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Causes of Death According to Death Certificates in Individuals with Dementia: A Cohort from the Swedish Dementia Registry

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OBJECTIVES: The causes of death in dementia are not established, particularly in rarer dementias. The aim of this study is to calculate risk of death from specific causes for a broader spectrum of dementia diagnoses.

DESIGN: Cohort study.

SETTING: Swedish Dementia Registry (SveDem), 2007–2012.

PARTICIPANTS: Individuals with incident dementia registered in SveDem (N = 28,609); median follow-up 741 days. Observed deaths were 5,368 (19%).

MEASUREMENTS: Information on number of deaths and causes of mortality was obtained from death certificates. Odds ratios for the presence of dementia on death certificates were calculated. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using Cox hazards regression for cause-specific mortality, using Alzheimer's dementia (AD) as reference. Hazard ratios for death for each specific cause of death were compared with hazard ratios of death from all causes (*P*-values from *t*-tests).

RESULTS: The most frequent underlying cause of death in this cohort was cardiovascular (37%), followed by dementia (30%). Dementia and cardiovascular causes appeared as main or contributory causes on 63% of certificates, followed by respiratory (26%). Dementia was mentioned less in vascular dementia (VaD; 57%). Compared to AD, cardiovascular mortality was higher in individuals with

VaD than in those with AD (HR = 1.82, 95% CI = 1.64–2.02). Respiratory death was higher in individuals with Lewy body dementia (LBD, including Parkinson's disease dementia and dementia with Lewy bodies, HR = 2.16, 95% CI = 1.71–2.71), and the risk of respiratory death was higher than expected from the risk for all-cause mortality. Participants with frontotemporal dementia were more likely to die from external causes of death than those with AD (HR = 2.86, 95% CI = 1.53–5.32).

CONCLUSION: Dementia is underreported on death certificates as main and contributory causes. Individuals with LBD had a higher risk of respiratory death than those with AD. *J Am Geriatr Soc* 64:e137–e142, 2016.

Key words: causes of death; dementia; death certificate; Alzheimer's; Lewy body dementia; respiratory death; survival analyses

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Survival of individuals with dementia varies widely and depends on the type of dementia.^{1–4} A recent study from the Swedish Dementia Registry (SveDem) confirmed that individuals with Alzheimer's disease (AD) have a lower mortality risk than those with other dementias, whereas frontotemporal dementia (FTD) is associated with particularly high risk in adjusted analyses.¹ Older age, poorer cognition, male sex, comorbidity,^{1,5} and lower body mass index (BMI) are associated with greater mortality.^{1,3,6} Previous research has shown that patterns of comorbidity differ according to dementia diagnosis;^{7–9} cardiovascular comorbidity is more prevalent in individuals with vascular dementia (VaD) and mixed AD and VaD,^{8,9} whereas individuals with dementia with Lewy bodies (DLB) are more likely to have respiratory comorbidity.⁷

Information on causes of death can be used to determine patterns of comorbidity and may help in customizing interventions to different groups of individuals.¹⁰ On death certificates, the underlying cause of death is more accurate for acute diseases than chronic conditions.¹¹ Physicians have trouble attributing main and contributing causes of death,

particularly in individuals with great multimorbidity.¹² For this reason, a multiple-cause-of-death approach, including all causes in any position on the death certificate, may be preferable with chronic diseases such as dementia.¹³

Causes of death in individuals with dementia differ between studies, although respiratory, cardiovascular, and infectious causes are the most frequently reported,^{2,10,14,15} whereas cancer-related deaths are less frequent.¹⁵ Cardiovascular causes dominate in individuals with VaD but are also the most-common cause of death in individuals with AD,² although previous studies did not report causes of death separately for a wide range of dementia diagnoses, and there is little information for less-frequent dementias.^{2,10} Likewise, previous studies reported two or three causes of death, without systematically assessing all chapters of the *International Classification of Diseases, 10th Revision* (ICD-10).^{2,10}

The aim of this study was to use data from SveDem to investigate a wide range of causes of death in individuals with different types of dementia and to calculate cause-specific risk of death using a multiple-cause-of-death approach. Additional aims were to identify causes of death for which individuals with specific types of dementia are at particularly high risk and to determine how often dementia itself is reported as a contributor to death.

METHODS

Study Population

SveDem is a nationwide register of incident dementia that has previously been described.^{1,3,16} Briefly, diagnoses are made according to ICD-10 criteria,¹⁷ with specific criteria for the different types of dementia. Variables include demographic characteristics, examination results, social aspects, medications, and cognition according to the Mini-Mental State Examination (MMSE).

For this study, individuals registered in SveDem diagnosed in primary or specialist care between 2007 and 2012 were included and followed until death or December 2012. Data from death certificates were obtained from the Swedish Board of Health and Welfare; in Sweden, a doctor completes the death certificate within a few days of death. SveDem registered 28,609 individuals during that period; seven were missing death certificate data, and 10 had an observation time of <1 day and were treated as missing in outcome variables.

Variable Codification and Statistical Analysis

Causes of death were obtained from death certificate records using ICD-10 coding.¹⁷ Thus, infection included all causes with codes A or B, cancer included codes C00 to D48, and endocrine E00 to E90. Diabetes was included within endocrine but also analyzed separately with codes E10 to E16. The chapter on mental and behavioral disorders was analyzed excluding dementia, with codes F10 to F99. Neurological diseases, excluding cerebrovascular syndromes and dementia, were those with ICD-10 codes G00 to G26, G32 to G44 and G47 to G99. Codes F00 to F99, G30, and G31 were used to identify individuals with dementia or delirium. Cardiovascular cause of death

included codes I00 to I99, excluding cardiac arrest (I46). Acute coronary disease (I20–I24) and stroke (ischemic or hemorrhagic—I60–I69) were also considered separately from cardiovascular disease in general. Respiratory causes included codes J00 to J99. Digestive causes included all codes beginning with K. Codes beginning with N are classified as genitourinary in the ICD-10,¹⁷ but comprised mostly renal diseases in this older population and will henceforth be referred to as renal causes. External causes of death (accidents and violent deaths) included codes starting with S, V, or W. For descriptive statistics, the underlying cause of death was calculated, as well as the total number of mentions in any place on the death certificate. For survival analyses, a multiple-cause-of-death approach was used, with codes appearing in any place on the death certificate counting as mentions. Thus, an individual with a death certificate mentioning decompensation of chronic obstructive pulmonary disease, myocardial infarction, and AD would be counted toward respiratory, cardiovascular, and dementia.

DLB and Parkinson's disease dementia (PDD) share pathological and clinical characteristics, and many authors consider them part of a continuum within the spectrum of Lewy body dementias (LBDs),^{18,19} so DLB and PDD were merged for this study as LBD. Diagnostic categories were thus AD, VaD, mixed AD and VaD (mixed), FTD, LBD, and other types of dementia, which included unknown diagnosis and other types of dementia not classified above. Because this last group did not correspond to a specific type of dementia, it was entered as a control but not reported in results.

For descriptive statistics, means and standard deviations and categories with numbers and percentages are provided as appropriate. Logistic regression models were used to calculate the odds of dementia appearing on death certificates according to dementia type. These were adjusted in the same way as the Cox hazards regression models described below.

Prospective analyses to identify factors associated with cause-specific mortality were performed using Cox proportional hazards regression models. For comparison, all-cause mortality hazard was also calculated. Hazard ratios (HRs) of death with 95% confidence intervals (CIs) are reported. Models with time-dependent covariates were used to test proportionality of hazards. Models were developed for all causes of mortality that appeared on 10% or more of death certificates. The fully adjusted model was controlled for age, sex, dementia diagnosis, MMSE, BMI, diagnostic unit (specialist or primary care), and number of medications. Beta coefficients obtained for specific causes of death were compared with those obtained for all-cause mortality using t-tests. SPSS version 21 (IBM Corp., Armonk, NY) and Stata version 12 (Stata Corp., College Station, TX) were used for analyses.

Ethical Issues

Participants and caretakers were informed orally and in writing about SveDem and could decline participation and withdraw consent. Data were collected locally and entered into the web-based database, coded, and anonymized before statistical analysis. The regional ethics committee in

Stockholm approved data collection and analytical procedures for this study, which complied with the Declaration of Helsinki.

RESULTS

Characteristics of the Study Population

Twenty-eight thousand six hundred nine individuals were included at the time of diagnosis. Median follow-up was 741 days, with 5,368 observed deaths (19%). Characteristics of study participants and their survival status are shown in Table 1. AD was the most common dementia type (32% of the sample), followed by mixed (19%) and VaD (17%). The majority of participants were in the mild stage of dementia according to their MMSE scores (mean 21.1 ± 5.1). A greater proportion of men died during the observation period (21% vs 17%).

Underlying and contributing causes of death were recorded on death certificates.

The most common underlying cause of death was circulatory ($n = 1,985$, 37% of death certificates), followed by dementia ($n = 1,613$, 30%) and cancer ($n = 550$, 10%).

When all causes of death appearing in any place on the death certificate were counted, there were a total of 26,822 mentions, with death certificates containing an average of 4.9 ± 2.2 mentions. Table 2 presents causes of death, with all causes in any place on the death certificate considered (multiple-cause approach); causes of death that appeared most frequently were dementia ($n = 3,381$, 63% of death certificates) and circulatory ($n = 3,361$, 63%). Respiratory diseases appeared on 1,396 death certificates (26%).

Dementia as a Cause of Death on Death Certificates

Dementia appeared on the death certificates of 69% of individuals with FTD and AD but on only 57% of those of individuals with other types of dementia (Table 3). The odds of dementia appearing in any place on a death certificate were calculated according to type of dementia. Individuals with VaD (odds ratio (OR) = 0.66, 95% CI = 0.56–0.78) and other types of dementia (OR = 0.58, 95% CI 0.49–0.69) were significantly less likely than those with AD to have dementia mentioned on their death certificate.

Survival Analysis

The results of age- and sex-adjusted and fully adjusted models were not substantially different, so only the latter are presented. Table 3 shows associations between types of dementia and causes of death after adjustment for age, sex, number of medication, MMSE score, unit (specialist or primary care), and BMI.

Participants with AD were at lower risk of all-cause, cardiovascular, and respiratory mortality than those with all other types of dementia. Individuals with VaD had the greatest risk of death from cardiovascular causes, with an 80% greater risk of cardiovascular death than those with AD (Table 3). Participants with VaD and mixed dementia

Table 1. Characteristics of Study Population According to Survival Status

	Total	Died	Follow-Up, Days, Median (Interquartile Range)
All, n (%)	28,609 (100)	5,368 (19)	741 (835)
Sex, n (%)			
Female	16,934 (59)	2,883 (17)	749 (826)
Male	11,675 (41)	2,485 (21)	714 (841)
Age, n (%)			
<80	13,146 (46)	1,722 (13)	787 (845)
≥80	15,463 (54)	3,646 (24)	774 (825)
Age, mean ± SD	79.8 ± 8.0		
Dementia diagnosis, n (%)			
AD	9,137 (32)	1,351 (15)	819 (864)
Mixed AD and VaD	5,478 (19)	1,303 (24)	769 (867)
VaD	5,255 (18)	1,243 (24)	696 (829)
Lewy body dementia ^a	1,054 (4)	254 (24)	769 (842)
Frontotemporal dementia	472 (2)	88 (19)	762 (789)
Other type	7,213 (25)	1,129 (16)	729 (766)
MMSE score, n (%)			
24–30	9,755 (34)	1,224 (13)	767 (828)
20–23	8,108 (28)	1,418 (17)	718 (820)
0–19	8,533 (30)	2,147 (25)	719 (853)
Not testable	834 (3)	296 (35)	691 (851)
Missing	1,379 (5)	283 (21)	699 (780)
MMSE score, mean ± SD	21.1 ± 5.1		
Number of medications, n (%)			
0–2	7,067 (25)	967 (14)	774 (855)
3–5	9,213 (32)	1,690 (18)	749 (834)
≥6	9,408 (33)	2,297 (24)	710 (852)
Missing	2,921 (10)	414 (14)	691 (744)
Number of medications, mean ± SD	4.7 ± 3.2		
Type of diagnostic unit, n (%)			
Specialist care	19,599 (69)	4,598 (23)	843 (861)
Primary care	9,010 (31)	770 (9)	501 (681)
Body mass index, kg/m ² , mean ± SD	24.7 ± 4.4		

Age categories were constructed around the median (79). Mini-Mental State Examination (MMSE) categories follow the tertile distribution plus categories for untestable and missing. Number of medication follows the tertile distribution in the sample.

^aParkinson's disease with dementia and dementia with Lewy bodies.

AD = Alzheimer's disease; VaD = vascular dementia; SD = standard deviation.

had a greater risk of stroke and death from coronary events than those with AD.

The likelihood of respiratory cause of death was highest in individuals with LBD, who had more than twice the likelihood of respiratory death as those with AD (HR = 2.16, 95% CI = 1.71–2.71). Death from external causes (accidents and violent deaths) was remarkably high for FTD (HR = 2.86, 95% CI = 1.53–5.32 vs AD; Table 3).

Because all-cause mortality could condition results from specific causes of death, significance testing was used to determine which causes of death appeared in excess of

Table 2. Causes of Death from Death Certificates According to Dementia Diagnosis (Multiple Causes of Death Shown)

Cause of Death	All Dementias, n = 5,368	AD, n = 1,351	Mixed AD and VaD, n = 1,303	VaD, n = 1,243	Lewy Body Dementia, ^a n = 254	Frontotemporal Dementia, n = 88	Other Types of Dementia, n = 1,129
	n (%)						
Infection	335 (6.2)	79 (5.8)	80 (6.1)	79 (6.4)	13 (5.1)	5 (5.7)	79 (7.0)
Cancer	846 (15.8)	248 (18.4)	207 (15.9)	173 (13.9)	24 (9.4)	16 (18.2)	178 (15.8)
Endocrine	737 (13.7)	149 (11.0)	195 (15.0)	207 (16.7)	21 (8.3)	10 (11.4)	155 (13.7)
Diabetes mellitus ^b	514 (9.6)	99 (7.3)	139 (10.7)	153 (12.3)	13 (5.1)	6 (6.8)	7 (0.6)
Dementia ^c	3,381 (63.0)	933 (69.2)	853 (65.5)	713 (57.4)	180 (70.9)	61 (69.3)	641 (56.8)
Circulatory ^d	3,361 (62.6)	740 (54.8)	885 (67.9)	879 (70.7)	115 (45.3)	36 (40.9)	706 (62.5)
Stroke	996 (18.6)	178 (13.2)	277 (21.3)	330 (26.5)	29 (11.4)	6 (6.8)	176 (15.8)
Acute coronary	521 (9.7)	119 (8.8)	131 (10.1)	139 (11.2)	17 (6.7)	7 (7.9)	108 (9.6)
Respiratory	1,396 (26)	329 (24.4)	340 (26.1)	317 (25.5)	97 (38.2)	22 (25.0)	291 (25.8)
Digestive	266 (5.0)	65 (4.8)	73 (4.9)	61 (4.9)	7 (2.8)	1 (1.1)	59 (5.2)
Renal	513 (9.6)	111 (8.2)	137 (10.5)	138 (11.1)	13 (5.1)	4 (4.5)	110 (9.7)
External	522 (9.7)	128 (9.5)	134 (10.3)	116 (9.3)	32 (12.6)	11 (12.5)	101 (8.9)

A multiple-cause-of-death approach was used, grouping underlying cause of death with contributing causes. Multiple causes of death are possible for each participant.

Circulatory death causes are given without including cardiac arrest. Causes of death were missing in six participants: Alzheimer's disease (AD), n = 3; vascular dementia (VaD), n = 1; other types of dementia, n = 2.

^aParkinson's disease with dementia and dementia with Lewy bodies.

^bDiabetes mellitus and other pancreatic disorders.

^cOrganic brain disorders, including dementia and delirium (F00–F09), AD (G30), and other neurodegenerative diseases (G31, G32).

^dExcluded the code for cardiac arrest (I46).

Table 3. Cause-Specific Mortality from Death Certificate Data Obtained Using Cox Hazard Models According to Type of Dementia (Reference Alzheimer's Disease (AD))

Cause of Death	Mixed AD and VaD	VaD	Lewy Body Dementia ^a	Frontotemporal Dementia
	Adjusted hazard ratio (95% confidence interval) P-value ^b			
All cause	1.29 (1.19–1.39)	1.56 (1.44–1.68)	1.59 (1.39–1.83)	2.08 (1.67–2.58)
Cancer	1.12 (0.93–1.36) .18	1.19 (0.98–1.46) .01	0.76 (0.50–1.17) .001	1.88 (1.13–3.12) .70
Endocrine	1.55 (1.24–1.92) .12	1.76 (1.42–2.19) .26	1.01 (0.64–1.61) .06	2.08 (1.09–3.97) .99
Circulatory	1.49 (1.36–1.65) .02	1.82 (1.64–2.02) .002	1.29 (1.06–1.58) .09	1.64 (1.17–2.29) .17
Respiratory	1.34 (1.15–1.57) .65	1.49 (1.28–1.76) .64	2.16 (1.71–2.71) .03	2.03 (1.31–3.13) .91
Renal	1.39 (1.07–1.79) .60	1.55 (1.19–2.00) .96	0.81 (0.45–1.43) .02	1.15 (0.42–3.13) .25
External	1.36 (1.06–1.74) .70	1.55 (1.19–2.02) .99	2.12 (1.43–3.14) .18	2.86 (1.53–5.32) .34

Results obtained from Cox hazards regression for the association between dementia diagnosis and all-cause and cause-specific mortality risk. Causes of death were obtained from death certificates. Results are adjusted for age, sex, number of medication, Mini-Mental State Examination (MMSE) score, diagnostic unit (specialist or primary care), and body mass index (BMI). For adjustments, two piecewise linearly represented variables (linear splines) were used for age; number of medication was entered as a linearly represented variable, with a category for missing. MMSE score was entered as a linearly represented variable, "untestable" and "missing." BMI was introduced as a linear variable, a quadratic variable, and a category for "missing." Age- and sex-adjusted hazard ratios were calculated. The number of mentions for each cause of death is shown in Table 1.

^aParkinson's disease with dementia and dementia with Lewy bodies.

^bStudent *t*-tests were used to compare beta coefficients from Cox hazard regressions for specific causes of death with those from all-cause mortality.

VaD = vascular dementia.

what would be expected from the results for all-cause mortality for each type of dementia. Risks of cardiovascular death and stroke (but not acute coronary disease) were significantly higher than those of all-cause mortality for individuals with mixed dementia and VaD (Table 3). The hazard of respiratory death in individuals with LBD was significantly higher than their hazard of death from all causes, indicating that their risk of respiratory death was higher than expected based on their all-cause mortality.

DISCUSSION

Underlying Cause of Death

Circulatory causes were the most frequently mentioned underlying cause of death (37%), irrespective of dementia diagnosis. Dementia was the underlying cause of death in 30%, followed by cancer. This distribution roughly matches that found in the general population in Sweden,

in which ischemic heart disease and stroke are the most common causes of death, followed by lung and colorectal cancers.²⁰ The older age of this population explains the inverted order of ischemic heart disease and stroke (with stroke more frequent in SveDem).²

Underreporting of Dementia on Death Certificates

All individuals in SveDem have a dementia diagnosis, but dementia was missing from 37% of death certificates. This confirms previous observations showing that dementia is underreported on death certificates.^{14,21,22} The focus on underlying cause of death might exacerbate the problem because clinicians might recognize dementia as a contributor to death but not prioritize the diagnosis in individuals with comorbidity. In one study, reported dementia mortality was three to four times as high when using a multiple-cause approach.²²

Survival Analyses

All other examined dementia disorders had higher general mortality than AD. When specific causes were considered, individuals with other dementia diagnoses were at greater risk of cardiovascular, respiratory, and external causes of death than those with AD. Because general mortality might condition the results for specific causes of death, the results from all-cause and specific-cause models were compared for each type of dementia to determine whether the risk of a specific cause of death was higher or lower than would be expected for a particular diagnosis.

Unsurprisingly, individuals with VaD had a high risk of cardiovascular death, and those with mixed dementia had an intermediate risk between AD and VaD, as found in previous cohorts² and suggested by their higher cardiovascular medication use⁸ and comorbidity profile.²³ It appears that stroke, which presented risks that were significantly higher than those obtained for all-cause mortality, rather than coronary disease was the cause of this high risk.

Individuals with LBD were at high risk of respiratory causes of death, with a likelihood that was significantly higher than expected from their all-cause mortality. Respiratory infections are a leading cause of morbidity and death in Parkinson's disease (PD)²⁴ and mortality is greater in individuals with PD who develop dementia,²⁵ but research has been scarce on causes of death in individuals with PDD or DLB. Previous SveDem research has demonstrated a 30% greater prevalence of respiratory comorbidity in individuals with DLB than in those with AD.⁷ Respiratory comorbidity in PD takes several forms, with airway obstruction or restrictive pulmonary dysfunctions appearing with high prevalence, and has been attributed to bradykinesia, rigidity, and musculoskeletal limitations of the spine.²⁶ The current study finding of a high risk of respiratory in among the LBD group fits well within the context of the parkinsonian symptoms that these individuals have, which could disrupt respiratory mechanics and lead to inefficient coughing and swallowing.²⁴

Mortality from external causes of death, including violent deaths and accidents, was almost three times as high in individuals with FTD as in those with AD; this was not significantly higher than results for all-cause mortality,

possibly because of the smaller size of this group. The personality disturbances and impulsivity that are common in this syndrome could contribute to high risk from external causes.²⁷

Strengths and Limitations

The present study had several limitations, among which was the absence of a cognitively intact control group. According to incidence estimates, SveDem captured more than one-third of all expected new dementia cases in Sweden. The quality of diagnoses is hard to assess, although diagnoses in SveDem follow general clinical practice, and adherence to national guidelines is good.¹⁶ Another concern is the quality of death certificate data; in individuals with comorbidity, different doctors might choose different diagnoses to report. The multiple-cause-of-death approach should mitigate this problem, which is impossible to eliminate completely using death certificate data. Previous studies have shown that reliability of Swedish death certificates is acceptable, especially at the chapter level in ICD coding, which is why the analyses were restricted to this level of coding.^{11,28} Another limitation is that data were not available on participants' cognition and stage of dementia at the time of death, because SveDem records data on MMSE at the time of diagnosis.

Strengths of this study are the large sample of individuals from throughout the country and a range of different types of dementia that reflect clinical and epidemiological reality. To the knowledge of the authors, this is the first study to examine a wide range of causes of death in a large cohort of individuals with diagnoses of several different types of dementia.

CONCLUSIONS

This study confirms previous reports that cardiovascular causes are the most frequent causes of death in individuals with dementia and supports the need to attend to cardiovascular risk factors in all dementia diagnostic groups. Stroke, rather than coronary disease, might be the cause of the excess cardiovascular risk in individuals with VaD and mixed dementia.

Individuals with AD had lower all-cause, cardiovascular, respiratory, and external mortality than those with other dementia diagnoses, and dementia was underreported on death certificates of individuals with all types of dementia.

Respiratory death was particularly high in individuals with LBD. Because cohorts of cognitively intact individuals with PD also have higher mortality from respiratory causes, the finding in LBD could be due to underlying parkinsonism.²⁵ Further research on respiratory health in individuals with LBD is needed. Prompt evaluation of swallowing difficulties is recommended in individuals with all types of dementia.

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Author Contributions: Sara Garcia-Ptacek (NVS, Center for Alzheimer Research, Division of Clinical Geriatrics, Karolinska Institutet) had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Garcia-Ptacek: concept and design, statistical analysis, interpretation of results, writing manuscript. Kåreholt, Rizzuto: concept and design, statistical analysis, interpretation of results, revision of manuscript for scientific content. Cermakova, Religa, Eriksson: concept and design, interpretation of results, revision of manuscript for scientific content.

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