Mortality in depressed and non-depressed primary care Swedish patients: a 12-year follow-up cohort study

Ranja Strömberg, Lars G Backlund, Sven-Erik Johansson and Monica Löfvander

Department of Neurobiology, Centre for Family Medicine, Karolinska Institutet, Huddinge, Centre for Clinical Research Västmanland—Uppsala University, Uppsala and Department of Public Health and Caring Sciences—Family Medicine and Preventive Medicine, Uppsala University, Uppsala, Sweden.

Correspondence to Ranja Strömberg, Department of Neurobiology, Centre for Family and Community Medicine, Caring Sciences and Society, Karolinska Institutet, Alfred Nobels allé 12, SE 141 83 Huddinge, Sweden. E-mail: Ranja.Stromberg@ki.se

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Background. Data regarding mortality among depressed patients in Swedish primary care is limited. Objectives. We compared mortality in a cohort of depressed and non-depressed patients at long-term follow-up and compared these values with standardized mortality rates (SMRs) in the Swedish population. Hazards ratios (HRs) for the relationship between death and depression, psychosocial factors and lifestyle were analysed, and we explored the proportion of unnatural causes of deaths. Methods. Mortality was studied in a cohort of 124 depressed and 280 non-depressed patients 12 years after being diagnosed with depression in primary care. Mortality and the mortality rates and SMRs in depressed and non-depressed patients were compared by gender. Cox regression was applied to calculate HRs for the risk of dying for explanatory variables, including depression, psychosocial factors and lifestyle.

Results. A larger number of depressed patients, 11% (n = 14), compared with non-depressed patients, 4% (n = 12), died (P = 0.008), with significantly higher values among depressed men (P = 0.014). SMRs did not differ from those of the Swedish population. Depression was the only variable associated with a significantly elevated risk of death (HR, 3.34; 95% CI, 1.38–8.08). Nearly one-third of deaths had unnatural causes when alcohol-related deaths were included.

Conclusion. This study underlines the importance of careful follow-up of all depressed patients’ mental and physical health and the intervention on unhealthy lifestyles. Large primary care database studies are needed to explore the association between depression, co-morbid somatic diseases, lifestyle and mortality.

Keywords. Depression, follow-up studies, mortality determinants, primary care, suicide.

Introduction

Depressed patients are frequently encountered in primary health care and most are treated by primary care physicians.1 When depression is severe, it is a serious illness and typically treated in psychiatric care, but these patients tend to have a poor prognosis regarding recurrence and mortality, as well as a high frequency of suicide.2 In contrast, there have been few studies examining mortality among depressed patients diagnosed and treated in primary care for patients with mild or moderate depression.3 A study from the Netherlands reported that nearly 12% of patients died within 10 years, but mortality did not differ from that of a matched control group and of all deaths, where 1.3% were by suicide and other unnatural causes.7 According to a literature review, suicide accounted for nearly 20% of the deaths in psychiatric samples but less than 1% in other medical and community samples.8 This review reported also that depression increased the risk of death, particularly by unnatural causes and cardiovascular diseases.

A cohort of depressed and non-depressed patients at a primary care centre in Stockholm, Sweden, was identified between 1997–2001 using the Beck’s Depression Inventory (BDI) and a diagnostic interview based on Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) criteria.6 The overall aim in this study was to explore the mortality in this cohort in a 12-year follow-up study.

There were four specific aims: first, we compared all-cause mortality and mortality rates by gender in depressed patients and non-depressed patients for a 12-year follow-up. Second, we compared standardized mortality rates (SMRs) by gender with SMRs in the general population.
Swedish population. A third aim was to calculate hazards ratio (HR) for the risk of death related to depression, psychosocial and lifestyle factors in sex- and age-adjusted models. Finally, we determined the proportion of unnatural causes of death among depressed patients.

We hypothesized that depressed patients in our cohort had a higher mortality rate than non-depressed patients and a higher rate than the general population in Sweden. Furthermore, we expected that unnatural causes of death were prevalent among depressed patients.

Methods

Setting and subjects
The setting was a primary care centre in Stockholm, Sweden.

The study cohort included patients aged 18–75 years who attended two family physicians’ 1-hour drop-in clinics from 1997–2001. Patients were enrolled on 2 days weekly beginning in October 1997. Women were enrolled until December 1998, while men were enrolled until January 2001 because of the lower prevalence of depression among men. Patients who agreed to participate were screened for depression using the BDI. Two physicians interviewed the patients with a BDI ≥10 within 2 weeks of applying the DSM-IV criteria for depression. Severity of depression was measured using the Montgomery Åsberg Depression Rating Scale.

A total of 124 depressed patients were diagnosed with depression, including 48 men and 76 women. The severity of depression was mild in two-thirds of the depressed men and in half of the depressed women. The remaining patients had moderate depression, except for one man and one woman with severe depression. The distribution of mild and moderate depression did not differ significantly between men and women.

Depressed patients were treated according to the national guidelines with selective serotonin reuptake inhibitors (SSRIs) combined with psychotherapy and follow-ups by their physicians. Treatment continued until the depression was resolved. No patients were treated with tricyclic antidepressants. Somatic health problems were treated according to guidelines. The patients who were also receiving care from psychiatric services (three men and four women) were not excluded from participation in the study. Patients with other psychiatric conditions, such as crisis reactions (11 men and 15 women), were excluded from this study so that we could specifically determine the mortality rate of depressed patients.

A reference group that included 280 non-depressed patients, 187 men and 93 women was composed of patients with BDI scores <10 and patients who were identified as having no psychiatric diagnosis during the diagnostic interview.

Follow-up time
The follow-up period was defined as the day of inclusion until the conclusion of the study on 25 September 2011. The median follow-up time was 12.3 years for men and 13.5 years for women.

Data sources and data preparations
Dates of deaths and all causes of death for depressed patients were obtained from The National Cause of Death Register, which documents all death certificates in Sweden. The dates of all causes of death among non-depressed patients were obtained from the Swedish National Registration. Mortality data for the Swedish population were obtained from Life Tables for 2001–2010, published by Statistics Sweden. Data regarding sociodemographics, psychosocial stressors, self-rated physical health, smoking habits and use of alcohol were obtained from a questionnaire distributed together with the BDI. Five fixed response alternatives were given, and the ratings were dichotomized. The outcome variable was mortality and mortality rate, including all causes of death. The explanatory variables were depression according to DSM-IV criteria or non-depressed, marital status categorized as married/cohabiting or living single, and perceived level of stress as very high level of stress or not (little or no stress). Perceived physical health was categorized as good (excellent, very good and good) or not good (poor or very poor), satisfaction with one’s family situation as good or unsatisfying and financial situation as good or poor. Employment was categorized as employed or unemployed. The length of education was categorized as ≥12 years or <12 years. Alcohol use was measured as the sum of weekly use of standard glasses (stgs) of alcohol. Less than 15 stgs/week for men and less than 10 stgs/week for women were categorized as safe levels. Daily smoking was categorized as yes or no.

Statistics
Differences between groups were tested using Pearson’s chi-square test or Fisher’s exact test. The mortality (percentage) and mortality rate per 10 000 person-years in the cohort were calculated by gender. SMRs were calculated by gender in relation to the reference (SMR = 1 = reference) consisting of the entire Swedish population (aged 18–75 years) based on Life Tables for 2001–2010 from Statistics Sweden. First, for each 1-year age group, the expected number of deaths was calculated. Second, the expected number of deaths for each 1-year age group was summed for depressed and non-depressed men and women. Finally, SMR was calculated as the ratio between the observed number of deaths and the expected number of deaths. Cox regression, adjusted for sex and age, was applied to calculate HRs for death related to explanatory variables: depression, sociodemographic data, psychosocial factors, perceived physical health, smoking use and alcohol use. Possible confounders/effect modifiers (sociodemographic data,
psychosocial factors, smoking use and alcohol use) were tested. A final main effect model adjusted for sex and age was developed to identify the most important factors. A test of proportionality for the main effect model was performed and the assumption was found to be satisfied. Interactions between depression and any of the included variables in the main effect model were tested but none were identified. Survival curves were constructed to illustrate the mortality rate among depressed versus non-depressed patients.

**Ethical approval**
Ethical approval was obtained from the Regional Ethical Review Board, Stockholm, Sweden.

**Results**
Sociodemographic characteristics and lifestyle choices among depressed and non-depressed men and women are shown in Table 1. No significant difference in age was observed between groups (mean ages, 44.2–47.9 years). Most patients had been educated at the university level. A significantly larger number of depressed patients were living single (51.2%) versus cohabitating (39.9%, \( P = 0.034; P < 0.05 \)). Additionally, unemployment was significantly more common among depressed patients than among non-depressed patients (8.9% versus 2.2%, \( P = 0.008; P < 0.01 \)), but the difference was statistically significant only among men (\( P = 0.018; P < 0.05 \)). Similarly, daily smoking was significantly more common among depressed patients compared with non-depressed patients (19.7% versus 9.3%, \( P = 0.004; P < 0.01 \)), but this value was only significant in depressed men (\( P = 0.001; P < 0.01 \)). No significant differences were observed between groups regarding use of alcohol exceeding the defined safe limits, neither among men nor among women.

Table 2 shows the number and frequencies of deaths during the follow-up period, mortality rates per 10 000 person-years and SMRs in the study cohort according to sex and depression.

Nearly 15% of depressed men and 9% of depressed women died during the follow-up period. Mortality was significantly higher among depressed patients than non-depressed patients (\( P = 0.008; P < 0.01 \)) but statistically significant only among men (\( P = 0.005; P < 0.01 \)). Additionally, the mortality rate was significantly and nearly 3-fold higher among all depressed patients compared with non-depressed patients (\( P = 0.016; P < 0.05 \)) but statistically significant only among men (\( P = 0.014; P < 0.05 \)).

Finally, the SMR of 1.77 in the depressed men was 77% higher than in the general male population in Sweden, but this difference was not statistically significant. Notably, SMR for non-depressed men was surprisingly and significantly lower than that in the Swedish male population.

SMR for depressed women was similar to that of the general population. Additionally, non-depressed women generally had lower SMR values than women in the Swedish female population (not significant).

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Frequencies (%) and mean values with 95% CIs of sociodemographic and lifestyle data of the depressed and non-depressed men and women at the start of the study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Totals</td>
</tr>
<tr>
<td></td>
<td>Depressed</td>
</tr>
<tr>
<td>N</td>
<td>124</td>
</tr>
<tr>
<td>Age, mean (95% CI)</td>
<td>470 (44.5–49.5)</td>
</tr>
<tr>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Single</td>
<td>51.2**</td>
</tr>
<tr>
<td>Children, yes</td>
<td>62.5</td>
</tr>
<tr>
<td>School ≥12 years</td>
<td>73.9</td>
</tr>
<tr>
<td>Employment</td>
<td></td>
</tr>
<tr>
<td>Work/study</td>
<td>74.2</td>
</tr>
<tr>
<td>Unemployed</td>
<td>8.9**</td>
</tr>
<tr>
<td>Pensioners</td>
<td></td>
</tr>
<tr>
<td>Old age</td>
<td>14.5</td>
</tr>
<tr>
<td>Disability</td>
<td>2.4</td>
</tr>
<tr>
<td>Life style variables</td>
<td></td>
</tr>
<tr>
<td>Daily smokers</td>
<td>19.7***</td>
</tr>
<tr>
<td>Alcohol/stgs above safe limit</td>
<td>13.1</td>
</tr>
</tbody>
</table>

\( P \) values by chi-square significance tests between groups.

*Missing values: \( n = 4 \).

1Missing values: \( n = 1 \).

\( *P < 0.05, **P < 0.01 \) and \( ***P < 0.001 \).
Table 3 shows HRs for the risk of dying during the follow-up period and its relationship to explanatory variables in sex- and age-adjusted models. The HR for depression (HR, 3.13; 1.38–7.10) was statistically significantly elevated. Additionally, other tested variables had elevated HRs, but the increase was not significant.

In the final model, including sex, age and smoking, only patients with diagnosed depression had a significantly higher risk of dying during the follow-up period (HR, 3.34, 1.38–8.08) compared with non-depressed patients.

Survival curves for the main effect model in Figure 1 show the difference in survival between depressed and non-depressed patients during the follow-up period.

The causes of death among depressed men and women are presented in Table 4. No significant differences in causes of death were identified between men and women. In summary, four deaths of 14 (29%) were regarded as having unnatural causes: alcohol-related liver cirrhosis (n = 2) and intoxication (n = 2, including one suicide).

Discussion

Key findings

Patients with mild or moderate depression at inclusion in the study had a nearly 3-fold higher mortality rate than non-depressed patients during the 12-year follow-up period; however, this difference was significant only among men. Depressed patients’ SMRs did not significantly differ from those in the Swedish general population. The risk of dying remained at 3-fold after adjusting for all other explanatory variables. Nearly one-third of subjects died of unnatural causes when alcohol-related liver disease was included.

Our hypotheses were confirmed except for the non-significant differences in SMRs of depressed men and women compared by gender to the general population in Sweden.

Comparison with previous studies

The mortality rate found in this study was comparable to that stated in an earlier primary care study from the Netherlands that reported a mortality of 12% over
The percentage of suicides in our study was higher than that in the study from Netherlands, which reported a suicide rate of 0.05% during their 10-year follow-up. We were not able to locate Swedish studies on suicide among depressed primary care patients. However, suicide SMRs among depressed patients once treated as inpatients in Swedish psychiatric hospitals were much higher, at 13 men and 16 women. In comparison, a Swedish population study reported 1.9% suicides among 3563 individuals during a follow-up of 56 years.

**Strengths and limitations**

A strength of this study was the careful methods used for diagnosing and measuring the severity of depression. Another strength was the long follow-up period. Limitations include the lack of data regarding the duration and recurrence rate of depression and that physical disorders and adherence to prescribed pharmacological therapy were not recorded. Lifestyle choices were identified at the start of the study; thus, the duration choices such as smoking are not known. In addition, the sample was small and the design was a single site cross-sectional follow-up study, limiting the generalizability of the results to districts with similar populations.

**Meaning of the study**

The higher mortality rate among depressed men attending family physicians’ drop-in hours is clinically important and was identified in a study cohort with favourable sociodemographic conditions. This finding indicates that depressed men should be viewed as high-risk patients that require careful follow-up of both their physical and mental health, as well as their lifestyles. Depression is likely a strong confounder to poor outcome of physical diseases and important for the physician to act upon.

In Swedish primary care, treatment for depression with SSRIs was in general use at the time of the study and had replaced treatment with tricyclic antidepressants. Depressed patients in the study were prescribed SSRIs and most were also referred to counselling with a psychotherapist. Nevertheless, we found that these patients had a higher mortality rate. We lack information regarding their adherence to the pharmacological therapy, and later studies have revealed low adherence to SSRI treatment. Better outcomes for such treatment has been demonstrated if carefully designed follow-up methods are applied, but such methods were not used to a full extent in this study. A 5-year follow-up study in Finland reported that approximately 70% of patients reached full recovery in a median time duration.

<table>
<thead>
<tr>
<th>Causes of death</th>
<th>Depressed patients</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td>124 (100)</td>
<td>48</td>
<td>76</td>
</tr>
<tr>
<td>Causes of death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All causes, N (%)</td>
<td>14 (11.2)</td>
<td>7 (14.6)</td>
<td>7 (9.2)</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>5</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Cancer</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Infection</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Alcohol-related liver disease</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Suicide and unnatural causes*</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

No significant differences between men and women ($P = 0.65$, Fisher’s exact test).

*One confirmed case of suicide and one case of intoxication.
of 20 months, but many patients spent about 30% of the follow-up time remaining depressed.16 Today, the Swedish guidelines for treating mild and moderate depression in primary care include psychological treatment with cognitive behaviour therapy. Studies have also shown that patients prefer treatment with psychotherapy rather than with SSRIs.17

Identifying extensive co-morbidity, including physical diseases such as diabetes, cardiac and pulmonary diseases, is important for understanding the mortality rate.18 It is suggested that mood disorders affect the course of medical illnesses.19 Depression is considered a risk factor for cardiac mortality and cardiac morbidity according to many studies.20,21 Additionally, among women, a strong relationship between depression and angina pectoris has been demonstrated.22 Diabetes together with depression is also an unfortunate combination.23 Consequently, in the UK, research programmes have been initiated for diagnosing depression in patients with coronary heart disease in primary care,24 and the latest guidelines for general practitioners in the UK include recommendations for identifying depression in patients with chronic physical health problems.25

Conclusion

This long-term follow-up study on mortality among depressed patients underlines the importance of careful follow-up of all depressed patients’ mental and physical health as they may be at risk for pre-term death. It is important to evaluate cardiovascular risk-factors and intervene in unhealthy lifestyle. Large database studies in primary care are needed to explore the association between depression, co-morbid somatic diseases, lifestyle and mortality.

Declaration


References