Association Between Depressive Symptoms and Mortality in Older Women

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Background: Major depression is associated with increased mortality, but it is not known whether patients who report depressive symptoms have greater mortality.

Subjects and Methods: We performed a prospective cohort study of 7518 white women 67 years of age or older who were recruited from population-based listings in Baltimore, Md, Minneapolis, Minn, Portland, Ore, and the Monongahela Valley, Pa. Participants completed the Geriatric Depression Scale (short form) and were considered depressed if they reported 6 or more of 15 possible symptoms of depression. Women were followed up for an average of 6 years. If a participant died, we obtained a copy of the official death certificate and hospital records, if available, and used *International Classification of Diseases, Ninth Revision,* codes to classify death attributable to cardiovascular, cancer, or noncancer, noncardiovascular cause.

Results: Mortality during 7-year follow-up varied from 7% in women with no depressive symptoms to 17% in those with 3 to 5 symptoms to 24% in those with 6 or more symptoms of depression ($P<.001$). Of 473 women (6.3%) with 6 or more depressive symptoms at baseline, 24% died (111 deaths in 2610 woman-years of follow-up) compared with 11% of women who reported 5 or fewer symptoms of depression (760 deaths in 41 460 woman-years of follow-up) ($P<.001$). Women with 6 or more depressive symptoms had a 2-fold increased risk of death (age-adjusted hazard ratio [HR], 2.14; 95% confidence interval [CI], 1.75-2.61; $P<.001$) compared with those who had 5 or fewer depressive symptoms. This association remained strong after adjusting for potential confounding variables, including history of myocardial infarction, stroke, diabetes mellitus, hypertension, chronic obstructive pulmonary disease, smoking, perceived health, and cognitive function (HR, 1.47; 95% CI, 1.14-1.88; $P = .003$). Depressive symptoms were associated with an increased adjusted risk of death from cardiovascular diseases (HR, 1.8; 95% CI, 1.2-2.5; $P = .003$), and noncancer, noncardiovascular diseases (HR, 1.8; 95% CI, 1.2-2.7; $P = .01$), but were not associated with deaths from cancer (HR, 1.0; 95% CI, 0.6-1.7; $P = .93$).

Conclusions: Depressive symptoms are a significant risk factor for cardiovascular and noncancer, noncardiovascular mortality but not cancer mortality in older women. Whether depressive symptoms are a marker for, or a cause of, life-threatening conditions remains to be determined.

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MANY STUDIES[1-13] have found that clinically diagnosed major depression is associated with increased mortality, but it is unclear whether depressive symptoms, such as those recognized in a routine office visit or on a simple screening instrument, predict mortality. Prior studies[14-20] have found that depressive symptoms are associated with poor health and functional status, as well as increased disability, health care utilization, and cost of health services. However, results have been inconsistent regarding a possible association between depressive symptoms and mortality.

Two large studies[21,22] found no association between baseline depressive symptoms and subsequent mortality, but 2 others[23,24] reported greater mortality in patients with depressive symptoms. Of these 2 studies, one[23] was limited to patients with preexisting coronary artery disease and the other[24] did not control for comorbid illnesses. Neither examined mortality from causes other than ischemic heart disease.

We measured depressive symptoms in a cohort of older women and followed them up for an average of 6 years. We examined the association between depressive symptoms and mortality from specific causes such as coronary heart disease, cerebrovascular disease, congestive heart failure, cancer, and chronic obstructive pulmonary disease.

SUBJECTS AND METHODS

SUBJECTS

A total of 9704 ambulatory women at least 65 years of age were recruited from population-based listings in Baltimore, Md, Minneapolis, Minn, Portland, Ore, and the Monongahela Valley, Pa, between 1986 and 1988 for the Study of Osteoporotic Fractures, a prospective cohort study designed to determine risk factors for osteoporotic fractures. At a second visit (1988-1990), 7518 of these women (80% of survivors) completed at least 10 of 15 items on the Geriatric Depression Scale. These 7518 women are the subjects of this secondary data analysis. The study was approved by the appropriate institutional review boards, and all subjects provided written informed consent.

MEASUREMENTS

Depressive Symptoms

At the second visit (1988-1990), we administered the Geriatric Depression Scale short form, a validated, reliable, 15-item, self-report, depressive symptoms checklist designed to detect the presence of current depression in the elderly.[25] Using a cutoff point of 6 or more symptoms, the Geriatric Depression Scale short form has a sensitivity of 88% and specificity of 62% compared with a structured clinical interview for depression.[26] We defined depression as 6 or more symptoms, with 6 to 7 symptoms indicating mild depression, 8 to 10 symptoms indicating moderate depression, and 11 or more symptoms indicating severe depression.[27] For participants who failed to complete all 15 items, we calculated the total number of depressive symptoms by dividing the reported number of symptoms by the proportion of items completed. To determine the effect of persistent depressive symptoms on subsequent mortality, we also administered the same instrument 4 years later (1992-1994) to 5837 of the original 7518 women (83% of survivors).

Other Measurements

Self-reported age, marital status, education, medical history, current perceived health status (excellent/good vs fair/poor/very poor), smoking, alcohol, and use of benzodiazepine, barbiturates, thiazide diuretics, and estrogen were determined from a questionnaire administered at the first visit and reviewed by an interviewer. Systolic and diastolic blood pressures were measured at the right brachial artery using a standard protocol.[28] Hypertension was defined as systolic blood pressure higher than 160 mm Hg, diastolic blood pressures higher than 90 mm Hg, or use of a thiazide diuretic. We measured social network by scoring answers to 11 questions regarding contact with spouse, relatives, and friends, then adding scores for the individual questions to create a total social network score. Higher scores indicate better social network.

Physical activity was estimated using a modified Paffenbarger scale that assesses the type and duration of weight-bearing activities in a variety of settings.[29] Participants were asked about the frequency with which they performed each of 40 activities at 4 time points during their lives (teenager, age 30 years, age 50 years, and previous year). For each of the 4 time points, the number of times per year each activity was performed was multiplied by 5.0 for low-intensity (eg, walking or gardening), 7.5 for medium-intensity (eg, dancing or tennis), or 10.0 for high-intensity activities (eg, jogging or skiing). Scores for these 4 time points were added to calculate lifetime physical activity.

At the second visit, weight was measured (in light indoor clothing with shoes removed) using a balance beam scale, and height was measured using a stadiometer.[30] Body mass index was calculated as weight in kilograms divided by the square of the height in meters. Cognitive function was measured by a trained examiner using Digit Symbol, a subtest of the Wechsler Adult Intelligence Scale.[31] Scores on Digit Symbol reflect the number correct within the timed trial; thus, lower scores indicate poorer performance.

RESULTS

The prevalence of depression (defined as a score ≥6 on the Geriatric Depression Scale short form) was 6.3% (473/7518). Compared with those who had 5 or fewer symptoms of depression, women with 6 or more symptoms were older and more likely to smoke or to report fair or poor health. They had a higher frequency of medical illnesses, worse functional status, and worse cognitive function. They were less likely to be married, well-educated, or physically active (**Table 1**). Follow-up was complete in 7406 women (99%) who completed the depression scale. Of the 112 women lost to follow-up, 5.4% had 6 or more depressive symptoms. Mortality varied from 7% in women with no depressive symptoms to 17% in those with 3 to 5 symptoms to 24% in those with 6 or more symptoms of depression ($P<.001$ for trend) (**Figure 1**).

Deaths occurred in 24% of women with 6 or more depressive symptoms (111 deaths in 2610 woman-years of follow-up) and 11% of women with 5 or fewer depressive symptoms (760 deaths in 41 460 woman-years of follow-up) ($P<.001$). Participants who subsequently died had a mean (±SD) depression score of 2.6 ± 2.7, compared with 1.6 ± 2.1 in participants who were alive at follow-up ($P<.001$).

Women with 6 or more depressive symptoms had a 2-fold increased risk of death (age-adjusted HR, 2.14; 95% CI, 1.75-2.61; $P<.001$) compared with those who had 5 or fewer symptoms. This association remained strong after adjusting for potential confounding variables (HR, 1.47; 95% CI, 1.14-1.88; $P = .003$) (**Table 2**). Each 1-symptom increase in number of depressive symptoms was associated with a 6% increase in all-cause mortality (HR, 1.06; 95% CI, 1.03-1.10; $P<.001$), adjusting for history of myocardial infarction, stroke, chronic obstructive pulmonary disease, diabetes mellitus, hypertension, smoking, perceived health, and cognitive function.

Of 473 women who had 6 or more depressive symptoms in 1988-1990, 297 completed the Geriatric Depression Scale short form again 4 years later, and 159 (53.5%)

Functional Status

To determine whether impaired functional status is an antecedent of depressive symptoms (ie, potential cause of both depression and mortality that should be adjusted for in the primary analysis) or an effect of depressive symptoms (ie, potential mechanism linking depressive symptoms and mortality that should not be adjusted for in the primary analysis), we measured functional status and depressive symptoms at 2 time points: at the 1988-1990 visit and again 4 years later.

Functional status was measured on a 39-point scale with up to 3 points (some difficulty, much difficulty, or unable to do) for each of 13 activities (eg, dressing, bathing, preparing meals, doing housework, shopping, or walking 2 or 3 blocks) based on a modified version of the Stanford Health Assessment Questionnaire.[32] We defined impaired functional status as a score of 14 or more because this number required that the respondent report much difficulty with at least 1 of the 13 activities.

To ascertain whether impaired functional status precedes the development of depressive symptoms, we first excluded women who had 6 or more depressive symptoms in 1988-1990, and then measured the incidence of depression (defined as a score ≥6 on the Geriatric Depression Scale in 1992-1994), comparing women who had impaired functional status in 1988-1990 with those who had normal functional status at that time. To ascertain whether impaired functional status is an effect of depressive symptoms, we first excluded women who had impaired functional status in 1988-1990, and then measured the incidence of impaired functional status (score ≥14) in the ensuing 4 years, comparing women who had 6 or more depressive symptoms in 1988-1990 with those who had 5 or fewer symptoms at that time.

Mortality

Mortality was ascertained for an average of 6 years (range, up to 7 years) following the initial depression measure. If a participant died, we obtained a copy of the official death certificate and hospital records, if available; the cause of death was assigned by one of us (W.S.B.) who was unaware of results from the Geriatric Depression Scale or other predictor measurements. We used *International Classification of Diseases, Ninth Revision* codes[33] to classify death due to cardiovascular (codes 394-402, 410-414, 424-444, and 798), cancer (codes 141-238 and 259), or noncancer, noncardiovascular cause. We specifically identified deaths from coronary heart disease (codes 410-414 and 429), cerebrovascular disease (codes 430-438), congestive heart failure (code 425), sudden death (code 798), lung cancer (codes 162-163), breast cancer (code 174), colon cancer (codes 153-154), chronic obstructive pulmonary disease (codes 491-496), pneumonia (code 486), accidents and trauma (codes 800-805, 852-994, and E812-E890), and natural causes (code 799.9). Three women who died from suicide were excluded from all analyses.

STATISTICAL ANALYSIS

Differences in baseline characteristics between women with and without depression were compared using χ^2 tests for dichotomous variables and *t* tests for continuous variables. The association between depressive symptoms and mortality was analyzed using proportional hazards models. We used forward stepwise proportional hazards regression to obtain adjusted risk estimates, adding those variables associated with mortality (at $P<.05$) to multivariate models that included depression. We verified the proportionality assumption of these models. The association between depressive symptoms and functional status was analyzed using logistic regression. For all analyses, we report the hazard ratio (HR) or odds ratio (OR) with 95% confidence intervals (CIs). Survival curves were estimated using an adjusted Cox proportional hazards model.[34] Analyses were performed with the use of SAS statistical software (SAS Institute Inc, Cary, NC).

of 297 had persistent depressive symptoms. Death occurred in 11.3% of women with 6 or more depressive symptoms at both time points (18 deaths in 971 woman-years of follow-up) and 4.3% of women with 5 or fewer depressive symptoms at both time points (223 deaths in 32 232 woman-years of follow-up) ($P<.001$). Women with persistent depressive symptoms had a 2.5-fold increased risk of death (age-adjusted HR, 2.53; 95% CI, 1.56-4.09; $P<.001$) compared with those who reported 5 or fewer symptoms at both time points, an association that persisted but did not remain statistically significant after adjusting for the variables listed in Table 2 (HR, 1.63; 95% CI, 0.86-3.07; $P = .13$).

We found that depressive symptoms are both a cause and an effect of impaired functional status. Among the 7045 participants who had 5 or fewer depressive symptoms in 1988-1990, those with impaired functional status (n = 172) had a mean (± SD) depression score of 3.5 ± 2.8 at follow-up compared with 1.6 ± 1.9 in women with normal functional status ($P<.001$); women with impaired functional status were more likely to develop depressive symptoms than those with normal functional status (24% vs 5%; OR, 5.4; 95% CI, 3.3-8.5; $P<.001$). Among the 7277 participants who had normal functional status in 1988-1990, women with 6 or more depressive symptoms had a mean (± SD) functional status score of 5.2 ± 6.1 at follow-up, compared with 2.1 ± 4.3 in women with 5 or fewer depressive symptoms ($P<.001$); those with 6 or more depressive symptoms were more likely to develop impaired functional status than those with 5 or fewer symptoms of depression (11% vs 3%; OR, 3.6; 95% CI, 2.4-5.3; $P<.001$). When added to the model in Table 2, adjustment for functional status (as a continuous variable) appeared to attenuate but not eliminate the association between depressive symptoms and mortality (HR, 1.31; 95% CI, 1.02-1.69; $P = .03$).

Mortality rates in women with and without depression did not appear to diverge until approximately 16 months of follow-up (**Figure 2**). In models adjusted for the variables listed in Table 2, women with depressive symptoms had an 80% increased risk of cardiovascular death and an 80% increased risk of noncancer,

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noncardiovascular death, including a 3-fold increased risk of death from chronic obstructive pulmonary disease, but no increased risk of death from cancer (**Table 3**).

COMMENT

Elderly women with 6 or more depressive symptoms had a 47% increased adjusted risk of all-cause mortality, including an 80% increased risk of dying of cardiovascular disease and noncancer, noncardiovascular disease, compared with women who reported 5 or fewer symptoms of depression. This increased risk is similar to that conferred by other cardiovascular risk factors, such as hypertension, cigarette smoking, hyperlipidemia, obesity, and diabetes.[35] Mortality increased with number of depressive symptoms, suggesting a dose-response relationship. Increased mortality in women with depression compared with women without depression did not occur until approximately 16 months of follow-up, indicating that depression is not simply a result of life-threatening conditions.

Table 1. Characteristics of Participants*

Variable	With Depression	Without Depression	*P*
Mean ± SD age, y	72.4 ± 5.3	71.3 ± 5.1	<.001
Married	40	51	<.001
Live alone	49	40	<.001
Mean ± SD education, y	11.8 ± 2.9	12.7 ± 2.8	<.001
Previous myocardial infarction	15	6	<.001
Previous stroke	4	3	.03
Chronic obstructive pulmonary disease	18	9	<.001
Diabetes mellitus	13	6	<.001
Hypertension	47	37	<.001
Current smoking	15	9	<.001
Current drinks per week	1.6 ± 3.8	1.9 ± 4.0	.08
Lifetime physical activity, weighted No. of times per year	3395 ± 2976	4383 ± 3345	<.001
Social network score	2.7 ± 0.7	3.2 ± 0.7	<.001
Current estrogen use	16	14	.48
Use of benzodiazepine in past 12 mo	32	14	<.001
Use of barbiturate in past 12 mo	3	1	.05
Fair/poor health	44	13	<.001
Body mass index, kg/m^2	27.0 ± 5.3	26.2 ± 4.6	<.001
Digit Symbol, No. correct	37.1 ± 11.6	43.9 ± 11.4	<.001
Impaired functional status	14	2	<.001

**N = 7518. Values are percentages, unless otherwise indicated.*

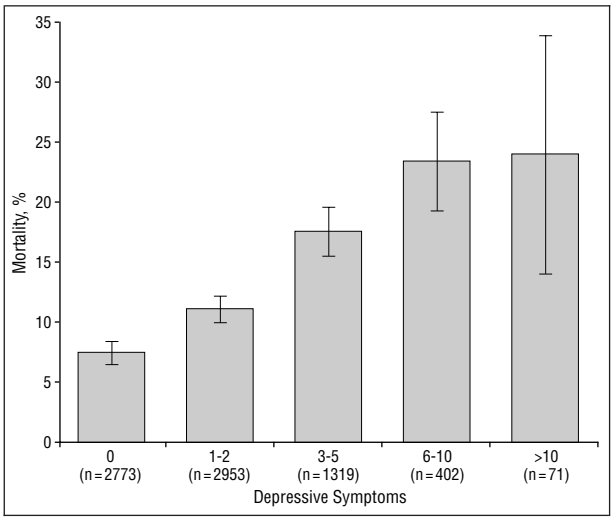

Figure 1. *Mortality during 7-year follow-up by number of depressive symptoms in 7518 elderly women. Bars represent 95% confidence intervals. P<.001 for trend.*

Why would women with depressive symptoms have increased mortality, and in particular increased cardiovascular mortality? Several possible mechanisms have been suggested. Electrocardiographic evidence of myocardial ischemia during daily life has been demonstrated in the hour following high levels of sadness, suggesting that myocardial ischemia may be a direct result of depressed mood.[36] Depression has been identified as a predictor of hypertension,[37] autonomic dysfunction as measured by higher plasma levels of norepinephrine and reduced heart rate variability,[38-45]

Table 2. Age-Adjusted Multivariate Hazard Model of Predictors of Mortality in 6176 Elderly Women*

Predictors of Mortality	Hazard Ratio (95% CI)	*P*
Depression†	1.47 (1.14-1.88)	.003
History of myocardial infarction	1.76 (1.41-2.20)	<.001
History of stroke	1.63 (1.18-2.27)	.003
Chronic obstructive pulmonary disease	1.61 (1.30-1.98)	<.001
Hypertension	1.29 (1.11-1.51)	.001
Diabetes mellitus	1.53 (1.20-1.96)	<.001
Current smoking	1.96 (1.57-2.45)	<.001
Fair/poor self-perceived health	1.32 (1.09-1.60)	.005
Better cognitive function (per 11-item increase on Digit Symbol)	0.81 (0.74-0.88)	<.001

**CI indicates confidence interval.*

†Further adjustment for marital status, living status, education, alcohol use, physical activity, social support, use of estrogen, benzodiazepine, and barbiturates, and body mass index (a measure of weight in kilograms divided by the square of the height in meters) did not affect this association.

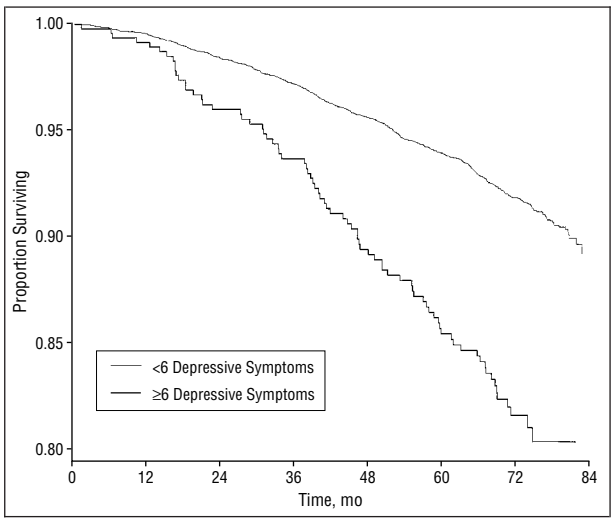

Figure 2. *Survival during 7-year follow-up in 6176 elderly women (adjusted for variables in Table 2).*

increased platelet reactivity,[46-48] and cardiovascular events including myocardial infarction.[6,11,22,24,49] Use of psychotropic medications, such as antidepressants, barbiturates, phenothiazines, and lithium, have been associated with mortality, although most likely as markers of depression rather than links in the pathway between depression and mortality.[11,50]

We did not measure hyperlipidemia as a potential risk factor for cardiovascular mortality among women with depressive symptoms, but it is unlikely that hyperlipidemia would explain the association between depressive symptoms and mortality because depression is probably associated with low rather than high cholesterol levels.[51-53] Patients with depression are less likely than patients without depression to adhere to prescribed exercise therapy,[54,55] and lack of exercise has been associated with poor health outcomes.[29,56,57] Our analysis adjusted for self-reported physical activity, but subsequent lack of exercise might have explained the association between depression and mortality.

Table 3. Relative Mortality From Specific Causes in Women With Depression Compared With Women Without Depression*

Cause (No. Deceased)†	Hazard Ratio (95% CI)‡	*P*
All cardiovascular disease (52, 273)	1.8 (1.2-2.5)	.003
Coronary heart disease (20,107)	1.7 (1.0-3.0)	.06
Cerebrovascular disease (15, 79)	1.7 (0.8-3.5)	.16
Congestive heart failure (6, 30)	3.2 (1.3-8.0)	.01
Sudden death (1, 17)	1.0 (0.1-8.0)	.98
Other cardiovascular disease (10, 40)	3.2 (1.1-9.0)	.03
All cancer (24, 271)	1.0 (0.6-1.7)	.93
Lung (6, 67)	0.9 (0.3-2.4)	.81
Breast (3, 27)	1.4 (0.3-5.8)	.68
Colon (0, 29)	. . .	.99
Other (15, 148)	1.3 (0.7-2.4)	.48
Noncardiovascular, noncancer conditions (35, 216)	1.8 (1.2-2.7)	.01
Chronic obstructive pulmonary disease (8, 23)	3.4 (1.4-8.5)	.01
Pneumonia (2, 16)	1.9 (0.4-8.4)	.41
Accidents and trauma (4, 11)	6.3 (1.7-23.8)	.01
Natural causes (8, 59)	2.0 (0.8-4.8)	.12
Other conditions (13, 107)	1.1 (0.5-2.3)	.83

**CI indicates confidence interval; ellipses, not applicable.*

†Numbers of deaths in women with, without depression.

‡Adjusted for age, history of myocardial infarction, stroke, chronic obstructive pulmonary disease, hypertension, diabetes, smoking, perceived health, and cognitive function.

Decreased compliance with medications[58] and lack of social support among patients with depressive symptoms also may contribute to the association between depressive symptoms and mortality.[59-61]

Another potential explanation is that the association between depressive symptoms and mortality may be partially confounded by impaired functional status. Our findings suggest that impaired functional status is both a cause and an effect of depression. To avoid overadjusting for the effects of depression in our primary analysis, we adjusted for impaired functional status in a separate analysis and found that the association between depressive symptoms and mortality was somewhat attenuated. We cannot determine whether this occurred because impaired functional status was a cause of depressive symptoms or a result of depressive symptoms that subsequently led to increased mortality.

Depressive symptoms could be a marker of other illnesses that are associated with increased mortality. If a greater prevalence of other illnesses explained the association between depressive symptoms and mortality, however, we would expect that mortality rates would diverge before 16 months of follow-up and that depressive symptoms also would be associated with increased cancer mortality. Prior studies[62-64] have yielded conflicting results regarding the possibility that stressful life events and depression contribute to the onset and progression of cancer, particularly breast cancer. We found no increased risk of subsequent death from cancer among women with depressive symptoms.

Our findings differ from those of 2 prior studies[21,22] that found no association between baseline depressive

symptoms and subsequent mortality. One study[21] enrolled members of a health maintenance organization who were younger than the participants in this study. The other[22] enrolled patients with hypertension and found that, although baseline depressive symptoms were not associated with mortality, an increase in number of depressive symptoms over time was associated with increased mortality, including fatal stroke and fatal myocardial infarction.

Several limitations deserve comment. First, only 80% of survivors from the initial cohort completed the depression measure; women included in this analysis may have been less depressed than those who did not complete the depression measure. Second, although we measured many potential confounding variables, the association between depressive symptoms and mortality may be influenced by unmeasured variables, such as use of antidepressant medications or chronic medical illnesses that were not identified by self-report. Third, we measured depressive symptoms rather than performing a clinical interview for depression; thus, we must conclude that depressive symptoms, and not necessarily the diagnosis of depression, are associated with increased mortality. Fourth, cause of death may be misclassified due to the potential inaccuracies of death certificates. Finally, we studied only elderly white women, whose characteristics may differ from those of other populations.

CONCLUSIONS

Depression is a common and readily treatable condition among older adults, but few receive appropriate treatment.[65] Depressive symptoms are associated with increased cardiovascular and noncancer, noncardiovascular mortality in older women. Although the effect of treatment for depressive symptoms on mortality remains to be determined, these findings suggest that treatment for depression may not only enhance quality of life but also reduce mortality among women with depressive symptoms. We should redouble our efforts to improve detection and treatment of depression.

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