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1 **Illness Beliefs Predict Mortality in Patients with Diabetic Foot Ulcers**

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26

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30 Structured Abstract

31 **Background:** Patients' illness beliefs have been associated with glycaemic control in diabetes and
32 survival in other conditions.

33 **Objective:** We examined whether illness beliefs independently predicted survival in patients with
34 diabetes and foot ulceration.

35 **Methods:** Patients (n=169) were recruited between 2002 and 2007. Data on illness beliefs were
36 collected at baseline. Data on survival were extracted and used to calculate number of days survived
37 from date of recruitment to the census point (1st November 2011).

38 **Results:** Logistic regressions revealed that mortality was predicted by ischemia and illness beliefs,
39 specifically beliefs regarding symptoms (identity beliefs): patients with less ischemia and who believed
40 their foot ulcer was associated with greater symptoms were more likely to die. Cox regressions
41 examined the predictors of time to death and again identified ischemia and identity beliefs as significant
42 predictors of time to death.

43 **Conclusions:** These data indicate that illness beliefs have a significant independent effect on survival
44 in patients with diabetes and foot ulceration.

45

46 **Keywords:** illness beliefs; mortality; diabetes; diabetic foot ulcers; self-regulatory model

47

48 INTRODUCTION

49 The psychological functioning of patients with diabetes has been shown to be of clinical importance.
50 For example, indices of psychological functioning have been associated with poorer metabolic
51 control(1); greater treatment non-adherence(2) and an increased risk of diabetic complications.(3)
52 Research with patients with diabetic foot ulcers has also been suggestive of a role for psychological
53 factors in predicting clinical outcomes. For example, in patients with, or at risk, from foot ulceration,
54 depression has been associated with an increased risk of ulceration,(4) delays in the rate of ulcer
55 healing(5) and a 2 fold greater risk of mortality.(6)

56 The evidence regarding the relationship between psychological functioning and outcomes in patients
57 with foot ulcers has, however, largely focussed on depression and remains equivocal. For example,
58 contrary to the studies cited above, data also exist to suggest that depression is not related to ulcer
59 recurrence(4, 6) or amputation.(7) Similarly, the effect of depression on ulcer healing has been shown
60 not to withstand adjustment for clinical predictors.(8) These observations lead us to speculate that a
61 focus on depression alone may be limiting our understanding of the ways in which psychological
62 functioning can influence clinical outcomes in diabetic foot ulceration; and that it may be necessary to
63 examine the role of other psychological processes.(5, 9)

64 If we are to extend our assessment of psychological factors beyond depression, which factors are worthy
65 of further enquiry? The influential self-regulatory model of illness(10) can inform this question. The
66 model asserts that patients form illness beliefs when contending with a health threat and that these
67 beliefs play a central role in determining patients' emotional and behavioural responses to their illness.
68 In this way, illness beliefs are 'upstream' from emotional responses, such as depression, to illness. A
69 recent systematic review provides evidence in support of illness beliefs being associated with glycaemic
70 control in diabetes.(11) Furthermore, a study comparing the effects of depression versus illness beliefs
71 in predicting dietary, quality of life and glycaemic control outcomes in diabetes, showed that illness

72 beliefs were more consistent and stronger determinants of these outcomes than depression.(12) Of
73 particular relevance, however, is recent work with patients with other patient groups which has shown
74 that illness beliefs predict mortality. For example, van Dijk and colleagues(13) reported in a cohort of
75 patients with end stage renal disease that beliefs regarding treatment control predicted mortality: with
76 death being more likely in patients who believed their treatment to be less effective. Similar findings
77 were subsequently reported by Chilcot, Wellstead and Farrington (2011) who also found negative
78 beliefs about the effectiveness of treatment predicted mortality in patients with end stage renal
79 disease.(14) More recently, Crawshaw, Rimington, Weinman and Chilcot (2015) reported that changes
80 in illness perceptions, specifically a change from positive to negative beliefs, predicted mortality in
81 patients who had undergone cardiac valve replacement.(15)

82 Taken together, the evidence suggests that illness beliefs may predict clinical outcomes, including
83 mortality, in patients with diabetes including those with diabetic foot ulcers. We report on findings from
84 a prospective cohort study in which we examined the effects of illness beliefs on mortality in patients
85 with active ulceration. In line with previous research we hypothesised that the risk of death would be
86 greater in patients with negative beliefs. Our predictive models were constructed to examine whether
87 illness beliefs predicted mortality after examining the role of potential demographic and clinical
88 determinants, as well as depression and coping. Depression was included in view of its prominence in
89 the literature as a determinant of mortality in diabetes.(6, 7, 16) Confrontational coping was also
90 considered a plausible determinant in light of evidence that ulcer history predicts mortality in patients
91 with diabetic foot ulcers(16) and earlier work with this cohort has shown that confrontational coping
92 predicts ulcer healing.(5)

93 **RESEARCH DESIGN AND METHODS**

94 **Patients**

95 A convenience sample of patients with diabetes mellitus and a foot ulcer was recruited from outpatient
96 podiatry clinics in secondary care in the UK between January 2002 and January 2007. Patients were
97 recruited into a longitudinal research programme examining psychological and behavioural aspects of
98 diabetic foot ulceration. This study was approved by the North Somerset & South Bristol Research
99 Ethics Committee and all participating patients provided written informed consent.

100 All clinics subscribed to a standard regimen of foot care, i.e., aggressive debridement at each visit,
101 treatment of infections with antibiotics and the use of removable Scotch-casts and other
102 footwear/devices for offloading ulcers on weight-bearing areas, minimising the likelihood of between-
103 centre variations in treatment outcomes. Inclusion/exclusion criteria ensured the population consisted
104 of patients with neuropathic or neuroischaemic ulcers. Patients were not eligible if they had: no palpable
105 pulses on the affected foot; a history of major amputation (i.e., any lower limb amputation greater than
106 a single digit); known large vessel peripheral vascular disease (e.g., previous bypass surgery,
107 angioplasty); advanced diabetic retinopathy with severe visual impairment; advanced nephropathy (e.g.,
108 on dialysis); other severe disabling medical conditions (e.g., stroke); or were being treated with platelet-
109 derived growth factor, tissue engineered skin or total contact casts.

110 One hundred and sixty-nine patients were recruited. In November 2011, survival data (i.e., deceased
111 versus alive at 1/11/11; and, if deceased, date of death) were requested from General Practitioners. Data
112 were available for 160 patients (n=104 alive at census point; n=32 deceased and date of death known;
113 n=24 deceased and date of death not known). No data were available for 9 patients. These patients were
114 excluded from the analyses. Analyses were conducted to compare patients with and without survival
115 data on all the predictor variables. No differences were evident between the groups on any variable (data
116 not shown), with the exception of age which approached significance ($p=0.056$): patients with missing
117 survival data were older (mean=65 years) compared with patients with complete data (mean=60 years).

118 **Measures**

119 **Illness beliefs:** Participants completed the Brief Illness Perceptions Questionnaire (BIPQ)(17) derived
120 from the self-regulatory model of illness.(10) This instrument is recommended in studies involving
121 older participants and/or ill participants and so was selected for the present study. The instrument
122 captured patients' beliefs regarding their foot ulcer in the following domains: identity ('How much do
123 you experience symptoms?'); consequences ('How much does your ulcer affect your life?'); timeline (How
124 long do you think your ulcer will continue?); personal control ('How much control do you feel you have over
125 your ulcer?'); treatment control ('How much do you think your treatment can help your ulcer?'); coherence
126 ('How well do you feel you understand your ulcer?') and emotional response ('How much does your ulcer
127 affect you emotionally?'). The range of scores for each subscale was 0-10, with higher scores indicating
128 a stronger belief in the relevant domain. The reliability, concurrent and predictive validity of the
129 instrument has been reported elsewhere.(17, 18)

130 **Depression:** Depression was measured using the depression subscale of the Hospital Anxiety and
131 Depression Scale (HADS).(19) The range of scores for this subscale was 0-21, with higher scores
132 reflecting higher levels of depression. The Cronbach's alpha reliability coefficient for the subscale in
133 the present study was 0.849.

134 **Confrontational coping:** Confrontation coping was measured using the confrontation subscale of the
135 Medical Coping Modes Questionnaire.(20) Range of scores for this subscale was 1-26, with higher
136 scores indicating a greater propensity towards confrontational coping. Confrontational styles are
137 characterised as being more controlling, competitive and extroverted. The Cronbach's alpha reliability
138 coefficient for the subscale in the present study was 0.709.

139 **Glucose control:** Glycated haemoglobin (HbA1c) was measured to provide a surrogate marker of
140 disease control 2-3 months prior to study entry. HbA1c was measured by cation exchange high
141 performance liquid chromatography using a Menarini HA-8140 analyser and associated reagents (A.
142 Menarini Diagnostics, Wokingham, UK). The assay was maintained in alignment with the Diabetes

143 Control and Complications Trial method,(21) with no significant assay drift and a between-batch
144 imprecision (CV) of 1.8% (at mean HbA1c 5.5% [37 mmol/mol]). All assays were performed on the
145 same instrument.

146 **Neuropathy and ischaemia assessments:** Neuropathy was assessed by applying a 10g nylon
147 monofilament to a number of sites on the affected foot and patients reporting the presence/absence of
148 sensation. Level of neuropathy was based upon the number of tested sites with sensory loss. Percentage
149 rather than absolute values were used as the number of sites assessed varied between podiatrists.
150 Ischaemia was assessed by measuring number of palpable pulses at the dorsalis pedis and posterior
151 tibial areas of the affected foot. All assessments were conducted by the treating podiatrist at each centre.

152 **Ulcer assessments:** Data were collected from clinical records on all patients regarding the number of
153 previous ulcers the size of the presenting ulcer and the presence/absence of infection in the presenting
154 ulcer. The assessment of ulcer size involved placing a disposable transparent film over the ulcer and
155 tracing the topical area of the ulcer. The tracing was then placed on a digital tablet (Visitrack: Smith
156 and Nephew, London, UK) and the area of the ulcer was re-traced with a stylus to produce a
157 measurement of absolute ulcer area (in mm²). These assessments were conducted by the treating
158 podiatrist at each centre.

159 **Statistical methods**

160 One way analysis of variance and chi-square analysis were conducted to compare patients with and
161 without missing survival data on all predictor variables. After checking that assumptions were satisfied,
162 survival analysis was undertaken using both logistic regression (to examine the predictors of whether
163 or not patients died over the observation period) and Cox regression models (to examine the predictors
164 of time to death). For the latter the survival outcome was number of days survived from the date of
165 recruitment to the census point (1/11/11) or death from any cause. Both survival analyses involved two
166 stages. In the first, all potential clinical and demographic predictors and the measures of depression and

167 coping were examined in univariate analyses to identify significant predictors. In the second step, all
168 seven belief measures were added to only those covariates identified as being significant in the first
169 step. Although this resulted in our models having up to ten predictors, this approach is in keeping with
170 contexts in which it is appropriate to relax the rule of ten predictors per number of outcomes(22); and
171 the self-regulatory model(10) which argues that a patients' understanding of their illness, and
172 subsequent behavioural and emotional responses, are influenced by all of the belief domains represented
173 in the model.

174 As both the predictor and outcome variables contained missing values, imputation methods were used
175 to maximise the available data for the survival analysis. The independent variables appeared to be
176 missing completely at random: Little's test(23) returned a p-value of 0.74. As only 79 out of the 160
177 patients contained no missing values, we imputed the missing predictor values using k-nearest
178 neighbours, with k=5, to ensure there was sufficient power.(24) For the outcome measures, survival
179 status was known for 160 patients. Of these, 24 were known to have died, but their date of death was
180 unknown. Thus, we performed multiple imputations to estimate the survival time for these patients. Five
181 imputation techniques were used, the first considered the patients to survive midway between their
182 inclusion into the study and study end date. The second identified the average proportion of time
183 between patients' start dates and the study end date for all the patients who died with a known date of
184 death and estimated the patient's death to be the same ratio between their start date and the study end
185 date. The third imputed survival time was based on the survival time of the patient with the closest start
186 date and the fourth survival time was based on the survival time of the four patients with the closest
187 start date. The fifth survival time was based on the average of the previous four survival times.

188 Using these datasets we then performed the logistic regression and Cox survival analysis. As the logistic
189 regression does not rely on survival time, we performed the logistic regression without survival
190 imputation. The Cox survival analysis was performed using all five predicted survivals.

191 Missing imputation methods were implemented using R, a free software environment for computing
192 and graphics.(25) All other analyses used SPSS, Version 19.

193 **Procedure**

194 Patients participated in a prospective observational study. At baseline, the following clinical and
195 demographic data were collected on all participants: age, gender, glycosylated haemoglobin (HbA1c),
196 number of previous ulcers, presence/absence of infection in ulcer, diabetes type, neuropathy and
197 ischemia and ulcer size. Participants also completed self-report measures of illness beliefs,(17)
198 depression(19) and confrontation coping(20) at baseline. Data on survival were collected after the
199 survival census point (1st November 2011).

200 **RESULTS**

201 **Cohort Characteristics**

202 Table 1 shows that the average period patients survived in this study was 6 years (range 57-3534 days);
203 the average age of participants was 60 years and, in keeping with the known prevalence of these ulcers,
204 two-thirds of our participants were male. The clinical data indicated moderately high levels of
205 neuropathy and ischemia and average HbA1c levels suggested poor glucose control. Most patients had
206 had an ulcer previously and for approximately one-third of patients the index ulcer was infected at study
207 entry. The psychological data revealed, on average, low levels of depression and modest levels of
208 confrontation coping. The illness beliefs measure indicated that patients reported that they experienced
209 few physical symptoms associated with their ulcers (identity beliefs); believed their ulcers had
210 significant consequences for them (consequence beliefs); and were likely to last a moderately long time
211 (timeline beliefs). Patients also reported moderate levels of personal control over their ulcers (personal
212 control beliefs), but had a greater belief in the effectiveness of treatment (treatment control beliefs).

213 Coherence beliefs suggested that patients' perceived they had a moderately good understanding of their
 214 ulcers and also believed that their ulcers affected their emotional well-being.

215 **Table 1: Clinical, demographic and psychological characteristics of the cohort**

	Mean (standard deviation) / Frequency	Available data (N)
Survival (days)	2233 (+/-912)	136
Gender	100 male / 36 female	136
Age	60.25 (+/-11.89)	136
HbA1c % [mmol/mol]	8.70 (+/-1.82); [72 +/-19.9]	129
Number of previous ulcers	1 (+/-3)	120
Ulcer infected at baseline	50 yes / 85 no	135
Diabetes type 1/2	Type 1=39/Type 2=94	133
Ulcer area at baseline (mm ²)	18.02 (34.68)	125
Neuropathy score (%)	72 (+/-33)	130
Ischemia score (%)	73 (+/-34)	131
Depression	5.78 (+/-4.28)	111
Confrontation coping	17.95 (+/-3.7)	109
Identity beliefs	2.99 (+/-2.86)	102
Consequence beliefs	6.53 (+/-2.07)	100
Timeline beliefs	5.97 (+/-1.85)	102
Personal control beliefs	6.03 (+/-2.46)	99
Treatment control beliefs	8.17 (+/-1.36)	101
Coherence beliefs	6.05 (+/-2.15)	102
Emotional response beliefs	5.61 (+/-2.66)	102

216

217 **Examining predictors of mortality**

218 The results from univariate logistic regression analyses examining the role of potential clinical and
 219 demographic predictors, and depression and coping, on mortality revealed that age (OR 1.035,
 220 p=0.022), diabetes type (1/2) (OR .419, p=0.033) and ischemia (OR .975, p <0.0001) were significant
 221 independent predictors of whether or not a patient had died by the census point (see Table 2). Neither

222 depression nor coping emerged as significant predictors. In the multivariate model, the inclusion of the
223 illness belief measures revealed that, although ischemia and diabetes type (1/2) continued to be
224 significant predictors of mortality, age was no longer significant. In addition, coherence beliefs emerged
225 as a significant predictor of mortality (OR .765, $p=0.027$); and identity beliefs approached significance
226 (OR 1.215, $p=0.092$). The direction of these associations suggested that patients were more likely to die
227 if they had less ischemia; type 1 diabetes; a poorer understanding of their condition and perceived they
228 had more symptoms. These analyses were repeated following imputation of missing data for the
229 predictor variables, as described above, and the results remained largely unchanged. Specifically, age,
230 diabetes type and ischemia emerged as the only significant predictors in the univariate analysis. The
231 inclusion of illness beliefs in the multivariate model identified only ischemia (OR 0.347 $p < 0.0001$) and
232 identity beliefs (OR 1.871, $p=0.054$) as significant predictors of mortality. The effects of age and
233 coherence beliefs were reduced to non-significant: $p=0.102$ and $p=0.197$ respectively (all other data not
234 shown).

235

236 **Table 2: Results from logistic regression examining effects of all clinical and demographic covariates and depression and coping**
 237 **(univariate analyses); and only significant covariates from step 1 with illness beliefs (multivariate analysis) on mortality status**

Univariate analyses				Multivariate analysis			
Covariate	Odds ratios	p	95%CI	Covariate	Odds ratios	p	95%CI
Age	1.035	.022	1.005-1.066	Age	1.003	.898	.960-1.048
Gender	1.351	.445	.625-2.922	Diabetes 1/2	0.288	.053	.081-1.018
Ulcer area at baseline (mm ²)	1.001	.893	.990-1.011	Ischemia	0.973	.000	.960-.987
Ulcer infected at baseline	.666	.231	.343-1.295	Consequence beliefs	0.866	.374	.6311-.189
Diabetes 1/2	.419	.033	.189-.931	Timeline beliefs	1.053	.722	.792-1.4
Number of previous ulcers	1.048	.523	.908-1.21	Personal control beliefs	1.137	.233	.921-1.404
HbA1c	.928	.429	.772-1.116	Treatment control beliefs	0.864	.456	.589-1.268
Depression	.946	.232	.864-1.036	Identity beliefs	1.215	.092	.969-1.523
Confrontation coping	1.014	.785	.919-1.118	Coherence beliefs	0.765	.027	.603-.970
Neuropathy	1.011	.072	.999-1.023	Emotional response beliefs	0.879	.234	.710-1.087
Ischemia	.975	.000	0.964-.985				

239 Examining predictors of time to death

240 As with the previous analysis, the first step involved univariate Cox regression models in which we
241 examined the role of potential clinical and demographic predictors and depression and coping. The
242 results revealed that only diabetes type (1/2) and ischemia were significant predictors of time to death
243 (see Table 3). In the multivariate model, the measures of illness beliefs were added to these significant
244 covariates. These results showed that ischemia remained a significant predictor of time to death (HR
245 0.976, $p < 0.0001$) and that, as with the logistic regression analyses, coherence (HR 0.775, $p = 0.036$) and
246 identity beliefs (HR 1.245, $p = 0.036$) also emerged as significant predictors, with treatment control
247 beliefs (HR 0.735), $p = 0.086$) approaching significance. Specifically, patients with less ischemia; a
248 poorer understanding of their condition; who perceived they had more symptoms; but also a greater
249 belief in the effectiveness of treatment were most likely to die (see Table 3).

250 **Table 3: Results from Cox regression analyses examining effects of all clinical and demographic covariates and depression and coping**
 251 **(univariate analyses); and only significant covariates from step 1 with illness beliefs (multivariate analysis) on time to death**

Univariate analyses				Multivariate analysis			
Covariate	Hazard ratios	p	95%CI	Covariate	Hazard ratios	p	95%CI
Age	1.021	.179	.990-1.053	Diabetes 1/2	.395	.107	.128-1.223
Gender	1.029	.945	.462-2.291	Ischemia score	.976	.000	.965-.987
Ulcer area at baseline (mm ²)	1.003	.585	.993-1.012	Consequence beliefs	.959	.817	.671-1.370
Ulcer infected at baseline	.792	.512	.394-1.592	Timeline beliefs	.993	.965	.717-1.374
Diabetes 1/2	.304	.026	.107-.868	Personal control beliefs	1.085	.465	.872-1.351
Number of previous ulcers	1.086	.182	.962-1.227	Treatment control beliefs	.735	.086	.517-1.045
HbA1c	.869	.181	.708-1.067	Identity beliefs	1.245	.036	1.014-1.529
Depression	.975	.579	.892-1.066	Coherence beliefs	.775	.036	.610-.983
Confrontation coping	1.014	.782	.918-1.120	Emotional response beliefs	.890	.274	.722-1.097
Neuropathy	1.005	.381	.994-1.017				
Ischemia score	.975	<.0001	.966-.985				

253 These analyses were repeated following imputation of missing predictor and outcome data as described
254 above, and the results remained largely unchanged. In particular, regardless of which of the 5 imputation
255 methods were used on the time to death variable, the univariate analyses revealed that only the measures
256 of ischemia, diabetes type (1/2) and age were significant independent predictors of time to death (data
257 not shown). Similarly, the multivariate analyses which included the illness belief measures revealed that
258 for all 5 imputation methods, only ischemia and identity beliefs were significant predictors (see Table
259 4).

260 **Table 4: Cox regression analyses using imputed data to examine effects of significant clinical and demographic and illness beliefs on**
 261 **time to death**

Covariate	Imputation 1			Imputation 2			Imputation 3			Imputation 4			Imputation 5		
	HR	p	95%CI	HR	p	95%CI	HR	p	95%CI	HR	p	95%CI	HR	p	95%CI
Age	1.283	.094	.958-1.717	1.315	.065	.983-1.760	1.257	.126	.938-1.684	1.252	.130	.936-1.676	1.272	.108	.949-1.705
Diabetes 1/2	1.661	.192	.775-3.561	1.691	.175	.792-3.609	1.631	.211	.758-3.509	1.715	.173	.790-3.721	1.647	.203	.764-3.552
Ischemia	.425	.000	.313-.578	.420	.000	.308-.573	.418	.000	.308-.566	.405	.000	.298-.551	.415	.000	.305-.564
Consequence beliefs	.732	.176	.465-1.151	.706	.133	.448-1.112	.848	.466	.545-1.32	.828	.407	.530-1.293	.807	.342	.518-1.257
Timeline beliefs	1.280	.236	.851-1.925	1.250	.279	.834-1.873	1.189	.381	.808-1.75	1.157	.460	.786-1.702	1.24	.286	.835-1.841
Personal control beliefs	1.277	.261	.834-1.954	1.276	.264	.833-1.954	1.206	.367	.803-1.812	1.182	.415	.791-1.766	1.228	.333	.810-1.860
Treatment control beliefs	.770	.145	.542-1.094	.746	.101	.526-1.059	.790	.186	.557-1.121	.799	.209	.563-1.134	.783	.173	.550-1.113

Identity beliefs	1.809	.017	1.113-2.940	1.995	.007	1.213-3.281	1.622	.05	1.001-2.628	1.654	.040	1.022-2.675	1.669	.038	1.028-2.71
Coherence beliefs	.796	.227	.550-1.152	.769	.161	.532-1.111	.828	.317	.573-1.198	.796	.220	.552-1.146	.808	.260	.557-1.172
Emotional response beliefs	.729	.120	.489-1.086	.733	.129	.491-1.095	.756	.156	.514-1.113	.737	.128	.497-1.092	.741	.134	.5-1.097

263 CONCLUSIONS

264 We examined the role of illness beliefs in predicting mortality and time to death in patients with diabetic
265 foot ulcers; controlling for other potential clinical and demographic determinants, as well as depression
266 and confrontational coping. These analyses were conducted with and without imputation of missing
267 data. The results from the multivariate models, without imputation, revealed that ischemia, coherence
268 and identity beliefs predicted both mortality and time to death. Specifically, death was more common
269 and occurred more quickly in individuals with less ischemia, who perceived their ulcers were associated
270 with greater symptoms and had a poorer understanding of their condition. When these analyses were
271 repeated with imputation of missing data for the predictor variables (logistic regressions) and imputation
272 of missing data for both the predictor and outcome variables (Cox regressions), the findings were largely
273 unchanged, with ischemia and identity beliefs emerging as significant predictors of both mortality and
274 time to death in all analyses. In view of the increased power associated with the imputed datasets, the
275 discussion of our findings will focus, primarily, on these results.

276 Our findings have several implications. First, they add to an existing literature which has shown that
277 patients' illness beliefs can influence clinical outcomes in diabetes (e.g., quality of life, glycaemic
278 control(11, 12)). In the present work, both survival analyses identified an independent role for illness
279 beliefs in predicting survival. These results are also in keeping with findings from other patient
280 groups(14, 15) and a recent systematic review(26) all of which have shown how negative beliefs
281 regarding one's illness is predictive of mortality over periods as short as 1.32 years(14) and as long as
282 10 years.(26)

283 Second, these results suggest that approaches to understanding mortality risk in this patient group(27)
284 may be improved through the inclusion of illness beliefs in risk models. Our data showed that, even
285 after controlling for other predictors, illness beliefs predicted survival; and that identity beliefs emerged
286 as being of particular importance. Indeed, evidence suggesting that illness beliefs are not only

287 modifiable, but that illness belief based interventions can produce significant changes in a range of
288 outcomes (e.g., adherence behaviours, mood, return to work) and across many different diseases,
289 including diabetes (28-31); suggests that the measurement of illness beliefs may not only improve our
290 understanding of the risk factors associated with mortality, but could also be incorporated into
291 interventions to improve survival. Although detailed consideration of the features and mechanisms of
292 such an intervention is beyond the scope of this paper, it could be hypothesised that evidence identifying
293 significant prospective relationships between illness beliefs and glycaemic control(11) and illness
294 beliefs and self-care behaviours(32) suggests that any such intervention could improve survival via these
295 pathways.

296 A related issue concerns the mechanisms underlying the seemingly central role of identity beliefs in
297 predicting mortality. Identity beliefs are concerned with an individual's perception of the extent to
298 which their condition is symptomatic and are often associated with more favourable outcomes (e.g.,
299 better adherence, attendance at cardiac rehabilitation, etc.(33, 34) However, in the present study, the
300 experience of greater symptoms was associated with an increased risk of death. This finding could
301 simply reflect the fact patients with greater symptoms had a greater burden of illness which resulted in
302 the greater risk of mortality. Alternatively, the seemingly counter-intuitive role of identity beliefs in this
303 patient group may be related to the unique nature of their condition. Specifically, our
304 inclusion/exclusion criteria were intended to enable us to recruit patients with ulcers which were
305 primarily neuropathic or neuroischemic. One of the defining features of such ulcers is that they are
306 largely pain-free due to the nerve damage associated with neuropathy. Thus, we hypothesise, that
307 patients with a largely painless condition who have high identity beliefs may have poorer outcomes
308 because they erroneously associate pain and related symptoms with severity. Thus, an absence of pain
309 may lead them to underestimate the seriousness of their ulcers; make them less likely to access
310 appropriate healthcare and this may, in turn, give rise to the poorer mortality outcomes observed in our
311 data.

312 A further issue relates to our finding that ischemia was associated with a survival advantage. As with
313 identity beliefs, ischemia was found to predict both mortality and time to death in all analyses, thereby
314 suggesting that, although counterintuitive, it was a robust finding. However, a number of issues should
315 be considered when interpreting this result. First, our approach to measuring ischemia involved a single
316 assessment (i.e., the measurement of the number of palpable pulses). However, the accurate
317 measurement of ischemia requires multiple, not single, methods.(35) Thus, our approach, while
318 pragmatic (we selected one method which could be conducted rapidly across all clinics), lacked
319 precision and this may have contributed to our finding. Second, as stated, our inclusion criteria were
320 intended to enable us to recruit patients with neuropathic or neuroischaemic ulcers i.e., patients with no
321 palpable pulses (severe ischemia) were excluded. As a result, the patients in this cohort with the greatest
322 levels of ischemia, were likely to be individuals with only moderate ischemic disease; and patients with
323 low levels of ischemia likely to be patients experiencing greater neuropathy. As the treatments for
324 microvascular complications such as neuropathy are considered not to be as effective as treatments for
325 macrovascular complications,(36) this might explain the apparent survival advantage in our patients
326 with moderate ischemia. In other words, moderate ischemia in this study may have been a marker of
327 less severe neuropathy thus contributing to the observed relationship with mortality and time to death.

328 The final issue relates to the observation that depression did not influence survival. This finding is
329 consistent with research showing that the effects of depression on clinical outcomes in diabetes are
330 equivocal.(27) Indeed, our data support a growing literature suggesting that a focus on depression in
331 isolation may not be helpful when considering how psychological factors, and psychological
332 interventions, influence clinical outcomes in diabetes.(12, 37, 38) In the case of the present work, we
333 were unable to detect a statistically significant independent effect of depression. However, it is worth
334 noting that post-hoc analyses (data not shown) revealed that depression was significantly positively
335 correlated with identity beliefs, thus suggesting the potential for an indirect effect of depression on
336 mortality outcomes.

337 In summary, our analyses have shown a significant independent effect of patients' illness beliefs on
338 survival in patients with diabetic foot ulcers. Potential limitations of this work relate to the modest
339 sample size and the exclusion of patients for whom we were unable to obtain survival data from clinical
340 records. However, it is worth noting that our sample size was greater than the mean sample size reported
341 in a systematic review of previous work examining the role of illness beliefs in survival(26); and our
342 excluded patients did not differ from the rest of the cohort on any of the predictors of survival. Finally,
343 our approach to measuring illness beliefs was pragmatic but lacked precision. Although the brief IPQ
344 is particularly suitable for studies with older and/or frail patients, it relies on single items for the
345 measurement of each belief domain and this necessarily precludes a detailed analysis of patients' beliefs.
346 Notwithstanding these limitations, these results broaden our understanding of the role of psychological
347 processes in diabetes and add to the growing literature suggesting that individuals' beliefs about their
348 illness may have prognostic significance.

349 **AUTHOR CONTRIBUTIONS**

350 KV designed the research, secured funding, conducted data analysis and wrote the manuscript. KV is
351 also the guarantor of this manuscript. KD contributed to data collection, analysis and discussion and
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354 study design and discussion and review of manuscript. CD contributed to study design and discussion
355 and review of manuscript. ND contributed to study design and discussion and review of manuscript. PP
356 contributed to study design and discussion and review of manuscript. JT contributed to study design
357 and discussion and review of manuscript. JW contributed to study design and discussion and review of
358 manuscript. AD contributed to study design and discussion and review of manuscript. RC contributed
359 to study design and discussion and review of manuscript. JR contributed to data analysis and discussion
360 and review of manuscript. DS contributed to data analysis and discussion and review of manuscript.

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367 **REFERENCES**

- 368 1. Lustman PJ, Anderson RJ, Freedland KE, de Groot M, Carney RM, Clouse RE. Depression and poor
369 glycemic control: a meta-analytic review of the literature. *Diabetes Care*. 2000 July 1, 2000;23(7):934-42.
- 370 2. Gonzalez JS, Peyrot M, McCarl LA, Collins EM, Serpa L, Mimiaga MJ, et al. Depression and Diabetes
371 Treatment Nonadherence: A Meta-Analysis. *Diabetes Care*. 2008 December 1, 2008;31(12):2398-403.
- 372 3. de Groot M, Anderson R, Freedland K, Clouse R, Lustman P. Association of depression and diabetes
373 complications: a meta-analysis. *Psychosomatic Medicine*. 2001 63(4):619-30.
- 374 4. Gonzalez JS, Vileikyte L, Ulbrecht JS, Rubin RR, Garrow AP, Delgado C, et al. Depression predicts first
375 but not recurrent diabetic foot ulcers. *Diabetologia*. 2010 2010/10/01;53(10):2241-8. English.
- 376 5. Vedhara K, Miles JNV, Wetherell MA, Dawe K, Searle A, Tallon D, et al. Coping style and depression
377 influence the healing of diabetic foot ulcers: observational and mechanistic evidence. *Diabetologia*. 2010
378 2010/08/01;53(8):1590-8. English.
- 379 6. Winkley K, Sallis H, Kariyawasam D, Leelarathna LH, Chalder T, Edmonds ME, et al. Five-year follow-up
380 of a cohort of people with their first diabetic foot ulcer: the persistent effect of depression on mortality.
381 *Diabetologia*. 2012 2012/02/01;55(2):303-10. English.
- 382 7. Winkley K, Stahl D, Chalder T, Edmonds ME, Ismail K. Risk factors associated with adverse outcomes in
383 a population-based prospective cohort study of people with their first diabetic foot ulcer. *Journal of Diabetes
384 and its Complications*. 2007 11//;21(6):341-9.
- 385 8. Takahashi PY, Kiemele LJ, Chandra A, Cha SS, Targonski PV. A Retrospective Cohort Study of Factors
386 that Affect Healing in Long-term Care Residents with Chronic Wounds. *Ostomy Wound Management*
387 2009;55(1):32-7.
- 388 9. Vedhara K, Beattie A, Metcalfe C, Roche S, Weinman J, Cullum N, et al. Development and preliminary
389 evaluation of a psychosocial intervention for modifying psychosocial risk factors associated with foot re-
390 ulceration in diabetes. *Behaviour Research and Therapy*. 2012 5//;50(5):323-32.
- 391 10. Leventhal H, Nerenz DR, Steele DJ. Illness representations and coping with health threats. In: Baum A
392 TS, Singer JE, editor. *Handbook of Psychology and Health Volume IV: Social Psychological Aspects of Health*.
393 Hillsdale, NJ: Erlbaum; 1984. p. p219-52.
- 394 11. McSharry J, Moss-Morris R, Kendrick T. Illness perceptions and glycaemic control in diabetes: a
395 systematic review with meta-analysis. *Diabetic Medicine*. 2011;28(11):1300-10.
- 396 12. Hampson SE, Glasgow RE, Strycker LA. Beliefs versus feelings: A comparison of personal models and
397 depression for predicting multiple outcomes in diabetes. *British Journal of Health Psychology*. 2000;5(1):27-
398 40.
- 399 13. van Dijk S, Scharloo M, Kaptein AA, Thong MSY, Boeschoten EW, Grootendorst DC, et al. Patients'
400 representations of their end-stage renal disease: relation with mortality. *Nephrology Dialysis Transplantation*.
401 2009 October 1, 2009;24(10):3183-5.
- 402 14. Chilcot J, Wellsted D, Farrington K. Illness Perceptions Predict Survival in Haemodialysis Patients.
403 *American Journal of Nephrology*. 2011;33(4):358-63.
- 404 15. Crawshaw J, Rimington H, Weinman J, Chilcot J. Illness Perception Profiles and Their Association with
405 10-Year Survival Following Cardiac Valve Replacement. *ann behav med*. 2015 2015/02/20:1-7. English.
- 406 16. Iversen MM, Tell GS, Riise T, Hanestad BR, Østbye T, Graue M, et al. History of Foot Ulcer Increases
407 Mortality Among Individuals With Diabetes: Ten-year follow-up of the Nord-Trøndelag Health Study, Norway.
408 *Diabetes Care*. 2009 December 1, 2009;32(12):2193-9.
- 409 17. Broadbent E, Petrie KJ, Main J, Weinman J. The Brief Illness Perception Questionnaire. *Journal of
410 Psychosomatic Research*. 2006 6//;60(6):631-7.
- 411 18. Broadbent E, Wilkes C, Koschwanez H, Weinman J, Norton S, KJ P. A systematic review and meta-
412 analysis of the Brief Illness Perception Questionnaire. *Psychology and Health*. 2015;30(11):1361-85.
- 413 19. Zigmond A, S. , Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatrica Scandinavica*.
414 1983;67(6):361-70.
- 415 20. Feifel H, Strack S, Nagy V. Coping strategies and associated features of medically ill patients.
416 *Psychosomatic Medicine*. 1987 49(6):616-25.

- 417 21. The Diabetes Control and Complications Trial Research Group. The Effect of Intensive Treatment of
418 Diabetes on the Development and Progression of Long-Term Complications in Insulin-Dependent Diabetes
419 Mellitus. *New England Journal of Medicine*. 1993;329(14):977-86. PubMed PMID: 8366922.
- 420 22. Vittinghoff E, McCulloch CE. Relaxing the Rule of Ten Events per Variable in Logistic and Cox
421 Regression. *American Journal of Epidemiology*. 2007 March 15, 2007;165(6):710-8.
- 422 23. Little RJA. A Test of Missing Completely at Random for Multivariate Data with Missing Values. *Journal*
423 *of the American Statistical Association*. 1988;83:1198-202.
- 424 24. Gustavo B, Monard M. A Study of K-Nearest Neighbour as an Imputation Method. *HIS* 2002;87:251-
425 60.
- 426 25. Maindonald JH, Braun WJ. Data analysis and graphics using R – an example based approach. Edition r,
427 editor. Cambridge: : Cambridge University Press; 2010.
- 428 26. Parfeni M, Nistor I, Covic A. A systematic review regarding the association of illness perception and
429 survival among end-stage renal disease patients. *Nephrology Dialysis Transplantation*. 2013 October 1,
430 2013;28(10):2407-14.
- 431 27. Markowitz SM, Gonzalez JS, Wilkinson JL, Safren SA. A Review of Treating Depression in Diabetes:
432 Emerging Findings. *Psychosomatics*. 2011 1//;52(1):1-18.
- 433 28. Petrie KJ, Perry K, Broadbent E, Weinman J. A text message programme designed to modify patients'
434 illness and treatment beliefs improves self-reported adherence to asthma preventer medication. *British*
435 *Journal of Health Psychology*. 2012;17(1):74-84.
- 436 29. Broadbent E, Ellis CJ, Thomas J, Gamble G, Petrie KJ. Further development of an illness perception
437 intervention for myocardial infarction patients: A randomized controlled trial. *Journal of Psychosomatic*
438 *Research*. 2009 7//;67(1):17-23.
- 439 30. Broadbent E, Ellis CJ, Thomas J, Gamble G, Petrie KJ. Can an illness perception intervention reduce
440 illness anxiety in spouses of myocardial infarction patients? A randomized controlled trial. *Journal of*
441 *Psychosomatic Research*. 2009 7//;67(1):11-5.
- 442 31. Jones CJ, Smith HE, Llewellyn CD. A systematic review of the effectiveness of interventions using the
443 Common Sense Self-Regulatory Model to improve adherence behaviours. *Journal of Health Psychology*. 2015
444 May 8, 2015.
- 445 32. Vedhara K, Dawe K, Wetherell MA, Miles JNV, Cullum N, Dayan C, et al. Illness beliefs predict self-care
446 behaviours in patients with diabetic foot ulcers: A prospective study. *Diabetes Research and Clinical Practice*.
447 2014 10//;106(1):67-72.
- 448 33. Chen S-L, Tsai J-C, Chou K-R. Illness perceptions and adherence to therapeutic regimens among
449 patients with hypertension: A structural modeling approach. *International Journal of Nursing Studies*. 2011
450 2//;48(2):235-45.
- 451 34. French DP, Cooper A, Weinman J. Illness perceptions predict attendance at cardiac rehabilitation
452 following acute myocardial infarction: A systematic review with meta-analysis. *Journal of Psychosomatic*
453 *Research*. 2006 12//;61(6):757-67.
- 454 35. Baker N, Marli-Krishnan S, Fowler D. A user's guide to foot screening, Part 2: peripheral arterial
455 disease. *The Diabetic Foot Journal*. 2005;8:58-70.
- 456 36. Fowler MJ. Microvascular and Macrovascular Complications of Diabetes. *Clinical Diabetes*. 2008 April
457 1, 2008;26(2):77-82.
- 458 37. Ismail K, Winkley K, Rabe-Hesketh S. Systematic review and meta-analysis of randomised controlled
459 trials of psychological interventions to improve glycaemic control in patients with type 2 diabetes. *The Lancet*.
460 2004 5/15//;363(9421):1589-97.
- 461 38. Alam R, Sturt J, Lall R, Winkley K. An updated meta-analysis to assess the effectiveness of
462 psychological interventions delivered by psychological specialists and generalist clinicians on glycaemic
463 control and on psychological status. *Patient Education and Counseling*. 2009 4//;75(1):25-36.

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