ORIGINAL ARTICLE

Minor and Major Depression and the Risk of Death in Older Persons

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Background: The association between depression and mortality in older community-dwelling populations is still unresolved. This study determined the effect of both minor and major depression on mortality and examined the role of confounding and explanatory variables on this relationship.

Methods: A cohort of 3056 men and women from the Netherlands aged 55 to 85 years were followed up for 4 years. Major depression was defined according to *DSM-III* criteria by means of the Diagnostic Interview Schedule. Minor depression was defined as clinically relevant depression (defined by a Center for Epidemiologic Studies Depression score ≥16) not fulfilling diagnostic criteria for major depression.

Results: After adjustment for confounding variables (sociodemographics, health status), men with minor depression had a 1.80-fold higher risk of death (95% confidence interval, 1.35-2.39) during follow-up than nondepressed men. In women, minor depression did not significantly increase the mortality risk. Irrespective of sex, major depression was associated with a 1.83-fold higher mortality risk (95% confidence interval, 1.09-3.10) after adjustment for sociodemographics and health status. Health behaviors such as smoking and physical inactivity explained only a small part of the excess mortality risk associated with depression.

Conclusion: Even after adjustment for sociodemographics, health status, and health behaviors, minor depression in older men and major depression in both older men and women increase the risk of dying.

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MORTALITY studies in psychiatry are important because they are an integral part of the effort to develop a comprehensive understanding of the development, course, and outcome of psychiatric disorders.[1] Previous mortality studies have concentrated either on major depression, as defined by *DSM-IV* criteria,[2] or on depressive symptoms in general, not specifically defining the type of depression. The latter mainly include cases of marked depressive symptoms below the severity threshold of major depression, often referred to as subthreshold or minor depression.[3,4]

The few community-based studies on major depression have described an increased mortality risk.[5-8] However, for minor depression, both the presence[9-11] and the absence[12-16] of an excess mortality risk have been described. Three studies found an increased mortality risk in depressed men but not in depressed women.[7,10,17]

Disparate findings regarding the effect of depression on mortality might partly be explained by failure to control for the effects of health status and socioeconomic status in some studies.[12] Since depressed persons usually have a lower socioeconomic status and a worse health status than their nondepressed peers,[18,19] these characteristics may partly be responsible for their increased mortality risk. To what extent a possibly increased mortality risk among depressed persons is caused by confounding by socioeconomic status and health status has not been extensively described. In addition, not many attempts have been made to understand the increased risk of dying among depressed persons. Depressed persons are known to be more likely than nondepressed persons to engage in smoking, excessive alcohol intake, physical inactivity, and unhealthy eating habits.[20,21] Whether these health behaviors explain part of their increased mortality risk has not been examined before, to our knowledge.

This community-based study examines the effects of both minor and major depression on mortality among older persons and explores the impact of potential

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PATIENTS AND METHODS

SAMPLE

Data for this study were collected in the Longitudinal Aging Study Amsterdam, a longitudinal study among persons aged 55 to 85 years. Data collection procedures and nonresponse have been described in depth.[22] In short, a random sample was drawn from the population registries of 11 municipalities in 3 geographic areas in the Netherlands. The sample was stratified by sex and age according to expected mortality at midterm of the Longitudinal Aging Study Amsterdam (after 5 years) to guarantee sufficient sample sizes for longitudinal analyses within age and sex strata. The cohort was originally recruited for the study Living Arrangements and Social Networks of Older Adults (N = 3805; response rate, 62.3%). Nonresponse was higher ($P<.001$) among the oldest old persons because of physical or cognitive impairment.[23] After 10 months, between September 1992 and September 1993, the Living Arrangements and Social Networks of Older Adults Study participants were approached again for the face-to-face Longitudinal Aging Study Amsterdam interview. A total of 3107 (81.7%) took part; 126 (3.3%) had died before approach; 44 (1.2%) could not be contacted; 134 (3.5%) were too ill or cognitively impaired to be interviewed; and 394 (10.4%) were unwilling to participate because of lack of interest. For the present study, 51 (1.6%) of the 3107 subjects were unavailable for subsequent analyses because of missing depression data, leaving a study sample of 3056.

DIAGNOSIS OF DEPRESSION

The Center for Epidemiologic Studies Depression Scale (CES-D)[24] was used to measure depressive symptoms experienced during the previous week. This 20-item self-report scale, ranging from 0 to 60, has proved to be a valid and reliable instrument in older populations.[25] In our study, the internal reliability was high (Cronbach $\alpha = .87$). The commonly used CES-D cutoff score of 16 was used to identify persons with a high level of depression. All subjects scoring above this cutoff were approached for a diagnostic interview, which was included in a second interview a few weeks after baseline (response rate, 86.0% relative to baseline). Nonresponse for the second interview was significantly higher among persons with higher age and more chronic diseases ($P<.001$), but was not related to sex. With the use of the Diagnostic Interview Schedule,[26] major depression (6-month recency) was defined according to *DSM-III* criteria.[27] Since a random sample of 330 screened negatives (CES-D score <16) also underwent a Diagnostic Interview Schedule interview, the criterion validity of the CES-D for major depression could be determined and appeared to be excellent (sensitivity, 100%; specificity, 88%).[25] The definition of minor depression was not exactly based on research diagnostic *DSM-IV* criteria (developed after the start of our study) but was in line with Angst and Merikangas' definition of subthreshold depression.[28] Subthreshold depression identifies persons with clinically relevant depressive syndrome (CES-D score ≥16) below the diagnostic severity threshold for major depressive disorder. In our study, 9.1% of the persons with minor depression fulfilled *DSM-III* criteria for dysthymia, and 62.3% still had a minor depression during a follow-up measurement after 5 months, illustrating the chronic nature of minor depression. In another study, it was shown that 43% of those with baseline minor depression were depressed during all 5 measurements during 1 year.[29] As expected, persons 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. Persons with a CES-D score of 16 or more and missing Diagnostic Interview Schedule data (18.7% of those with a CES-D score ≥16) were categorized as having minor depression. Some of these per-

confounding variables (sociodemographics, health status) and explanatory variables (health behaviors) in these effects.

RESULTS

Mean age of the 3056 respondents was 70.6 years, and 51.6% were female. Of the respondents, 2603 (85.2%) were not depressed, 392 (12.8%) had a minor depression, and 61 (2.0%) had a major depression. As compared with the nondepressed, subjects with minor depression were significantly older; more often female; less educated; more often living in urbanized areas; more diseased, physically disabled, and physically inactive; and more often current smokers ($P<.01$) (**Table 1**). Most of these characteristics were also found, although to a lesser extent, for major depression. However, a striking difference emerged for age: persons with major depression were significantly younger than those with minor depression.

In total, 561 subjects (18.4%) died during the follow-up of, on average, 50 months. In univariate analysis, significant predictors ($P<.01$) of mortality were advanced age ($P<.001$), male sex ($P<.001$), low level of education ($P<.001$), high urbanization level ($P = .002$), presence of all specific chronic diseases except arthritis ($P<.001$), physical disability ($P<.001$), current smoking ($P = .02$), low or high BMI ($P = .04$ and $P = .003$, respectively), and physical inactivity ($P<.001$). The crude mortality rate per 1000 person-years was 39.5 for the nondepressed, 71.4 for persons with minor depression, and 60.7 for those with major depression (**Table 2**). Persons with minor depression had a significant 1.84-fold higher risk of dying than nondepressed persons (95% confidence interval [CI], 1.49-2.27). This risk was reduced somewhat after adjustment for sex and age (relative risk [RR], 1.65; 95% CI, 1.33-2.04). However, the age-adjusted mortality risk of minor depression was much higher in men (RR, 2.02; 95% CI, 1.53-2.67) than in women (RR, 1.27; 95% CI, 0.92-1.76) (**Figure**). The significance of this interaction by sex was tested by adding the sex × minor depression interaction term in the age- and sex-adjusted model. Since the interaction term was statistically significant ($P = .05$), the remainder of the findings for minor depression will be presented for men and women separately. For major depression, the unadjusted mortality risk was 1.55 (95% CI, 0.92-2.58). Adjustment for sex and age increased the mortality risk to

sons might have been misclassified because they could have had major depression. To check the effect of missing Diagnostic Interview Schedule data, all analyses were repeated after excluding persons with missing second-interview data.

DEATH

Death certificates were traced through the registries of the municipalities in which the 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*. The following causes of death were distinguished (*International Classification of Diseases, Ninth Revision,*[30] codes in parentheses): cardiovascular disease (401-429, 440-459), stroke (430-438), diabetes (250), gastrointestinal tract disease (530-579), cancer (140-208), respiratory disease (460-519), accidents (E800-E929), suicide (E950-E959), and other causes (remaining codes).

OTHER VARIABLES

Potentially confounding covariates were sociodemographics and health status at baseline. Sociodemographics included age, sex, education, and level of urbanization. Chronic disease status was assessed by self-reports of heart disease, peripheral atherosclerosis, stroke, diabetes mellitus, lung disease, cancer, and arthritis. Physical disability in daily life was assessed by a 3-item questionnaire[31] and classified as none, moderate (1 disability), and severe (≥2 disabilities). Disability can be considered a rough indicator of illness severity and, consequently, is a potential confounder of the association between depression and mortality. However, since depression in itself also results in subsequent physical decline and disability,[32-37] disability may also be part of the explanatory mechanism by which depression links to mortality. Consequently, the consideration of disability as a pure confounder would result in an overadjusted estimate of the mortality risk of depression. In this study, disability is considered a potential confounder as well as a potential explanatory variable.

Other potentially explanatory variables included health behaviors such as smoking (none, former smoker, or current smoker), excessive alcohol consumption (an average of 3 drinks or more per day), and body mass index (BMI) (computed as weight in kilograms divided by the square of height in meters). Physical activity was assessed by asking respondents whether they had engaged in walking, bicycling, light and heavy household activities, gardening, and sports activities in the previous 2 weeks. Based on the total number of activities reported, physical activity was classified as low (0-2 activities), moderate (3-4 activities), or high (5-6 activities).

STATISTICAL ANALYSES

Respondents were divided into 3 depression categories: no depression, minor depression, and major depression. Study characteristics across these groups were compared by means of χ^2 statistics. Mortality rates per 1000 person-years were calculated according to depression status. Overall estimates of the relative risk of death were computed from Cox proportional hazards regression models. In multivariate models, the effect of depression on mortality was studied after successive adjustment for potential confounders (sociodemographics, chronic diseases) and potential explanatory variables (health behaviors). To rule out possible interaction between depression and covariates in predicting mortality, the significance of product terms between depression and covariates was tested.

2.32 (95% CI, 1.38-3.89) (Figure). No interaction by sex was present for major depression (*P* of interaction term, .53).

In men, adjustment for age, education and urbanization, and chronic diseases reduced the mortality risk of minor depression to 1.80 (**Table 3**). Adjustment for physical disability further reduced the mortality risk considerably, but minor depression remained significantly associated with mortality (1.57). Adjustment for BMI, smoking, and physical activity reduced the mortality risk to 1.45 (95% CI, 1.08-1.95). In women, minor depression was not significantly associated with mortality after adjustment for age (Table 3) and became even smaller than 1.0 after further adjustment for confounders and explanatory variables.

After adjustment for sociodemographics and chronic diseases, persons with major depression had a 1.83-fold higher risk of dying than those who were not depressed (Table 3). Adjustment for physical disability, BMI, smoking, and physical activity reduced the mortality risk for major depression, but the risk was still significantly increased (RR, 1.68; 95% CI, 1.00-2.84).

The increased mortality risks for major and minor depression were not caused by suicide. Only 3 persons committed suicide: 1 woman with minor depression and 1 man and 1 woman without depression at baseline (**Table 4**). A large proportion (46.7%) of the persons with major depression died because of cardiovascular disease, but, probably because of small numbers, this was not signficantly different from the proportions in nondepressed persons (31.1%) and those with minor depression (29.4%). Nondepressed persons had significantly more cancer mortality, whereas persons with minor depression died somewhat more often because of respiratory disease.

The minor depression category included 73 persons who scored above the CES-D cutoff but did not participate in the second interview. Consequently, these persons 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 second-interview data. These analyses yielded similar results for minor depression: the mortality risk adjusted for chronic diseases and sociodemographics was 1.97 (95% CI, 1.42-2.72) in men and 1.09 (95% CI, 0.74-1.61) in women.

As expected, anxiety disorders (defined by *DSM-III* criteria) were more prevalent among the depressed.[38]

Table 1. Baseline Characteristics by Depression Status

	%			*P*		
	No Depression (n = 2603)	Minor Depression (n = 392)	Major Depression (n = 61)	No vs Minor	No vs Major	Minor vs Major
Age, y						
55-64	34.5	23.2	39.3			
65-74	31.7	28.1	37.7	<.001	.21	.001
75-85	33.8	48.7	23.0			
Sex						
Male	50.4	38.5	23.0	<.001	<.001	.02
Female	49.6	61.5	77.0			
Education, y						
≤8	42.0	56.6	49.2			
9-11	43.8	32.9	37.7	<.001	.53	.54
≥12	14.2	10.5	13.1			
Urbanization, addresses/m^2						
<1000	42.6	29.1	24.6			
1000-2500	36.8	38.8	55.7	<.001	.006	.03
>2500	20.6	32.1	19.7			
Cardiac disease	18.6	25.8	21.3	<.001	.59	.46
Peripheral arteriosclerosis	8.7	15.1	18.0	<.001	.01	.55
Stroke	4.8	10.5	9.8	<.001	.08	.88
Diabetes mellitus	7.3	10.5	13.1	.03	.09	.53
Lung disease	10.3	19.6	18.0	<.001	.05	.77
Cancer	8.5	13.5	13.1	.002	.20	.93
Arthritis	33.0	45.9	42.6	<.001	.11	.63
Physical disability*						
No	63.7	29.6	47.5			
Moderate	18.7	20.9	24.6	<.001	.004	.03
Severe	17.6	49.5	27.9			
Physical activity†						
Low	16.6	39.7	27.8			
Moderate	47.9	43.1	38.9	<.001	.09	.02
High	35.5	17.2	33.3			
Smoking						
Nonsmoker	30.4	32.1	38.3			
Former smoker	45.5	36.1	30.0	.003	.06	.58
Current smoker	24.2	31.8	31.7			
Alcohol use‡						
No or moderate	96.1	96.4	95.1	.91	.69	.61
Excessive	3.9	3.6	4.9			
Body mass index, kg/m^2						
<20	2.2	3.9	6.7			
20-28	64.9	59.9	65.0	.09	.07	.38
>28	32.9	36.2	28.3			

**Moderate indicates 1 physical limitation; severe, 2 or more physical limitations.*

†Physical activity was measured by engagement in walking, bicycling, light and heavy household activities, gardening, and sports; low indicates 0 to 2 activities; moderate, 3 to 4 activities; and high, 5 to 6 activities.

‡Excessive alcohol use was considered to be 3 or more drinks per day.

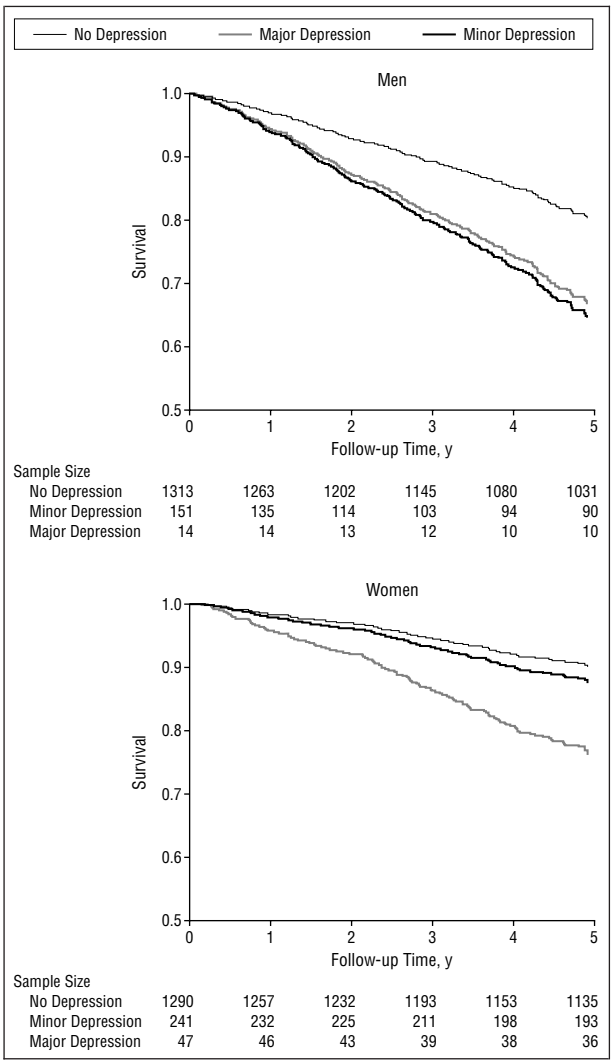
However, anxiety disorders were not significantly associated with mortality (adjusted risk, 1.04; 95% CI, 0.59-1.82), and adjustment for anxiety disorders did not influence the mortality risks for depression. In addition, we checked whether the results for minor depression could be caused by the 6 somatic items of the CES-D scale. After these items were deleted, minor depression (defined by a score ≥11 using the remaining 14 CES-D items) was even slightly more predictive of mortality in men (for sociodemographics and diseases, adjusted RR, 2.05; 95% CI, 1.53-2.74) and not in women (adjusted RR, 0.95; 95% CI, 0.66-1.37). Finally, to rule out possible interaction by sociodemographics or health status, product terms between depression and covariates were entered in the regression models. No interactions were found; effects of major and minor depression were similar across strata of age, education, urbanization, and disease status.

COMMENT

The present study provides evidence that minor depression among older men and major depression among older men and women increase the risk of dying during 50 months of follow-up. Major depression was defined according to diagnostic *DSM-III* criteria, whereas minor depression was defined as subthreshold depression including syndromes

Table 2. Association Between Minor and Major Depression and Mortality

	No.	Deaths	Person-Years	Rate per 1000 Person-Years	Relative Risk (95% Confidence Interval)	
					Unadjusted	Sex and Age Adjusted
Total population						
No depression	2603	437	11 060	39.5	1.0	1.0
Minor depression	392	109	1516	71.4	1.84 (1.49-2.27)	1.65 (1.33-2.04)
Major depression	61	15	247	60.7	1.55 (0.92-2.58)	2.32 (1.38-3.89)
Men						
No depression	1313	282	5472	51.5	1.0	1.0
Minor depression	151	61	524	116.4	2.30 (1.75-3.04)	2.02 (1.53-2.67)
Major depression	14	4	58	69.0	1.35 (0.50-3.58)	1.71 (0.63-4.58)
Women						
No depression	1290	155	5588	27.7	1.0	1.0
Minor depression	241	48	999	48.4	1.75 (1.26-2.42)	1.27 (0.92-1.76)
Major depression	47	11	189	58.2	2.10 (1.14-3.86)	2.57 (1.39-4.74)



Cumulative probability of survival for men (top) and women (bottom) according to depression status, adjusted for age. For men, when compared with no depression, survival probability was lower for major depression (mortality risk, 1.71; P = .29) and minor depression (mortality risk, 2.02; P < .001). For women, when compared with no depression, survival probability was lower for major depression (mortality risk, 2.57; P = .003), but not for minor depression (mortality risk, 1.27; P = .15).

such as dysphoria, dysthymia, and adjustment disorder. The mortality risks were statistically significant after adjustment for sociodemographics and health status. A small part of the mortality risk of depression was caused by health behaviors, mainly smoking and physical inactivity, which are more common in depressed than in nondepressed older persons. However, even after adjustment for these health behaviors, the detrimental effects of major depression (in general) and minor depression (in men only) remained significantly present.

In line with our findings, an increased mortality risk for major depression has been found consistently.[5-8] Minor depression was associated with mortality in some studies[9-11] but not in others.[12-16] These disparate findings may result from the different age ranges in earlier mortality studies. Gallo et al[35] suggested that minor depression may be expressed differently in the elderly, with more emphasis on hopelessness and despair and less on sadness. Consequently, our findings for minor depression may be specific to the older population. Another explanation for previous disparate findings is that many mortality studies did not differentiate the effects between men and women. In line with other studies,[7,10,17] our findings show that an increased mortality risk for minor depression was found in men but not in women. There might be some reasons for such a sex difference. First, women's physiological and behavioral reactions to stress may differ from those of men.[39] Second, men more often die because of cardiovascular disease than women do. Other study results[17,40] suggest that depression is a stronger risk factor for cardiovascular death than for other causes of death. Our findings support this suggestion for major depression but not for minor depression. Third, women and men may psychologically define events differently. Since major depression is defined by more rigorous clinical criteria, a sex difference in its conceptualization is less likely. However, for minor depression, Angst and Dobler-Mikola[41] found that men reported fewer depressive symptoms than women at the same degree of impairment of psychosocial functioning, thereby possibly causing an artifactual female preponderance. Also, effects of life events

Table 3. Relative Risks Relating Minor and Major Depression to Mortality After Successive Adjustment for Potential Confounders and Potential Explanatory Variables*

	Minor Depression		Major Depression, Men + Women (n = 3056)
	Men (n = 1478)	Women (n = 1578)	
Unadjusted	2.30 (1.75-3.04)	1.75 (1.26-2.42)	1.55 (0.92-2.58)
Adjustment for confounders			
Age	2.02 (1.53-2.67)	1.27 (0.92-1.76)	2.32 (1.38-3.89)
Education	1.94 (1.47-2.57)	1.26 (0.91-1.75)	2.26 (1.34-3.79)
Urbanization	1.91 (1.45-2.54)	1.23 (0.89-1.72)	2.16 (1.29-3.64)
Chronic diseases	1.80 (1.35-2.39)	1.11 (0.79-1.56)	1.83 (1.09-3.10)
Adjustment for explanatory variables			
Physical disability†	1.57 (1.17-2.10)	1.00 (0.71-1.41)	1.74 (1.03-2.93)
Smoking	1.53 (1.15-2.06)	0.96 (0.68-1.15)	1.74 (1.03-2.93)
Body mass index	1.52 (1.13-2.04)	0.94 (0.67-1.32)	1.71 (1.01-2.90)
Physical activity	1.45 (1.08-1.95)	0.92 (0.65-1.34)	1.68 (1.00-2.84)

**Data are given as relative risk (95% confidence interval).*
†*Physical disability may be a confounder as well as an explanatory variable.*

Table 4. Causes of Death Across Depression Status

	No. (%)			
Cause of Death	No Depression (n = 437)	Minor Depression (n = 109)	Major Depression (n = 15)	P*
Cardiovascular disease	136 (31.3)	32 (29.4)	7 (46.7)	.40
Stroke	42 (9.6)	10 (9.2)	1 (6.7)	.92
Diabetes	9 (2.1)	5 (4.6)	0 (0.0)	.26
Gastrointestinal tract disease	10 (2.2)	2 (1.8)	1 (6.7)	.51
Cancer	143 (32.7)	23 (21.1)	3 (20.0)	.04
Respiratory disease	34 (7.8)	19 (17.4)	2 (13.3)	.009
Accidents	5 (1.1)	1 (0.9)	0 (0.0)	.90
Suicide	2 (0.5)	1 (0.9)	0 (0.0)	.87
Other causes of death	56 (12.8)	16 (14.7)	1 (6.7)	.67

**By χ^2 test.*

and changing social networks on minor depression were found to be greater in older women than in older men.[42,43] For men, it has been suggested that minor depression partly represents a premonitory sign of subclinical disease.[17] Differing minor depression concepts in older women and men[44] might be responsible for the sex-differential effect of minor depression.

Our findings provide insight into the role of confounders and explanatory variables in the effect of depression on mortality. Adjustment for the fact that persons with minor depression are older, less educated, and more diseased and more often live in urbanized areas than nondepressed persons reduced the excess mortality risk for minor depression considerably. Persons with major depression, however, were younger and more often female than the nondepressed, which caused an increase in the mortality risk for major depression after adjustment for sociodemographics and health status. In addition, differences in health behavior between depressed (both major and minor) and nondepressed persons explained part of the excess mortality risk. Depressed persons were found to be substantially less physically active, were more often smokers, and more often had a lower BMI, which might partly reflect lack of appetite. Adjustment for these factors further decreased the mortality risk for depression.

Even after adjustment for health behaviors, minor depression in men and major depression in both men and women significantly increased the risk of dying. Therefore, other explanations should be considered as well. First, as shown in clinical populations, a direct consequence of (major) depression is suicide. However, as in other community-dwelling older samples,[8,17,45] suicide was rare in our study (only 3 cases) and did not explain the increased mortality risks for depression. Second, it has been hypothesized that depressed persons are less likely to comply with treatment recommendations,[46] which could have unfavorable health consequences. Third, depression itself may cause physiological changes that enhance susceptibility to disease and, consequently, lead to death. Depression has been found to adversely affect endocrine, neurologic, and immune processes by increasing the sympathetic tone, decreasing vagal tone, and causing immunosuppression.[47-49] Alternative explanations are that depression represents a reaction to subclinical disease that places subjects at greater risk for mortality, or that a third factor, related to both, causes the depression and mortality link.

The identification of major depression and minor depression as risk factors for mortality in old age is important. Earlier studies have shown that major and minor depression have a large range of unfavorable consequences: they affect well-being, physical function, morbidity, and utilization of services.[32-36,50-53] Our study adds mortality to this list and supports that the adverse health consequences of depression are very diverse. Depression is a potentially modifiable condition, but, unfortunately, it is often unrecognized and untreated in older persons.[54] The results of this study support ongoing efforts to achieve a more active policy regarding major as well as minor depression in late life.

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