

Depression and Death in Diabetes; 10-year follow up of all cause and cause specific
mortality in a diabetic cohort

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ABSTRACT

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Background: When depression co-occurs with type 2 diabetes, adverse bidirectional interactions increase the burden of both illnesses. In addition to affecting patient's health, functioning, and quality of life, this relationship also results in increased mortality as compared to those with depression or diabetes alone.

Objective: The purpose of this study was to examine the relationship between depression and all cause as well as cause specific mortality in patients with type 2 diabetes by extending findings from our 5-year mortality study. Specifically, we re-examined the risk of depression and all cause, cardiovascular, cancer and non-cardiovascular, non-cancer related deaths.

Method: We used an ICD-10 algorithm combined with death certificate data to classify mortality types among type 2 diabetic patients who participated in the Pathways Epidemiologic Study. Cox proportional hazard modeling was used to examine the relationships between depression status and mortality over a 10-year period

Results: We found a significant, positive relationship between depression and all cause as well as non-cardiovascular, non-cancer mortality in this sample (n=4128).

Cardiovascular mortality failed to reach significance in fully adjusted models, and, in contrast to the 5-year data, no trend or significant relationship was observed between depression status and cancer related deaths.

Conclusions: Our study confirmed a significant, positive relationship between depression and mortality in patients with type 2 diabetes. Major depression demonstrated a stronger relationship than did minor depression, and among cause specific groups, non-cardiovascular, non-cancer death types demonstrated the largest magnitude of association with depression status.

INTRODUCTION:

Depression and type 2 diabetes are among the most prevalent chronic conditions in primary care. Individually, they are present in approximately 10% of primary care patients (1, 2) and both contribute significantly to decreased health, functioning and quality of life (3, 4). Depression and diabetes are also independently associated with a marked increase in healthcare expenditures (5).

When depression co-occurs with type 2 diabetes, a bidirectional relationship increases the burden of both illnesses (6). In the presence of diabetes, depression prevalence increases to up to 30% depending on definition (screening measure versus structured psychiatric interview) and the population surveyed (7, 8). In addition, duration of depression in the majority of diabetic patients lasts 2 years or longer (9) and relapse rates are high (10). Functional disability associated with comorbid depression and diabetes is more than additive, leaving patients more functionally impaired than those suffering from either diabetes or depression alone (11-13).

The impact of type 2 diabetes is also amplified by depression. In addition to greater deficits in self care including adherence to diet, exercise, smoking cessation and taking medications as prescribed, comorbid depression is associated with increased medical symptom burden (14), medical morbidity (15), increased risk of subsequent microvascular and macrovascular complications (16, 17), hospitalization (18) and dementia (19, 20). Comorbid depression in patients with diabetes has also been shown to be significantly associated with increased risk of mortality (21-31).

Literature examining the association between depression, diabetes and death has suggested a possible causative role of depression in risk of mortality. In addition to multiple studies showing that comorbid depression is associated with increased risk of all cause mortality (death from any cause) in patients with diabetes, the magnitude of the association between depression and death has been shown in some studies to increase as the severity of depression increases (22, 28, 29). Moreover, the highest risk of mortality is observed when both depression and diabetes are present together compared to when patients have only one or neither of these conditions (23, 27, 28). Few studies have examined cause specific mortality in patients with depression and diabetes, but among those that have, most have focused on cardiovascular mortality. Our research group has previously published a study showing that comorbid depression and diabetes was associated with non-cardiac, non-cancer mortality and that similar but non-significant trends were evident for cardiovascular and cancer related mortality (22).

The purpose of this study is to further examine the relationship between depression and cause specific mortality in diabetic patients. Specifically, we will extend the findings from our 5 year study in order to examine 10 year trends in the relationship between depression and cardiovascular as well as cancer related deaths. We will also examine all cause mortality and report on which specific types of mortality are most common among the non-cardiovascular, non-cancer deaths.

METHODS:

Setting and cohort selection:

This study was conducted using data from the Pathways Epidemiologic study, which is a prospective cohort study of diabetic patients from the Group Health Cooperative (GHC) health care system in western Washington. GHC is a large, mixed model healthcare organization that insures approximately half a million members representative of the greater Seattle area and provides primarily outpatient services including primary care and behavioral health services. A full explanation of the setting, study design and cohort selection has been reported elsewhere (9, 22).

Briefly, diabetic patients from nine GHC primary care clinics were selected from a diabetes registry to participate in the Pathways study (see figure 1). Nine thousand and sixty-four diabetic patients were identified between 2000 and 2002 and 7,841 were eligible for the study. These patients were sent baseline surveys and 4,623 patients (61.7%) successfully completed and returned the questionnaire. Among the 4,623 patients who returned the baseline Pathways study questionnaire, 73 were excluded after loss to follow-up or because vital status was unknown. Of the remaining 4,550, 102 refused consent for follow up and 324 were missing predictor, outcome or other covariate data. These losses resulted in a cohort of 4,128 patients (53% of those originally eligible or 89% of those who successfully completed and returned the survey) for this analysis. Differences between responders and non-responders included that non-responders were younger (mean age of 58.9 years vs 64.6 years), less likely to have had a recent glycosylated hemoglobin (HbA_{1c}), less likely to be on an antidepressant (23% vs 26%), less likely to be treated with insulin (25% vs 30%), and had less medical comorbidity (RxRisk, mean 2,873 vs 3,490). Of those non-responders who did have a recent HbA_{1c},

non-responders were more likely to have glycosylated hemoglobin that exceeded 8% (50% vs 37%).

Measures:

All patient data was gathered at baseline. The patient survey included information on socioeconomic status (age, sex, race, education level, and employment status), diabetes duration, diabetes treatment intensity (none, oral, insulin or both), and health risk behaviors (smoking, physical activity defined as 0 vs 1 day/week of exercise or more (32)). Medical record review and automated laboratory data were utilized to obtain the following: presence of hypertension, body mass index (BMI), and HbA_{1c} levels in the year before entry into the study. Computerized pharmacy records were used to calculate a modified RxRisk for study participants (22). The RxRisk has been shown to predict health care expenditures and patient mortality in previous studies (33, 34) and was used as a measure of medical comorbidity. Depression was measured using the Patient Health Questionnaire 9 (PHQ-9), a diagnostic self-report instrument validated in primary care populations (35) and based on the Diagnostic and Statistical Manual of Mental Disorders IV (DSM IV) symptoms of depression. Each of the nine DSM-IV symptoms are scored on a likert scale from 0 (no days per week) to 3 (nearly every day). Minor depression was defined as scoring 2 or more on either depressed mood or anhedonia in addition to scoring 2 or more on at least one other symptom of depression without meeting criteria for major depression. Major depression was defined as scoring 2 or more on either depression or anhedonia and a 2 or more on at least four other symptoms.

Cause of Death and Mortality:

Death certificate data was obtained as part of GHC's yearly, computerized match of enrollees with Washington state death data, and cause of death was assigned based on the underlying cause of death as listed on participant death certificates. A Charlson Comorbidity and ICD-10 code based algorithm was used to sort underlying cause of death into groups by death type (36, 37). This method for identifying cause of death was different from the method we used in our previous report, which utilized primarily clinician chart review according to the protocol described in the Women's Health Initiative study (38). In order to assess the validity of the algorithm in this study, we applied the algorithm to our five-year data and compared causes of death as determined by case review versus algorithm. The comparison produced an overall kappa of 0.81 (0.77, 0.85) across three cause specific subgroups suggesting there was "substantial" to "almost perfect agreement" between the two methods with regard to their ability to classify cause of death. For the cause specific deaths, three major categories were formed based on the absolute number of events or power to detect an association, and these included cardiovascular related deaths, cancer related deaths and non-cardiovascular, non-cancer related deaths. Cardiovascular deaths included those caused by coronary artery disease, peripheral vascular disease and stroke. Cancer deaths included death related to any cancer. The non-cardiovascular, non-cancer deaths represented death due to all other causes including non-coronary related cardiac deaths such as arrhythmia and valvular disease as well as suicide.

Statistical Analysis:

Survival analysis was performed using Cox proportional hazard models. Our predictor was depression status defined as not depressed, minor depression or major depression with each group being mutually exclusive. The outcome of interest was death, and this was examined as all cause and cause specific mortality. Other variables were used as covariates to control for demographic information (age, race, sex, education level, and marital status), clinical characteristics (medical comorbidity, hypertension, diabetes duration, and treatment intensity), and health behaviors and diabetes control measures (smoking, physical activity, BMI and HbA_{1c}). Three survival models were created with sequential inclusion of each group of covariates in order to control for baseline differences or confounding. Proportional hazard assumptions were examined using Schoenfeld residuals and no violation was observed.

The cause specific analysis was performed using a cumulative incidence approach (Fine and Gray (39)) due to the presence of competing risks (39-41) by death type. Time to death was calculated by subtracting enrollment date from date of death or the date subjects were censored due to study exit.

Given the relative increase in number of cardiac-related deaths due to non-coronary causes between the five and ten year time periods (1.4% of non-CVD, non-CA deaths at 5 years and 6.7% of deaths at 10 years), we performed a sensitivity analysis to examine the effect of including all cardiac deaths (coronary and due to heart disease but not

coronary in origin) under the major cardiovascular related death grouping. All statistical analysis was performed using STATA 12.0.

RESULTS:

Patients with major depression were significantly younger, more likely to be female, more likely to receive treatment with insulin, less likely to be physically active and more likely to be smokers compared to those without depression. They also had a higher HbA_{1c}, greater medical comorbidity, and higher BMI. Those with minor depression were less likely to have graduated high school, more likely to be treated with insulin, and less likely to be active compared to those without depression. They also had an average duration of diabetes greater than subjects without depression and had increased medical comorbidity (Table 1).

Of the 4,128 patients, 1217 deaths occurred during the follow up period including 97 deaths due to unknown causes. We observed the following number of deaths by depression status: 766/3,279 (23.4%) for the non-depressed, 102/343 (29.7%) of those with minor depression and 142/495 (28.7%) of those with major depression. Of the 1120 deaths for which we were able to determine cause of death, 437 were identified as due to cardiovascular causes, 270 due to cancer and 413 due to non-cancer, non-cardiovascular causes. Table 2 describes the breakdown by subgroups with a comparison to our five-year results. Average time until event in the study was 7.2 years with a standard deviation of 2.1 years.

In Cox proportional hazard models (Table 3) major depression was significantly associated with all cause mortality. The strength of the association decreased as each model became more inclusive with the demographically, clinically and fully adjusted models hazard ratios at 1.97 (95% CI 1.64, 2.37), 1.62 (95% CI 1.35, 1.96), and 1.52 (95% CI 1.25, 1.85) respectively. The association between minor depression and all cause mortality was of lesser magnitude than that observed with major depression, but followed a similar trend with the fully adjusted model HR of 1.22 (95% CI 0.99, 1.52). Cause specific modeling demonstrated that major depression trended positively with cardiovascular associated deaths, though it only reached significance in the demographically adjusted model with a HR of 1.71 (95% CI 1.27, 2.31). Minor depression was not associated with cardiovascular deaths in demographically, clinically or fully adjusted models. Neither minor nor major depression demonstrated any association with cancer related deaths. Of all mortality categories, minor and major depression showed the strongest relationships with non-cardiovascular, non-cancer death types. Respective risks for these fully adjusted models were 1.42 (95% CI 1.02, 1.99) for minor depression and 1.61 (95% CI 1.17, 2.22) for major depression. Data from our five year study was very similar to the 10-year data with the exception that in the 5-year data hazard ratios were generally larger in magnitude and there appeared to be a larger but non significant, positive trend between depression and risk of cancer related deaths. Minor differences included that the relationship between five-year minor depression and non-cardiovascular, non-cancer mortality just failed to reach statistical significance (HR of 1.54 95% CI 0.98, 2.42). Sensitivity analysis revealed no significant differences when all

types of cardiac related deaths were combined including both coronary and non-coronary related cardiac deaths.

DISCUSSION:

Our study demonstrates a clear association between depression and 10-year all cause mortality with the non-cardiovascular, non-cancer death types accounting for the majority of this association. However, the association between depression and cardiovascular mortality failed to reach significance in our cohort. In comparison to our five-year data, the 10-year study helped to better characterize some of the 5-year trends. For example, in addition to the lack of significance between depression and cardiovascular deaths mentioned above, the association between depression and cancer deaths, which trended positive in the 5-year study, disappeared completely in the 10-year data. It was also apparent that non-cardiovascular, non-cancer mortality was most strongly associated with depression in both the 5-year and 10-year results. Other notable findings include that depression severity (major vs minor depression) was associated with mortality in all categories. This “dose-response” relationship supports a possible causative role for depression in all cause and cause specific mortality within this diabetic cohort. However, a large treatment study in patients with comorbid depression and diabetes is needed to determine whether improving depression outcomes decreases mortality risk.

Our study did not find that major or minor depression increased the risk of cardiovascular deaths in patients with type 2 diabetes. However, a recent meta-analysis (42) found that major depression was associated with an increase risk of cardiovascular

mortality in patients with diabetes across four studies. The hazard ratio found in this meta-analysis was actually quite similar to the one found in the present study but confidence intervals showed greater certainty (meta-analysis HR=1.21 95% CI:1.05, 1.37 vs HR=1.24 95% CI:0.88, 1.76 from our study). These data suggest our study may have been underpowered to show a significant risk of depression with cardiovascular mortality. Our analyses are also likely conservative because we controlled for covariates that are both potential confounders and mediators of the relationship between depression, diabetes and death type. Type 2 diabetes often occurs up to five years earlier in patients with depression (43), and depression has been shown in longitudinal studies to be a risk factor for poor glycemic control as well as macrovascular and microvascular complications. Depression often begins early in adult life and is also a risk factor for smoking, obesity and becoming less physically active. Depression is also associated with psychobiologic risk factors such as increased cortisol levels, dysregulation of the autonomic nervous system, and increased inflammatory factors, all of which could lead to earlier development of diabetes and poor control of diabetes (44, 45). Our analyses conservatively controlled for indicators of diabetes severity (insulin use, number of diabetes complications, and HbA1c) and health risk behaviors (smoking, physical activity and BMI), which likely affected the association of depression with mortality. Taking these adjustments into consideration and their tendency to decrease the risk of mortality associated with depression may explain why the relationship between major depression, diabetes and cardiovascular mortality was significant in the demographically adjusted model with a HR of 1.71 (1.27, 2.31), but became non-significant in the more fully adjusted models.

Given the high risk of cardiovascular related death among those with diabetes and in the general US population, it is understandable why most studies have focused on the relationship between depression and cardiovascular mortality. However, this study adds to the more limited literature showing that the strongest relationship between depression, diabetes and death is within the non-cardiovascular, non-cancer death types. Behavioral mediators such as lack of adherence to medications, diet and exercise may account for the effects of depression on cardiovascular death types, but this relationship is not as easily explained when examining the stronger link between depression and non-cardiovascular, non-cancer death types. Of the mortality types in this group, non-coronary heart disease (7%), infection (7%), and dementia and other CNS (6%) related deaths were most common. Low numbers of these death types precluded statistical analysis, however, known associations already exist between depression and risk of infection in aging, diabetic populations (46) as well as depression and risk of dementia (19, 20) in patients with diabetes.

The strengths of this study include that analysis was performed on data from a large, prospective cohort that was well characterized with regard to many potentially confounding factors. Other strengths include that it was conducted longitudinally over a 10-year time period and allows for comparisons between 5 and 10-year outcomes. Limitations include that predictor and covariate data were collected only at baseline, however, we believe this should subject us to a conservative bias, ultimately underestimating the magnitude of the association between depression and all cause and cause specific mortality. We estimate the bias to be conservative because we would expect the magnitude of the association between depression and mortality to decrease

over time in lieu of repeat depression measurement. Comparison of the magnitude of 5-year vs 10-year hazard ratio's within each subgroup supports this conclusion.

Generalizability is also a concern given the 62% rate of returning survey data and recruitment from a diabetes registry.

In conclusion, our study found a significant positive association between depression and all cause mortality in patients with diabetes that increased with depression severity. The largest magnitude of association among cause specific death types was non-cardiovascular, non-cancer mortality. The relationship between depression and diabetes and cardiovascular mortality did not reach significance in models that adjusted for baseline diabetic and medical indicators of disease severity and health risk behaviors. Finally, we updated trends from our 5-year data and conclude that that non-coronary cardiovascular, infection and dementia/CNS death types were most common within the non-cardiovascular, non-cancer mortality group and that depression status is unrelated to cancer mortality in our cohort. All told, our research suggests that depression may significantly influence mortality associated with non-coronary heart disease, infection and CNS disorders including dementia in patients with diabetes. These findings should be replicated and further research is needed to determine if effective treatment of depression will result in abatement of the increased risk of death. Possible implications of this research include that screening and treatment of depression in diabetic patients should be emphasized to insure good care.

Conflicts of Interest:

Dr. Von Korff receives funding from Pfizer through a sub-contract with Geisinger for research related to low back pain. Dr. Katon has been funded for CME and talks from Lilly, Pfizer, Wyeth and Forest. Drs. Lin and Coleman have no conflicts of interest to report.

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Figure 1: Recruitment of Epidemiologic Cohort Study to Assess Mortality

*adapted from the original publication

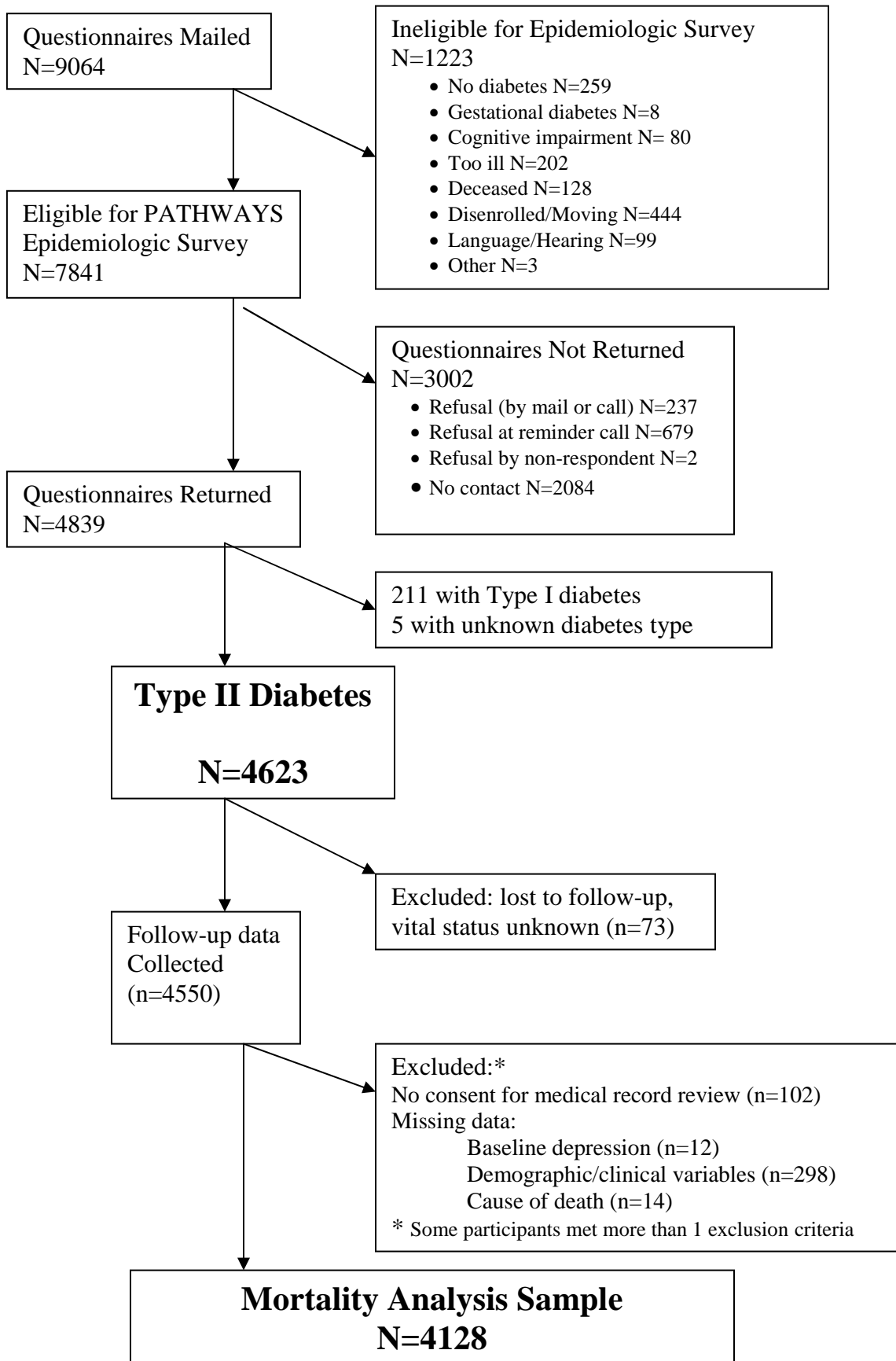


Table 1- Baseline Clinical and Demographic Characteristics by Depression Status

Variable	Total	No Depression N (%)	Minor Depression N (%)	Major Depression N (%)
N	4128	3,279 (79.4)	343 (8.3)	495 (12.0)
Age, mean (SD)	63.4 (13.4)	64.0 (13.2)	64.2 (13.8)	59.4 (13.8)
Female, N (%)	1,987 (48.1%)	1,525 (46.5%)	165 (48.1%)	291 (58.8%)
Non-white, N (%)	821 (19.5%)	554 (16.9%)	74 (21.6%)	94 (19.0%)
Highschool or less, N (%)	983 (23.8%)	741 (23.1.2%)	107 (31.7%)	135 (28%)
Marital Status (single, %)	1503 (36.4%)	1040 (34.8%)	131 (38.2%)	227 (45.9%)
Diabetes duration – mean years (SD)	9.6 (9.4)	9.5 (9.5)	10.6 (9.8)	9.6 (8.3)
Hb _{A1C} mean % (SD)	7.8 (1.6)	7.7 (1.5)	7.9 (1.6)	8.2 (1.7)
Treatment, N (%)				
-none or diet	1043 (25.3%)	871 (26.6%)	82 (23.9%)	87 (17.6%)
-hypoglycemic only	1825 (44.2%)	1475 (45.0%)	147 (42.9%)	196 (39.6%)
-any insulin	1260 (30.5%)	814 (24.8%)	114 (33.2%)	212 (42.8%)
Hypertension, N (%)	2578 (62.5%)	2026 (61.8%)	229 (66.8%)	316 (63.8%)
Body Mass Index, mean (SD)	31.5 (7.3)	31.0 (6.8)	32.1 (7.1)	34.8 (9.3)
Physical Activity (≤1 day/week), N (%)	1336 (32.4%)	955 (29.1%)	151 (44.0%)	234 (46.1%)
Current Smoking, N (%)	347 (8.4%)	241 (7.3%)	35 (10.2%)	71 (14.3%)
RXRisk*	3135 (2444)	3058 (2367)	3424 (2543)	3431 (2794)

* Medical co-morbidity, excluding co-morbidity associated with diabetes and depression

**Adapted form the original publication

Statistically significant differences between non depressed and depressed are bolded

Table 2 – Cause of Death and Specific Death Type

Cause of Death	5 yr N (%)	10 yr N (%)
Atherosclerotic Cardiovascular Disease	248 (42.7)	437 (35.9)
Coronary disease	202 (34.8)	334 (27.4)
Stroke	43 (17.3)	95 (21.7)
Peripheral vascular disease	11 (1.9)	8 (0.7)
Cancer	156 (26.9)	270 (22.2)
Lung	32 (5.5)	57 (4.7)
Colorectal	17 (2.9)	18 (1.5)
Prostate	12 (2.1)	29 (2.4)
Breast	12 (2.1)	21 (1.7)
Other and unknown primary site	83 (14.3)	145 (11.9)
Non-CVD, Non-cancer	177 (30.5)	413 (33.9)
Cardiac, non-coronary	8 (1.4)	81 (6.7)
Infection	44 (7.6)	79 (6.5)
Dementia and other CNS disease	33 (5.7)	76 (6.2)
Renal failure	17 (2.9)	32 (2.6)
COPD and other respiratory disease	27 (4.6)	56 (4.6)
Cirrhosis and other GI disease	18 (3.1)	43 (3.5)
Accident	5 (0.9)	22 (1.8)
Suicide	4 (0.7)	6 (0.5)
Other	13 (2.2)	18 (1.5)
Total	581 (100)	1217 (100)

*adapted from the original publication

Table 3 – All Cause and Cause Specific Numbers and Hazard Ratios by Model and Depression Status

	Cause of Death			
	All-Cause	Cardiovascular	Cancer	Non-CVD, Non-Cancer
Number (%) of Events				
Not Depressed	766 (23.4%)	337 (10.3%)	219 (6.7%)	298 (9.1%)
Minor Depression	102 (29.7%)	42 (12.2%)	22 (6.4%)	50 (14.6%)
Major Depression	142 (28.7%)	58 (11.7%)	26 (5.3%)	63 (12.7%)
Adjusted for Demographic Characteristics,¹ Hazard ratio (95% Confidence Interval)				
Minor Depression 5 year	1.48 (1.14,1.93)	1.51 (1.02,2.24)	1.04 (0.59,1.85)	1.87 (1.19,2.93)
Major Depression 5 year	2.26 (1.79,2.85)	2.00 (1.37,2.94)	1.61 (0.99,2.59)	3.35 (2.30,4.89)
Minor Depression 10 year	1.39 (1.12, 1.71)	1.24 (0.88, 1.76)	0.88 (0.54, 1.41)	1.58 (1.14, 2.19)
Major Depression 10 year	1.97 (1.64, 2.37)	1.71 (1.27, 2.31)	1.05 (0.70, 1.59)	2.26 (1.68, 3.03)
Adjusted for Demographic¹ & Clinical Characteristics²				
Minor Depression 5 year	1.29 (0.99,1.68)	1.27 (0.86,1.89)	0.99 (0.56,1.76)	1.59 (1.01,2.49)
Major Depression 5 year	1.62 (1.28,2.06)	1.35 (0.91,1.99)	1.36 (0.83,2.22)	2.26 (1.52,3.35)
Minor Depression 10 year	1.23 (1.0, 1.53)	1.05 (0.72, 1.51)	0.82 (0.50, 1.34)	1.42 (1.02, 1.97)
Major Depression 10 year	1.62 (1.35, 1.96)	1.30 (0.93, 1.80)	1.00 (0.66, 1.53)	1.83 (1.36, 2.46)
Adjusted for Demographic¹, Clinical Characteristics², Health Habits and Disease Control Measures³				
Minor Depression 5 year	1.24 (0.95,1.61)	1.20 (0.81,1.78)	0.94 (0.53,1.68)	1.54 (0.98,2.42)
Major Depression 5 year	1.52 (1.19,1.95)	1.25 (0.83,1.86)	1.27 (0.77,2.10)	2.15 (1.43,3.24)
Minor Depression 10 year	1.22 (0.99, 1.52)	1.04 (0.71, 1.51)	0.82 (0.50, 1.36)	1.42 (1.02, 1.99)
Major Depression 10 year	1.52 (1.25, 1.85)	1.27 (0.90, 1.78)	1.0 (0.65, 1.53)	1.61 (1.17, 2.22)

*adapted from the original publication

Statistically significant HR's are bolded

1. Demographic characteristics at baseline: age, gender, race, education and marital status.
2. Clinical characteristics at baseline: diabetes duration, treatment intensity, medical comorbidity (excluding diabetes, depression) and hypertension diagnosis.
3. Health behaviors and disease control measures at baseline: BMI, smoking, limited physical activity, and Hb_{A1C}

