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Depression and All-Cause Mortality Among Persons With Diabetes: Are Older Adults at Higher Risk? - Results from the Translating Research Into Action for Diabetes (TRIAD) Study

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Abstract

Background/Objectives—Several studies have found that depression leads to an increased risk of mortality among patients with diabetes. Our goal is to compare the strength of the association between depression and mortality between the elderly and non-elderly population.

Design—A survival analysis conducted in a longitudinal cohort study of persons with diabetes to test the association of depression and mortality among Medicare-aged and non-Medicare aged persons.

Setting—Managed care.

Participants—3341 persons aged 18 and over with diabetes who participated in the wave 2 survey of the Translating Research Into Action for Diabetes (TRIAD) study.

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Author Contributions: Lindsay Kimbro is the primary author of this manuscript. She conducted the literature review, participated in the analysis meetings, and wrote the final manuscript. Neil Steers is the lead analyst on the study. Carol Mangione, Kenrik Duru, Laura McEwen, and Andrew Karter all contributed to the manuscript during the analyses phases and during the manuscript review process. Susan Ettner acted as the senior author giving consistent feedback throughout the entire process.
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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.

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 (PHQ8).

Results—After controlling for age, gender, race/ethnicity, income, and other comorbidities, mortality risk among depressed persons with diabetes was 49% higher than among non-depressed persons with diabetes. However, our results varied by age. After controlling for the same variables, mortality risk among persons over the age 65 years and older with depression was 78% greater than among elderly persons without depression. For the less than 65-year-old cohort, the effect of depression on mortality was smaller and not statistically significant.

Conclusion—This analysis suggests that the effect of depression on mortality among persons with diabetes is most significant for older adults. Because there is evidence in the literature that treatment of depression in the elderly can lead to lower mortality, our results may suggest that older adults with diabetes should be considered a high priority population for depression screening and treatment.

Keywords

Depression; Diabetes; Mortality; Elderly

INTRODUCTION

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

However, 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 looked at differences in the association of depression with mortality between Medicare-age and non-Medicare-age populations with diabetes. Thus, although the literature is consistent that depression is associated with an increased rate of mortality among people with diabetes, it does not adequately show how this effect may vary with age. Using data from the Translating Research Into Action for Diabetes (TRIAD) Study, we examined the association of depression with increased mortality among persons with diabetes, stratified by age group (below 65 versus 65 and over). Given the worsening health effects of age-related comorbidities and the increased risks of depression-related non-adherence to diabetes care among the elderly, we hypothesize that the magnitude of the association of depression and mortality will be greater among the Medicare-aged population than among younger persons.

METHODS

Study Design and Participants

TRIAD is a multicenter prospective longitudinal study of persons with diabetes in managed care settings. The study cohort consisted of enrollees from 10 health plans from 8 different states. Eligible persons were 18 years of age and older, community dwelling, not pregnant, had diabetes for more than 1 year, spoke English or Spanish, were continuously enrolled in their health insurance plan for 18 months or more, used at least 1 diabetes-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 analyzes data from the 2003 wave (wave 2) of TRIAD, in which a depression screener was administered to a patient sample with diabetes. 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 due to missing data on at least one chart variable in our analyses, leaving 4,241 persons with complete medical record data. The sample size was further reduced by 900 persons due to missing data on at least one survey variable in our analyses, leaving an analytic sample size of 3,341 (N=1,402 age 65 and over; N=1,939 under age 65) with complete survey and chart data.

Variables

The outcome variable was time-to-mortality, which was measured as days until death following 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 (NCHS), 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 on all decedents. Each individual participant has 6 to 7 years of mortality follow-up data, dependent upon their interview date. NDI data were obtained through 2009.

The primary predictor variable was depression. Depression was measured using the Patient Health Questionnaire (PHQ8),[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, and marital status,

which came from the patient survey. Except for duration with diabetes and the Charlson Index, all of the independent variables were treated as categorical in order to discern any possible non-linear effects. They were represented using a series of indicators for each category, with one omitted reference category. Age was divided into 7 categories: 18-<35, 35-<45, 45-<55, 55-<65, 65-<75 (the reference category), 75-<85, and 85+ years. Income was divided into 4 categories: less than $15k, $15k-$39,999k, $40k-$75k, and over $75k (the reference category). Education was classified as follows: less than high school graduate, high school graduate, some college, and college graduate or higher (the 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, we used descriptive statistics to compare the mean age, duration of diabetes, physical functioning score as estimated by the PCS-12, and number of comorbidities to estimate how representative the analytic sample was of the original TRIAD Wave 2 cohort.

Statistical Analysis

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

RESULTS

To determine if our analytic sample (N=3341) was comparable to the larger sample of TRIAD participants completing wave 2 surveys (N=6760), we compared the age distributions in both groups, and found thatin the full wave 2 sample, 53% were age 64 and under, whereas in the analytic sample, 58% were age 64 and under. We also compared duration with diabetes, PCS12 scores and comorbidities, and the magnitudes of these differences were very small. Those in the analytic sample were approximately three years younger, had diabetes for 1 less year, scored one half-point higher on the PCS12 scores (range: 0-100), and had only a fraction of a comorbidity (0.16) less than those participants excluded from the analytic sample.

Descriptive statistics for key outcomes and covariates in the depressed and non-depressed groups 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 were found to differ significantly between the depressed and not depressed groups. Unadjusted mortality rates differed significantly between the depressed and non-depressed groups, with 27% of the depressed being classified as deceased compared to 18% of the non-depressed group.

We conducted survival analyses of days until death controlling for the demographics and clinical characteristics listed in Table 1. Table 2 shows the results of these analyses expressed as three different sets of hazard ratios. The first shows the hazard ratios for the entire cohort, which is similar to previous studies in both the analytic methods and results.[3-8] The estimates stratified by age group are displayed in the second and third columns, respectively. Before running the stratified analyses, we evaluated the need for stratification by testing the equality of the structure of our model between the age-65-and-older subsample and the under-age-65 subsample. A significant difference in model structure was found (chi-square = 60.82, $p < 0.001$), thus indicating the need for stratification. For the analysis of the entire cohort, as shown in the first column of the table, depressed persons were 49% more likely to die on any given day than their non-depressed counterparts even when controlling for age. These results are similar to those of previous studies.[3-7] However, in the age-stratified analyses that allow for the effects of depression and the other predictors to vary for the elderly vs. the non-elderly, we found that depressed persons in the 65 and over age stratum were nearly 80% more likely to die on any given day than their non-depressed counterparts. In contrast, among the younger population, the association between depression and mortality becomes small and is no longer statistically significant.

We conducted two sensitivity analyses. In our first analysis, we examine whether cardiovascular disease, diabetic nephropathy, or smoking confounded the effect of depression on mortality. Although all three did show a significant association with mortality, their inclusion in the model did not change the magnitude of the association of depression with mortality. Due to missing data and the resulting decrease in the number of available observations (from 3341 to 2698), as well as concerns that these measures may partly mediate the effects of depression on mortality, these variables were excluded from the main analyses.

In the second sensitivity analysis, we examined whether the use of depression medication caused a change in the association of depression with mortality. The results of these analyses are shown in Table 3. Instead of using depression (defined as having a PHQ8 score > 9) as a variable, we examined the association of mortality with having depression and no antidepressant use as well as with having a history of antidepressant use within the 18 months prior to the chart abstraction (with or without current depression). The reference group contains those with no current depression (i.e., a PHQ8 ≤ 9) and no history of antidepressant use within the 18 months prior to the chart abstraction. The results showed that among the entire cohort, both the “depressed/no antidepressant group” and the “antidepressant group” had a 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 while the direction of the estimated effects remained the same, the statistical significance changed substantially. Among the <65 years cohort, neither the “depressed/no antidepressant group” nor the “antidepressant group” had a significantly higher mortality risk than the reference group. Among the ≥65 year cohort, the “depressed/no antidepressant group” had a 90% higher mortality rate than the reference group, but those with a history of antidepressant use were not statistically different from the reference group. Due to missing data and the resulting

decrease in the number of observations (from 3341 to 2799), these results are presented as a sensitivity analysis rather than as the main analyses.

DISCUSSION

Our study examines the association between depression and mortality within a large, diverse group of persons with diabetes. In addition, our study also examines these associations stratifying by Medicare-aged versus younger age. Our results from the age-stratified analyses suggests that the significant associations between depression and mortality found in other full-population studies may be driven by the elderly population. In our sample, being ≥ 65 years of age had a substantial effect modification on the relationship between depression and mortality. This effect modification is missed when simply controlling for age alone. There are possibly differential attrition rates by age. However, if participants with the most severe depression were more likely to die prior to the wave 2 survey, then the observed significance associated may be an underestimate. In contrast, if patients with greater comorbidity and age had an observed likelihood of dying from other conditions, our group of healthier survivors at wave 2 may have had a greater observed magnitude of association between depression and mortality than what may have been observed in the cohort overall.

Because depressed persons are less likely to be adherent to their medications than non-depressed persons regardless of age[7, 13-15], the resulting higher depression-associated mortality among the elderly could be due to a stronger effect of non-adherence to diabetes medication on mortality among this group as compared to the younger population. Depressed persons have also been shown to have low levels of adherence to critical diabetes care treatment such as diet, exercise, and glucose self-monitoring regimine.[13,15] This non-adherence can be particularly detrimental to the elderly who may already be suffering from age-related comorbidities. These age-related changes include both physical and psychological changes that can have a negative effect on both the severity of depression and other diabetic factors[7] These cyclical effects may be what caused this drastic increase of mortality risk associated with depression among older adults as compared to the younger cohorts of diabetic persons.

There is evidence of under-treatment of depression in primary care settings among 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 among elderly person with diabetes. 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 among older adults as compared to the younger cohort. An alternative hypothesis could be that depression is simply a prodromal marker for increasing disease severity and does not have a causal effect on mortality. Several studies have found a strong association of disease severity with comorbid depression among diabetics but have concluded that further research is needed to determine the pathways and biological mechanisms associated with this interaction.[18-21] In this study, we have tried to control for the possibility of confounding by controlling for duration with diabetes and the Charlson Index. Importantly, we were not able to control for cognitive impairment. As previous studies have shown, depression, and cognitive impairment are

linked, especially in individuals with diabetes.[22-24] Therefore, the observed effect of depression on mortality among the elderly group may be partially due to unmeasured cognitive impairment. However, this limitation is somewhat mitigated by the fact that each individual in the sample was required to give informed consent in order to be included in the study and had to be able to complete a 45 minute survey without assistance, thus likely excluding those with major cognitive impairment.

Our study has some limitations. First, our measure for depression was the PHQ8 questionnaire, which is a screening test and not a diagnostic tool. Although PHQ8 scores above 9 are correlated with depression[11], they do not confirm the diagnosis. Also, in TRIAD, we did not have information about those who are receiving treatment for their depression other than pharmacotherapy. Second, we were unable to control for other potentially important unmeasured factors such as family history of other diseases or other environmental factors. Third, our sample included only TRIAD participants for whom wave 2 data were collected and only for those who had complete data capture. Finally, as our sample was limited to persons with diabetes with managed care insurance, it may not generalize to those with other forms of coverage or to the uninsured.

Our results, along with the earlier evidence of complications[25] and increased medical costs[26] that result from untreated depression among those with diabetes, reinforce the importance of screening for depression, particularly among older adults. A previous study analyzing the effectiveness of depression diagnosis and treatment found that older depressed patients with diabetes were less likely to die within a 5-year interval if their primary care clinics were implementing depression care management programs.[27]These results, combined with our hypothesis-generating finding that older adults with diabetes and depression did not have higher mortality among those with a history of antidepressant treatment, suggests that clinical recognition and treatment of depression may be particularly important for older adults with diabetes. Using depression screeners such as the PHQ-8 or even the abbreviated PHQ-2[28] can be an effective way of recognizing depression before it results in unnecessary health risks that can lead to death. Older adults with diabetes, in virtually all clinical settings, should be considered a top priority for these screenings. Using a two-item screener, such as the PHQ-2 will help physicians identify diabetes patients with 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.[29] However, further research will need to be conducted to determine the “best practices” for the treatment of depression in diabetic persons, as there are mixed reviews on the effectiveness of treatment as depression worsens.[30-32] Therefore, it is of vital importance, particularly among the elderly, to screen and treat depression as soon as possible.

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Table 1

Demographic and Health Characteristics of Study Cohort

Variable	N	Not Depressed	Depressed*	P-value
Total	3341	81.7%	18.3%	
Gender				<0.01
Female	1777	50.6%	64.9%	
Insulin Treatment	648	18.9%	23.9%	<0.01
Married or Living together	2065	63.9%	52.5%	<0.01
Age				<0.01
18- <35	69	2.0%	2.5%	
35- <45	254	7.0%	10.2%	
45- <55	688	19.6%	25.1%	
55- <65	928	27.3%	29.8%	
65- <75	885	27.7%	21.3%	
75- <85	483	15.4%	10.2%	
85+	34	1.0%	1.0%	
Race/Ethnicity				<0.01
White	1890	57.2%	53.8%	
Hispanic	532	16.0%	15.6%	
Black	599	17.0%	22.1%	
Asian/Pacific Islander	131	4.4%	2.0%	
Other	189	5.5%	6.6%	
Income				<0.01
<$15,000	818	20.7%	41.3%	
$15,000 - <$40,000	1073	32.1%	32.1%	
$40,000 - <$75,000	821	26.0%	18.2%	
$75,000+	629	21.2%	8.4%	
Education Level:				<0.01
<High School graduate	607	15.7%	29.2%	
High School graduate	897	26.4%	29.0%	
Some College	1072	32.9%	28.4%	
College grad or higher	765	25.0%	13.4%	
Mean duration with Diabetes (in years)	3341	13.0	13.3	0.5
Charlson Index Mean	3341	2.0	2.4	<0.01
Deceased	666	18.4%	26.7%	<.01

**6-7 year follow up depending on interview date.

* Depressed is defined as a PHQ8 score of > 9

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Table 2

Hazard Ratios of Survival Analyses of Persons with Diabetes Overall and When Stratified by Younger than or Equal to and Older than Age 65

Variable	Entire Cohort N= 3341			Older Cohort ≥ 65 years old N = 1402			Younger Cohort < 65 years old N =1939		
	Hazard Ratio for Mortality	**HR CI (Low)**	**HR CI (High)**	**Hazard Ratio for Mortality**	**HR CI (Low)**	**HR CI (High)**	**Hazard Ratio for Mortality**	**HR CI (Low)**	**HR CI (High)**
Depressed*	**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	1.01	1.00	1.01	1.01	1.00	1.02	1.00	0.99	1.02
Insulin Treatment	1.20	.98	1.46	1.10	0.84	1.44	1.31	0.97	1.78
Married or Living together	**0.77**	**0.65**	**.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- <35	**0.08**	**0.01**	**0.56**	--	--	--	**Ref**	--	--
35- <45	**0.15**	**0.07**	**0.31**	--	--	--	1.96	0.24	16.02
45- <55	**0.58**	**0.43**	**0.76**	--	--	--	**7.47**	**1.03**	**54.09**
55- <65	0.81	0.66	1.01	--	--	--	**10.26**	**1.42**	**73.94**
65- <75	**Ref**	--	--	**Ref**	--	--	--	--	--
75- <85	**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/Ethnicity (ref: White/Caucasian)									
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/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 (ref: >$75,000)									
<$15,000	**2.39**	**1.65**	**3.45**	**2.01**	**1.25**	**3.26**	**2.83**	**1.58**	**5.08**
$15,000 - <$40,000	**2.38**	**1.72**	**3.30**	**1.99**	**1.28**	**3.07**	**3.08**	**1.86**	**5.11**
$40,000 - <$75,000	**1.71**	**1.22**	**2.39**	**1.80**	**1.15**	**2.84**	1.35	0.80	2.28
Education Level (ref: College grad or higher)									
< High School grad	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

*Depressed is a PHQ8 score of >9

Table 3

Hazard Ratios of Survival Analyses of Persons with Diabetes overall and When Stratified by Younger than or Equal to and Older than Age 65 and by Depression Medication Use.

	Entire Cohort N=2799 (100%)			**Older Cohort ≥ 65 years old N = 1119**			**Younger Cohort < 65 years old N =1680**		
Variable*	**Hazard Ratio for Mortality**	**HR CI (Low)**	**HR CI (High)**	**Hazard Ratio for Mortality**	**HR CI (Low)**	**HR CI (High)**	**Hazard Ratio for Mortality**	**HR CI (Low)**	**HR CI (High)**
Depressed - no history of antidepressant use**	**N = 309 (11% of entire cohort) HR = 1.65**	**1.30**	**2.11**	**N = 113 (10% of older cohort) HR = 1.9**	**1.39**	**2.59**	N = 196 (12% of younger cohort) HR = 1.27	0.86	1.89
History of antidepressant use***	**N = 525 (19% of entire cohort) HR = 1.30**	**1.04**	**1.63**	N = 142 (13% of older cohort) HR = 1.12	0.81	1.56	N = 383 (23% of younger cohort) HR = 1.38	0.99	1.93

* Reference category was anyone with a PHQ8 score ≤9 and no history of antidepressant use.

** Those who were classified depressed with a PHQ8 score of greater than 9 but have no history of antidepressant use.

*** Those who have any history of antidepressant use.