

Mortality Risk after Dementia Diagnosis by Dementia Type and Underlying Factors: A Cohort of 15,209 Patients based on the Swedish Dementia Registry

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Handling Associate Editor: Alberto Villarejo

Accepted 2 February 2014

Abstract.

Background: Knowledge on survival in dementia is crucial for patients and public health planning. Most studies comparing mortality risk included few different dementia diagnoses.

Objectives: To compare mortality risk in the most frequent dementia disorders in a large cohort of patients with an incident diagnosis, adjusting for potential confounding factors.

Methods: 15,209 patients with dementia from the national quality database, Swedish Dementia Registry (SveDem), diagnosed in memory clinics from 2008 to 2011, were included in this study. The impact of age, gender, dementia diagnosis, baseline Mini-Mental State Examination (MMSE), institutionalization, coresidency, and medication on survival after diagnosis were examined using adjusted hazard ratios (HR) with 95% confidence intervals (CI).

Results: During a mean follow-up of 2.5 years, 4,287 deaths occurred, with 114 (95% CI 111–117) deaths/1,000 person-years. Adjusted HR of death for men was 1.56 (95% CI 1.46–1.66) compared to women. Low MMSE, institutionalization, and higher number of medications were associated with higher HR of death. All dementia diagnoses demonstrated higher HR compared to Alzheimer's disease, with vascular dementia presenting the highest crude HR. After adjusting, frontotemporal dementia had the highest risk with a HR of 1.91 (95% CI 1.52–2.39), followed by Lewy body dementia (HR 1.64; 95% CI 1.39–1.95), vascular dementia (HR 1.55; 95% CI 1.42–1.69), Parkinson's disease dementia (HR 1.47; 95% CI 1.17–1.84), and mixed Alzheimer's disease and vascular dementia (HR 1.32; 95% CI 1.22–1.44).

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Conclusion: Worse cognition, male gender, higher number of medications, institutionalization, and age were associated with increased death risk after dementia diagnosis. Adjusted risk was lowest in Alzheimer's disease patients and highest in frontotemporal dementia subjects.

Keywords: Alzheimer's disease, cohort studies, dementia, frontotemporal dementia, mortality, Parkinson's disease, vascular dementia

INTRODUCTION

Knowledge of mortality risk in dementia is crucial for resource planning and valuable information for patients and families [1, 2]. Dementia shortens life expectancy but survival estimates range from 1 to 13 years depending on dementia type, gender, cognitive level, neuropathology, cohort, and study design [2–9]. The availability of data on survival varies greatly by dementia type. Numerous studies have examined mortality in Alzheimer's disease (AD) [1, 6, 7, 9–11] or vascular dementia (VaD) [11, 12], although prospective cohorts of incident cases are rarer [1, 7, 9, 10, 13]. Less information exists on other dementia types [2, 14, 15]. Furthermore, comparisons of mortality risk between different dementia diagnoses are infrequent with most studies only including two [7, 14–17] or three diagnoses [13, 18, 19]. Two clinic-based [6, 20] and one population-based study [21] included more dementia types, but large prospective studies of incident cases with a wide range of diagnoses are lacking. AD seems to present longer survival than other dementia types [2, 7, 19], although others do not confirm this finding [3, 22].

A number of factors have been identified as being associated with mortality in dementia. Higher age [1, 3, 7, 10, 22] and lower cognition [4, 11, 16] increase mortality risk, while female gender appears to be protective [1, 3, 6, 7, 12, 16, 18, 22–24], although some studies contradict these findings [10, 25] and others propose that the association between gender and mortality might differ by dementia diagnosis [2, 13, 26, 27]. AD patients living alone may suffer higher mortality [28], and comorbidity plays a role and appears reflected in the higher mortality rates associated with institutionalization [5, 7, 22]. For this reason, studies exploring mortality after dementia diagnosis need to take these aspects into consideration.

The Swedish Dementia Registry (SveDem) is a web-based quality initiative that records subjects with incident dementia diagnosis nationwide. To date, the database contains more than 28,000 individual patient entries. The aim of this study is to explore mortality risk in the most frequent dementia disorders in a large prospective cohort. We report mortality risk

associated with baseline factors including dementia diagnosis, gender, age, medications, living arrangements, and Mini-Mental State Examination (MMSE) for 15,209 incident dementia patients.

MATERIALS AND PATIENTS

Study population

SveDem was created in 2007 to improve quality of care [29–32] for dementia patients throughout Sweden. Newly diagnosed patients meeting ICD-10 [33] criteria for dementia, diagnosed at either memory clinics or primary care, are included in the database. The national guidelines published by the Swedish National Board of Health and Welfare [34] that an established basal dementia work-up be administered to patients with suspicion of dementia are followed in over 85% of diagnoses [35], and testing can be expanded if necessary. These same guidelines encourage early diagnosis [35]. Quality control of the database is performed by random cross-checks of histories and entries [35]. Based on estimates of dementia incidence in the general Swedish population, in 2011 SveDem captured around 25% of all new dementia cases in Sweden [35]. The coverage for specialist memory clinics was 93% [35]. Changing diagnoses within the first year of follow-up are about 5%. SveDem is collated with the national population registry to record deaths.

Dementia diagnoses are coded as AD, VaD, AD and VaD (mixed), Lewy Body Disease (LBD, McKeith criteria [36]), Parkinson's-Disease Dementia (PDD, Movement Disorder Society Task Force criteria [37]), frontotemporal dementia (FTD, Manchester criteria [38]), unspecified dementia (where specific dementia diagnosis is not ascertained), and other dementia types (grouping miscellaneous dementia disorders such as corticobasal degeneration or alcohol related dementias). Simultaneously, age, gender, and baseline MMSE are entered, as are coresidency status (living alone versus cohabiting) and place of residence (home versus institution). The number of medication that the patient takes regularly at the beginning of diagnostic workup comprises all medications that the patient takes that appear in the official Swedish Drug Index [39].

This variable is used as a proxy for comorbidity [32, 40], since it has been shown to be better than other medication-based comorbidity scores at predicting morbimortality [40]. The presence of cardiovascular medication, antidepressants, antianxiety, neuroleptics, and sleeping aids is recorded. Cholinesterase inhibitors and N-Methyl-D-aspartate (NMDA) antagonists prescribed upon diagnosis are entered.

For this study, we selected patients included in SveDem who had received a dementia diagnosis from specialist memory clinics from 2008 through 2011 and for whom complete data on dementia diagnosis, age, gender, and survival was available. The decision to exclude primary care was due to later and more irregular inclusion of these units in the registry, uncertainty over national coverage levels and differences in diagnostic process compared to specialist care [30]. Of 15,224 patient entries, 15 (0.1%) patients were excluded for incomplete data on diagnosis, age, gender, or time of death. A total of 15,209 patients were thus included in the analysis. Survival was examined according to the above variables.

To eliminate potential bias from the exclusion of patients from primary care, the final analyses were repeated *post-hoc* in all 28,722 patients (from both specialist and primary care) included in the register between 2007 and 2012.

Statistical analyses

Prospective analyses to identify factors associated with mortality risk were performed using Cox proportional hazards regression models and are shown as hazard ratios (HR) of death with 95% confidence intervals (CI). Kaplan-Meier survival curves and models with time-dependent covariates were employed to test if the assumption of proportional hazards was met. In the instances in which mortality hazards were not proportional, the hazard at the beginning of the observation period and the hazard at day 1,000 of follow-up were calculated in addition to the average hazard over the whole observation period. Person-years (PY) at risk were calculated individually for all patients from dementia diagnosis to date of death or end of follow-up, on February 2013. Standardized mortality ratios (SMR) of the SveDem cohort relative to the general Swedish population were calculated. In order to minimize the number of persons with dementia present in the general Swedish population figures, mortality rates for ICD-10 codes F00 (dementia due to AD), F01 (VaD), F02 (dementia in other disease), F03 (unspecified dementia), and F05 (delirium, not

substance induced) were subtracted from the general Swedish population mortality rates [33]. For descriptive statistics, means and standard deviations (SD) are provided where appropriate. SPSS® version 21 and PROC PHREG in the Statistical Analysis System (SAS®) version 9.3 were used for analyses.

Age was explored as a continuous variable and also divided into four categories (under 65, 65–74, 75–84, and 85 and above). The first cut point for age (under 65) was selected to represent the distinction between early and late-onset dementia [41], with further cut points every 10 years of age. Number of medication was categorized as 0–1, 2–5, 6–9, and 10 or more habitual drugs at time of diagnostic workup. MMSE score was classified as not assessable, severe (0–9), moderate (10–19), mild (20–24), and slight impairment (25 and over). These categories result from the tertile distribution of MMSE in our sample (<19, 20–24, and over 25) with a further subdivision in the lowest MMSE category so as not to group patients with very different cognitive performance. Gender, coresidency and place of residence were treated as dichotomous variables.

Crude and age and gender adjusted HR were calculated (results not shown). All presented HR estimates were adjusted for age, gender, dementia diagnosis, MMSE, and number of medication unless otherwise stated. The interaction between gender and dementia type and gender and MMSE were analyzed. A previous study conducted on SveDem showed reduced mortality with cholinesterase inhibitors [42], so additional models were repeated controlling for these medications, as well as for presence or absence (as dichotomous variables) of cardiovascular medication, antidepressants, neuroleptics, antianxiety medication, and sleeping aids.

Standard protocol approvals and patient consent

The data collection and analysis procedures were approved by the regional ethics committee in Stockholm (approval number 2009/209-31). Patients and caretakers were informed orally and in writing about SveDem, and could decline participation and withdraw consent at any time. Data was collected locally and entered into the web-based database, and coded and anonymized before statistical analysis.

RESULTS

A total of 15,209 patients were included. Characteristics of the study subjects are shown in Tables 1 and 2. Fifty-nine percent of the study subjects were women.

Table 1
Characteristics of study subjects

	Number of patients (%)	Deaths	PY at risk	Deaths/ 1000 PY
All	15209 (100)	4287	37619	114
Gender				
Women	8910 (58.6)	2279	22602	101
Men	6299 (41.4)	2008	15017	134
Age				
<65	1018 (6.7)	91	2857	32
65–74	3434 (22.6)	557	9089	61
75–84	7307 (48.0)	2035	18301	111
≥85	3450 (22.7)	1604	7372	218
Mean (SD)	78.1 (8.2)			
MMSE				
≥25	4382 (28.8)	738	11685	63
20–24	5515 (36.3)	1423	13858	103
10–19	4164 (27.4)	1559	9707	161
<10	395 (2.6)	174	842	207
Not assessable	384 (2.5)	223	727	307
Missing	369 (2.4)	170	800	213
Mean (SD)	21.3 (5.1)			
Coresident				
No	6868 (45.2)	2086	17024	123
Yes	7791 (51.2)	1961	19626	100
Missing	550 (3.6)	240	969	248
Residency				
Home	13870 (91.2)	3637	34969	104
Institution	1321 (8.7)	676	2606	259
Missing	18 (0.1)	13	44	295
Number of medication before diagnosis				
<2	2541 (16.7)	434	6799	64
2–5	6778 (44.6)	1736	17260	101
6–9	4148 (27.3)	1361	9817	139
>10	1306 (8.6)	592	2770	214
Missing	436 (2.9)	164	974	168
Mean (SD)	4.7 (3.3)			

PY, person-years; SD, standard deviation.

Table 2
Distribution of dementia types, age, and number of medication at diagnosis

	Patients n (%)	Mean age (SD)	Mean medication (SD)	Deaths n	PY at risk	Deaths/1000 PY
All	15,209 (100)	78 (8.2)	4.7 (3.3)	4,287	37,619	114
AD	5,641 (37.1)	77 (8.3)	3.7 (2.9)	1,107	15,003	74
Mixed	3,732 (24.5)	81 (6.6)	5.2 (3.1)	1,182	8,932	132
VaD	2,832 (18.6)	79 (7.6)	6.2 (3.23)	1,050	6,476	162
LBD	461 (3.0)	77 (7.0)	4.7 (2.9)	155	1,103	141
PDD	283 (1.9)	75 (6.8)	6.4 (3.2)	84	658	128
FTD	348 (2.3)	69 (9.3)	3.3 (2.9)	81	862	94
Unspecified	1,559 (10.3)	79 (8.9)	5.0 (3.5)	530	3,675	144
Other	353 (2.3)	73 (10.1)	4.6 (3.3)	98	910	108

Distribution of dementia types, age and number of medication at diagnosis. PY, person-years; SD, standard deviation; AD, Alzheimer's disease; Mixed, mixed Alzheimer's disease and vascular dementia; VaD, vascular dementia; LBD, Lewy body dementia; PDD, Parkinson's disease dementia; Unspecified, diagnosis not specified or unknown; Other, any other established diagnosis other than AD, mixed, VaD, LBD, or PDD.

Mean age was 78.1 years (SD 8.2), mean MMSE was 21.3 (SD 5.1), and mean number of medications taken by the patient at the beginning of the diagnostic workup was 4.7 (SD 3.3). Thirty-seven percent were diagnosed as AD and forty-five percent lived alone.

Patients were followed-up for an average of 2.5 years (range 0 to 1869 days) for a total of 37,619 PY at risk

and 4,287 observed deaths (114 deaths/1,000 PY; 95% CI 111 to 117). The mortality rate was 134 deaths per 1,000 PY among men and 101 among women. Table 3 shows an age and gender adjusted mortality comparison between the cohort and the general Swedish population. Included in Table 4 are HRs of death associated with different variables. Non-proportional

Table 3
Standardized mortality ratios in SveDem relative to the general Swedish population

	Men			Women			All		
	Observed deaths per year	SMR	95% CI	Observed deaths per year	SMR	95% CI	Observed deaths per year	SMR	95% CI
45–54	2	14.29	1.71–51.57	1	11.11	0.28–61.89	3	12.46	2.58–36.43
55–64	6	2.04	0.75–4.43	9	4.33	1.98–8.23	15	2.96	1.66–5.47
65–74	86	3.07	2.46–3.79	53	2.61	1.95–3.41	139	2.84	2.39–3.35
75–84	264	1.61	1.42–1.81	264	1.75	1.54–1.97	528	1.66	1.53–1.81
>85	251	1.66	1.46–1.88	340	1.80	1.61–2.00	591	1.21	1.11–1.31
All ages	609	1.76	1.62–1.90	667	1.84	1.70–1.98	1276	1.49	1.41–1.58

Comparison of ratio of observed to expected deaths in SveDem relative to the general Swedish population. Population data was obtained from Socialstyrelsen (Swedish National Board of Health and Welfare) for 2011. Observed deaths per year in each gender and age group in SveDem appear in the first column. Standardized mortality ratios (SMR) and 95% confidence intervals (CI) are shown.

Table 4
Results of Cox proportional hazard regression examining mortality associated to baseline factors

	HR (95% CI)	p-value
Gender		
Women	ref	
Men	1.56 (1.46–1.66)	<0.000
Age		
<65	ref	
65–74	1.96 (1.57–2.44)	<0.000
75–84	3.32 (2.72–4.17)	<0.000
≥85	6.17 (4.97–7.65)	<0.000
MMSE		
≥25	ref	
20–24	1.45 (1.32–1.58)	<0.000
10–19	2.14 (1.96–2.34)	<0.000
0–9	2.91 (2.47–3.44)	<0.000
Not assessable	3.72 (3.19–4.35)	<0.000
Coresident		
No	ref	
Yes	1.02 (0.96–1.09)	0.485
Residency		
Home	ref	
Institution	1.42 (1.27–1.57)	<0.000
Number of medications		
0–1	ref	
2–5	1.25 (1.12–1.39)	<0.000
6–9	1.53 (1.37–1.71)	<0.000
≥10	2.14 (1.88–2.44)	<0.000

Results of Cox proportional hazard regression examining mortality associated to baseline factors. Results are given as hazard ratios (HR), 95% confidence intervals (CI) for relative mortality, and p-values for parameter estimates (Cox regression) adjusted for all baseline factors as they appear on the table, as well as by dementia diagnosis. First category of each variable serves as reference (ref).

hazard ratios were detected for LBD, unspecified and other dementia types, so time-dependent covariates for these diagnoses were included in the model (Table 5).

Mortality by gender, age, and baseline characteristics

Men had an increased risk of death compared to women in crude and adjusted analyses (Table 4). Similar gender differences were obtained when data was

stratified by MMSE. The interaction terms between gender and MMSE, and gender and dementia type were non-significant. When analyses were stratified by diagnosis, men had significantly higher mortality risk than women in all diagnostic groups, except in FTD where there was no association (HR 1.02, 95% CI 0.64–1.61, $p=0.94$) and in LBD where differences were not statistically significant (HR 1.41, 95% CI 0.96–2.07, $p=0.077$). The largest difference between men and women occurred in PDD with a HR for men of

Table 5
Hazard ratios (HR) of death associated with dementia diagnosis compared to Alzheimer's disease (AD)

	Crude		Adjusted		
	HR (95% CI)	<i>p</i> -value	HR (95% CI)	<i>p</i> -value	
AD	ref		ref		
Mixed	1.84 (1.70–2.00)	<0.001	1.33 (1.22–1.44)	<0.001	
VaD	2.27 (2.09–2.47)	<0.001	1.56 (1.43–1.70)	<0.001	
PDD	1.80 (1.44–2.24)	<0.001	1.47 (1.17–1.84)	<0.001	
FTD	1.29 (1.03–1.62)	0.026	1.91 (1.52–2.40)	<0.001	
LBD	Average	1.96 (1.66–2.32)	<0.001	1.75 (1.47–2.08)	<0.001
	Beginning of follow-up	1.49 (1.09–2.05)	0.013	1.23 (0.89–1.68)	0.211
	After 1000 days	2.22 (1.83–2.71)	<0.001	1.89 (1.55–2.31)	<0.001
Unspecified	Average	1.99 (1.79–2.20)	<0.001	1.43 (1.29–1.59)	<0.001
	Beginning of follow-up	2.52 (2.13–2.99)	<0.001	1.75 (1.47–2.08)	<0.001
	After 1000 days	1.74 (1.52–1.98)	<0.001	1.28 (1.12–1.46)	<0.001
Other	Average	1.45 (1.18–1.79)	<0.001	1.35 (1.09–1.67)	<0.001
	Beginning of follow-up	2.05 (1.43–2.94)	<0.001	1.92 (1.33–2.77)	<0.001
	After 1000 days	1.22 (0.92–1.61)	0.169	1.13 (0.85–1.49)	0.406

HR, 95% confidence intervals (CI), and *p*-values comparing different dementia diagnosis with AD. Results were obtained from Cox regression analysis and Cox regression with time-dependent covariates. Crude results in left-hand columns. In right-hand columns, HRs adjusted for age, gender, Mini-Mental State Exam, coresident, residential setting, and number of medication at the beginning of diagnostic workup. Lewy body dementia (LBD), unspecified dementia, and other dementia diagnoses had significantly non-proportional hazards compared to AD: for these, average HR for the whole follow-up period is given together with the HR at the beginning of follow-up and HR at 1,000 days of follow-up. Mixed, mixed Alzheimer's disease and vascular dementia; VaD, vascular dementia; PDD, Parkinson's disease dementia; Unspecified, diagnosis not specified or unknown; Other, any other established diagnosis other than AD, mixed, VaD, LBD, or PDD; ref, AD group served as a reference category.

1.71 (95% CI 1.04–2.79) and in other dementias (HR 1.73; 95% CI 1.12–2.66) (data not presented in tables).

In crude analyses, each additional year of age increased mortality by 8%. In the final adjusted analysis, compared to patients under 65, each subsequent category was associated with increased mortality risk (Table 4).

Compared with the patients scoring high on MMSE (≥ 25), those scoring lower had higher risk of death, with risk increasing with decreasing cognition (Table 4). Patients in whom MMSE could not be administered, judged not assessable, had the highest risk (HR 3.72, 95% CI 3.19–4.35).

Higher number of medications was associated with increased mortality, with the highest HR occurring among patients taking 10 or more medications (Table 4). Living in an institution was associated with increased risk of death (Table 4).

Mortality by dementia diagnosis

As shown in the survival functions in Fig. 1, lower mortality risk was observed among AD patients compared to all other dementia diagnoses. In Cox regression, the highest crude HR corresponded to VaD (HR 2.27, 95% CI 2.08–2.47) (Table 5). This relationship remained unchanged after adjusting for gender. After adjusting for age and gender, PDD had the highest risk (Fig. 1A). However, after number of medication

was introduced as a covariate, FTD had the highest risk.

When the whole follow-up period was examined, in the final multivariate model, all other dementia diagnoses were significantly associated with higher mortality risk compared to AD (Table 5; Fig. 1B). Mixed dementia presented a HR of 1.32 (95% CI 1.22–1.44), intermediate between AD and VaD, while FTD presented the highest risk (HR 1.91; 95% CI 1.52–2.39). LBD, unspecified dementia, and other dementia had significant non-proportional mortality hazards, meaning that death risk diverged from AD over time. For LBD, the average death risk over the whole observation period was significantly higher than for AD. Death risk relative to AD increased significantly over time (*p*-value for change over time is not presented). A statistically significant difference was not demonstrated at the beginning of the observation period, but a higher HR for death was evident at 1,000 days.

For unspecified and other dementia diagnoses, mortality risk relative to AD decreased over time (Table 5).

Additional adjustment for cholinesterase inhibitors and individual medications (such as cardiovascular treatment or antidepressants) as potential confounding factors showed no substantial changes in results (results not presented).

Post-hoc analyses were rerun on all 28,704 patients in the register (including primary care). The gradation of mortality risk relative to AD did not change, with

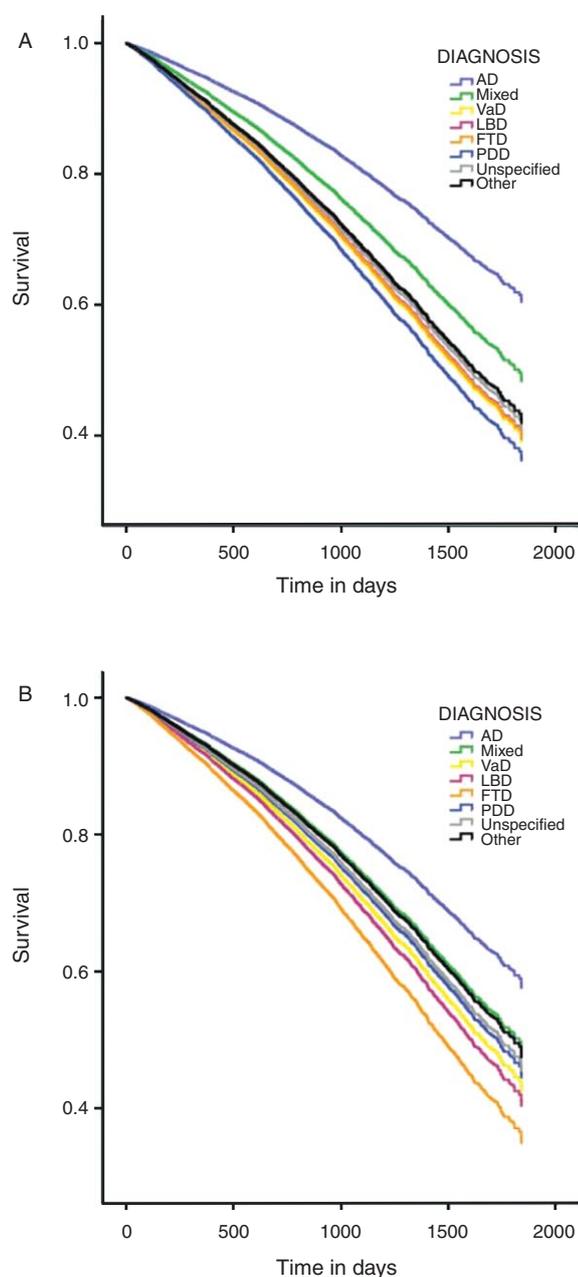


Fig. 1. Age and gender adjusted survival function from Cox hazard regression. Y-axis: estimated survival percentages. X-axis: number of days. When not adjusting for age, patients with vascular dementia (VaD) has the highest mortality risk. A) Age-and-gender adjusted mortality risk was highest for Parkinson's disease with dementia (PDD). B) In the final model, after adjusting for age, gender, Mini-Mental State Exam, co-residence, residential setting and number of medication at the beginning of diagnostic workup, frontotemporal dementia (FTD) presented the highest risk. AD, Alzheimer's disease; Mixed, mixed Alzheimer's disease and vascular dementia; LBD, Lewy body dementia; Unspecified, unspecified dementia; Other, other dementia diagnoses.

HRs remaining roughly similar to those obtained from the cohort containing only specialist memory clinic patients.

DISCUSSION

The results of this study show that worse cognition, male gender, institutionalization, higher number of medications, and higher age are associated with increased mortality after dementia diagnosis regardless of dementia type. AD exhibits better survival than other dementias while FTD has the highest mortality after adjusting for age, gender, MMSE, number of medication, institutionalization, and coresidency.

Our incident dementia cohort presented a mortality rate of 134 deaths per 1000 PY among men and 101 among women. The age and gender adjusted SMR indicated excess mortality in SveDem compared to the general Swedish population (Table 3). Caution must be taken in interpreting these results as higher age groups in the general Swedish population are likely to contain a significant proportion of persons with dementia. We have attempted to control for this by subtracting the mortality rates corresponding to the ICD-10 codes for dementia and non-alcoholic delirium (F00, F01, F02, F03, and F05) from the general rates, but this only accounts for a fraction of these persons. Our finding of 111 deaths per 1000 PY in the 75–84 age group compares to the 172 deaths per 1000 PY reported in patients with incident stroke in the same age group in Sweden [43]. Our rates were lower than those described in other dementia cohorts. In the same age group, the NEDICES cohort [11], reported mortality rates of 224 and 166 deaths per 1000 PY for men and women respectively, which is higher than the 138 deaths per 1000 PY for men and 94 for women observed in our study. This is despite the NEDICES cohort being a prevalent cohort in which length bias might have suggested lower mortality rates. A Swedish study conducted on the +77 group within the Kungsholmen [7] project on incident dementia reported mortality rates for the 77–84 age group of 288 deaths per 1000 PY for men and 175 for women. Both these studies are population-based and comparisons with our register-based study must be tentative. Both had longer follow-up than ours, which might lower our mortality rates since a proportion of patients would foreseeably die in later years. Additionally, both these studies were conducted in the 1990s: greater quality of care and changes in clinical practice with diagnostic boundaries shifting toward the mild end of the dementia spectrum might reduce mortality in present-day patients.

Lower mortality risk was found in women across all cognitive levels. Our findings confirm the general trend in published literature of lower mortality with female gender [1, 3, 6, 7, 12, 16, 18, 22–24]. This trend is not without exceptions [10, 25], and some authors have found a different gender effect with different dementia diagnoses [2, 13, 26, 27] with women afflicted with VaD [13] or LBD [44] faring worse. In our study, lower risk for women was apparent in all dementia types, except FTD and LBD, where results were not statistically significant. Insufficient sample size or different gender effects in these dementia types could explain these results.

Not surprisingly, age is associated with increased mortality in dementia [1, 3, 7, 10, 22]. The study on the +77 subgroup of the Swedish Kungsholmen project [7] reported a 10% increase in mortality risk for each 1-year increase in age. This compares with our finding of 8% per year.

The present study indicates that worse baseline cognition, as represented by MMSE, is associated with higher mortality risk. This increased risk is already apparent from the rather mild levels of cognitive impairment represented by the MMSE 20–24 group and increases with further decline. Previously, some studies only demonstrated increased mortality at severe stages of cognitive decline [11, 16] while a meta-analysis by Dewey et al. [4] found increased mortality even with moderate impairment. Despite not having a non-demented control group for comparison, our finding of 63 deaths per 1000 PY in the MMSE ≥ 25 and 103 deaths per 1000 PY in the 20–24 category is not negligible, and suggests that even mild dementia is associated with increased mortality. The group deemed “non assessable” presented the highest risk. If most of these patients are incapable of taking the test because of low cognition, this would hint at a floor effect in the MMSE test and would signify that mortality continues to increase when cognitive deterioration progresses below the test threshold. However, this group is heterogeneous, comprising patients who refuse to take the test and those who cannot due to advanced dementia or coexisting conditions, which might be associated with increased mortality. Our existing data are insufficient to support one hypothesis over the other.

Comorbidity and disability have been reported to increase mortality after dementia diagnosis [5, 7, 22]. The higher risk among institutionalized patients reflects this. In our cohort, the number of medications was associated with increased mortality. We recently showed that treatment with cholinesterase-inhibitors for AD was associated with reduced mortality in AD

patients in SveDem [42], so this variable was included in the analysis as a potential confounder. The presence of cholinesterase inhibitors in the models did not alter the other results, and neither did other individual medication types.

In our large national cohort, different dementia diagnoses were associated with significantly different mortality rates, with all dementia types showing increased risk relative to AD. VaD displayed the highest crude mortality risk, but FTD was the most lethal dementia after adjusting. This could reflect the fact that FTD disproportionately affects younger individuals who suffer from less comorbidity. In our cohort, the average age in the FTD group was lower than in AD, and they took less medication (Table 2). The FTD group had few patients in the over 85 group ($n = 7$), so we repeated Cox regression analyses only with patients under 85, with similar results.

The lower mortality associated with AD remained after stratifying for gender and adjusting for potential covariates, including MMSE, age, and medications. As expected given the etiopathology of the condition, mixed dementia presented a HR that was significantly higher than AD but lower than VaD. The difference between AD and LBD increased over time. The heterogeneity of the “other dementia” category makes it harder to interpret results. Previous literature reports conflicting results on the influence of different dementia diagnosis on mortality, although most publications report either lower risk with AD [2, 6, 7] or fail to demonstrate a significant difference [11, 18, 19, 21, 22]. Most studies compare AD and VaD (sometimes including mixed dementia) [7, 11, 18, 45, 46] or AD with LBD [9, 15, 25, 26, 47] but few analyze a wider spectrum of diagnoses [6, 9, 20]. When comparing AD and VaD, most studies either fail to demonstrate a difference in survival [7, 11, 18, 45, 46] or suggest lower risk with AD [12, 27]. The cardiovascular risk factors that contribute to a VaD diagnosis would naturally drive up cardiovascular mortality, the main cause of death across cohorts according to previous publications [11]. Landi and colleagues [48] found that AD patients had fewer comorbid conditions than VaD, even after excluding cardiovascular risk factors, making AD a “healthier” demented cohort. The only proxy for co-morbidity available in our study is the number of medication at the beginning of workup, which was 3.7 in the AD group compared to the sample average of 4.7 and the 6.2 average among VaD. This might support the idea of less co-morbidity in the AD group. However, our survival analyses were controlled for number of medication. The same analyses run without

controlling for number of medication showed similar results, with a slight increase in the HR for VaD and PDD. Cholinesterase inhibitors were also examined and did not alter results. In a previous study, VaD was found to increase mortality relative to AD, with mixed dementia presenting intermediate risk [13]. These findings mirror our own and fit with the presumed etiopathology of mixed dementia as a condition with both AD and VaD features.

Previous studies found that LBD presented worse prognosis than AD [15, 26], even after controlling for cognitive level [25], although others find no differences in survival or age at death [47]. In our cohort, multivariate Cox analyses run with LBD as index category showed a significantly increased risk relative to AD and mixed dementia, but no difference with VaD or PDD diagnoses. This could reflect a lack of statistical power, or physiopathological similarities between the LBD and PDD diagnoses.

Frontotemporal degeneration survival estimates range from 3 [49] to 9.5 [50] years but vary depending on variant type [49], presence of motor neuron disease [49], and symptoms at onset [50]. FTD survival compares unfavorably to AD in most studies [6, 20]. With our available data, we cannot ascertain the variant type proportion in our FTD group.

No statistically significant differences were found between mortality risk in different dementia types in a population-based cohort of 828 patients that examined AD, VaD, LBD, and combined dementias [21]. This was probably due to the low number of dementia cases ($n = 275$), particularly LBD ($n = 12$). Two clinic-based studies have compared a wider variety of diagnoses. Koedam et al. [20] found lower mortality risk for AD, with the highest HR for LBD, although differences in risk estimates were not significant. Steenland and colleagues [6] found the highest mortality in motor neuron disease, followed by FTD, LBD, Parkinson's disease (PD), AD, and mild cognitive impairment compared to controls. Their PD group included PD patients without cognitive impairment, but otherwise their gradation of mortality by disease type matches our findings.

Weaknesses of this study are the absence of cognitively normal controls and its descriptive nature. Our follow-up time, from January 2008 to February 2013, might have been too short. SveDem contains a lower proportion of AD diagnosis than previously observed [51], but this is probably due to classifying mixed dementia as separate from AD. Length bias refers to the overestimation of survival due to failure to include patients with rapidly progressive disease who die before recruitment, and appears whenever studies

mix incident and prevalent cases [3]. Our inclusion of only incident cases should help control this bias. However, neurodegeneration in dementia is thought to begin years or decades before diagnosis, and determining the exact moment of dementia incidence is probably impossible.

The exclusion of patients from primary care could be a source of bias since the patient population differs from specialist care. Primary care diagnoses extremely few patients with PDD or LBD, for example, so joint analyses of primary and specialist patient groups are problematic. Still, analyses were repeated with all 28,722 patients from both memory clinics and primary care included in SveDem from 2007 and 2012: the gradation of mortality by diagnosis, and even the hazard ratios for different factors remained roughly similar. This should assuage concerns of a biased sample.

The reliability of clinical diagnoses of dementia is always a concern in studies of this nature. To complicate matters, the correlation between clinical diagnosis and pathology is not straightforward [52]. The fact remains that in clinical practice patients are diagnosed and treated with a clinical diagnosis. As such, mortality information from SveDem is relevant to the clinical process.

In 2011, SveDem captured an estimated 25% of all new dementia cases in Sweden. These calculations are based on the estimated incidence of dementia, but the percentage of new dementia cases who undergo dementia work-up and receive a diagnosis each year is unknown [35]. The coverage in specialist care is 93%, making SveDem uniquely representative among this population. However, there might be baseline differences between the population in SveDem and populations with incident dementia who do not receive a diagnosis or who are diagnosed by units not included in SveDem.

Strengths of our study are its inclusion of a wider variety of dementia disorders than previously published and that all diagnoses were made in specialist clinics, improving reliability. A review of literature indicates that this is the largest prospective study of its type examining mortality in incident dementia.

CONCLUSION

In our study, male gender, higher age, institutionalization, lower cognitive status measured by MMSE, and higher number of medications before dementia diagnosis were independently associated with increased mortality risk. VaD showed the highest crude

mortality rate and FTD the highest adjusted mortality. This might translate the fact that FTD predominantly affects younger and healthier individuals.

Our findings concur with published literature showing that AD has a more benign course than other dementias, but the reasons remain unclear. Coexistent comorbidities or factors relating to the cognitive profile of different diseases might play a role. The underlying neurodegenerative disease process might directly impact mortality.

ACKNOWLEDGMENTS

The authors are grateful to SveDem (<http://www.svedem.se>) for providing data for this study as well as many thanks to all participants in SveDem (patients, caregivers, and staff). This study was supported financially by the Swedish Brain Power network, the Swedish association of local authorities and regions, the Stockholm County Council and Alzheimerfonden. Sara Garcia-Ptacek 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. Sara Garcia-Ptacek, Bahman Farahmand, Dorota Religa, and Maria Eriksson contributed to study concept and design and analysis and interpretation of data. Maria Luz Cuadrado and Ingemar Kåreholt participated in analysis and interpretation of data. All authors contributed to drafting the article and revising for intellectual content as well as approved the final version. Conflicts of interest: Sara Garcia Ptacek is supported by SveDem.

Authors' disclosures available online (<http://www.j-alz.com/disclosures/view.php?id=2135>).

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