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

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What's new?

- What's known: Self-management influences both ulceration and healing in people living with diabetes.

- Intervention adherence could prevent up to 75% of foot ulcers.

- This study found that: In people without previous ulcers, moderate quality evidence suggests both depression and poorer foot self-care increase the risk of ulceration.

- In people with previous ulcers, low-/very low-quality evidence suggests little association between psychosocial/behavioural factors and ulceration.

- Evidence on ulcer healing is inconclusive.

- Further research is needed.

- Clinical implications: Depression and poor foot self-care may increase ulceration risk in people living with diabetes with no ulceration history.

history of ulcers or amputation [9-12]. Prognostic factors for non-healing include: loss of protective sensation, peripheral arterial disease, infection, increased age, male sex and plantar stress [4,13-15]. Some factors are modifiable by intervention.

For preventative management, guidelines recommend identification of the at-risk foot, regular surveillance, ensuring routine wearing of appropriate footwear, and risk factor modification [16]. Interventions for treating active ulceration include pressure offloading and ulcer protection, restoration of tissue perfusion, treatment of infection, ulcer debridement and callus removal [16]. People living with diabetes play an essential role in managing their own risk of ulceration and promoting healing of active ulcers. Systematic review evidence shows some preventative interventions may have large effects on ulcer prevention (e.g. customized orthoses, giving a 64% relative risk reduction) [17]. However, reviews also highlight the role of adherence to interventions [16,18], suggesting that up to 75% of foot ulcers could be prevented if adequate adherence to interventions could be achieved [19].

In this review, we look beyond the physical and pathophysiological prognostic factors described above to determine whether psychosocial and behavioural factors predict future adverse foot outcomes (ulceration, non-healing and amputation). Psychosocial factors can be emotional (e.g. depression), cognitive (e.g. coping) and social (e.g. social support); behavioural factors related to feet include foot self-care and adhering to offloading [20].

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.

Search

We searched Ovid MEDLINE, Ovid Embase, PsychINFO, CINAHL and Cochrane CENTRAL for articles and conference abstracts published from inception to 29 March 2019, using the search shown in Appendix S3 (based on foot ulcer terms, study design terms and psychosocial/behavioural factors). We did not restrict the language of articles. Two researchers independently assessed titles and abstracts of retrieved studies, and then full text of all potentially relevant studies. We also examined references of included studies and review papers. We did not contact study authors.

Data extraction and quality assessment

Data were extracted by one reviewer into a piloted data extraction spreadsheet, and checked by a second reviewer.

Two reviewers independently assessed risk of bias, using an approach based on the Quality In Prognosis Studies (QUIPS) tool [22,23], which addresses domains of study participation, study attrition, prognostic factor measurement, outcome measurement, confounding, and statistical analysis and reporting. We rated each domain as having high, moderate or low risk of bias, and produced an 'overall risk of bias' for each prognostic factor–outcome combination: overall high risk of bias if high risk of bias for at least two domains; low risk of bias if all domains were at low risk of bias; and moderate risk of bias if there was high risk of bias for one domain or moderate risk of bias for at least two domains (with the rest at low risk of bias).

In the study participation domain, we considered how representative the participants were of our review population, whether those recruited were very different from those not participating in terms of key prognostic factors, and whether the participation rate was low. We considered whether RCTs (analysed as cohort studies) were a selected population, and also assessed the data source (including any funding).

To assess the confounding domain, we first conducted a literature review to determine key confounding factors: we examined independent prognostic factors for healing or ulceration, and then investigated significant associations between psychosocial/behavioural factors and these key prognostic factors, ensuring that the confounder was unlikely to be on the causal pathway between the psychosocial factor and the outcome. We also drew on clinical experience for any missing important confounders. For ulceration, we considered four key confounders: gender, education, age and ethnicity. For healing or amputation, we considered five key confounders: education, ulcer area, and less importantly, age, ethnicity and longstanding illness. We also compared results from adjusted and unadjusted analyses. For further details see Appendices S1 and S2.

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

Table 1 Risk of bias assessments

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	High	Moderate	HIGH
Crews 2016 [30] Physical activity–healing	Moderate	Moderate	High	Moderate	High	Moderate	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	Moderate	MODERATE
Iwase 2018 [32] Physical activity–ulcer incidence	High	Low	Moderate	Moderate	Moderate	High	HIGH
Lemaster 2003 [33] Physical activity–ulcer recurrence	High	Low	Moderate	Low	Low	Low	MODERATE
Marston 2006 [34] Physical activity–healing	High	Moderate	Moderate	Moderate	High	Low	HIGH
Monami 2008 [35] Depression–ulcer recurrence	High	Low	High	Moderate	Moderate	Moderate	HIGH
Monami 2008 [35] Depression–healing	Moderate	Low	Moderate	Moderate	High	Moderate	MODERATE
Najafi 2017 [36] Physical activity–healing	High	Low	Moderate	Low	High	High	HIGH
Siersma 2014 [37] Anxiety-depression–healing	High	Low	Moderate	Moderate	Moderate	Moderate	MODERATE
Siersma 2014 [37] Anxiety-depression–amputation	High	Low	Moderate	Low	Moderate	Moderate	MODERATE
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	Moderate	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	Moderate	Low	MODERATE
Winkley 2007 [41] Depression–amputation	Moderate	Moderate	Low	Low	High	Low	MODERATE
Yazdanpanah 2018 [42] Foot self-care activities–ulcer incidence	High	High	Moderate	Moderate	Moderate	Moderate	HIGH
Yazdanpanah 2018 [42] Physical activity–ulcer incidence	High	High	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 ≥ OR ≤ 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).


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┌─────────────────────────────────────┐
│ Total number of records = 6,047     │
│ 4,090 screened after duplicates     │
│ removed                             │
└─────────────────────────────────────┘
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              │        ┌──────────────────────┐
              ├───────▶│ Records clearly not  │
              │        │ relevant = 3,792     │
              ▼        └──────────────────────┘
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│ Total number of records obtained    │
│ at full text = 298                  │
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              ├───────▶│ Studies excluded     │
              │        │ with reasons = 259   │
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│ Number of studies included          │
│ = 27 in 39 reports                  │
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│ Number of studies analysed =15 in 27│
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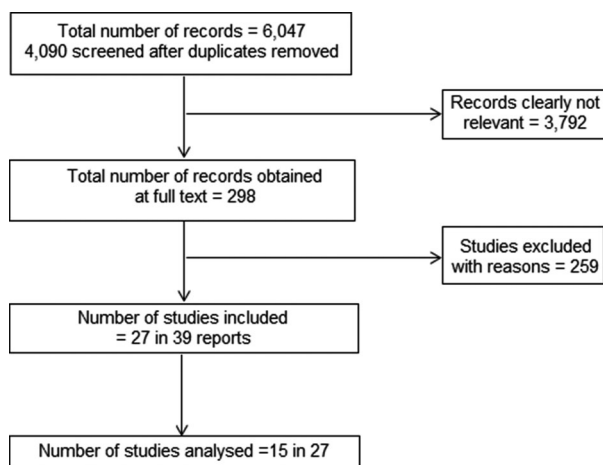
FIGURE 1 Flow diagram for inclusion of studies.

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

Table 2 Summary of findings

Population	Factor – Association – Outcome	Quality of evidence	No. of studies (people)	Comments
Depression				
Prior ulcer	Depression: unclear association with ulceration	Very low	3 (387)	Inconsistency, but 2 studies at moderate risk of bias show no association [31,35,41]
No prior ulcer	More depression associated with more ulcers	Moderate	3 (8634)	Dose response [31,32,43]
Current ulcer	More depression associated with amputation	Very low	1 (233)	Very wide confidence interval (CI) [41]
Current ulcer	Depression: unclear association with healing	Very low	3 (328)	Inconsistency [35,38,45]
Anxiety				
With or without prior ulcer: no evidence on ulceration				
Current ulcer	More anxiety associated with more healing	Very low	1 (169)	Wide confidence interval [38]
Current ulcer	Anxiety-depression (EQ-5D subscale) not associated with healing	Low	1 (1232)	Wide confidence interval [37]
Current ulcer	Anxiety-depression (EQ-5D): unclear association with amputation	Very low	1 (1232)	Very wide CI; inconsistency by dose [37]
Coping				
Current ulcer	Coping: acceptance-resignation not associated with healing	Very low	1 (169)	[38]
Current ulcer	Coping: avoidant not associated with healing	Very low	1 (169)	[38]
Current ulcer	More confrontation coping associated with less healing	Very low	1 (169)	[38]
Prior ulcer and 36% prior ulcer	More examining feet and checking shoes associated with no or slightly more ulcers	Low	2 (390)	[29,31]
No prior ulcer and 98% with no prior ulcer	More examining feet and checking shoes associated with fewer ulcers	Low	2 (804)	[31,46]
36% prior ulcer and 2% prior ulcer	Moisturising lotion: unclear association with ulceration	Low	2 (390)	Inconsistency – slightly more ulcers for 36% prior ulcer. Fewer ulcers for 2% prior ulcer (wide CI) [42,46]
36% prior ulcer and 2% prior ulcer	Washing of feet not associated with ulceration	Low	2 (390)	Consistency [42,46]
36% prior ulcer and 2% prior ulcer	Drying of feet after washing: unclear association with ulceration	Low	2 (390)	Inconsistency – no association with ulcer development for 36% prior ulcer. Fewer ulcers for 2% prior ulcer (wide CI) [42,46]
36% prior ulcer and 2% prior ulcer	More foot self-care (overall) associated with more ulcers	Moderate and very low	2 (390)	Overall score and preventative foot care [42,46]
Adherence				
Prior ulcer	Adherence to footwear not associated with ulceration	Low	1 (171)	[39]
Current ulcer	More adherence to offloading associated with more healing	Low	1 (79)	1 study (2 reports) [30,47]
Current ulcer	Less adherence to clinic appointments associated with amputation	Low	1 (165)	Large association (Odds Ratio = 4) [28]
Physical activity				
Prior ulcer	More physical activity associated with fewer ulcers	Very low	1 (400)	Wide confidence interval [33]
98% with no prior ulcer	More physical activity associated with fewer ulcers	Very low	1 (566)	Wide confidence interval [42]
Prior ulcer	Number of steps / day over 3 months not associated with ulceration	Moderate	1 (171)	[39] outcome at 18 months
Prior ulcer	Variation in number of steps over 3 months associated with fewer ulcers	Moderate	1 (171)	[39] outcome at 18 months
Current ulcer	Physical activity: unclear association with healing	Very low	2 (288)	Not associated when adjusted for adherence to off-loading [34,36]

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 twice 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).
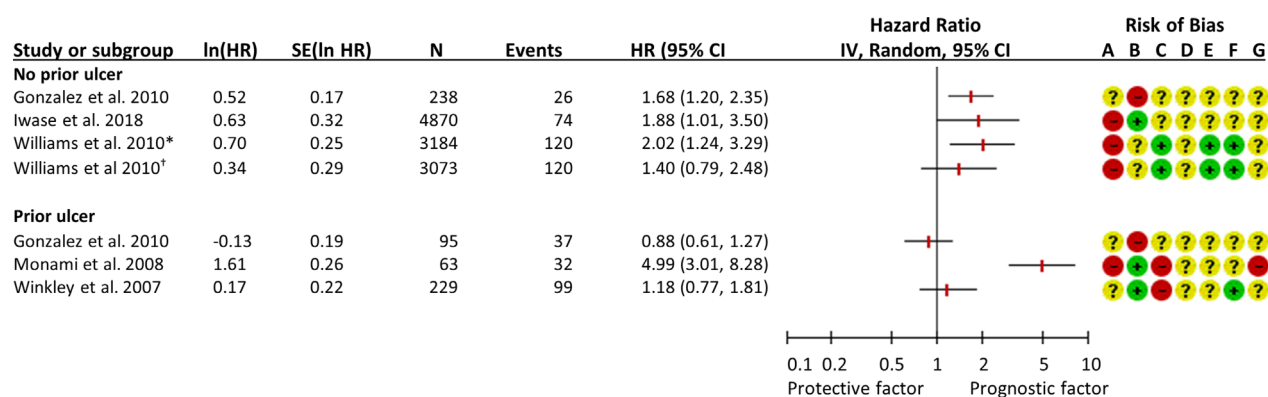
Behavioural factors: foot self-care

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

Study or subgroup	ln(HR)	SE(ln HR)	N	Events	HR (95% CI)
No prior ulcer					
Gonzalez et al. 2010	0.52	0.17	238	26	1.68 (1.20, 2.35)
Iwase et al. 2018	0.63	0.32	4870	74	1.88 (1.01, 3.50)
Williams et al. 2010*	0.70	0.25	3184	120	2.02 (1.24, 3.29)
Williams et al 2010†	0.34	0.29	3073	120	1.40 (0.79, 2.48)
Prior ulcer					
Gonzalez et al. 2010	-0.13	0.19	95	37	0.88 (0.61, 1.27)
Monami et al. 2008	1.61	0.26	63	32	4.99 (3.01, 8.28)
Winkley et al. 2007	0.17	0.22	229	99	1.18 (0.77, 1.81)

FIGURE 2 Depression as a prognostic factor for the development of foot ulcers in people with diabetes. *Major depression vs. no depression. †Minor depression vs. no depression. The following scales were used: Hospital Anxiety and Depression Scale continuous (z-score), Gonzalez *et al.* [31]; Center for Epidemiologic Studies Depression Scale (≥ 16 vs. < 16), Iwase *et al.* [32]; Patient Health Questionnaire·9, Williams *et al.* [43]; 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.

[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; β-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 moderate 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; β = 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 (β = 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
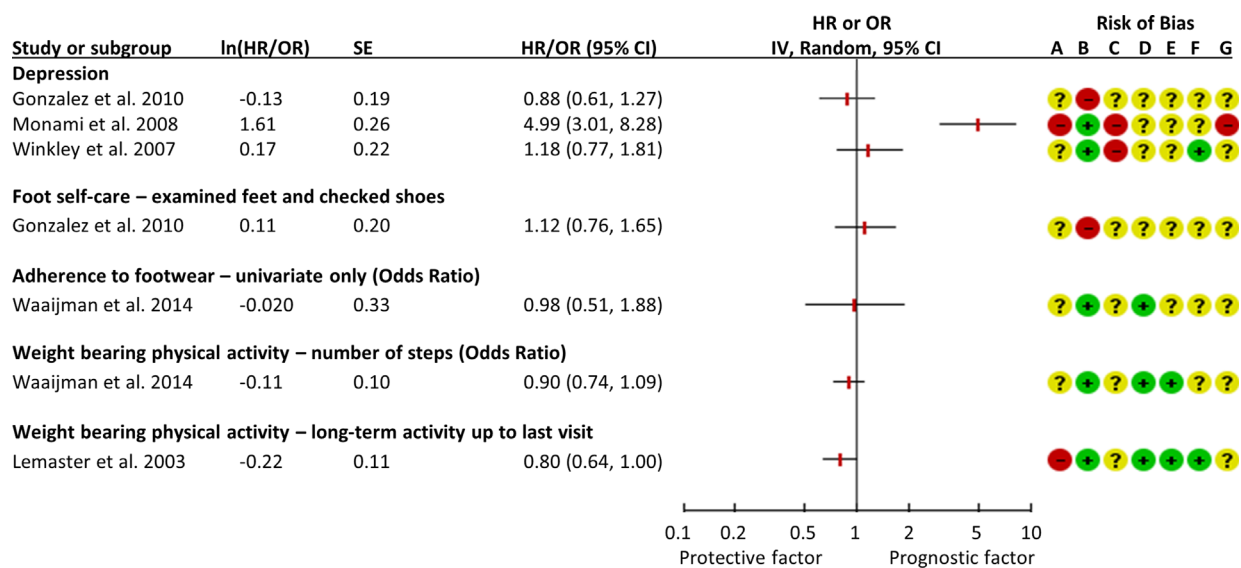
FIGURE 3 Development of foot ulcers in people with diabetes and with prior ulcers. The following scales were used: Hospital Anxiety and Depression Scale continuous (z-score), Gonzalez *et al.* [31]; Geriatric Depression Scale (≥ 10 vs. < 10), Monami *et al.* [35]; DSM IV (depression vs. no depression), 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.

Competing interests

None declared.

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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.