A Cohort Study of People With Diabetes and Their First Foot Ulcer

The role of depression on mortality

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OBJECTIVE — The aim was to evaluate over 18 months whether depression was associated with mortality in people with their first foot ulcer.

RESEARCH DESIGN AND METHODS — A prospective cohort design was used. Adults with their first diabetic foot ulcer were recruited from foot clinics in southeast London, U.K. At baseline, the Schedules for Clinical Assessment in Neuropsychiatry 2.1 was used to define those who met DSM (*Diagnostic and Statistical Manual of Mental Disorders*)-IV criteria for minor and major depressive disorders. Potential covariates were age, sex, marital status, socioeconomic status, smoking, antidepressant use, A1C, macro- and microvascular complications, and University of Texas classification–based severity and size of ulcer. The main outcome was mortality 18 months later, and A1C was the secondary outcome. The proportion who had an amputation, had recurrence, and whose ulcer had healed was recorded.

RESULTS — A total of 253 people with their first diabetic foot ulcer were recruited. The prevalence of minor and major depressive disorder was 8.1% ($n = 21$) and 24.1% ($n = 61$), respectively. There were 40 (15.8%) deaths, 36 (15.5%) amputations, and 99 (43.2%) recurrences. In the adjusted Cox regression analysis, minor and major depressive disorders were associated with an approximately threefold hazard risk for mortality compared with no depression (3.23 [95% CI 1.39–7.51] and 2.73 [1.38–5.40], respectively). There was no association between minor and major depression compared with no depression and A1C ($P = 0.86$ and $P = 0.43$, respectively).

CONCLUSIONS — One-third of people with their first diabetic foot ulcer suffer from clinical depression, and this is associated with increased mortality.

Diabetes Care 30:1473–1479, 2007

Diabetic foot ulcers are one of the most common, disabling, and costly complications of diabetes (1–3). The incidence and prevalence for foot ulcers is estimated at 2% and 5–7% per year, respectively (3,4). Duration of diabetes, persistent hyperglycemia, and peripheral neuropathy (associated with reduced pain sensation) are considered to be well-known biological risk factors for the onset and recurrence of foot ulcers (5–7). Primary and secondary prevention of diabetic foot ulcers can be achieved by daily foot examinations for painless ulcers or injuries, regular podiatrist visits, use of appropriate foot wear, and maintenance of optimal diabetes self-care (8). Despite this, adverse outcomes following the onset of foot ulcers are poor, and they are the most common reason for amputation (9). The rate of recurrence of foot ulcers is estimated at 34, 61, and 70% in 1, 3, and 5 years, respectively (1). Around 15% develop osteomyelitis, and there is a twofold increase in mortality compared with people with diabetes without a foot ulcer (3, 10,11). Could psychological factors such as depressive disorders help to explain the high rates of mortality and morbidity?

The pooled prevalence of depressive disorders in people with diabetes when diagnostic criteria are used is estimated at 11%, which is two times more common than the general population, and the estimated pooled prevalence of depressive symptoms using self-report measures is 31% (12). In cross-sectional studies (13,14), depressive disorders and symptoms are associated with poor glycemic control and complications. Emerging evidence from the U.S. shows that depressive symptoms are associated with increased mortality in diabetes, including a dose-response–type association with severity of depression (15–20) based on self-reported measures of depression and/or diabetes. The received wisdom is that the mediating mechanism is via glycemic control, but prospective evidence for this association is still lacking (21). People with early diabetic foot disease are likely to fear the worst, such as gangrene or loss of a limb, but there is little epidemiological evidence to support the role of psychological factors on adverse outcomes (15,19). Depression, which can be treated, often goes undetected in people with diabetes, and, even when detected, treatment is not optimized (22). Our main hypothesis was that in people with diabetes, depression was associated with increased risk of mortality following the onset of their first foot ulcer compared with those who were not depressed. The secondary hypothesis was that depression was prospectively associated with worsening glycemic control.

RESEARCH DESIGN AND METHODS

— The study protocol was approved by the ethics committees of the Institute of Psychiatry, King's College London, and the local partici-

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Received for publication 10 November 2006 and accepted in revised form 7 March 2007.

Published ahead of print at http://care.diabetesjournals.org on 15 March 2007. DOI: 10.2337/dc06-2313.

Abbreviations: DSM, *Diagnostic and Statistical Manual of Mental Disorders*; SCAN 2.1, Schedules for Clinical Assessment in Neuropsychiatry 2.1.

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

pating National Health Service trusts. All participants gave written informed consent.

A population-based cohort of adults, aged ≥18 years with diabetes based on World Health Organization criteria (23) and presenting with their first (baseline) foot ulcer was recruited between August 2000 and October 2002 and prospectively followed for 18 months. The setting and sampling frame constituted all the community chiropody and hospital foot clinics within five National Health Service health authorities in south London, U.K. (Lambeth, Southwark, Lewisham, North Croydon, and Bexley and Greenwich), representing a population of 6 million, of which 80,000 are estimated to have diabetes (24,25). A similar model of multidisciplinary medical care of the diabetic foot ulcer was used in each of these health authorities based on accepted local guidelines (26).

We screened all people presenting with their first ulcer within the sampling frame. They were identified through a rotating review of the preceding fortnight of new and follow-up appointments at each clinic. After an introduction by the podiatrist, the researcher contacted the patient for an appointment to obtain informed consent and used a standardized checklist to assess for study eligibility. We invited all of those eligible to participate. We defined a clinically significant diabetic foot ulcer as follows: *1*) the ulceration was in the anatomical foot, *2*) there had to be a full-thickness break in the epithelium with a minimum width of 5 mm, and *3*) the arm-to-ankle ratio was ≥0.5 at either the dorsalis pedis or anterior tibial sites using Doppler pressure readings (to exclude severe ischemia) (27). When subjects had more than one ulcer, the largest ulcer was defined as the baseline ulcer. Exclusion criteria were *1*) ulcer present for >1 year, *2*) poor fluency in English, *3*) independent comorbid medical conditions associated with lower-extremity ulcers such as rheumatoid arthritis, and *4*) severe mental illness such as schizophrenia or bipolar disorders, as they have mental health needs usually requiring specialist services. Severity of the ulcer was classified as superficial (grade 1) versus deep (grade 2 or 3) based on the University of Texas classification (28), and the surface area in centimeters squared (cm^2) was measured using digital photography (29).

Main explanatory variable

Depression was measured using the Schedules for Clinical Assessment in Neuropsychiatry 2.1 (SCAN 2.1) (30). Three categories of depression were measured: those who met the *Diagnostic and Statistical Manual of Mental Disorders* (DSM)-IV criteria for major or minor depressive disorders and those who did not meet either (defined as no depression). The SCAN 2.1 is a semistructured diagnostic interview with good reliability and validity and was administered by a trained nurse (K.W.) (31). The SCAN 2.1 closely resembles the clinical psychiatric interview and allows the interviewer to clarify the nature and severity of psychiatric symptoms and to exclude depressive symptoms judged secondary to the direct physiological effects of their medical condition. Computerized algorithms generated the presence or absence of a major depressive disorder (DSM-IV) (32). Current symptoms present in the preceding 4–6 weeks were assessed to reduce the bias of recalling symptoms of longer duration, as this period is considered the minimum necessary to capture depressive symptoms present over 2 weeks, which is the minimum duration criterion for DSM-IV. Inter-rater reliability for major depressive disorders was assessed (K.W. and K.I.) independently, conducting SCAN 2.1 interviews of 10 people with diabetes not involved in the study. A continuous measure of depressive symptoms was derived from the sum of the raw scores on all depression items in the SCAN 2.1 using a separate algorithm (33).

Main outcome measures

The date and cause of death was obtained through the U.K.'s Central Register Office and coded according to ICD-10 codes. A1C was measured at baseline and at 12 and 18 months (34). First amputation, first recurrence, and healing status were measured during the 18 months using a standardized checklist completed by the clinic podiatrist, who was blind to the patient's depression status at each patient clinic visit. Recurrence of foot ulcers was defined as a recurrence of a full-thickness break in the epithelium with a minimum width of 5 mm at the same or different site to the baseline ulcer. Healing was defined as the complete closure of the ulcer with skin intact (complete epithelialization) and without drainage or sinus formation (35).

Potential covariates

Age, sex, self-reported ethnicity, socioeconomic status (36), smoking status (current, ex-, or nonsmoker), alcohol use (using the Alcohol Use Disorders Identification Test: score ≥8 represented clinically significant alcohol problems, and <8 represented no problems) (37), and antidepressant treatment were assessed at baseline. Type and duration of diabetes (in years) and presence of complications were recorded from medical notes. Macrovascular complications were defined as prior myocardial infarction, coronary and peripheral angioplasty, coronary artery bypass grafting, or cerebrovascular accident. Microvascular complications were defined as retinopathy (background or proliferative), measured using digital fundal examination; nephropathy (macroalbuminuria defined by a raised 24-h protein or dialysis); and neuropathy (vibration perception threshold ≥25 volts). We used the diet, exercise, and foot care subscales of the Summary of Diabetes Self-Care Activities questionnaire, which is a brief and valid measure of adherence to diabetes self-management (38). Participants are asked to score, on a Likert scale of 0–7, how often they have carried out self-care activities over the last 7 days.

Statistical analysis

STATA 9 (Stata, College Station, TX) was used. Completers and dropouts at 18 months were compared on baseline data using the *t* test and χ^2 test for homogeneity. The distribution of the main explanatory variables and potential confounders at baseline and of the outcomes was computed using percentage proportions or means ± SD. We derived the mean A1C from available measures at baseline and at 12 and 18 months to capture the assumed close temporal association between glycemic control and risk of ulceration.

At baseline, univariate associations between the association of baseline and minor and major depressive disorders compared with no depression and potential explanatory variables were calculated. Cox proportional hazards regression was used to study the relationship between baseline DSM-IV minor and major depressive disorders compared with no depression, with the binary outcome of mortality adjusting for baseline potential covariates that were either significantly associated with depression or were clinically important, such as macrovascular complications and type of diabetes, and presented as hazard ratios and 95% CIs.

The estimated survival curve was reported such that the adjusted hazard ratios were standardized (in other words, all things being equal) by the average values of those covariates that were included in the final prediction model (except for severity of ulcer in which case we standardized as if the ulcer was severe [University of Texas grade 2 or 3]). The regression was repeated using depression as a continuous variable. In a secondary analysis, missing observations of mean A1C were replaced with estimates using the expectation maximization imputation method. Quadratic effect of A1C was also assessed in the regression model to assess if this improved the fit. The overall fit of the model was assessed using Cox-Snell generalized residual analysis (not presented), and robust standard errors were used to adjust for potential misspecification (39). To examine change in A1C over time in minor and major depressive disorders compared with those who were not depressed, taking into account the baseline A1C and other covariates, we did an ANCOVA. The association between mortality with amputation, recurrence, and healing status was assessed using the ϕ coefficient

The calculation of the sample size was based on the pooled prevalence of major depression of 14%, based on contemporaneous pooled data (40) that 30% of the nondepressed subjects would have an adverse outcome such as a recurrence of foot ulcer 18 months later (1), a risk ratio of 2.00 as the minimum clinically significant effect of major depression, a two-tailed type 1 error of 0.05, and a power of 80%. We estimated that 162 nondepressed and 27 depressed subjects were needed. Anticipating a drop-out rate of 25%, our final estimated sample was 250 subjects.

RESULTS — A total of 262 patients presented with their first diabetic foot ulcer. Two hundred and sixty met the study criteria, and of these 253 consented and constituted the cohort. Our follow-up rates were 100% for mortality outcome; 92.0, 93.7, and 90.5% for amputation ($n = 233$), healing ($n = 237$), and recurrence ($n = 229$), respectively; and 72.3% for A1C at 18 months (including those whose A1C was missing because they had died at 18 months). There were six (2.4%) patients for whom there was no A1C measurement at any time point. There was 90% agreement for major depressive disorder based on the 10 interviews conducted by the two SCAN 2.1 raters.

The baseline characteristics of the cohort are reported in Table 1. Ten patients were prescribed an antidepressant (tricyclic [$n = 7$] and selective serotonin reuptake inhibitor [$n = 3$]), 6 of 10 had major depressive disorder, and the remaining 4 had no depression. People with major depressive disorder were more likely to be younger and have more severe and larger baseline ulcers (Table 1) than those who were not depressed. People with minor depressive disorder were more likely to have a larger baseline ulcer than those who were not depressed. There were no differences in the diet, exercise, and foot care subscales of the Summary of Diabetes Self-Care Activities scores between the three categories of depression, except that people with major depressive disorder were less likely to adhere to their diet compared with those with no depression ($P = 0.002$).

During the 18 months of follow-up, there were 40 (15.8%) deaths. All deaths were due to natural causes such as infection ($n = 14$), cardiovascular disease ($n = 10$), cerebrovascular accident ($n = 10$), cancer ($n = 4$), renal failure ($n = 1$), and complications from liver disease ($n = 1$). Of 10 people who had been prescribed an antidepressant, only 1 died. No patients were receiving any psychological treatments. In the Cox regression analysis ($n = 246$), after adjusting for covariates (age, University of Texas severity, sex, smoking, mean A1C, marital status, and socioeconomic status) baseline minor and major depressive disorders were both significantly associated with an approximately threefold increase in the likelihood of death (hazard ratio 3.23 [95% CI 1.39–7.51] and 2.73 [1.38–5.40], respectively) (Fig. 1) compared with those who had no depression. The only other covariates that were significantly associated with mortality were age (1.08 [1.05–1.11]) and, inversely, mean A1C (0.74 [0.56–0.99]). The association between minor and major depressive disorder compared with no depression with mortality did not significantly change if the presence of macrovascular complications (3.25 [1.39–7.62] and 2.74 [1.38–5.44], respectively) or type of diabetes (3.25 [1.39–7.64] and 2.73 [1.38–5.40], respectively) were added to the model. Adding mean A1C as a quadratic term did not improve the fit. A missing value analysis replacing six missing values for mean A1C did not alter the results. There was a significant association between depression, when measured as a continuous variable, and mortality (1.03 [1.01–1.06], $P = 0.009$; $n = 213$).

During the 18-month follow-up, the proportion who underwent their first amputation was 15.5% ($n = 36$) (all due to diabetic foot disease) and those who had their first recurrence was 43.2% ($n = 99$). The coefficients of association, ϕ, of mortality with amputation, healing, and recurrence were of small effect sizes: -0.04 ($P = 0.81$), -0.24 ($P < 0.001$), and 0.25 ($P < 0.001$), respectively.

At 18 months, mean A1C for no depression ($n = 127$), minor depressive disorder ($n = 11$), and major depressive disorder ($n = 42$) was 8.2 ± 1.8%, 8.2 ± 1.8%, and 8.6 ± 1.9%, respectively. In ANCOVA, when adjusted for baseline A1C and the covariates used in the survival analysis, the association between minor and major depressive disorders with A1C at 18 months was not significant when compared with no depression (adjusted mean differences 0.1% [95% CI −0.9 to 1.1] and 0.2% [−0.4 to 0.8], respectively). There was also no difference between major depressive and minor depressive disorders at baseline and 18-month A1C (0.2% [−1.0 to 1.3]).

CONCLUSIONS — We found that one-third of people presenting with their first diabetic foot ulcer had clinically significant depression (combining minor and major depressive disorders), and this was associated with an approximately threefold increased risk of death 18 months later. There was no association between depression at baseline and glycemic control 18 months later.

The advantages of this study is that it was representative of hospital and community settings practicing a similar model of medical care for foot ulcers in a diverse socioeconomic and ethnic population. We used a standardized semistructured psychiatric interview to generate the diagnosis of depression based on an internationally recognized psychiatric classification. We captured the dimensional nature of depression by including minor and major depressive disorders and by deriving a continuous measure of depressive symptoms from the raw scores. The prospective design as well as podiatrists remaining blind to depression status aimed to reduce bias in the assessment of outcomes. We achieved excellent follow-up rates for mortality, but there were missing data for the 18-month A1C, which was partly attributable to the high rates of

Table 1—*Baseline characteristics of total study population and stratified by DSM-IV depressive disorder*

	Total population	Major depressive disorder	Minor depressive disorder	No depressive disorder	*P* value*
n	253	61	21	171	
Mean age (years)	62.0 ± 13.9	57.4 ± 14.5	65.2 ± 13.6	63.3 ± 13.4	0.01
Sex					
Female	92 (36.4)	26 (42.6)	7 (33.3)	59 (34.5)	0.50
Male	161 (63.6)	35 (57.4)	14 (66.7)	112 (65.5)	
Social class†					
I/II	85 (33.6)	16 (26.2)	9 (42.9)	60 (35.1)	0.40
III	94 (37.2)	22 (36.1)	8 (38.1)	64 (37.4)	
IV/V	74 (29.2)	23 (37.7)	4 (19)	47 (27.5)	
Marital status					
Married/cohabiting	125 (49.6)	28 (45.9)	11 (55)	86 (50.3)	0.74
Single/divorced/widowed	127 (50.4)	33 (54.1)	9 (45)	85 (49.7)	
Ethnicity					
White	182 (71.9)	43 (70.5)	15 (71.4)	124 (72.5)	0.95
Black/Asian/other	71 (28.1)	18 (29.5)	6 (28.6)	47 (27.5)	
Current smoking status					
Non- or ex-smoker	213 (84.2)	48 (78.7)	20 (95.2)	145 (84.8)	0.19
Smoker	40 (15.8)	13 (21.3)	1 (4.8)	26 (15.2)	
Alcohol problems					
AUDIT <8	214 (88.1)	52 (89.7)	18 (90)	144 (87.3)	0.86
AUDIT ≥8	29 (11.9)	6 (10.3)	2 (10)	21 (12.7)	
Type of diabetes					
Type 1	43 (17.0)	14 (23.0)	2 (9.5)	27 (15.8)	0.28
Type 2	210 (83)	47 (77.0)	19 (90.5)	144 (84.2)	
Microvascular complications					
None	32 (12.6)	6 (9.8)	1 (4.8)	25 (14.6)	0.33
One or more	221 (87.4)	55 (90.2)	20 (95.2)	146 (85.4)	
Macrovascular complications					
None	185 (73.1)	48 (78.7)	11 (52.4)	126 (73.7)	0.06
One or more	68 (26.9)	13 (21.3)	10 (47.6)	45 (26.3)	
Mean duration of diabetes (years)	14.7 ± 13.2	13.0 ± 10.4	19 ± 18	14.7 ± 13.4	0.2
Mean duration of ulcer (months)	3.1 ± 3.6	3.1 ± 3.4	2.6 ± 3.5	3.2 ± 3.7	0.77
Mean A1C (%)	8.2 ± 1.7	8.5 ± 1.8	7.5 ± 1.7	8.2 ± 1.7	0.12
University of Texas severity of ulcer					
Superficial (grade 1)	188 (74.3)	38 (62.3)	7 (33.3)	35 (20.5)	0.02
Deep ulcer (grade 2 or 3)	65 (25.7)	23 (37.7)	14 (66.7)	136 (79.5)	
Mean ulcer size (cm^2)	3.2 ± 6.7	4.7 ± 10.5	5.5 ± 8.5	2.3 ± 4	0.01
Vibration perception threshold (volts)					
<25	47 (18.6)	11 (18.0)	1 (4.8)	35 (20.5)	0.22
≥25	206 (81.4)	50 (82.0)	20 (95.2)	136 (79.5)	
Arm-to-ankle ratio					
≥0.9	193 (76.3)	44 (72.1)	16 (76.2)	133 (77.8)	0.67
≥0.5 to <0.9	60 (23.7)	17 (27.9)	5 (23.8)	38 (22.2)	

Data are means ± SD or *n* (%). *χ^2 Test for categorical variables or *t* test for continuous variables. †Social class occupations: I, professional; II, managerial; III, skilled; IV, semiskilled; and V, unskilled. AUDIT, Alcohol Use Disorders Identification Test.

mortality. This may have led to biased estimates of the association between depression and glycemic control.

The limitations of our study are that we may have missed a small group of institutionalized or house-bound people, those whose ulcer was not accurately recorded or diagnosed by the podiatrist, and those who did not attend appointments. There is a small possibility of residual confounding from other diabetes complications and related conditions, but this is unlikely as we explored this in the modeling stage and we adjusted for the University of Texas classification and for macrovascular complications. We did not measure the presence of related depressive syndromes that do not meet the criteria for minor or major depressive disorders, such as adjustment disorders and dysthymia, but this was unlikely to alter our findings as the prevalence of these disorders is approximately six times lower than major depressive disorders, and they have significant comorbidity with major depression (41,42). The high rates of depression are in keeping with the literature that people with diabetes and complications are about two to three times more likely to have depressive dis-

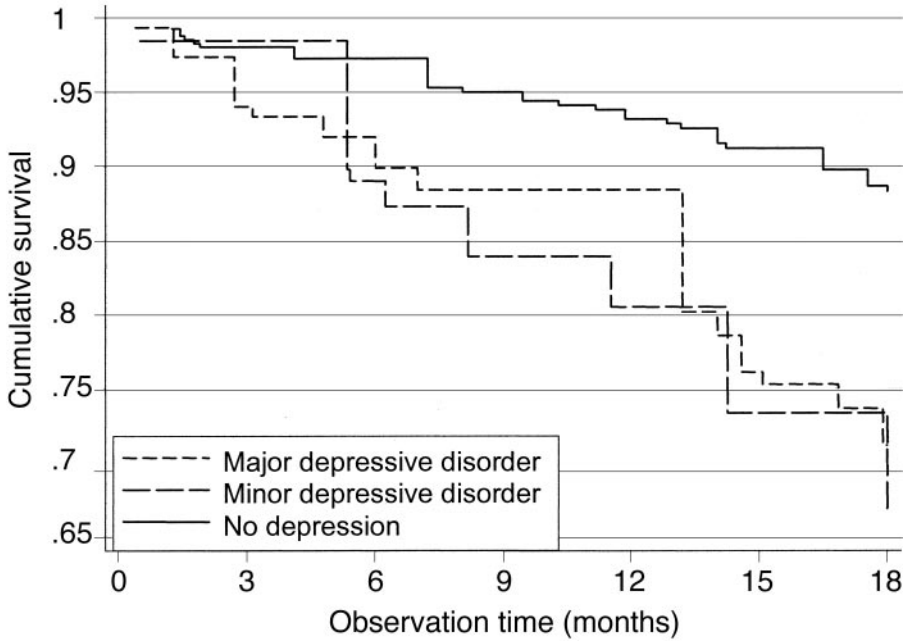

Figure 1—*Predicted survival curve for subjects with and without DSM-IV depressive disorder.*

orders, even when diagnostic criteria are used, and depressive symptoms than those without complications (14).

Why do patients with depression and diabetes have a significantly increased risk of death compared with those who are not depressed? One possibility is that depression may lead to behavioral difficulties in adhering to the intensive medical regime, as reported in cross-sectional community studies (43). There are several reasons why this mechanism is not the whole story. First, there was no association between depression at baseline and glycemic control 18 months later, which is contrary to pooled data from cross-sectional studies (13). Second, behavioral difficulties secondary to depression do not fully explain the increased mortality in people with other chronic diseases. In a prospective study, unhealthy lifestyles and poor adherence were not sufficient explanations for increased mortality in people with depressive symptoms and cardiovascular disease (44). In our study, we also did not find a consistent association between depression and diabetes self-care, but this may have been partly due to the well-recognized difficulties of subjective measures of adherence. Third, the possibility of competing events, which are events that prevent or modify the occurrence of other events, may have been present (45), such as whether amputation led to increased or decreased risk of mortality, although in our correlational analysis we did not observe any associations between morbidity outcomes and mortality.

Although there is emerging evidence that depression increases mortality and morbidity in people with diabetes, the mediating mechanisms are less clear. Some large-scale population-based prospective studies have reported that minor and major depression is associated with increased mortality in people with diabetes (17,18,20), but in randomized controlled trials of interventions for depression in diabetes, whereas depression scores tend to improve, glycemic control does not always improve (46–53).

Several alternative pathophysiological processes that have been proposed to explain the increased mortality in people with depressive disorders and cardiac mortality (44,54,55) may also apply to diabetes. Mechanisms proposed include decreased heart rate variability secondary to changes in autonomic tone (56), perhaps secondary to diabetic autonomic neuropathy; impairment of platelet function (57); cytokine activation (58,59); and activation of the hypothalamic-pituitary-adrenal axis (60), which may increase the susceptibility to infection and cardiovascular disease, which were the most common causes of death in this study (61). Antidepressants, especially tricyclics, are cardiotoxic, but in our study antidepressant prescribing was very low and there was only one death while on antidepressants (55).

We did not observe a difference between minor and major depression in the risk of mortality, which is in contrast to findings in community samples (18). This was substantiated by the positive association between depressive symptoms and mortality. One possible explanation is that depression in people with diabetes complications may have a chronic and/or fluctuating course, as they have a greater burden of disease. The handful of studies on the course of depression suggest that it is chronic and disabling in diabetes (62,63).

Our study demonstrates that a quarter of those presenting with their first diabetic foot ulcer are suffering from a major depressive disorder, a further 8% have a minor depressive disorder, and both are associated with around a threefold-increased mortality compared with those who are not depressed. Improvements in the screening, detection, and treatment of depression in this high-risk group could potentially lead to improved psychological and physical outcomes.

Acknowledgments— The funding body was not involved in the design and conduct of the study; the collection, management, analysis, and interpretation of the data; or the preparation, review, or approval of the manuscript.

We thank the Wellcome Trust for funding this project. We thank Maureen Bates and Melanie Doxford, Diabetic Foot Clinic, King's College Hospital, and Ian Aitkenhead for their time and thoughts at the pilot stage. We also thank all the participating patients and staff for their time. We thank Professor Traolach Brugha and Dr. Trevor Hill, University of Leicester, U.K., for converting the SCAN 2.1 raw scores. Parts of this article were presented at the 42nd European Association for the Study of Diabetes Annual Meeting, Copenhagen-Malmoe, Denmark-Sweden, 14–17 September 2006.

References

1. Apelqvist J, Larsson J, Agardh C: Long-term prognosis for diabetic patients with foot ulcers. *J Intern Med* 233:485–491, 1993
2. Williams D: The size of the problem: epidemiological and economic aspects of foot problems in diabetes. In *The Foot in Diabetes*. Boulton A, Connor H, Cavanagh P, Eds. Chichester, John Wiley, 1994, p. 15–24
3. Ramsey SD, Newton K, Blough D, McCulloch DK, Sandhu N, Reiber GE, Wagner EH: Incidence, outcomes, and cost of foot ulcers in patients with diabetes. *Diabetes Care* 22:382–387, 1999
4. Walters D, Gatling W, Mulle M, Hill R:

The distribution and severity of diabetic foot disease: a community study with comparison to a non-diabetic group. *Diabet Med* 9:354–358, 1992
5. Apelqvist J, Larsson J, Agardh C: The influence of external precipitating factors and peripheral neuropathy on the development and outcome of diabetic foot ulcers. *J Diabetes Complications* 4:21–25, 1990
6. Moss S, Klein R, Klein B: The prevalence and incidence of lower extremity amputation in a diabetic population. *Arch Intern Med* 152:610–616, 1992
7. Boyko E, Ahroni J, Stensel V, Forsberg R, Davignon D, Smith D: A prospective study of risk factors for diabetic foot ulcer: the Seattle Diabetic Foot Study. *Diabetes Care* 22:1036–1042, 1999
8. National Institute for Clinical Excellence: Type 2 diabetes: footcare [article online], 2004. Available at: http://www.nice.nhs.uk/page.aspx?o=cg010. Accessed 23 March 2006
9. Siitonen O, Niskanen L, Laakso M, Siitonen J, Pyorala K: Lower-extremity amputations in diabetic and non diabetic patients: a population based study in eastern Finland. *Diabetes Care* 16:16–20, 1993
10. Boyko E, Ahroni J, Smith D, Davignon D: Increased mortality associated with diabetic foot ulcer. *Diabet Med* 13:967–972, 1996
11. Moulik P, Mtonga R, Gill G: Amputation and mortality in new-onset diabetic foot ulcers stratified by etiology. *Diabetes Care* 26:491–494, 2003
12. Anderson R, Freedland K, Clouse R, Lustman P: The prevalence of comorbid depression in adults with diabetes: a meta-analysis. *Diabetes Care* 24:1069–1078, 2001
13. Lustman P, Anderson R, Freedland K, de Groot M, Carney R, Clouse R: Depression and poor glycaemic control: a meta-analytic review of the literature. *Diabetes Care* 23:934–942, 2000
14. de Groot M, Anderson R, Freedland K, Clouse R, Lustman P: Association of depression and diabetes complications: a meta-analysis. *Psychosom Med* 63:619–630, 2001
15. Carrington A, Mawdsley S, Morley M, Kinsey J, Boulton A: Psychological status of diabetic people with or without lower limb disability. *Diabetes Res Clin Pract* 32:19–25, 1996
16. Rosenthal M, Fajardo M, Gilmore S, Morley J, Naliboff B: Hospitalization and mortality of diabetes in older adults: a 3-year prospective study. *Diabetes Care* 21:231–235, 1998
17. Egede L, Nietert P, Zheng D: Depression and all-cause and coronary heart disease mortality among adults with and without diabetes. *Diabetes Care* 28:1339–1345, 2005
18. Katon W, Rutter C, Simon G, Lin E, Ludman E, Ciechanowski P, Kinder L, Young B, Von Korff M: The association of comorbid depression with mortality in patients with type 2 diabetes. *Diabetes Care* 28:2668–2672, 2005
19. Nabuurs-Franssen M, Huijberts M, Nieuwenhuijzen Kruseman A, Willems J, Schaper N: Health-related quality of life of diabetic foot ulcer patients and their caregivers. *Diabetologia* 48:1906–1910, 2005
20. Zhang X, Norris S, Gregg E, Cheng Y, Beckles G, Kahn H: Depressive symptoms and mortality among persons with and without diabetes. *Am J Epidemiol* 161:652–660, 2005
21. Nakahara R, Yoshiuchi K, Kumano H, Hara Y, Suematsu H, Kuboki T: Prospective study on influence of psychosocial factors on glycemic control in Japanese patients with type 2 diabetes. *Psychosomatics* 47:240–246, 2006
22. Lustman P, Harper G: Nonpsychiatric physicians' identification and treatment of depression in patients with diabetes. *Compr Psychiatry* 28:22–27, 1987
23. World Health Organization: *Definition, Diagnosis and Classification of Diabetes Mellitus and Its Complications: Report of a WHO Consultation. Part 1: Diagnosis and Classification of Diabetes Mellitus*. Geneva, World Health Org., Department of Noncommunicable Disease Surveillance, 1999
24. Office of National Statistics: Census 2001 [article online], 2003. Available at http://www.statistics.gov.uk/census2001/pyramids/pages/1b.asp. Accessed 23 March 2006
25. *Yorkshire and Humber Public Health Observatory PBS Diabetes Population Prevalence Model: Phase 2*. York, Yorkshire & Humber Public Health Observatory, University of York, 2005
26. Edmonds M, Foster A: *Managing the Diabetic Foot*. Oxford, Blackwell Science, 2000
27. International Working Group on the Diabetic Foot: *The International Consensus on the Diabetic Foot*. Amsterdam, the Netherlands, International Working Group on the Diabetic Foot, 1999
28. Armstrong D, Lavery L, Harkless L: Validation of a diabetic wound classification system: the contribution of depth, infection, and ischemia to risk of amputation. *Diabetes Care* 21:855–859, 1998
29. Rajbhandhari S, Harris N, Sutton M, Lockett C, Eaton S, Gadour M, Tesfaye S, Ward J: Digital imaging: an accurate and easy method of measuring foot ulcers. *Diabet Med* 16:339–342, 1999
30. World Health Organization: *SCAN: Schedules for Clinical Assessment in Neuropsychiatry. Version 2.1*. Geneva, World Health Org., 1997
31. Rijnders C, van den Berg J, Hodiamont P, Nienhuis F, Furer J, Mulder J, Giel R: Psychometric properties of the Schedules for Clinical Assessment in Neuropsychiatry (SCAN-2.1). *Soc Psychiatry Psychiatric Epidemiol* 35:348–352, 2000
32. Çelik C: I-Shell SCAN: SCAN Version 2.1. Geneva, World Health Org., 1999
33. Der G, Wing J: ICD 10 program for WHO SCAN: version 1.0. MS DOS. Geneva, World Health Org., 1992
34. Hoelzel W, Miedema K: Development of a reference system for the international standardisation of HbA1c/glycohemoglobin determinations. *J Int Fed Clin Chem* 9:62–67, 1996
35. Sinacore D: Total contact casting for diabetic neuropathic ulcers. *Phys Ther* 76:296–301, 1996
36. Office of Population Censuses and Surveys: *Standard Occupational Classification*. London, Her Majesty's Stationary Office, 1991
37. Saunders J, Aasland O, Thomas B, de la Fuente J, Grant M: Development of the Alcohol Use Disorders Test (AUDIT): WHO collaborative project on the early detection of persons with harmful alcohol consumption. *Addiction* 88:791–804, 1993
38.. Toobert D, Hampson S, Glasgow R: The summary of diabetes self-care activities measure: results from 7 studies and a revised scale. *Diabetes Care* 23:943–950, 2000
39. Cleves M: *Introduction to Survival Analysis Using Stata*. College Station, TX, Stata Corporation, 2004
40. Gavard J, Lustman P, Clouse R: Prevalence of depression in adults with diabetes: an epidemiological evaluation. *Diabetes Care* 16:1167–1178, 1993
41. Judd L, Akiskal H, Maser J, Zeller P, Endicott J, Coryell W, Paulus M, Kunovac J, Leon A, Mueller T, Rice J, Keller M: A prospective 12-year study of subsyndromal and syndromal depressive symptoms in unipolar major depressive disorders. *Arch Gen Psychiatry* 55:694–700, 1998
42. Ayuso-Mateos J, Vazquez-Barquero J, Dowrick C, Lehtinen V, Dalgard O, Casey P, Wilkinson C, Lasa L, Page H, Dunn G, Wilkinson G: Depressive disorders in Europe: prevalence figures from the ODIN study. *Br J Psychiatry* 179:308–316, 2001
43. Ciechanowski P, Katon W, Russo J: Depression and diabetes: impact of depressive symptoms on adherence, function, and costs. *Arch Intern Med* 160:3278–3285, 2000
44. Penninx B, Beekman A, Honig A, Deeg D, Schoevers R, van Eijk J, van Tilburg W: Depression and cardiac mortality: results from a community-based longitudinal study. *Arch Gen Psychiatry* 58:221–227, 2001
45. Klein J, Andersen P: Regression modeling of competing risks data based on pseudovalues of the cumulative incidence function. *Biometrics* 61:223–229, 2005
46. Lustman P, Griffith L, Clouse R, Freedland K, Eisen S, Rubin E, Carney R,

McGill J: Effects of nortriptyline on depression and glycaemic control in diabetes: results of a double-blind, placebo-controlled trial. *Psychosom Med* 59:241–250, 1997
47. Lustman P, Griffith L, Freedland K, Kissel S, Clouse R: Cognitive behavior therapy for depression in type 2 diabetes mellitus: a randomized, controlled trial. *Ann Intern Med* 129:613–621, 1998
48. Lustman P, Freedland K, Griffith L, Clouse R: Fluoxetine for depression in diabetes: a randomized double-blind placebo-controlled trial. *Diabetes Care* 23:618–623, 2000
49. Huang X, Song L, Li T: The effect of social support on type II diabetes with depression. *Chinese Journal of Clinical Psychology* 9:187–189, 2001
50. Katon W, Von Korff M, Lin E, Simon G, Ludman E, Russo J, Ciechanowski P, Walker E, Bush T: The Pathways Study: A randomized trial of collaborative care in patients with diabetes and depression. *Arch Gen Psychiatry* 61:1042–1049, 2004
51. Williams J, Katon W, Lin E, Noel P, Worchel J, Cornell J, Harpole L, Fultz B, Hunkeler E, Mika V, Unutzer J, the IMPACT Investigators: The effectiveness of depression care management on diabetes-related outcomes in older patients. *Ann Intern Med* 140:1015–1024, 2004
52. Lustman P, Clouse R, Nix B, Freedland K, Rubin E, McGill J, Williams M, Gelenberg A, Ciechanowski P, Hirsch I: Sertraline for prevention of depression recurrence in diabetes mellitus: a randomized, double-blind, placebo-controlled trial. *Arch Gen Psych* 63:521–529, 2006
53. Lin E, Katon W, Rutter C, Simon G, Ludman E, Von Korff M, Young B, Oliver M, Ciechanowski P, Kinder L, Walker E: Effects of enhanced depression treatment on diabetes self-care. *Ann Fam Med* 4:46–53, 2006
54. Frasure-Smith N, Lesperance F, Talajic M: Depression following myocardial infarction: impact on 6-month survival. *JAMA* 270:1819–1825, 1993
55. Carney R, Freedland K, Miller G, Jaffe A: Depression as a risk factor for cardiac mortality and morbidity: a review of potential mechanisms. *J Psychosom Res* 53: 897–902, 2002
56. Carney R, Blumenthal J, Stein P, Watkins L, Catellier D, Berkman L, Czajkowski S, O'Connor C, Stone P, Freedland K: Depression, heart rate variability, and acute myocardial infarction. *Circulation* 104: 2024–2028, 2001
57. Musselman D, Tomer A, Manatunga A, Knight B, Porter M, Kasey S, Marzec U, Harker L, Nemeroff C: Exaggerated platelet reactivity in major depression. *Am J Psychiatry* 153:1313–1317, 1996
58. Owen B, Eccleston D, Ferrier I, Young H: Raised levels of plasma interleukin-1 beta in major and postviral depression. *Acta Psychiatr Scand* 103:226–228, 2001
59. Suarez E, Krishnan R, Lewis J: The relation of severity of depressive symptoms to monocyte-associated proinflammatory cytokines and chemokines in apparently healthy men. *Psychosom Med* 65:362–368, 2003
60. Harris T, Borsanyi S, Messari S, Stanford K, Brown GW, Cleary S, Shiers H, Herbert J: Morning cortisol as a risk factor for subsequent major depressive disorder in adult women. *Br J Psychiatry* 177:505–510, 2000
61. Chrousos G: The hypothalamic-pituitary-adrenal axis and immune-mediated inflammation. *N Engl J Med* 332:1351–1363, 1995
62. Lustman P, Griffith L, Freedland K, Clouse R: The course of major depression in diabetes. *Gen Hosp Psychiatry* 19:138–43, 1997
63. Peyrot M, Rubin R: Persistence of depressive symptoms in diabetic adults. *Diabetes Care* 22:448–52, 1999