Is There an Increased Risk of Dying after Depression?

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Although a lot of research has been performed on the relation between depression and subsequent mortality, the results show contradictory findings. In this study, the authors investigated mortality in depressed people compared with nondepressed people in a large-scale retrospective cohort study based in general practice in the province of Limburg, the Netherlands. All subjects diagnosed with depression between 1975 and 1990 were included and compared with subjects matched on birth year who never were diagnosed with depression. Follow-up ended on April 30, 2000. Hazard ratios and their 95% confidence intervals were calculated using stratified Cox proportional hazards models adjusted for age, sex, and socioeconomic status. Subgroups based on sex and age at the diagnosis of depression were evaluated separately.

A total of 68,965 patients were followed for an average of 15 years. Among 1,362 depressed subjects 132 died, and among 67,603 nondepressed subjects 4,256 died. The adjusted hazard ratio for depressed versus nondepressed subjects was 1.39 (95% confidence interval: 1.16, 1.65). A significant interaction was observed between the age at diagnosis of depression and sex. A moderate positive association between depression and subsequent mortality was identified.

cohort studies; depression; mortality

Abbreviations: CI, confidence interval; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders: DSM-IV; ICHPPC-2, International Classification of Health Problems in Primary Care; ICPC, International Classification of Primary Care; RNH, RegistratieNet Huisartspraktijken (Registration Network Family Practices).

Clinical depression is associated with social, occupational, and physical impairment and mortality (1), but results from studies on mortality in depressed people are not always clear. Although some studies have shown a strong positive association between depression and mortality (2–7), others found no increased risk (8–10). In their review on depression and subsequent mortality, Wulsin et al. (11) included 57 studies of which 51 percent showed a positive association, 23 percent showed a negative association, and 26 percent showed different results for males and females. Some of these contradictory findings may be explained by differences among studies in the definition of depression, study populations, length of follow-up, and number and choice of additional characteristics for which the authors controlled. Psychiatric patient studies and hospital patient studies, for example, generally show a higher risk of dying for depressed people than community studies do (12). The present general practice-based cohort study is distinguished from most other studies on this subject by the absence of selection of patients, the large number of subjects, the long follow-up time, the fact that we included a broad range of ages, and the special focus on mortality related to suicide/accidents. On the basis of the data of a general practice-based morbidity and mortality registry, we examined the relation between depression and the subsequent risk of dying, with a special focus on mortality related to suicidal and accidental deaths.
MATERIALS AND METHODS

The Registration Network Family Practices

A retrospective cohort study based on the RegistratieNet Huisartspraktijken (RNH, Registration Network Family Practices) was carried out. The RNH is a continuous and computerized database in which 53 general practitioners working in 21 practices in the south of the Netherlands are participating (13).

In the RNH, all relevant health problems of a patient are registered, including all relevant past health problems. A health problem is defined as “anything that has required, does, or may require health-care management and has affected or could significantly affect a person’s physical or emotional well-being” (13). Health problems are coded by the general practitioners only if they are permanent (no recovery expected), chronic (duration longer than 6 months), or recurrent (more than three recurrences within 6 months), or if they have lasting consequences for the functional status or prognosis of the patient. Problems are coded according to the International Classification of Primary Care (ICPC) (14) using the criteria of the International Classification of Health Problems in Primary Care (ICHPPC-2) (15). Subjects who die are coded as such with the date of death. The cause of death is registered using ICPC codes. For this analysis, only those deaths resulting from suicide or accidents were distinguished from other causes. The registration of death in general practice is fully comprehensive in the Netherlands, because the general practitioner either confirms the death himself or is informed by a colleague general practitioner who is on duty, a hospital specialist, or a forensic physician in the case of suspicious death. The health insurance company will inform the general practitioner about the deaths of patients with public health insurance. Furthermore, as a result of the traditional relation between the general practitioner and the family, relatives often contact the general practitioner after the death of a family member.

The database also contains background information on the patient’s sex, date of birth, living arrangement, level of education, and type of health insurance (the latter two being used as an indicator of socioeconomic status). The registered data are continuously updated and historically cumulated for each patient. Membership of the RNH population ends only by migration, institutionalization, or death. With regard to demographic characteristics, the population in this database is comparable with the regional Dutch population (16).

Diagnostic criteria

Diagnostic criteria

According to the coding rules of the RNH, depression can be coded by one of two ICPC codes: depressive disorder (ICPC code P76) or affective psychosis (ICPC code P73). A separate code (ICPC code P03) can be used for depressive feelings. For the diagnosis of a depressive disorder (ICPC code P76), patients should not be psychotic but should comply with three criteria out of the following six: 1) sadness or melancholy more than can be explained by the psychosocial stress; 2) suicidal thoughts or attempt; 3) indecisiveness, decreased interest in usual activities, or diminished ability to think; 4) feelings of worthlessness, self-reproach, or inappropriate or excessive guilt; 5) early morning waking, hypersonnia, or early morning fatigue; and 6) anxiety, hyperirritability, or agitation. An affective psychosis (ICPC code P73) is diagnosed when the disorder is predominantly in the area of mood, with either severe depression or marked elation and expansiveness, or the two alternating, distinguishable from the usual range of emotion. Furthermore, subjects are not able to meet the ordinary demands of life and, in the case of a unipolar disorder, there are also disorders of thought. Alcohol or drug use must be excluded as a cause of the above-mentioned symptoms. Patients presenting with depressive feelings, but not complying with the requirements for a depressive disorder or affective psychosis, are coded under depressive feelings (ICPC code P03). For this study, the cause of death was classified as suicide and accidents, natural causes, or unknown.

Study design

Using data from all subjects that ever were registered in the database (n = 105,762), we applied a retrospective cohort design. Depressed subjects in our study were those subjects who were diagnosed with ICPC code P76 (depressive disorder) or ICPC code P73 (affective psychosis) for the first time between January 1, 1975, and January 1, 1990. Furthermore, they had to be aged 20 or more years when the depression was diagnosed; 1,362 depressed people were available for analysis.

Our reference group consisted of subjects who never had a diagnosis of depression (ICPC code P73 or ICPC code P76). Each time a depressed person was included in the study, all nondepressed subjects from the same year of birth as the depressed subject were included as control subjects. The date of diagnosis of the depressed subject was assigned to the nondepressed subjects as a starting date for study. When more than one subject from the same year of birth was diagnosed with depression, the different dates of diagnosis were randomly assigned to all nondepressed subjects from the same birth year. Thereafter, all nondepressed subjects who had moved or died before the assigned starting date were excluded, leaving 67,603 nondepressed subjects for analysis. Both depressed and nondepressed subjects were followed for a diagnosis of mortality. Follow-up of subjects ended on April 30, 2000, or earlier in the case of failure or censoring.

Analysis

The time to death was analyzed with a Cox proportional hazards model, using SPSS statistical software package version 9.0 for Windows (17). Since depression was not a time-dependent variable, we applied a standard Cox regression analysis, stratifying on birth year. In a separate analysis, we added a time-dependent covariate to check whether the risk of dying for depressed persons was dependent on the time since depression. In multivariable analysis, the results were adjusted for age, sex, and socioeconomic status. Education and type of health insurance were used as indicators for socioeconomic status. To examine whether males and females differed regarding their association of depression with mortality, we added an interaction term of depression.
and sex (subgroup analyses based on sex were also applied). Similarly, we investigated whether there was a different association for depression diagnosed before age 50 or afterward. As a sensitivity analysis, we added subjects with depressive complaints (ICPC code P03) not complying with the requirements for ICPC code P76 or ICPC code P73 to our depressed patients group while they were consequently removed from our reference group.

**RESULTS**

The descriptive characteristics of the study population are displayed in table 1. A total of 1,362 depressed and 67,603 nondepressed subjects were included in the analyses.

Mortality was observed in 4,388 subjects (6.4 percent). Among depressed subjects 132 (9.7 percent) died, and among nondepressed subjects 4,256 (6.3 percent) died. Follow-up ranged from 2.2 years to 25.3 years among depressed subjects and from 0.2 years to 25.4 years among nondepressed subjects. The average overall follow-up period was 14.9 years; 235 (17.3 percent) depressed and 10,969 (16.2 percent) nondepressed patients were lost to follow-up. This was caused by a change of general practitioner in 91 percent and 86 percent, respectively, for the depressed and the nondepressed. Seventeen depressed and 273 nondepressed subjects were deregistered because they were institutionalized (of which the large majority were probably admitted to a nursing home). People who are referred to specialist care but who are not institutionalized keep their own general practitioner. The mean age at the start of the study was 43.9 (standard deviation, 13.6) years among depressed subjects and 37.8 (standard deviation, 14.7) years among nondepressed subjects. There were more females, more subjects with a lower level of education, and more subjects with public health insurance in the depressed group compared with the group of nondepressed subjects.

In table 2, the associations between depression and mortality are shown. The hazard ratio of dying after correction for age, sex, and socioeconomic status was 1.39 (95 percent confidence interval (CI): 1.16, 1.65) for depressed versus nondepressed subjects. In subgroups of males and females, the estimated hazard ratios adjusted for age and socioeconomic status were 1.51 (95 percent CI: 1.15, 1.97) and 1.33 (95 percent CI: 1.05, 1.68), respectively. In subgroups of depression diagnosed before age 50 years or afterward, the hazard ratios were 1.15 (95 percent CI: 0.79, 1.67) and 1.46 (95 percent CI: 1.20, 1.77), respectively.

Because a significant interaction was observed for the association among depression, age at diagnosis of depression, and sex, we included these interaction terms in our subgroup analysis. In subgroups of depression diagnosed before age 50 years or afterward, the hazard ratios were, respectively, 1.66 (95 percent CI: 1.08, 2.53) and 1.33 (95 percent CI: 1.15, 1.97).

**TABLE 1.  Descriptive characteristics of the study population, province of Limburg, the Netherlands, 1975–2000**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Subjects with depression (n = 1,362)</th>
<th>Subjects without depression (n = 67,603)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. %</td>
<td>No. %</td>
</tr>
<tr>
<td>Mean age in years*</td>
<td>43.9 (13.6)†</td>
<td>37.8 (14.7)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>465 34.1</td>
<td>33,048 48.9</td>
</tr>
<tr>
<td>Females</td>
<td>897 65.9</td>
<td>34,555 51.1</td>
</tr>
<tr>
<td>Type of health insurance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Public</td>
<td>1,046 76.8</td>
<td>46,659 69.0</td>
</tr>
<tr>
<td>Private</td>
<td>316 23.2</td>
<td>20,944 31.0</td>
</tr>
<tr>
<td>Educational level‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>762 55.9</td>
<td>29,630 43.8</td>
</tr>
<tr>
<td>Medium</td>
<td>309 22.7</td>
<td>19,543 28.9</td>
</tr>
<tr>
<td>High</td>
<td>98 7.2</td>
<td>6,944 10.3</td>
</tr>
<tr>
<td>Mean follow-up years§</td>
<td>15.8 9.7</td>
<td>14.9 6.3</td>
</tr>
<tr>
<td>Deceased subjects</td>
<td>132 9.7</td>
<td>4,256 6.3</td>
</tr>
</tbody>
</table>

* Mean age at the date of inclusion in the cohort.
† Numbers in parentheses, standard deviation.
‡ For 14.2% of the subjects with depression and 17.0% of the subjects without depression, this information was missing or not updated; “low” is defined as primary school and/or lower vocational education, “medium” as secondary school and/or medium-level vocational education, and “high” as higher vocational education and/or university.
§ For subjects with depression, the range was 2.2–25.3 years; for subjects without depression, the range was 0.2–25.4 years.
In depressed patients, the period between a diagnosis of depression and death ranged between 2.2 and 24.0 years (mean, 13.3 years; standard deviation, 5.5 years). Deaths were more or less equally spread over this time period.

In table 3, the causes of death for depressed and nondepressed people are shown. Causes of death were not available for 31 (23.5 percent) depressed subjects and 1,454 (34.2 percent) nondepressed subjects. Among deceased patients for whom the cause of death was available, suicide and accidental deaths accounted for 2.97 percent and 2.25 percent in depressed and nondepressed patients, respectively (relative risk = 1.32, 95 percent CI: 0.42, 4.11).

After the addition of subjects with depressive complaints (ICPC code P03) to our exposed group, revealing a total of 2,271 cases and 67,124 noncases with 227 and 4,149 deceased subjects, respectively, the adjusted hazard ratio was 1.37 (95 percent CI: 1.16, 1.65) after adjustment for age, sex, and socioeconomic status.

**DISCUSSION**

In this study, we observed a moderate positive association (hazard ratio = 1.39) between depression and mortality, which was statistically significant after adjustment for age, sex, and socioeconomic status. Our subgroup analysis showed that the positive association between depression and mortality in the group of young men was slightly higher than the average, while the positive association in the group of old men was not significant. A nonsignificant negative association was observed in the group of young women.

The subjects included in our study are a largely unselected group of persons, since almost all people in the Netherlands are registered in a general practice. The population in the RNH, therefore, may be considered to be representative for the regional general population. To ensure the quality of the RNH database, regular instruction and training sessions are provided.

**TABLE 2. Age-adjusted and multivariate-adjusted hazard ratios of mortality, province of Limburg, the Netherlands, 1975–2000**

<table>
<thead>
<tr>
<th>Exposure</th>
<th>No. of deceased subjects</th>
<th>HR*†</th>
<th>95% CI*</th>
<th>HR‡</th>
<th>95% CI</th>
<th>HR§</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All subjects</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not depressed¶</td>
<td>4,256</td>
<td>1.02</td>
<td>1.00, 1.05</td>
<td>1.27</td>
<td>1.15, 1.41</td>
<td>1.39</td>
<td>1.15, 1.65</td>
</tr>
<tr>
<td>Depressed</td>
<td>132</td>
<td>1.21</td>
<td>1.02, 1.44</td>
<td>1.27</td>
<td>1.06, 1.51</td>
<td>1.39</td>
<td>1.16, 1.65</td>
</tr>
<tr>
<td><strong>Males</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not depressed¶</td>
<td>2,349</td>
<td>1.12</td>
<td>1.01, 1.24</td>
<td>1.52</td>
<td>1.29, 1.81</td>
<td>1.54</td>
<td>1.27, 1.88</td>
</tr>
<tr>
<td>Depressed</td>
<td>57</td>
<td>1.46</td>
<td>1.12, 1.91</td>
<td>1.52</td>
<td>1.16, 1.98</td>
<td>1.51</td>
<td>1.15, 1.97#</td>
</tr>
<tr>
<td><strong>Females</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not depressed¶</td>
<td>1,907</td>
<td>1.01</td>
<td>0.91, 1.12</td>
<td>1.35</td>
<td>1.13, 1.62</td>
<td>1.33</td>
<td>1.05, 1.68#</td>
</tr>
<tr>
<td>Depressed</td>
<td>75</td>
<td>1.27</td>
<td>1.01, 1.61</td>
<td>1.35</td>
<td>1.07, 1.71</td>
<td>1.33</td>
<td>1.05, 1.68#</td>
</tr>
<tr>
<td><strong>Depression before age 50 years</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not depressed¶</td>
<td>993</td>
<td>1.07</td>
<td>0.73, 1.55</td>
<td>1.10</td>
<td>0.75, 1.60</td>
<td>1.15</td>
<td>0.79, 1.67</td>
</tr>
<tr>
<td>Depressed</td>
<td>28</td>
<td>1.07</td>
<td>0.73, 1.55</td>
<td>1.10</td>
<td>0.75, 1.60</td>
<td>1.15</td>
<td>0.79, 1.67</td>
</tr>
<tr>
<td><strong>Depression at age 50 or more years</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not depressed¶</td>
<td>3,263</td>
<td>1.26</td>
<td>1.03, 1.53</td>
<td>1.32</td>
<td>1.09, 1.61</td>
<td>1.46</td>
<td>1.20, 1.77</td>
</tr>
<tr>
<td>Depressed</td>
<td>104</td>
<td>1.26</td>
<td>1.03, 1.53</td>
<td>1.32</td>
<td>1.09, 1.61</td>
<td>1.46</td>
<td>1.20, 1.77</td>
</tr>
</tbody>
</table>

* HR, hazard ratio; CI, confidence interval. † Unadjusted. ‡ Adjustment for age. § Adjustment for age, sex, and socioeconomic status. ¶ Reference group. # Not adjusted for sex.
Studies that reported suicide rates as a percentage of deaths. However, in their review on the mortality of depression and mortality. Our first thoughts are combined into one item (reduced appetite and loss of energy/tiredness), while two symptoms of the DSM-IV classification are not included (28, 32). From this study, however, we have no evidence to support this hypothesis.

An explanation for the fact that the positive association between depression and mortality was not significant in the group younger than 50 years may be that depression in the older age group, but not in the younger one, is a sign of an underlying chronic condition that increases the risk of dying. Another explanation may be that depression has a greater physiologic impact on older people than it has on younger people. In this respect, it is striking to see that the same pattern has been identified earlier with respect to the relation between depression and the emergence of subsequent dementia (33).

In summary, we observed a moderate positive association between depression and mortality in a large-scale, general practice-based study with a long period of follow-up. This finding could not be explained by an increased number of accidental or suicidal deaths.
ACKNOWLEDGMENTS

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