Early-onset dementia
Early-onset dementia is associated with higher mortality

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Abstract

Objective
To compare mortality risks of patients with early- and late-onset dementia with non-demented controls of the same age range, and to analyse mortality risks in subtypes of dementia.

Methods
We included 1203 subjects from our memory clinic. Patients with dementia were subdivided into two groups, with early (< 65 years) or late-onset dementia (≥ 65 years), and compared with non-demented controls of the same age range. We used Cox proportional hazard models to estimate mortality risks.

Results
When compared to non-demented controls of the same age range, patients with early-onset dementia had a strongly elevated mortality risk (Hazard Ratio (95% Confidence interval), HR= 43.3 (3.1 – 600.4)), while patients with late-onset dementia had a moderately increased mortality risk compared to older controls (HR (95% CI) = 3.4 (1.8 – 6.2)). An additional analysis showed that, adjusted for age, AD seemed to have the most benign course, with a fourfold increased mortality risk. DLB and VaD (frequently seen at older age) and FTLD and ‘other dementia’s’ (frequently seen at younger age) had a six- to eightfold increased mortality risk.

Conclusion
Dementia is a risk factor for death. Especially in young patients the impact of dementia on mortality is high.
Introduction
Dementia typically is considered a disorder of the elderly and the prevalence increases exponentially with age \(^1,2\). In general, increasing age is the most important risk factor for death. Moreover, dementia in itself is an important risk factor for death \(^3-8\). Estimates of survival in demented persons are useful for patients, caregivers and clinicians, bearing relevance to counselling patients and caregivers and planning special health and social services.

Patients suffering from dementia die earlier than healthy subjects of the same age \(^4\). It is unclear whether age modifies the risk of death in demented patients. Some studies found no effect of age at onset on mortality risk \(^9,10\). Other studies showed that subjects with a dementia onset at a younger age have a lower mortality risk and live relatively longer than older patients with dementia, but still have a higher mortality risk when compared to the general population \(^5,6,8,11,12\). Finally, the opposite effect has also been found. In several studies the mortality risk in demented subjects decreased with age \(^3,7,13,14\), implicating that dementia with an onset at a younger age has a more malignant course.

Dementia is a general term which describes a syndrome of progressive deterioration of cognitive function \(^15\). Alzheimer’s disease (AD) is the most common cause of dementia, both at older and younger age \(^16-19\). Vascular dementia (VaD) and dementia with Lewy bodies (DLB), common causes of dementia after AD, are typically seen in the elderly \(^20-22\). Frontotemporal Lobar Degeneration (FTLD) and more sporadic of dementia such as Creutzfeld Jacob Disease (CJD) and Corticobasal Degeneration (CBD) are relatively more prevalent at younger age \(^1,17-19\). Information about mortality in specific forms of dementia is limited, as most studies analysed mortality in AD \(^5,6,9,12,13\). Mortality in FTLD has been reported to be either comparable with AD or higher than AD \(^23,24\). For both DLB and VaD a higher mortality risk when compared to AD has been reported \(^22,25-27\). However, studies are difficult to compare due to methodological differences; some studies were performed in a memory clinic setting, while others were population based. Moreover, none of the studies compared a wider spectrum of dementia types with non-demented controls.

In the present study, our aim was twofold. Firstly, we investigated the mortality risk in patients with early-onset dementia and patients with late-onset dementia in comparison with non-demented controls of the same age range. Secondly, we analysed mortality risks associated with specific types of dementia.

Methods
Patients
We included 1203 patients that visited the outpatient memory clinic at the Alzheimer Center of the VU University Medical Center between 1993 and 2006. For the diagnostic procedure all subjects underwent a standard battery of investigations including medical history, physical and neurological examination
including mini-mental state examination (MMSE) \(^\text{28}\), laboratory tests, neuropsychological assessment, EEG and MRI of the brain. The diagnosis was made by consensus in a multidisciplinary team. Clinical criteria of the National Institute of neurological and Communicative Disorders and Stroke- Alzheimer’s Disease and Related Disorders (NINCDS-ARDA) were used for AD \(^\text{29}\), Neary and Snowden criteria for FTLD \(^\text{30}\), National Institute of Neurological Disorders and Stroke- Association Internationale pour la Recherche et l’Enseignement en Neuroscience (NINDS-AIREN) criteria for VaD \(^\text{31}\) and the current clinical criteria for DLB \(^\text{32}\). As a control group, we used patients who presented at our memory clinic with subjective complaints, but who –after careful investigation- were considered to be cognitively normal. The groups of demented patients included 589 patients with AD (n = 570 probable AD, n = 19 possible AD), 129 with FTLD, 80 with VaD, 52 with DLB and 43 patients with another type of dementia (3 CJD, 9 Progressive Supranuclear Palsy, 3 Huntington’s disease, 2 M. Parkinson dementia, 5 CBD, 4 alcohol dementia, 1 CADASIL and 16 dementia not otherwise specified). Patients with dementia were dichotomised according to age at diagnosis (age < 65 years versus ≥ 65 years). There were 273 patients with early-onset dementia (158 AD, 72 FTLD, 19 VaD, 3 DLB and 21 other dementia) and 620 patients with late-onset dementia (431 AD, 57 FTLD, 61 VaD, 49 DLB and 22 other dementia). Controls were also dichotomised according to age (age < 65 years and age ≥ 65 years). There were 186 young non-demented controls and 124 older non-demented controls.

In 2006 a questionnaire was sent to all the general practitioners enquiring if the patient had died or was still alive. If the questionnaire was not returned, data on survival were collected from the patient file. From 64% of the subjects we collected the data through the questionnaire and in 36% data were collected from the patient files. Follow up time was defined as the time from the date of first visit until the date of death or last known date of being alive. By design, follow up time varies between patients, as consecutive patients in a clinical setting were included (follow up time (years) mean ± SD: 2.5 ± 2.0, median: 2.0 (max. 10.4)) All subjects gave written informed consent for their clinical data to be used for research purposes.

Statistical analysis

SPSS 12.0.1 for Windows was used. Group differences were examined using Chi-squared test for categorical data and analysis of variance (ANOVA) with post hoc Bonferroni t-tests for continuous data. Cox proportional hazards models and Kaplan Meier survival curves, that account for varying follow up times, were used to investigate the risk of death associated with dementia. Data are presented as hazard ratio and accompanying 95% confidence interval (HR (95% CI)). The first analyses compared early-onset and late-onset dementia with separate groups of non-demented controls of the same age range. In a second set of analyses, the risk of mortality associated with specific types of dementia compared with non-demented controls (young and old controls pooled together) was assessed.
The first model shows the crude risk estimates. In the second model we corrected for age and sex. Significance was set at \( p < 0.05 \).

Results
Demographic and clinical characteristics of the patient sample according to dementia status are shown in table 1. Patients with early-onset dementia were older than young non-demented controls. MMSE score was comparable between the two dementia groups and between both control groups. In total, 212 subjects died. In the young demented group 43 patients (16%) died, but no subjects died in the young control group. Most deaths, 158 (26%), occurred in the elderly demented group. In the older control group 11 subjects (9%) died.

Table 1. Demographic and clinical characteristics by patient groups

<table>
<thead>
<tr>
<th></th>
<th>&lt; 65 years</th>
<th>≥ 65 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Controls</td>
<td>Dementia</td>
</tr>
<tr>
<td>N</td>
<td>186</td>
<td>273</td>
</tr>
<tr>
<td>Age</td>
<td>53 (8)</td>
<td>58 (5)*~</td>
</tr>
<tr>
<td>Females</td>
<td>87 (47%)</td>
<td>131 (48%)</td>
</tr>
<tr>
<td>MMSE</td>
<td>29 (2)</td>
<td>21 (6)*</td>
</tr>
<tr>
<td>Death</td>
<td>0 (0%)</td>
<td>43 (16%)*~</td>
</tr>
<tr>
<td>Time to death</td>
<td>Median 2.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.4 (2.8)</td>
</tr>
<tr>
<td>Time to last</td>
<td>Median 2.0</td>
<td></td>
</tr>
<tr>
<td>known date alive</td>
<td></td>
<td>2.5 (2.1)</td>
</tr>
<tr>
<td></td>
<td>Median 1.9</td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as mean (SD) and median or N (%)

* MMSE available for 1069 subjects
*\( p < 0.05 \) compared to young controls
#\( p < 0.05 \) compared to elderly controls
~\( p < 0.05 \) compared to late-onset dementia
Figure 1 shows the Kaplan Meier survival curves of patients with early- and late-onset dementia and young and old non-demented controls (Log-rank test: $p < 0.001$). Cox proportional hazard models showed that patients with late-onset dementia had a more than threefold increased risk of dying (HR (95% CI) = 3.4 (1.8 – 6.2)) compared to older non-demented controls. Patients with early-onset dementia had a strongly increased mortality risk (HR (95% CI) = 43.3 (3.1 – 600.4)) compared to non-demented controls of the same age range. After correction for age and sex, the mortality risk for patients with late-onset dementia did not change (HR (95% CI) = 3.3 (1.8 – 6.1)). The mortality risk for patients with early-onset dementia became incalculably high (HR = $\infty$).
Figure 1. Kaplan Meier curve

Cumulative proportion surviving from date of diagnosis was determined for early-onset dementia (n = 273) and late-onset dementia (n = 620) and young (n = 186) and older non-demented controls (n = 124). The line-dot line represents the young non-demented controls, the dotted line represents the older non-demented controls, the broken line represents the patients with early-onset dementia and the straight line the patients with late-onset dementia (Log-rank test: p< 0.001).

Patients at risk

<table>
<thead>
<tr>
<th></th>
<th>Young controls</th>
<th>Elderly controls</th>
<th>Early-onset dementia</th>
<th>Late-onset dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>186</td>
<td>124</td>
<td>273</td>
<td>620</td>
</tr>
<tr>
<td>Patients at risk</td>
<td>93</td>
<td>78</td>
<td>132</td>
<td>305</td>
</tr>
<tr>
<td>Survival (years)</td>
<td>39</td>
<td>34</td>
<td>64</td>
<td>124</td>
</tr>
</tbody>
</table>
In a second set of analyses we analysed the mortality risk in specific forms of dementia compared to the pooled group of non-demented controls. The diagnostic groups differed with respect to age (table 2, p < 0.05). Patients with AD, DLB and VaD were older than non-demented controls, while the groups of FTLD and ‘other dementia’ had a comparable age to controls. The group of AD patients had the highest proportion of women and the group of VaD patients the lowest. Among the patients with dementia, patients with FTLD had the highest MMSE and AD the lowest.

Table 3 shows that all forms of dementia were associated with an increased risk of death compared with non-demented controls. After correction for age and sex, AD, the most common type of dementia at younger and older age, was associated with a fourfold increased risk of death. A six- to eightfold increased mortality risk was found in VaD and DLB, frequently seen at older age, and in FTLD and the group of ‘other dementia’, with relatively young patients. In comparison with other types of dementia, AD seemed to have the most benign course in terms of risk of mortality, while DLB and ‘other dementia’ had the highest mortality risk, although risk estimates did not differ significantly among the different types of dementia.
Table 2. Demographic and clinical characteristics by specific dementia groups

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Age (SD)</th>
<th>Females (N %)</th>
<th>MMSE a</th>
<th>Death (N %)</th>
<th>Time to death</th>
<th>Time to last known date alive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>310</td>
<td>62 (12)</td>
<td>150 (48%)</td>
<td>28 (2)</td>
<td>11 (4%)</td>
<td>2.7 (2.2)</td>
<td>2.6 (1.9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Median 2.0</td>
<td>Median 2.2</td>
</tr>
<tr>
<td>AD</td>
<td>589</td>
<td>71 (10)</td>
<td>337 (57%)</td>
<td>20 (5)</td>
<td>123 (21%)</td>
<td>3.4 (2.2)</td>
<td>2.3 (2.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Median 3.0</td>
<td>Median 1.9</td>
</tr>
<tr>
<td>VaD</td>
<td>80</td>
<td>72 (9)</td>
<td>25 (31%)</td>
<td>22 (6)</td>
<td>27 (34%)</td>
<td>2.0 (1.6)</td>
<td>2.9 (2.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Median 1.6</td>
<td>Median 2.1</td>
</tr>
<tr>
<td>DLB</td>
<td>52</td>
<td>75 (7)</td>
<td>17 (33%)</td>
<td>22 (5)</td>
<td>16 (31%)</td>
<td>1.9 (1.6)</td>
<td>1.9 (1.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Median 1.3</td>
<td>Median 1.5</td>
</tr>
<tr>
<td>FTLD</td>
<td>129</td>
<td>64 (8)</td>
<td>48 (37%)</td>
<td>24 (5)</td>
<td>26 (20%)</td>
<td>2.9 (2.4)</td>
<td>2.1 (1.8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Median 1.8</td>
<td>Median 1.8</td>
</tr>
<tr>
<td>Other dementia’s</td>
<td>43</td>
<td>65 (12)</td>
<td>20 (47%)</td>
<td>21 (6)</td>
<td>9 (21%)</td>
<td>0.8 (0.7)</td>
<td>2.2 (1.8)</td>
</tr>
</tbody>
</table>

Data are presented as mean (SD) and median or N (%)

* significant difference p < 0.05 compared to controls

° significant difference p < 0.05 compared to FTLD

- significant difference p < 0.05 compared to AD

+ significant difference p < 0.05 compared to DLB

a MMSE available for 1069 subjects

<sup>a</sup> MMSE available for 1069 subjects

<sup>+</sup> significant difference p < 0.05 compared to DLB

<sup>°</sup> significant difference p < 0.05 compared to FTLD
Table 3. Mortality risk associated with specific dementia types

<table>
<thead>
<tr>
<th></th>
<th>Model 1</th>
<th>Model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>1 (ref.)</td>
<td>1 (ref.)</td>
</tr>
<tr>
<td>AD</td>
<td>5.6 (3.0 - 10.5)</td>
<td>4.3 (2.3 – 8.0)</td>
</tr>
<tr>
<td>VaD</td>
<td>8.7 (4.3 – 17.5)</td>
<td>6.6 (3.3 – 13.3)</td>
</tr>
<tr>
<td>DLB</td>
<td>13.0 (6.0 – 28.2)</td>
<td>8.3 (3.8 – 18.1)</td>
</tr>
<tr>
<td>FTLD</td>
<td>6.3 (3.1 – 12.8)</td>
<td>6.4 (3.2 – 13.1)</td>
</tr>
<tr>
<td>Other dementia’s</td>
<td>8.8 (3.6 – 21.3)</td>
<td>7.6 (3.1 – 18.4)</td>
</tr>
</tbody>
</table>

Hazard ratios and 95% confidence intervals, HR (95% CI) were calculated for all dementia types. Model 1 shows the crude estimates, in model 2 we adjusted for age and sex.

Discussion

We found that dementia is associated with an increased risk of death compared to non-demented controls. The impact of dementia on mortality in patients with early-onset dementia was higher than in patients with late-onset dementia. In addition we found that specific types of dementia were all associated with an increased risk of death compared to non-demented controls.

It has been suggested by several studies that early-onset dementia has a more malignant course than late-onset dementia. One study calculated survival in 199 patients with AD, divided in early- and late-onset (< 65 years versus ≥ 65 years). They found that survival was decreased in patients with early-onset dementia compared to patients with late-onset dementia. Another prospective population-based cohort study evaluated the survival and risk factors of mortality with dementia in 3675 initially non-demented participants. They found a lower impact of dementia (AD, VaD and other dementia) on mortality with increasing age, although all patients were initially already older than 65 years of age. A German study analysed survival in 115 patients with FTLD and found that patients with an earlier disease onset had a higher mortality risk (age at onset 42–73 years). In line with these earlier findings, we confirm that patients with early-onset dementia have a high risk of death compared to controls of the same age range. These results add to the growing body of evidence that early-onset dementia has a more malignant course than late-onset dementia.

In our study the different types of dementia were all associated with an increased mortality risk. AD, the most common form of dementia, seemed to have the most
benign course with a fourfold increased risk of death, after correction for age and sex. In unadjusted analyses the highest mortality risk was found in VaD and DLB, confirming results from other studies 22,25-27. Both forms of dementia are most commonly seen at older age 20-22. The high mortality risk seemed to be partly attributable to the older age, as after correction for age, the mortality risk decreased and became comparable with the mortality risk we found in FTLD and ‘other dementia’, both more commonly observed among younger patients. Most earlier studies focus on mortality in AD and FTLD. It has been suggested that especially FTLD is a highly malignant disease with limited life expectancy 24,33. Our study did not confirm these results, although risk estimates for FTLD were higher than risk estimates found for AD. We included all patients from our memory clinic and we did find that rare types of dementia, such as CJD and PSP (combined in our ‘other dementia group’), progress rapidly.

Among the limitations of our study is the fact that we used clinical diagnosis of dementia, as neuropathological diagnoses were not available. Therefore we cannot exclude the unavoidable uncertainty of a clinical diagnosis in dementia and the presence of mixed pathology. However, all patients were carefully screened and fulfilled clinical criteria for specific types of dementia. Data on causes of death were not available and further study is necessary to determine the causes of death in early- and late-onset dementia and the different types of dementia. Second, our non-demented controls consisted of subjects with subjective complaints. It cannot be excluded that these controls develop dementia at some stage, as it has been demonstrated that patients with subjective complaints are at increased risk of dementia 34,35. On the other hand, with increasing age all subjects are at increased risk of dementia, so we believe that our results give a good impression of the increased mortality risk in dementia. Furthermore, we compared our results to data on mortality rates in the Dutch general population from an interdisciplinary cohort study on predictors and consequences of changes in autonomy and well-being in the aging population in the Netherlands (LASA) 36. Mortality rates among 998 younger subjects (55-65 years) and 1305 elder subjects (> 65 < 85 years) with 5 years follow up were 0.8% per year in the younger age group and 3.3% per year in the older age group. In our study the mortality rate of patients with early-onset dementia was 6% per year and 10% for patients with late-onset dementia. Although it is impossible to make a formal comparison between the data from our study and these results, due to differences in study set up, these numbers provide further support for our finding that dementia at a younger age has a larger impact on the mortality risk than dementia at older age. Third, it is conceivable that our results are influenced by lag time bias, as survival was calculated from date of first visit, while the first symptoms of the disease may have started years before. However, we feel that the use of date of first visit to our memory clinic is preferable as a starting point, as it is a clearly defined point in time for both patients and controls, while defining the year in which the first symptoms started can be difficult, inevitably leading to a noisy estimate.
Moreover, we feel that our risk estimate from time of first visit has important clinical value, as these data provide information on prognosis, which is important for both patients and caregivers. Finally, rather than an epidemiological, population based study where a given number of subjects is followed for a fixed number of years, our study is a cohort study in a clinical setting. In our study we included patients between 1993 and 2006 with all different types of dementia as encountered in a memory clinic. As a consequence of our study set-up, we have a high variability in duration of follow up, which was accounted for in the statistical analyses. The large confidence interval in the hazard ratio of early-onset dementia is due to the small numbers in the younger groups, especially because no one died in the young control group.

This cohort represents a very important selection of patients, as these patients all presented at a memory clinic and the findings of our study do provide important information about the mortality risk in patients with dementia in a memory clinic setting. This information is of great value for caregivers, patients and healthcare professionals.

Reference List


