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Survival following dementia onset: Alzheimer's disease and vascular dementia

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Abstract

Survival following the onset of dementia has been reported to vary from 3 to over 9 years. We examined mortality in 3602 participants of the Cardiovascular Health (CHS) Cognition Study in four US communities evaluated for dementia incidence between 1992 and 1999 and followed for 6.5 years. By June 2000, 33 of 62 (53.2%) participants who developed vascular dementia (VaD) had died compared to 79 of 245 (32.2%) with Alzheimer's disease (AD), 66 of 151 (43.7%) with both AD and VaD, and 429 of 2318 (18.5%) with normal cognition. Using Cox proportional hazards regression with a time-dependent covariate for dementia status adjusted for age, gender and race, individuals with VaD were more than four times as likely to die during follow-up than those with normal cognition (HR: 4.4, 95% CI: 3.1–6.3). The hazard ratios were 2.1 (95% CI: 1.6–2.7) for AD and 2.5 (95% CI: 1.9–3.3) for both types. Adjusted accelerated life models estimated median survival from dementia onset to death as 3.9 years for those with VaD, 7.1 years for AD, 5.4 years for mixed dementia, and 11.0 years for matched controls with normal cognition. While persons with VaD died primarily from cerebrovascular disease, those with AD/mixed dementia died more frequently from dementia/failure to thrive.

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Keywords: Survival; Mortality; Dementia; Alzheimer's disease; Vascular dementia; Mixed dementia; Cause of death

1. Introduction

As life expectancy increases and the number of older adults developing dementia continues to grow, information on survival following the onset of dementia has become an important public health issue. In terms of healthcare expenditures, the formal costs related to medical care for demented persons can be considerable. In the United States, costs for care have been estimated to average over \$27,500 per patient annually [1]. While "cost" is traditionally thought of as the financial burden of medical care and use of healthcare resources, there are also informal costs incurred

including the value of the caregiver's time and loss of income, out-of-pocket expenditures for formal caregiving costs, and the caregiver's excess health costs [2]. These have been estimated to range between an additional \$10,000–\$35,000 per person per year [1]. Finally, nonfinancial burden of this disease, including the psychological distress and the effect on quality of life for both patient and caregiver alike, plays an important part in the public health impact of dementia [3]. Estimates of the risk of mortality and length of survival in persons after dementia onset are important to help in the planning of resources needed for care.

Although it is generally agreed that the diagnosis of dementia reduces life expectancy, the estimated number of years for survival following the onset of dementia varies. One of the longest estimates for median survival following dementia was 9.3 years [4]; this sample consisted of outpatients with Alzheimer's disease (AD). Three studies

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have estimated length of survival for both AD and vascular dementia (VaD) in the same sample. Molsa et al. [5] estimated overall survival for dementia inpatients to be 5 years for both AD and “multi-infarct” dementia. Correcting for “length bias” which overestimates survival due to the lack of severe cases entering studies [6], Wolfson et al. [7] calculated survival after probable AD to be 3.1 years, 3.5 for possible AD, and 3.3 years for VaD. Most recently, Knopman et al. [8] estimated median survival for AD to be 6.1 years and for VaD to be 3.3 years. The need for prospective studies to evaluate mortality following dementia using standardized criteria has been emphasized [9]. In the Cardiovascular Health (CHS) Cognition Study, a population-based cohort evaluated for dementia incidence, date of onset was determined for dementia cases using prospectively collected longitudinal data, thus allowing for estimates of survival to be calculated eliminating length bias.

2. Materials and methods

2.1. The cohort

The Cardiovascular Health Study (CHS) was initiated in 1989 to evaluate risk factors for cardiovascular disease in adults age 65 or older [10]. A total of 5201 individuals were recruited from Medicare eligibility lists in four US communities: Forsyth county, NC, Washington county, MD, Sacramento county, CA, and Pittsburgh, PA [11]. In 1992, an additional 687 African-Americans were recruited into the study. Informed consent was obtained from all participants at entry into the study and at periodic intervals. Institutional Review Board approval was received at all sites collecting and analyzing data. In brief, CHS participants completed up to 10 annual clinic visits at which thorough physical examinations and medical data were collected at each. This included data on demographics, anthropometry, blood pressure, psychosocial interviews, depression, medical history, health behaviors, physical function, hematology, and medications. Cognitive function was collected using the Modified Mini-Mental State Exam [12], Digit Symbol Substitution Test [13], Benton Visual Retention Test [14]. Several other procedures were done throughout follow-up including carotid ultrasound, echocardiography, retinal imaging, electrocardiograms, and spirometry. Cranial magnetic resonance imaging (MRI) was done twice, once in 1992–1994 and again in 1997–1999 following a standardized protocol on eligible participants [15]. Extensive evaluation of cardiovascular events, all hospitalizations, and mortality was done during study follow-up through 2002 [16].

2.2. Evaluation of dementia

An ancillary study to the CHS, the CHS Cognition Study, was initiated in 1998 to evaluate dementia in a subset of the cohort. Detailed methodology for this study has been

described elsewhere [17,18]. Eligibility for the study included completion of an MRI and 3MSE in 1992–1994. Dementia status was ascertained through the year 2000 on 3602 participants using data already collected in the CHS supplemented with additional cognitive measures. Individuals were screened using the 3MSE and other parameters. Those failing the screening and still living were invited back to the clinic for detailed neuropsychological testing. If the participant was deceased or unwilling to come into the clinic, additional data were collected from medical records, physician questionnaires and interviews with the participant or family members including the Telephone Interview for Cognitive Status [19], Neuropsychiatric Inventory [20], IQCode [21], and/or Dementia Questionnaire [22].

A committee of neurologists and psychiatrists from all four clinical centers evaluated data to classify dementia in participants. A clinical definition of dementia was used based on a progressive or static cognitive deficit of sufficient severity to affect the subjects’ activities of daily living, and history of normal intellectual function before the onset of cognitive abnormalities. Participants were also required to have impairments in two cognitive domains, which did not necessarily include memory [17]. This correlates very closely to DSM-IV criteria [23]. Individuals who did not meet criteria for dementia but who were documented with cognitive deficits were classified as having mild cognitive impairment (MCI) [24]. Type of dementia was classified using several standardized criteria and the MRIs available for each participant. For these analyses, the National Institute of Neurological and Communicative Diseases and Stroke–Alzheimer Disease and Related Disorders Association (NINCDS-ADRDA) criteria [25] was used to ascertain AD and the State of California Alzheimer’s Disease Diagnostic and Treatment Centers (ADDTC) criteria [26] was used for VaD. Year of onset was determined by review of the longitudinal cognition exams collected in the main study as well as annual measures of depression, medication use, activities of daily living, hospitalizations, and by family member input collected in the Dementia Questionnaire. Cause of death was classified independently by a separate committee of CHS physicians with expertise in geriatrics [16]. This group of physicians used medical records, death certificates, physician questionnaires, nursing home notes and informant interviews when making their determination.

2.3. Statistical analyses

Individuals with prevalent dementia at entry into the cohort and classified with mild cognitive impairment were excluded from these analyses. The Statistical Package for the Social Sciences, version 11.0 [27], and STATA [28] were used to analyze data for this study. Descriptive statistics were presented and chi-square tests or analysis of variance tested for differences between dementia status groups for categorical or continuous variables, respectively.

Cox proportional hazards regression estimated relative risk of mortality by dementia type compared to those with normal cognition using a time-dependent covariate for dementia status. Both crude models and those adjusted for age, gender and race were done. To estimate median survival for participants with dementia, we used accelerated failure time models based on time from dementia onset until death or censor date adjusted for age, race and gender [29]. These models can extrapolate survival time when follow-up has not yet reached specific time parameters. In order to calculate a comparable median survival for persons without dementia, we matched each case by age (5-year age group) and gender to a participant with normal cognition and set the control's index date to the date of dementia onset of the matched case. There was not a sufficient number of minorities in the cohort to match on race, and thus race could only be included as a covariate in the models. Time from index date until death or censor date was used to estimate median survival for these controls. To determine if effect modification were present, we also examined risk of death by several strata including gender. If apparent, results by strata were presented.

3. Results

Of the 3602 CHS Cognition Study participants evaluated for dementia, 577 with dementia prevalent at entry into the cohort and 227 determined to have mild cognitive impairment (for which we did not have a date of onset)

were excluded leaving 2318 persons with normal cognition and 480 with subsequent incident dementia for analyses. Of those with dementia, 245 were classified with NINCDS-ADRDA AD (no VaD), 151 with mixed dementia, 62 with ADDTC VaD (no AD) and 22 had other types including Parkinson's disease dementia and dementia with Lewy bodies. For calculation of median survival, 480 matched controls with normal cognition were identified and utilized.

At entry into the cohort, average age was 75.1 years and participants were followed for an average of 6.5 years. Examining baseline characteristics, participants with dementia were found to be older, of nonwhite race, and with lower levels of education (Table 1). Those with vascular and mixed dementia also had a higher baseline prevalence of coronary heart disease and hypertension and a history of stroke. Individuals with AD were more likely to carry the $\epsilon 4$ allele of the APOE genotype. By June 2000, 33 of 62 (53.2%) participants who had developed VaD had died compared to 79 of 245 (32.2%) with AD, 66 of 151 (43.7%) with both AD and VaD, and 429 of 2318 (18.5%) with normal cognition.

Using Cox proportional hazards regression with a time-dependent covariate for dementia status adjusted for age, gender and race (Table 2), individuals with dementia had an increased risk of death almost four times that of persons without dementia (unadjusted HR: 3.9; 95% CI: 3.2–4.6). This hazard ratio remained at 2.8 (95% CI: 2.3–3.4) when adjusted for age, race and gender. Differences were found when the three dementia types were modeled separately.

Table 1

Selected characteristics of individuals classified with incident Alzheimer's disease, vascular dementia, or normal cognition after enrollment in the CHS Cognition Study, 1992–1994

Characteristic	Normal cognition	Alzheimer's disease ^a	Mixed dementia ^b	Vascular dementia ^c	<i>p</i> ^d
<i>N</i>	2318	245	151	62	
	<i>N</i> (%) or mean (S.D.)	<i>N</i> (%) or mean (S.D.)	<i>N</i> (%) or mean (S.D.)	<i>N</i> (%) or mean (S.D.)	
Mean age (years)	76.2 (5.2)	80.1 (5.7)	79.8 (6.3)	78.3 (5.2)	<0.001
Male gender	951 (41.0)	83 (33.9)	65 (43.0)	33 (53.2)	0.03
Non-white race	216 (9.3)	42 (17.1)	21 (13.9)	11 (17.7)	<0.001
Education					
Some high school or less	443 (19.2)	91 (37.1)	42 (27.8)	17 (27.4)	<0.001
High school graduate	680 (29.4)	57 (23.3)	40 (26.5)	20 (32.3)	
Some college	611 (26.4)	45 (18.4)	32 (21.2)	10 (16.1)	
College degree or higher	579 (25.0)	52 (21.1)	37 (24.5)	15 (24.2)	
History of CHD	425 (18.3)	56 (22.9)	39 (25.8)	22 (35.5)	0.001
History of Stroke	86 (3.7)	3 (1.2)	20 (13.2)	16 (25.8)	<0.001
Hypertension	983 (42.4)	107 (43.7)	81 (53.6)	40 (64.5)	<0.001
Smoking status					
Never	1030 (44.5)	126 (51.4)	81 (53.6)	20 (32.3)	0.03
Former	1083 (46.7)	99 (40.4)	60 (39.7)	33 (53.2)	
Current	204 (8.8)	20 (8.2)	10 (6.6)	9 (14.5)	
APOE-4 allele	465 (21.7)	81 (39.1)	45 (33.8)	11 (19.0)	<0.001
Deceased during follow-up	429 (18.5)	79 (32.2)	66 (43.7)	33 (53.2)	<0.001

^a AD only (no VaD) using NINCDS-ADRDA criteria.

^b Classified with both AD and VaD.

^c VaD only (no AD) using ADDTC criteria.

^d Chi-square or ANOVA *p*-value.

Table 2
Associations of incident dementia and type of dementia with risk of mortality following onset in participants of the CHS Cognition Study

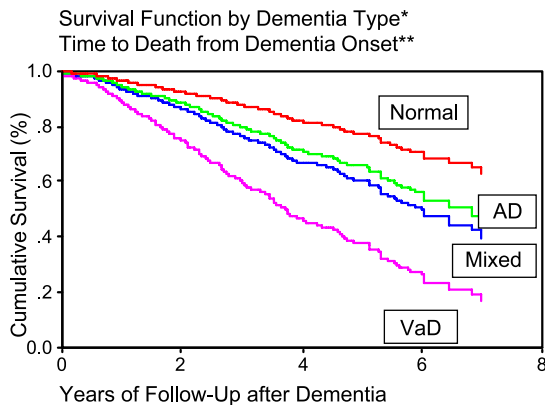
Dementia status	Deaths/N	Unadjusted HR (95% CI)	Adjusted HR (95% CI) ^a
Normal cognition	429/2318	1.0 (reference)	1.0 (reference)
Total dementia	190/480	3.9 (3.2–4.6)	2.8 (2.3–3.4)
AD only ^b	79/245	3.0 (2.3–3.8)	2.1 (1.6–2.7)
Mixed dementia ^c	66/151	3.8 (2.9–4.9)	2.5 (1.9–3.3)
VaD only ^d	33/62	5.7 (4.0–8.2)	4.4 (3.1–6.3)

^a Adjusted for age at entry into the cohort, gender and race.
^b AD only (no VaD) using NINCDS-ADRDA criteria.
^c Classified with both AD and VaD.
^d VaD only (no AD) using ADDTC criteria.

Adjusted for age, race, and gender, persons with VaD were more than four times as likely to die during follow-up than those with normal cognitive status (HR: 4.4, 95% CI: 3.1–6.3). The hazard ratios were 2.1 (95% CI: 1.6–2.7) for AD and 2.5 (95% CI: 1.9–3.3) for both types.

The survival function showing relative rates of mortality following dementia onset from Cox survival analysis is presented in Fig. 1. Dementia status was significantly associated with risk of death adjusted for age, race and gender in this model ($p < 0.0001$). Adjusted for age, gender and race, median survival from dementia onset to death was less for those with all types of dementia compared to those with normal cognition (Table 3). Median survival was estimated to be 3.9 (3.5–4.2) years for those with VaD only, 7.1 (6.7–7.5) years for those with AD only, and 5.4 (5.2–6.0) years for those with both types of dementia. This is compared to a median survival of 11.0 (10.5–11.7) years for those without dementia.

Cause of death also differed significantly by dementia status (Table 4). Most persons classified with dementia died



* AD was classified using NINCDS-ADRDA criteria and VaD used ADDTC criteria.
 ** Follow-up begins at date of onset for dementia cases and at the index date for controls matched to cases on age and gender.

Fig. 1. Survival function from dementia onset (or index date) to death by type of dementia for participants of the CHS Cognition Study using Cox proportional hazards regression adjusted for age at entry into the cohort, race and gender. Rates for participants with Alzheimer's disease (AD), mixed dementia (both AD and VaD), vascular dementia (VaD) and controls matched to cases on age and gender with normal cognition are shown.

Table 3
Estimated median survival by type of dementia using accelerated life models adjusted for age, race and gender

Type of dementia	Median survival (years)	95% Confidence limits
Normal cognition ^a	11.0	10.5–11.7
Alzheimer's disease ^b	7.1	6.7–7.5
Mixed dementia ^c	5.4	5.2–6.0
Vascular dementia ^d	3.9	3.5–4.2

^a Controls matched to dementia cases by age and gender and index date set to onset of dementia of the case.
^b AD only (no VaD) using NINCDS-ADRDA criteria.
^c Classified with both AD and VaD.
^d VaD only (no AD) using ADDTC criteria.

of causes other than the dementia syndrome itself. Individuals with VaD were more likely to die of cerebrovascular disease (42.4%) than those with AD (8.8%), both types (9.1%) or with normal cognition (7.5%). Those with normal cognition were more likely to die from cancer (40.1%) or coronary heart disease (25.4%) compared to persons with dementia.

When examining risk of death for each type of dementia by gender, there were little differences between men and women for those with AD or mixed dementia (Fig. 2). However, women with vascular dementia were at a greater risk of death than were men. Adjusted for age and race, the

Table 4
Cause of death in 607 CHS Cognition Study participants classified with dementia prior to death by dementia type (chi-square $p < 0.001$)

Cause of death	Type of dementia			
	Normal cognition	Alzheimer's disease ^a	Mixed dementia ^b	Vascular dementia ^c
Total N deceased	429	79	66	33
	N (%)	N (%)	N (%)	N (%)
Coronary heart disease	109 (25.4)	15 (19.0)	15 (22.7)	4 (12.1)
Cerebrovascular disease	32 (7.5)	7 (8.8)	6 (9.1)	14 (42.4)
Other cardiovascular disease	23 (5.4)	4 (5.1)	2 (3.0)	1 (3.0)
Cancer	172 (40.1)	14 (17.7)	7 (10.6)	3 (9.1)
Dementia/failure to thrive	2 (0.5)	15 (19.0)	17 (25.8)	2 (6.1)
Pneumonia/respiratory conditions	35 (8.1)	6 (7.6)	7 (10.6)	5 (15.1)
Sepsis/infection	7 (1.6)	4 (5.1)	2 (3.0)	2 (6.1)
Accident/trauma	14 (3.3)	0 (0.0)	3 (4.6)	0 (0.0)
Other non-cardiovascular	35 (8.1)	14 (17.7)	7 (10.6)	2 (6.1)

^a AD only (no VaD) using NINCDS-ADRDA criteria.
^b Classified with both AD and VaD.
^c VaD only (no AD) using ADDTC criteria.

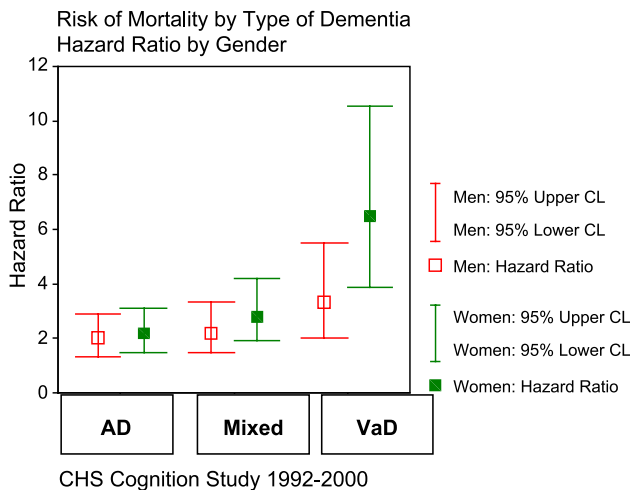


Fig. 2. Risk of mortality following dementia onset by type of dementia showing results for men and women separately. Hazard ratios and 95% upper and lower confidence limits (CL) are shown for Alzheimer's disease (AD), vascular dementia (VaD) and mixed dementia (both AD and VaD).

hazard ratio for risk of death was 6.5 (3.9–10.9) for women while it was 3.3 (2.0–5.5) for men.

4. Discussion

Death following dementia onset was examined in the CHS Cognition Study, a prospective cohort followed for an average of 6.5 years after entry into the study. Risk of death after onset of dementia was highest for those classified with VaD (HR 4.4, 95% CI: 3.1–6.3 adjusted for age, race and gender) than for AD (HR: 2.1, 95% CI: 1.6–2.7) or mixed dementia (HR: 2.5, 95% CI: 1.9–3.3). Similarly, estimated median survival was shortest for those with VaD (3.9 years) compared to those with AD (7.1 years), mixed dementia (5.4 years) or with normal cognition (11.0 years). Cause of death and estimated median survival differed by type of dementia. Women with VaD were at a higher risk of death than were men.

The estimates for survival produced here using prospectively collected data for date of onset resulted in median survival estimates within the range of those reported by others. Our results are closest to those reported by Knopman et al. [8] who found differences in survival by type of dementia (6.1 years for AD and 3.3 years for VaD) as well as by criteria used to classify type. The other two studies assessing both AD and VaD did not find differences between the two dementia types. While our estimate for VaD is similar to Wolfson et al.'s estimate of 3.3 years [7], our AD estimate is much longer than theirs of 3.1 years for probable AD and 3.5 years for possible AD. The overall estimate by Molsa et al. of 5 years [5], who also found no difference by type, is midway between our two estimates for VaD and AD. In terms of studies only examining AD, our result is less than that of the 9.3 years estimated by Walsh et al. [4] but right within the range of 3.9–8.3 years estimated

by Brookmeyer et al., who found survival to differ by age at diagnosis [30]. A fourth study examining both AD and VaD had reported length of survival to be 6.1 years with no difference between AD or VaD; however, this study focused on presenile dementia in men and women age 45–64 years [31] which may not be directly comparable to data from other studies of older adults.

A number of reasons may be involved in the differences reported among studies. As Knopman et al. [8] has shown, the criteria used for defining type of dementia has a great impact on differences in survival estimated for each type. This is most likely a major explanation for many of the discrepancies found between these studies. The data available to make the classification of dementia type is of critical importance, especially access to imaging when determining the presence of VaD. Methods for assessing onset will also affect duration of survival. Whereas in our study, the annually collected cognitive scores were primarily used to determine onset, many other studies rely on presentation to a physician or formal clinical diagnosis from medical records. It is also possible that differences in demographics including age distribution, gender mix, and geographic region may have influenced results in these studies. Differences in median survival by age at diagnosis have also been reported [31]. Persons diagnosed at age 65, for example, had a median survival of 8.3 years compared to 3.4 years for those diagnosed at age 90. The primary difference between the Wolfson et al.'s shorter survival estimates involved their application of a correction formula for length bias, which is assumed to occur because persons with rapidly progressive illness die before they can be included in dementia studies [7]. As our estimates involved a cohort free of dementia at entry into the study and used prospectively collected data to determine onset of dementia, length bias should not be an issue here. Thus, our data show that survival differs by type of dementia and that it is longer for those with AD than VaD.

The reasons for differences in survival for AD and VaD should be considered. Based on clinical aspects of disease progression, it appears that both underlying mechanisms as well as comorbidities may be involved. As the onset and progression of AD is very gradual, there is no evidence that interim effects are lethal until the disease process affects basic human functionality—that is, unless death is caused by a comorbid disease. VaD, however, is characterized by cerebral infarcts representing various levels of severity of cerebrovascular disease. As is shown by the distribution of cause of death, over 40% of persons with VaD died from stroke or a related cerebrovascular condition which may have a very sudden onset. Data on the comorbid conditions of the Cognition Study cohort also show higher prevalence of coronary heart disease and hypertension for those with VaD. Although these were not direct causes of death, they may have contributed. An explanation for the intermediate survival length attributed to mixed dementia is more difficult to understand. Although this category may repre-

sent less severe stages of VaD or both AD/VaD, it is also possible that this category includes less certainty as to dementia type, and may reflect greater misclassification. An examination of the APOE gene frequency, however, tends to support the study's classification results; the $\epsilon 4$ allele was highest for those with AD only (39%), lowest for those with VaD only (19%) and between these frequencies for those with both types (34%). Thus, the distribution and severity of AD and VaD in those with mixed dementia may be the most likely explanation for survival estimated here.

Cause of death in this study also shows differences by type of dementia. While cerebrovascular accidents were the major cause of death for participants with VaD, those with AD or mixed dementia died more frequently from either the dementia syndrome itself or from coronary heart disease. Although it may be surprising to find that patients with VaD have no greater mortality from CHD than AD patients, this may reflect the high prevalence of CHD in the elderly. Many other studies have reported pneumonia to be the most frequently cited cause of death in dementia patients. In a sample of demented persons examined by autopsy for cause of death in the United Kingdom, pneumonia accounted for 57% of deaths followed by cardiovascular disease (16%) and pulmonary embolism (14%). Differences between AD and VaD were not found [32]. Another autopsy study found similar results with cardiovascular disease and bronchopneumonia being the most common immediate causes of death [33]. This study reported no differences between demented and non-demented persons, although cardiac causes of death were more common in persons with VaD than AD or mixed dementia. Dementia was always reported as an underlying, never a primary, cause of death here. Although bronchopneumonia was the leading cause of death for persons with AD (71%) in a study in Scotland, it was somewhat lower for those with VaD (52%) [34]. Place of death was associated with differences in immediate cause of death. Differences in methodology are the most likely reasons for discrepancies between our study and others. While immediate cause of death is reported in these studies, the CHS attempted to classify underlying cause of death using a variety of sources including the death certificate and medical records.

The finding that women were at a greater risk of death after onset of VaD than men is at odds with general reports of survival and gender. Although age and physical function tend to be the strongest predictors of death in persons with dementia [35–37], studies evaluating gender tend to show no differences or men to be at a greater risk of mortality. Male gender was associated with an increased risk of mortality in AD [38,39], VaD [39] and in unspecified dementia [35,36,40], but no gender differences were found in others studies [31,41]. A study of population attributable risk (PAR), however, found that although the survival was higher in demented women than men, dementia predicted 49.7% of deaths in women compared to 30.7% of deaths in men [42]. In addition, VaD was a stronger predictor of death in women than was AD.

The strengths of this study include the large sample size and prospectively collected longitudinal data on cognition and functionality that were used to determine dementia onset. In addition, the ability to have observed cognition prior to entry into the Cognition cohort for most participants and to begin follow-up with all participants free of dementia is important in estimating survival. Finally, the amount of information available for classification of dementia type, especially access to MRIs for all participants in the study, allowed for use of standardized criteria and more accuracy in the classification. The study was limited by the lack of longitudinal neuropsychiatric data on participants and the use of alternative data collected when neuropsychiatric testing could not be done. In addition, as medical records were used to determine cause of death, the mortality review committee was aware of a dementia diagnosis when assessing cause of death. Finally, as is common with many recruited cohort studies, the CHS participants had more education and higher incomes than the general population [11], and a healthy cohort effect may have been present that would affect generalizability of results.

As the general health of the world improves, and the prevention or treatment of infectious as well as other chronic conditions increases the average age of populations in both developed and developing countries, information on the consequences of diseases impacting the elderly is crucial. Although new treatments and interventions may help improve the quality of life for some patients, estimates of survival for specific types of dementia may help in planning for the resources and services needed to care for the afflicted individuals. Until medical science can discover preventive measures or a cure for dementing illnesses, epidemiologic data describing the course of these diseases are of great value to dementia patients' providers and caregivers.

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