Depression predicts first but not recurrent diabetic foot ulcers

J. S. Gonzalez · L. Vileikyte · J. S. Ulbrecht ·
R. R. Rubin · A. P. Garrow · C. Delgado ·
P. R. Cavanagh · A. J. M. Boulton · M. Peyrot

Received: 24 February 2010 / Accepted: 30 April 2010 / Published online: 17 June 2010
© Springer-Verlag 2010

Abstract

Aims/hypothesis This study examined the relationship between symptoms of depression and the development of diabetic foot ulcers.

Methods Participants were 333 patients (71% male; mean age 62 years; 73% with type 2 diabetes) with diabetic peripheral neuropathy (DPN), but without peripheral vascular disease

(PVD). Severity of DPN and the presence of PVD were assessed by clinical examination. Depression, other diabetes complications and foot self-care were assessed by self-report. Cox regression tested whether depression was an independent predictor of foot ulceration over 18 months, whether this relationship was moderated by foot ulcer history, and whether foot self-care mediated this relationship.

Results During follow-up, 63 patients developed a foot ulcer. Those with prior foot ulcers had more than four-fold greater risk of subsequent foot ulceration compared with those without a history of foot ulcer. A significant interaction effect showed that depression was significantly related to the development of first but not recurrent foot ulcers. This relationship was independent of biological risk factors. In the final model, each standard deviation increase in depression symptoms was significantly associated with increased risk of developing first foot ulcers (HR 1.68, 95% CI 1.20–2.35), while foot self-care was associated with lower risk (HR 0.61, 95% CI 0.40–0.94). Foot self-care did not mediate the relationship between depression and foot ulceration.

Conclusions/interpretation These data suggest that depression is associated with increased risk of first foot ulcers in DPN patients and that this relationship is independent of biological risk factors and foot self-care. Interventions that target depression and foot self-care before the development of foot ulcers may maximise the likelihood of successful prevention of foot ulceration.

Keywords Depression · Depressive symptoms · Diabetes · Diabetic peripheral neuropathy · Foot self-care · Foot ulcers · Longitudinal

J. S. Gonzalez
Ferkau Graduate School of Psychology, Yeshiva University,
Rousso Building, 1300 Morris Park Avenue,
Bronx, NY 10461, USA

J. S. Gonzalez (✉)
Albert Einstein College of Medicine,
Bronx, NY, USA
e-mail: jeffrey.gonzalez@einstein.yu.edu

L. Vileikyte · A. P. Garrow · C. Delgado · A. J. M. Boulton
University of Manchester,
Manchester, UK

L. Vileikyte · A. J. M. Boulton
University of Miami,
Miami, FL, USA

J. S. Ulbrecht
Pennsylvania State University,
State College, PA, USA

R. R. Rubin · M. Peyrot
Johns Hopkins University School of Medicine,
Baltimore, MD, USA

P. R. Cavanagh
University of Washington,
Seattle, WA, USA

M. Peyrot
Loyola University Maryland,
Baltimore, MD, USA

Abbreviations

DPN Diabetic peripheral neuropathy
NDS Neuropathy disability score

PVD	Peripheral vascular disease
HADS	Hospital Anxiety and Depression Scale
SDSCA	Summary of Diabetes Self-Care Activities
VPT	Vibration perception threshold

Introduction

Diabetic foot complications are common throughout the world and cause an extensive burden on individuals, the healthcare system and society [1]. Persons with diabetes have a 12–25% lifetime risk of developing a foot ulcer [2, 3], and those with established diabetic peripheral neuropathy (DPN), a key risk factor for foot ulceration, have an annual first ulcer incidence of 5–7% [3]. Recurrence rates among those with successfully treated foot ulcers may be as high as 60% [4]. Foot ulcers are the most important risk factor for lower-extremity amputations [5, 6] and are associated with substantial treatment costs [7]. Moreover, foot ulceration impacts negatively on quality of life [8] and, perhaps most strikingly, diabetes patients with a history of foot ulceration have a twofold increased risk for mortality as compared with those without foot ulcers [9–12].

Previous studies have almost invariably focused on biological foot ulcer risks, with little consideration of potentially important psychological factors such as depression. For example, while a meta-analysis of 12 studies suggests that depressive symptoms are significantly associated with DPN [13], these studies did not evaluate foot ulceration as an outcome, despite the fact that depression is consistently and negatively associated with diabetes self-care [14], including foot self-care [15], which is believed to play a crucial role in foot ulcer prevention [16, 17].

Our previous work using standardised diagnostic criteria for neuropathy [18] demonstrated a significant association between DPN severity and increased depressive symptoms, but failed to demonstrate a relationship between past foot ulceration and either concurrent [19] or subsequent depression [20]. Consistent with our findings, recent data from a large population-based study of diabetes patients with past foot ulceration also found that these patients reported more symptoms of depression than patients without diabetes, but their level of depression symptoms did not differ from diabetes patients who had not had a foot ulcer [12].

Whether depression is a risk factor for subsequent foot ulceration has received little empirical investigation. One group reported that symptoms of depression were associated with foot ulcer recurrence in a small sample of elderly patients with type 2 diabetes [21]. However, it is unclear from the report whether analyses adequately controlled for potential confounding between neuropathy severity and depression; others using a larger population-based sample

have failed to find this relationship [22]. As neuropathy, a well-established risk factor for foot ulceration [3], is also a risk factor for elevated depressive symptoms [19, 20], this may be a major limitation of previous research.

The primary aim of the current study was, therefore, to prospectively investigate the independent role of depression in the development of foot ulceration, after controlling for biological foot ulcer risks. Given that incident foot ulceration risk is reported to be 2.5 times to more than five times greater among those with a history of foot ulceration as compared with those without [23–25], we examined whether past foot ulceration moderated the association between depression and incident foot ulceration. Additionally, we examined foot self-care behaviour as a potential mediator of the relationship between depression and foot ulceration. We hypothesised that depression would be an independent risk factor for incident foot ulceration and that this association would be mediated by poorer foot self-care.

Methods

Participants

Data for these analyses were obtained from a sample of individuals at high risk for foot ulceration participating in a 2 year longitudinal UK and USA collaborative study on the psychological determinants of adherence to foot self-care and foot ulceration. The details of this sample have been reported previously [19, 20]. The sample was drawn from 522 patients with established peripheral neuropathy and either type 1 (onset prior to 40 years of age and prescription of insulin within 2 years of diagnosis) or type 2 diabetes (all other types of diabetes) attending three diabetes treatment centres (Manchester, UK; Baltimore, MD, USA; and State College, PA, USA) between 2001 and 2003. Of these patients, 495 agreed to participate, giving a 5% refusal rate. The Central Manchester Research Ethical Review Committee and the Institutional Review Boards at the Johns Hopkins University and the Pennsylvania State University approved this study and all participants provided informed consent.

In accordance with the international diagnostic guidelines for neuropathy [18], two semi-quantitative tests were used to diagnose neurological dysfunction: the neuropathy disability score (NDS) and the vibration perception threshold (VPT, as described in the ‘Measures’ section). Each of these measures has been found to predict foot ulceration [3, 25]. Participants were diagnosed as having neuropathy if they had an NDS ≥ 3 and a mean VPT of ≥ 25 volts; thus, patients with mild neuropathic deficits were excluded from the study. For the current analysis, patients were also excluded if they had: peripheral vascular disease (based on clinical examination and defined as no palpable foot pulse in either foot—at least

one pulse per foot had to be palpated for inclusion); a history of major amputation (any lower limb amputation proximal to the mid-foot); evidence of Charcot deformity; or other severe chronic medical diseases or complications of diabetes precluding participation (such as dialysis-treated end-stage renal disease, stroke or widespread malignant disease). Patients were also excluded if they were unable to understand English sufficiently well to complete the psychological assessment or had insufficient (corrected) vision to complete the questionnaires without assistance. Of the original baseline sample, 333 participants were followed for the development of a foot ulcer and re-evaluated at approximately 9 and 18 months after the baseline assessment. Patients were included in the current analysis if they provided data for at least one re-evaluation.

Measures

Depressive symptoms The Hospital Anxiety and Depression Scale (HADS) [26] was designed to avoid the confounding of somatic symptoms of concurrent physical disorders such as sleep problems and/or pain, with the assessment of anxious and depressive symptoms in medically ill persons. The HADS measures the absence of both positive affect and pleasure from everyday tasks with seven items. Items are coded so that higher scores indicate greater severity of depression; examples of statements on the scale are: ‘I still enjoy the things I used to enjoy’ or ‘I can laugh and see the funny side of things.’ A review of the literature suggests that a score of 8 on the HADS is the optimal cut-off for identifying clinical cases of depression [27].

Clinical tests of neuropathy severity The NDS, a composite measure of both large- and small-fibre dysfunction, was assessed using a Neurotip (Owen Mumford, Woodstock, UK) to record awareness of pin-prick sensation, a 128 Hz tuning fork to assess awareness of vibration, warm and cool rods to assess temperature sensation on the dorsal surface of the foot, and a tendon hammer to record the presence and strength of the Achilles reflex. The sensory modalities were scored as present=0 or reduced/absent=1 for each side. Reflexes were scored as normal=0, present with reinforcement=1, or absent=2 for each side. The maximum score is 10, with a score of 0 representing a totally normal peripheral nervous system examination [25]. The VPT, a quantitative measure of large-fibre dysfunction, was assessed at the big (great) toe of both feet as an average of three measurements of the initial perception of vibration, using a neurothesiometer [3] (Horwell, Nottingham, UK).

Foot ulceration A history of foot ulceration was obtained by asking each participant: ‘Have you ever had a foot ulcer (an open sore on your foot)?’ The presence of foot ulcers

was determined by a medical examination at the time of the baseline interview and patients with an active ulcer at this examination were also coded as having a positive history of ulceration. A foot ulcer was defined as a full-thickness skin break below the malleolus (foot–ankle junction). At the follow-up evaluations, patients were asked whether they had developed a new foot ulcer since the previous study visit. They were also asked to provide information to determine the month and year of foot ulceration. A minimum duration for the foot ulcer was not specified due to the likelihood that patients would be inaccurate reporters for ulcer duration over the follow-up. A foot examination was performed to determine the presence of any ulcer at each follow-up visit. All patients who reported the onset of a foot ulcer with a date following the baseline evaluation or who had a foot ulcer discovered by physical examination were coded as having developed a foot ulcer during the follow-up. The number of months between the baseline visit and the reported onset date was calculated to determine time to event. In cases where patients reported that more than one ulcer had developed over the follow-up interval, we coded the earliest ulcer for the analyses presented below.

Foot self-care Two items were used to assess patients’ practise of foot self-care and were based on the subscale from the Summary of Diabetes Self-Care Activities (SDSCA) [28]. The two-item foot-care SDSCA subscale was negatively related to depression symptoms in a primary sample of type 2 diabetes patients [15]. The items asked patients how often over the past week they: (1) examined their feet; and (2) checked the inside of their shoes. While the SDSCA uses a response scale consisting of the number of days over the past week the behaviour was performed, our response scale was scored as follows: 1, never; 2, once; 3, twice; 4, every other day; 5, once a day; and 6, twice daily.

Control variables While indicators of neuropathy severity were our primary controls for biological risk associated with ulcers, we also considered a number of additional variables that have been reported to predict ulceration in patients with diabetes: age [29]; sex [30, 31]; duration of diabetes [30, 31]; nephropathy [4, 30]; retinopathy/poor vision [23, 24, 30]; and macrovascular complications [29]. Each of these variables was assessed by self-report at the baseline evaluation. The following questions were used to evaluate the presence of nephropathy, retinopathy, and cardiovascular complications of diabetes: ‘Have you been told of any kidney damage from the diabetes?’ ‘Do you have any diabetes damage in the back of your eyes (retina) that you have been told about or have you had laser therapy?’ ‘Have you had a stroke or a transient ischaemic

attack (mini-stroke)’ and ‘Do you have angina (heart pain), or have you had a heart attack or heart bypass surgery?’

Statistical methods

All data were analysed using SPSS 11.0. Descriptive statistics were calculated for all variables and the data distributions were examined for normality. Missing data were imputed with the mean score for each respective variable to reduce the impact of list-wise deletion on the total sample size for the analysis. Out of our sample of 333 participants for whom follow-up data were available, the maximum number of imputed values for any variable was six (diabetes duration). No other variable had more than two missing values.

The analysis examined the relationship between baseline symptoms of depression and time-to-onset of foot ulceration over the follow-up using Cox regression survival analyses. Time-to-onset was calculated as the number of months from baseline until the development of the first foot ulcer. Participants who did not develop a foot ulcer were censored at the point of their last evaluation in the study. To facilitate interpretation of the results, for the regression analyses we converted depression symptoms and foot care behaviour to *z* scores where the mean is zero and each one unit corresponds to a standard deviation in the original scoring of the scales (see Table 1 for SDs). In preliminary analyses, we examined each of the potential control variables separately in bivariate Cox regression models to identify variables significantly related to ulceration for inclusion in the multivariate model. We also examined depression, foot ulcer history, NDS and VPT in bivariate models. For our multivariate analysis, we examined a model that included depression *z* score as the primary

predictor of interest and added covariates that were significant in bivariate analyses (age and retinopathy), indicators of neuropathy severity (NDS, VPT) and history of foot ulceration. Addition of covariates was performed with a single stepwise entry command using $p < 0.05$ as the criterion for entry. Next, we added the interaction term between depression score and history of foot ulceration to examine evidence for moderation of the depression effect by foot ulcer history. Finally, we repeated the model, stratifying the analysis by foot ulcer history. Where significant effects for depression were found, we tested an additional model including foot self-care behaviour as a potential mediator and followed standard procedures for the evaluation of mediation [32].

Results

Demographic and clinical characteristics of our study population are presented in Table 1. With respect to biological risk factors for foot ulceration, 28.5% either reported a prior foot ulcer or had an active foot ulcer at baseline. Further, as per our inclusion criteria, patients had moderate to severe neuropathy ([mean $\pm$ SD] VPT=40.3 $\pm$ 9.8, NDS=7.2 $\pm$ 2.3). Cardiovascular complications of diabetes and retinopathy were reported by 66.7% and 45% of the overall sample, respectively. Patients who reported a prior foot ulcer at baseline were significantly more likely to be younger, to have retinopathy, to have more severe DPN and to be engaging in more frequent foot self-care.

As can be seen in Table 2, patients with a history of foot ulcers experienced a much higher rate of foot ulceration over the follow-up compared with those without a prior foot ulcer (4.33:1), with an 81% greater chance of developing a foot ulcer sooner than those without a prior

Table 1 Baseline characteristics of the study population

Characteristic	Overall sample ($n=333$)	No prior ulcer ($n=238$)	Prior ulcer ($n=95$)
Sex (% male)	70.6	68.5	75.8
Age (years)*	62.2 $\pm$ 11.1	63.0 $\pm$ 11.3	60.0 $\pm$ 10.5
Duration of diabetes (years)	17.0 $\pm$ 11.5	16.4 $\pm$ 11.5	18.6 $\pm$ 11.5
Retinopathy (%)***	45.0	39.1	60.0
Nephropathy (%)	14.1	11.8	20.0
Cardiovascular complications (%)	66.7	66.4	67.4
NDS***	7.2 $\pm$ 2.3	6.8 $\pm$ 2.2	8.2 $\pm$ 2.1
VPT***	40.3 $\pm$ 2.3	38.7 $\pm$ 9.7	44.3 $\pm$ 8.7
HADS (raw score)	4.9 $\pm$ 3.9	4.9 $\pm$ 4.0	5.1 $\pm$ 3.6
Foot self-care (raw score)***	3.6 $\pm$ 1.4	3.4 $\pm$ 1.4	4.1 $\pm$ 1.2

Results are presented as percentages and mean $\pm$ SD

χ^2 tests were used to evaluate categorical variables and independent sample *t* tests were used to evaluate continuous variables

Significant differences between the no prior ulcer and prior ulcer groups are denoted by asterisks in the first column: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

Table 2 Cox regressions: bivariate relationships with ulcer risk

Characteristic	Overall sample (<i>n</i> =333)	No prior ulcer (<i>n</i> =238)	Prior ulcer (<i>n</i> =95)
Sex (male)	1.04 (0.61–1.78)	1.29 (0.59–2.85)	1.18 (0.56–2.51)
Age (years)	0.98 (0.96–0.99)*	0.98 (0.95–1.01)	0.98 (0.96–1.01)
Duration of diabetes (years)	1.01 (0.99–1.04)	1.02 (0.99–1.06)	1.00 (0.97–1.03)
Retinopathy	2.04 (1.23–3.40)**	2.91 (1.29–5.53)**	0.93 (0.48–1.80)
Nephropathy	0.85 (0.41–1.80)	1.03 (0.31–3.43)	0.50 (0.19–1.28)
Cardiovascular complications	1.06 (0.63–1.79)	1.01 (0.50–2.27)	1.10 (0.55–2.19)
Prior ulcer	4.33 (2.62–7.16)***	NA	NA
NDS	1.32 (1.15–1.50)***	1.33 (1.09–1.62)**	1.12 (0.95–1.32)
VPT	1.05 (1.02–1.09)***	1.06 (1.01–1.10)*	1.02 (0.98–1.06)
HADS <i>z</i> score	1.21 (0.96–1.52)	1.57 (1.14–2.15)**	0.88 (0.61–1.27)
Foot care <i>z</i> score	1.18 (0.92–1.51)	0.89 (0.61–1.29)	1.12 (0.76–1.65)

Data are hazard ratios and 95% confidence intervals

* $p<0.05$; ** $p<0.01$;

*** $p<0.001$

NA, not applicable

foot ulcer. Of the total 63 foot ulcers, 37 (59%) occurred in this group with an average time-to-onset from baseline of approximately 9 months (9.1 ± 6.7) vs more than 12 months average time-to-onset in the first ever foot ulcer group (12.7 ± 6.5). In the overall sample, patients of younger age and who reported retinopathy also had significantly higher hazard rates. In addition, VPT and NDS were significantly associated with increased risk of ulceration. Neither depression nor foot self-care behaviour was significantly associated with ulcer risk in the overall sample in the bivariate analysis. Table 2 also reports bivariate relationships stratified by ulcer history for comparison with the multivariate results presented in Table 3.

As seen in Table 3, for the overall sample in multivariate analysis, higher depression, younger age, higher NDS scores and prior foot ulceration were independently and significantly associated with a higher risk of foot ulceration. Moreover, there was a significant interaction between foot ulcer history and depression in predicting time to foot ulcer incidence in the overall sample. Stratified analyses controlling for the significant positive associations of retinopathy

and VPT with foot ulceration rate showed that each one standard deviation increase in depression score was associated with a 48% increase in the rate of foot ulceration in those with no prior foot ulcer (HR 1.48, 95% CI 1.08–2.03). We next examined evidence for foot self-care as a potential mediator of this relationship between depression and foot ulceration risk in the group with no prior foot ulcers. We found that depression was significantly correlated ($r=0.21$, $p=0.001$) with more frequent foot self-examination and this significant relationship persisted in a multivariate linear regression ($\beta=0.19$, $p=0.004$) controlling for the biological risk covariates. VPT ($\beta=0.17$, $p=0.009$) and retinopathy ($\beta=0.12$, $p=0.065$) were similarly positively associated with foot self-care in this model. However, when foot self-care behaviour was added as a predictor of foot ulceration rate in the final Cox regression model for the group with no prior foot ulcer (see Table 3), the relationship between depression and foot ulceration rate was not attenuated; it was enhanced. The relationship between foot self-care and foot ulcer risk was significant in this model, with each standard unit increase in foot self-

Table 3 Multivariate Cox regression: predictors of time to foot ulceration

Predictor	Overall sample (<i>n</i> =333)	No prior ulcer (<i>n</i> =238)	Prior ulcer (<i>n</i> =95)
Depression			
HADS <i>z</i> score	1.38 (1.01–1.89)*	1.68 (1.20–2.35)**	0.88 (0.61–1.27)
Demographic/biological covariates			
Age	0.97 (0.95–0.99)*	–	–
Retinopathy	–	4.43 (1.89–10.14)**	–
Objective neuropathy severity			
NDS	1.22 (1.07–1.40)**	–	–
VPT	–	1.07 (1.02–1.13)**	–
Ulcer history			
Prior ulcer	3.56 (2.05–6.17)***	N/A	N/A
Prior ulcer $\times$ depression score	0.58 (.035–0.97)*	N/A	N/A
Foot self-care mediation			
Foot self-care <i>z</i> score	–	0.61 (0.40–0.94)*	–

Data are hazard ratios and 95% confidence intervals

Dashes (–) denote that the variable did not enter the analysis on the stepwise command

* $p<0.05$; ** $p<0.01$;

*** $p<0.001$

NA denotes ‘not applicable’ because the analysis was stratified by foot ulcer history

care associated with a significant decrease in the risk of foot ulceration, once other predictors were taken into account. In the prior foot ulcer group, there was no significant relationship between depression and rate of foot ulceration; no other predictors were significantly associated with foot ulceration (Table 3). Foot self-care behaviour was not associated with depression in the prior foot ulcer group ($r=0.05$, $p=0.731$).

Antidepressant use was reported by 55 participants over the follow-up but was not related to foot ulcer risk; controlling for antidepressant use did not appreciably alter the results of the multivariate models reported above (data not shown). Further analyses controlling for total number of self-reported comorbid medical illnesses, which was also unrelated to foot ulcer risk, did not change the results of the multivariate models (data not shown).

Discussion

This prospective study of a well-defined sample of patients at high risk for foot ulceration provides evidence that severity of depression symptoms is an independent risk factor for the development of first foot ulcers. Our analyses compellingly demonstrate the interplay between biological, psychological and behavioural foot ulcer risks. Depression was significantly associated with an increased rate of developing foot ulcers among those patients with no prior foot ulceration but not among those who had previously had a foot ulcer. This relationship between depression and foot ulcer rates was independent of biological risk factors. The relationship was also substantial; each standard deviation increase in depressive symptom severity was associated with a 68% increase in risk of first foot ulcers. One standard deviation above the mean in our sample, for example, corresponded to a value that is just above the cut-off for identifying clinical depression [27]. Importantly, this relationship was based on continuously measured depression severity and the increased risk for first foot ulcers associated with each standard deviation increase applies to the full range of observed HADS depression scores (0–19).

We did not find evidence for the hypothesised mediation by foot self-care of the relationship between depression and the development of initial foot ulcers. While depression, foot self-care and incident foot ulceration were significantly associated with each other, higher depression scores were associated with greater frequency of foot self-care which, in turn, was associated with lower foot ulceration risk in multivariate analysis. Adding behaviour to the multivariate model increased rather than reduced the strength of the unique association between depression and foot ulcer risk. While at first glance these results may appear paradoxical, we believe they suggest that the association between

depression and foot ulceration may involve at least two countervailing components. First, patients engaging in more frequent foot self-care may have been more aware of their heightened health risk and, thus, more likely to experience symptoms of depression. While in this way depression was associated with lower risk of foot ulceration through its relationship with more frequent foot self-care, depression was also associated with higher risk of ulceration through pathways that were not identified by our analyses. When foot self-care was controlled for, the component of depression that was associated with lower foot ulcer risk (through its association with foot self-care) was removed from the estimate of the depression effect, thus increasing the strength of the positive effect between depression and foot ulcer risk.

Whether depression represents an indicator of biological risk that was not captured by the risk factors measured by the current study or whether it truly is a causal agent in the development of first diabetic foot ulcers, acting via mechanisms other than foot self-care, is an important question that deserves further investigation. It is also possible that our measure of foot self-care does not capture the full impact of foot self-care on the risk for ulceration, so that a more comprehensive measure might mediate the relationship between depression and foot ulceration. The fact that depression, like foot self-care, was associated with foot ulcer risk only in those without a history of foot ulcers suggests that the effects of these psychological and behavioural factors may not be robust enough to come into play in the context of very high levels of risk (i.e. in patients with prior history of foot ulceration). Although there is a strong evidence base to suggest that depression is associated with poorer self-care and non-adherence to diabetes treatment [14], depression is also associated with alterations in immune system responses to infection and injury [33], and neuroendocrine changes—specifically activation of the hypothalamic–pituitary–adrenal axis and sympathetic nervous system [34]. While preliminary findings suggest that such pathways may be important in explaining the link between depression and impaired foot ulcer healing [35], the role of these pathways in explaining risk of new foot ulcer development is less clear and deserves further investigation.

The results of the current study are consistent with emerging findings suggesting that depression is associated with negative outcomes in patients at risk for foot ulcers. Depression has been prospectively associated with a three-fold increased risk of mortality over 18 months in patients presenting with their first foot ulcer, even after controlling for glycemic control, foot ulcer severity, smoking, socioeconomic status and other covariates [36]. Depression has also been associated with worse healing of foot ulcers over time and cross-sectionally associated with more severe and

larger foot ulcers [36]. More broadly, depression is also associated with increased mortality in diabetes patients in general [37, 38]. Recent research in primary care patients with type 2 diabetes also suggests that depression is associated with increased risk of microvascular and macrovascular complications over time, even after controlling for diabetes severity and self-care activities [39]. The mechanisms that might explain these relationships have yet to be identified. The elucidation of the mechanisms for these relationships has important implications for prevention and treatment. Our finding that depression predicts the onset of only first diabetic foot ulcers in at-risk patients suggests that preventive efforts may need to be focused on high-risk individuals who have not yet experienced diabetes complications.

Our findings should be considered within the context of our design. For example, we excluded patients with peripheral vascular disease, advanced renal disease and blindness. Although not the focus of the current analyses, our ability to identify relationships between these complications and risk for foot ulcer may have been limited by these restrictions and by our use of self-reporting to measure some of these variables. Also, our measurement of foot ulcers relied on patients' ability to remember whether they had had a foot ulcer since their last study visit. This could have biased our results, although we expect that the potential for under-reporting was greater than that for over-reporting. Furthermore, all patients received in-person education about the definition of a foot ulcer as part of their participation in the study and self-reports were supplemented by physical examinations at each study visit. Finally, while we selected covariates based on empirical support in the literature, we used stepwise entry to reduce the total number of covariates in our model and to preserve a reasonable ratio of events to predictors in our equations. Larger studies with a higher number of foot ulcer events are needed to more fully investigate the full set of contributors to foot ulcer risk.

The strength of the current study is enhanced by a number of factors including: our ability to prospectively assess the relationship between depression and incidence of foot ulcers; our inclusion of controls for biological risk factors for foot ulceration; clinical assessments of DPN; and our examination of the role of behaviours thought to be associated with foot ulceration risk. Our moderation analyses support further investigation into the moderating influence of biological risk in the relationship between depression and diabetes complications. Our results demonstrate that depression and self-care have important relationships to foot ulcer risk that are independent of biological risk factors in those who have not yet had a foot ulcer. This suggests that preventive efforts that address these factors may have greater efficacy in patients who have not yet

reached the highest level of risk. Addressing depression and foot self-care only in patients already presenting with foot ulcers may be 'too little, too late.'

Acknowledgements This work was supported by grants from Diabetes UK (RD00-0002009; L. Vileikyte, Principal Investigator) and the American Diabetes Association (1-00-CR-11; R. R. Rubin, Principal Investigator). L. Vileikyte is supported by NIH/NIDDK R01DK71066.

Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

References

1. Boulton AJM, Vileikyte L, Ragnarson-Tennvall G, Apelqvist J (2005) The global burden of diabetic foot disease. *Lancet* 366:1710–1724
2. Singh N, Armstrong DG, Lipsky BA (2005) Preventing foot ulcers in patients with diabetes. *JAMA* 293:217–228
3. Abbott CA, Vileikyte L, Williamson S, Carrington AL, Boulton AJ (1998) Multicenter study of the incidence of and predictive risk factors for diabetic neuropathic foot ulceration. *Diab Care* 21:1071–1075
4. Ghanassia E, Villon L, Thuan dit Dieudonne J, Boegner C, Avignon A, Sultan A (2008) Diabetic patients hospitalized for diabetic foot ulcers: a 6.5-year follow-up study. *Diab Care* 31:1288–1292
5. Pecoraro R, Reiber GE, Burgess EM (1990) Pathways to diabetic limb amputation. *Diab Care* 13:513–521
6. Margolis DJ, Allen-Taylor L, Hoffstad O, Berlin JA (2005) Diabetic neuropathic foot ulcers and amputation. *Wound Repair Regen* 13:230–236
7. Rogers LC, Lavery LA, Armstrong DG (2008) The right to bear legs—an amendment to health care: how preventing amputation can save billions for the US healthcare system. *J Am Podiatr Med Assoc* 98:166–168
8. Vileikyte L (2001) Diabetic foot ulcers—a quality of life issue. *Diab Metab Res Rev* 17:246–249
9. Ramsey SD, Newton K, Blough D et al (1999) Incidence, outcomes, and cost of foot ulcers in patients with diabetes. *Diab Care* 22:382–387
10. Boyko EJ, Ahroni JH, Smith DG, Davignon D (1996) Increased mortality associated with diabetic foot ulcer. *Diabet Med* 13:967–972
11. Moulik PK, Mtonga R, Gill GV (2003) Amputation and mortality in new-onset diabetic foot ulcers stratified by etiology. *Diab Care* 26:491–494
12. Iversen MM, Tell GS, Riise T et al (2009) A history of foot ulcer increases mortality among persons with diabetes: 10-year follow-up of the Nord-Trøndelag Health Study, Norway. *Diab Care* 32:2193–2199
13. de Groot M, Anderson R, Freedland KE, Clouse RE, Lustman PJ (2001) Association of depressive symptoms and diabetes complications: a meta-analysis. *Psychosom Med* 63:619–630
14. Gonzalez JS, Peyrot M, McCarl LA et al (2008) Depression and diabetes treatment nonadherence: a meta-analysis. *Diab Care* 31:2398–2403
15. Gonzalez JS, Safren SA, Delahanty LM et al (2008) Symptoms of depression prospectively predict poorer self-care in patients with type 2 diabetes. *Diabet Med* 25:1102–1107
16. National Institute for Clinical Excellence (2004) Type 2 diabetes: prevention and management of foot problems. Clinical Guideline

10. London: National Institute for Clinical Excellence, 2004. Available from www.nice.org.uk/nicemedia/pdf/CG010NICEguideline.pdf, accessed 23 February 2010
17. International Working Group on the Diabetic Foot (1999) International consensus on the diabetic foot. International Diabetes Foundation, Amsterdam
18. Boulton AJ, Vinik AI, Arezzo JC et al (2005) Diabetic neuropathies: a statement by the American Diabetes Association. *Diab Care* 28:956–962
19. Vileikyte L, Leventhal H, Gonzalez JS et al (2005) Diabetic peripheral neuropathy and depressive symptoms: the association revisited. *Diab Care* 28:2378–2383
20. Vileikyte L, Peyrot M, Gonzalez JS et al (2009) Predictors of depressive symptoms in persons with diabetic peripheral neuropathy: a longitudinal study. *Diabetologia* 52:1265–1273
21. Monami M, Longo R, Desideri CM, Masotti G, Marchionni N, Mannucci E (2008) The diabetic person beyond a foot ulcer: healing, recurrence, and depressive symptoms. *J Am Podiatr Med Assoc* 98:130–136
22. Winkley K, Stahl D, Chalder T, Edmonds ME, Ismail K (2007) Risk factors associated with adverse outcomes in a population-based prospective cohort study of people with their first diabetic foot ulcer. *J Diab Complications* 21:341–349
23. Boyko EJ, Ahroni JE, Stensel V, Forsberg RC, Davignon DR, Smith DG (1999) A prospective study of risk factors for diabetic foot ulcer. *Diab Care* 22:1036–1042
24. Boyko EJ, Ahroni JE, Cohen V, Nelson KM, Heagerty PJ (2006) Prediction of diabetic foot ulcer occurrence using commonly available clinical information: the Seattle Diabetic Foot Study. *Diab Care* 29:1202–1207
25. Abbott CA, Carrington AL, Ashe H et al (2002) The North-West Diabetes Foot Care Study: incidence of, and risk factors for, new diabetic foot ulceration in a community-based patient cohort. *Diabet Med* 19:377–384
26. Zigmond AS, Snaith RP (1983) The hospital anxiety and depressive symptoms rating scale. *Acta Psychiatr Scand* 67:361–370
27. Bjelland I, Dahl AA, Haug TT, Neckelmann D (2002) The validity of the hospital anxiety and depression scale: an updated literature review. *J Psychosom Res* 52:69–77
28. Toobert DJ, Hampson SE, Glasgow RE (2000) The summary of diabetes self-care activities measure: results from 7 studies and a revised scale. *Diab Care* 23:943–950
29. Iversen MM, Midtjell K, Ostbye T et al (2008) History of and factors associated with diabetic foot ulcers in Norway: the Nord-Trøndelag Health Study. *Scand J Public Health* 36:62–68
30. Lavery LA, Armstrong DG, Vela SA, Quebedeaux TL, Fleischli JG (1998) Practical criteria for screening patients at high risk for diabetic foot ulceration. *Arch Intern Med* 148:157–162
31. Pham H, Armstrong DG, Harvey C, Harkless LB, Giurini JM, Veves A (2000) Screening techniques to identify people at high risk for diabetic foot ulceration. *Diab Care* 23:606–611
32. Baron RM, Kenny DA (1986) The moderator/mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. *J Pers Soc Psychol* 51:1173–1182
33. Robles TF, Glaser R, Kiecolt-Glaser JK (2005) Out of balance: a new look at chronic stress, depression, and immunity. *Curr Dir Psychol Sci* 14:111–115
34. Golden S (2007) A review of the evidence for a neuroendocrine link between stress, depression and diabetes mellitus. *Curr Diab Rev* 3:252–259
35. Vileikyte L, Shen B-J, Hardman MJ et al. (2010) Emotional distress impedes diabetic foot ulcer healing through elevated levels of interleukin-6: preliminary findings. *Diabetologia* 53 (Suppl 1, in press)
36. Ismail K, Winkley K, Stahl D et al (2007) A cohort study of people with diabetes and their first foot ulcer: the role of depressive symptoms on mortality. *Diab Care* 30:1473–1479
37. Lin EH, Heckbert SR, Rutter CM et al (2009) Depression and increased mortality in diabetes: unexpected causes of death. *Ann Fam Med* 7:414–421
38. Egede L, Nietert P, Zheng D (2005) Depression and all-cause and coronary heart disease mortality among adults with and without diabetes. *Diab Care* 28:1339–1345
39. Lin EHB, Rutter CM, Katon W et al (2010) Depression and advanced complications of diabetes: a prospective cohort study. *Diab Care* 33:264–269