Adjustment for education and age was significant, but modeling educational level in different groups made little difference, and modeling age as a single linear term produced results fairly close to those presented.

The 1990 projections from the EBSHP are shown in Figs. 3 and 4, and the 2003 projections from CHAP are shown in Figs. 5 and 6. The results are reasonably similar: The 1990 estimates using EBSHP data and 1980 U.S. Census population estimates suggest that AD prevalence in the U.S. population will increase from 2.88 million in 1980 to 10.2 million in 2050 and will equal 5.12 million in the current year, 2010. The 2003 estimates using CHAP data and 2000 U.S. Census population estimates suggest that AD prevalence in the U.S. population will increase from 4.5 million in 2000 to 13.2 million in 2050 and will equal 5.1 million in the current year, 2010.

In the 2003 projections, the number of affected persons projected in 2050 is higher than in the 1990 estimates as the methodology used in 2003 assumes that projected increases in survival will affect both persons with and without AD, with the ratio of survival among unaffected persons to survival among affected persons remaining constant at its present level whereas the 1990 methods did not. Some of the closeness of the estimates is likely because of chance. Some of the closeness, despite the diagnosis of AD being made by different skilled clinicians in the EBSHP and CHAP, is likely because of both studies using NINCDS-ADRDA criteria for the clinical diagnosis of AD and implementing these criteria in a very similar way in the field with strong emphasis on fully structured and specified methods[1].

Three series of U.S. Census population growth estimates—the high, middle, and low series—are used to form the projections both in the 1990 effort (Fig. 3) and in the 2003 effort (Figure 5). Use of these three series of estimates may be considered as very roughly analogous in purpose to the use of a confidence interval about an estimate: the middle series represents the best estimate of population growth with current knowledge and reasonable expectations. The high and low series are projections that "do not represent likely scenarios in themselves, but purport to represent the extremes between which most likely outcomes should fall" [17]. Thus, the high and low series estimates represent brackets about the more likely middle series estimate of population growth.

Similar points deserve emphasis about both sets of estimates. The projected increase in the number of people affected by AD in the U.S. population aged >65 years by 2050 is large. In the 1990 projections, the projected increase is from 2.88 million in 1980 to 10.2 million (middle series) by 2050. In the 2003 projections, the projected increase is from 4.5 million in 2000 to 13.2 million (middle series) by 2050. Perhaps most importantly, in the two sets of projections presented here, this increase in number of people affected by AD is solely attributable to the increase in size of the oldest age groups of the population. These projections assume that the factors underlying the occurrence of AD will remain constant over this period. That is, they represent what will happen if society does not take any effective steps to prevent this disease over this period. Projected declines in death rates among people aged >65 years will both increase the number and proportion of people who will survive to the ages at which this disease becomes most prevalent and results in increased survival of people affected by AD.

As illustrated by Figs. 4 and 6, the projected overall increase in the number of people with AD in the U.S. population is largely driven by the growth in size of the over-85 subgroup of the population aged >65 years, and by the high occurrence of AD in this subgroup. The over-

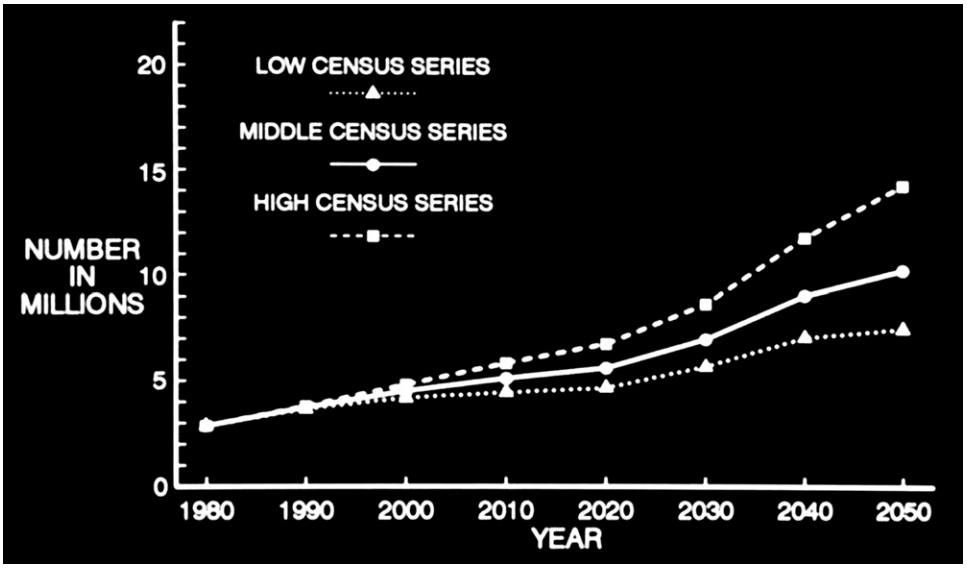


Fig. 3. Projected number of people aged ≥65 years with clinically diagnosed probable AD in the U.S. population from 1980 through 2050 using low, middle, and high U.S. Census projections of population growth and AD prevalence data from the East Boston Senior Health Project in East Boston, Massachusetts [15].

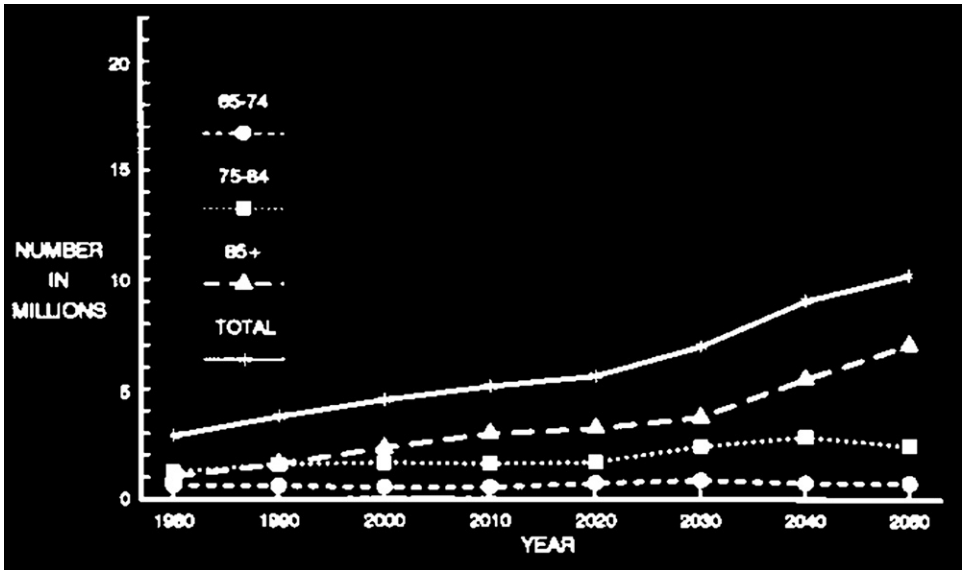


Fig. 4. Projected number of people aged ≥65 years with clinically diagnosed probable AD in the U.S. population from 1980 through 2050 by three age subgroups using the U.S. Census middle series projection of population growth and AD prevalence data from the East Boston Senior Health Project [15].

85 subgroup is the oldest subgroup shown in the figures and the oldest population subgroups are the ones increasing most rapidly in the populations of the United States and of all other developed countries. Although the number of cases of AD in over-85 subgroup increases sharply, it increases moderately in the 75 to 84 year-old subgroup and remains nearly constant in the 65 to 74 year-old subgroup. A substantial limitation of both the 1990 and the 2003 estimates is that both are based on AD estimates from a single population study, and no single community, including either East Boston, Massachusetts, or Chicago, Illinois, is likely to be truly representative of the entire U.S. population in many ways.

Projections of AD prevalence in the U.S. population have varied substantially. In general, the differences between various estimates reflect primarily the differences in source studies, not those in projection methodology. These differences include study size, study design features, whether a single source study or multiple studies were used, and whether the source study or studies are population-based. In studies using a two-stage design, the following two differences are especially important: first, whether second-stage evaluation for AD is completely or mostly restricted to subjects who fail a brief first-stage cognitive screening procedure, or whether selection for second-stage evaluation is random from all strata of first-stage cognitive performance; second, whether second-stage clinical evaluators are efficiently masked to the first-stage cognitive test performance of the subject. The assumption that efficiently masked skilled clinical examiners will detect AD solely among study subjects who fail a brief cognitive tests and never or very rarely among those who score above a cut-off is unlikely, especially as, for efficiency, the proportion failing the test is generally set to be substantially smaller than the proportion passing [18]. Thus, source studies using screening test failure to identify subjects for further evaluation are very likely to result in lower estimates of disease occurrence. Another important design feature of the

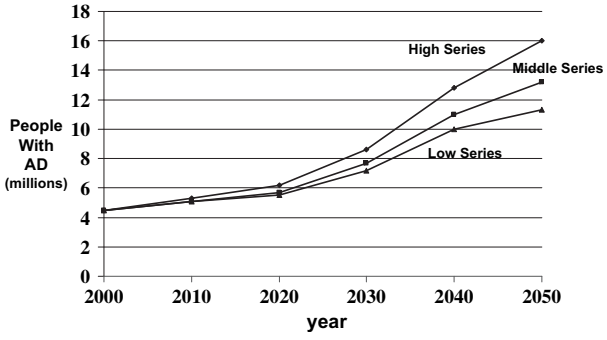


Fig. 5. Projected number of people aged ≥65 years with clinically diagnosed probable AD in the U.S. population from 2000 through 2050 using low, middle, and high U.S. Census projections of population growth and AD incidence data from the CHAP [13].

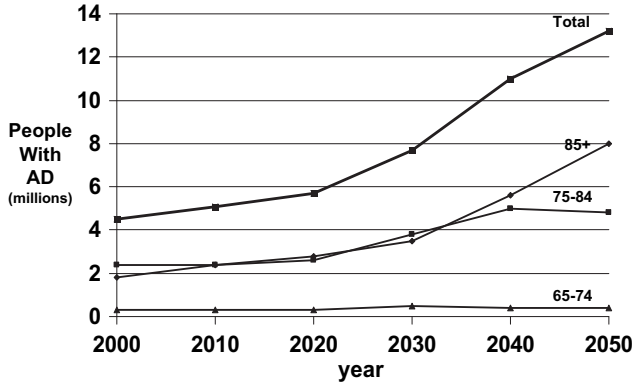


Fig. 6. Projected number of people aged ≥65 years with clinically diagnosed probable AD in the U.S. population from 2000 through 2050 by three age subgroups using the U.S. Census middle series projection of population growth and AD incidence data from the CHAP [13].

source study is whether receipt of healthcare is a necessary feature of AD ascertainment, as AD and other dementing illnesses are typically substantially under-recognized in healthcare settings [19]. The criteria used in the diagnosis of AD and their implementation can also affect the estimates reached. This source of variation is increased because reasonable investigators can implement the same criterion system for AD in a very different manner. An especially difficult matter is that the clinical and pathological manifestations of AD typically develop and progress by minute degrees, often over a long period. AD prevalence or incidence estimates require placing a diagnostic cut point along the continuum between normality and disease. Because it is not clear exactly where this cut point should be placed, different investigators, each using the same diagnostic criteria, will place the cut point differently. In contrast, the methods of referring the source study estimates to the U.S. population vary somewhat, but not greatly, and estimates of future U.S. population growth vary little; usually U.S. Census estimates are used.

Comparing the results of a previous projection [3] with the ones presented here is instructive about how the source studies used influence projection results. Brookmeyer et al [3] used four source studies [20–23], strong methods of referring estimates from these studies to the U.S. population, and U.S. Census estimates of population growth. One of the source studies used [23] was the incidence phase of the EBSHP, which used stratified random sampling to ascertain disease (The prevalence phase of the EBSHP was also the source study used for the 1990 projections described here.). However, the other three studies used methodologies that gave lower estimates of AD, especially in the oldest age groups. One study [21] used only medical records to identify cases; another [22] eliminated the low-scoring 10% of persons from the dementia-free cohort and used a restrictive protocol to detect incident disease. Another [20] examined a highly educated volunteer cohort which was possibly healthier than the total population. These differences in the source studies resulted in fairly large differences in current estimates of AD prevalence in the U.S. population. The 1997 estimate by Brookmeyer et al [3] was 2.32 million, substantially lower than the 2000 estimate by Hebert et al [4] of 4.5 million. However, both studies used similar U.S. Census estimates of U.S. population growth and similar projection methods, and Brookmeyer et al estimated that AD prevalence in the U.S. population would increase to 8.64 million by 2047, an increase of 372%, whereas Hebert et al estimated that AD prevalence in the U.S. population would increase to 13.2 million by 2050, an increase of 293%.

In conclusion, there is substantial variation in current estimates of AD prevalence in the U.S. population. Much of this variation is likely because of methodological variations in the source studies used to form these estimates or is intrinsic to the nature of the disease. AD, like many other common chronic diseases, usually arises over time by minute degrees so that it is difficult for even highly skilled examiners to place a cut point between normality and disease precisely and uniformly even when using the same disease criteria. There is much less variation in estimating future changes in AD prevalence. With a reliable forecast for a rapid increase in the oldest population age groups for both the U.S. population and for the populations of all other developed countries, the increase in AD prevalence in future will be large and this strongly emphasizes the need to find preventive measures for this disease in the near future.

## 4. Informative probability sampling and major prevalence findings from the ADAMS

ADAMS was designed to provide nationally representative data on the antecedents, prevalence, outcomes, and costs of dementia and CIND, using a unique study design based on the Health and Retirement Study (HRS). ADAMS is the first population-based study of dementia and CIND in the United States to include subjects from all regions of the country, while at the same time using a single standardized diagnostic protocol in a community-based sample. A sample of 856 individuals aged $\geq$71 years who were participants in the ongoing HRS received an extensive in-home clinical and neuropsychological assessment to determine a diagnosis of normal, CIND, or dementia [1]. Linkage of data from the ADAMS with detailed HRS longitudinal data on health, healthcare utilization, informal care, and economic resources and behavior allows for in-depth investigations into the risk factors and outcomes of CIND and dementia, as well as the lifetime costs of dementia in the population.

### *4.1. ADAMS sampling methodology*

The nationally representative HRS sample provided the sample frame for ADAMS [24,25]. From the larger nationally representative sample of approximately 7000 HRS respondents aged $\geq$70 years, a stratified, random subsample of 1770 individuals was selected for participation in ADAMS. The goal of the ADAMS was to obtain clinical assessments on 850 individuals. ADAMS sample selection, initial consent, and final data management for the project were conducted by staff of the University of Michigan Survey Research Center, Ann Arbor. In-home evaluations for cognitive impairment and consensus conferences to establish final diagnoses were directed by experienced teams at the Duke University Program in Epidemiology of Dementia [5].

Early in the design stage of ADAMS, the investigators recognized that a field period of $\geq$2 years would be required to complete 850 in-home assessments with the nationally distributed subsample of HRS panel members. To maximize efficiencies in the field and to minimize the elapsed time between an HRS cognitive assessment and the ADAMS evaluation, the baseline sample was drawn in two phases. Each phase was based on a random half sample of the full HRS multi-stage sample design. All HRS respondents aged $\geq$70 years at the time of the HRS 2000 interview were eligible for the initial ADAMS selection in phase 1 sample areas. Similarly, all HRS respondents in phase 2 areas aged $\geq$70

years at the time of the 2002 HRS interview were eligible for phase 2 sample selection.

To achieve a sufficient number of ADAMS respondents across the full range of cognitive ability, the phase 1 and 2 samples were stratified on the basis of cognitive test scores, gender, and age. Respondents were classified into major cognitive strata on the basis of their performance on the cognitive measures in the designated HRS interview (either 2000 or 2002, depending on the ADAMS Phase assignment). Self-respondents were classified into cognition strata on the basis of the entire set of HRS cognitive tests (aggregate scores ranging from 0 to 35). Proxy respondents were classified on the basis of scores ranging from 1.0 to 5.0 on the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) scale. (More details on the self- and proxy-respondent scales are available in documentation at the HRS Web site [26]). The combination of stratification criteria—HRS self or proxy interview status, cognition stratum, age, and gender—yielded 18 explicit strata for the ADAMS baseline sample selection. The stratified sample for ADAMS Phase 1 areas was selected on the basis of HRS 2000 cognition scores. A final stratified sample for the phase 2 areas was selected on the basis of updated cognition measures obtained in the HRS 2002 interview. A detailed description of the ADAMS sample design is available in a documentation report at the HRS Web site [27].

Table 1 summarizes the final disposition of the entire sample of 1770 ADAMS selectees. In the total sample, ADAMS clinical evaluations and diagnostic assessments were completed with a total of 856 sample individuals (48.4% of the sample, 55.6% of persons known to be alive at the time the ADAMS contact was attempted). In the time window between the 2000 or 2002 HRS interview and the subsequent ADAMS assessment attempt, 228 (12.9%) of the designated sample members died. An additional 59 (3.3%) sample members were believed to be alive but could not be located at the time of the scheduled assessment. A total of 499 (28.2%) sample individuals refused to participate in the ADAMS baseline assessment and an additional 128 (7.2%) could not participate for other reasons (including health and lack of a suitable proxy).

Table 1 also illustrates the very different pattern of ADAMS sample dispositions for persons who were self-respondents or proxy respondents in the 2000 and 2002 HRS interviews that determined their sample stratum and sample selection status.

Table 1
ADAMS baseline sample dispositions by respondent type

| Sample disposition | Total N = 1770 | Self respondent n = 1238 | Proxy respondent n = 532 |
|---|---|---|---|
| Assessed | 48.4% | 53.1% | 37.3% |
| No contact | 3.3% | 2.8% | 4.7% |
| Non-interview, other | 7.2% | 7.8% | 6.0% |
| Refused | 28.2% | 28.6% | 27.2% |
| Deceased | 12.9% | 7.8% | 24.8% |
| Cooperation among survivors | 56% | 57% | 50% |

ADAMS, Aging, Demographics, and Memory Study.

The percentages of original sample cases that proved to be no contact, other noninterview, or refusals are very similar for the two respondent type groups but as expected the short-term mortality rates were much higher for persons who required a proxy respondent in the preceding HRS interview.

Because the in-depth ADAMS assessments occurred at varying lengths of time after the 2000 or 2002 HRS interview used to determine an individual panel member's eligibility and sample stratum assignment and the sample was subject to nonresponse, an in-depth analysis was performed of the potential selection bias because of differential mortality or other sources of selective attrition in the ADAMS baseline sample [27]. These analyses suggested that the natural process of mortality among the members of the original ADAMS sample did not introduce significant selection/attrition bias into the final sample of 856 ADAMS assessments for surviving members aged >70. Among the surviving members of the ADAMS sample, an investigation into factors associated with nonresponse identified being a man and pre-existing mental health conditions as significant factors in increased response propensity for sample persons who were self-reporters in the preceding HRS wave. For ADAMS sample members who required a proxy reporter at the previous HRS interview, lower cognitive functioning status is associated with slightly increased likelihood of an ADAMS assessment. To attenuate potential selection bias caused by differential participation, the final ADAMS analysis weights include an attrition adjustment that controls for original cognitive stratum, gender, and age.

### 4.2. Prevalence findings

Table 2 provides sample characteristics for the 856 ADAMS participants on the basis of dementia status. The sample is well distributed across the range of age and education levels with a significant number of individuals aged ≥90 years and also a large percentage with 8 or fewer years of education.

Standard design-based methods were used to estimate the population prevalence of AD, vascular dementia (VaD), all dementia, and CIND based on the initial in-home assessments of the ADAMS sample. Descriptive estimates of prevalence and model-based analyses of risk factors incorporated survey weights to reflect the differential probability of selection for the subjects in the ADAMS cognition strata and for nonresponse in the ADAMS assessment. The final weighted ADAMS prevalence estimates were initially poststratified to 2000 Census population controls for household and nursing facility and/or extended care populations and then to July 2002 total population controls by age and gender. Standard errors for all descriptive estimates and model parameters account for the ADAMS complex sample design.

#### 4.2.1. AD, VaD, and dementia

Diagnoses were anchored by Diagnostic and Statistical Manual of Mental Disorders (DSM)-III-R and DSM-IV

Table 2
Characteristics of the ADAMS sample that completed a baseline assessment*

| Characteristic | All | All demented N (%) | AD N (%) | VaD N (%) | Dementia, undetermined etiology N (%) | Non-demented N (%) |
|---|---|---|---|---|---|---|
| Overall | 856 (100%) | 308 (100%) | 229 (100%) | 48 (100%) | 23 (100%) | 548 (100%) |
| Age (years) | | | | | | |
| 71–79 | 355 (58.6%) | 62 (20.9%) | 37 (14.0%) | 14 (23.7%) | 8 (64.2%) | 293 (64.7%) |
| 80–89 | 366 (33.7%) | 158 (58.6%) | 119 (62.7%) | 25 (56.8%) | 10 (29.1%) | 208 (29.7%) |
| 90+ | 135 (7.7%) | 88 (20.5%) | 73 (23.3%) | 9 (19.5%) | 5 (6.7%) | 47 (5.6%) |
| Gender | | | | | | |
| Men | 355 (39.3%) | 95 (31.5%) | 59 (28.5%) | 20 (37.9%) | 13 (43.0%) | 260 (40.6%) |
| Women | 501 (60.7%) | 213 (68.5%) | 170 (71.5%) | 28 (62.1%) | 10 (57.0%) | 288 (59.4%) |
| Education (years) | | | | | | |
| 0–8 | 291 (17.4%) | 125 (33.5%) | 93 (32.2%) | 18 (33.8%) | 12 (48.0%) | 166 (14.7%) |
| 9–11 | 144 (16.1%) | 53 (15.3%) | 39 (16.1%) | 7 (9.9%) | 4 (17.4%) | 91 (16.3%) |
| 12 | 203 (29.4%) | 71 (27.2%) | 55 (29.2%) | 10 (32.2%) | 4 (6.4%) | 132 (29.8%) |
| >12 | 218 (37.1%) | 59 (24.0%) | 42 (22.5%) | 13 (24.1%) | 3 (28.2%) | 159 (39.2%) |
| Race/ethnicity | | | | | | |
| Non-Hispanic white | 613 (87.1%) | 218 (83.4%) | 162 (82.1%) | 36 (87.3%) | 15 (86.4%) | 395 (87.7%) |
| Non-Hispanic African American | 159 (7.6%) | 67 (12.4%) | 49 (12.9%) | 9 (10.5%) | 7 (12.3%) | 92 (6.9%) |
| Hispanic | 84 (5.2%) | 23 (4.2%) | 18 (5.0%) | 3 (2.2%) | 1 (1.3%) | 61 (5.4%) |

AD, Alzheimer's disease; VaD, vascular dementia; ADAMS, Aging, Demographics, and Memory Study.
* Ns are unweighted, percentages are weighted and calculated within columns.

criteria for dementia, and other currently accepted diagnostic criteria for AD and other subtypes of dementia were used. Table 3 shows the overall national prevalence estimates for AD and all dementia, stratified by gender and 9- or 10-year age ranges. As expected, the national prevalence of AD and all dementia increased with age, reaching 37.2% dementia prevalence among individuals aged ≥90 years.

Overall, AD accounted for approximately 69.9% of all dementia, whereas VaD accounted for 17.4%. Other types of dementia such as "dementia, undetermined etiology," Parkinson's dementia, normal pressure hydrocephalus, frontal lobe dementia, alcoholic dementia, traumatic brain injury, and Lewy body dementia accounted for the remaining 12.7% of cases. With increasing age, AD accounted for progressively more cases of dementia so that in the age group of ≥90 years, AD accounted for 79.5% of the dementia cases compared with 46.7% among those aged 71 to 79 years.

The estimated number of individuals nationwide aged ≥71 years with AD was 2.3 million (95% CI: 2.8–4.0 million) and an estimated 577,000 (319,000–834,000) had VaD. The estimated number of individuals aged ≥71 years in the United States in 2002 with any type of dementia was 3.3 million (2.8–4.0 million).

#### 4.2.2. Cognitive impairment not dementia

CIND was defined as (1) mild cognitive or functional impairment reported by the participant or informant that did not meet criteria for dementia; or (2) performance on neuropsychological measures that was both below expectation and ≥1.5 standard deviations below published norms on any test. Diagnostic subcategories for CIND were used in an effort to reflect the variation in clinical presentation and potential differences in the etiology of the impairment. Further details are available in this issue of the *Journal* on how the definition of CIND was operationalized in ADAMS [1].

Table 4 shows the national prevalence estimates for CIND and some of its more frequent subtypes, stratified by 9- or 10-year age ranges. The overall prevalence of CIND in the United States for individuals aged ≥71 years was 22%. CIND prevalence increased with age, affecting nearly 39% of individuals aged ≥90 years. The prevalence of prodromal AD increased substantially with age, accounting for 8% of those aged >70 years.

Table 3
National prevalence of dementia and Alzheimer's disease, by age categories

| | All dementia | | | Alzheimer's disease | | |
|---|---|---|---|---|---|---|
| Age (years) | Combined | Men | Women | Combined | Men | Women |
| 71–79 | 4.97 (2.61–7.32) | 5.25 (1.25–9.25) | 4.76 (1.82–7.70) | 2.32 (1.26–3.37) | 2.30 (0.80–3.81) | 2.33 (0.95–3.70) |
| 80–89 | 24.19 (19.28–29.11) | 17.68 (11.66–23.70) | 27.84 (20.41–35.28) | 18.10 (13.47–22.74) | 12.33 (5.82–18.84) | 21.34 (14.44–28.24) |
| 90+ | 37.20 (25.36–49.03) | 44.59 (21.70–67.47) | 34.69 (23.36–46.02) | 29.60 (18.59–40.61) | 33.89 (10.00–57.77) | 28.15 (17.61–38.69) |
| Total | 13.67 (11.21–16.12) | 10.80 (7.55–14.50) | 15.53 (12.23–18.83) | 9.51 (7.41–11.61) | 6.77 (4.25–9.85) | 11.29 (8.35–14.23) |

Weighted percentages and (95% confidence interval).

### 4.3. Discussion

ADAMS has produced the first prevalence estimates of dementia, AD, VaD, and CIND in a nationally representative sample in the United States that included individuals from all regions of the country. To allow comparison with findings from previous studies using a lower minimum age (i.e., either age 60+ years or 65+ years), the estimates from ADAMS for individuals aged ≥71 years were combined with those from other studies for ages 60 to 70 years. This resulted in an estimated total of 3.7 million individuals with dementia and just over 2.5 million with AD in the United States. The sole previous national estimate of dementia prevalence was 2.9 million, based on a Delphi consensus review of previously published studies in the United States [28]. The four previous national estimates of AD prevalence differed by greater than two-fold and ranged from 2.1 [29] to 4.5 million [2,4]. The lowest estimate came from a meta-analysis of 18 U.S. and European studies; the highest from the East Boston and Chicago community studies [2,4]. Variability in prevalence estimates of AD because of geographic factors has been discussed. In addition to the issue of extrapolation from regional samples, one likely source for variation among AD prevalence estimates is the use of different criteria for dementia. Some studies used criteria that do not require evidence of impaired functional performance [16], whereas most used criteria requiring significant impairment in social or occupational functioning. Another possible source of study variation is the use of different methods to identify the "border" between CIND and dementia. To explore this point, additional analyses of ADAMS data were performed that included longitudinal 18-month follow-up assessments of those diagnosed with CIND. For these analyses, all those individuals who progressed to AD at follow-up were considered to have had "AD at baseline." Because the ADAMS sample consisted of individuals aged ≥71 years, prevalence estimates of dementia for age 60 to 71 years were obtained from other studies and combined with estimates from the present study. This resulted in an estimate of 3.1 million individuals aged ≥60 years with AD in the United States, which is an increase from the previous estimate of 2.3 million. These figures are still substantially lower than the highest AD prevalence estimates of 4.5 million [2,4].

In ADAMS, the prevalence of CIND is 22% or about 5.3 million individuals aged ≥71 years in the United States. These results suggest that the number of individuals with CIND in the United States is about 70% higher than the number with dementia. In the 71- to 79-year-old age group, 16% had CIND, whereas an additional 5% had dementia, suggesting that more than one in five individuals in this age group has cognitive impairment as well as considerable life expectancy. To date, there are no other national estimates of the number of individuals with CIND in the United States to compare with these ADAMS estimates. Studies of the frequency of other medical conditions, such as stroke, hypertension, and cancer, suggest substantial regional variation throughout the United States. Thus, similar regional differences for cognitive impairment are possible. Reviews often report CIND prevalence ranging widely from 5% to 29% [30,31]. Even so, it is striking that estimates from the few available U.S. regional and Canadian samples report CIND prevalence figures of 17% to 23% [32–34], closely bracketing the ADAMS estimate of 22%. Selected European population studies using different CIND criteria report prevalence rates ranging from 21% to 27% [35,36].

ADAMS has several strengths: a representative, directly assessed sample of the U.S. population aged ≥71 years; the inclusion of large numbers of individuals with few years of education; a sizeable sample of individuals aged >90 years; and the inclusion of long-term care residents. All of these groups have a high prevalence of CIND and dementia. In addition, using a single, experienced assessment team, successfully used in other population studies, and one common expert case review panel likely minimized diagnostic variability.

Some limitations also exist. The participation rate was lower than hoped for but comparable with other population studies of this age group, such as the Cardiovascular Health Study (participation rate of 57.3%) and the Canadian Study of Health and Aging (68.5%). Both studies have made major scientific contributions toward improved understanding of health and memory in late life. Nonparticipation in all such studies could result in selection bias. ADAMS has addressed potential nonresponse bias using detailed archived information from previous interviews, although models based on measures collected 6 to 18 months before the ADAMS assessment may not fully capture selection bias.

Table 4
National prevalence of cognitive impairment not dementia (CIND), by age categories

| Age (years) | All CIND N = 241 | Prodromal AD* N = 98 | Vascular CIND and stroke N = 54 | Medical conditions N = 55 |
|---|---|---|---|---|
| 71–79 | 16.0% (11.5–20.5) | 5.5% (2.6–8.4) | 3.57% (1.4–5.6) | 4.7% (1.2–8.3) |
| 80–89 | 29.2% (24.3–34.1) | 9.7% (6.4–13.1) | 10.1% (6.4–13.9) | 5.4% (2.1–8.7) |
| 90+ | 38.8% (25.6–52.0) | 22.1% (11.8–32.3) | 2.7% (0.00–6.0) | 9.4% (0.2–18.6) |
| Total | 22.0% (18.5–25.5) | 8.1% (6.3–9.8) | 5.7% (3.8–7.6) | 5.3% (2.5–8.0) |

AD, Alzheimer's disease.
Unweighted N's. Weighted percentages and (95% confidence interval).
*Includes mild cognitive impairment subtype of CIND.

However, given the range of available measures, it is possible that the response propensity models and the associated weighting adjustments do capture the major factors that could contribute to any significant selection bias in population estimates on the basis of the ADAMS data.

As the elderly U.S. population grows, the number of individuals with CIND and dementia will also increase, thereby making the planning for the long-term care needs of these individuals increasingly important. The value of ADAMS, the first study of CIND and dementia in a nationally representative sample in the United States, extends beyond just estimating prevalence to being able to address many key questions in preparing for the care of older adults with CIND and dementia. These prevalence estimates provide the framework necessary to assess the effect of treatment advances as they become available. In the years to come, the ADAMS methodology can provide a marker of how well the country is doing with respect to the control and treatment of AD and other dementias. Regional studies in the United States will now have a national estimate with which to compare when exploring regional differences in disease patterns. The ADAMS data can also be enriched with other data collected from the ongoing HRS and with linked Medicare administrative records, allowing researchers to explore questions that might increase our understanding of, and ability to successfully address, the needs of an aging U.S. population.

The ADAMS prevalence findings and accounts of how they were produced have been described previously [5–7].

## 5. Discussion

In principle, to determine prevalence one enumerates the underlying population and counts all its members who meet criteria for disease on a given day. Although it sounds simple, the task is not easy to accomplish. Sampling design, response factors, and diagnostic procedures all play key roles in determining the level of prevalence and its validity when proportions are applied to the U.S. population structure over a span of calendar years. Stratified sampling schemes designed to estimate a proportion, like prevalence, have their precision and variability tied to the number of strata, the expected prevalence in each stratum, and the allocation or sampling fraction within each stratum [37]. Researchers may opt for proportional sampling from strata, for so-called optimal sampling, or for other designs to achieve the overall estimate.

Before undertaking estimation of prevalence, it is important to ask why one would want to know prevalence. In other words, what would be the purpose of estimating prevalence of AD or dementia? Focusing on the prevalence of severe cognitive impairment and disability might allow the estimation of the number of nursing home beds, or demand for institutional care or home healthcare. Focusing on newly diagnosed cases might reveal the need for family and caregiver counseling and training to develop coping skills. Expanding beyond currently available data to estimate prevalence of asymptomatic cases might indicate "treatment demand" (should disease modifying treatments become available). Current prevalence data are tied to estimates of clinically diagnosable dementia and, therefore, reflect a more general disease-disability burden or cost-and-suffering index visited on society. Average prevalence proportions can be used to project numbers of beds or other resources required to adequately care for affected persons. Age-specific prevalence estimates have tended to vary, depending on the method used to ascertain cases and statistical methods used to calculate them. However, regardless of variation in prevalence proportions, the slopes of the age-prevalence curves appear to be rather similar. Specifically, estimated prevalence is reported to approximately double for every 5 years of age regardless of study [38].

Several elegant methods of estimating the prevalence of dementia and its subtypes were presented in this article. First, Brookmeyer's forward calculation method (section 2 and [8]) uses a carefully selected set of disease incidence estimates from existing published studies, coupled with survival estimates and competing risk data, to produce overall and age-specific prevalence proportions. The resulting prevalence estimates are then a function of both the rate at which new cases occur (incidence), and how long individuals live with the disease (duration or survival). Survival with the disease is also associated with their risk of dying from another disease (competing risks). Competing risks of death also vary by age, in kind, and in magnitude, and influence the observed dementia disease duration through their effects.

Both Brookmeyer (section 2 and [3]) and Evans and Hebert (section 3 and [4]) applied the forward calculation method to produce U.S. national prevalence estimates of AD. Brookmeyer uses source data from multiple studies, whereas Evans and Hebert use source data only from CHAP. Conceivably, the use of source data from multiple studies leads to an "average" definition of dementia and its onset may have some stability—so the composite prevalence is approximately equal to the incidence $\times$ the disease duration. The Evans and Hebert prevalence estimates were substantially higher than those of Brookmeyer.

Evans and Hebert, using a different projection approach, produced a second set of national prevalence estimates of AD on the basis of source data from EBSHP. Essentially they projected prevalence proportions from EBSHP to the larger national setting, taking into account various demographic variables. The resulting national estimates were very similar to those produced using CHAP incidence data and the forward calculation method (section 3 and [2]). It is worth noting that both EBSHP and CHAP were completed by virtually the same team of investigators in different cities (Boston and Chicago) using very similar, if not identical, disease criteria and definitions. Both studies used accepted sampling designs and techniques to conduct a two-stage case-finding approach.

ADAMS resulted from a national probability sample of persons aged >70 years (section 4 and [5,6]). Prevalence estimates were produced that were more similar to those

of Brookmeyer (section 2 and [3]) than they were to those generated from EBSHP and CHAP (section 3 and [2,4]). Despite careful design, only about half (n = 856) of the 1700 persons sampled agreed to participate, 308 of those were found to be demented, and an additional 241 were diagnosed as cognitively impaired. However, accounting for sampling design, the estimated prevalence proportions were somewhat lower than given by these raw numbers alone. Diagnosis was assigned primarily by an expert panel review of data collected through in-home neuropsychological testing and interview of the subjects selected. Despite its strong points and detailed arguments to the contrary, some skepticism is still raised by the relative low response rates, potentially causing bias in the estimates and the relatively small sample overall used to project nationwide numbers of affected persons. Brief in-home cognitive testing as a basis for case ascertainment could also have affected the determination of prevalence in unpredictable ways. In addition, the disease definition applied by the expert panel was somewhat different from those used in EBSHP and CHAP [1,13,15]. The ADAMS investigators realized many of these potential limitations and attempted to address and explain their possible effect.

For ADAMS, EBSHP, and CHAP, all participants were screened with a cognitive battery, and on that basis were stratified into those more likely to have dementia and those less likely to have the condition. Other demographic variables were also used to refine further the stratification. Then a stratified sample of persons (across all strata) was selected and provided with detailed evaluations. Strata with lowest scores (i.e., more likely dementia) may have had higher sampling fractions that those with higher scores (i.e., less likely dementia). Although the actual sampling fractions and stratum weights are somewhat unclear, it raises the possibility that, for EBSHP and CHAP, a few "cases" identified through clinical evaluation among those included in a stratum defined by higher scores, younger ages, and so forth, could cause the estimated overall prevalence estimate to be greater because of the weight they add to the stratum. This is presented only as a technical caveat for interpretation or explanation of why prevalence estimates could differ because of sampling methodology. Certainly the sampling methods and techniques used in part to ascertain prevalent or incident cases in ADAMS, EBSHP, and CHAP were well established and justified; thus, it may be more likely that differences in other factors could have lead to differences in estimates.

So, which estimate is "right" and which ones are left? It may come back to the purpose in formulating such estimates. Each study described earlier in this article has strong points as well as limitations. Agreement of figures from ADAMS and the forward calculation results of Brookmeyer, while interesting, does not diminish the greater estimated prevalence from EBSHP and CHAP. CHAP uses a forward calculation method similar to the one used in the Brookmeyer study, yet CHAP and EBSHP use the same disease definitions and arrive at similar prevalence estimates. Thus, differences in disease definition and threshold seem to drive differences in prevalence.

Adding earlier stage or milder cases from along the clinical disease continuum, or broadening the definition of disease could certainly affect projections of disease burden. More recently, it has also been hypothesized, through the results of imaging and biomarker studies [39] as well as neuropathological studies, that certain pathological features of AD may form many years before any symptoms are observable clinically. This has led the research field to conceive of asymptomatic prevalence, but prevalence studies of that construct seem far off in the future. Or maybe not.

Although delaying symptom onset may decrease clinical prevalence (primarily because of competing risks of death), delaying symptom progression could potentially increase prevalence if the force of competing mortality risks were not as strong in those affected with dementia. Thus, the way in which neurodegeneration of AD affects body systems, other than simply cognition, may contribute to the estimated prevalence. For example, neurodegeneration and vascular pathology may interact synergistically [40], resulting in an increased symptom progression and a decreased survival. These hypothetical scenarios await substantiation but at the same time raise new potential prevalence targets for estimation. Estimating prevalence by disease severity strata for example, consistent with the Clinical Dementia Rating [41] or other common metric, may be additionally informative. Competing risks are also likely to vary by ethnicity and other factors. As more is learned and researchers are able to apply diagnostic biomarkers together with the probability of clinical disease expression, more useful and consistent prevalence estimates should become evident and would be tailored to specific purposes.

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