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Depression and All-Cause Mortality in Persons with Diabetes Mellitus: Are Older Adults at Higher Risk? Results from the Translating Research Into Action for Diabetes Study

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OBJECTIVES: To compare the strength of the association between depression and mortality between elderly and younger individuals with diabetes mellitus.

DESIGN: A survival analysis conducted in a longitudinal cohort study of persons with diabetes mellitus to test the association between depression and mortality in older (≥65) and younger (18–65) adults.

SETTING: Managed care.

PARTICIPANTS: Persons aged 18 and older with diabetes mellitus who participated in the Wave 2 survey of the Translating Research Into Action for Diabetes (TRIAD) Study (N = 3,341).

MEASUREMENTS: The primary outcome was mortality risk, which was measured as days until death using linked data from the National Death Index. Depression was measured using the Patient Health Questionnaire.

RESULTS: After controlling for age, sex, race and ethnicity, income, and other comorbidities, mortality risk in persons with diabetes mellitus was 49% higher in those with depression than in those without, although results varied according to age. After controlling for the same variables, mortality risk in persons aged 65 and older with depression was 78% greater than in those without. For those younger than 65, the effect of depression on mortality was smaller and not statistically significant.

CONCLUSION: This analysis suggests that the effect of depression on mortality in persons with diabetes mellitus is most significant for older adults. Because there is evidence in the literature that treatment of depression in elderly adults can lead to lower mortality, these results may suggest that older adults with diabetes mellitus should be considered a high-priority population for depression screening and treatment. **J Am Geriatr Soc 62:1017–1022, 2014.**

Key words: depression; diabetes mellitus; mortality; elderly

As of 2011, 25.8 million children and adults in the United States had diabetes mellitus, and 79 million had pre-diabetes mellitus.[1] Persons with diabetes mellitus have a mortality rate that is twice as high as persons of similar age without diabetes mellitus.[1] Individuals with diabetes mellitus have also been found to have twice the odds of being depressed as those without diabetes mellitus.[2] In a population of persons with type 2 diabetes mellitus in an integrated healthcare delivery system in Washington State, it was found that persons with depression had a significantly higher mortality risk than those without, and the greater risk was not limited to cardiovascular causes.[3] Other studies, including those limited to elderly populations with diabetes mellitus, have found similar results.[4–8]

None of the prior studies examined the effect modification that increasing age has on depression-related mortality. No prior studies in this area have specifically examined differences in the association between depression and mortality in younger and older populations with diabetes mellitus. Thus, although the literature is consistent that depression is associated with greater mortality in people with diabetes mellitus, it does not adequately show how this effect may vary with age. Using data from the Translating Research Into Action for Diabetes (TRIAD) Study, the association between depression and mortality in persons with diabetes mellitus was examined, stratified

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according to age (<65 vs ≥65). Given the effects of age-related comorbidities and the risk of depression-related nonadherence to diabetes mellitus care in elderly adults, it was hypothesized that the magnitude of the association between depression and mortality would be greater in older than younger adults.

METHODS

Study Design and Participants

TRIAD is a multicenter, prospective, longitudinal study of persons with diabetes mellitus in managed care settings.[9] The study cohort consisted of enrollees from 10 health plans from eight states. Eligible persons were aged 18 and older, community dwelling, and not pregnant; had had diabetes mellitus for more than 1 year; spoke English or Spanish; had been continuously enrolled in their health insurance plan for 18 months or more; used at least one diabetes mellitus–related medical service; and were able to provide informed consent. The institutional review boards at each participating site approved the study, and all participants provided informed consent.

This report specifically analyzed data from the 2003 wave (Wave 2) of TRIAD, in which a depression screen was administered to a sample of participants with diabetes mellitus. These analyses include Wave 2 data from five of the six study sites included in the original baseline survey. The data were collected from TRIAD participants using a mailed survey or a computer-assisted telephone interview supplemented by a medical record review for the same subjects to gather information on clinical variables.

TRIAD originally enrolled a sample of 11,927 adults, with 8,334 completing the initial Wave 1 survey and medical record review. Although 6,760 persons completed the Wave 2 survey, no medical chart data were available for 1,928 (28.5%) subjects, leaving 4,832 persons with both sources of data. The sample size was further reduced by 591 persons because of missing data on at least one chart variable in the analyses, leaving 4,241 persons with complete medical record data. The sample size was further reduced by 900 persons because of missing data on at least one survey variable in the analyses, leaving an analytical sample size of 3,341 (1,402, ≥65; 1,939, <65) with complete survey and chart data.

Variables

The outcome variable was time to mortality, which was measured as days until death after the interview date and calculated using mortality data and dates of death obtained from the National Death Index (NDI). The NDI service, maintained by the National Center for Health Statistics, is a computerized index of death record information compiled from state vital statistics offices and has been found to have a high degree of validity.[10] The NDI is updated annually, approximately 12 months after the end of the calendar year. Each TRIAD research site submitted the participant's first name, last name, Social Security number, date of birth, and state of residence to the NDI. NDI responded with a verification of death and the date of death for all decedents. Each participant had 6 to 7 years of mortality follow-up data, depending on their interview date. NDI data were obtained through 2009.

The primary predictor variable was depression. Depression was measured using the Patient Health Questionnaire (PHQ-8),[11] in which anyone with a score greater than 9 points was classified as depressed. The Charlson Comorbidity Index, which is associated with mortality risk,[12] was a covariate and was scored from comorbidity data in the participant's medical record. Other variables used as covariates in the survival analyses included sex, age, race and ethnicity, income, education, insulin treatment, duration of diabetes mellitus, and marital status, which came from the survey. Except for duration with diabetes mellitus and the Charlson Index, all of the independent variables were treated as categorical to discern any possible nonlinear effects. They were represented using a series of indicators for each category, with one omitted reference category. Age was divided into seven categories (18–34, 35–44, 45–54, 55–64, 65–74 (reference category), 75–84, ≥85). Income was divided into four categories (< $15,000, $15,000–39,999, $40,000–74,999, and ≥$75,000 (reference category)). Education was classified as less than high school graduate, high school graduate, some college, and college graduate or higher (reference category). The categorical cut-points for these variables were selected to ensure that there were sufficient participants in each category for the analysis.

Because 28% of the Wave 2 sample did not have medical record data and could not be included in these analyses, descriptive statistics were used to compare the mean age, duration of diabetes mellitus, physical functioning score as estimated using the PCS-12, and number of comorbidities to estimate how representative the analytical sample was of the original TRIAD Wave 2 cohort.

Statistical Analysis

Cox regression models, adjusted for demographic and health variables and fixed effects for research site were specified to determine the associations between depression and time to death. Adjusted associations between each predictor variable and days until death were expressed as hazard ratios along with their associated 95% confidence intervals. The same analysis was conducted stratified according to age to compare the associations between depression and mortality between the cohort aged 18 to 64 and that aged 65 and older. Finally, two sensitivity analyses were conducted. The first added cardiovascular disease, diabetic nephropathy, and smoking to the regression model, and the second examined the use of antidepressant medication.

RESULTS

To determine whether the analytical sample (N = 3,341) was comparable with the larger sample of TRIAD participants completing Wave 2 surveys (n = 6,760), the age distributions in both groups were compared, and it was found that 53% of the full Wave 2 sample and 58% of the analytical sample was younger than 65. Duration with diabetes mellitus, PCS12 score, and comorbidities were also compared, and the magnitudes of these differences

were small. Those in the analytical sample were approximately 3 years younger, had had diabetes mellitus for 1 year less, scored 0.5 points higher on the PCS12 (range 0–100), and had only a fraction of a comorbidity (0.16) less than participants excluded from the analytical sample.

Descriptive statistics for important outcomes and covariates in the groups with and without depression and unadjusted tests of differences between the two groups for each of these variables are shown in Table 1. All covariates except duration with diabetes mellitus were found to differ significantly between the groups with and without depression. Unadjusted mortality differed significantly between the groups with and without depression, with 27% of those with depression having died, compared with 18% of those without. Survival analyses of days until death were conducted, controlling for the demographic and clinical characteristics listed in Table 1. Table 2 shows the results of these analyses expressed as three sets of hazard ratios. The first shows the hazard ratios for the entire cohort, which is similar to previous studies in the analytical methods and results.[3–8] The estimates stratified according to age are displayed in the second and third columns. Before running the stratified analyses, the need for stratification was evaluated by testing the equality of the structure of the model between the age subsamples. A significant difference in model structure was found (chi-square = 60.82, $P < .001$), indicating the need for stratification. For the analysis of the entire cohort, as shown in the first column of Table 2, participants with depression were 49% more likely to die on any given day than those without even after controlling for age. These results are similar to those of previous studies,[3–7] although in the age-stratified analyses that allow for the effects of depression and the other predictors to vary for the older and younger participants, persons aged 65 and older with depression were nearly 80% more likely to die on any given day than those without. In contrast, in the younger population, the association between depression and mortality was smaller and not statistically significant.

Table 1. Demographic and Health Characteristics of Study Cohort

Characteristic	N	Not Depressed	Depressed[a]	*P*-Value
Total,%	3,341	81.7	18.3	
Female,%	1,777	50.6	64.9	<.001
Insulin treatment,%	648	18.9	23.9	.002
Married or living together,%	2,065	63.9	52.5	<.001
Age, %				
18–34	69	2.0	2.5	<.001
35–44	254	7.0	10.2	
45–54	688	19.6	25.1	
55–64	928	27.3	29.8	
65–74	885	27.7	21.3	
75–84	483	15.4	10.2	
≥85	34	1.0	1.0	
Race and ethnicity, %				
White	1,890	57.2	53.8	.002
Hispanic	532	16.0	15.6	
Black	599	17.0	22.1	
Asian and Pacific Islander	131	4.4	2.0	
Other	189	5.5	6.6	
Income, $,%				
<15,000	818	20.7	41.3	<.001
15,000–39,999	1,073	32.1	32.1	
40,000–74,999	821	26.0	18.2	
≥75,000	629	21.2	8.4	
Education,%				
<High school graduate	607	15.7	29.2	<.001
High school graduate	897	26.4	29.0	
Some college	1,072	32.9	28.4	
≥College graduate	765	25.0	13.4	
Years with diabetes mellitus, mean	3,341	13.0	13.3	.50
Charlson Index, mean	3,341	2.0	2.4	<.001
Deceased,%[b]	666	18.4	26.7	<.001

[a] Patient Health Questionnaire score > 9.

[b] Six- to 7-year follow-up depending on interview date.

Two sensitivity analyses were conducted. In the first, whether cardiovascular disease, diabetic nephropathy, or smoking confounded the effect of depression on mortality was examined. Although there was a significant association between each of the three and mortality, their inclusion in the model did not change the magnitude of the association between depression and mortality. Because of missing data and the resulting decrease in the number of available observations (from 3,341 to 2,698), as well as concerns that these measures may partly mediate the effects of depression on mortality, these variables were excluded from the main analyses.

Whether the use of depression medication caused a change in the association of depression with mortality was examined in the second sensitivity analysis. The results of these analyses are shown in Table 3. Instead of using depression (defined as having a PHQ-8 score >9) as a variable, the association between mortality and having depression and no antidepressant use, as well as between mortality and having a history of antidepressant use within the 18 months before the chart abstraction (with or without current depression) was examined. The reference group contained participants with no current depression (a PHQ-8 ≤ 9) and no history of antidepressant use within the 18 months before the chart abstraction. The results showed that, in the entire cohort, the depressed–no antidepressant group and the antidepressant group had significantly higher mortality risk than those who were not depressed and had no history of antidepressant use. When this analysis was replicated with the same age stratification as the main analyses, the results showed that, although the direction of the estimated effects remained the same, the statistical significance changed substantially. Of those younger than 65, neither the depressed–no antidepressant group nor the antidepressant group had significantly greater mortality risk than the reference group. In the group aged 65 and older, the depressed–no antidepressant group had 90% greater mortality than the reference group, but those with a history of antidepressant use were not statistically different from the reference group. Because of

Table 2. Survival Analyses of Persons with Diabetes Mellitus Stratified According to Age

Variable	Hazard Ratio (95% Confidence Interval)		
	Entire Cohort, N = 3,341	Age≥65, n = 1,402	Age<65, n = 1,939
Depressed[a]	1.49 (1.24–1.80)	1.78 (1.39–2.27)	1.15 (0.86–1.54)
Female	0.53 (0.44–0.62)	0.61 (0.49–0.76)	0.45 (0.34–0.59)
Duration with diabetes mellitus	1.01 (1.00–1.01)	1.01 (1.00–1.02)	1.00 (0.99–1.02)
Insulin treatment	1.20 (0.98–1.46)	1.10 (0.84–1.44)	1.31 (0.97–1.78)
Married or living together	0.77 (0.65–0.92)	0.83 (0.66–1.04)	0.68 (0.51–0.91)
Charlson Index	1.31 (1.26–1.36)	1.28 (1.21–1.35)	1.39 (1.30–1.48)
Age			
18–34	0.08 (0.01–0.56)		Reference
35–44	0.15 (0.07–0.31)		1.96 (0.24–16.02)
45–54	0.58 (0.43–0.76)		7.47 (1.03–54.09)
55–64	0.81 (0.66–1.01)		10.26 (1.42–73.94)
65–74	Reference	Reference	
75–84	1.69 (1.39–2.07)	1.69 (1.38–2.07)	
≥85	4.78 (3.12–7.33)	4.53 (2.94–6.98)	
Race or ethnicity (reference white)			
Hispanic	0.67 (0.51–0.88)	0.83 (0.60–1.15)	0.45 (0.27–0.74)
Black	0.67 (0.53–0.85)	0.55 (0.38–0.79)	0.77 (0.55–1.08)
Asian and Pacific Islander	0.20 (0.07–0.54)	0.29 (0.09–1.92)	0.11 (0.02–0.81)
Other	0.89 (0.65–1.23)	1.08 (0.74–1.58)	0.58 (0.32–1.05)
Income, $ (reference ≥$75,000)			
<15,000	2.39 (1.65–3.45)	2.01 (1.25–3.26)	2.83 (1.58–5.08)
15,000–39,999	2.38 (1.72–3.30)	1.99 (1.28–3.07)	3.08 (1.86–5.11)
40,000–74,999	1.71 (1.22–2.39)	1.80 (1.15–2.84)	1.35 (0.80–2.28)
Education (reference ≥college graduate)			
< High school graduate	1.04 (0.80–1.37)	0.95 (0.68–1.33)	1.18 (0.73–1.90)
High school graduate	0.95 (0.74–1.22)	0.92 (0.68–1.26)	0.96 (0.62–1.48)
Some college	1.01 (0.80–1.28)	0.97 (0.71–1.31)	1.07 (0.72–1.59)

[a] Patient Health Questionnaire score >9.

Table 3. Survival Analyses of Persons With Diabetes Mellitus Overall and Stratified According to Age and Antidepressant Use

Variable	Entire Cohort, N = 2,799		Older Cohort, n = 1,119		Younger Cohort, n = 1,680	
	n (%)	HR (95% CI)	n (%)	HR (95% CI)	n (%)	HR (95% CI)
Depressed---no history of antidepressant use	309 (11)	1.65 (1.30–2.11)	113 (10)	1.9 (1.39–2.59)	196 (12)	1.27 (0.86–1.89)
History of antidepressant use	525 (19)	1.30 (1.04–1.63)	142 (13)	1.12 (0.81–1.56)	383 (23)	1.38 (0.99–1.93)

Reference category was a Patient Health Questionnaire score ≤9 (not depressed) and no history of antidepressant use.
HR = hazard ratio; CI = confidence interval.

missing data and the resulting decrease in the number of observations (from 3,341 to 2,799), these results are presented as a sensitivity analysis rather than as the main analysis.

DISCUSSION

This study examined the association between depression and mortality in a large, diverse group of persons with diabetes mellitus. It also examined these associations stratifying according to age. Results from the age-stratified analyses suggest that the elderly population may be driving the significant associations between depression and mortality found in other full-population studies. Being aged 65 and older had a substantial effect modification on the relationship between depression and mortality. This effect modification is missed when controlling for age alone. There may be differential attrition rates according to age, but if participants with the most-severe depression were more likely to die before the Wave 2 survey, then the observed significance may be an underestimate. In contrast, if participants with greater comorbidity and older age had an observed likelihood of dying from other conditions, the group of healthier survivors at Wave 2 may have had a greater observed magnitude of association between depression and mortality than in the cohort overall.

Because individuals with depression are less likely to adhere to their medications than those without regardless of age,[7,13–15] the resulting higher depression-associated mortality in elderly adults could be due to a stronger effect of nonadherence to diabetes mellitus medication on mortality in this group than in the younger population. Individuals with depression have also been shown to have low levels of adherence to critical diabetes mellitus care treatment such

as diet, exercise, and a glucose self-monitoring regimen.[13,15] This nonadherence can be particularly detrimental to elderly adults, who may already have age-related comorbidities. These age-related changes include physical and psychological changes that can have a negative effect on the severity of depression and other diabetic factors.[7] These cyclical effects may be what caused this drastically greater mortality risk associated with depression in older adults than in younger cohorts of individuals with diabetes mellitus.

There is evidence of undertreatment of depression in primary care settings in elderly persons.[16,17] The results of the sensitivity analysis in Table 3 regarding antidepressant use suggests that effective depression treatment may greatly attenuate the strong link between depression and mortality in elderly person with diabetes mellitus. It is also possible that lower rates of treatment for depression may contribute to the difference in the magnitude of the association between depression and mortality in older adults and that in younger adults. An alternative hypothesis could be that depression is simply a prodromal marker for disease severity and does not have a causal effect on mortality. Several studies have found a strong association between disease severity and comorbid depression in individuals with diabetes mellitus but have concluded that further research is needed to determine the pathways and biological mechanisms associated with this interaction.[18–21] It was attempted in the current study to control for the possibility of confounding by controlling for duration with diabetes mellitus and Charlson Index. It was not possible to control for cognitive impairment. As previous studies have shown, depression, and cognitive impairment are linked, especially in individuals with diabetes mellitus.[22–24] Therefore, the observed effect of depression on mortality in the elderly group may be partially due to unmeasured cognitive impairment, although the fact that each individual in the sample was required to give informed consent to be included in the study and to complete a 45-minute survey without assistance, thus likely excluding those with major cognitive impairment, somewhat mitigated this limitation.

This study has some limitations. First, the measure for depression was the PHQ-8, which is a screening test and not a diagnostic tool. Although PHQ-8 scores above 9 are correlated with depression,[11] they do not confirm the diagnosis. Also, information was not available in TRIAD about individuals who were receiving treatment other than pharmacotherapy for their depression. Second, it was not possible to control for other potentially important unmeasured factors such as family history of other diseases or other environmental factors. Third, the sample included only TRIAD participants for whom Wave 2 data were collected and only for those who had complete data capture. Finally, because the sample was limited to persons with diabetes mellitus with managed care insurance, it may not generalize to those with other forms of coverage or to those who are uninsured.

These results, along with the earlier evidence of complications[18] and greater medical costs[25] that result from untreated depression in individuals with diabetes mellitus, reinforce the importance of screening for depression, particularly in older adults. A previous study analyzing the effectiveness of depression diagnosis and treatment found that older individuals with depression and diabetes mellitus were less likely to die within a 5-year interval if their primary care clinics were implementing depression care management programs.[26] These results, combined with the hypothesis-generating finding that older adults with diabetes mellitus, depression, and a history of antidepressant treatment did not have higher mortality than those without depression, suggests that clinical recognition and treatment of depression may be particularly important for older adults with diabetes mellitus. Using depression screens such as the PHQ-8 or even the abbreviated PHQ-2[27] can be an effective way of recognizing depression before it results in unnecessary health risks that can lead to death. Older adults with diabetes mellitus, in virtually all clinical settings, should be considered a top priority for these screenings. Using a two-item screen such as the PHQ-2 will help physicians identify individuals with diabetes mellitus at high risk of depression during a routine visit and should facilitate timely diagnosis with the PHQ-9 or referral to confirm diagnosis and treat if needed,[6] but further research will need to be conducted to determine the best practices for the treatment of depression in individuals with diabetes mellitus because there are mixed reviews on the effectiveness of treatment as depression worsens.[28–30] Therefore, it is of vital importance, particularly in elderly adults, to screen and treat depression as soon as possible.

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Conflict of Interest: The editor in chief has reviewed the conflict of interest checklist provided by the authors and has determined that the authors have no financial or any other kind of personal conflicts with this paper.

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Author Contributions: Kimbro L.: primary author of this manuscript. She conducted the literature review,

participated in the analysis meetings, and wrote the final manuscript. Neil Steers W.: lead analyst on the study. Mangione C., Kenrik Duru O., McEwen L., and Karter A.: contributed to the manuscript during the analysis phases and manuscript review process. Ettner S. L.: acted as the senior author, giving consistent feedback throughout the entire process.

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