Is Depression in Elderly People followed by Dementia? A Retrospective Cohort Study based in General Practice

F. BUNTINX, A. KESTER, J. BERGERS, J. A. KNOTTNERUS

Summary
We used a retrospective cohort study design to test the hypothesis of a relation between old-age depression and subsequent dementia. The study sample comprised 19,103 patients aged 50 or more and born after 1910, included in a family-practice-based registration network. We estimated odds ratio (OR) and 95% confidence interval (95% CI) for a diagnosis of dementia in patients with or without previous late-onset depression and survival analysis, including hazard ratios resulting from Cox regression analysis.

The OR for a diagnosis of dementia subsequent or not to late-onset depressions was 2.38 (95% CI 1.08-5.06). No significant difference between patients with or without old-age depression was found at survival analysis: \( p = 0.26 \) (log rank test). Hazard ratio for patients with and without previous old age depression was 2.55 (95% CI 1.19—5.47). We conclude that there is a significant relation between old-age depression and subsequent dementia in patients aged 50 or more and born after 1910. This supports the hypothesis of old-age depression being a predictor, and possibly a causal factor, of subsequent dementia.

Introduction
Since the late 1800s, the relation between depression in elderly people and dementia has been the subject of research [1–4]. Symptoms of depression have been found to occur more frequently in patients with dementia than in the healthy elderly population [5–7]. In the Eurodem study [8, 9], six case–control studies assessing the relation between depression and Alzheimer’s dementia were re-analysed and their results were pooled. Four studies assessing the relation between depression and subsequent Alzheimer's disease onset produced an odds ratio (OR) of 1.82 with a 95% confidence interval (95% CI) of 1.16–2.83. This positive relation was confined however to late-onset disease (OR 2.44; 95% CI 1.36–4.36). No relation was found with antidepressant treatment or life events.

It has been hypothesized that depression in late life could be a predictor, and even an aetiopathological factor for dementia [5, 7, 9, 11]. Among elderly patients with depression, between 3% after 1 year and 79% after 4–18 years have been found demented at follow-up [1]. For major depression and Alzheimer’s disease, an overlap in the neuropathological and neurochemical substrate has been suggested [1, 7, 10]. If a causal relation between depression and dementia existed, this could have consequences for clinical care. The influence of psychosocial and pharmacological treatment on this relation would then have to be explored [7, 11]. There have been no cohort studies comparing the risk of developing dementia in patients with or without late-onset depression and living at home.

We therefore compared the risk of a diagnosis of dementia after a previous diagnosis of old-age depression with the risk in patients without any diagnosed depression in a retrospective cohort study of a population sample derived from a network of general practices.

Methods
This study was carried out within the context of the Registration Network of Family Practices (Registratie Netwerk Huisartspraktijken = RNH), consisting of 15 practices continuously registering basic data (including birth date, sex, level of education and type of household) as well as health problems of their patients via a computerized record system [12]. Health problems recorded are either permanent, chronic or recurrent. Data are coded following the ICPC-classification [13] and collected in a central database. The RNH uses the diagnostic criteria of the International Classification of Health Problems in Primary Care (ICHPPC-2 defined) [14]. Currently the database contains data concerning 60,000 patients. Practices are situated in both rural and urban regions of the province. Since all Dutch inhabitants are registered in a general practice except when institutionalized, the RNH register represents the local general population. The database is used for cohort or case–control studies. Data from patients who have moved or died are stored and were also used for this analysis.
Quality control: Internal quality control of the database is assured by an automated thesaurus of the ICPC classification including ICHPPC criteria, by automated checking for erroneous or missing entries, by continuous training of the GPs (including consensus meetings and coding of dummy patients) and by automated data control in the central database with regular feedback to the GPs [15]. Completeness and reliability of the data were demonstrated by a comparison of the RNH's cancer data with the data of the regional Cancer Registry [16] and a comparison of the RNH's epilepsy data with the data of the Maastricht Epilepsy case register [15].

Diagnostic criteria: For the diagnosis of dementia, the International Classification of Health Problems in Primary Care (ICHPPC-2 defined) requires a progressive decrease of intellectual capacities, with a deterioration of at least three functions out of five: orientation in time, place or persons, short-term memory, abstracting, making simple calculations and affective alterations or personality disorders [14]. For the diagnosis of depression, patients should not be psychotic and comply with three criteria out of a list of six [14].

Patients: This study relates to all RNH-patients, aged 50 or above at 31 December 1993 and born after 1910. The latter restriction was introduced because the data collection was feared to be less reliable with respect to death and transfer to an institution in the period before 1960. Patients with a diagnosis of dementia before age 50 were excluded from this study. All 489 patients with a diagnosis of depression (ICPC code P76) entered after reaching age 50 (old-age depression) were identified. In this group, patients were identified who had a diagnosis of dementia (ICPC code P70) included after the depression had been diagnosed. For comparison, using the same age criteria, patients who did not develop depression (n = 18 614) were identified and in this group the occurrence of dementia was also established.

Analysis: The relation between previous late-onset depression and subsequent dementia was assessed by estimating the odds ratio with its 95% CI for a diagnosis of dementia in patients with or without a previously diagnosed depression. In patients showing a dementia following diagnosis of depression, the time period between both diagnoses was also evaluated.

Separate Kaplan–Meier survival curves, starting at age 50, were produced for patients with or without late-onset depression to compare time to diagnosis of dementia. Censor events consisted of death, leaving the RNH practices or reaching the end of the follow-up period (31 December 1993). Survival times in the two groups of patients were compared using the log rank test.

A Cox regression model was fitted to adjust for sex, year of birth, education and number of co-morbid medical problems known to the general practitioner. Depression was modelled as a time-dependent covariable.

All calculations were made using BMDP software [17].

Results

Crude data analysis: Of the 489 patients with a diagnosis of depression, eight (1.6%) had a subsequent history of dementia. The odds ratio of dementia in patients with versus without previous old age depression was 2.38 (95% CI 1.08–5.06) (Table). In this group, the estimated fraction of dementia attributable to previous depression was 57% (95% CI 14–79). In the eight patients with a diagnosis of dementia following a diagnosis of depression, the time period between the diagnoses ranged between 1 and 10 years.

Survival analysis: Kaplan–Meier survival curves for patients with or without old-age depression are presented in the Figure. Survival of the groups did not differ significantly (p = 0.26) (log rank test). Cox regression analysis: The hazard ratio for patients with or without old age depression was 2.55; 95% CI 1.19–5.47. Based on the likelihood ratio χ², the p value was 0.03.

Sex, education and number of medical problems did not reach statistical significance. Year of birth, however, was highly significant (p < 0.001).

Discussion

This paper reports on the first cohort study examining the relationship between old-age depression and subsequent dementia. It follows a series of case-control studies suggesting such a relationship with a pooled OR of 1.82 [9]. Our crude data analysis also shows a significant relation with an OR of the same magnitude (OR 2.38). Statistical significance disappeared, however, when using survival analysis. When Cox regression analysis was used, adjusting for the...

Table. New cases of subsequent dementia in patients aged 50 or more, with and without a previous old-age depression

<table>
<thead>
<tr>
<th>Previous old-age depression</th>
<th>Subsequent dementia</th>
</tr>
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<tbody>
<tr>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Yes</td>
<td>8</td>
</tr>
<tr>
<td>No</td>
<td>129</td>
</tr>
<tr>
<td>Total</td>
<td>137</td>
</tr>
<tr>
<td>p = 0.03</td>
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Figure. Kaplan-Meier survival curves for patients with or without old age depression.
covariables that previously proved to be relevant determinants of the incidence and prevalence of dementia [18], the hazard ratio was very similar to the odds ratio in the crude data analysis and significance was reached again: HR 2.55; 95% CI 1.19–5.47.

Our previous study [18] estimated the crude prevalence rate of dementia in our group to be 1.5% for patients aged 65 or more. This is within the range of the estimates of other data from general practice as reviewed by Muskens et al. [19]. The prevalence of depression in our study is lower than decreased elsewhere for the same age groups [20]. This difference could result from the definition of depression used. Only patients with ICPC code P76 (depression) were selected, without including patients with ICPC code P03 (depressive mood). This choice was made because we were most interested in the impact of well developed and clinically manifest cases of depression.

Many hypotheses have been formulated with respect to the reasons for a relation between old-age depression and subsequent dementia, including obscurity in the differentiation between both diseases, confounding by life events, the impact of antidepressant treatment and an overlap in the neuropathological or neurochemical substrates (1, 7, 10, 21–23). Misclassification bias is never impossible. However, as the time period between the diagnosis of depression and subsequent dementia ranges between 1 and 10 years and is 4 years or more in six out of eight cases, this study does not support the explanation based on diagnostic obscurity and classification bias. From case-control studies, the impact of antidepressant treatment or confounding by life events seems minor [9]. As only a small proportion of the patients with old-age depression will develop dementia, there certainly exists no simple cause and effect relation between the diseases. This leaves the hypothesis of a common genetic, neuropathological or neurochemical basis, favouring the development of both diseases or the existence of changes resulting from old-age depression and causing an increased vulnerability or sensitivity to other risk factors for dementia.

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References

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