Alzheimer's Disease as a Cause of Death in the United States

Donna L. Hoyert, PhD
Harry M. Rosenberg, PhD

Drs. Hoyert and Rosenberg are with the Mortality Statistics Branch, Division of Vital Statistics, National Center for Health Statistics, Centers for Disease Control and Prevention. Dr. Hoyert is a Statistician (Demographer), and Dr. Rosenberg is the Chief of the Branch.

Address correspondence to Dr. Hoyert, Mortality Statistics Branch, NCHS, 6525 Belcrest Rd., Rm. 820, Hyattsville MD 20782; tel. 301-436-8884; fax 301-436-7066; e-mail <dlh7@cdc.gov>.

SYNOPSIS

Objective. To describe the scope of mortality from and trends in Alzheimer's disease, to show how Alzheimer's disease ranks as a leading cause of death, to describe a methodological change regarding ranking, and to discuss issues related to the reporting of Alzheimer's disease on death certificates.

Methods. The authors analyzed mortality data from the National Vital Statistics System.

Results. Alzheimer's disease has increasingly been reported as a cause of death on death certificates in the United States; however, this increase may represent a variety of factors including improved diagnosis and awareness of the disease or changes in the perception of Alzheimer's disease as a cause of death. In 1995, Alzheimer's disease was identified as the underlying cause of 20,606 deaths. Overall, Alzheimer's disease was the 14th leading cause of death in 1995; for people 65 years of age or older, it was the 8th leading cause of death. Both death rates and cause-of-death ranking differed by selected demographic variables.

Conclusions. In recognition of the importance of the condition as a major public health problem, Alzheimer's disease was added to the list of causes eligible to be ranked as leading causes of death in the United States beginning with mortality data for 1994. Several issues need to be kept in mind in interpreting mortality data on Alzheimer's disease, including how diagnoses are made, how the condition is classified, and the purpose of death certificates.

In recent decades, Alzheimer's disease has been recognized as an important public health problem that has individual, familial, and societal implications for health, finances, and well-being.[1,2] While the debilitating features of this and other dementing conditions have long been noted, widespread realization that the various conditions are distinct from normal aging and recognition that therapeutic, curative, and even preventive action may be possible are more recent developments.[2,3] Increasing awareness has led to an infusion of research funds for the study of causes, diagnosis, treatment, and other aspects of Alzheimer's disease.[2,4–6]

Although definite diagnosis of the condition still requires autopsy evidence, the criteria developed by the National Institute of Neurological and Commu-

nicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) have set standards for the clinical diagnosis of possible, probable, and definite Alzheimer's disease.[7] While use of standard diagnostic criteria promotes comparability across research studies, statistical estimates of the prevalence of Alzheimer's disease continue to vary widely (from 2.4% to 11.3% of the population ages 65 years and older), in part because of differences between studies (such as in how criteria are operationalized, in populations examined, or in geographic areas studied).[1–3,5]

Information from Death Certificates

Using information available from the National Vital Statistics System, the authors examined data on Alzheimer's mortality. Data in the National Vital Statistics System come from death certificates filed in the 50 states and the District of Columbia.[8] The National Center for Health Statistics (NCHS) has cooperative agreements with each state to compile their data into a national data file.

Medical information collected on the death certificate is provided in a two-part format as recommended by the World Health Organization.[9] Generally, more than one cause of death is reported on the death certificate, and together these causes are referred to as "multiple causes of death." For each death certificate, one of the causes is referred to as an "underlying cause of death," defined as the disease or injury that initiated the train of events leading directly to death or the circumstances of the accident or violence that produced the fatal injury.[8] To classify medical terms on the death certificate, NCHS uses the *International Classification of Diseases* (*ICD*).[8,10] Generally, the underlying cause is the item tabulated and presented for statistical purposes in the United States and other countries.[8]

The availability of data on Alzheimer's disease has increased as a result of revisions in the *ICD*. Under the *Eighth Revision* of the *ICD* (*ICDA-8*)—in effect in the United States from 1968 through 1978—deaths reported as caused by Alzheimer's disease were classified under the title "Senile and presenile dementia" (*ICDA-8* 290) in the U.S. Vital Statistics System.[11] It was specifically mentioned as one of the conditions included under the detailed title "Presenile dementia" (*ICDA-8 290.1*). With implementation of the *Ninth Revision* in 1979 (*ICD-9*), a separate title was introduced for Alzheimer's disease (*ICD-9* 331.0).[9]

Since the adoption of *ICD-9*, NCHS publications have used seven tabulation lists in presenting data on underlying causes of death.[8,12] Among them are the "each cause list," which is the entire tabular list of valid causes of mortality as delineated in *ICD-9*; the "list of 282 causes," which includes all of the causes of death required by the World Health Organization for international reporting purposes; and the List of 72 Selected Causes of Death, or "72 cause list," which is designed especially for presentation of health problems considered to be of greatest public health relevance in the United States. NCHS implemented the "72 cause list" beginning with 1979 data.

Inclusion of a specific condition or disease on the "72 cause list" makes data on that condition or disease more accessible to researchers because NCHS publishes routine information for this list of causes and determines the leading causes of death using this list.[13] However, although Alzheimer's disease has its own code in *ICD-9*, it is not separately identified in the "72 cause list" because of its low frequency as a reported cause of death when the list was developed; it is included in a residual category called "All other diseases."[14]

NCHS uses a standardized ranking procedure, developed and first recommended for use in the 1950s by a working group made up of state and Federal representatives, to identify diseases of public health importance.[13,15] Rankings are based on the number of deaths for which each of the 37 rankable causes from the "72 cause list" is recorded as the underlying cause of death (Figure 1).[13,14,16] NCHS determined which causes were eligible to be ranked at the same time that the seven tabulation lists were developed. Like the tabulation lists, the eligible causes are similar to those used in the preceding revision and reflect long-standing decisions about ranking procedures.[9] However, the "72 cause list" and the eligible causes from this list were modified to reflect changes between *ICD* revisions, mortality trends, and suggestions from other Federal agencies about proposed tabulation lists. HIV infection was added as a cause eligible to be ranked as a leading cause of death in the United States beginning with mortality data for 1987, and Alzheimer's disease was added starting with 1994 data.[12,16,17]

A description of the process leading to death is provided on the death certificate by physicians—including medical examiners or coroners—based on all available evidence and their medical knowledge. This statistical information provides baseline data on a wide assortment of diseases, information that is used for a variety of purposes including decisions about levels of research funding.[10]

Research on Alzheimer's Disease

Current research—on risk factors, biological and genetic markers, and potential causes—seeks to find ways to identify people at risk for Alzheimer's disease before the onset of symptoms, with the ultimate goal of delaying, if not preventing the disease.[6] Until that is possible, diagnosis and death set the bounds on the experience of living with Alzheimer's disease. Knowing what contributes to death provides information about the progression of the disease.[18,19] Kukull et al. have suggested that early in the course of the disease, people tend to die of unrelated conditions for which recognition or management are compromised by the existence of Alzheimer's.[19] They also contend that in the case of more severe or advanced disease, Alzheimer's disease and related diseases play a more direct role in death.[19]

The purpose of this paper is to describe the scope of and trends in mortality from Alzheimer's disease, to show how

List of 37 rankable causes of death from the "72 cause list" used by the National Center for Health Statistics, United States, 1979–1998

Condition	*ICD-9* code
Shigellosis and amebiasis	004,006
Tuberculosis	010–018
Whooping cough	033
Streptococcal sore throat, scarlatina, and erysipelas	034–035
Meningococcal infection	036
Septicemia	038
Acute poliomyelitis	045
Measles	055
Viral hepatitis	070
Syphilis	090–097
Malignant neoplasms, including neoplasms of lymphatic and hematopoietic tissues	140–208
Benign neoplasms, carcinoma in situ, and neoplasms of uncertain behavior and of unspecified nature	210–239
Diabetes mellitus	250
Nutritional deficiencies	260–269
Anemias	280–285
Meningitis	320–322
Diseases of heart	390–398,402,404–429
Hypertension with or without renal disease	401,403
Cerebrovascular diseases	430–438
Atherosclerosis	440
Acute bronchitis and bronchiolitis	466
Pneumonia and influenza	480–487
Chronic obstructive pulmonary diseases and allied conditions	490–496
Ulcer of stomach and duodenum	531–533
Appendicitis	540–543
Hernia of abdominal cavity and intestinal obstruction without mention of hernia	550–553,560
Chronic liver disease and cirrhosis	571
Cholelithiasis and other disorders of gallbladder	574–575
Nephritis, nephrotic syndrome, and nephrosis	580–589
Infections of kidney	590
Hyperplasia of prostate	600
Complications of pregnancy, childbirth, and the puerperium	630–676
Congenital anomalies	740–759
Certain conditions originating in the perinatal period[a]	760–779
Accidents and adverse effects	E800–E949
Suicide	E950–E959
Homicide and legal intervention	E960–E978

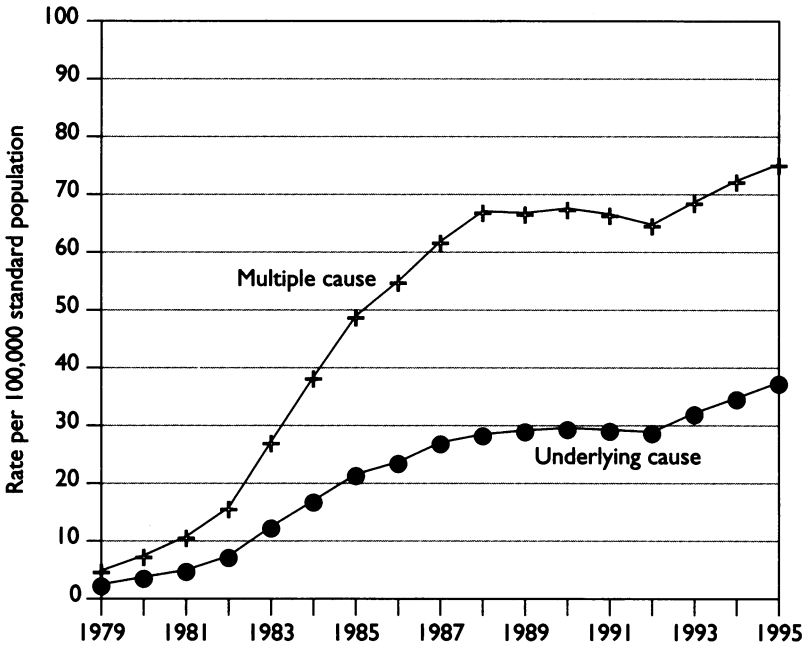
[a]Includes, among others, birth trauma, intrauterine hypoxia, birth asphyxia, and respiratory distress syndrome.
ICD-9 = Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death, 9th revision

Alzheimer's disease ranks as a leading cause of death, to describe changes in NCHS ranking procedures that make it possible for Alzheimer's disease to be ranked, and to discuss issues associated with reporting of Alzheimer's disease on death certificates. The usefulness of mortality data for the total population is limited by underreporting of Alzheimer's disease on death certificates;[20] however, these data can provide the public health community with useful estimates of the annual numbers of deaths at national and subnational levels, can show the ranking of Alzheimer's disease relative to other causes of death, and can provide information on the interrelationship of conditions that lead to death.

Methods

We used mortality data from the National Vital Statistics System for the analyses reported in this paper. To show the number of deaths for 1979 to 1995 that were reported to

Figure 1. Age-adjusted death rates per 100,000 standard population for Alzheimer's disease as an underlying cause of death or one of multiple causes of death, decedents ages 65 years and older, United States, 1979–1995



NOTE: Rates for Alzheimer's disease as one of multiple causes includes deaths for which the disease is listed as the underlying cause and deaths for which it is mentioned as one of the causes.

SOURCE: National Center for Health Statistics, National Vital Statistics System

involve Alzheimer's disease, we compiled underlying and multiple cause counts for Alzheimer's disease deaths (*ICD-9* 331.0*)*. The *underlying cause count* reflects physicians' reports of Alzheimer's disease as the underlying cause of death—the cause most important in explaining why death occurred at the time. We also used underlying cause counts in determining the ranking of causes and the ranking of leading causes of death. *Multiple cause counts* reflect any mention of Alzheimer's disease on the death certificate, regardless of the specific role the physician indicated Alzheimer's disease had in causing the death.

We calculated age-specific death rates to show mortality risk for dying of Alzheimer's disease for the population of a given age and to use in computing age-adjusted death rates. (The age-specific death rates are multiplied by a standard population of the same age, summed, and divided by the total of the standard population to get age-adjusted death rates.) The age-adjusted death rates are used to make comparisons between groups and over time.[8,16] This procedure removes the effect of changes in the population age distribution over time and of differences in the distribution between groups. Since most people with Alzheimer's disease reported on their death certificates are 65 years of age or older, we computed a parallel set of death rates for people in that age group. These rates were adjusted to remove the effect of changes in the population age distribution at 65 years of age or older.

Results

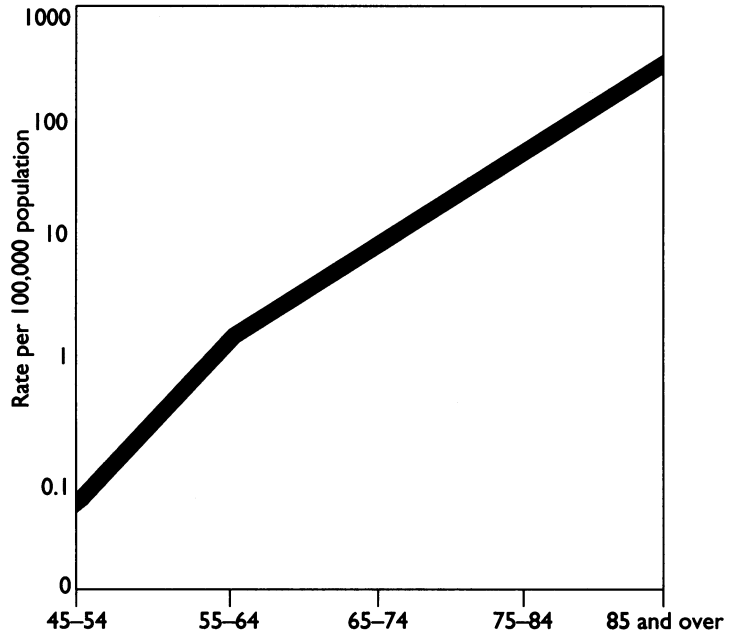
1995 mortality and 1979–1995 trends. In 1995, Alzheimer's disease was reported as the underlying cause of 20,606 deaths, with 20,230 of these deaths to people 65 years of age or older. Multiple cause data indicate that in 1995, Alzheimer's disease was listed as one of the causes of death on a total of 41,419 death certificates for all ages and 40,836 for people 65 years of age and older. Thus the total number of death certificates in which Alzheimer's disease was either recorded as the underlying cause of death or mentioned elsewhere on the death certificate was twice the number for which it was recorded only as the underlying cause of death (Figure 2).

As underlying cause. The trend for 1979 through 1995 in death rates for Alzheimer's disease as an underlying cause showed an increase (Figure 2), but the reasons for this increase in reporting are not clear, as discussed below. The age-adjusted death rate increased from 0.2 deaths per 100,000 standard population in 1979 to 2.7 deaths per 100,000 standard population in 1995. The corresponding age-adjusted death rate for people 65 years and older (Figure 2) increased from 2.5 deaths per 100,000 standard population in 1979 to 37.5 deaths per 100,000 standard population in 1995. While increases occurred throughout the time period, the rate of increase diminished substantially after 1985. Nevertheless, Alzheimer's disease showed the highest increase from 1994 to 1995 in the age-adjusted death rate of the 15 leading causes of death (data not shown).

Death rates for Alzheimer's disease as an underlying cause differed across age groups. In 1995, death rates ranged from 0.1 deaths per 100,000 population for people 45 to 54 years of age to 274.7 for people 85 years and older (Figure 3). The ratio of death rates for those 85 and older to death rates for those 45 to 54 years of age has increased over time as reporting has increased at the older ages. From 1994 to 1995, death rates for people 65 to 74 years old increased merely 1% while the increase for people 75 to 84 years of age was 10% and for those 85 years and older it was 9%.

Differentials persists in death rates for Alzheimer's dis-

Figure 2. Death rates for Alzheimer's disease as the underlying cause of death, by age group, United States, 1995



SOURCE: National Center for Health Statistics, National Vital Statistics System

ease as underlying cause by other demographic characteristics such as ethnicity and sex.[21] In 1995, age-adjusted rates for older males (37.7 per 100,000 standard population) were not significantly different from those for older females (37.1 per 100,000 standard population), in contrast to the roughly 70% difference in 1979 (Table 1).

Age-adjusted death rates for Alzheimer's disease tended to be greater for states in the Northeast and Northwest than for the United States overall (Figure 4); however, the differential between states diminished somewhat over time. For people 65 years or older, the highest age-adjusted state death rate for the period 1990–1994 was just under four times greater than the lowest age-adjusted state death rate, down from 4.25 times the lowest rate during the period 1979–1983.

Ranking. In 1994, Alzheimer's disease was the 14th leading cause of death for all ages combined, and the 9th for people ages 65 years and older (Table 2). In 1995 Alzheimer's was ranked as the 14th leading cause for all age groups combined but 8th for people 65 years old and older.[22] As in many other causes of death, Alzheimer's disease death rates differ by demographic characteristics. In 1995, Alzheimer's disease's ranking as a leading cause of death varied dramatically between the younger and older age groups (Table 2). The rank was higher in 1995 than in 1994 for males and for males and females 65 years and older. If Alzheimer's disease had been ranked before 1994, it would have been the 11th leading cause of death for people 65 years or older for 1987–1993 and the 15th leading cause of death for people of all ages in 1993.[16]

Discussion

Physicians are increasingly reporting Alzheimer's disease as a cause of death on death certificates. The reasons for this increase are not clear; however, some possibilities will be offered in this discussion.

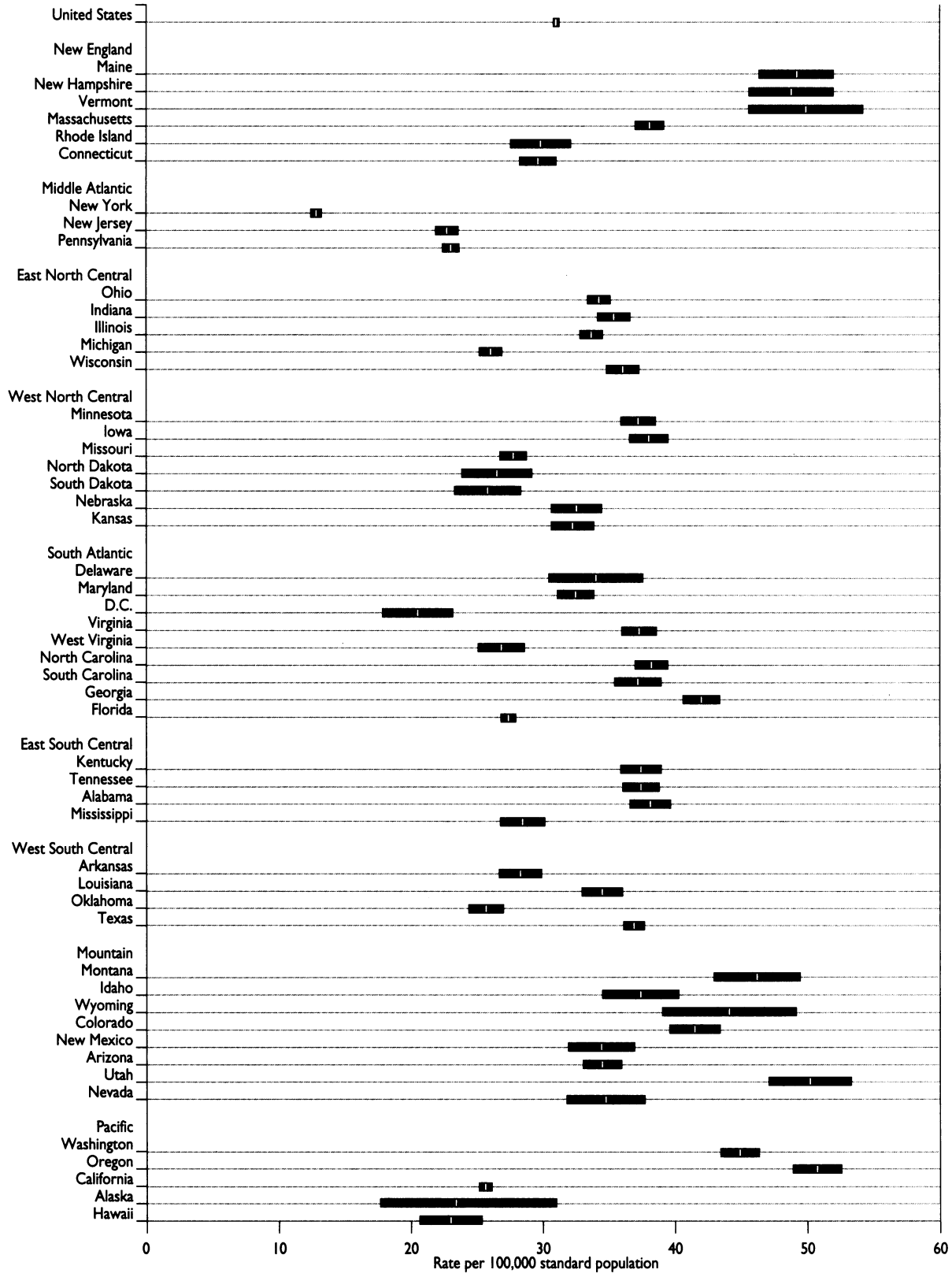
Flexibility versus comparability. The United States has routinely published mortality data using information from death certificates throughout this century. Having comparable data is important in order to analyze trends; however, scientific fields and their terminology evolve. A built-in means for staying abreast of the evolution in terminology is the periodic revision of the *ICD* and routine evaluation studies of the effects of changes in classification on mortality statistics. However, occasionally changes need to be made between *ICD* revisions.

Since the implementation of *ICD-9*, HIV infection emerged and quickly became a major public health issue and Alzheimer's disease was increasingly recognized as an important public health issue as well.[2] In response to these two developments, access to data on these causes was improved by adding tabular material to routine publications and making both causes eligible for ranking. The addition of HIV infection to the list of rankable causes of death effective in 1987 and the addition of Alzheimer's disease as a rankable cause of death effective in 1994 demonstrate a needed flexibility on the part of NCHS in the presentation of health data for the identification and surveillance of health problems. Yet NCHS tabulation lists using *ICD-9* codes remained as they were when *ICD-9* was first introduced, ensuring comparability and continuity in mortality tabulations over time.

Issues in the use and interpretation of data.

Categorization. Categorization of Alzheimer's disease in mortality statistics depends on the way the disease is reported on death certificates. The specific terms used to report a dementing condition will determine how a death is categorized under the classifications outlined in the *ICD*. It is possible that some Alzheimer's disease deaths will be classified under titles other than the separate category of Alzheimer's disease. In some circumstances, it may be useful for researchers to aggregate data on a group of dementing conditions. This might be done, for example, to examine mortality in people with similar symptoms or to include deaths that may have been due to Alzheimer's disease but were not reported specifically as such.

Figure 3. Age-adjusted death rates per 100,000 standard population and 95% confidence intervals for decedents 65 years of age and older, by state, United States, 1990 to 1994



SOURCE: National Center for Health Statistics, National Vital Statistics System

Table 1. Age-adjusted death rates per 100,000 standard population for Alzheimer's disease as the underlying cause of death, United States, 1979 and 1995

	1979		1995	
	All ages	65 and older	All ages	65 and older
Sex	0.2	2.5	2.7	37.5
Men	0.3	3.1	2.7	37.7
Women	0.2	2.0	2.7	37.1

SOURCE: National Center for Health Statistics, National Vital Statistics System

Reporting and diagnosis. Medical personnel reporting deaths on the death certificate are reporting their opinion of the causes or sequence of causes contributing to death based on their medical knowledge and the available evidence. Thus, they should have diagnostic evidence that a condition existed, believe in general that the condition could be a cause of death, and believe that the condition contributed to death in this specific case. If the physician (including medical examiners or coroners) does not believe that Alzheimer's disease played a role in causing a death even if the decedent was thought to have suffered from the disease, then Alzheimer's disease should not be reported. For this reason, the death certificate is not an appropriate source of data on incidence or prevalence.

The accuracy of mortality data is dependent on the ability of medical personnel to identify the condition. Some suggest that Alzheimer's disease should always be reported on the death certificate for every decedent diagnosed as having the disease;[23–25] however, this view is not universally held. Interest or willingness to make a diagnosis of any disease may reflect awareness, training, and knowledge; the potential benefits for treatment in making a diagnosis; and the tools available to make a diagnosis. While diagnostic tools and knowledge and awareness of Alzheimer's disease have increased,[6] treatment options are still fairly limited.

Several studies have documented that Alzheimer's disease is not necessarily reported on the death certificate for people diagnosed as having the disease.[19,20,24,26] Reporting is more likely when the condition is more severe.[19,20] A few studies have found reporting differences depending on the place of death (nursing home versus hospital), but this is not consistent across studies.[20,27,28] Inclusion on death certificates does not seem to differ by sex.[20,27]

While researchers have begun to examine the characteristics and settings that are associated with reporting on the death certificate, factors affecting individual physicians' decisions about putting Alzheimer's disease on the death certificate have not been examined. Possibly, diagnostic evidence is more likely to be available in nursing home records than in hospital records or perhaps nursing home medical personnel are more familiar with individual medical histories. Diagnosis is more likely when the condition is more severe. However, these studies have not examined the possibility of medical personnel dismissing Alzheimer's disease as a possible cause of death even when the diagnosis is made. Finally, some research suggests that reporting levels are improving over time,[27,29] which may reflect changes in awareness within the medical community.[20,25]

While a research study can control and standardize diagnostic criteria, death certification relies upon variable diagnostic evidence. The existence of a set of standard diagnostic criteria[2,7,30] such as those in the NINCDS-ADRDA guidelines has the potential for raising the adequacy of diagnosis in the general population to the point that measures of prevalence and mortality are reasonable for surveillance purposes. The degree to which medical personnel do a diagnostic workup probably reflects the benefits they perceive of having that diagnostic evidence and may depend on the specialty of the physician.[31] Failure to diagnose Alzheimer's disease would still result in underreporting on death certificates; on

Table 2. Rank of Alzheimer's disease among 15 leading causes of death and number of deaths in which Alzheimer's disease was reported as the underlying cause of death by selected characteristics, United States, 1994 and 1995

Characteristic	1994		1995	
	Rank	Number of deaths	Rank	Number of deaths
All ages	14	18,584	14	20,606
Male	...[a]	6377	15	6999
Female	8	12,207	8	13,607
Under 65 years of age	...[a]	367	...[a]	376
Male	...[a]	175	...[a]	162
Female	...[a]	192	...[a]	214
65 years of age or older	9	18,217	8	20,230
Male	10	6202	9	6837
Female	8	12,015	8	13,393

NOTE: Ranking based on number of deaths for which the condition was reported as the underlying cause of death.

[a]Alzheimer's disease was not one of the 15 leading causes of death for this group.

SOURCE: National Center for Health Statistics, National Vital Statistics System

the other hand, reporting influenced by diagnostic fashion could be overinclusive, which would result in overreporting.[32]

Changes in diagnostic practices having an impact on mortality statistics is not without precedent. For example, in the case of brain tumors, an analysis of mortality trends concluded that technological advances in diagnosis as well as increasing willingness to do diagnostic workups for the elderly resulted in increasing death rates over time.[33] In part, the trend in Alzheimer's disease may also reflect changes in awareness and diagnostic testing.

Demographic differentials. As reporting of Alzheimer's disease has increased, differentials by ethnicity, sex, and geography have attenuated while those by age have increased. Increases in reporting of Alzheimer's deaths, particularly among the very old, probably reflects improvements in reporting on death certificates. Strong positive associations between age and Alzheimer's disease incidence and prevalence are repeatedly found in studies.[3,5] Mortality data from vital statistics indicate that males are at a survival disadvantage compared to women; however, for Alzheimer's disease this differential lessened over time between 1979 and 1995. There is some evidence in the literature to support the finding of a differential between males and females in death rates,[5] but perhaps the attenuation of the differential over time in vital statistics represents improvement in mortality information available in recent years.[27] It is likely that for Alzheimer's disease as for other causes of death some of the geographic differences represent diagnostic and reporting differences rather than real differences in mortality risk from this cause.

Leading causes. Work by Katzman[23] is often cited in the literature to suggest that Alzheimer's disease is the fourth or fifth leading cause of death.[20] In 1976 when Katzman was writing about Alzheimer's disease, mortality data were classified according to *ICDA-8*.[11] Alzheimer's disease was not classified separately but was included in the specific category of "Presenile dementia" (*ICDA-8* 290.1) and broader category "Senile and presenile dementia (*ICDA-8* 290), for which relatively few deaths were reported. Instead of using the reported number of deaths for the broader category, which ignores the distinction by age of onset, Katzman estimated the number of deaths of people dying "with senile dementia" using estimates of the prevalence and mortality risk of Alzheimer's disease.[23] This estimated number of deaths placed Alzheimer's disease around the fifth leading cause of death at the time.

Katzman's procedure, however, differs from the NCHS procedures, which require explicit reporting of the condition on the death certificate as the underlying cause and require that the condition be among the rankable causes of death. Katzman's method seems to assume that in all of the estimated 60,000 to 90,000 deaths, Alzheimer's disease would be reported as the underlying cause of death on the death certificate. However, we suspect that even if Alzheimer's disease had been reported, in a substantial percent of cases it was likely to have been reported as contributing rather than causing death. The 60,000 to 90,000 estimate for Alzheimer's disease as a multiple cause would have placed it around the eighth leading cause of death relative to the multiple cause counts for causes eligible for ranking in the 1970s.

ICD-10. NCHS uses the *ICD* to classify mortality data, and the *ICD* is revised periodically. Currently, NCHS is using the *Ninth Revision,* but a *Tenth Revision* has been developed.[34] NCHS plans to implement the *Tenth Revision* for data year 1999. NCHS's recent addition of Alzheimer's disease to the list of rankable causes of death anticipates changes that will take place with the implementation of *ICD-10* in addition to fulfilling current public interest in getting better access to these data. Under *ICD-10,* Alzheimer's disease is one of the conditions listed separately in WHO's recommended "General Mortality—Selected List"[34] and therefore will also be included in the *ICD-10* version of the tabulation list, which is currently being developed.

Conclusions

While the number of people afflicted with Alzheimer's disease may be increasing simply because the population is aging, some research suggests that the prevalence has increased as well.[35] Data from death certificates also indicate an increasing trend for mortality; however, the reasons for the mortality trend are not straightforward. It is likely that this trend primarily reflects improvements in reporting and diagnosis. However, the rate of increase in reporting slowed substantially after 1985. In recognition of the frequency with which Alzheimer's disease is reported as a cause of death and the high level of interest in this condition, NCHS has made several changes to make data on this condition more accessible to the public (such as making it eligible for ranking, adding tabular material to routine publications, and putting tables up on Internet sites).

Alzheimer's disease causes substantial functional impairment for many in the elderly population, creates an increasingly demanding role for informal and formal caregivers, complicates treatment of other medical conditions, and, in the end, shortens many elderly people' lives.[6,19] The public health community attempts to play a role by developing programs to respond to each of the various effects of Alzheimer's disease; statistics on this disease provide an essential basis for developing these programs. Statistics on the size of the community afflicted and the numbers dying with the condition provide information on the resources needed to solve specific problems. Information on how the disease unfolds and relationships between Alzheimer's disease and other conditions contribute to current palliative care and point out further research needed.

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