Chapter 5

Does depression in old age increase cardiovascular mortality?

Abstract

Background Depression in old age is associated with an increased mortality risk of cardiovascular disease but the mortality risk from non-cardiovascular causes is disputed.

Objective To investigate the effect of depression on cardiovascular and non-cardiovascular mortality in old age.

Methods We prospectively followed 500 subjects from age 85 years onwards within the population-based Leiden 85-plus Study. Depressive symptoms were assessed annually with the 15-item Geriatric Depression Scale (GDS-15). Mortality risks were estimated in a Cox proportional-hazards model with the annual assessment of depression (GDS-15 ≥ 4 points) as a time-dependent covariate.

Results During 1654 person-years of follow-up (mean per person, 3.2 years), depression was associated with a two-fold increase of all cause mortality (Relative Risk [RR], 1.83; 95 % Confidence Interval [CI], 1.24 - 2.69) that was not explained by comorbid conditions. Both cardiovascular mortality and non-cardiovascular mortality contributed equally to the excess mortality (RR 1.95 and 1.75 respectively).

Conclusion Depression in old age contributes to an increase of both cardiovascular and non-cardiovascular mortality. Motivational depletion may play an important role in the increased mortality in elderly with depression.
Introduction

The presence of depressive symptoms in the elderly is associated with increased mortality\(^1\)\(^2\). Relatively little is known about the etiological relationship between depression and mortality\(^3\). Depression could influence mortality through various behavioural and biological mediators or by accompanying medical illness and disability, which are related to increased mortality\(^4\)\(^5\)\(^6\)\(^7\).

Population-based studies demonstrated an increased cardiovascular mortality in elderly persons with depressive symptoms\(^8\)\(^9\)\(^10\)\(^11\)\(^12\). These findings supported the view that excess mortality in depression is due to cardiovascular mechanisms such as low heart rate variability, elevated plasma catecholamines, hypothalamic-pituitary-adrenal (HPA) axis disturbances, and platelet and immune activation\(^13\)\(^14\)\(^15\). Other studies, however, showed that depressive symptoms in community dwelling elderly increased not only cardiovascular mortality but also non-cardiovascular mortality\(^16\)\(^17\)\(^18\).

Because it remains unclear by which means depression increases mortality in the elderly, we studied the effect of depression on cardiovascular and non-cardiovascular mortality in the Leiden 85-plus Study, a population-based prospective study of the oldest old.

Methods

Subjects

The Leiden 85-plus Study is a prospective population-based study of all 85-year old inhabitants of Leiden, The Netherlands. The study and characteristics of the cohort were described in detail previously\(^19\). In short, between September 1997 and September 1999 all members of the 1912 to 1914-birth cohort were asked to participate in the month after their 85\(^{\text{th}}\) birthday. There were no selection criteria for health or demographic characteristics. Of the 705 eligible subjects, 14 died before they could be enrolled and 92 refused to participate. In total, 599 subjects were enrolled (response 87\%). All subjects gave informed consent. For cognitively impaired subjects informed consent was obtained from a guardian. The Medical Ethical Committee of the Leiden University Medical Center approved the study. Subjects were visited annually at home for face-to-face interviews, collection of blood samples, and recording of an electrocardiogram.

Depressive symptoms

Depressive symptoms were annually assessed with the 15-item Geriatric Depression Scale (GDS-15), a questionnaire especially developed as a screening instrument for depression in the elderly\(^20\). Cognitive functioning was measured with the Mini Mental State Examination\(^21\). In order to obtain reliable results of the GDS-15 in the presence of impaired cognitive function, the GDS-15 was administered only in those with a Mini-Mental State Examination score above 18 points.

Depression was considered present when the GDS-15 score was at least 4 points, because this cut-off point yielded the most efficient distribution of sensitivity and specificity in our population\(^22\). Depression was assumed to be present or absent during the year after the annual assessment of the GDS-15.
Does depression in old age increase cardiovascular mortality?

Mortality
All subjects were followed up for mortality until 1 September 2002. Survival time was defined as the period from the 85th birthday until 1 September 2002 (censoring date) or the day of death as obtained from the civic registry. Shortly after the civic registry reported the death of a subject, the treating physician (general practitioner or nursing home physician) was interviewed to obtain the cause of death using a standardized questionnaire. Two senior specialists of internal medicine, who were unaware of the presence of depression in the participants, determined the causes of death by consensus according to the tenth version of the International Classification of Diseases (ICD-10)\(^{23}\). Causes of death were divided into two groups: cardiovascular mortality (ICD-codes I00-I99, I20-I25 and I60-I69) and non-cardiovascular mortality (all other ICD-codes). Cardiovascular mortality was defined as myocardial infarction (I20-I25), stroke (I60-I69), and other cardiovascular causes (I00-I99). Non-cardiovascular mortality was defined as infection (A00-B99), cancer (C00-D48), and other non-cardiovascular causes (all other ICD-codes).

Possible confounders
All subjects’ treating physicians were interviewed annually to assess the presence of cardiovascular disease. In addition, electrocardiograms of all subjects were recorded each year on a Siemens Siccard 440 and transmitted by telephone to the ECG Core Lab in Glasgow for automated Minnesota coding\(^{24}\). As described earlier\(^{25}\), subjects were classified as having cardiovascular disease in case of a positive history of arterial surgery, stroke, intermittent claudication, myocardial infarction or angina pectoris. Subjects with an ECG revealing myocardial infarction or ischemia were also classified as having cardiovascular disease.

Socio-demographic characteristics and living arrangements were obtained for all subjects. Level of education was dichotomised on a maximum of six years of schooling. Alcohol consumption was considered high when more than two drinks were consumed daily. Smoking history was classified as no smoking, smoking in the past and current smoking. The treating physician of each participant was interviewed annually using structured questionnaires to assess the presence of diabetes mellitus, chronic obstructive pulmonary disease (COPD), arthritis, malignancy, dementia and Parkinson Disease. Moreover, we checked the computerised pharmacy registries for the use of medication which are specific for the presence of diabetes mellitus, COPD or Parkinson Disease. Diabetes mellitus was also considered present in case of a glucose level of 11.0 mmol/L or higher in obtained blood samples. Chronic diseases were defined as cardiovascular disease, diabetes mellitus, COPD, arthritis, malignancy, dementia and Parkinson’s disease\(^{26}\). Independency in daily living was defined as being able to do all nine basic activities of daily living independently as measured using the Groningen Activity Restriction Scale (GARS)\(^{27}\).

Statistical Analysis
Cardiovascular and non-cardiovascular mortality were calculated per 1000 observed person-years at risk for person years with depression and without depression separately. Cardiovascular and non-cardiovascular mortality risks (RRs) and 95 % confidence intervals (95% CIs) were estimated in a Cox proportional-hazards model using the annual categorical assessment of depression as a time-dependent covariate. This model incorporates the course of depression during follow-up. Adjustments were made for potential distorting variables, including gender, smoking, alcohol consumption, and the cumulative number of chronic diseases. Additionally, cardiovascular and non-cardiovascular mortality risks were analysed in strata of subjects with and without cardiovascular disease at baseline.
Results

From the 599 participants at baseline, all 500 subjects with a MMSE score of more than 18 points completed the GDS-15 at baseline (table 5.1). At baseline, 119 subjects (24 % of the study sample) were depressed as measured by a GDS-15 score of at least 4 points.

During follow-up, 1654 person-years were observed (mean per person, 3.2 years), 424 person-years (26%) with depression (GDS-15 ≥ 4 points) and 1230 person-years (74%) without depression (GDS-15 ≤ 3 points). In total, 116 subjects (23 % of the study sample) died. The all cause mortality was 57 per 1000 person years without depression (70 events during 1230 person-years at risk) and 108 per 1000 person-years with depression (46 events during 424 person-years at risk). When depression was present, the all cause mortality risk was twofold increased (RR 1.83, 95 % CI 1.24 - 2.69) after adjustment for gender, smoking, alcohol consumption, and chronic disease.

To further explore whether the increased all cause mortality in depressed participants was due to comorbid conditions, we repeated the analyses in healthy persons only. In subjects with a baseline MMSE score of at least 24 points (n = 415), the all cause mortality was still increased in depressed participants (RR 2.02, 95% CI 1.31 - 3.12), as it was in subjects who were independent in their activities of daily living (n = 456; RR 1.69, 95% CI 1.09 - 2.62), and in subjects without chronic diseases (n = 77; RR 9.96, 95% CI 1.02 - 98.99).

Table 5.1 Baseline demographic and clinical characteristics of the 85-year old participants of the Leiden 85-plus Study with a MMSE score of more than 18 points (n = 500).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>184 (37 %)</td>
</tr>
<tr>
<td>Independent living</td>
<td>444 (89 %)</td>
</tr>
<tr>
<td>Widowed</td>
<td>277 (55 %)</td>
</tr>
<tr>
<td>Low level of education</td>
<td>303 (61 %)</td>
</tr>
<tr>
<td>High alcohol consumption(^a)</td>
<td>51 (10%)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>82 (16 %)</td>
</tr>
<tr>
<td>Chronic disease present(^b)</td>
<td>423 (85 %)</td>
</tr>
<tr>
<td>Depression present(^c)</td>
<td>119 (24 %)</td>
</tr>
</tbody>
</table>

\(^a\) Alcohol consumption was considered high when more than 2 drinks per day were consumed.

\(^b\) Chronic diseases included cardiovascular disease, diabetes mellitus, COPD, arthritis, malignancy, dementia and Parkinson’s disease.

\(^c\) Depression was considered present when GDS-15 score was 4 points or more.
From the 116 deceased subjects, 46 subjects (40%) died from cardiovascular causes and 70 subjects (60%) from non-cardiovascular causes. Cardiovascular mortality consisted of 25 subjects (54%) who died from myocardial infarction, 11 subjects (24%) who died from stroke, and 10 subjects (22%) who died from other cardiovascular causes. Non-cardiovascular mortality consisted of 16 subjects (23%) who died from infection, 26 subjects (37%) who died from cancer, and 28 subjects (40%) who died from other non-cardiovascular causes. No deaths from suicide were reported. Figure 5.1 shows the cardiovascular and non-cardiovascular mortality per 1000 person-years in subjects with and without depression, illustrating an increase of both cardiovascular and non-cardiovascular mortality when depression was present. Cardiovascular as well as non-cardiovascular mortality were significantly 1.95-fold and 1.75-fold increased in participants with depression (Table 5.2).
Table 5.2 Cardiovascular and non-cardiovascular mortality risks dependent on depression\(^a\).

<table>
<thead>
<tr>
<th>Depression(^b)</th>
<th>No(^c)</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cause mortality</td>
<td>1</td>
<td>2.07 (1.35 - 3.17)(^e)</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>1.83 (1.24 - 2.69)(^e)</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>1</td>
<td>2.10 (1.07 - 4.13)(^e)</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>1.95 (1.07 - 3.56)(^e)</td>
</tr>
<tr>
<td>Non-cardiovascular mortality</td>
<td>1</td>
<td>2.05 (1.18 - 3.56)(^e)</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>1.75 (1.05 - 2.91)(^e)</td>
</tr>
</tbody>
</table>

\(^a\) Mortality risks were estimated with Cox proportional-hazards models with the annual assessment of depression as a time-dependent covariate.

\(^b\) Depression was considered present when GDS-15 score was 4 points or more.

\(^c\) Reference category.

\(^d\) Adjusted for gender, smoking, alcohol consumption, and number of chronic diseases.

\(^e\) \(p < 0.05\).

The relation between depression and mortality was also studied separately in subjects with and without cardiovascular disease at baseline. In participants with cardiovascular disease at baseline, the risk of cardiovascular mortality was 2.25-fold (95% CI 1.14 - 4.47) increased for subjects with depression compared to those without depression (Table 5.3). On the other hand, the risk of non-cardiovascular mortality was 3.17 times (95% 1.10 – 9.18) increased among depressed subjects without a history of cardiovascular disease. The risk of non-cardiovascular mortality remained increased when subjects (n=73) who developed cardiovascular diseases during follow-up were excluded from this group (RR 2.63, 95% CI 0.79 – 8.77).

Table 5.3 Mortality risks dependent on depression stratified for the presence of cardiovascular disease at baseline\(^a\).

<table>
<thead>
<tr>
<th>Depression(^b)</th>
<th>No(^c)</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular disease at baseline (n=306)</td>
<td>1</td>
<td>1.76 (1.13 - 2.75)(^d)</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>2.25 (1.14 - 4.47)(^d)</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>1.50 (0.83 - 2.71)</td>
</tr>
<tr>
<td>No cardiovascular disease at baseline (n=192)</td>
<td>1</td>
<td>2.21 (0.98 - 4.97)</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>1.34 (0.34 - 5.20)</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>3.17 (1.10 - 9.18)(^d)</td>
</tr>
</tbody>
</table>

\(^a\) Mortality risks were estimated with Cox proportional-hazards models with the annual assessment of depression as a time-dependent covariate, adjusted for gender, smoking, alcohol consumption, and number of chronic diseases not including cardiovascular disease. Presence of cardiovascular disease missing for two subjects.

\(^b\) Depression was considered present when GDS-15 score was 4 points or more.

\(^c\) Reference category.

\(^d\) \(p < 0.05\).
Conclusion

In the oldest old depression is associated with a two-fold increased all cause mortality. Both cardiovascular mortality and non-cardiovascular mortality contribute equally to this excess of mortality. Our finding that depression in the oldest old is associated with increased all cause mortality is in line with the increased all cause mortality as described in depressed elderly of younger age groups. As earlier reported by other studies, we also found that depression was associated with increased cardiovascular mortality. However, the non-cardiovascular mortality in depressed elderly of the Leiden 85-plus Study was increased to the same extent. Some other authors reported the same findings in younger elderly but this has not yet been reported for older people. Thus, in the oldest old depression does increase the all cause mortality, but not specifically the cardiovascular mortality.

The landmark study of Frasure-Smith et al in 1993 raised attention to the specifically increased cardiovascular mortality in depressed patients who had suffered from myocardial infarction. In line with their observations, we also found cardiovascular mortality to be more pronounced in depressed subjects with a history of cardiovascular disease. However, in subjects without a history of cardiovascular disease, we found a more pronounced increase of non-cardiovascular mortality. The fact that Frasure-Smith et al studied only subjects with a history of severe cardiovascular disease, and consequently mainly cardiovascular deaths, may explain their conclusion that depression specifically increases cardiovascular mortality.

Within the Leiden 85-plus Study we performed repeated annual measurements of depressive symptoms in a representative sample of community dwelling elderly subjects. Although the GDS-15 was validated to screen for depression in the oldest old, the fact that depression was not formally diagnosed could be seen as a limitation of this study. Nevertheless, it becomes increasingly clear that both depressive symptoms and depressive disorders, pointed out as minor and major depression respectively, have the same serious consequences in the elderly. So, depression may better be interpreted as a continuum of depressive symptoms than the mere presence or absence of a depressive disorder.

How does depression in old age increase mortality? Within the Leiden 85-plus Study, we found an increased mortality risk for depressed elderly even after adjustments for comorbid conditions. In line, the mortality risks of depressed participants remained increased in participants who were independent in activities of daily living, in participants with good cognitive function, and in those without chronic diseases. These results demonstrate that the excess of mortality is not only caused by co-morbidity and frailty, as was already mentioned by other authors. Furthermore, antidepressive pharmacotherapy was almost nonexistent in our population, which makes it unlikely that treatment effects of depression increase mortality. Earlier, we found that the prognosis of depression in terms of mortality is especially poor when accompanied by feelings of loneliness. Depressed subjects who suffered from feelings of loneliness were at a 2.1 higher mortality risk, whereas depressed subjects who did not suffer from feelings of loneliness were at a 1.2 higher increased mortality risk. Following this observation, social isolation could underlie the excess mortality in depression. Subjects who ”give up” are likely to disengage from health promoting behaviour leading to decreased mobility, nutritional deficiency, reduced compliance to prescribed medication, and finally to earlier death. Thus, motivational depletion may play an important role in the increased mortality in depressed elderly.
References

Does depression in old age increase cardiovascular mortality?
