Depression and Advanced Complications of Diabetes

A prospective cohort study

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OBJECTIVE — To prospectively examine the association of depression with risks for advanced macrovascular and microvascular complications among patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS — A longitudinal cohort of 4,623 primary care patients with type 2 diabetes was enrolled in 2000–2002 and followed through 2005–2007. Advanced microvascular complications included blindness, end-stage renal disease, amputations, and renal failure deaths. Advanced macrovascular complications included myocardial infarction, stroke, cardiovascular procedures, and deaths. Medical record review, ICD-9 diagnostic and procedural codes, and death certificate data were used to ascertain outcomes in the 5-year follow-up. Proportional hazard models analyzed the association between baseline depression and risks of adverse outcomes.

RESULTS — After adjustment for prior complications and demographic, clinical, and diabetes self-care variables, major depression was associated with significantly higher risks of adverse microvascular outcomes (hazard ratio 1.36 [95% CI 1.05–1.75]) and adverse macrovascular outcomes (1.24 [1.0–1.54]).

CONCLUSIONS — Among people with type 2 diabetes, major depression is associated with an increased risk of clinically significant microvascular and macrovascular complications over the ensuing 5 years, even after adjusting for diabetes severity and self-care activities. Clinical and public health significance of these findings rises as the incidence of type 2 diabetes soars. Further research is needed to clarify the underlying mechanisms for this association and to test interventions to reduce the risk of diabetes complications among patients with comorbid depression.

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D epression is adversely associated with diabetes, from incidence to mortality (1–3). Compared with individuals with diabetes alone, those with comorbid depression have increased disease burden, greater symptom severity, increased work disability, and increased medical services use (4–6). Comorbid depression is also associated with substantially higher health care costs among patients with a range of diabetes complications (7).

Both biologic and behavioral factors may play a role in the relationship between depression and diabetes complications. Depression and chronic psychological stress can activate the hypothalamic-pituitary-adrenal axis, stimulate the sympathetic nervous system, increase inflammatory and platelet aggregation responses, and contribute to poor diabetes control (8). Poor glycemic control increases the risk of diabetes complications (9). Depression may also impair glycemic control through negative effects on self-care behaviors (adherence to diet, exercise, checking blood glucose, and taking medications as prescribed) (10–12).

The relationship between depression and type 2 diabetes is bidirectional (1). Individuals with depression, but no diabetes, are at higher risk for developing diabetes at follow-up. Conversely, individuals with no depression, but receive diabetes treatment, are at a higher risk for developing depression at follow-up. For example, patients with diabetes complications such as nephropathy requiring hemodialysis or retinopathy and resulting blindness face significant impairment in their daily lives. These daily stressors can be overwhelming and, in turn, precipitate or worsen depression.

A meta-analysis of 27 studies found a significant association between depression and a wide variety of diabetes complications (neuropathy, retinopathy, nephropathy, macrovascular complications, and sexual dysfunction) (13). The conclusions that can be drawn from individual studies are limited given their relatively small samples, which included patients with both type 1 and type 2 diabetes. While meta-analyses can combine information to overcome problems with small samples in individual studies, measurement problems remain a limitation of these studies. The diabetes complications considered included both mild and advanced pathophysiologic changes (e.g., both microalbuminuria and stroke) and both self-reported symptoms (e.g., pain severity or impotence) and objectively documented disorders (e.g., retinopathy or glomerular filtration rate). In addition, depression assessment often used symptom-severity scales and lacked diagnostic measures. The greatest limitation of these studies was their cross-sectional design.

Cross-sectional studies cannot clarify whether patients are depressed because they have disabling and worrisome diabetes complications or whether having depression could actually precede occurrence of severe and clinically significant diabetes complications.

In the only large-scale prospective study, Black et al. (2) found in a sample of 2,830 elderly Mexican Americans with type 2 diabetes (aged ≥65 years) that comorbid depression at baseline was associated with an increased risk of macrovascular and microvascular complications over a 7-year period. This study was limited to an elderly population from one ethnic group, and presence of diabetes and complications were based on patient self-report. The analyses also did not account for potential clinical confounders or mediators such as glycemic control, severity of medical comorbidity, or health habits. This prospective study investigates whether there is a link between depression and subsequent development of clinically significant diabetes complications in a large cohort of primary care patients. We aim to close three gaps in prior research. First, we examined only advanced and medical chart–verifiable microvascular and macrovascular complications. Second, we adjusted for clinical confounders and variables that may mediate the relationship between depression and diabetes. Third, we assessed depression using a measure that has been validated against the gold standard diagnostic interview for a clinical affective disorder (14).

RESEARCH DESIGN AND
METHODS — Group Health is a mixed-model prepaid health plan serving approximately half a million members in Washington state. Most Group Health members receive medical services within the integrated group practice, which includes 30 primary care clinics in western Washington. The Group Health enrollment is demographically similar to the area population. All study procedures were approved by institutional review boards at Group Health and the University of Washington. This research was supported by grants from the National Institutes of Health (MH 073686).

The cohort for this longitudinal prospective study, the Pathways Epidemiologic Follow-Up Study, was initially sampled between 2000 and 2002 from adults in the Group Health diabetes registry who received care at any of nine pri-

mary care clinics in the Seattle/Puget Sound area selected because of the socioeconomic, racial, and ethnic diversity of the patients they serve (15). The Group Health diabetes registry includes all Group Health members meeting any of the following eligibility criteria in the preceding 12 months: filled prescription for insulin or an oral hypoglycemic agent, two fasting plasma glucose levels ≥126 mg/dl, two random plasma glucose levels ≥200 mg/dl, two outpatient diagnoses of diabetes, or any inpatient diagnosis of diabetes (15).

Surveys were mailed to 9,063 potentially eligible patients, but 1,222 patients were later found to be ineligible due to reasons such as death, disenrollment, erroneous diagnosis of diabetes, or cognitive impairment. Among 7,841 eligible patients, 4,839 subjects (61.7% of eligible patients) returned the baseline questionnaire. Patients with type 1 diabetes ($n = 216$) were excluded, and 4,623 patients with type 2 diabetes participated in the study and comprised the original Pathways Epidemiologic Study cohort (16).

Pathways Epidemiologic Follow-Up Study
Approximately 5 years after enrollment, surviving members of the original cohort of patients with type 2 diabetes were recontacted by mailed letter and follow-up telephone call during 2005–2007. Consenting patients completed a 20-min telephone interview and were asked for permission to review their electronic and paper medical records for information on medical conditions. Waiver of consent to review electronic and paper medical records was approved by the human subjects review committee for patients who had died since enrollment in the cohort.

Assessment of clinical adverse outcomes of diabetes
Using medical record review, ICD-9 diagnostic and procedure code data, and Washington state death certificate data, we identified physician-diagnosed and objectively documented macrovascular and microvascular complications of diabetes, before baseline and during follow-up. Microvascular complications included end-stage renal disease (ESRD), low vision or blindness, proliferative retinopathy or photocoagulation procedures for diabetes, foot ulcers, and amputations. Macrovascular complications included myocardial infarction, stroke, congestive heart failure (CHF), cardiovascular procedures

(percutaneous coronary artery intervention, coronary artery bypass grafting, and abdominal aortic aneurysm repair), and revascularization of the lower extremity. Deaths due to coronary, cerebrovascular, or peripheral arterial disease were include as adverse macrovascular events, and deaths due to ESRD were included as adverse microvascular events (3). The specific codes and definitions for some of these adverse diabetes outcomes were adopted from the Women's Health Initiative Study (17). Please see the online appendix (available at http://care.diabetesjournals.org/cgi/content/full/dc09-1068/DC1) for codes and definitions used to identify these advanced microvascular and macrovascular complications.

Assessment of depression
The Patient Health Questionnaire-9 (PHQ-9) (18) was used to ascertain probable major and minor depression at baseline and follow-up. The PHQ-9 is a self-report measure of depression symptoms based on the American Psychiatric Association's DSM-IV criteria for diagnosis of depressive episode and has been found to have an adequate sensitivity and high specificity in relation to a diagnosis of major depression based on structured interviews (14,18). Following a standardized method, each item was scored as positive if endorsed as "more than half the time" or "nearly all the time," and a diagnosis of probable major depression required a positive response to one of the two core symptoms (depressed mood or loss of interest) and a total of five positive symptoms for at least the last 2 weeks. Criteria for probable minor depression required at least one core symptom (depressed mood or loss of interest) and a total of two to four positive symptoms for at least the last 2 weeks.

Covariates: demographic, clinical, and self-care characteristics
Potential confounders and mediators for the association of depression and adverse diabetes outcomes were selected a priori, as covariates. We use the term "mediator" to refer to variables that maybe on the causal pathway in the relationship between depression and adverse events, even though these mediators were assessed at the same time as depression. The mailed survey included sociodemographic characteristics (age, sex, race, educational attainment, and marital status), diabetes duration, diabetes treatment (none or diet, oral hypoglycemic only, or

any insulin), height, weight, and health habits from the Summary of Diabetes Self-Care Questionnaire (smoking, physical activity, diet, and blood glucose monitoring) (19). Review of paper and electronic medical records provided data on hypertension and glycemic control (A1C). Medical comorbidity was adjusted using RxRISK, an empirically derived comorbidity measure based on medications patients take to manage chronic diseases (20). This pharmacy-based comorbidity adjustor has been found to yield good prediction of hospitalization and mortality risks, in addition to total health care costs. For this study, antidepressant and hypoglycemic medications were not included in the calculation of the RxRisk score. Thus, the modified RxRisk score should be considered a measure of overall medical comorbidity other than depression or diabetes.

Statistical analyses

We estimated the association between depression and adverse outcomes using a proportional hazards model (21). Because the length of follow-back (i.e., years of observation prior to baseline survey) varied across individuals, analyses were stratified by years of follow-back to account for variations in the amount of prior data available. These models adjusted for evidence of a prior history of adverse outcomes. We also explored whether prior adverse outcome history modified the effect of depression by including the interaction between depression and prior adverse outcomes. Sensitivity analyses examined the effect of depression among individuals with no indication of a prior adverse outcome.

Proportional hazards models censor individuals at the time of disenrollment, death from other causes (i.e., attributed to neither macrovascular nor microvascular events), or the end of follow-up, whichever comes first. We fit four proportional hazards models to each adverse outcome, with each sequential model adding covariates. The first model included only baseline depression (major, minor, or none) and an indicator of prior adverse outcomes within the same class (microvascular or macrovascular). The second model added demographic characteristics (age, sex, race, education, and marital status). The third model added clinical characteristics at baseline (diabetes duration, treatment type, RxRisk score, and hypertension diagnosis). The fourth model added baseline clinical characteristics and

Figure 1—*Pathways Epidemiologic Follow-Up sample recruitment.*

health habits or self-care behaviors that may be affected by depression (A1C, BMI, smoking, and limited physical activity) (10,16).

RESULTS — Figure 1 describes the Pathways Epidemiologic and Follow-Up Study sample recruitment. Among 4,623 patients with type 2 diabetes surveyed at baseline, 12 (0.2%) were not eligible for follow-up due to disenrollment or refusal. Among 4,611 sample eligible for the 5-year follow-up, data were collected for 3,922 (85.1%). We excluded participants for the following reasons: 632 (13.7%) refused medical record review, 49 (1.0%) were non-English speakers; 8 (0.2%) had incomplete medical records (missing paper chart), 12 (0.003%) had missing depression status, and 199 (0.05%) had

missing demographic or clinical variables. This resulted in a final sample size of 3,723 patients for the analysis. Another 3 were missing the date of a microvascular outcome, and 39 were missing the date of a macrovascular outcome and were unable to be included in the time-to-event analysis.

The mean duration of follow-back was (means ± SD) 4.5 ± 0.97 years. Mean duration of follow-up was 20.8 years (ranging from 6 months to 54 years, median 22 years, SD 10.9 years). Clinical and demographic characteristics of the Pathways Epidemiologic Follow-Up Study cohort by baseline depression status are summarized in Table 1. As reported in a prior article, diabetic patients with major depression were slightly younger; had higher A1C, BMI, and med-
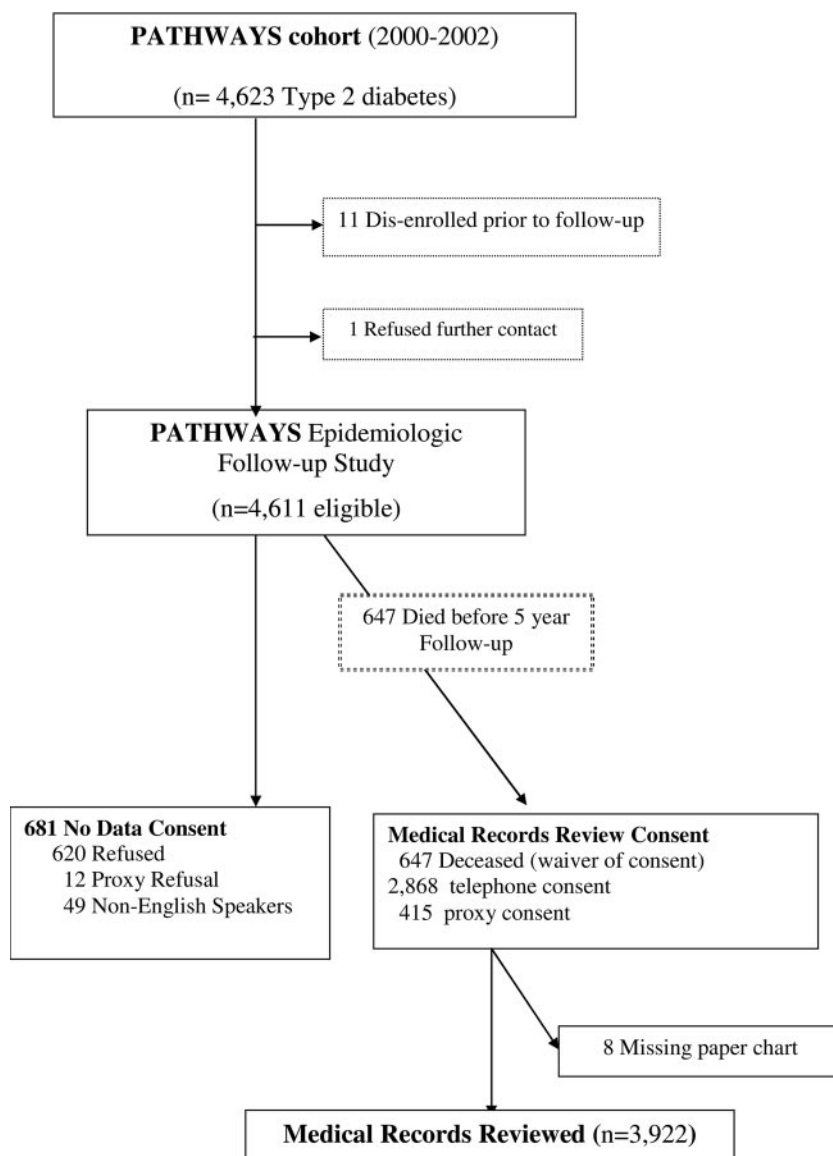
Table 1—*Baseline clinical and demographic characteristics by depression*

Characteristics	Total sample	No depression	Minor depression	Major depression
n	3,723	2,965	315	443
Female	1,782 (47.9)	1,369 (46.2)	152 (48.3)	261 (58.9)
Nonwhite	726 (19.5)	555 (18.7)	81 (25.7)	90 (20.3)
High school education or less	919 (24.7)	696 (23.5)	101 (32.1)	122 (27.5)
Marital status single	1,245 (33.4)	941 (31.7)	112 (35.6)	192 (43.3)
Treatment				
None or diet	947 (25.4)	798 (26.9)	71 (22.5)	78 (17.6)
Oral hypoglycemic agent only	1,746 (46.9)	1,422 (48.0)	143 (45.4)	181 (40.9)
Any insulin	1,030 (27.7)	745 (25.1)	101 (32.1)	184 (41.5)
Hypertension	2,392 (64.3)	1,887 (63.6)	217 (68.9)	288 (65.0)
Physical activity (≤1 day/week)	1,223 (32.9)	873 (29.4)	140 (44.4)	210 (47.4)
Any prior microvascular event	750 (20.2)	580 (19.6)	77 (24.4)	93 (21.0)
Any prior macrovascular event	1,042 (28.1)	788 (26.7)	108 (34.4)	146 (33.0)
Age	64.3 ± 12.5	64.9 ± 12.3	64.7 ± 13.2)	60.1 ± 13.0)
Diabetes duration (years)	8.8 ± 8.4	8.6 ± 8.4	10.2 ± 9.2)	9.0 ± 7.5)
A1C	7.8 ± 1.6	7.7 ± 1.5	7.9 ± 1.6	8.1 ± 1.7
BMI	31.8 ± 7.2	31.2 ± 6.8	32.3 ± 7.0	35.0 ± 9.1
RxRisk*	3,203 ± 2,410	3,124 ± 2,320	3,475 ± 2,517	3,536 ± 2,846

Data are *n* (%) or means ± SD. *Medical comorbidity and expected cost in USD excluding diabetes and depression.

ical comorbidity; and more likely to be treated with insulin as compared with those with no depression (16). The group with major depression included a higher proportion of women and current smokers.

Adverse clinical outcomes of diabetes

In this primary care type 2 diabetic cohort, 14.3% (533 of 3,723) of patients had a clinically significant microvascular outcome during the follow-up period, with 13.3% (394 of 2,965) of patients with no depression (0.06 events per person-year risk or 1 event per 15.8 person-

years risk), 18.7% (59 of 315) of patients with minor depression (0.07 events per person-year risk or 1 event per 13.6 person-years risk), and 18.1% (80 of 443) of patients with major depression (0.07 events per person-year risk or 1 event per 13.7 person-years risk) having a microvascular event. Nearly a quarter (24.0%, 893 of 3,723) of patients had a clinically significant macrovascular outcome, with 23.7% (702 of 2,965) of patients with no depression (0.03 events per person-year risk or 1 event per 29.1 person-years risk), 25.7% (81 of 315) of patients with minor depression (0.05 events per person-year risk or 1 event per 18.6

person-years risk), and 24.8% (110 of 443) of patients with major depression (0.05 events per person-year risk or 1 event per 19.4 person-years risk) having a macrovascular event.

Table 2 shows estimated hazard ratios for four models and the two types of severe complications in patients with minor and major depression relative to the no depression group. Major depression was associated with a higher risk of both microvascular and macrovascular severe complications across all four models. The association between major depression and severe adverse events strengthened with addition of demographic covariates

Table 2—*Hazard ratios (95% CIs) for microvascular and macrovascular outcomes in patients with diabetes*

Covariate adjustment	Microvascular		Macrovascular	
	Minor depression	Major depression	Minor depression	Major depression
Unadjusted	1.54 (1.16–2.03)	1.48 (1.16–1.88)	1.17 (0.92–1.47)	1.20 (0.98–1.47)
Adjusted for				
Any prior event*	1.49 (1.13–1.97)	1.47 (1.15–1.87)	1.09 (0.86–1.37)	1.13 (0.92–1.38)
Any prior event and demographic characteristics*†	1.48 (1.11–1.95)	1.67 (1.30–2.15)	1.11 (0.88–1.40)	1.49 (1.21–1.83)
Any prior event, demographic characteristics, and clinical characteristics*†‡	1.33 (1.00–1.76)	1.38 (1.07–1.77)	1.06 (0.83–1.33)	1.34 (1.08–1.65)
Any prior event, demographic characteristics, clinical characteristics, and self-care and diabetes control measures*†‡§	1.31 (0.98–1.74)	1.36 (1.05–1.76)	1.00 (0.79–1.27)	1.25 (1.00–1.54)

Hazard ratios compare individuals with minor or major depression to those without depression at baseline and are based on models that match on years of follow-back. *Any prior microvascular or macrovascular event. †Demographic characteristics at baseline, including age, sex, race, education, and marital status.‡Clinical characteristics at baseline, including diabetes duration, treatment intensity, expected costs (RxRisk), and hypertension diagnosis. §Self-care behaviors and disease control measures at baseline, including BMI, smoking, limited physical activity, and A1C.

and lessened with subsequent adjustment for clinical characteristics and, to a lesser extent, potential mediators (i.e., health habits and A1C levels).

We also found a significant association between minor depression and severe microvascular complications in three of four models. When potential clinical mediators such as diabetes self-care and A1C were added, this relationship became nonsignificant. Results from sensitivity analyses that examined the effect of depression on microvascular and macrovascular complications only among individuals with no prior indication of these complications produced very similar results that led to the same conclusions.

CONCLUSIONS — Among adults with type 2 diabetes, we found that individuals with depression were at increased risk of clinically significant subsequent micro- and- macrovascular complications, relative to individuals without depression at baseline. Over a 5-year period, patients with major depression and diabetes had a 36% higher risk of developing advanced microvascular complications, such as ESRD or blindness, and a 25% higher risk of developing advanced macrovascular complications, such as myocardial infarction or stroke, compared with diabetic patients without depression. The strength of the association between depression and risk of adverse events generally increased with adjustment for demographic variables but decreased with adjustment for clinical characteristics. Adjustment for differences in health habits and glycemic control also reduced the association between depression and macrovascular complications but did not change the association between depression and microvascular complications.

We observed similar patterns in estimated associations between minor depression and microvascular and macrovascular complications, though the estimated increase in risk associated with minor depression was less than estimated increases associated with major depression. Associations between minor depression and macrovascular complications were not statistically significant.

Biological, psychological, or behavioral responses to stressors facing patients with diabetes and comorbid depression may all play important roles in the development of adverse diabetes outcomes (9,12,13,22). Interestingly, our data showed that health habits such as physical inactivity and dietary factors (BMI) increased the risk for macrovascular complications such as myocardial infarction and stroke but had little effect on the association of depression and development of microvascular complications such as blindness and ESRD. Results from a recent study (23) demonstrated that physical inactivity played a significant role in the association of depressive symptoms and subsequent cardiovascular events among patients with coronary heart disease. However, more research is needed to clarify the role of health risk behaviors (smoking, physical activity, and diet) on development of microvascular complications.

Activation of the hypothalamic-pituitary-adrenal axis (increased cortisol secretion), the sympathetic nervous system (increased catecholamine release), proinflammatory and procoagulation responses (increased levels of cytokines or platelet/endothelial cell adhesion molecule-1) associated with depression may provide a unifying pathophysiologic explanation for disease progression found in patients with type 2 diabetes in this study. Depression has consistently been linked to hypothalamic-pituitary-adrenal axis dysregulation, sympathetic nervous system activation, and proinflammatory and procoagulation markers among patients with coexisting cardiovascular disorders (8,11). Perhaps these neuroendocrine and inflammatory responses accompanying depression also play similar roles in the progression of microvascular and macrovascular complications among patients with type 2 diabetes. Evidence that depression is associated with more negative appraisals of insulin therapy could also contribute to higher A1C levels and increased risk for complications (24). Depressed patients would be less willing to start insulin therapy than nondepressed diabetic patients, thus delaying benefits from insulin treatment.

Limitations of this study include that depression was only measured at one point in time. However, depression runs a chronic or recurrent course among patients with coexisting diabetes. Approximately 75% of patients with depression and diabetes (recruited from same cohort) had a lifetime history of chronic depression lasting >2 years. Moreover, >80% of this cohort who met criteria for major depression at the 5-year follow-up also had major or minor depression at baseline (22). Data on the number of prior depressive episodes were not collected to permit ascertainment of whether recurrent depression versus an initial depressive episode would have greater impact on adverse outcomes. The study was completed in one geographic region of the U.S., possibly limiting generalizability. Strengths of this study include prospective follow-up of a large sample of primary care patients with type 2 diabetes; structured assessment of depression; use of physician diagnoses, automated laboratory, pharmacy data, and chart review to confirm diagnosis; and the ability to control for important clinical covariates (e.g., prior adverse events medical comorbidity, glycemic control) and diabetes self-care activities (e.g., smoking and exercise). Finally, the focus on severe and documented adverse diabetes outcomes adds to the clinical significance and public health importance of these findings.

Major depression is associated with a 25% increased risk of advanced macrovascular complications and a 36% increased risk of microvascular complications among patients with type 2 diabetes. Given the rapidly increasing rates of type 2 diabetes, this increased risk has important clinical and public health implications. This work demonstrates a need for further research to test interventions that may reduce risks of diabetes complications among patients with comorbid depression and to explore explanatory biological mechanisms.

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