ORIGINAL ARTICLE

Depression and Cardiac Mortality

Results From a Community-Based Longitudinal Study

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Background: Depression may be a potential risk factor for subsequent cardiac death. The impact of depression on cardiac mortality has been suggested to depend on cardiac disease status, and to be stronger among cardiac patients. This study examined and compared the effect of depression on cardiac mortality in community-dwelling persons with and without cardiac disease.

Methods: A cohort of 2847 men and women aged 55 to 85 years was evaluated for 4 years. Major depression was defined according to psychiatric *DSM-III* criteria. Minor depression was defined by Center for Epidemiologic Studies-Depression Scale scores of 16 or higher. Effects of minor and major depression on cardiac mortality were examined separately in 450 subjects with a diagnosis of cardiac disease and in 2397 subjects without cardiac disease after adjusting for demographics, smoking, alcohol use, blood pressure, body mass index, and comorbidity.

Results: Compared with nondepressed cardiac patients, the relative risk of subsequent cardiac mortality was 1.6 (95% confidence interval [CI], 1.0-2.7) for cardiac patients with minor depression and 3.0 (95% CI, 1.1-7.8) for cardiac patients with major depression, after adjustment for confounding variables. Among subjects without cardiac disease at baseline, similar increased cardiac mortality risks were found for minor depression (1.5 [95% CI, 0.9-2.6]) and major depression (3.9 [95% CI, 1.4-10.9]).

Conclusion: Depression increases the risk for cardiac mortality in subjects with and without cardiac disease at baseline. The excess cardiac mortality risk was more than twice as high for major depression as for minor depression.

Arch Gen Psychiatry. 2001;58:221-227

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DEPRESSION has a large range of adverse health consequences, including impaired physical function, increased morbidity, and an increased risk of death.[1-5] Several findings suggest that cardiac disease plays a central role in the development of these consequences.[6-8] Among patients hospitalized with a myocardial infarction, a psychiatric diagnosis of major depression has been shown to be associated with a 2- to 4-fold increased risk for cardiac mortality.[9-13] Whether this risk is specific for the period of hospitalization or whether it also exists among cardiac patients living in the community has not yet been examined. Among persons initially free of cardiac disease, some studies[14-18] but not others[19,20] found that significant depressive symptoms, often referred to as subthreshold or minor depression, increase the risk for fatal cardiac events.[21]

In their review of the literature, Glassman and Shapiro[6] suggested that the impact of depression on cardiac mortality depends on baseline cardiac disease status; the risk for cardiac events that depression confers seems to be smaller in subjects without cardiac disease than in cardiac patients. However, because of large differences in study settings (outpatient vs inpatient) and depression measurements (depressive symptoms vs major depression), an indirect comparison of previous results for cardiac patients and for

See also page 229

subjects without cardiac disease is only of limited value. Whether depression indeed has more adverse cardiac consequences for cardiac patients than for subjects without cardiac disease is crucial for our further understanding of the (pathophysiological) link between depression and cardiac disease. In addition, since depression is a potentially preventable and treatable condition, the identification of subjects for whom depression has the strongest cardiac consequences has im-

SUBJECTS, MATERIALS, AND METHODS

SAMPLE

Data are from the Longitudinal Aging Study Amsterdam (LASA), a study among men and women aged 55 to 85 years. Data collection procedures and response have been described in detail previously.[2] In short, a random sample of community-dwelling older persons, stratified by age and sex, was drawn from the population registries of 11 municipalities in the Netherlands. The cohort was originally recruited for the study, Living Arrangements and Social Networks of Older Adults (LSN) (N=3805 [response rate, 62.3%]). After 10 months, between September 1992 and September 1993, participants were approached to participate in the baseline LASA interview. A total of 3107 (81.7%) gave informed consent and took part; 126 (3.3%) had died; 44 (1.2%) could not be contacted; 134 (3.5%) were too ill or impaired to be interviewed; and 394 (10.4%) refused to participate.

Because of missing baseline depression data, 51 (1.6%) of the 3107 subjects were lost to subsequent analyses. For 209 (6.8%) of the remaining 3056 respondents, a cardiac disease diagnosis could not be confirmed or ruled out with complete certainty, because of contradictory (n=110) or incomplete (n=99) data on cardiac disease status. These 209 subjects were somewhat older, more often male, and more often had minor depression than subjects without cardiac disease, but were somewhat younger, less often male, and less often had minor depression than those with ascertained cardiac disease. Also, they had more cardiac deaths during follow-up (11.5%) than subjects without cardiac disease (3.8%) ($P<.001$), but less than those with ascertained cardiac disease (20.7%) ($P=.004$). The 209 subjects with an uncertain cardiac disease diagnosis were left out in further analyses, leaving 2847 participants for the analyses.

MEASUREMENTS

Depression

As in previous publications,[2,5] a measurement of both minor and major depression is used. At baseline, the Center for Epidemiologic-Depression Scale (CES-D[22]) was used to assess depressive symptoms experienced during the previous week. This 20-item self-report scale, ranging from 0 to 60, has been shown to be a valid and reliable instrument in older populations.[23] In our study, the internal consistency was high (Cronbach $\alpha=.87$). Four weeks after baseline, all subjects scoring above the commonly used CES-D cutoff score of 16 were approached for a diagnostic interview (response, 86.0% relative to baseline). Nonresponse of this interview was higher among subjects with higher age and more chronic diseases ($P<.001$), but not related to sex. Using the Diagnostic Interview Schedule (DIS[24]), a psychiatric diagnosis of major depression (6-month recency) was defined according to *DSM-III* criteria.[25] The criterion validity of the CES-D for major depression seemed to be excellent (sensitivity, 100%; specificity, 88%).[23] Minor depression was considered present if subjects scored above the CES-D cutoff, but did not fulfill the diagnostic severity threshold for major depression. This definition of minor depression identifies subjects with a clinically relevant level of depressive symptoms, often referred to as a subthreshold depressive syndrome.[21] As expected, subjects with major depression had a higher mean CES-D score (25.9) than those with minor depression (22.3) ($P<.01$), which confirms more severe depressive symptoms in major depression. The minor depression category included 69 subjects who scored above the CES-D cutoff but did not participate in the follow-up diagnostic DIS interview. Consequently, these subjects could have had major depression instead of minor depression. To check the effect of this potential misclassification, analyses were repeated after excluding those with missing DIS interview data.

portant clinical implications. This study examines and compares the effect of significant depressive symptoms (minor depression) and major depression on cardiac mortality in a community-dwelling sample of older subjects both without and with cardiac disease.

RESULTS

The mean (SD) age of the 2847 participants was 70.5 years (8.7 years) and 52.0% were female. Of the respondents, 278 (9.8%) had angina pectoris, 278 (9.8%) had a history of myocardial infarction, and 178 (6.3%) had congestive heart failure. Four hundred fifty subjects (15.8%) had a confirmed diagnosis of cardiac disease. Cardiac patients were significantly older, more often male, less educated, more often past smokers, and more often had diabetes, stroke, or lung disease than subjects without cardiac disease (**Table 1**). Minor depression was significantly ($\chi^2_1=11.0$, $P<.001$) more often present among subjects with cardiac disease (17.8%) than among those without cardiac disease (12.0%). The prevalence of major depression was not significantly ($\chi^2_1=0.9$, $P=.35$) associated with cardiac disease status: 1.8% and 2.4% of the subjects without and with cardiac disease, respectively, had major depression.

Five hundred one subjects (17.8% of baseline sample) died during the follow-up period of, on average, 50 months. Of these deaths, 184 (36.7%) were cardiac deaths and 108 (21.6%) were CHD deaths. The cardiac mortality rate for the total sample was 15.3 per 1000 person-years. As expected, this rate was much higher among subjects with cardiac disease (53.1 per 1000 person-years) than among those without cardiac disease (8.3 per 1000 person-years). In univariate regression analyses, other significant predictors ($P<.05$) of cardiac mortality were higher age, male sex, lower education, current smoker, low body mass index, stroke, diabetes, and lung disease.

In subjects without cardiac disease at baseline, the crude cardiac mortality rate per 1000 person-years was 7.7 in the nondepressed, but much higher in those with minor (16.2) and major (22.3) depression (**Figure 1**).

Cardiac Disease

Cardiac disease was present when a diagnosis of either coronary heart disease (CHD) (angina pectoris or a history of myocardial infarction) or congestive heart failure was confirmed. These diagnoses were ascertained by combining 3 data resources: self-reported (symptoms of) cardiac disease, medication use during the past 2 weeks registered by medical interviewers, and reports of cardiac disease by subject's general practitioners. Angina pectoris was considered present when at least 2 of the following criteria were met: (1) self-reported cardiac disease with symptoms of pain or a heavy, uncomfortable feeling in the chest during exertion that disappeared within 10 minutes after stopping or taking sublingual nitroglycerine; (2) the current use of nitroglycerine; and (3) a confirmed cardiac disease diagnosis given by the general practitioner. A history of myocardial infarction was considered present when (1) a subject reported having had a myocardial infarction in the past and (2) a confirmed cardiac disease diagnosis was given by the general practitioner. Congestive heart failure was considered present when at least 2 of the following criteria were met: (1) self-reported cardiac disease with symptoms of edema of the lower extremities when waking up in the morning and/or having to sleep with more than 1 pillow because of shortness of breath; (2) the current use of diuretic medication and either a digitalis or vasodilator preparation; and (3) a confirmed cardiac disease diagnosis by the general practitioner.

Cardiac Mortality

Death certificates were traced through the registries of the municipalities in which respondents were registered. Vital status ascertainment was 100% complete. All deaths that occurred between the baseline interview and October 1, 1997, were recorded. The follow-up period lasted on average 50 months (4.2 years), ranging from 1 to 60 months. Information about causes of death was obtained through the Dutch Central Bureau of Statistics and coded according to the *International Classification of Diseases, Ninth Revision (ICD-9* codes).[26] *International Classification of Diseases, Ninth Revision* codes 410 through 429 identify all cardiac deaths, and *ICD-9* codes 410 through 414 identify deaths by CHD.

COVARIATES

Potentially confounding factors, assessed at study baseline, included age, sex, level of education, smoking status (nonsmoker or former or current smoker), excessive alcohol intake (an average of ≥3 drinks per day), and body mass index, computed as weight in kilograms divided by the square of height in meters. The average of 2 readings of the blood pressure, measured using an oscillometric digital finger blood pressure monitor (Omron model HEM-812F; Omron Healthcare Inc, Vernon Hills, Ill), was classified as normotensive (systolic pressure, <140 mm Hg, and diastolic pressure, <90 mm Hg); systolic hypertension (diastolic pressure, <90 mm Hg; and systolic pressure, ≥140 mm Hg); and diastolic hypertension (diastolic pressure, >90 mm Hg). The presence of comorbid conditions was indicated by self-reported stroke, diabetes mellitus, lung disease, or cancer.

STATISTICAL ANALYSES

Characteristics of subjects with and without cardiac disease were compared using χ^2 statistics for categorical variables and *t* statistics for continuous variables. Subjects with no cardiac death were censored on October 1, 1997, or at the time of death, whichever occurred first. For subjects with and without cardiac disease, cardiac and CHD mortality rates per 1000 person-years were calculated according to depression status. Cox proportional hazards regression models were used to examine the effects of minor and major depression on time to cardiac mortality. Relative risks (RRs) and 95% confidence intervals (CIs) were used as the measure of association and adjusted for confounding variables. The assumption of proportionality of hazard was checked with log minus log plots and by tests of the interaction of time with exposure (minor and major depression).

In these subjects, the same trend was found for CHD mortality, with rates of 3.9, 6.3, and 16.7 in subjects with no, minor, and major depression, respectively. The age- and sex-adjusted Cox proportional hazards model among subjects without cardiac disease (**Table 2**) showed that minor depression was associated with a 1.7-fold increased risk for cardiac mortality (95% CI, 1.0-2.8). This mortality risk reduced somewhat after further adjustment for education, smoking, drinking, hypertension, body mass index, stroke, diabetes, lung disease, and cancer (RR, 1.5 [95% CI, 0.9-2.6]). Subjects with major depression were 4.9 times and, after full adjustment 3.9 times, more likely to have a cardiac death than nondepressed subjects. When the outcome was restricted to CHD mortality only, major depression, but not minor depression, significantly increased the risk for dying (adjusted RR, 5.2; 95% CI, 1.5-17.7).

Similar analyses were conducted among the 450 cardiac patients. Again, the crude cardiac mortality rate per 1000 person-years was much lower in the nondepressed (47.1) than in those with minor depression (72.4) and major depression (126.8) (Figure 1). A similar pattern was observed for CHD mortality, with rates of 30.1, 55.1, and 101.4, respectively. Among cardiac patients, the fully adjusted RR for cardiac mortality was 1.6-fold increased when minor depression was present (95% CI, 1.0-2.7) and 3.0-fold increased when major depression was present (95% CI, 1.1-7.8) (Table 2). When only CHD mortality was considered, fully adjusted RRs were even higher (minor depression: RR, 2.1; 95% CI, 1.1-3.8; major depression: RR, 3.9; 95% CI, 1.3-11.8). Overall, Table 2 shows increased risks for cardiac mortality associated with minor depression and, most pronounced, with major depression. These risks seem to be similar for subjects with and without cardiac disease. An analysis among all subjects confirms that the risks in both groups were not dissimilar, since the interaction term between cardiac disease and depression status was not significant ($P = .53$).

The minor depression category included 69 persons who scored above the CES-D cutoff but did not participate in the second interview. Consequently, these per-

Table 1. Population Characteristics According to Baseline Cardiac Disease Status

Characteristic	No Cardiac Disease, % (n = 2397)	Cardiac Disease, %* (n = 450)	χ^2 or F Value†	*P*
Age, mean (SD)	69.8 (8.7)	74.0 (7.9)	91.2	<.001
Female	54.5	38.4	39.3	.001
Higher education (>12 years)	56.9	50.9	5.6	.02
Smoking				
Nonsmoker	32.0	23.7	18.2	<.001
Past smoker	42.0	53.4		
Current smoker	26.0	22.9		
Excessive alcohol intake‡	4.3	2.7	2.6	.11
Body mass index (kg/m^2)				
<20, kg/m^2	2.5	3.0	0.7	.71
20-28, kg/m^2	64.6	62.6		
>28, kg/m^2	32.9	34.4		
Blood pressure level§				
Normotensive	75.2	80.4	5.1	.08
Systolic hypertension	18.2	15.2		
Diastolic hypertension	6.6	4.4		
Diabetes	6.1	15.6	47.8	<.001
Stroke	4.1	12.2	48.5	<.001
Lung disease	10.5	15.6	9.8	.002
Cancer	8.7	10.4	1.4	.24
Minor depression	12.0	17.8	11.7	.001
Major depression	1.8	2.4	0.9	.34

**Unless otherwise indicated.*

*†χ^2 Statistics (*df *= 1) for categorical variables and F statistics (*df *= 2846) for continuous.*

‡Given as drinks per day with more than 3 representing excessive alcohol intake.

§Normotensive is defined as a systolic pressure of less than 140 mm Hg and a diastolic pressure of less than 90 mm Hg; systolic hypertension, as a diastolic pressure of less than 90 mm Hg and systolic pressure of 140 mm Hg or greater; and diastolic hypertension, as a diastolic pressure of greater than 90 mm Hg.

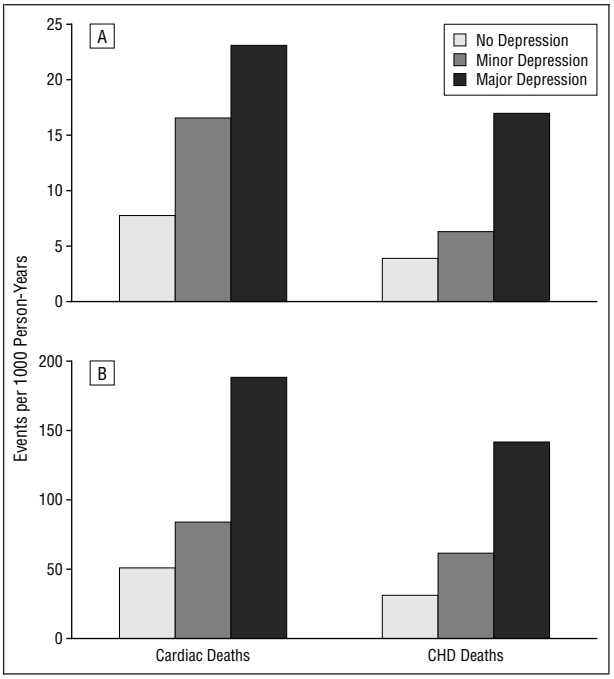

Figure 1. *Cardiac death and cardiac heart disease (CHD) death rates per 1000 person-years by depression status in subjects without cardiac disease (n=2397) (A) and in subjects with cardiac disease (n=450) (B). Note that the scales for the upper and lower graphs are different.*

sons could have had major depression instead of minor depression. Analyses were repeated after excluding those with missing DIS interview data. These analyses yielded similar cardiac mortality risk estimates for minor depression in subjects without cardiac disease (fully adjusted RR, 1.5; 95% CI, 0.8-2.7) and in cardiac patients (RR, 1.9; 95% CI, 1.1-3.3), which confirms that potential misclassification of those with missing DIS data did not influence our results (**Figure 2**).

Table 3 presents adjusted RRs for cardiac mortality and CHD mortality in 6 groups according to depression and cardiac disease status. When compared with nondepressed subjects without cardiac disease (reference group), minor and major depression in subjects without cardiac disease significantly increased the risk for cardiac mortality (RRs, 1.6 and 3.8, respectively). Nondepressed cardiac patients had a significant 3.4-fold increased risk for cardiac mortality when compared with the reference group. In cardiac patients with minor and major depression, RRs were 5.1 and 10.5, respectively. The RRs for CHD mortality were even more pronounced; compared with nondepressed subjects without cardiac disease, RRs were 1.4 and 5.1 for subjects without cardiac disease with minor and major depression, respectively, 4.5 for nondepressed cardiac patients, 8.5 for cardiac patients with minor depression, and 17.7 for cardiac patients with major depression. Finally, we checked whether there was a sex difference in the effect of depression on cardiac mortality by entering an interaction term sex×depression in the Cox proportional hazards analysis. However, no significant interaction could be demonstrated (P=.68), and stratified analyses confirmed that the RR estimates for depression were comparable for men and women.

COMMENT

This study shows that depressed older persons were significantly more likely to die because of cardiac disease during 50 months of follow-up than nondepressed older persons. The increased cardiac mortality risk associated with depression was present—and very similar—in both subjects with and without cardiac disease. The risk for cardiac mortality was about 1.6 times increased in persons with minor depression and more than 3 times increased in persons with major depression. When causes of death were restricted to CHD deaths, the risks associated with minor and major depression were even somewhat more increased.

In their review of the literature, Glassman and Shapiro[6] suggested that depression has 2 times stronger prognostic consequences for cardiac patients than for persons free of cardiac disease. Our study is the first to examine and directly compare the effect of depression on cardiac mortality in community-dwelling older subjects with and without cardiac disease. We did not find

Table 2. Relative Risks (RRs) for Cardiac and Ischemic Heart Disease (IHD) Mortality According to Depression Status in Subjects Without and With Cardiac Disease*

		Cardiac Mortality			IHD Mortality		
	No. of Patients	No. of Deaths	Age- and Sex-Adjusted, RR (95% CI)	Fully Adjusted,† RR (95% CI)	No. of Deaths	Age- and Sex-Adjusted, RR (95% CI)	Fully Adjusted,† RR (95% CI)
Subjects without cardiac disease							
No depression ‡	2072	69	1.0	1.0	35	1.0	1.0
Minor depression	282	18	1.7 (1.0-2.8)	1.5 (0.9-2.6)	7	1.4 (0.6-3.2)	1.3 (0.6-3.1)
Major depression	43	4	4.9 (1.8-13.7)	3.9 (1.4-10.9)	3	6.9 (2.1-22.7)	5.2 (1.5-17.7)
Subjects with cardiac disease§							
No depression‡	361	67	1.0	1.0	43	1.0	1.0
Minor depression	78	21	1.6 (1.0-2.6)	1.6 (1.0-2.7)	16	1.9 (1.1-3.5)	2.1 (1.1-3.8)
Major depression	11	5	3.6 (1.4-9.0)	3.0 (1.1-7.8)	4	4.7 (1.6-13.4)	3.9 (1.3-11.8)

*CI indicates confidence interval
†Adjusted for age, sex, education, smoking status, alcohol use, hypertension, body mass index, diabetes mellitus, stroke, lung disease, and cancer.
‡Reference group.
§Includes coronary heart disease (angina pectoris or history of myocardial infarction) and congestive heart failure.

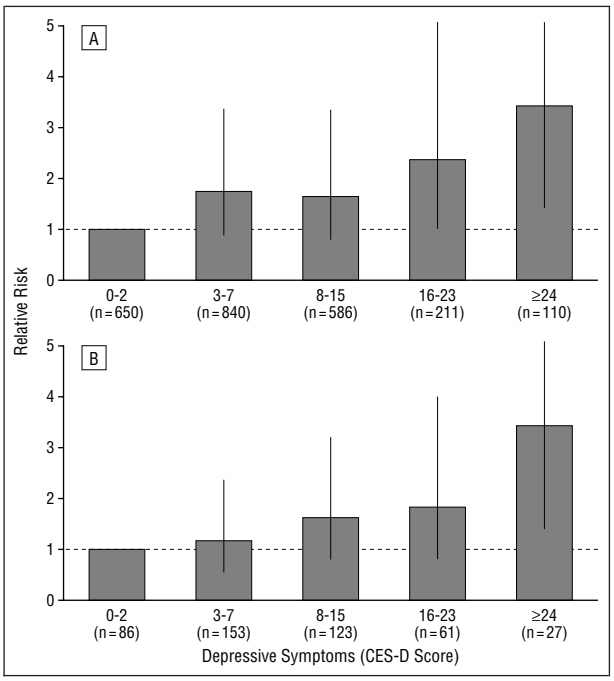

Figure 2. *Adjusted relative risk for cardiac death according to level of depressive symptoms in subjects without cardiac disease (n=2397) (A) and in subjects with cardiac disease (n=450) (B). All depression groups are compared to the lowest level of depressive symptoms (Center for Epidemiologic Studies-Depression Scale [CES-D] score of 0-2). Bars indicate relative risks; lines indicate 95% confidence intervals.* P=.06, *for trend, in subjects without cardiac disease.* P=.04, *for trend, in subjects with cardiac disease.*

Table 3. Adjusted Relative Risks (RRs) for Cardiac and Ischemic Heart Disease (IHD) Mortality According to Cardiac Disease Status and Depression Status*†

	No. of Patients	Cardiac Mortality, RR (95% CI)	IHD Mortality, RR (95% CI)
No cardiac disease, no depression‡	2072	1.0	1.0
No cardiac disease, minor depression	282	1.6 (1.0-2.8)	1.4 (0.5-3.1)
No cardiac disease, major depression	43	3.8 (1.4-10.6)	5.1 (1.6-16.9)
Cardiac disease, no depression	361	3.4 (2.4-4.9)	4.5 (2.8-7.1)
Cardiac disease, minor depression	78	5.1 (3.1-8.6)	8.5 (4.5-16.1)
Cardiac disease, major depression	11	10.5 (4.1-26.7)	17.7 (6.0-51.9)

*CI indicates confidence interval.
†Relative risks are adjusted for age, sex, education, smoking status, alcohol use, hypertension, body mass index, diabetes mellitus, stroke, and cancer.
‡Reference group.

evidence of a stronger adverse cardiac effect of depression in cardiac patients than in subjects without cardiac disease: in both subgroups the excess risk for cardiac mortality associated with depression was present and very similar. However, cardiac mortality risks did differ according to level of depression: risks were about twice as high for major depression as for minor depression. These results suggest that the severity of depression shows a gradient of risk for subsequent cardiac mortality. Consequently, measurement differences for depression (symptoms vs psychiatric diagnosis) in earlier studies may explain a large part of the earlier reported differences in the prognostic strength of depression for cardiac mortality.

Several plausible mechanisms for the link between depression and cardiac mortality exist, of which pathophysiological and behavioral ones are the most important. Direct pathophysiological alterations caused by depression have been described, including impairment of platelet functions[6,7,27,28] and a decreased heart rate variability as a consequence of an imbalance in the autonomic tone.[29] Also, immune activation and hypercortisolemia as stress responses to depression[30-33] may result in decreased insulin resistance and increased steroid production and blood pressure, thereby increasing the risk of cardiac disease.[34] Unhealthy lifestyles have been found to be more common among depressed than among nondepressed persons.[5,8] Although we adjusted the analyses for smoking and drinking, it is likely that depressed people are less compliant with treatment recommendations and less willing to exercise and eat healthy, which

may explain part of our results. Also, the link between depression and cardiac mortality may be caused by pharmacotherapeutic treatment. Antidepressants, in particular tricyclic antidepressants, may have a cardiotoxic effect.[35] However, in our community-based sample, antidepressants were used only sparingly and dosages were generally low.[2] Adjustment for antidepressants in the analyses did not change the RRs for minor and major depression, and therefore cannot explain our results. Finally, it is possible that depression may be an indirect indication of disease severity or it may represent a reaction to (sub)clinical cardiovascular symptoms (eg, dyspnea) that places subjects at greater risk for cardiac mortality.[16,19] The community-based setting of our study made it impossible to collect detailed clinical information about the severity of cardiac disease among cardiac patients. However, the strength of the elevated cardiac mortality risks, the community-based setting of our sample, and the fact that similar elevated risks were found among persons without cardiac disease suggest that depression is not only a surrogate marker of cardiac disease severity but that it has effects in itself. Our large sample size, the detailed measurement of depression and the inclusion of subjects both with and without cardiac disease, provided the unique opportunity to gain more insight into the prognostic importance of depression for subsequent cardiac mortality in a community-based sample.

The described potential mechanisms explaining the excess cardiac mortality risk among depressed subjects can operate in both subjects with and without cardiac disease. Our findings suggest that these mechanisms are active irrespective of baseline cardiac disease status. We could not demonstrate an interaction (ie, multiplicative effects) between depression and baseline cardiac disease status in predicting cardiac mortality. Consequently, it is not very likely that some mechanisms are triggered only when cardiac disease is present. Baseline cardiac disease and depression rather seem to have independent, additive effects on cardiac mortality.

Depression is common in older community-dwelling populations. The prevalence of a psychiatric diagnosis of major depression in our study was 2%, and a further 13% suffered from minor depression. These prevalences are in line with other community-based studies.[36] Despite its high prevalence, depression often goes unrecognized.[37] Untreated, minor and major depression are not self-limiting disorders. The vast majority (62%) of those with a minor depression in our study were still depressed after 5 months,[38] illustrating the chronic nature of depression. Our results show that minor depression and, most strongly, major depression place both community-dwelling cardiac patients and persons free of cardiac disease at an increased risk for cardiac mortality. Since the "basis" risk for fatal cardiac events is substantially elevated when cardiac disease is already present, especially cardiac patients with (major) depression should be recognized as a high-risk population. Prevention and treatment of depression may be one of the most effective targets for interventions aimed at reducing the risk for fatal cardiac events. Future clinical trials should point out whether more appropriate care for depressed persons may prevent fatal cardiac events.

Accepted for publication July 20, 2000.

The Longitudinal Aging Study Amsterdam is largely funded by the Ministry of Welfare, Health, and Sports, the Hague, the Netherlands.

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