# Depression Predicts Increased Incidence of Adverse Health Outcomes in Older Mexican Americans With Type 2 Diabetes

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**OBJECTIVE** — To examine the separate and combined effects of depression and diabetes on the incidence of adverse health outcomes among older Mexican Americans.

**RESEARCH DESIGN AND METHODS** — Longitudinal data from the Hispanic Established Population for the Epidemiologic Study of the Elderly (EPESE) survey were used to examine the main effects and interaction effects of diabetes and depressive symptoms (measured with the Center for Epidemiologic Study of Depression) or clinical diagnostic criteria (measured with the Composite International Diagnostic Interview Depression Module) on the development of macrovascular complications (including cardiovascular disease, stroke, and kidney disease), microvascular complications (including nephropathy, neuropathy, retinopathy, and amputations), functional disability, and mortality over 7 years in a sample of 2,830 Mexican Americans aged ≥65 years.

**RESULTS** — The interaction of diabetes and depression was found to be synergistic, predicting greater mortality, greater incidence of both macro- and microvascular complications, and greater incidence of disability in activities of daily living, even when controlling for sociodemographic characteristics such as sex, age, education, acculturation, and marital status. Importantly, this interaction was found to predict not only greater incidence but also earlier incidence of adverse events in older adults.

**CONCLUSIONS** — Whether a marker for underlying disease severity, an indicator of diminished self-care motivation, or the result of physiologic changes, the interaction of depression and diabetes has a synergistic effect on the health of older Mexican Americans, increasing the risk for poor outcomes. This is of particular clinical importance because although depression is often underrecognized in older adults, effective treatment is available and can result in improved medical outcomes.

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Depression, long recognized as a consequence of physical illness (1), is increasingly being perceived as a potential risk factor for compromised health, particularly among older adults (2). A number of recent studies have shown that depression predicts the onset of many medical conditions, including hypertension, heart disease, cancer, stroke, and angina, as well as type 2 diabetes (3–7).

Several studies have also shown depression as a predictor of mortality (8) as well as the onset of disability (9). Indeed, it has been projected that by 2020, depression will be the second leading cause of disability worldwide (10). Depression has also been shown to impact adherence to treatment regimens and the cost of health care among individuals with chronic disease (11), including diabetes (12). Despite this evidence, few studies have examined the influence of depression on the course of chronic disease, particularly in large samples of older adults living in the community.

In earlier studies from the Hispanic Established Population for the Epidemiologic Study of the Elderly (EPESE) survey, we demonstrated that depressive symptoms were associated with a number of poor health indicators among older diabetic Mexican Americans, including elevated rates of comorbid medical conditions, greater functional disability, and increased health care utilization (2,13). Moreover, death rates among individuals with both diabetes and depression were found to be three times higher than rates among diabetic individuals without depression (2). Little is known, however, regarding the impact of depression on other adverse health outcomes in diabetes, such as increasing disease severity, disability, and comorbidity of disease.

In the present study, longitudinal data from the Hispanic EPESE survey were used to assess the separate and combined influences of depression and diabetes on the incidence of macrovascular and microvascular complications, functional disability, and mortality among older Mexican Americans. This is a particularly appropriate population in which to examine this relationship because older Mexican Americans experience elevated rates of both diabetes and depression: 25–30%

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**Abbreviations:** CESD, Center for Epidemiologic Studies Depression Scale; CIDI, Composite International Diagnostic Interview; DSM-IV, Diagnostic and Statistical Manual, Fourth Edition; EPESE, Established Population for the Epidemiologic Study of the Elderly.

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



**See accompanying editorial, p. 2952.**

of Mexican Americans aged ≥65 years have type 2 diabetes, and as many as 25% of these individuals report significant levels of depression (14).

## RESEARCH DESIGN AND METHODS

### Sample

The baseline interview of the Hispanic EPESE was conducted from 1993 to 1994 in Texas, Colorado, New Mexico, Arizona, and California, the region in which most older Mexican Americans reside. Area probability sampling resulted in a representative sample of 3,050 community-dwelling Mexican Americans aged ≥65 years who completed in-home face-to-face interviews in either Spanish or English. The baseline sample was designed to be representative of the ~500,000 Mexican Americans aged ≥65 years residing in the southwestern U.S. The initial baseline wave of interviews was followed by three waves of follow-up: the first was conducted from 1995 to 1996, the second was conducted from 1998 to 1999, and the third wave of follow-up was conducted from 2000 to 2001.

Depressive symptoms were assessed at baseline. Individuals who were too ill or cognitively impaired to complete face-to-face interviews at baseline were not included in the present analyses, which resulted in 2,830 individuals with complete data for analyses predicting mortality. Analyses predicting incident diabetic complications or disability reflect only the reports of the 2,462 individuals who were not deceased by the first follow-up. Clinical diagnostic criteria for depression were assessed at the first wave of follow-up and yielded a total of 2,092 individuals with complete data for analyses predicting mortality, incident complications, and disability.

As can be seen in Table 1, older women comprised ~59% of the sample. Just over two-thirds of the participants were aged 65–74 years and ~10% had completed high school. Just over half of the participants in the sample were currently married; older men were much more likely to have been married than older women ($\chi^2 = 308.2$, $P < 0.0001$).

**Table 1—*Baseline characteristics and diabetic/depressive classes***

| | Depressive symptoms class* ($n$ = 2,830) | | Depressive diagnosis class† ($n$ = 2,092) | |
|---|---|---|---|---|
| | *n* | % | *n* | % |
| Men | 1,173 | 41.4 | 846 | 40.4 |
| Women | 1,657 | 58.6 | 1,246 | 59.6 |
| Age | | | | |
| 65–74 years | 1,898 | 67.1 | 1,433 | 68.5 |
| 75+ years | 932 | 32.9 | 659 | 31.5 |
| Education | | | | |
| 12+ years | 276 | 9.8 | 207 | 9.9 |
| <12 years | 2,554 | 90.2 | 1,885 | 90.1 |
| Marital status | | | | |
| Currently married | 1,574 | 55.6 | 1,184 | 56.6 |
| Not married | 1,256 | 44.4 | 908 | 43.4 |
| Diabetes | 636 | 22.5 | 453 | 21.7 |
| Minor depression* | 678 | 24.0 | — | — |
| Depressive symptoms class* | | | | |
| No diabetes/minimal depression | 1,704 | 60.2 | — | — |
| No diabetes/minor depression | 490 | 17.3 | — | — |
| Diabetes/without any symptoms | 79 | 2.8 | — | — |
| Diabetes/minimal depression | 369 | 13.1 | — | — |
| Diabetes/minor depression | 188 | 6.6 | — | — |
| Lifetime depressive disorder† | — | — | 188 | 9.0 |
| Depressive diagnosis class† | | | | |
| No diabetes/no depression | — | — | 1,503 | 71.8 |
| No diabetes/lifetime depression | — | — | 136 | 6.5 |
| Diabetes/no depression | — | — | 401 | 19.2 |
| Diabetes and lifetime depression | — | — | 52 | 2.5 |

*Based on CESD scores, "minor" is a score of 16 or more, "minimal" is a score of 1–15, "without any" is a score of 0; †CIDI/DSM-IV criteria for any lifetime major depression or dysthymia.

### Measures

**Diabetes and diabetic complications.** At baseline and both follow-up interviews, the presence of diabetes was assessed by asking the respondents whether they had ever been told by a physician that they had diabetes. All individuals who responded affirmatively were then asked whether they had type 1 or type 2 diabetes; all respondents indicated that they had been diagnosed with type 2 diabetes. Individuals reporting impaired glucose tolerance were not designated as having diabetes in the present analyses. Respondents were also asked whether they had experienced any kidney problems (nephropathy), eye problems (retinopathy), circulation or nerve problems (neuropathy), or amputations as a result of having diabetes. Respondents were then categorized as having any incident microvascular complications at each wave of follow-up if they reported any complications that were not present at baseline.

At baseline and all three waves of follow-up interviews, respondents were asked whether they had ever received a physician's diagnosis of other medical conditions that are often sequelae of diabetes, including cardiovascular disease, stroke, and kidney disease. Respondents were categorized as having incident macrovascular complications at each wave of follow-up if they reported any conditions that were not reported at baseline.

**Functional disability.** Disability in activities of daily living was measured with a modified version of the Katz Activities of Daily Living scale (15), which included walking across a small room, bathing, grooming, dressing, eating, transferring from a bed to a chair, and using the toilet. Respondents were categorized as having incident disability at each wave of follow-up if they reported any difficulties with activities of daily living that were not reported at baseline.

Sociodemographic characteristics included the sex, age, years of education, level of acculturation, and marital status at baseline. Vital status (mortality) was assessed at each follow-up interview. The

actual date of death was then ascertained by reviewing death certificates.

Depression was measured in two ways in this study. Depressive symptoms were measured at baseline with the Center for Epidemiologic Studies Depression Scale (CESD) (16), the most commonly used survey measure of depressive symptomatology in studies of older adults. Found to be reliable and valid when used in elderly individuals, the scale consists of 20 items that ask how often specific symptoms were experienced during the week preceding the interview, and responses are scored on a four-point scale, with potential total scores ranging from 0 to 60. These scores were used to delineate three categories of respondents: those with minor depression (based on a CESD score of ≥16), those with minimal depression (CESD scores of 1–15, often referred to as subthreshold depressive syndrome), and those without any depressive symptoms (CESD score of 0). The cutoff for minor depression, although not indicative of a diagnosis of clinical depression, has previously been shown to effectively identify individuals with clinically significant levels of depressive symptoms in other studies of older adults (17) as well as with this sample of older Mexican Americans (2).

Depressive diagnoses were assessed at the second wave (first follow-up interview) with a modified version of the depression module of the Composite International Diagnostic Interview (CIDI) (18), which matches the criteria for depressive disorders as delineated in the Diagnostic and Statistical Manual, Fourth Edition (DSM-IV) of the American Psychiatric Association (19). Developed by the Alcohol, Drug Abuse, and Mental Health Administration and the World Health Organization, the CIDI was designed specifically for large-scale psychiatric epidemiologic research with populations from diverse cultures and education levels. Earlier versions of these criteria have been extensively used to yield valid and reliable diagnoses of depressive disorders in survey research, including surveys of the elderly. The Hispanic EPESE specifically used the depression module from the Fresno CIDI (20), which was culturally and linguistically adapted for Mexican Americans.

In the present study, depressive diagnoses included reporting of any lifetime major depressive episode (requiring an affirmative response to five of nine depressive symptoms experienced in a 2-week period, at least one of which was depressed mood or anhedonia) or lifetime dysthymia (requiring an affirmative response to three depressive symptoms that lasted ≥2 years, without absence of symptoms for at least 2 months, at least one of which was depressed mood, among individuals not concomitantly meeting the criteria for major depression) (19). Individuals who reported that symptoms were in response to bereavement of no more than 2 months' duration were not included in the depressed group.

Two sets of diabetic/depressive classes were derived. The depressive symptom classes included six categories: *1*) respondents with no diabetes and a total absence of any depressive symptoms (CESD score of 0), *2*) respondents with no diabetes and with only minimal levels of depressive symptoms (CESD scores of <16), *3*) respondents with minor depression (CESD scores of ≥16) but no diabetes, *4*) respondents with diabetes but with a total absence of any depressive symptoms (CESD score of 0), *5*) respondents with diabetes and minimal depression (CESD scores of 1–15), and *6*) respondents with diabetes and minor depression (CESD scores of ≥16). The depressive diagnosis classes included four categories: *1*) respondents with no diabetes or lifetime depressive diagnoses, *2*) respondents with lifetime depressive diagnoses but no diabetes, *3*) respondents with diabetes but no lifetime depressive diagnoses, and *4*) respondents with diabetes and lifetime depressive diagnoses.

### Analyses

The rates of incident macrovascular and incident microvascular complications, incident disability, and mortality over the 7 years of study were assessed across sociodemographics, diabetic status, minor depression alone, lifetime depression alone, and across each of the two sets of diabetic/depressive classes. Cumulative rates were derived at each follow-up wave and differences were assessed with $\chi^2$ analyses. Initial logistic regression models were used to assess the main effects and interaction effects of diabetes and depression. Interaction effects were assessed by entering a second-order term for depression and diabetes into the main effects model (21). Survival analysis was then used to estimate the hazard ratios and survival function estimates associated with the diabetic/depressive classes, while controlling for sociodemographic characteristics (22). The PHREG procedure for Cox proportional hazards regression in the SAS statistical software (SAS Institute, Cary, NC) was used to estimate these functions. This procedure was particularly appropriate because it easily accommodates both discrete (for incident complications and disability) and continuous (for mortality) measurement of event times and allows testing of time dependency, that is, whether the event occurs earlier or later in association with an independent variable. All analyses were adjusted for design effects using SUDAAN statistical software (SAS Institute) (23).

## RESULTS

### Prevalence of diabetes and depression

Almost 23% of individuals in the sample group reported a physician's diagnosis of type 2 diabetes; no variation by sex was noted (Table 1). Approximately 24% of subjects reported minor depression; however, older women reported a substantially higher rate (28.6%) than older men (17.4%). Approximately 9.0% met criteria for any lifetime diagnosis of major depressive episode or dysthymia; however, the rate among older women (11.5%) was more than twice that of older men (5.3%). Categorizing by depressive symptoms, 13% of subjects had neither diabetes nor any depressive symptom, 47% had diabetes with only minimal depressive symptoms, 17.3% had minor depression but no diabetes, 2.8% had diabetes without any depressive symptoms, 13.1% had diabetes with minimal depression, and 6.6% had both diabetes and minor depression. Categorizing by lifetime depressive diagnoses, 71.8% of the sample had neither diabetes nor lifetime depression, 6.5% had lifetime depression but no diabetes, 19.2% had diabetes but no lifetime depression, and 2.5% had both diabetes and lifetime depression.

### Rates of adverse outcomes

By the final wave of follow-up, 35% of individuals in the sample group had macrovascular complications that were not present at baseline, >14% had new microvascular complications, 24% had incident disability, and 28% had died. At all

three waves of follow-up, the older men were less likely to have incident disability but more likely to have died than the older women. Individuals who were aged ≥75 years at baseline were more likely to have incident disability and to have died at all three waves of follow-up. Respondents with ≥12 years of formal education were less likely to have developed macrovascular complications and disability and were less likely to have died at all three waves of follow-up. Those who were married at baseline were less likely to have developed disability and less likely to have died at all three waves of follow-up. Individuals with diabetes or minor depression at baseline, as well as those who met criteria for any lifetime diagnosis of depressive disorders had much higher rates of all four adverse events at all three waves of follow-up (lifetime depressive disorders were measured at the first follow-up and, therefore, could predict death only at the final two waves of follow-up).

Among the diabetic/depressive symptom classes, respondents with both diabetes and minor depression had dramatically higher rates of all four adverse events. For example, by the final wave of follow-up, 44% of subjects with both conditions had macrovascular complications, compared with only 30% who had neither condition. Similar rate differences were apparent for microvascular complications (43% with both conditions versus 36% with only diabetes and only 3% with neither condition), disability (38% with both conditions versus 14% with neither condition), and mortality (45% with both conditions versus 17% with neither condition). The rates for subjects with only diabetes and those with only minor depression were comparable across adverse events, with the exception that those with only diabetes were more likely than those with only minor depression to develop microvascular complications by any of the waves of follow-up.

Importantly, subjects who had diabetes but no depressive symptoms whatsoever (CESD score of 0) were at much lower risk for all adverse outcomes than those with both conditions and at comparable risk to individuals with only minor depression (again, with the exception of microvascular complications).

Similar results were found among the diabetic/depressive diagnosis classes: respondents with both diabetes and any lifetime depressive disorders also had dramatically higher rates of all four adverse events. For example, by the final wave of follow-up, 64% of subjects with both conditions had macrovascular complications compared with only 38% of those with neither condition. Approximately 52% of those with both conditions developed microvascular complications versus 42% of those with only diabetes and 7% of those with neither condition. Incident disability occurred in 52% of subjects with both conditions versus 23% of those with neither condition, and 56% of those with both conditions died by the final wave of follow-up compared with only 18% of those with neither condition. Respondents with neither diabetes nor any lifetime depressive disorder had the lowest rates of all four adverse events, and the rates for those with only diabetes and those with only lifetime depression were comparable across all adverse events, again with the exception that those with only diabetes were more likely than those with only depression to develop diabetic complications.

## Multivariate findings

The elevated risk associated with the interaction of diabetes and depression was even more apparent in the results of the multivariate analyses. Results of preliminary logistic regression models (not shown in the tables) predicting the incidence of all four adverse outcomes indicated that both diabetes and the two measures of depression had significant main effects, with the exception that neither measure of depression predicted the incidence of microvascular complications. More importantly, however, the effects of the interaction between diabetes and depression were striking. First, the effects of the interaction seemed to be synergistic (that is, greater than the additive main effects of diabetes and depression). For example, regarding mortality, the risk associated with the interaction between diabetes and depression (odds ratio [OR] 4.04, 95% CI 2.70–6.02) was greater than the additive main effects of diabetes (1.32, 1.02–1.71) and any lifetime depressive diagnosis (1.29, 1.01–1.69; additive effects for these main effects would be 1.32 × 1.29 or 1.70). Similarly, regarding incident disability, the risk associated with the interaction (4.11, 2.72–6.23) was greater than the additive main effects of diabetes (1.74, 1.26–2.63) and minor depression measured with depressive symptoms (1.27, 1.02–1.81; additive effects for these main effects would be 1.74 × 1.27 or 2.21).

Second, these initial results also indicated that the interaction effects were more substantial earlier than later during the follow-up period. For example, the risk for microvascular complications associated with the interaction between diabetes and any lifetime depressive disorder was considerably higher at the second follow-up (6.58, 4.16–10.39) than at the third follow-up (5.13, 3.32–7.95). Similarly, the risk for mortality associated with the interaction between diabetes and minor depression declined from the first follow-up (5.43, 3.52–8.38) to the second follow-up (3.72, 2.65–5.23) to the third follow-up (3.30, 2.39–4.51). Based on these findings, a series of survival analyses were conducted for each of the four adverse outcomes.

**Macrovascular complications.** Table 2 shows the hazard ratio (HR) for each of the four adverse events associated with the combined risk factors over the 7 years of follow-up, controlling for the influence of sociodemographic characteristics. These results were derived from a set of survival analyses subsequent to the preliminary logistic regression models. As can be seen in Table 2, older Mexican Americans with both diabetes and minor depression had not only a significantly higher risk of comorbid disease than those with neither condition (HR 2.40, 95% CI 1.71–3.36) but also a higher risk than respondents with only minor depression (1.33, 1.14–1.70) or those with diabetes and minimal depression (1.56, 1.21–2.00). Importantly, those who had diabetes but no depressive symptoms whatsoever (CESD score of 0) were at much the same risk (1.35, 1.06–2.27) as individuals with only minor depression, lower than the risk even for those with diabetes and minimal depression. Importantly, these findings illustrate a gradient of risk from diabetic individuals with no depressive symptoms to those with minimal depression to those with minor depression. Similar results were found for incident microvascular complications, incident disability, and mortality (Table 2).

The risks associated with the diabetic/depressive diagnosis classes are also shown in Table 2. Respondents with both diabetes and any lifetime depressive diagnoses had a significantly higher risk of

**Table 2—*HRs for incident adverse outcomes among older Mexican Americans**

| | Macrovascular complications | | Microvascular complications | | Disability | | Mortality | |
|---|---|---|---|---|---|---|---|---|
| | HR | 95% CI | HR | 95% CI | HR | 95% CI | HR | 95% CI |
| Diabetes and depressive symptoms | | | | | | | | |
| Men | 1.03 | 0.90–1.18 | 0.99 | 0.86–1.14 | 0.95 | 0.83–1.09 | 1.73 | 1.49–2.02 |
| Aged 75 years or older | 1.03 | 0.90–1.19 | 0.98 | 0.86–1.12 | 1.27 | 1.11–1.45 | 2.45 | 2.12–2.83 |
| High school education | 0.83 | 0.66–1.02 | 0.83 | 0.66–1.04 | 0.83 | 0.67–1.04 | 1.11 | 0.87–1.42 |
| Married | 0.98 | 0.85–1.12 | 0.97 | 0.84–1.11 | 0.94 | 0.82–1.08 | 0.82 | 0.71–0.96 |
| Minimal depression only† | 1.22 | 0.98–1.50 | 1.26 | 1.01–1.55 | 1.27 | 1.04–1.59 | 1.39 | 1.06–1.82 |
| Minor depression only‡ | 1.33 | 1.14–1.70 | 1.28 | 1.01–1.64 | 1.36 | 1.07–1.74 | 2.02 | 1.50–2.73 |
| Diabetes without any depressive symptoms | 1.35 | 1.06–2.27 | 2.31 | 1.58–3.39 | 1.62 | 1.18–2.52 | 1.91 | 1.19–3.06 |
| Diabetes with minimal depression† | 3.56 | 1.21–2.00 | 2.43 | 1.90–3.14 | 1.71 | 1.32–2.20 | 2.59 | 1.92–3.50 |
| Diabetes with minor depression‡ | 2.40 | 1.71–3.36 | 8.63 | 5.40–13.79 | 6.89 | 4.46–10.64 | 4.94 | 3.30–7.38 |
| Time dependence | 0.73 | 0.95–1.16 | 0.29 | 0.18–0.49 | 0.27 | 0.17–0.44 | 0.59 | 0.37–0.93 |
| Diabetes and lifetime depressive diagnoses | | | | | | | | |
| Men | 1.09 | 0.94–1.26 | 0.77 | 0.61–0.97 | 0.66 | 0.55–0.80 | 1.68 | 1.41–2.000 |
| Aged 75 years or older | 0.98 | 0.85–1.14 | 0.81 | 0.63–1.04 | 2.21 | 1.87–2.63 | 2.85 | 2.41–3.37 |
| High school education | 0.83 | 0.66–1.05 | 0.85 | 0.59–1.22 | 0.86 | 0.64–1.17 | 0.98 | 0.73–1.31 |
| Married | 0.98 | 0.84–1.13 | 1.07 | 0.84–1.34 | 0.82 | 0.69–0.98 | 0.87 | 0.73–1.04 |
| Lifetime depression only‖ | 1.58 | 1.23–2.03 | 0.94 | 0.49–1.79 | 1.38 | 1.02–1.90 | 1.64 | 1.17–2.28 |
| Diabetes only | 1.37 | 1.16–1.62 | 9.30 | 7.38–11.15 | 1.84 | 1.51–2.24 | 1.51 | 1.23–1864 |
| Diabetes and lifetime depression‖ | 2.64 | 1.73–4.04 | 11.32 | 8.76–15.43 | 3.94 | 2.31–6.73 | 4.59 | 2.12–9.93 |
| Time dependence | 0.70 | 0.33–1.15 | 0.60 | 0.30–0.84 | 0.58 | 0.27–0.82 | 0.31 | 0.12–0.62 |

*$n$ = 2,830 for mortality analyses and 2,462 for all other analyses with depressive symptoms, and $n$ = 2,092 for all analyses with lifetime depression; †CESD scores of 1–15; ‡CESD scores of 16 or more; §CESD score of 0; ‖CIDI/DSM-IV criteria for any lifetime major depression or dysthymia.

disability than those with neither condition (3.94, 2.31–6.73). Those with both conditions also had a higher risk than respondents with only depressive diagnoses (1.38, 1.02–1.90) or only diabetes (1.84, 1.51–2.24). Again, similar results were evident for incident macrovascular complications, incident microvascular complications, and mortality.

Importantly, the results from testing for time dependency in regards to having both depression and diabetes (Table 2) indicate that the comorbidity of the two conditions was predictive not only of greater risk but also of earlier risk of all adverse outcomes, with the exception of macrovascular complications. This finding was evident for both the comorbidity of diabetes and minor depression and the comorbidity of diabetes and lifetime depressive disorder.

Because the nature and course of major depression and dysthymia vary considerably, analyses were also conducted that compared the hazards associated with diabetes comorbid with lifetime major depression versus diabetes comorbid with lifetime dysthymia. Although not shown, these results indicated no substantial differences in the risk associated with either depressive disorder, with the exception that lifetime dysthymia was a somewhat stronger predictor of mortality than lifetime major depression.

**CONCLUSIONS** — Our findings provide compelling evidence that the interaction between diabetes and depression, whether measured by clinical diagnostic criteria or by self-reported depressive symptoms, has a synergistic effect on adverse health outcomes in older Mexican Americans. We provide evidence for a gradient response such that the risk of adverse outcomes increases with the increasing severity of depression present with diabetes. Importantly, we also found that the interaction between diabetes and depression predicts not only increased mortality, complications, and disability but also earlier occurrence of all of these adverse outcomes, with the exception of macrovascular complications.

Speculation regarding the pathways by which depression impacts diabetes falls into two broad categories: psychobehavioral and pathophysiological. Depression may influence diabetes through decreased motivation to maintain behaviors that will protect against the development or worsening of diabetes, such as proper weight, diet, and exercise (24). The increased risk of negative diabetic outcomes may also be the result of biologic changes that occur as a result of depression, including neurohormonal or neurotransmitter abnormalities (25), or lowered immune functioning, or inhibited cortisol release, which in turn increase vulnerability to diabetes (26,27). It may also be possible that both depression and diabetes share common pathogenesis, such as actions of the autonomic or sympathetic nervous systems (28,29), polymorphism of genes associated with obesity, insulin resistance, and sensitivity to stress (30), reduction of glucose use and increased insulin resistance (31), common neuroendocrine pathways (32), or the disruption of the hypothalamic-pituitary-adrenal axis (33). The link between depression and diabetes may also be the direct or indirect result of risk factors common to both conditions, such as obesity, inactivity, medication use, and other preexisting psychological and physical conditions (34).

Importantly, psychobehavioral and pathophysiological mechanisms may act independently or in conjunction. There

may also be differences in the timing of actions of psychobehavioral versus pathophysiological mechanisms. A recent study by Peyrot and Rubin (24) suggests that the influence of factors such as stress and social support may engage in response to life circumstances, whereas factors such as disease severity, blood glucose, and other biologic measures may be more consistent, long-term influences.

It should be noted that this study has several limitations. First, diabetes was measured by self-reported physician diagnosis because no measure of fasting blood glucose was available in the study. Self-reports of chronic conditions, however, have been widely used in population-based surveys and have proven to be highly reliable, including self-reports of diabetes (35). Second, although the methods used to assess depression are standard and well validated for use in epidemiologic studies, there is no absolute certainty regarding diagnosis. In addition, the assessment for lifetime depressive disorder did not occur until the first follow-up interview. The fact that similar results were found for both clinical diagnostic criteria and high levels of depressive symptoms and the evidence of a gradient in severity of depression, however, suggest that our findings are robust and generalizable. In addition, we could not account for the transition between depressive states over time. Depression can occur once for a short time period, consistently over a long time period, or can come and go repeatedly over the course of time. Future work will need to incorporate these transitions. Finally, the present study was limited to older Mexican Americans with type 2 diabetes. It is not clear whether the interaction between depression and diabetes is consistent across racial and ethnic groups, across age-groups, or in both type 1 and type 2 diabetes.

This study is unique, however, in that it is the first large, population-based study to show that the interaction between depression and diabetes has a synergistic effect on mortality and the development of complications and disability. In other words, the effects of concomitant depression and diabetes on negative health outcomes are multiplicative, that is, greater than simply the sum of the main effects of each individual condition. Furthermore, our results also show that the interaction results in earlier occurrence of macrovascular complications, microvascular complications, disability, and mortality.

Our study findings hold particular clinical importance because effective treatment is available for both diabetes and depression. Close case management of diabetes that includes assessment and treatment for depression has been shown to be beneficial. Treatment for depression in patients with diabetes can result in improved medical outcomes, as well as improved psychological well-being. Most importantly, treatment for depression has been found to be associated with improved glycemic control (36). Treatment for depression has also been found to result in weight reduction and improvements in diabetic neuropathy (37). Treatment for diabetes has been demonstrated to reduce functional disability, alleviate psychological distress in depressed individuals, and increase overall well-being (38). As it has been amply demonstrated that improved glycemic control results in reductions of the microvascular and macrovascular consequences of diabetes, including mortality (39) and reduction of diabetic symptoms (38), treatment for depression that leads to improved glycemic control is essential for depressed diabetic adults.

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