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Depressive Symptoms and Mortality among Persons with and without Diabetes

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Although people with diabetes mellitus have a high risk of depression and depression may increase mortality among people with other conditions, the impact of depression on mortality risk among people with diabetes needs further examination. Using survival analysis, the authors analyzed longitudinal data from the NHANES I Epidemiologic Follow-up Study (1982–1992). The findings showed that the presence of severe depressive symptoms significantly elevated mortality risk among US adults with diabetes; the same pattern was not observed among people without diabetes. After results were controlled for sociodemographic, lifestyle, and health-status variables, diabetic persons with Centers for Epidemiologic Studies Depression (CES-D) Scale scores of 16 or more had 54% greater mortality than those with scores under 16 ($p = 0.004$). After exclusion of participants who died during the first year of follow-up, mortality remained higher among those with CES-D scores greater than or equal to 22 as compared with those with CES-D scores less than 16, but not among those with CES-D scores between 16 and 21. No significant relation between depression and mortality was found in the nondiabetic population. This analysis indicates that diabetes modifies the effect of depression on mortality. It also demonstrates the importance of observing subgroups, rather than aggregated populations, when examining the effect of depression on mortality.

depression; diabetes mellitus; mortality

Abbreviations: CES-D, Centers for Epidemiologic Studies Depression [Scale]; NHANES I, First National Health and Nutrition Examination Survey; NHEFS, NHANES I Epidemiologic Follow-up Study.

The prevalence of diabetes mellitus in the United States has increased rapidly in recent years, with a 49 percent increase in diagnosed diabetes being observed between 1990 and 2000 (1). During 2002, it was estimated that 18.2 million Americans had the disease—13.0 million diagnosed and 5.2 million undiagnosed (2). Diabetes is a leading cause of death in the United States. During 2000, the disease accounted directly for 69,301 deaths and contributed to 213,062 deaths among persons aged 25 years or older (1). Diabetes is also a major cause of loss of quality-adjusted life years, largely because of vascular complications (3).

Diabetes is associated with depression and depressive symptoms, but the strength and causal direction of these associations are unclear (4–10). In two recent studies that used data from the First National Health and Nutrition Examination Survey (NHANES I) but utilized different instruments to measure depressive symptoms, investigators came to different conclusions about the role of depression as a cause of diabetes mellitus (11, 12). Saydah et al. (12), using the Centers for Epidemiologic Studies Depression (CES-D) Scale, found no evidence to support an etiologic relation between depression and diabetes. Conversely, Carnethon et al. (11), using the General Well-Being Depression subscale, found that if social factors such as educational attainment are taken into account, depressive symptoms predict an increased incidence of diabetes among

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people with less than a high school education. Depression has also been found to affect glycemic control and both macrovascular and microvascular complications (13–20), but it is unclear whether there is a reverse causal relation (i.e., whether diabetes causes depression) (7, 21, 22). In a review, Talbot and Nouwen (21) stated that there is no solid evidence that the initial occurrence of clinically significant depression results either from biochemical changes directly attributable to type 2 diabetes or its treatment or from the psychosocial demands imposed by the illness or its treatment.

A similar ambiguity exists with regard to the relation between depression and mortality. As many studies report that depression is associated with increased mortality in general populations, especially among older adults (21, 23–27), as indicate no such relation (28–33). In a systematic review of the relation between depression and mortality, Wulsin et al. (34) identified 57 studies carried out between 1966 and 1996, of which 29 demonstrated positive results, 13 negative results, and 15 mixed results. Further examination (35–42) revealed that a relation may exist between depression and excess mortality only when subjects have certain illnesses—such as coronary artery disease (42), myocardial infarction (35, 36, 40), stroke (38, 41), congestive heart failure (39), or ischemic heart disease (37)—or when subjects have a disadvantaged social position with low income or less education or are socially isolated (43–45). However, we have not identified any study that directly compares the depression-associated mortality rates of populations with and without medical conditions at baseline.

In this study, we examined the association between depression and diabetes by studying the relation between depressive symptoms and mortality among people with diabetes. We used a nondiabetic population as a comparator to determine whether depressive symptoms played the same role in mortality among persons with and without diabetes while controlling for sociodemographic, lifestyle, and health-status variables.

MATERIALS AND METHODS

This study used data from the NHANES I Epidemiologic Follow-up Study (NHEFS). The NHEFS is a follow-up study of adults who participated in NHANES I, which was conducted from 1971 to 1975. NHANES I included four follow-up surveys; the first one was conducted between 1982 and 1984, the second one in 1986, the third one between 1987 and 1989, and the last one between 1990 and 1992. The NHEFS study population was drawn from a probability sample of noninstitutionalized civilian US adults aged 25–74 years (n = 14,407). In the NHEFS, the vital status of 93 percent of the original NHANES I sample was traced through 1992.

This study included the subgroup of NHEFS adult participants who had baseline diabetes status and depressive symptoms assessed in 1982–1984 at age $\geq$32 years (n = 9,990). The vital status of these participants was ascertained for the period 1982–1992. Because data from the physical examination conducted at baseline did not provide adequate information by which diabetes could be identified (i.e., plasma glucose level, fasting plasma glucose level, or results of oral glucose tolerance testing), diabetes was assessed by self-report, with information derived from two survey questions: ''Did a doctor ever tell you that you had diabetes or sugar diabetes?'' and ''Are you now taking medicine for this condition (diabetes)?'' In total, 714 (7.1 percent) persons with diabetes and 9,276 persons without diabetes were identified. Using information from each follow-up survey question on the subject's vital status, we identified 229 deceased cases in the diabetic population and 1,614 deceased cases in the nondiabetic population. This vital status information was based on death certificates (98.7 percent of death cases) and proxies' reports (1.3 percent of death cases). Because of missing or incomplete information on date of loss to follow-up and CES-D scores, 156 participants with diabetes and 2,213 participants without diabetes were excluded from our analysis. Thus, the analyzed diabetic population was reduced to 558 (276 deaths, 282 survivors), and the analyzed nondiabetic population was reduced to 7,063 (1,499 deaths, 5,564 survivors).

Survival time, or the amount of time that elapsed from the date of the 1982–1984 interview to the date of death or censoring, was the outcome variable in our survival analysis. Survival time (in weeks) was defined in terms of the following variables: 1) date of interview in the 1982–1984 follow-up survey, 2) date of later follow-up interview, and 3) date of loss to follow-up or date on which the subject was last known to be alive as reported by a proxy (date of censoring). Survival time was calculated as the date of death or censoring minus the date of interview in the 1982 survey.

Independent variables evaluated included depressive symptom score, demographic characteristics, lifestyle, and health status. The first group of variables constituted the explanatory variables of primary interest, and the other groups of variables were potential confounders.

We assessed depressive symptoms using the CES-D questionnaire, which consists of 20 descriptive statements of depressed mood; feelings of worthlessness, hopelessness, and loneliness; loss of appetite; sleep disturbances; concentration problems; and psychomotor retardation. Although in previous studies a score of $\geq$16 was defined as clinical depression (46) and a score of <16 was defined as ''not depressed'' (47), we treated the cutoff score not as diagnosed depression but as an indicator of risk for clinically significant impairment. We also categorized persons as having either moderate (scores of 16–21) or severe (scores >21) depressive symptoms. The CES-D questionnaire is reliable and valid (48), with high sensitivity and adequate specificity as a screening instrument for depression (49). Scoring for the four positively worded items was reversed in this study. Consequently, the 20 items, which were scored on a standard four-point scale from 0 to 3, had a potential range of 0–60, with the higher scores representing responses in the depressed range. Only persons who answered all 20 items on the questionnaire were included in our primary analysis (50, 51).

We controlled for age, gender, race, marital status, residential area (rural vs. urban), education, work status, and income, since there are known correlations between

mortality and these sociodemographic variables (52–55). We also included five lifestyle variables as control factors, since they are known to be associated with mortality (56, 57): ever having smoked at least 100 cigarettes, current smoking, alcohol consumption (number of drinks per day), currently being on a diet for weight loss, and physical activity level (on a three-point scale: quite inactive (1 point), moderately active (2 points), or very active (3 points)). Because health status has been found to be a good predictor of mortality (58, 59), we also adjusted for eight health-status variables: self-rated health; body mass index (weight (kg)/height $(m)^2$); a history of cancer, hypertension, heart attack, or stroke; blindness; and current use of antidepressants.

The analyses were conducted in three steps. First, using survival analysis, we examined the individual effects of explanatory and control variables on mortality. Variables that were significantly related to mortality in either diabetic or nondiabetic subgroups were used in our final model. Second, using survival analysis and the Cox proportional hazards model, we examined the association between depressive symptoms—as measured by the CES-D Scale—and mortality while controlling for physical health-status variables. We categorized CES-D results in two different ways. First, participants were stratified by CES-D score: <16 vs. ≥ 16. Second, participants were stratified into three groups based on their CES-D scores: <16 (group 1), 16–21 (group 2), and ≥ 22 (group 3). Finally, in order to examine the possibility that the relation between depressive symptoms and mortality was explained by concurrent terminal illness, severe disease, or severe depression, we conducted a sensitivity analysis to examine differences among subjects after excluding participants who died within the first year of follow-up. We also compared mortality among participants who answered all 20 items on the questionnaire with mortality among participants who answered at least 17 items. We performed these analyses using the SPSS statistical software package (version 9.0 for Windows (60)).

RESULTS

Baseline descriptive data for the outcome variable and its covariates are presented in table 1, along with the differences found between the diabetic and nondiabetic population groups. Within the diabetic and nondiabetic populations, we observed no significant differences in sociodemographic characteristics, CES-D scores, lifestyle variables, or physical health-status variables between the total original sample and the subgroup of respondents who had both adequate CES-D scores and acceptable dates of death or loss to follow-up (statistics for the total original sample are not shown here). With 276 deaths and 282 presumed survivors in the diabetic subgroup (49.5 percent cumulative mortality) and 1,499 deaths and 5,564 survivors in the nondiabetic subgroup (21.2 percent cumulative mortality), during the period 1982–1992, the average survival time was 7 years in the diabetic population and 8.5 years in the nondiabetic population. The prevalence of CES-D scores greater than or equal to 16 in the diabetic cohort was 26.3 percent (age-adjusted: 25.9 percent), and the prevalence in the nondiabetic cohort was 15.8 percent (age-adjusted: 16.2 percent),

In the cohort of 7,621 adults who were included in our primary analysis, nondiabetic participants, as compared with diabetic participants, were younger (mean age = 56.8 years vs. 64.2 years); were more likely to be White (86.8 percent vs. 76.3 percent), married (68.7 percent vs. 57.4 percent), highly educated (11.4 years of schooling vs. 9.6 years), and employed (17.2 percent vs. 9.9 percent); and had higher incomes (mean score on a six-point income scale (see table footnotes): 4.0 vs. 3.1). The nondiabetic cohort was also healthier than the diabetic cohort on the basis of self-reported better health (mean score on a five-point Likert scale: 2.5 vs. 3.6) and lower body weight (body mass index: 25.3 vs. 29.8); were less likely to have a history of cancer (4.4 percent vs. 5.6 percent), hypertension (35.1 percent vs. 64.3 percent), heart attack (5.1 percent vs. 15.4 percent), or stroke (1.0 percent vs. 5.0 percent); were less likely to have blindness (1.4 percent vs. 3.6 percent); and were less likely to currently use antidepressants (2.3 percent vs. 3.6 percent). In addition, the nondiabetic cohort, as compared with the diabetic cohort, was more likely to have smoked at least 100 cigarettes (54.4 percent vs. 49.5 percent), to smoke currently (27.3 percent vs. 19.5 percent), and to consume more alcohol (mean number of drinks per day: 1.4 vs. 0.8) and was less likely to be dieting for weight loss (4.6 percent vs. 24.7 percent). Finally, the nondiabetic cohort, in comparison with the diabetic cohort, was more physically active (mean physical activity scale score: 2.1 vs. 1.8).

Figures 1 and 2 show the unadjusted survival functions stratified by CES-D scores. These functions demonstrate the expected positive relation between depression and mortality—that is, the group with lower CES-D scores had longer survival. The two survival functions in each figure are parallel, suggesting that depression satisfies the proportional hazards assumption. However, although the survival functions were significantly separated from each other in the diabetic cohort, they were not so in the nondiabetic cohort.

Before constructing our final model of survival analysis, we identified the following independent variables that were not significantly related to mortality ($\alpha = 0.05$) when entered individually into the model: rural residence, current smoking, alcohol consumption per day, and current use of antidepressants. Using an identical model, we examined depression-associated mortality among people with and without diabetes after excluding the insignificant variables identified above (table 2). When results were controlled for sociodemographic, lifestyle, and health-status variables, depression played a significant role in mortality risk among people with diabetes. Compared with respondents with CES-D scores less than 16, respondents with scores of 16 or higher had death hazards that were increased by 54 percent ($p = 0.004$). Although depression slightly increased hazard ratios among people without diabetes, the relation was not statistically significant ($p = 0.67$). Increased levels of physical activity and health status significantly reduced mortality rates in both population groups. Income significantly decreased mortality risk among people without diabetes but not among people with diabetes.

TABLE 1. Baseline characteristics of participants included in the survival analysis, NHANES I* Epidemiologic Follow-up Study, 1982–1992

Variable	Original study participants (n = 9,990; 714 diabetic, 9,276 nondiabetic)	
	Diabetic population with CES-D* score and date of survival (n = 558; 276 deaths, 282 survivors)	Nondiabetic population with CES-D score and date of survival (n = 7,063; 1,499 deaths, 5,564 survivors)
Dependent variable		
Mean survival time (weeks)	366.2 (160.2)†	440.3 (114.0)‡
Independent variables		
Mean CES-D score	11.5 (9.7)	8.3 (8.3)‡
Category of CES-D score (%)		
0–15	73.7	84.2‡
16–21	10.9	8.5
≥22	15.4	7.3‡
≥16	26.3	15.8‡
Demographic and socioeconomic characteristics		
Mean age (years)	64.2 (12.6)	56.8 (14.8)‡
Female gender (%)	61.3	63.5
White race (%)	76.3	86.8‡
Married (%)	57.4	68.7‡
Rural residence (%)	39.8	38.8
Mean amount of education (years)	9.6 (3.7)	11.4 (3.5)‡
Currently employed (%)	9.9	17.2‡
Mean annual income§	3.1 (1.8)	4.0 (1.8)‡
Lifestyle variables		
Ever smoking ≥100 cigarettes (%)	49.5	54.4‡
Current smoking (%)	19.5	27.3‡
Mean alcohol consumption (drinks/day)	0.8 (1.5)	1.4 (1.9)
Currently being on a weight-loss diet (%)	24.7	4.6‡
Physical activity level (%)		
Quite inactive (1 point)	32.8	16.5‡
Moderately active (2 points)	53.8	56.3
Very active (3 points)	13.4	27.2‡
Health-status variables		
Self-rated health (%)		
Excellent (1 point)	3.8	22.6‡
Very good (2 points)	11.6	28.2‡
Good (3 points)	29.7	28.8
Fair (4 points)	33.2	14.7‡
Poor (5 points)	21.7	5.7‡
Mean body mass index¶	29.8 (6.5)	25.3 (4.9)‡
Disease history (%)		
Cancer	5.6	4.4
Hypertension	64.3	35.1‡
Heart attack	15.4	5.1‡
Stroke	5.0	1.0‡
Blindness (%)	3.6	1.4‡
Current use of antidepressant medication (%)	3.6	2.3‡

* NHANES I, First National Health and Nutrition Examination Survey; CES-D, Center for Epidemiologic Studies Depression [Scale].

† Numbers in parentheses, standard deviation.

‡ Significant difference between diabetic and nondiabetic populations with adequate CES-D scores and survival dates (t test or chi-squared test, two-sided, $p < 0.05$).

§ Income was categorized as follows: 1 = <$5,000; 2 = $5,000–$10,000; 3 = $10,001–$15,000; 4 = $15,001–$20,000; 5 = $20,001–$25,000; and 6 = >$25,000.

¶ Weight (kg)/height $(m)^2$.

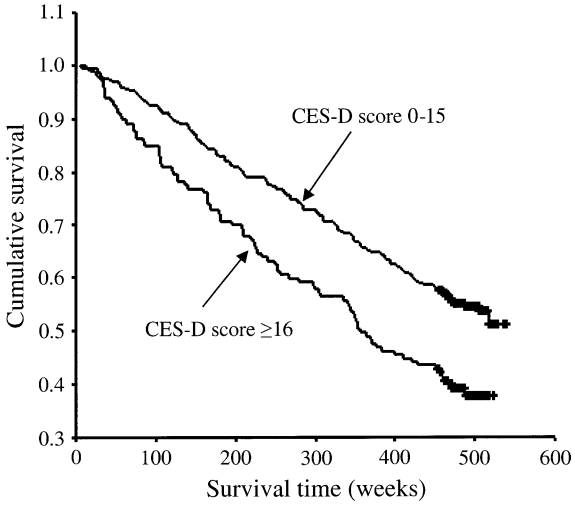

FIGURE 1. Survival functions in a diabetic population stratified by Centers for Epidemiologic Studies Depression (CES-D) Scale score, NHANES I Epidemiologic Follow-up Study, 1982–1992.

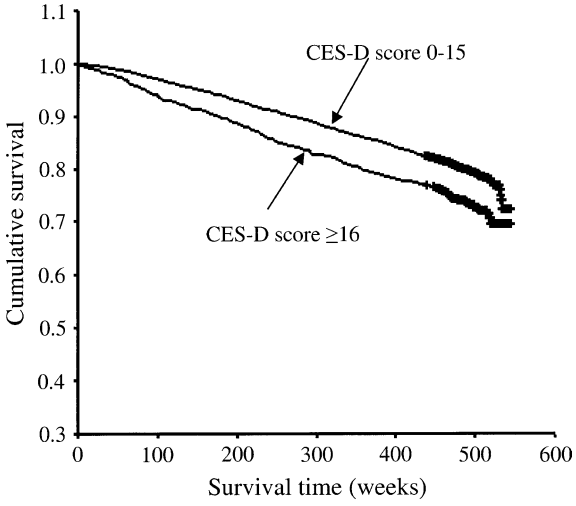

FIGURE 2. Survival functions in a nondiabetic population stratified by Centers for Epidemiologic Studies Depression (CES-D) Scale score, NHANES I Epidemiologic Follow-up Study, 1982–1992.

We further examined the relation between depressive symptoms and mortality by stratifying participants according to their CES-D scores (table 2). Using CES-D scores less than 16 for comparison, we categorized people with CES-D scores of 16–21 as having moderate depressive symptoms and those with scores of $\geq$22 as having severe depressive symptoms. Again, depressive symptoms were associated with increased mortality risk among people with diabetes. Other things being equal, respondents with moderate depressive symptoms had a hazard ratio that was increased by 63 percent ($p = 0.016$), and respondents with severe depressive symptoms had a ratio increased by 49 percent ($p = 0.029$). No such relation was found in any subgroup among people without diabetes ($p = 0.45$ and $p = 0.12$, respectively).

We examined the relation again after excluding respondents who died during the first year of follow-up. Moderate depressive symptoms no longer significantly increased the risk of mortality among persons with diabetes, whereas mortality risk remained increased in respondents with severe depressive symptoms (hazard ratio = 1.46, 95 percent confidence interval: 1.01, 2.13). Using the same model, no significant relation between depression and mortality was found among people without diabetes.

We conducted sensitivity analyses using an enlarged group of respondents ($n = 8{,}007$), including those who answered 17–19 items on the CES-D questionnaire. We found no significant difference in depression-associated mortality between respondents who answered all 20 items and respondents who answered at least 17 items in either the diabetic population or the nondiabetic population. We also tested for bias introduced by missing data by including the subsample of respondents who did not provide answers for certain questions (the most commonly missing data were those related to family income, where 7.2 percent of the data were missing). After the mean value for family income was assigned to these cases, no significant difference in depression-associated mortality was found between the subgroup with complete data and the subgroup with missing data.

DISCUSSION

Using prospective data from the NHEFS, we examined the relation between depressive symptoms and mortality among persons with and without diabetes at baseline. Our findings addressed the following three questions: 1) Do patients with diabetes have higher levels of depressive symptoms compared with a healthy population? 2) Do depressive symptoms significantly increase mortality risk in general populations as they did in a population with diabetes? 3) How does diabetes modify the depression-mortality association? Our findings not only confirm that people with diabetes are prone to be depressed but also demonstrate that depressive symptoms play a more important role in mortality among people with diabetes than among people without diabetes. Compared with respondents with CES-D scores less than 16, respondents with scores of 16 or more had death hazards that were increased by 54 percent. However, no such relation was found among people without diabetes. We found the same patterns after stratifying depressive symptoms and excluding respondents who had died within the first year of follow-up.

Our findings also demonstrate that diabetes is more likely to be related not only to worse mental and physical health but also to a disadvantaged social position. Compared with nondiabetic people, people with diabetes are more likely to suffer from depression; to rate their health as worse; to report more cases of cancer, hypertension, heart attack, stroke, and blindness; to be physically inactive; to be

TABLE 2. A comparative model of the depression-mortality association between diabetic and nondiabetic populations, NHANES I* Epidemiologic Follow-up Study, 1982–1992†

Variable	Study participants			
	Diabetic population		Nondiabetic population	
	HR* or e^{β}	95% CI*	HR or e^{β}	95% CI
Analysis with dichotomized CES-D* scores‡				
Demographic and socioeconomic variables				
Age (per year)	1.07	1.06, 1.09	1.08	1.07, 1.09
Female gender	0.48	0.34, 0.67	0.52	0.46, 0.59
White race	0.88	0.62, 1.23	1.00	0.85, 1.17
Married	0.82	0.60, 1.11	0.79	0.69, 0.90
Education (per year)	0.99	0.95, 1.03	1.01	0.99, 1.02
Currently employed	0.64	0.34, 1.20	0.96	0.78, 1.17
Annual income§	0.99	0.89, 1.10	0.92	0.89, 0.96
Lifestyle variables				
Ever smoking ≥100 cigarettes	1.45	1.10, 1.92	1.47	1.30, 1.66
Currently being on a weight-loss diet	0.86	0.61, 1.22	0.87	0.62, 1.21
Physical activity level¶	0.76	0.62, 0.95	0.81	0.74, 0.89
Health-status variables				
Self-rated health#	1.16	1.01, 1.34	1.17	1.11, 1.24
Body mass index**	1.01	0.99, 1.03	1.01	0.99, 1.02
Disease history				
Cancer	2.03	1.27, 3.24	1.68	1.38, 2.03
Hypertension	1.21	0.90, 1.63	1.16	1.03, 1.30
Heart attack	1.30	0.93, 1.81	1.50	1.27, 1.77
Stroke	1.11	0.63, 1.98	1.47	1.06, 2.03
Blindness	1.33	0.75, 2.38	1.19	0.88, 1.61
CES-D score ≥16	1.54	1.15, 2.07	1.03	0.89, 1.19
Analysis with categorized CES-D scores††,‡‡				
Moderate depressive symptoms (CES-D scores 16–21)	1.63	1.10, 2.42	0.93	0.77, 1.12
Severe depressive symptoms (CES-D scores ≥22)	1.49	1.04, 2.12	1.17	0.96, 1.41
Analysis with categorized CES-D scores and a 1-year lag††,§§				
Moderate depressive symptoms (CES-D scores 16–21)	1.33	0.85, 2.08	0.97	0.80, 1.17
Severe depressive symptoms (CES-D scores ≥22)	1.46	1.01, 2.13	1.13	0.92, 1.38

* NHANES I, First National Health and Nutrition Examination Survey; HR, hazard ratio; CI, confidence interval; CES-D, Center for Epidemiologic Studies Depression [Scale].

† Covariates included age, female gender, White race, being married, education, currently being employed, annual income, ever having smoked at least 100 cigarettes, currently being on a weight-loss diet, physical activity level, self-rated health, body mass index, history of cancer, hypertension, heart attack, or stroke, and blindness.

‡ For diabetic population: omnibus tests, L^2 (baseline) = 2,916; −2 log likelihood = 2,672 (18 df); model χ^2 improvement = 244 ($p < 0.001$). For nondiabetic population: omnibus tests, L^2 (baseline) = 23,128; −2 log likelihood = 20,845 (18 df); model χ^2 improvement = 2,283 ($p < 0.001$).

§ Income was categorized as follows: 1 = <$5,000; 2 = $5,000–$10,000; 3 = $10,001–$15,000; 4 = $15,001–$20,000; 5 = $20,001–$25,000; and 6 = >$25,000.

¶ Assessed on a three-point Likert scale: quite inactive (1 point), moderately active (2 points), or very active (3 points).

Assessed on a five-point Likert scale: excellent (1 point), very good (2 points), good (3 points), fair (4 points), or poor (5 points).

** Weight (kg)/height $(m)^2$.

†† Adjusted for the same variables as in the above model. Details on the full models can be obtained from the first author upon request.

‡‡ For diabetic population: omnibus tests, L^2 (baseline) = 2,916; −2 log likelihood = 2,672 (19 df); model χ^2 improvement = 244 ($p < 0.001$). For nondiabetic population: omnibus tests, L^2 (baseline) = 23,128; −2 log likelihood = 20,842 (19 df); model χ^2 improvement = 2,286 ($p < 0.001$).

§§ For diabetic population: omnibus tests, L^2 (baseline) = 2,629; −2 log likelihood = 2,409 (19 df); model χ^2 improvement = 220 ($p < 0.001$). For nondiabetic population: omnibus tests, L^2 (baseline) = 21,723; −2 log likelihood = 19,584 (19 df); model χ^2 improvement = 2,139 ($p < 0.001$).

less well-educated; to have lower incomes; and to be unemployed.

This is the first study we are aware of that has examined the relation between depressive symptoms and mortality among people with and without diabetes using a nationwide longitudinal follow-up sample. Although many studies claim that depression elevates humans' susceptibility to diabetes (4–10) and that depression further deteriorates diabetic patients' health status by affecting their glycemic control and their macrovascular and microvascular complications (13–20), much contradictory evidence also exists (7, 12, 21, 22, 61). By demonstrating a significant relation between depressive symptoms and excess mortality among persons with diabetes, this study indicates that an association does exist between depression and diabetes.

Using a nondiabetic subgroup as a comparator, this study design may exclude other potential confounders. After we controlled for sociodemographic characteristics, lifestyle, and health status, our results showed that depression significantly elevates mortality only among persons with diabetes. This finding implies that diabetes modifies the depression-mortality association.

This study also clarifies the relation between depressive symptoms and mortality among general populations. Previous studies carried out in restricted populations have indicated that a relation exists between depression and excess mortality only when subjects have certain cardiovascular illnesses—such as coronary artery disease (42), myocardial infarction (35, 36, 40), stroke (38, 41), congestive heart failure (39), or ischemic heart disease (37)—or when subjects have a disadvantaged social position, such as a low income, less education, or social isolation (43–45). However, we have not identified any study that uses a comparison group to examine the relation between depression and mortality. We found that diabetes, similarly to other chronic diseases, significantly affects the depression-mortality association. This relation was not observed in the nondiabetic comparison population. Our findings demonstrate the importance of examining subgroups, rather than aggregated populations, when examining the effect of depression on mortality.

Our study had several strengths. First, the data we used came from a nationwide longitudinal survey with 10 years of follow-up. Second, the most important confounding variables, such as sociodemographic, health-status, and lifestyle variables, were controlled for when we examined the relation between depression and mortality. Third, an identical model was used to analyze two different populations, and the comparison confirmed a relation between depressive symptoms and diabetes. Fourth, sensitivity analyses provided a degree of methodological validity.

Our study also had various limitations. First, depressive symptoms were measured only at baseline, and the CES-D scale was used as a time-independent variable in our model. As a result, any change in depressive symptoms was not reflected in our survival analysis. Second, baseline characteristics in the diabetic and nondiabetic populations differed, which decreased the explanatory power of the comparison model. Third, information on specific causes of death was not available, and this affected the generalizability of our findings. Fourth, the diabetic population was identified by self-report—an approach that may have introduced misclassification. However, this methodological approach has been found to cause only minor bias, with high agreement between personal interviews and medical records in diabetic populations ($\kappa = 0.7$) (62).

We recognize that our study does not provide a causal explanation for the relation between depression and excess mortality. Because the major explanatory variable, CES-D score, was used as a time-independent variable, our model more likely demonstrates a valid association. Further investigation should focus on the mechanism of how depression affects mortality among persons with diabetes. Two paradigms are available for further investigation of such mechanisms (5, 63–67); one paradigm relates to physiology and psychology, and the other relates to health behavior. Depression and diabetes may be linked by neurohormonal changes mediated through the hypothalamic-pituitary-adrenal axis. Depression has been found to increase levels of counterregulatory hormones, particularly cortisol (66) and catecholamines (64, 65, 67). By activating the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system, the counterregulatory hormones related to depression increase human susceptibility to obesity, insulin resistance, and type 2 diabetes (5, 63). In addition, depression activates the central sympathetic nervous system and leads to increased catecholamine levels and subsequent insulin resistance (5, 63). These physiologic processes may contribute to morbidity and mortality risk.

Depressive symptoms may be related to health behaviors associated with diabetes (68). Depressed persons may be more likely to adopt unhealthy behaviors, such as a sedentary lifestyle and a poor diet, which are associated with a greater likelihood of obesity and type 2 diabetes (68, 69). Depressed persons may isolate themselves and be less likely to contact other people, decreasing the availability of social support, which could be crucial for glycemic control, treatment compliance, and survival (20, 70, 71).

Our study found an association between diabetes and depressive symptoms at baseline. Thereafter, depressive symptoms appeared to play a significant role in elevating mortality risk among persons with diabetes but not among persons without diabetes during a 10-year period. Our findings also help clarify the contradictory findings on the association between depression and mortality among general populations. Depression should probably be considered a target for diabetes management interventions (72). In addition, however, more investigation is needed to clarify the nature and etiology of the interaction between diabetes and depression.

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