Systematic Review or Meta-analysis

Psychosocial and behavioural prognostic factors for diabetic foot ulcer development and healing: a systematic review

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Abstract

Aim To investigate whether ulceration, amputation and healing of foot ulcers in people living with diabetes are associated with psychosocial and behavioural factors.

Methods We searched MEDLINE, Embase, PsychINFO, CINAHL and The Cochrane Library to March 2019 for longitudinal studies with multivariable analyses investigating independent associations. Two reviewers extracted data and assessed risk of bias.

Results We identified 15 eligible studies involving over 12,000 participants. Clinical and methodological heterogeneity precluded meta-analysis, so we summarize narratively. Risk of bias was moderate or high. For ulceration, we found significantly different results for people with and without an ulcer history. For those with no ulcer history, moderate quality evidence suggests depression increases ulcer risk [three studies; e.g. hazard ratio (HR) 1.68 (1.20, 2.35) per Hospital Anxiety and Depression Scale (HADS) standard unit]. Better foot self-care behaviour reduces ulcer risk [HR 0.61 (0.40, 0.93) per Summary of Diabetes Self-Care Activities scale standard unit; one study]. For people with diabetes and previous ulcers, low- or very low-quality evidence suggests little discernible association between ulcer recurrence and depression [e.g. HR 0.88 (0.61, 1.27) per HADS standard unit], foot self-care, footwear adherence or exercise.

Low-quality evidence suggests incomplete clinic attendance is strongly associated with amputation [odds ratio (OR) 3.84 (1.54, 9.52); one study]. Evidence for the effects of other psychosocial or behavioural factors on ulcer healing and amputation is very low quality and inconclusive.

Conclusions Psychosocial and behavioural factors may influence the development of first ulcers. More high quality research is needed on ulcer recurrence and healing. (Open Science Framework Registration: https://osf.io/ej689)

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Introduction

One complication of diabetes is foot ulceration, which may affect up to 25% of people with diabetes during their lifetime [1,2]. The annual incidence of diabetic foot ulcers was 2.2% in the UK general population in 1996–1998 [3] and 6.3% in the global population of people with diabetes [4].

Foot ulcers in people with diabetes are difficult to heal and 65% of those affected may have recurrent ulcers within 5 years of healing [4]. People with unhealed foot ulcers have poorer quality of life [5,6], increased risk of amputation and higher 5-year mortality rates [4,7], resulting in increased burden on health services [4,8]. The physical and emotional burden of ulceration is considerable: for example, 32% of people with foot ulcers are depressed and this is associated with a threefold greater risk of mortality [9].

Prognostic factors for developing foot ulcers include: increased age, male sex, longer duration of diabetes, loss of protective sensation, peripheral arterial disease and previous
We hypothesize that psychosocial and behavioural factors are independent prognostic factors for ulceration and wound healing. Potential mechanisms could involve psychosocial and behavioural factors affecting pathophysiological processes or impacting on lifestyle factors such as smoking (which may influence ulceration and healing, by affecting tissue perfusion) or influencing the effectiveness of interventions, especially those involving self-management. Psychosocial factors may themselves influence behavioural factors.

As far as we are aware, this is the first systematic review of evidence pertaining to independent effects of psychosocial and behavioural prognostic factors on future ulceration, amputation and healing. Potentially, the review will inform the development of interventions to improve adverse foot outcomes.

**Participants and methods**

Full methods are given in Appendices S1 and S2 and in our review protocol, which is registered with the Open Science Framework (https://osf.io/ej689).

**Study selection**

We included reports of longitudinal studies that investigated the prognostic value of psychosocial and behavioural factors for foot ulceration, healing or amputation in people with diabetes [21]. We included randomized controlled trials (RCTs) analysed as cohort studies, provided the studies took account of interventions in their analyses. We included case–control studies only if there were no cohort studies for a particular prognostic factor–outcome combination. We did not consider cross-sectional studies (because of the likely substantial risk of bias associated with reverse causation) or qualitative studies, and did not specify a minimum follow-up period. We only included studies that identified independent prognostic factors using multivariable analysis (or similar).

We included studies in people living with diabetes (any type) and a foot ulcer for the investigation of healing and amputation, and studies in people without a current ulcer for investigating the development of ulceration. We accepted study authors’ definitions of foot ulcers and healing.

We considered four types of prognostic factor: emotional (e.g. depression, anxiety, stress, mood, guilt and blame); cognitive (e.g. coping, illness beliefs and self-efficacy); social (e.g. social support and social isolation); and behaviour related to feet (e.g. inspecting feet, reporting changes in foot health, using recommended footwear, adherence to offloading and taking physical activity). Lifestyle factors unrelated directly to feet (e.g. smoking and alcohol) were excluded, as were education and knowledge, non-modifiable social factors (such as socio-economic class) and psychosocial factors at a population level.

We included the following primary outcome measures, regardless of follow-up duration; for development of foot ulcers: foot ulceration, changes in foot risk and ulcer-free
time; for healing: complete healing (secondary outcome was rate of reduction in ulcer area); and for amputation: major (above the ankle) and minor amputation.

For binary outcomes, we reported results as the log hazard ratio (HR) and its 95% confidence interval (CI); failing this, we considered the odds ratio (OR) or risk ratio (RR) at the longest time point. For continuous outcomes, we reported the beta-coefficient and its standard error (SE) or dichotomous data with any cut-point.

**Data synthesis and analysis**

We stratified the analyses by prognostic factor, determining direct associations between prognostic factor and outcome. We also considered whether behavioural factors were intermediates in mechanisms linking psychosocial factors with the outcome.

We planned to conduct meta-analyses using Review Manager Version 5.3 (The Cochrane Collaboration, Nordic Cochrane Centre, Copenhagen, Denmark, 2014) with a random-effects generic inverse variance meta-analysis model. However, we did not conduct meta-analyses because the studies were not sufficiently similar in terms of population, prognostic factor measurement (including cut-off points), outcome measurement and type of analysis. Instead, we summarized the data narratively, including all results for a given prognostic factor-outcome combination on the same forest plot.

We examined the forest plots for variability in the point estimates, taking account of CIs. We investigated heterogeneity using sensitivity analyses to explore overall risk of bias (restricting to low and moderate risk of bias), and a conducted a pre-specified subgroup analysis based on prior history of ulcers (with vs. without prior ulcers).

If studies conducted multivariable analyses involving two or more psychosocial or behavioural factors, we considered whether these factors were independent or if one was a mediator, using the method described in Appendix S1.

We summarized the review findings using an approach modified from the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) framework to assess the quality of the evidence for each prognostic factor-outcome combination [23-25]. We rated the strength of a body of evidence as ‘high’, ‘moderate’, ‘low’ or ‘very low’, considering the within-study risk of bias, applicability of evidence, heterogeneity, precision of association statistics, risk of publication bias and two ‘up-rating’ factors: large effect and dose effect [25,26]. We assessed the narrative summaries in this review on the basis of the strength and consistency of results, and considered imprecision across studies in terms of imprecision in each primary study: taking into account whether there were fewer than 10 outcome events for each prognostic variable (for dichotomous outcomes) or fewer than 100 cases per regression or fewer than two participants per prognostic
| Study / Year | Prognostic Factor | Foot Outcome Combination | Study Participation Bias | Attrition Bias | Prognostic Factor Measurement Bias | Outcome Measurement Bias | Adjustment Bias | Analysis and Reporting Bias | Overall Risk of Bias |
|-------------|-------------------|--------------------------|--------------------------|----------------|----------------------------------|-------------------------|----------------|----------------------------|---------------------|
| Beaney 2016 [28] | Adherence to appointments—amputation | High | Moderate | Moderate | Low | High | Moderate | HIGH |
| Chin 2014 [29] | Foot self-care activities—ulcer incidence | High | Low | Moderate | Moderate | Low | Low | MODERATE |
| Crews 2016 [30] | Adherence to off-loading—healing | Moderate | Moderate | High | Moderate | Moderate | Moderate | MODERATE |
| Crews 2016 [30] | Depression—healing | Moderate | Moderate | High | Moderate | Moderate | High | HIGH |
| Crews 2016 [30] | Physical activity—healing | Moderate | Moderate | High | Moderate | Moderate | High | HIGH |
| Gonzalez 2010 [31] | Depression—ulceration | Low | High | Moderate | Moderate | Moderate | Low | MODERATE |
| Gonzalez 2010 [31] | Foot self-care activities—ulceration | Low | High | Moderate | Moderate | Moderate | Low | MODERATE |
| Gonzalez 2010 no prior [31] | Depression—ulcer incidence | Moderate | High | Moderate | Moderate | Moderate | Moderate | MODERATE |
| Gonzalez 2010 no prior [31] | Foot self-care activities—ulcer incidence | Moderate | High | Moderate | Moderate | Moderate | Moderate | MODERATE |
| Gonzalez 2010 prior [31] | Depression—ulcer recurrence | Moderate | High | Moderate | Moderate | Moderate | Moderate | MODERATE |
| Gonzalez 2010 prior [31] | Foot self-care activities—ulcer recurrence | Moderate | High | Moderate | Moderate | Moderate | Moderate | MODERATE |
| Iwase 2018 [32] | Depression—ulcer incidence | High | Low | Moderate | Moderate | Moderate | High | HIGH |
| Iwase 2018 [32] | Physical activity—ulcer incidence | High | Low | Moderate | Moderate | Moderate | High | HIGH |
| Lemaster 2003 [33] | Physical activity—ulcer recurrence | Low | Low | Low | Low | Low | Moderate | MODERATE |
| Mantle 2006 [34] | Physical activity—healing | High | Moderate | Moderate | Moderate | Moderate | High | Low | HIGH |
| Monami 2008 [35] | Depression—ulcer recurrence | High | Low | Moderate | Moderate | High | Moderate | MODERATE |
| Monami 2008 [35] | Depression—healing | Moderate | Low | Moderate | Moderate | High | Moderate | MODERATE |
| Najafi 2017 [36] | Physical activity—healing | High | Low | Moderate | Moderate | Moderate | High | HIGH |
| Siersma 2014 [37] | Anxiety—depression—amputation | Low | Moderate | High | Moderate | Moderate | Moderate | HIGH |
| Vedhara 2010 [38] | Depression—healing | High | High | Moderate | Moderate | Moderate | Moderate | HIGH |
| Vedhara 2010 [38] | Anxiety—healing | High | High | Moderate | Moderate | Moderate | Moderate | HIGH |
| Vedhara 2010 [38] | Coping—healing | High | High | Moderate | Moderate | Moderate | Moderate | HIGH |
| Waaijman 2014 [39] | Adherence to footwear—ulcer recurrence | Moderate | Low | Moderate | Low | Low | Moderate | MODERATE |
| Waaijman 2014 [39] | Physical activity—ulcer recurrence | Moderate | Low | Moderate | Low | Low | Moderate | MODERATE |
| Williams 2010 [43] | Depression—ulcer incidence | High | Moderate | Low | Moderate | Low | Low | MODERATE |
| Winkley 2007 [41] | Depression—ulcer recurrence | Moderate | Low | High | Moderate | Low | Low | MODERATE |
| Winkley 2007 [41] | Depression—amputation | Moderate | Low | High | Moderate | Low | Low | MODERATE |
| Yazdanpanah 2018 [42] | Foot self-care activities—ulcer incidence | High | Moderate | Moderate | Moderate | Moderate | Moderate | HIGH |
| Yazdanpanah 2018 [42] | Physical activity—ulcer incidence | High | Moderate | Moderate | Moderate | Moderate | Moderate | HIGH |
factor (for continuous outcomes). We also considered the width of the CIs in each study, together with the number and size of studies contributing evidence. The grade of evidence is interpreted as the extent to which one can be confident that an estimate of association is close to the true quantity of specific interest.

We present detailed GRADE ‘Summary of Findings’ in the supporting information, with separate rows for outcomes of healing, amputation and foot ulceration. We report narratively, listing the association statistics with 95% CIs for each relevant study and giving an overall grading of the evidence. We also summarize the findings more concisely in a table in the main text.

We defined the clinical importance of observed associations for binary factors as small (OR < 1.5), moderate (1.5 \( \leq \) OR \( \leq \) 2), or large (OR > 2) [27].

### Results

#### Search results

We retrieved 4090 records from electronic searches and included 27 studies in 39 reports in the review (Fig. 1). Twelve studies were not analysed because they did not report useable data or were case control studies (for references, see Appendix S4), leaving 15 included studies [28-42].

#### Study and participant characteristics

The 15 studies included 12,312 participants (details in Table S1). Eleven studies had a cohort design, ten prospective [29-32,35,37-38,41-43] and one retrospective [28]; four analysed data from RCTs, adjusting for the randomized interventions [33-34,36,39]. Most participants had type 2 diabetes and nine studies recruited > 70% men. The median (overall range) sample size was 233 (49, 4923).

### Prognostic factors and outcomes

We grouped results under the subheadings of emotional, cognitive, foot self-care behaviour, adherence behaviour and physical activity. No study investigated social factors, and evidence was lacking for some of the psychosocial and behavioural factors listed in the Methods. Six studies included two or more psychosocial/behavioural factors in the same multivariable analysis (see Table S2).

Nine studies reported ulceration; follow-up ranged from 12 months to a median 5.4 years [29,31-33,35,39,41-43]. Five studies reported ulcer healing, with follow-up 12 weeks to 12 months [34-38]; and another reported the reduction in ulcer size at 6 weeks [30]. Three studies reported amputation at 12 months [28,37] and 18 months [41] in people with foot ulcers at baseline. Two studies reported healing then recurrence in the same study and we analysed associations with depression for each outcome.

#### Risk of bias assessment

Risk of bias assessments for each prognostic factor–outcome combination are summarized in Table 1, with detail given in Table S3: none had low risk of bias for all domains. We assessed 12 prognostic factor–outcome combinations in eight studies to be at overall high risk of bias [28,30,32,34-36,38,42].

#### Evidence synthesis

High clinical and/or methodological heterogeneity precluded meta-analysis. The evidence in the review was mainly low or very low quality. We give the full results in Table S4 and summarize the results in Table 2.

### Psychosocial factors: emotional

Exploring the relationship between depression and ulceration. Five studies (9021 people) analysed depression as a prognostic factor for ulceration with long term follow-up (1 to 5.4 years) [31-32,35,41,43]. Studies differed by participants’ history of ulceration and depression scales (Table S2).

There was high statistical heterogeneity in the association between depression and ulceration across studies. Sensitivity analysis by risk of bias showed heterogeneity remained after removal of one study at overall high risk of bias.

Subgroup analysis by ulcer history. We undertook prespecified subgroup analyses by participants’ ulcer history (present vs. absent), considering both within- and between-study comparisons (for which the former is considered more reliable) [44]. One within-study subgroup analysis for the association between depression and ulceration showed a
significant difference between people with and without prior ulcers, reflected in a significant interaction term in the multivariable analysis (see Table S4).

In the between-study subgroup analysis by ulcer history (Fig. 2), the distinction between subgroups was less clear than for the within-study analysis. We found extensive
heterogeneity within the subgroup of three studies in people with prior ulcers, which may have been attributable to risk of bias. Restricting the analysis to studies at moderate risk of bias suggested no association in this subgroup between depression and ulcer recurrence, but we note this risk of bias assessment is subjective. The subgroup of three studies in people without prior ulcers showed a consistent association between increased depression and higher ulcer incidence. One study in people without prior ulcers showed ulceration was even more likely with severe depression, indicating a ‘dose effect’.

As a result of these subgroup analyses, we report the evidence separately for studies in people with and without prior ulcers (Table S4). In people without prior ulcers, moderate quality evidence (downgraded once each for risk of bias and imprecision, but upgraded for dose effect) suggested greater depression is associated with more ulceration [e.g. HR 1.68 (1.20, 2.35) per HADS standard unit; this means as the HADS score increased by one standard unit, the risk of ulceration nearly doubled at any follow-up time]. For people with diabetes and prior ulcers, very low-quality evidence (downgraded once for risk of bias and imprecision, and twice for inconsistency) suggested depression may not be associated with ulcer recurrence [e.g. HR 0.88 (0.61, 1.27) per increase in HADS standard unit], but there is much uncertainty.

Exploring the relationship between depression and ulcer healing or amputation. Three studies (328 participants) analysed whether depression was associated with ulcer healing over 6 months [35,38] or 6 weeks [45]. The evidence was inconsistent in the direction of association and rated as very low quality (downgraded once for inconsistency and once for risk of bias). Only one study (233 participants) reported on amputation [41], giving a possible association between depression and amputation at 18 months [HR 1.38 (0.70, 2.72)]. This too was very low-quality evidence (downgraded once for risk of bias and twice for imprecision).

Exploring the relationship between anxiety and ulcer healing or amputation. Two studies in 169 and 1232 participants, respectively considered prognostic factors of anxiety for healing at 6 months [38] and the EQ-5D anxiety-depression scale for associations with healing or amputation at 12 months [37]. The evidence was very low quality for both anxiety–healing and anxiety–depression with amputation combinations. There was little or no association between increased scores for anxiety–depression and healing [e.g. HR for severe problems vs. none: 1.15 (0.81, 1.63)] This was low-quality evidence (downgraded once each for risk of bias and imprecision).

Psychosocial factors: cognitive

Exploring the relationship between coping and ulcer healing. No studies investigated cognitive factors for ulceration. One study in 169 participants explored the relationship between coping and ulcer healing at 6 months for three independent types of coping style [38]. The results suggested there may be little or no association with healing for acceptance–resignation coping and avoidant coping, but a negative association for confrontation coping. The evidence was of very low quality (downgraded twice each for risk of bias and imprecision).

### Behavioural factors: foot self-care

Exploring the relationship between foot self-care and ulceration. Three studies with 1094 participants explored foot care behaviour as a potential prognostic factor for ulceration [29,31,42]. Studies differed in the participants’ history of ulceration and ways of assessing self-care (Table S2). All studies reported the degree to which participants applied a range of foot self-care behaviours, two studies reporting foot self-care as a continuous variable and the third considering each foot self-care factor as either present or absent. Foot self-care was often not included in multivariable analyses because of a lack of significance in univariate analysis, either due to few events or because of small associations. We report the results of univariate analyses where appropriate.

We give full results for each foot self-care factor in Table S4 and focus here on two combined factors (foot examination and checking shoes). There was some inconsistency in the association between foot self-care and ulceration across studies, which we investigated in ulcer history subgroup analyses, both within- and between-study.

Subgroup analysis by ulcer history—examining feet and/or checking shoes. One within-study subgroup analysis of 333 participants reported separate results for people with and without prior ulcers. In 238 people without prior ulcers, multivariable analysis (including depression) suggested reduced risk of ulceration in those who both examined their feet and checked their shoes [HR 0.61 (0.40, 0.93) per Summary of Diabetes Self Care Activities (SDSCA) standard unit]. However, there was little or no association for people with prior ulceration [HR 1.12 (0.76, 1.65) per standard unit, in univariate analysis]. This evidence is low quality for each subgroup (downgraded once each for risk of bias and imprecision).

In a between-study subgroup analysis, different results were found by ulcer history: in people without prior ulcers, one study in a largely (98%) ulcer-naive population and the subgroup of people without prior ulcers in the above study showed a consistent association between decreased foot self-care and ulceration [e.g. HR 0.61 (0.40, 0.93) per SDSCA standard unit]. This was low-quality evidence (downgraded for risk of bias and imprecision). Two studies that included people with a history of ulceration [95 participants, all of whom had prior ulcers and 106 of 295 (36%) with prior ulcers], suggested a small positive association, or none, between examining feet and/or checking shoes and ulceration...
[e.g. examining the bottom of feet, HR 1.10 (0.97, 1.25) per point on a 5-point scale]. This is low-quality evidence (downgraded for risk of bias and imprecision).

Other foot self-care—applying moisturizer and drying feet. Two studies (one of which had 98% of participants without prior ulcers; the other had 36% of participants with prior ulcers) gave inconsistent results for other single prognostic factors—applying moisturizer and drying feet after washing. For each factor, the first study (without prior ulcers) reported less ulceration with increased foot self-care and the other (some prior ulcers) reported little or no association. This is low-quality evidence (downgraded for risk of bias and inconsistency/imprecision).

Behavioural factors: adherence

Three studies including 415 participants explored relationships between adherence to various interventions (attending clinic appointments [28], wearing footwear [39] and offloading [30]) and different foot outcomes (amputation, ulceration and healing, respectively). Adherence was determined objectively using concealed monitoring devices in two studies, and from patient records in the other study. In each case, the evidence is low quality (downgraded for risk of bias and imprecision/indirectness).

Exploring the relationship between adherence and ulceration. One RCT, comparing two types of footwear in 171 participants with prior ulcers, observed no association between any measure of adherence to footwear at 3 months and ulceration over 18 months in univariate analyses.

Exploring the relationship between adherence and ulcer healing or amputation. Poorer adherence to clinic appointments (<100% vs. 100% attendance) showed an association with a much greater risk of amputation at 12 months [OR 3.84 (1.54, 9.52)]. Increased adherence to offloading (proportion of activity offloaded) showed an association with better healing (reduction in wound size at 6 weeks; b-coefficient 0.15, P < 0.05).

Behavioural factors: physical activity

Exploring the relationship between physical activity and ulceration. Three studies with 1137 participants investigated whether there was an association between physical activity and ulceration over 18 months and 2 years [33,39,46]; two were RCTs of footwear in people with prior ulcers, and in the other study, 98% of participants had no previous ulcer [46]. Physical activity was measured in different ways at different times (Table S2).

Univariate results from one study with 566 participants (98% previously ulcer-free) suggested that moderate- to high-intensity physical activity at baseline may be associated with a reduced risk of ulceration [HR 0.66 (0.28, 1.53]. This was low-quality evidence (downgraded twice for imprecision and once for risk of bias).

One RCT analysed as a cohort study (171 participants with prior ulcers) suggested no association between the number of steps per day (after at least 3 months) and ulceration over 18 months [OR 0.99 (0.97, 1.01) per 100 steps in a univariate analysis]. In multivariable analysis, variation in the number of steps resulted in fewer foot ulcers [OR 0.93 (0.89, 0.97) per 100 steps] This is low-quality evidence (downgraded for risk of bias).

Another RCT analysed as a cohort study (400 participants with prior ulcers) reported that increases in the average number of active hours from enrolment to 2 years was associated with a decrease in 2-year ulceration [HR 0.80 (0.64, 1.00) per hour]. This is low-quality evidence (downgraded for risk of bias and imprecision).
Exploring the relationship between physical activity and ulcer healing. Three studies with 373 participants looked at physical activity as a prognostic factor for healing at 12 weeks [34,36] and reduction in ulcer size at 6 weeks [30]. The results are inconsistent: one study (in 145 participants) reported no association between increased duration of weight-bearing activity averaged over 12 weeks and healing [HR 1.03 (0.96, 1.10) per hour], but did not adjust for offloading. Another study (79 participants) suggested an association between higher baseline daily step count and healing (reduction in wound size at 6 weeks; $\beta = 0.16; P < 0.05$; adjusted for baseline wound size only). However, when multivariable analyses were adjusted for adherence to offloading, the association was removed. The third study (49 participants) reported insufficient information to determine the association with healing. Overall the evidence for the physical activity–healing combination was of very low quality, downgraded twice for risk of bias, some indirectness and imprecision.

Investigation of mediation: two or more psychosocial or behavioural factors for ulceration. Two studies in 3711 people included depression and foot self-care in the same analysis for ulceration, giving potential to investigate whether the two factors were independent or were part of the same pathway [31,43]. One further study included depression and physical activity in 4870 ulcer-naive participants, but there was insufficient information to investigate mediation [32].

Foot self-care as a possible mediator. Two studies investigated foot self-care as a possible mediator for the association between depression and ulceration in people without prior ulcers [31,43]. One study (238 people) found a slight enhancement in the association for depression with ulcer incidence when adjusted for foot self-care: the HR increased from 1.57 (1.14, 2.15) per standard unit for the univariate association to 1.68 (1.20, 2.35) per standard unit for the multivariable association including foot self-care. Depression was associated with a higher frequency of foot self-care ($\beta = 0.19, P = 0.004$) in multivariable linear regression. Foot self-care was negatively associated with ulceration in both univariate analysis [HR 0.89 (0.61, 1.29) per standard unit] and in multivariable analysis, that included depression [HR 0.61 (0.40, 0.94) per standard unit]. It was, therefore, unclear whether foot self-care was a mediator (low-quality evidence because of risk of bias and imprecision).

A second study in 3473 people found the addition of foot self-care to the multivariable model did not affect the depression–ulceration association.

Investigation of mediation: two or more psychosocial or behavioural factors for healing

One study in 79 participants investigated two pairs of factors for ulcer healing in different analyses [30,45,47]: depression and adherence to offloading; and depression and physical activity. However, the previously determined inconsistency for both depression–healing and physical activity–healing associations precluded further investigation of mediators.

Discussion

This systematic review is the first to examine evidence in support of psychosocial and behavioural factors influencing foot ulcer outcomes (ulceration, healing and amputation). We included 15 studies involving 12 312 people, investigating psychosocial and behavioural factors, with the most evidence for depression; other factors were adherence behaviours, foot self-care and physical activity. Prognostic factors and outcomes were too disparate to allow meta-analysis and we summarized narratively.

Summary of results

Evidence from three studies consistently suggests depression may be associated with increased risk of ulceration in people with diabetes but without prior ulcers, but it is unclear whether this association exists for people with prior ulcers. Evidence from one study suggests depression may be associated with amputation, but the findings for healing were inconsistent in three studies. Evidence for anxiety and coping was limited and restricted to associations with healing: one small study suggested confrontation coping may be associated with less healing and there was uncertainty around the association with anxiety. One large study suggested scores on the EQ-5D anxiety–depression subscale show little or no association with healing and its impact on amputation is uncertain.

Evidence from three studies on foot self-care behaviours suggests that people with diabetes but without prior ulcers, and who examine their feet and check their shoes, are less likely to develop foot ulcers, but no clear association is evident for people with prior ulcers. Three small studies investigated different adherence behaviours. These suggest adherence to footwear may not be associated with ulceration in people with diabetes and prior ulcers, adherence to offloading may be associated with increased healing, and poorer adherence to clinic appointments may be associated with greater risk of amputation. Evidence from two studies suggests that physical activity may be associated with less ulceration both for people with and those without prior ulcers. It is unclear whether physical activity is associated with healing, a relationship that may depend on adherence to offloading.

Evidence quality

Evidence for depression in people with diabetes but without prior ulcers is consistent and of moderate quality. However, most other evidence is low or very low quality using GRADE
because of high or moderate risk of bias, inconsistency in the direction of association, and imprecision (i.e. wide confidence intervals due to small sample sizes and/or low numbers of events per covariate). All studies are at high or moderate risk of bias, often because they did not fully adjust for what we considered were key confounding factors, namely, for ulceration: age, sex, education and ethnicity, and for healing: education, ulcer area, age, ethnicity and longstanding illness.

**Differences according to ulcer history**

Evidence from both within- and between-study subgroup analyses suggests that ulcer history may affect the magnitude and direction of the prognostic factor–ulceration association. In people with diabetes but without previous ulcers, depression and poor foot self-care behaviour (lack of foot examination and shoe checking) are independently prognostic for ulceration.

By contrast, in people who have already experienced an ulcer, there may be a general lack of association of psychosocial and behavioural factors with ulceration (see Fig. 3). However, the evidence for people with prior ulcers is of low or very low quality and there may be alternative explanations for differences between ulcer history populations, such as treatment of previous ulcers and contact with health professionals. Further research is required in people with prior ulcers.

**Mechanisms involving psychosocial and behavioural factors**

Very few studies explored possible mechanisms; those that did were limited to examining the role of foot self-care as a mediator of the association between depression and ulcer incidence. No clear conclusions could be drawn due to equivocal findings and low evidence quality.

**Strengths and limitations**

This systematic review has summarized the best available evidence for the impact of psychosocial and behavioural factors on adverse foot outcomes. We only included longitudinal cohort studies and RCTs with multivariable analyses. Most studies used time-to-event analysis over acceptable follow-up durations. We assessed risk of bias using a reliable measure (QUIPS) and the quality of the evidence according to GRADE for prognostic factor studies. Following investigation of heterogeneity, we identified very different effects in people with and without prior ulcers, an important finding. The review is, however, limited by the analytical approaches adopted by the primary studies and the disparate methods of measurement of the psychosocial and behavioural factors.

**Conclusions**

The evidence suggests that psychosocial and behavioural factors may be determinants of foot ulcer outcomes such as first ulceration, healing and amputation. We found moderate quality evidence in people with no previous episodes of ulcers for associations between depression and increased ulceration risk. There was also low-quality evidence in this population group for associations between better foot self-care and decreased ulceration risk. However, more research is needed to examine whether psychosocial and behavioural factors involving psychosocial and behavioural factors

| Study or subgroup | ln(HR/PR) | SE | HR/OR (95% CI) | A | B | C | D | E | F | G |
|------------------|----------|----|---------------|---|---|---|---|---|---|---|
| **Depression**   |          |    |               |   |   |   |   |   |   |   |
| Gonzalez et al. 2010 | -0.13    | 0.19 | 0.88 (0.61, 1.27) |   |   |   |   |   |   |   |
| Monami et al. 2008 | 1.61     | 0.26 | 4.99 (3.01, 8.28) |   |   |   |   |   |   |   |
| Winkley et al. 2007 | 0.17     | 0.22 | 1.18 (0.77, 1.81) |   |   |   |   |   |   |   |
| **Foot self-care – examined feet and checked shoes** |          |    |               |   |   |   |   |   |   |   |
| Gonzalez et al. 2010 | 0.11     | 0.20 | 1.12 (0.76, 1.65) |   |   |   |   |   |   |   |
| **Adherence to footwear – univariate only (Odds Ratio)** |          |    |               |   |   |   |   |   |   |   |
| Waaijman et al. 2014 | -0.020   | 0.33 | 0.98 (0.51, 1.88) |   |   |   |   |   |   |   |
| **Weight bearing physical activity – number of steps (Odds Ratio)** |          |    |               |   |   |   |   |   |   |   |
| Waaijman et al. 2014 | -0.11    | 0.10 | 0.90 (0.74, 1.09) |   |   |   |   |   |   |   |
| **Weight bearing physical activity – long-term activity up to last visit** |          |    |               |   |   |   |   |   |   |   |
| Lemaster et al. 2003 | -0.22    | 0.11 | 0.80 (0.64, 1.00) |   |   |   |   |   |   |   |

**FIGURE 3** Development of foot ulcers in people with diabetes and with prior ulcers. The following scales were used: Hospital Anxiety and Depression Scale continuous (z-score), Gonzalez et al. [31]; Geriatric Depression Scale (≥ 10 vs. < 10), Monami et al. [35]; DSM IV (depression vs. no depression), Winkley et al. [41]. Risk of bias: A, participation bias; B, missing data bias; C, prognostic factor measurement bias; D, outcome measurement bias; E, confounding factor bias; F, analysis and reporting bias; G, overall risk of bias. Red (-), high risk of bias; yellow (?), moderate risk of bias; green (+), low risk of bias. HR, hazard ratio; OR, odds ratio.
factors affect ulceration, healing and amputation in people with a history of ulceration, and to explore the mechanisms by which psychosocial and behavioural factors may influence foot outcomes in people living with diabetes. Meanwhile, we would argue that there remains a need for clinicians (and clinical guidelines) to consider psychosocial and behavioural factors alongside pathophysiology.

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Competing interests

None declared.

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References

1 Raglan M, Scammell B. Diabetic foot ulcers: ‘Just chop it off’? Bone & Joint 360 2016; 5: 2–6.
2 Singh N, Armstrong DG, Lipsky BA. Preventing foot ulcers in patients with diabetes. JAMA 2005; 293: 217–228.
3 Abbott CA, Carrington AL, Ashe H, Bash S, Every LC, Griffiths J et al. 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 2002; 19: 377–384.
4 Armstrong DG, Boulton AJM, Bus SA. Diabetic foot ulcers and their recurrence. N Engl J Med 2017; 376: 2367–2375.
5 Nabuurs-Franssen MH, Huijberts MSP, Nieuwenhuijzen Kruseman AC, Willems J, Schaper NC. Health-related quality of life of diabetic foot ulcer patients and their caregivers. Diabetologia 2005; 48: 1906–1910.
6 Ribu L, Hanestad BR, Moum T, Birkeland K, Rustoen T. Health-related quality of life among patients with diabetes and foot ulcers: association with demographic and clinical characteristics. J Diabetes Complications 2007; 21: 227–236.
7 Faglia E, Favales F, Morabito A. New ulceration, new major amputation, and survival rates in diabetic subjects hospitalized for foot ulceration from 1990 to 1993. Diabetes Care 2001; 24: 78–83.
8 Steel A, Reece J, Daw A-M. Understanding the relationship between depression and diabetic foot ulcers. J Soc Health Diabetes 2016; 4: 17.
9 Ismail K, Winkle K, Stahl D, Chalder T, Edmonds M. A cohort study of people with diabetes and their first foot ulcer: the role of depression on mortality. Diabetes Care 2007; 30: 1473–1479.
10 Boyko EJ, Ahroni JH, Cohen V, Nelson KM, Hegarty PJ. Prediction of diabetic foot ulcer occurrence using commonly available clinical information: the Seattle Diabetic Foot Study. Diabetes Care 2006; 29: 1202–1207.
11 Crawford F, Cezard G, Chappell FM, Murray GD, Price JF, Sheikh A et al. A systematic review and individual patient data meta-analysis of prognostic factors for foot ulceration in people with diabetes: the international research collaboration for the prediction of diabetic foot ulcerations (PODUS). Health Technol Assess 2015; 19: 1–210.
12 Lyons T. Management of diabetic foot complications. In: Veves A, Malik R, editors. Contemporary Diabetes: Diabetic Neuropathy: Clinical Management, 2nd edn. Totowa, NS: Humana Press, 2008.
13 Falanga V. Wound healing and its impairment in the diabetic foot. Lancet 2005; 366: 1736–1743.
14 Leese G, Schofield C, McMurray B, Libby G, Golden J, MacAlpine R et al. Scottish foot ulcer risk score predicts foot ulcer healing in a regional specialist foot clinic. Diabetes Care 2007; 30: 2064–2069.
15 Prompers L, Schaper N, Apelqvist J, Edmonds M, Jude E, Mauricio D et al. Prediction of outcome in individuals with diabetic foot ulcers: focus on the differences between individuals with and without peripheral arterial disease. The EURODIABLE Study. Diabetologia 2008; 51: 747–755.
16 Schaper NC, van Netten JJ, Apelqvist J, Bus SA, Hinchliffe RA, Lipsky BA. IWGDF Guidelines on the Prevention and Management of Diabetic Foot Disease. Available at www.iwgdf.guidelines. org Last accessed 4 May 2020.
17 Ulbrects JS, Hurley T, Mauger DT, Cavanagh PR. Prevention of recurrent foot ulcers with plantar pressure-based in-shoe orthoses: the CareFUL Prevention Multicenter Randomized Controlled Trial. Diabetes Care 2014; 37: 1982–1989.
18 van Netten JJ, Price PE, Lavery LA, Monteiro-Soares M, Rasimus A, Jubiz Y et al. Prevention of foot ulcers in the at-risk patient with diabetes: a systematic review: prevention of foot ulcers in the at-risk patient with diabetes. Diabetes Metab Res Rev 2016; 32: 84–98.
19 Bus SA, van Netten JJ. A shift in priority in diabetic foot care and research: 75% of foot ulcers are preventable: prevention of foot ulcers in diabetes. Diabetes Metab Res Rev 2016; 32: 195–200.
20 Vedhara K, Beattie A, Metcalfe C, Roche S, Weinman J, Cullum N et al. Development and preliminary evaluation of a psychosocial intervention for modifying psychosocial risk factors associated with foot re-ulceration in diabetes. Behav Res Ther 2012; 50: 323–332.
21 Hayden JA, Coté P, Steenstra IA, Bombardier C. QUIPS-LBP Working Group. Identifying phases of investigation helps planning, appraising, and applying the results of explanatory prognosis studies. J Clin Epidemiol 2008; 61: 552–560.
22 Hayden JA, van der Windt DA, Cartwright JL, Coté P, Bombardier C. Assessing bias in studies of prognostic factors. Ann Intern Med 2013; 158: 280–286.
23 Hayden JA, Tougas ME, Riley R, Iles R, Pincus T. Individual recovery expectations and prognosis of outcomes in non-specific low back pain: prognostic factor exemplar review. Cochrane Database Syst Rev 2014. Available at http://doi.wiley.com/10.1002/14651858.CD001284 Last accessed 26 January 2018.
24 Guyatt GH, Oxman AD, Schönemann HJ, Tugwell P, Knottnerus A. GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology. J Clin Epidemiol 2011; 64: 380–382.
25 Iorio A, Spencer FA, Falavigna M, Alba C, Lang E, Burnand B et al. Use of GRADE for assessment of evidence about prognosis: rating confidence in estimates of event rates in broad categories of patients. BMJ 2015; 350: h870.
26 Schönemann HJ, Oxman AD, Higgins JPT, Vist G, Glasziou P, Guyatt GH. Chapter 11: Presenting results and ‘Summary of findings’ tables. In: Higgins JPT, Green S, editors. Cochrane Handbook for...
Systematic Reviews of Interventions. Version 5.1.0. Available at www.cochrane-handbook.org Last accessed 26 January 2018.

27 Hemingway H, Marmot M. Psychosocial factors in the aetiology and prognosis of coronary heart disease: systematic review of prospective cohort studies. BMJ 1999; 318: 1460–1467.

28 Beaney AJ, Nunney I, Gooday C, Dhatariya K. Factors determining the risk of diabetes foot amputations—a retrospective analysis of a tertiary diabetes foot care service. Diabetes Res Clin Pract 2016; 114: 69–74.

29 Chin Y-F, Liang J, Wang W-S, Hsu BR-S, Huang T-T. The role of foot self-care behavior on developing foot ulcers in diabetic patients with peripheral neuropathy: a prospective study. Int J Nurs Stud 2014; 51: 1568–1574.

30 Crews RT, Shen B-J, Campbell L, Lamont PJ, Boulton AJM, Peyrot M et al. Role and determinants of adherence to off-loading in diabetic foot ulcer healing: a prospective investigation. Diabetes Care 2016; 39: 1371–1377.

31 Gonzalez JS, Vileikyte L, Ulbrecht JS, Rubin RR, Garrow AP, Delgado C et al. Depression predicts first but not recurrent diabetic foot ulcers. Diabetologia 2010; 53: 2241–2248.

32 Iwase M, Fuji H, Nakamura U, Okhuma T, Ide H, Jodai-Kitamura T et al. Incidence of diabetic foot ulcer in Japanese patients with type 2 diabetes mellitus: the Fukushima diabetes registry. Diabetes Res Clin Pract 2018; 137: 183–189.

33 Lemaster JW, Reiber GE, Smith DG, Heagerty PJ, Wallace C. Daily weight-bearing activity does not increase the risk of diabetic foot ulcers. Med Sci Sports Exerc 2003; 35: 1093–1099.

34 Marston WA. Risk factors associated with healing chronic diabetic foot ulcers: the importance of hyperglycemia. Ostomy Wound Manage 2006; 52: 26–28, 30, 32.

35 Monami M, Longo R, Desideri CM, Masotti G, Marchionni N, Mannucci E. The diabetic person beyond a foot ulcer: healing, recurrence, and depressive symptoms. J Am Podiatr Med Assoc 2008; 98: 130–136.

36 Najafi B, Grewal GS, Bharara M, Menzies R, Talal TK, Armstrong DG. Can’t stand the pressure: the association between unprotected standing, walking, and wound healing in people with diabetes. J Diabetes Sci Technol 2017; 11: 657–667.

37 Siersma V, Thornsen H, Holstein PE, Mars K, Apelqvist J, Jude EB et al. Health-related quality of life predicts major amputation and death, but not healing, in people with diabetes presenting with foot ulcers: the Eurodiale study. Diabetes Care 2014; 37: 694–700.

38 Vedhara K, Miles JNV, Wetherell MA, Dawe K, Searle A, Tallon D et al. Coping style and depression influence the healing of diabetic foot ulcers: observational and mechanistic evidence. Diabetologia 2010; 53: 1590–1598.

39 Waaijman R, de Haart M, Arts MLJ, Wever D, Verlouw AJWE, Nollet F et al. Risk factors for plantar foot ulcer recurrence in neuropathic diabetic patients. Diabetes Care 2014; 37: 1697–1705.

40 Williams LH, Miller DR, Fincke G, Laframe J-P, Erzioni R, Maynard C et al. Depression and incident lower limb amputations in veterans with diabetes. J Diabetes Complications 2011; 25: 175–182.

41 Winkley K, Stahl D, Chalder T, Edmonds ME, Ismail K. Risk factors associated with adverse outcomes in a population-based prospective cohort study of people with their first diabetic foot ulcer. J Diabetes Complications 2007; 21: 341–349.

42 Yazdanpanah L, Shahbazian H, Nazari I, Hesam S, Ahmadi F, Cheraghian B et al. Risk factors associated with diabetic foot ulcer-free survival in patients with diabetes. Diabetes Metab Syndr 2018; 12: 1039–1043.

43 Williams LH, Rutter CM, Katon WJ, Reiber GE, Ciechanowski P, Heckbert SR et al. Depression and incident diabetic foot ulcers: a prospective cohort study. Am J Med 2010; 123: 748–754.e3.

44 Sun X, Briel M, Walter SD, Guyatt GH. Is a subgroup effect believable? Updating criteria to evaluate the credibility of subgroup analyses. BMJ 2010; 340: c117–c117.

45 Vileikyte Shen BJ, Crews RT, Boulton AJM, Peyrot MF. Depression and diabetic foot ulcer healing: the association revisited. Diabetes 2013; 62(Suppl): A171.

46 Yazdanpanah L, Shahbazian H, Nazari I, Arti HR, Ahmadi F, Mohammadianinejad SE et al. Incidence and risk factors of diabetic foot ulcer: a population-based diabetic foot cohort (ADFC study) – two-year follow-up study. Int J Endocrinol 2018; 1–9. https://doi.org/10.1155/2018/7631659.

47 Vileikyte L, Shen B, Brouwn S, Boulton A, Kirsner R, Reeves N et al. Depression, physical activity, and diabetic foot ulcer healing. American Diabetes Association 77th Scientific Sessions, 9–13 June, 2017, San Diego, CA, USA. Diabetes 2017; 66(Suppl): A168.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1. Methods.
Appendix S2. Key confounding factors.
Appendix S3. Search strategy: MEDLINE.
Appendix S4. Studies ineligible for the analysis.
Table S1. Characteristics of included studies—summary.
Table S2. Prognostic factors: scales, cut-off points and baseline values.
Table S3. Risk of bias.
Table S4. GRADE summary of findings.