Chapter 4

The natural history of depression in old age

Abstract

**Background** Despite its negative consequences, little is known about the natural history of depression in the oldest old.

**Aim** To study the incidence, course and predictors of depression in the general population of the oldest old.

**Methods** The Leiden 85-plus Study is a prospective population-based study of 500 subjects from age 85 through 89 years. Depressive symptoms were annually assessed with the 15-item Geriatric Depression Scale (GDS-15), using a cut-off of 5 points.

**Results** During a mean follow-up of 3.9 years, the annual risk for the emergence of depression was 6.8 percent. Poor daily functioning and institutionalisation predicted the incidence of depression. Within the 77 participants with depression at baseline (prevalence 15 percent) the annual remission rate was 14 percent. In more than half of the participants with a remission of depression, we observed a relapse of depression during follow up. No predictors of remission could be identified.

**Conclusions** Among the oldest old, depression is frequently occurring and highly persistent. More active case finding and treatment is potentially rewarding.


**Introduction**

Depression ranks among the most significant health problems in the elderly and is potentially treatable at all ages\(^1\). The consequences of both major and minor depression in the elderly are known to be severe, including diminished quality of life, functional decline, marked disability, increased service utilisation and high mortality from comorbid medical conditions\(^2\)\(^3\)\(^4\). To date, few studies have been published on the incidence of depression in the oldest of old and none about its course\(^5\)\(^6\)\(^7\). Given the rapidly increasing number of elderly subjects in society, we studied the incidence and course of depression in the oldest old within the Leiden 85-plus Study, a population-based prospective study of a large cohort of community-dwelling elderly in Leiden, the Netherlands.

**Methods**

*Sampling and procedures*

The Leiden 85-plus Study is a prospective population-based study of inhabitants in Leiden, the Netherlands. The study was described in detail elsewhere\(^8\). In short, between 1997 and 1999 all members of the 1912 to 1914 birth cohort living in Leiden were enrolled in the month of their 85th birthday. No ‘a priori’ selection criteria on health, cognitive functioning or living situation were applied. Demographic characteristics were representative for the general Dutch population of 85-year-old persons. Upon enrolment, information was given by mail; further contact was made by telephone or a home visit to ask for approval. Subjects were then visited at their place of residence by medical staff and research nurses. During the baseline visits structured face-to-face interviews were conducted and blood samples were collected. Follow through-interviews were carried out in all eligible participants each year during the study period of 4 years. The Medical Ethical Committee of the Leiden University Medical Centre approved the study.

*Depression*

Each year we assessed the 15-item Geriatric Depression Scale (GDS-15), a questionnaire especially developed as a screening instrument for the presence of depressive symptoms in elderly populations\(^9\). Depression was considered present when the score of the GDS-15 was 5 points or more. This cut-off gives the best sensitivity and specificity for the presence of major depression in the general population\(^9\), in geriatric inpatients\(^10\), in primary care settings\(^11\)\(^12\), and in medical inpatients\(^13\), and was found to have a good specificity (0.85) in a representative sample of community-dwelling oldest old for the presence of major depression\(^14\). Because the reliability and the validity of the GDS-15 are compromised in elderly with serious cognitive impairment, the GDS-15 was not administered in participants with an Mini-Mental State Examination score less than 19 points\(^15\).

*Incidence and course*

The incidence of depression was studied by following up the participants without depression at baseline, defined as having a GDS-15 score of 0 - 2 points at age 85, during a four-year period. Incident depression was considered to be present when the GDS-15 increased to 5 points or more during the follow-up measurements of these participants.
The course of depression was studied by following the participants with depression at baseline, defined as a GDS-15 score of 5 points or more, during a follow-up of four years. Remission of depression was defined as gaining a GDS-15 score of 0 - 2 points at any measurement during follow-up.

Risk factors
Demographic variables, including gender, marital state, living arrangements, loss of a spouse, income and institutionalization were recorded. The level of education was dichotomised at 6 years and income at the level of state pension.

Disability in daily functioning was measured with the Groningen Activity Restriction Scale (GARS)\textsuperscript{16}. Poor daily functioning was defined as a GARS-score above 23 points (33rd percentile)\textsuperscript{17}. Furthermore, the self rated presence of loneliness was assessed.

Health related correlates included the use of medication obtained from the pharmacist’s registers, and data on chronic diseases. The latter included cardiovascular disease (stroke, myocardial infarction or ischemia, arterial surgery, intermittent claudication), malignancy, Parkinson Disease, diabetes mellitus, chronic obstructive pulmonary disease, and arthritic disease at baseline or in the past. Data were obtained from a structured questionnaire and based on diagnoses of the general practitioner. Diabetes was considered present in case of a positive medical history, or current use of antidiabetic medication, or a nonfasting glucose concentration of 11.1 mmol/l or higher.

Statistical analysis
First, the cumulative incidence and the cumulative remission rate of depression with the corresponding 95 % Confidence Intervals (95% CI) were calculated in life tables. The assumption was made that depression developed or remitted halfway the follow-up period in which the participant passed the GDS-15 cut-off point. Second, relative risks (and 95% CI) of risk factors for the incidence and the remission of depression were calculated in a Cox proportional-hazards model, with the assumption that depression developed or remitted halfway the follow-up period in which the participant passed the GDS-15 cut-off point.

Results
During the study period 705 inhabitants of Leiden reached the age of 85 years and were eligible to participate. Fourteen subjects died before they could be enrolled and 92 subjects refused to participate. At baseline the response rate was 87 percent, resulting in a sample of 599 participants. There were no significant differences for various sociodemographic characteristics and the presence of depressive symptoms between the 599 participants and the source population\textsuperscript{18}. Of these, 500 participants had MMSE-scores above 18 points and were included in the present analysis.

Of the 500 participants at baseline, 334 (67 %) had no significant symptoms of depression, as measured with GDS-scores of 0 - 2 points. During follow-up, the mean total GDS-15 score increased significantly from 0.96 (SD 0.8) at baseline to 2.3 points (SD 2.7) at age 89 (paired t-test, p < 0.001). Table 4.1 describes the incidence of depression, defined as GDS-15 scores of 5 points or more, in the 334 participants without depression at baseline. During a follow-up of 827 person years at risk depression occurred in 56 participants (incidence rate 68 per 1000 person years, 95% CI: 50 to 85) amounting to an annual risk of 6.8 %. Figure 4.1 illustrates the cumulative incidence of depression from age 85 through 89 years.
Table 4.1 The incidence of depression during a four-year follow-up of 334 participants without depression at baseline (as measured with a GDS-score of 0 to 2 points) from age 85 onwards\(^a\).

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Number at start</th>
<th>Reasons for attrition</th>
<th>GDS completed</th>
<th>GDS &gt; 4 points</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Dead</td>
<td>Refusal</td>
<td>Severe Cl(^b)</td>
</tr>
<tr>
<td>85-86</td>
<td>334</td>
<td>19</td>
<td>24</td>
<td>14</td>
</tr>
<tr>
<td>86-87</td>
<td>269</td>
<td>14</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>87-88</td>
<td>220</td>
<td>17</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>88-89</td>
<td>171</td>
<td>14</td>
<td>8</td>
<td>8</td>
</tr>
</tbody>
</table>

\(^a\) Incident depression was considered present when the score on the GDS-15 was above 4 points.

\(^b\) Severe CI = Severe cognitive impairment was considered present when the MMSE-score was below 19 points.

Figure 4.1 The cumulative incidence of depression in 334 participants without depression at baseline, defined as a GDS-15 score between 0 and 2 points, from 85 to 89 years onwards. Incident depression was defined as a GDS-15 score above 4 points during any of the follow-up measurements.
Table 4.2 shows the impact of various risk factors for the emergence of depression. Neither demographic characteristics nor any of the health related characteristics contributed to the incidence of depression. Institutionalisation and poor daily functioning were associated with an increased risk for development of depression. Also, the GDS-score at baseline was associated with an almost twofold increased risk per point increase. After adjustment for the GDS-score at baseline the increased risks of depression for institutionalisation (RR 2.8, 95% CI: 1.3 - 6.4) and poor daily functioning (RR 1.9, 95% CI: 1.1 - 3.4) sustained.

Table 4.2 The risk of depression during follow-up in 334 participants without depression at baseline dependent on socio-demographic characteristics, daily functioning and health characteristics.

<table>
<thead>
<tr>
<th></th>
<th>N (%)</th>
<th>Relative risk (95% CI)^a</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female gender</td>
<td>209 (63%)</td>
<td>1.1 (0.6-1.9)</td>
<td>ns</td>
</tr>
<tr>
<td>Low educational level</td>
<td>195 (58%)</td>
<td>1.0 (0.6-1.7)</td>
<td>ns</td>
</tr>
<tr>
<td>Low income</td>
<td>53 (16%)</td>
<td>1.6 (0.8-3.1)</td>
<td>ns</td>
</tr>
<tr>
<td>Not married                   ^b</td>
<td>204 (61%)</td>
<td>0.8 (0.4-1.5)</td>
<td>ns</td>
</tr>
<tr>
<td>Living alone                   ^b</td>
<td>194 (58%)</td>
<td>1.1 (0.7-2.0)</td>
<td>ns</td>
</tr>
<tr>
<td>Loss of a spouse               ^b ^c</td>
<td>56 (17%)</td>
<td>0.9 (0.5-1.7)</td>
<td>ns</td>
</tr>
<tr>
<td>Presence of loneliness         ^b</td>
<td>29 (9%)</td>
<td>1.3 (0.5-3.3)</td>
<td>ns</td>
</tr>
<tr>
<td>Institutionalization            ^b</td>
<td>23 (7%)</td>
<td>3.4 (1.5-7.5)</td>
<td>0.003</td>
</tr>
<tr>
<td>Poor daily functioning         ^b ^d</td>
<td>173 (52%)</td>
<td>2.2 (1.3-3.8)</td>
<td>0.006</td>
</tr>
<tr>
<td>Presence of chronic diseases    ^b ^e</td>
<td>249 (75%)</td>
<td>1.1 (0.6-2.1)</td>
<td>ns</td>
</tr>
<tr>
<td>MMSE 19-23 points              ^b</td>
<td>41 (12%)</td>
<td>0.3 (0.04-2.1)</td>
<td>ns</td>
</tr>
<tr>
<td>Use of analgesics              ^b</td>
<td>81 (24%)</td>
<td>1.2 (0.7-2.2)</td>
<td>ns</td>
</tr>
<tr>
<td>Use of benzodiazepines         ^b</td>
<td>56 (17%)</td>
<td>1.1 (0.5-2.2)</td>
<td>ns</td>
</tr>
<tr>
<td>GDS-score at baseline (per point)  ^b</td>
<td>-</td>
<td>1.9 (1.3-2.6)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

^a Relative risks are estimated with Cox's proportional-hazard models.
^b Adjusted for sex, educational level and income.
^c Loss of a spouse was introduced in the model as a time dependent covariate.
^d Poor daily functioning defined as a GARS- score of 24 to 72 points.
^e Chronic diseases included cardiovascular disease, diabetes mellitus, Chronic Obstructive Pulmonary Disease, arthritis, Parkinson Disease, and malignancy.

From the 500 participants at baseline, 77 participants had GDS-scores of five points or more, indicating depression (prevalence 15 %, 95 % CI: 12 - 18 %). During the four-year follow-up we observed a remission in 16 participants with an annual remission probability of 14 percent (figure 4.2). Remission sustained in seven from the 16 participants whereas in nine participants there was a relapse during follow-up. None of the predictors as described in table 2 significantly predicted remission (data not shown).
Figure 4.2 The cumulative persistence of depression in 77 participants with depression at baseline, defined as a GDS-15 score above 4 points, from 85 to 89 years onwards. Remission was defined as a GDS-score of 0 to 2 points during any of the follow-up measurements.

**Discussion**

Here, we show that the population-based oldest old are at a high risk of developing depression and that, when present, depression is highly persistent. Predictors for the incidence of depression in the oldest of old were institutionalisation and poor daily functioning, while no predictors were identified for remission.

In one of the few longitudinal studies of depression in the old-old (79-85 years), Palsson et al. reported an incidence of depression according to DSM III R criteria of 44 per 1000 person years, associated with female sex. Their lower incidence rate compared to our estimate of 70 per 1000 person years is possibly due to the younger age of their participants. An age associated increase of the incidence rate of depression is further strengthened by the findings of Meller et al., who described a high incidence rate of 140 per 1000 person years in a population of octo- and nonagenarians (85-103 years). Changes in living situation and dementia were the main risk factors in their study, without reaching statistical significance. As changes of living situation in this age spectrum means usually moving to institutionalised living, this seems to be in line with our predictor institutionalisation. The lower incidence rate of depression in the study of Haynie et al. in the “OCTO-twin study” may be explained by their selection of very healthy persons at entry.
In contrast to these studies on the incidence of depression, no data were available on its course in the oldest old. Earlier on, a strong tendency to chronicity of depression was reported in younger elderly\textsuperscript{19}. Here, it becomes clear that the persistence of depression as observed in younger elderly can be extrapolated to the oldest old.

In the present study, we have annually assessed the presence of depression in a large representative sample of community-dwelling oldest old persons. Although depression was not formally diagnosed, it becomes increasingly clear that depressive symptoms in the elderly have as distinct effects as depressive disorders\textsuperscript{20}. In addition, it could be questioned whether the GDS-15 is able to detect changes in depressive symptoms over time. Within the Leiden 85-plus Study, we have demonstrated that the loss of a partner, a major negative life event, was associated with a significant increase of more than two points on the GDS-15\textsuperscript{21}. Thus, the chosen GDS-15 criteria for the incidence and remission of depression should enable us to measure a relatively robust change in depressive symptoms over time.

Although the initial response rate in this study was very high, substantial attrition due to mortality and cognitive decline is an intrinsic part of all prospective studies of depression in oldest of old people. In an earlier analysis, we found an almost twofold increased risk of death for depressed oldest old participants of the Leiden 85-plus Study, which sustained when corrected for demographic and health related factors\textsuperscript{22}. In the present study, refusal was not related to depression at baseline\textsuperscript{18}, but it may be that participants with incident depression refused more often at follow-up. Participants who developed serious cognitive impairment (MMSE $\leq$ 18 points) were excluded from the study, another reason for a possible underestimation of the incidence rate. Confounding by effects of specific treatment is probably very limited because, as reported before, use of antidepressants was almost non-existent at baseline\textsuperscript{23}. We did not identify determinants that predicted remission, but as depression is associated with refusal and mortality, it may be that the numbers in our study were too small to detect these effects.

From a clinical perspective, we should be aware that depression occurs often in the oldest old and has a poor prognosis. Poor daily functioning and institutionalisation are strong predictors of incident depression in the oldest old. In an earlier study among the oldest of old\textsuperscript{23}, the recognition of depression by the general practitioner was low and antidepressive treatment virtually non-existent. Taken together with the results of the present study, it is clear that more active case finding is warranted as treatment of depression in the oldest old is as well potentially rewarding as in people of younger age.
References