Depression and All-Cause and Coronary Heart Disease Mortality Among Adults With and Without Diabetes

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OBJECTIVE — The aim of this study was to evaluate the effect of depression on all-cause and coronary heart disease (CHD) mortality among adults with and without diabetes.

RESEARCH DESIGN AND METHODS — We studied 10,025 participants in the population-based National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study who were alive and interviewed in 1982 and had complete data for the Center for Epidemiologic Studies Depression Scale. Four groups were created based on diabetes and depression status in 1982: *1*) no diabetes, no depression (reference group); *2*) no diabetes, depression present; *3*) diabetes present, no depression; and i4) diabetes present, depression present. Cox proportional hazards regression models were used to calculate multivariate-adjusted hazard ratios (HRs) of death for each group compared with the reference group.

RESULTS — Over 8 years (83,624 person-years of follow-up), 1,925 deaths were documented, including 522 deaths from CHD. Mortality rate per 1,000 person-years of follow-up was highest in the group with both diabetes and depression. Compared with the reference group, HRs for all-cause mortality were no diabetes, depression present, 1.20 (95% CI 1.03–1.40); diabetes present, no depression 1.88 (1.55–2.27); and diabetes present, depression present, 2.50 (2.04–3.08). HRs for CHD mortality were no diabetes, depression present, 1.29 (0.96–1.74); diabetes present, no depression 2.26 (1.60–3.21); and diabetes present, depression present, 2.43 (1.66–3.56).

CONCLUSIONS — The coexistence of diabetes and depression is associated with a significantly increased risk of death from all causes, beyond that due to having either diabetes or depression alone.

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Depression is highly prevalent in the U.S., affecting ~18.8 million adults or about 9.5% of the U.S. population aged ≥18 in a given year (1). Depression is a leading cause of disability, workplace absenteeism, diminished or lost productivity, and increased use of health care resources (2,3). There is fairly consistent evidence that depression is associated with increased mortality (4–9). A recent meta-analysis, which included 25 studies and 106,628 subjects, found that the hazard ratio (HR) for all-cause mortality in depressed subjects was 1.81 (95% CI 1.58–2.07) compared with that for nondepressed subjects (10).

Diabetes is also highly prevalent in the U.S. (11), and multiple studies have documented an increased prevalence of depression in individuals with diabetes (12). It is estimated that 10–30% of people with diabetes have coexisting depression and that people with diabetes have twofold increased odds of having depression compared with individuals without diabetes (12,13). The coexistence of depression and diabetes is known to be associated with poor glycemic control (14,15), an increased risk of complications (16–18), a decreased quality of life (19), an increased disability burden (20,21), and increased health care use and costs (19,22,23). However, no study has examined whether the coexistence of depression and diabetes is associated with increased risk of mortality. In particular, there are no data that compares the effect of depression on the risk of death in people with and without diabetes.

To address these issues, we examined mortality in a large nationally representative cohort of adults aged 25–75 years in 1971–1975 (24), who were reinterviewed in 1982 and followed until 1992 (25,26). We compared all-cause and coronary heart disease (CHD) mortality among four subsets of participants based on their disease status at the 1982 interview.

RESEARCH DESIGN AND METHODS

— The National Health and Nutrition Examination Survey (NHANES) I was a multistage, stratified, national probability sample of the civilian noninstitutionalized population of the U.S. aged 1–74 years (24). The survey was conducted between 1971 and 1975 and included a standardized examination and questionnaires that addressed various health topics. Persons living in poverty

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Abbreviations: CES-D, Center for Epidemiologic Studies Depression Scale; CHD, coronary heart disease; NHANES, National Health and Nutrition Examination Survey; NHEFS, National Health and Nutrition Examination Epidemiologic Follow-up Study.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

areas, women of childbearing age (25–44 years), and elderly persons (≥65 years) were oversampled. The NHANES I sample included 20,729 persons 25–74 years of age, of whom 14,407 (70%) were medically examined.

The NHANES I Epidemiologic Follow-up Study (NHEFS) is a longitudinal study of participants who were between 25 and 74 years old during the 1971–1975 interviews (25,26). The first follow-up study was conducted in 1982 and included all persons aged 25–74 years at the NHANES I assessment (n = 14,407). Participants were subsequently interviewed in 1986, 1987, and 1992. The 1982 follow-up interview included data on self-reported medical conditions and an assessment of depression based on the Center for Epidemiologic Studies Depression Scale (CES-D). For this investigation, we analyzed data on participants in the NHEFS cohort who completed the CES-D in 1982 and were followed until the 1992 interview date.

Definition of depression

The CES-D is a self-report scale designed to measure depression in the general population (27). The scale consists of 20 items rated on a four-point scale with response categories indicating the frequency of occurrence of each item in the previous week. The four-point scale ranges from 0 (rarely or none of the time) to 3 (most or all of the time). Scores for items 4, 8, 12, and 16 are reversed before scores for the 20 items are summed. Total scores range from 0 to 60 with higher scores indicating more depressive symptoms. A cutoff of ≥16 has been used extensively for distinguishing depressed from nondepressed patients. The CES-D is a valid and reliable instrument for assessing depression in community samples with high internal consistency, good construct and concurrent validity, and modest test-retest reliability (27–30).

Defining the study cohort

Of the 14,407 respondents eligible for inclusion in the 1982 follow-up study, 13,383 were traced, 11,361 were living, and 10,523 were interviewed (25). We defined our cohort as the 10,025 individuals who were alive and interviewed in 1982 and who had complete data for the CES-D. We excluded 498 individuals who either did not have complete data for the CES-D or were missing data for covariates. We divided the cohort into four groups based on the presence or absence of self-reported diabetes and depression (defined as CES-D ≥16) in 1982 as follows: *1*) individuals without diabetes and without depression, *2*) individuals without diabetes but with depression, *3*) individuals with diabetes but without depression, and *4*) individuals with both diabetes and depression.

Baseline data collection

Demographic, lifestyle behavior, and comorbidity information were collected as part of the 1982 interview. We included age (in years) as a continuous variable. Race/ethnicity was categorized as white versus black/other. Poverty:income ratio was defined as percentage of the U.S. federal poverty level and classified as <125%, 125–399%, and ≥400%. Education was categorized as <high school graduate, high school graduate, or >high school graduate, and marital status was classified as not married or married. BMI was calculated from self-reported weight and height and categorized as normal weight (18.5–24.9), overweight (25.0–29.9), and obese (≥30.0+). Smoking was grouped as never, former, or current smoker, and physical activity based on the individual's engagement in usual recreational activity was categorized as regular, light, or sedentary. Self-reported aspirin use was dichotomized as yes versus no.

In addition, respondents were asked to report previously diagnosed medical conditions, including diabetes, hypertension, heart disease, stroke, and cancer. The diagnosis of diabetes was based on a "yes" response to the question, "Have you ever been told by a doctor that you have diabetes?" A similar approach was used to establish prior diagnosis of the other self-reported medical conditions.

Outcome measures

Main outcome measures were all-cause mortality and CHD mortality across the four groups in the cohort. Follow-up data were collected in four waves: 1982–1984, 1986, 1987, and 1992. For each wave, patient or proxy interviews were conducted and health care facility records as well as death certificates were obtained. Death for each cohort member was ascertained through a search of the National Death Index or through tracing of vital status via a proxy interview. The underlying causes of death on the death certificates were classified according to ICD-9. End points for this study were deaths from all causes and deaths related to CHD (ICD-9 codes 410–414). The reliability of the National Death Index for epidemiological studies has been previously validated (31,32). Length of follow-up for each individual was calculated from the date of the baseline interview (1982–1984) to either the date of death or the date of last follow-up.

Statistical analysis

Statistical analysis was performed with SAS (Cary, NC) (33) and SUDAAN (Research Triangle Park, NC) (34) and the approach recommended by the National Center for Health Statistics for analyzing the NHEFS was used (35). Means or proportions of baseline risk factors were calculated for the reference group (individuals without diabetes and without depression) and the other three groups (individuals without diabetes but with depression, individuals with diabetes but without depression, and individuals with both diabetes and depression). All-cause and CHD mortality rates per 1,000 person-years of follow-up were calculated for the four groups. Life expectancy and survival times for the four groups were estimated by the Kaplan-Meier product-limit method.

Cox proportional hazards regression models were used to calculate multivariate-adjusted HRs of death for each group compared with the reference group. Simulation data have shown that the Cox model is preferred to the cumulative logistic or person-time logistic regression models for analyzing data from the NHEFS because it takes into account differential follow-up time and does not require the survival time to be exponentially distributed (35). Two multivariate models were developed: a minimal model (model 1) that included confounding sociodemographic variables that were unlikely to be mediators of the relationship between diabetes/depression and mortality and a full model (model 2) that included variables in model 1 and additional variables that were likely to be mediators of the relation between diabetes/depression and mortality. Model 1 included age in 1982, sex, race/ethnicity, poverty:income ratio, education, and marital status. In addition to the variables in model 1, model 2 included smoking,

Table 1—*Baseline characteristics in 1982 by presence or absence of diabetes and depression*

	No diabetes, not depressed	No diabetes, depressed	Diabetes, not depressed	Diabetes, depressed
n	7,032	2,278	453	262
Mean age (years)	55.7	56.9	62.6	64.2
Sex (%)				
Male	40.0	28.4	43.5	28.6
Female	60.0	71.6	56.5	71.4
Race/ethnicity (%)				
White	87.9	83.1	75.9	72.9
Black/other	12.1	16.9	24.1	27.1
Poverty:income ratio (%)				
<125	16.6	26.1	31.5	36.1
125–399	61.6	59.8	52.0	54.1
≥400	21.8	14.1	16.5	9.8
Education (%)				
<High school graduate	36.7	50.0	59.7	70.6
High school graduate	30.7	27.0	23.1	16.1
>High school graduate	32.6	23.0	17.2	13.3
Marital status (%)				
Not married	28.5	38.7	38.3	48.1
Married	71.5	61.3	61.7	51.9
Physical activity (%)				
Regular	17.3	13.3	9.1	8.4
Light	52.2	41.1	42.8	29.1
Sedentary	30.5	45.6	48.1	62.5
Mean BMI (kg/m^2)	25.9	26.1	28.7	29.0
BMI category (%)				
Normal weight (18.5–24.9 kg/m^2)	47.3	47.8	28.5	25.4
Overweight (25.0–29.9 kg/m^2)	36.1	33.6	37.2	37.5
Obese (≥30 kg/m^2)	16.6	18.6	34.3	37.1
Smoking (%)				
Never smoked	44.8	45.6	48.6	51.5
Former smoker	27.6	23.7	30.9	27.5
Current smoker	27.6	30.7	20.5	21.0
Cancer (%)	3.5	5.4	4.4	5.7
Hypertension (%)	40.6	48.6	69.5	74.4
Heart disease (%)	13.5	22.1	30.9	45.0
Stroke (%)	0.6	1.9	3.1	8.4
Aspirin use (%)	21.7	30.8	25.6	30.9

physical activity, BMI, aspirin use, and comorbid medical conditions at baseline (cancer, hypertension, heart disease, and stroke). In these models, age at death (or age at last contact for censored subjects) was used as the dependent variable. The assumption of proportionality of hazard was assessed for the four diabetes/depression classification groups and each study covariate; all multivariate models satisfied this assumption.

RESULTS — In this nationally representative sample of 10,025 adults followed for an average duration of 8 years (83,624 person-years of follow-up), 1,925 (19%) of the study subjects died. CHD accounted for 522 (27%) of all deaths. Table 1 shows the baseline characteristics of the study participants. In general, the group of individuals with both diabetes and depression were older, included more women, included more ethnic minorities, were more likely to have sedentary lifestyles, more likely to be overweight/obese, and more likely to have history of hypertension, heart disease, and stroke at baseline compared with the other three groups. On the contrary, individuals with both diabetes and depression were poorer, were less educated, and were less likely to be married at baseline compared with individuals in the other three groups.

Table 2 presents mortality rates and multivariate-adjusted HRs of death from all-cause and CHD according to diabetes and depression diagnoses at the 1982 interview. Mortality rate per 1,000 person-years of follow-up from all causes and from CHD were highest in individuals with both diabetes and depression and lowest in individuals without diabetes and without depression. Multivariate-adjusted HRs of deaths from all causes were significantly higher for people with diabetes but highest for those with both diabetes and depression. For model 1, compared with the reference group (individuals without diabetes and without depression), the adjusted HR of death was threefold higher for those with both diabetes and depression. After further multivariate adjustment (model 2), the HR of death was 2.5-fold higher for people with both diabetes and depression.

Post hoc comparisons showed that adjusted hazards for all-cause mortality were significantly higher in people with both diabetes and depression compared with those with only diabetes in both the minimal (odds ratio [OR] 1.67 [95% CI 1.30–2.14]) and the full (1.33 [1.02–1.74]) models. Similarly, adjusted hazards for all-cause mortality were significantly higher in people with both diabetes and depression compared with those with only depression in both the minimal (2.44 [1.97–3.03]) and the full (2.08 [1.68–2.59]) models.

For CHD mortality, both the minimal and full multivariate-adjusted models suggested that HRs were higher for people with diabetes but highest for those with both diabetes and depression compared with the reference group. However, post hoc comparisons showed that adjusted hazards for CHD mortality were not significantly higher in people with both diabetes and depression compared with those with only diabetes in both the minimal (OR 1.38 [95% CI 0.89–2.12]) and the full (1.07 [0.67–1.71]) models. In contrast, CHD mortality was significantly higher in people with both diabetes and depression compared with those with only depression in both the minimal (2.37 [1.57–3.58]) and the full (1.88 [1.23–2.87]) models. Figures 1 and 2 show Kaplan-Meier curves of unadjusted

Table 2—*HR of death from all causes and coronary heart disease according to diabetes and depression diagnoses in 1982*

	No diabetes, not depressed	No diabetes, depressed	Diabetes, not depressed	Diabetes, depressed
n	7,032	2,278	453	262
Person-years of follow-up	59,934	18,616	3,371	1,703
All-cause mortality				
Deaths (*n*)	1,147	478	166	134
Mortality rate (per 1,000)	19.1	25.7	49.2	78.7
Hazard ratio (95% CI)				
Multivariate model 1	1.00 (reference)	1.34 (1.16–1.54)	1.96 (1.63–2.35)*	3.27 (2.66–4.01)*
Multivariate model 2	1.00 (reference)	1.20 (1.03–1.40)	1.88 (1.55–2.27)†	2.50 (2.04–3.08)†
CHD mortality				
Deaths (*n*)	301	125	55	41
Mortality rate (per 1,000)	5.0	6.7	16.3	24.1
HR (95% CI)				
Multivariate model 1	1.00 (reference)	1.46 (1.09–1.95)	2.51 (1.81–3.47)‡	3.46 (2.41–4.96)‡
Multivariate model 2	1.00 (reference)	1.29 (0.96–1.74)	2.26 (1.60–3.21)§	2.43 (1.66–3.56)§

Mortality rate was calculated with person-years of follow-up as denominator. CHD was defined by ICD-9 codes 410–414. Multivariate model 1 was adjusted for age in 1982 (years), sex, race/ethnicity (white vs. black/other), poverty:income ratio (<125, 125–399, ≥400%), education (<high school, high school, >high school), marital status (not married vs. married). Multivariate model 2 included additional adjustments for smoking (never, former, current), physical activity (light, regular, sedentary), BMI (<18.5, 18.5–24.9, 25.0–29.9, ≥30 kg/m^2), aspirin use (yes vs. no), and comorbid conditions at baseline (cancer, hypertension, heart disease, stroke). *Comparison of diabetes, depressed vs. diabetes, and not depressed for model 1 significantly different (OR 1.67 [95% CI 1.30–2.14]). †Comparison of diabetes, depressed vs. diabetes, and not depressed for model 2 significantly different (OR 1.33 [1.02–1.74]). ‡Comparison of diabetes, depressed vs. diabetes, and not depressed for model 1 significantly different (OR 1.38 [0.89–2.12]). §Comparison of diabetes, depressed vs. diabetes, and not depressed for model 2 significantly different (OR 1.07 [0.67–1.71]).

life expectancy and survival times for both all-cause and CHD mortality during the periods of follow-up for the four groups.

CONCLUSIONS — This is the first study to compare the effects of depression on mortality in people with and without diabetes. The study provides evidence that over a mean follow-up period of 8 years, the coexistence of diabetes and de-

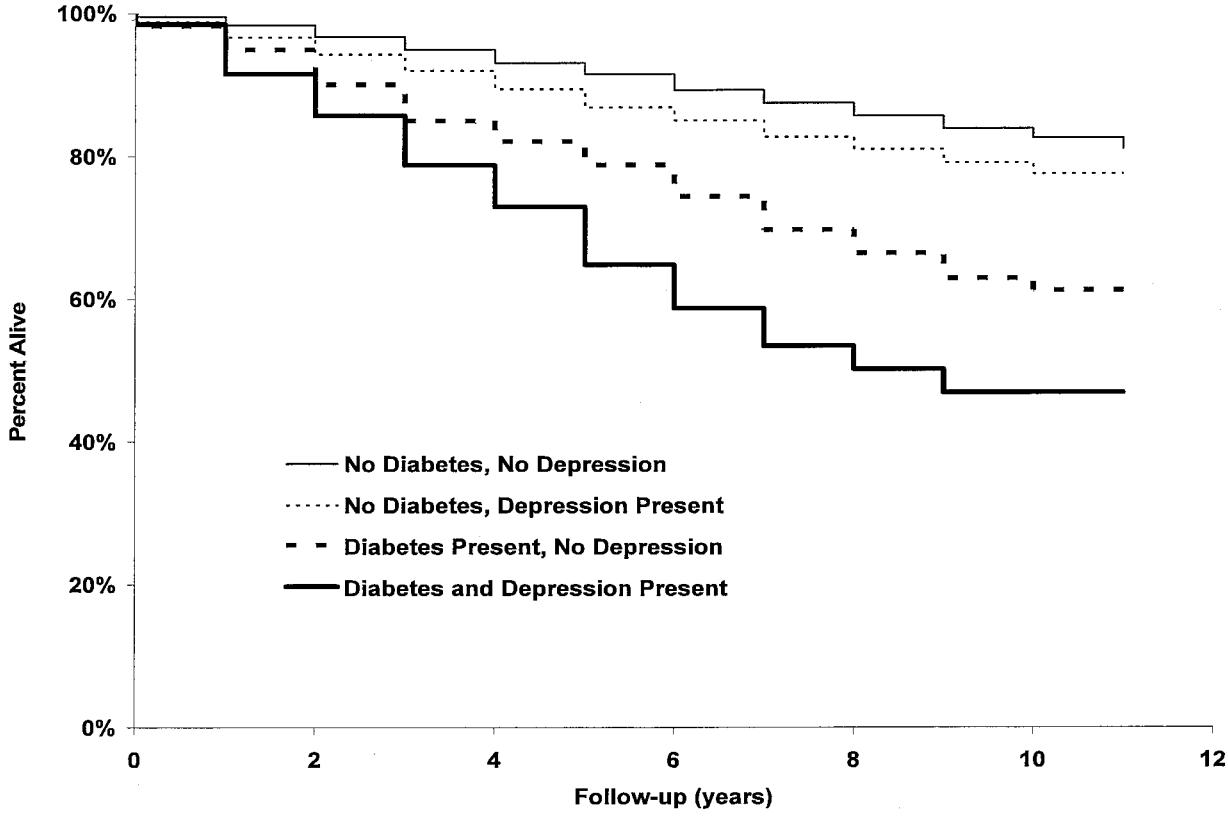

Figure 1—*Estimated probability of survival (all-cause mortality) according to diabetes and depression diagnosis in 1982.*

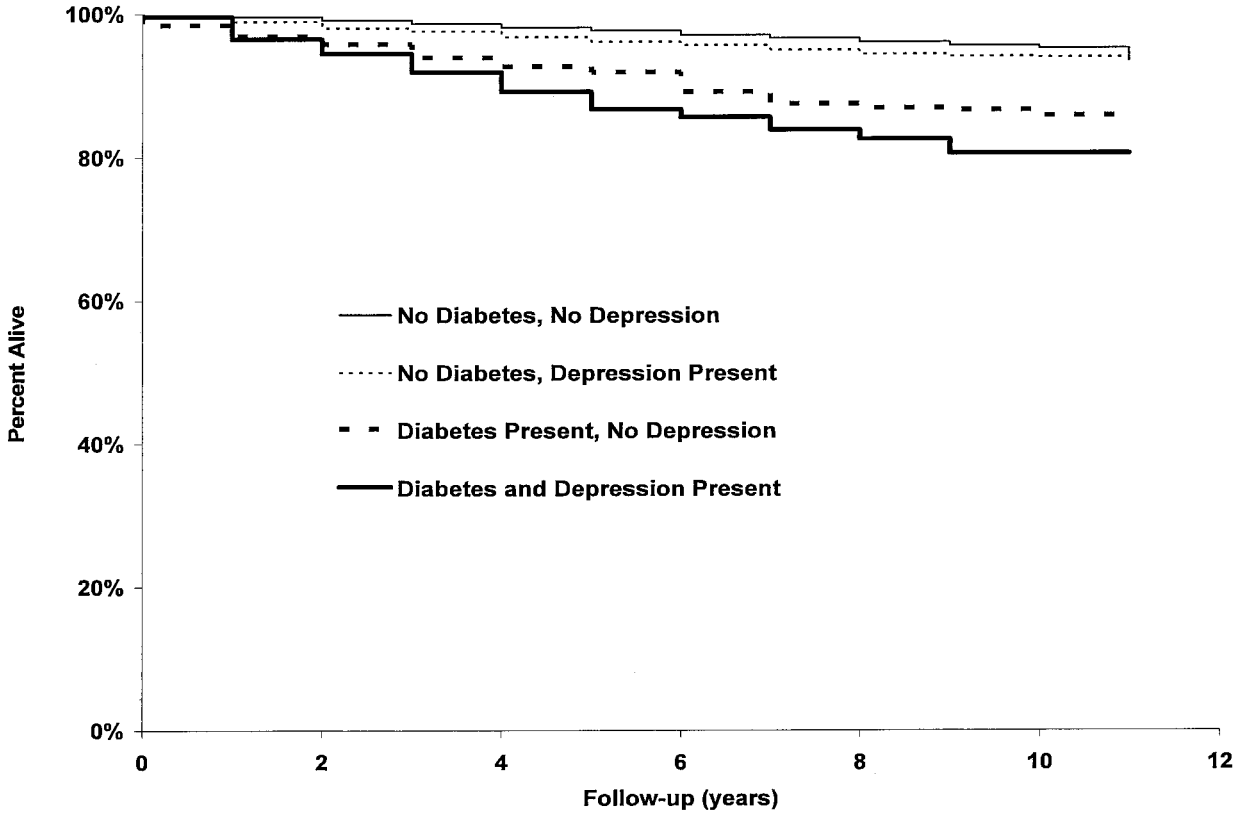

Figure 2—*Estimated probability of survival (CHD mortality) according to diabetes and depression diagnosis in 1982.*

pression is associated with significantly increased risk of death from all causes beyond that due to having either diabetes or depression alone. After adjusting for clinically relevant confounders, people with both diabetes and depression had a 1.3-fold increased risk of death from all causes compared with people with only diabetes, a 2-fold increased risk of death from all causes compared with people with only depression, and a 2.5-fold increased risk of death compared with people without either diabetes or depression.

We found that in comparison with individuals without diabetes, the risk of death associated with diabetes was approximately twofold (minimal and full models). This is consistent with the findings of other investigators, who have shown that diabetes is associated with a 1.5- to 2-fold increased risk of death (36–40). Our estimates of the risk of death associated with depression ranged from 1.2 to 1.3. This seems lower than estimates from some previous studies (4,7,10) but appears consistent with those from other studies (5,6). It seems that these inconsistencies are due to differences in study design, diagnostic criteria for depression, and duration of follow-up.

In this study, the coexistence of diabetes and depression seems to have a synergistic effect on all-cause mortality. In the full model (model 2), depression alone was associated with a 1.2-fold increased risk of death, diabetes alone was associated with a 1.9-fold increased risk of death, but the combination of diabetes and depression was associated with a 2.5-fold increased risk of death. In post hoc comparisons, people with diabetes and comorbid depression had significantly higher adjusted HRs for all-cause mortality than people with only depression (OR 2.08 [95% CI 1.68–2.59]) and people with only diabetes (1.33 [1.02–1.74]). This is consistent with the findings of Black et al. (17) on the synergistic effects of depression on health outcomes in elderly Mexican Americans with type 2 diabetes.

There is considerable evidence that diabetes is a leading cause of CHD and that it is associated with increased CHD mortality (11). Similarly, there is accumulating evidence that depression is associated with significantly increased CHD mortality (8,41–43). Our results confirm these earlier findings. Compared with individuals without diabetes or depressive symptoms, those with depressive symptoms had 1.3- to 1.5-fold increased CHD mortality and those with diabetes had 2.3- to 2.5-fold increased CHD mortality. However, even though individuals with both diabetes and depression had significantly higher risk of CHD mortality compared with the reference group and those with only depression, their risk was not significantly higher than people with diabetes alone. This finding suggests that diabetes is a stronger predictor of CHD mortality than depression in this cohort. Additionally, these findings suggest that the presence of diabetes accounts for most of the increased risk of CHD mortality seen in people with diabetes and comorbid depression.

Although several studies have shown an association between depression and increased morbidity and mortality, the underlying mechanisms are unclear. Suicide is a known mechanism through which depression increases the risk of death (1). In addition, depression is hypothesized to decrease physical health by

a combination of biological and psychological mechanisms. Psychological distress and subsequent neurohormonal and immunological changes are thought to increase susceptibility to disease, persistent somatic symptoms of depression are thought to worsen physical health over time, and depressed mood is thought to interfere with physical recovery by impeding treatment seeking, adherence to treatment, and adoption of healthy lifestyles (44,45).

Our results suggest that the effect of depression on all-cause mortality and possibly CHD mortality in people with and without diabetes is independent of sociodemographic characteristics, major cardiac risk factors, and comorbidity. Future studies need to explore other plausible mechanisms that were not addressed in this study, including the role of nonadherence to medical treatments, inflammatory responses, potential cardiotoxic effects of antidepressants, depression-mediated immune suppression, and altered cardiac autonomic tone (44,45).

The major implication of the results of this study is the need for the health care community, especially health professionals who treat people with diabetes, to pay more attention to the recognition and treatment of depression. A growing body of literature suggests that coexisting depression has a negative impact on health in people with diabetes. Previous studies have shown that depression is associated with poor glycemic control, increased risk of complications, decreased quality of life, and increased health care utilization and cost (14–16,19,22). Coexisting depression has recently been shown to increase the odds of functional disability, days lost from work, and days spent in bed among people with diabetes (20,21). This study now shows that the combination of diabetes and depression is associated with increased risk of death beyond that due to having either diabetes or depression alone. Therefore, more aggressive strategies need to be implemented to initiate and optimize treatment for depression among individuals with diabetes.

Strengths of this study include its large sample size, the prospective design, its nationally representative nature, its 8 years of follow-up, and the availability of data on several key risk factors. Nonetheless, the study has several potential limitations. First, the data were based on self-report, making them prone to misclassification. However, studies have shown that self-reported data on diabetes, chronic diseases, and several cardiovascular risk factors are reliable (46–48). Second, the diagnosis of depression was not based on the "gold standard" of a clinical interview. However, the CES-D is a widely accepted, valid, and reliable tool for identification of depression in community samples (27–30). Third, we were unable to precisely differentiate type 1 from type 2 diabetes. However, as suggested by Gu et al. (36), the older age of the NHANES I cohort and the high proportion of type 2 diabetic patients in the U.S. indicate that our findings reflect mortality in type 2 diabetic patients. Fourth, participants without diabetes in 1982 may have developed diabetes during follow-up and yet were counted as not having diabetes. Similarly, it is possible that participants without depression in 1982 developed depression during the follow-up period. These individuals would be expected to have higher mortality than individuals who never developed diabetes or depression, which probably lowered our hazard estimates of death for the groups with diabetes. Finally, due to the absence of data on both disease duration and disease severity for diabetes and depression, their independent effects on mortality could not be assessed. Future studies will need to explore their independent effects on mortality.

Despite these potential limitations, the results of this study remain important. The coexistence of diabetes and depression is associated with a significantly increased risk of death from all causes, beyond that due to having either diabetes or depression alone. After adjusting for clinically relevant confounders, people with both diabetes and depression had a 1.3-fold increased risk of death from all causes compared with people with only diabetes, a 2-fold increased risk of death from all causes compared with people with only depression, and a 2.5-fold increased risk of death compared with people without either diabetes or depression.

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