Preventing foot ulceration in diabetes: systematic review and meta-analyses of RCT data

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Abstract
Aims/hypothesis Foot ulceration is a serious complication for people with diabetes that results in high levels of morbidity for individuals and significant costs for health and social care systems. Nineteen systematic reviews of preventative interventions have been published, but none provides a reliable numerical summary of treatment effects. The aim of this study was to systematically review the evidence from RCTs and, where possible, conduct meta-analyses to make the best possible use of the currently available data.

Methods We conducted a systematic review and meta-analysis of RCTs of preventative interventions for foot ulceration. OVID MEDLINE and EMBASE were searched to February 2019 and the Cochrane Central Register of Controlled Trials to October 2018. RCTs of interventions to prevent foot ulcers in people with diabetes who were free from foot ulceration at trial entry were included. Two independent reviewers read the full-text articles and extracted data. The quality of trial reporting was assessed using the Cochrane Risk of Bias tool. The primary outcome of foot ulceration was summarised using pooled relative risks in meta-analyses.

Results Twenty-two RCTs of eight interventions were eligible for analysis. One trial of digital silicone devices (RR 0.07 [95% CI 0.01, 0.55]) and meta-analyses of dermal infrared thermometry (RR 0.41 [95% CI 0.19, 0.86]), complex interventions (RR 0.59 [95% CI 0.38, 0.90], and custom-made footwear and offloading insoles (RR 0.53 [95% CI 0.33, 0.85]) showed beneficial effects for these interventions.

Conclusions/interpretation Four interventions were identified as being effective in preventing foot ulcers in people with diabetes, but uncertainty remains about what works and who is most likely to benefit.

Keywords Diabetes · Evidence-based healthcare · Foot ulcer · Meta-analysis · Prevention · Systematic review

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Introduction

Foot ulceration is a serious complication of diabetes that can result in high levels of morbidity for individuals and burdens health and social care systems with huge costs [1, 2]. Predicting those people most likely to develop a foot ulcer has been the subject of much research and the independent risk factors have been established [3, 4]. However, the value of prediction models to inform treatment decisions depends on the availability of effective interventions to modify risk [5].

As part of a wider research project to create a cost-effective, evidence-based pathway for assessing and managing the foot in diabetes, we conducted an overview of existing systematic reviews to synthesise the available evidence on treatment effects (PROSPERO registration: CRD42016052324). Although the overview identified 19 published reviews [6–24], it failed to provide reliable numerical summaries of effects because of limitations of the reviews in scope, overlap and quality [25]. A comprehensive review of RCTs was required to enable us to make the best possible use of the data currently available and re-explore the possibility of performing meta-analyses.

Methods

Our aim was to systematically review data from RCTs of interventions used to prevent foot ulcerations in diabetes, and to conduct meta-analyses to obtain pooled estimates of their effects. We included data from RCTs only, as this is the only method of clinical evaluation that controls for known, unknown and unmeasured confounding.

The protocol can be viewed at www.journalslibrary.nihr.ac.uk/programmes/hta/1517101.

Eligibility criteria

Trials were permitted to include people of any age with a diagnosis of type 1 or type 2 diabetes, with or without a history of ulceration, but free from foot ulceration at trial entry.

Simple interventions (e.g. education aimed at individuals with diabetes or physicians, or the provision of footwear) and complex interventions (where several interventions were provided together) were eligible for inclusion. Standard care or active treatment were eligible as comparators.
Outcomes

Primary outcomes We were primarily interested in foot ulcers (incident, primary and recurrent) reported as binary outcomes (present/absent). These could be defined, for example, as ‘a full-thickness skin defect that requires more than 14 days to heal’ [26] or according to a system of ulcer classification [27]. Primary outcomes were the absolute numbers of incident primary ulcers and of incident recurrent ulcers.

Secondary outcomes In reports where foot ulceration was the primary outcome we also sought data on amputation (minor: involving the foot [intrinsic to the foot]; or major: involving the foot and leg); mortality; gangrene; infection; adverse events; harms; time to ulceration; quality of life (measured using the EuroQol five-dimensions questionnaire or the six- or 12-item Short Forms); timing of screening; self-care; hospital admissions; psychological (knowledge/behaviour); and adherence to therapy.

Searches

We searched OVID MEDLINE (see electronic supplementary material [ESM] Table 1) and OVID EMBASE (from inception to February 2019) and the Cochrane Central Register of Controlled Trials (to October 2018) for eligible RCTs, without language restrictions. ClinicalTrials.gov was searched for ongoing clinical trials (search date: 21 February 2019).

Trial selection and data extraction

One reviewer screened all titles and abstracts and a 10% random sample was checked by a second reviewer. Two reviewers working independently screened full-text articles and extracted data (D. J. Nicholson, and either F. Crawford or A. E. Amanna) about the included populations, including the risk classification, interventions, comparators and outcomes. For each trial we extracted absolute numbers on an intention-to-treat basis, where the numbers randomised to each group were available, and calculated RRs and 95% CIs. Where reports lacked information or clarity, we contacted the trial authors. Non-English language reports were translated.

Risk of bias (quality) assessment

We assessed the quality of trial reporting using the Cochrane Risk of Bias tool [28]. The five domains we assessed were: random sequence generation, allocation concealment, blinding of assessors to the outcome, incomplete outcome data and selective reporting [28]. We also noted whether an a priori sample size calculation was reported [29].

Data analysis

Absolute numbers were extracted and RRs and 95% CIs were calculated. Where it made clinical and statistical sense to pool the data, we undertook meta-analyses with trial data weighted according to the inverse variance method and assessed heterogeneity using the $I^2$ statistic [28]. Analyses were conducted using R version 3.4.2 (https://cran.r-project.org).

Results

From 10,488 studies, 22 RCTs met our eligibility criteria [30–51]. A flow diagram showing the flow of information throughout the process of screening and selecting studies for inclusion in the review is presented in Fig. 1 and the characteristics of the included trials are described in Table 1. Table 1 also incorporates the results from the risk of bias assessment; only five of the 22 trials [36, 39, 42, 46, 50] were judged to be at low risk of bias.

Overall, the included trials assessed eight different types of interventions to prevent foot ulceration, which we grouped as follows: (1) education alone (three trials) [34–36]; (2) dermal infrared thermometry (four trials) [37–40]; (3) complex interventions (five trials) [41–45]; (4) custom-made footwear and offloading insoles (six trials) [46–51]; (5) digital silicone device (one trial) [32]; (6) antifungal treatment (one trial) [30]; (7) elastic compression stockings (one trial) [31]; and (8) podiatric care (one trial) [33].

Education alone

Three RCTs evaluated single-session education interventions of varying length and content for people at high risk of foot ulceration [34–36].

Meta-analysis ($n = 423$) (Fig. 2a) showed no statistically significant difference in the incidence of foot ulceration at 6 months compared with standard care and advice (RR 1.04 [95% CI 0.54, 1.97]) [34–36]. The quality of the included trials was variable, with only one trial [36] judged to be at low risk of bias across all domains. Other sources of potential bias arose from one trial [34] being stopped early and another [35] reporting an interim analysis before target recruitment was reached [52].

Secondary outcomes Two trials of education interventions reported data on amputation [34, 36], mortality [34],
knowledge [34], behaviour [36] and/or quality of life [36]. No amputations were recorded for participants in either arm at 6 months’ follow-up in one trial [34]. The other trial reported 3/85 amputations in the intervention arm vs 0/85 in the control arm at 6 months, and no difference (n = 9 in both arms) at 12 months [36].

One trial [34] reported that two participants, one in each arm, had died by 6 months. In the same trial, a statistically significant difference in knowledge (as measured by the Patient Interpretation of Neuropathy knowledge score) was observed in the intervention arm [34].

One trial [36] reported on quality of life and found no differences between the two arms on the Diabetic Foot Scale, but higher scores for those in the education arm on the Nottingham Assessment of Functional Footcare questionnaire, which assesses behaviour, compared with the control group.

**Dermal infrared thermometry**

Four RCTs involving 468 participants with diabetes were identified [37–40]. In one trial [37], the numbers of participants randomised to either dermal infrared thermometry or standard care were not known, and so an RR and 95% CI could not be calculated.

**Meta-analysis** A pooled analysis of data from three RCTs (n = 243) [38–40] found that dermal infrared thermometry reduced the number of foot ulcers in people with a history of foot ulceration (RR 0.41 [95% CI 0.19, 0.86]) (Fig. 2b). Outcomes were collected between 6 and 15 months. The quality of these trials was variable, with only one trial [39] judged to be at low risk of bias across all domains.

**Secondary outcomes** Trials of dermal thermometry variously reported on amputation following infection [37], quality of life (36-item Short Form [SF-36]) [37], adherence to therapy [38, 39] and time to ulceration [39, 40].

In one trial, amputations following infections occurred in 0/41 participants in the intervention group vs 2/44 in the comparator group [38]. In the same trial there was no statistically significant difference in quality of life measured using SF-36 in any category or in the overall score [38].

Two trials [39, 40] found no statistically significant difference between the dermal thermometry group and the comparator group in the time that prescribed footwear and insoles were worn, as measured using a self-report questionnaire containing an ordinal scale of <4 to >12 h/day. The time to ulceration was statistically significantly longer in the dermal thermometry treatment group compared with standard care in one trial [39] but not in another [40].

**Complex interventions**

Five RCTs evaluated the effects of complex interventions (i.e. integrated combinations of patient- or physician-level interventions and structural interventions) on the development of a foot ulcer [41–45].

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**Fig. 1** Flow diagram of study selection
| Author | Population characteristics | Details of experimental and control interventions | Standard care | Outcomes (unit of analysis) | Risk of bias | Length of follow-up |
|--------|-----------------------------|--------------------------------------------------|---------------|-----------------------------|-------------|--------------------|
| Monami 2015 [34] | n=121 (I= 61, C = 60) Male: 60% Mean age: 71 years Previous ulcers: 11% T2DM: 100% Mean diabetes duration: 15 years Ulcer risk: high Participants defined as 'high risk' if neuropathy diagnosed, previous diabetic foot ulcer or foot abnormalities | Intervention: brief educational programme 2 h programme provided by a physician (for 15 min) and nurse (for 105 min) to groups of five to seven participants: 30 min face-to-face lesson on risk factors for foot ulcers and 90 min interactive session with practical exercises on behaviours for reducing risk Control: brief leaflet and standard care | All participants had previously received standard multidisciplinary education for diabetes (with a structured group programme at diagnosis or first contact, and follow-up meetings every 2 years) | Ulcers (n), amputation (n), mortality (n), knowledge score, time spent for intervention and ulcer care in control group (min per participant) | Sequence generation: + Allocation concealment: + Assessor blinding to outcome data: - Incomplete data addressed: - Selective reporting: + Sample size calculated: + |
| Amersten Gershater 2011 [35] | n=131 (I= 61, C = 70) Male: 73% Mean age: 64 years Previous ulcers: 100% T2DM: 67% Mean diabetes duration: NR Ulcer risk: high (IWGDF) | Intervention: group session of foot care education from a registered diabetes nurse Oral and written instructions on self-care based on IWGDF guidelines 1× 60 min plus standard care Control: standard information, oral and written instructions on self-care based on IWGDF guidelines | Routine care from staff Adjusted shoes for indoor and outdoor use and individually fitted insoles | Ulcers (n), cause of ulcers (stress, trauma, other), location of ulcer (big toe or other, plantar, other including heel) | Sequence generation: + Allocation concealment: + Assessor blinding to outcome data: - Incomplete data addressed: - Selective reporting: + Sample size calculated: + |
| Lincoln 2008 [36] | n=172 (I= 87, C = 85) Male: 67% Mean age: NR Previous ulcers: 100% T2DM: 77% Mean diabetes duration: NR Ulcer risk: high (10 g monofilament, Neurotip, VPT ≥25 V) | Intervention: 1 h structured foot care education session provided by the researcher in participants' own homes Control: standard care and the same foot care leaflets as the intervention group | Regular podiatry and suitable orthoses when appropriate Overall medical care followed national UK clinical guidelines | Ulcers (n), amputations (n), quality of life (DFS-SF), mood (HADS, HADS-anxiety, HADS-depression), protective foot care behaviours (NAPFF) | Sequence generation: + Allocation concealment: + Assessor blinding to outcome data: - Incomplete data addressed: - Selective reporting: + Sample size calculated: + |
| Dermal infrared thermometry Armstrong 2007 [37] | n=225 (I= NR, C = NR) Male: 96% Mean age: 69 years Previous ulcers: unclear T2DM: 100% Mean diabetes duration: 13 years Ulcer risk: IWGDF risk group 2/3 | Intervention: infrared thermometry and a complex intervention provided by attending physicians Control: a complex intervention only | Footwear, education and professional foot care | Ulcers (n), rate of ulcer (HR), temperature difference at ulcer site (survival curve) | Sequence generation: + Allocation concealment: + Assessor blinding to outcome data: + Incomplete data addressed: + Selective reporting: + Sample size calculated: + |
| Lavery 2004 [38] | n=85 (I = 41, C = 44) Male: 49% Mean age: 55 years Previous ulcers: 41% T2DM: NR Mean diabetes duration: 14 years Ulcer risk: IWGDF risk group 2/3 | Intervention: infrared thermometry and a complex intervention provided by treating physician (evaluation), nurse case manager (contact) and podiatrist (follow-up) Control: complex intervention; foot evaluation by a podiatrist every 10–12 weeks, therapeutic footcare, diabetic foot education | Footwear, education and professional foot care | Foot complications: ulcers, Charcot foot, infection and amputation (n) Quality of life: pre- and post-physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, mental health (SF-36 scores) | Sequence generation: + Allocation concealment: + Assessor blinding to outcome data: + Incomplete data addressed: + Selective reporting: + Sample size calculated: + |
| Lavery 2007 [39] | n=173 (I = 99, I2 = 56, C = 58) Male: 54% Mean age: 65 years Previous ulcers: 100% T2DM: 95% Mean diabetes duration: 13 years | Infrared thermometry and a complex intervention; study nurse for contact, treating physician for foot evaluations, podiatrist for assessing shoes/insoles | Lower-extremity evaluation, education programme, therapeutic insoles and footwear All participants received a pedometer to record their daily activity in a log book | Foot ulcers (n), foot trauma, fracture, death, osteomyelitis, time to ulceration (days) | Sequence generation: + Allocation concealment: + Assessor blinding to outcome data: + Incomplete data addressed: + Selective reporting: + Sample size calculated: + |
| Author | Population characteristics | Details of experimental and control interventions | Standard care | Outcomes (unit of analysis) | Risk of bias<sup>a</sup> |
|--------|-----------------------------|-----------------------------------------------|----------------|-----------------------------|-----------------------|
| Skafjeld 2015 [40] | Male: 56% | Male: 58 years | Previous ulcers: 100% | T2DM: 71% | Mean diabetes duration: 18 years | Ulcer risk: high (10 g monofilament, VPT ≥ 225 V, palpation of pulses, Doppler, ankle brachial index ≥ 0.7) | 11: enhanced care with infrared thermometry Control: standard care 12: structured care with a structured daily foot self-inspection Control: standard care | Participants were told to inspect their feet daily and to contact a nurse if necessary | Ulcer (n), increased skin temperature (°C), customised footwear worn (h/day), contacts with study nurse | Follow-up: 12 months | Sequence generation: + Allocation concealment: ? Assessor blinding to outcome data: + Incomplete data addressed: + Selective reporting: + Sample size calculated: – |
| Complex interventions | | | | | | | | | | |
| Cisneros 2010 [41] | Male: 62% | Male: 66 years | Previous ulcers: 28% | T2DM: 96% | Mean diabetes duration: 14.5 years | Ulcer risk: IWGDF risk group 3 | Intervention: complex intervention Therapeutic education in groups of eight, 4 × 90 min provided by researcher, two pairs of protective shoes, testing for neuropathy Control: information on regular foot care and footwear use according to individual consultations with the researcher | Routine care from staff, instructions on foot care when requested, testing for neuropathy | Ulcer occurrence (n), ulcer recurrence (n), time to foot ulceration (survival time – quarterly evaluations) | Follow-up: 24 months | Sequence generation: ? Allocation concealment: ? Assessor blinding to outcome data: + Incomplete data addressed: ? Selective reporting: + Sample size calculated: – |
| LeMaster 2008 [42] | Male: 51% | Mean age: 60 years | Previous ulcers: 42% | T2DM: 94% | Mean diabetes duration: 11 years | Ulcer risk: moderate or high risk | Intervention: complex intervention Part 1 (1–3 months): physical therapist led exercises to strengthen lower-extremity muscles and promote balance over eight sessions Part 2 (4–12 months): increase in moderately intense activity by 50% over 12 months among community-dwelling participants Provided by physical therapist and study nurse Control: standard care | Foot-related self-care skill education, daily foot examination Usual medical care from their own healthcare providers Participants were referred to orthotists or podiatrists for therapeutic footwear at enrolment | Foot ulcer rates (lesions/lesion episode, full-thickness ulcer/ulcer episode) | Follow-up: 12 months | Sequence generation: + Allocation concealment: + Assessor blinding to outcome data: + Incomplete data addressed: + Selective reporting: + Sample size calculated: + |
| Liang 2012 [43] | Male: 56% | Mean age: 56 years | Previous ulcers: 0% | T2DM: 87% | Mean diabetes duration: 11 years | Ulcer risk: ADA risk category 1/2/3 High risk, n = 100% | Intervention: complex intervention Foot care kit containing foot care cream, 10 g monofilament, thermometer to measure water temperature for washing feet, alcohol cotton pieces and a mirror Daily foot care and diabetes education classes provided by a diabetes nurse-led multidisciplinary team (three endocrinologists, four nurses and one dietitian) Control: standard care | Conventional care alone according to ADA standards; medication adjustment, foot assessment and 2 h of education about diabetes foot care | Ulcers (n, %), amputation (n, %), HbA1c (%), diabetes knowledge, foot care behaviour | Follow-up: 24 months | Sequence generation: ? Allocation concealment: ? Assessor blinding to outcome data: ? Selective reporting: ? Incomplete data addressed: + Sample size calculated: – |
| Litzelman 1993 [44] | Male: 19% | Mean age: 60 years | Previous ulcers: NR | T2DM: 100% | | Intervention: participant education sessions, self-foot care, reinforced through telephone follow-up (2 weeks) and postcard reminder (1 and 3 months) Control: standard care | 1 year after the initial assessment, all participants underwent a repeated history and physical examination performed by nurse clinicians blind to | Participant outcomes: participant behaviour (scale) | Behaviour of healthcare provider (%) Physical findings (ulcers, physical examination, dry/cracked skin, corns, calluses, ingrown nails, | Sequence generation: ? Allocation concealment: ? Assessor blinding to outcome data: + Incomplete data addressed: ? |
| Author                        | Population characteristics                                                                 | Details of experimental and control interventions                                                                 | Standard care                                                                 | Outcomes (unit of analysis)                                                                 | Risk of bias^a |
|------------------------------|---------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|---------------|
| McCabe 1998 [45]             | Sample size calculated: 1997 randomised (I = 997, C = 1000) Mean: 53% Mean age: 60 years Previous ulcers: unclear T2DM 89% Mean diabetes duration: NR Ulcer risk: low, moderate, high Ankle brachial index ≤0.75, history of foot/leg infections = high risk | Informational flow sheets on foot-related risk factors for amputation in individuals with diabetes Prompts for healthcare providers to: (1) ask that participants remove their footwear; (2) perform foot examinations; and (3) provide foot care education Provided by nurses clinicians Control: care as usual plus standard care | Participants’ randomised treatment Fungal infections, improperly trimmed nails, foot/leg cellulitis, leg deformity, sensory examination (%) Follow-up: 12 months | Sample size calculated: + Sequence generation: ? Allocation concealment: ? Assessor blinding to outcome data: ? Selective reporting: + Incomplete data addressed: + Sample size calculated: + |
| Custom-made footwear and offloading | Sample size calculated: 171 (I = 85, C = 86) Mean: 82.5% Mean age: 62 years Previous ulcers: 100% T2DM: 71% Mean diabetes duration: 17 years Ulcer risk: high (assessed by 10 g monofilament and vibration perception plus pedis tests) | Intervention: custom-made footwear, of which the offloading properties were improved and subsequently preserved based on in-shoe plantar pressure measurement and analysis | Each participant received written and verbal instructions on foot care and on proper use of footwear All footwear in both study groups was evaluated at delivery and at 3 month follow-up visits (pressure measurements, temperature monitoring and activity monitor) | Ulcer recurrence (participants with ulcer, previous ulcer location, complicated foot ulcers); ulcer recurrence according to adherence and non-ulcerative lesions (all in n), %; in-shoe peak pressure, daily step count; adherence (mean ± SD) Follow-up: 18 months | Sequence generation: + Allocation concealment: + Assessor blinding to outcome data: + Selective reporting: + Incomplete data addressed: + Sample size calculated: + |
| Reiber 2002 [47]             | Sample size calculated: 400 (I1 = 121, I2 = 119, C = 160) Mean: 77% Mean age: 62 years Previous foot ulcers or infection requiring antibiotics: 100% T2DM 93% Mean diabetes duration: ≤6 years: 33% 6-24 years: 11% ≥25 years: 56% Ulcer risk: high (assessed by 10 g monofilament and presence of foot deformity) | Intervention: therapeutic shoes with two types of inserts and standard care, provided by the study pedorthist and evaluated by a panel of three foot care specialists Intervention 1: three pairs of therapeutic shoes and customised medium-density cork inserts with a neoprene closed-cell cover Intervention 2: three pairs of therapeutic shoes and prehilitrated, tapered polyurethane inserts with a brushed nylon cover Control: usual footwear and standard care | Participants continued to receive regular healthcare and foot care from the VA or GHC A lightweight terry-cloth house slipper (Tru-Stitch Footwear, Malone, NY, USA) with no internal seam and a textured sole was designed for all participants to use to minimise differences in out-of-shoe exposure | Lesions and ulcers (ulcers, non-ulcerative, total, person-years of follow-up; incidence per person (n participants with ≥1 ulcer, cumulative incidence per person, RR); incidence per person-year ( ulcer and ulcer episode, n; incidence, RR); pivotal events for ulcer episodes (shoe and non-shoe related) (all in n and 95% CI) Follow-up: 24 months | Sequence generation: + Allocation concealment: ? Assessor blinding to outcome data: + Selective reporting: + Incomplete data addressed: + Sample size calculated: + |
Table 1 (continued)

| Author         | Population characteristics | Details of experimental and control interventions | Standard care | Outcomes (unit of analysis) | Risk of bias |
|----------------|----------------------------|--------------------------------------------------|---------------|-----------------------------|-------------|
| Rizzo 2012 [48] | n = 296 (I = 148, C = 150) | Intervention: orthoses and shoes, plus standard care | Foot ulcer (participants n), new foot ulcers (n), cumulative incidence of ulcerers and recurrences (3 and 5 years; χ², % and p value), ulcer due to trauma or hyperpressure (n, %), VPT (mean ± SD), cost evaluation (€) | Follow-up: 12 months | Sequence generation: + Allocation concealment: ? Assessor blinding to outcome data: – Incomplete data addressed: + Selective reporting: + Sample size calculated: – |
| Lavey 2012 [49] | n = 299 (I = 149, C = 150) | Intervention: shear-reducing insole and complex intervention | Ulcers (%), footwear compliance (4, 4–8, 8–12, 12–16 h/day; n, %), time to ulcer (HR) | Follow-up: 18 months | Sequence generation: ? Allocation concealment: ? Assessor blinding to outcome data: + Incomplete data addressed: + Selective reporting: + Sample size calculated: + |
| Ulbrecht 2014 [50] | n = 150 (I = 79, C = 71) | Intervention: bespoke orthoses with offloading properties, provided by study coordinators (clinicians) | Ulcers (%), peak barefoot plantar pressure vs lesion (ulcer, non-ulcerative, no lesion; kPa) Questions about quality of life (scales 0 to 100), foot self-care (0–10), fear of falling (scale to 100), participant satisfaction (five-point Likert scale) | Follow-up: 1, 3 and 6 weeks, then every 3 months another 15 months (potential 16.5 months) | Sequence generation: + Allocation concealment: + Assessor blinding to outcome data: + Incomplete data addressed: + Selective reporting: + Sample size calculated: + |
| Uccioli 1995 [51] | n = 69 (I = 33, C = 36) | Intervention: therapeutic shoes with custom insoles specially designed for individuals with diabetes (Podiabete by Buratto Italy) | Ulcer relapses (n, %), cumulative incidence of relapse (multiple regression analysis), ulcer relapse between groups (χ², %, p value), ulcer-free time, peripheral neuropathy (VPT, peripheral vascular disease), ankle brachial index (mean ± SD), use of therapeutic shoes | Follow-up: 12 months | Sequence generation: ? Allocation concealment: ? Assessor blinding to outcome data: – Incomplete data addressed: + Selective reporting: + Sample size calculated: – |
| Digital silicone devices | n = 167 (I = 89, C = 78) | Intervention: digital silicone orthoses (Podikon, Epitrich, Saccocengole, Italy) and regular care at the diabetic foot clinic | Ulcers (%), hyperkeratosis (plantar, dorsal, interdigital; %), skin hardness (%), Stable deformities (%), Podobarometric evaluationb (pre- and post-evaluation in mean ± SD) | Follow-up: 3 months | Sequence generation: + Allocation concealment: ? Assessor blinding to outcome data: + Incomplete data addressed: + Selective reporting: + Sample size calculated: – |
| Armstrong 2005 [30] | n = 70 (I = 34, C = 36) | Intervention: antifungal treatment (ciclopirox 8%) and self-management (daily inspection) | Ulcers, unexpected visits, missed appointments, tinea pedis/ hyperkeratosis at start and end of study (%) | Follow-up: 12 months | Sequence generation: + Allocation concealment: ? Assessor blinding to outcome data: ? Incomplete data addressed: + Selective reporting: + Sample size calculated: – |
| Author         | Population characteristics | Details of experimental and control interventions | Standard care | Outcomes (unit of analysis) | Length of follow-up | Risk of biasa |
|---------------|----------------------------|---------------------------------------------------|---------------|-----------------------------|---------------------|----------------|
| Elastic compression stockings Belcaro 1992 [31] | Mean diabetes duration: 12 years Ulcer risk: high (IWGDF risk group 2/3) | A staff podiatrist examined each participant at recruitment | NA, NR | Ulcers (n, %), number of limbs (n) Deterioration of microcirculation Supine resting flux (mean ± SD) Venoarteriolar response (median and range) | Follow-up: 48 months | Sample size calculated: – |
|               | n = 160 (I = 80, C = 80)  | Mean age: 53 years Previous ulcers: none T2DM: NR | NR | | | |
|               | Male: 50% Mean diabetes duration: 15 years Ulcer risk: microangiopathy measured with laser Doppler, VPT also measured | | | | |
| Podiatric care Plank 2003 [33] | Mean diabetes duration: 16 years Ulcer risk: high (reduced sensation assessed by 128 Hz tuning fork, 5.07 monofilament) | | Instruction on the possible benefits of regular chiropody care and the aim of the study | Ulcers (feet and participants), death, amputation (n, %). | Follow-up: 12 months | |
|               | n = 91 (I = 47, C = 44)  | Male: 56% Mean age: 65 years Previous ulcers: 100% T2DM: 93% | | | | |
|               | Mean age: 65 years Previous ulcers: 100% T2DM: 93% | | | | |

aRisk of bias: low (+), uncertain (?) or high (–)

bIncludes total surface of the foot (cm²), average weight-bearing pressure (kPa), weight distribution compared with the total (%), weight distribution compared with the rear foot (%), static maximum peak pressure (kPa) and dynamic maximum peak pressure (kPa)

C, control; DFS-SF, Diabetic Foot Scale-Short Form; GHC, Group Health Co-operative; HADS, Hospital Anxiety and Depression Scale; I, intervention; IWGDF, International Working Group on the Diabetic Foot; NAFF, Nottingham Assessment of Functional Footcare; NR, not reported; T2DM, type 2 diabetes mellitus; VA, Veterans Affairs; VPT, vibration perception threshold
### a

| Study | Education | Control | RR 95% CI | Fixed weight % | Random weight % |
|-------|-----------|---------|-----------|----------------|-----------------|
| Monami et al (2015) [34] | 0 61 | 6 60 | 0.08 (0.02, 1.31) | 1.6 | 4.8 |
| Gerhater et al (2011) [35] | 19 61 | 22 70 | 1 (0.59, 1.64) | 50.3 | 48 |
| Lincoln et al (2008) [36] | 26 87 | 18 85 | 1.42 (0.83, 2.37) | 47.9 | 47.3 |
| **Total** | **209** | **215** | | | |

Heterogeneity: $I^2$ 55%, $p = 0.111$

### b

| Study | Digital thermometry | Control | RR 95% CI | Fixed weight % | Random weight % |
|-------|---------------------|---------|-----------|----------------|-----------------|
| Lavery (2004) [38] | 1 41 | 7 44 | 0.15 (0.02, 1.19) | 7.5 | 11.6 |
| Lavery et al (2007) [39] | 5 59 | 17 58 | 0.28 (0.12, 0.73) | 36.4 | 38.9 |
| Skafjeld et al (2015) [40] | 7 21 | 10 20 | 0.66 (0.32, 1.40) | 56.3 | 49.4 |
| **Total** | **121** | **122** | | | |

Heterogeneity: $I^2$ 33%, $p = 0.224$

### c

| Study | Complex intervention | Control | RR 95% CI | Fixed weight % | Random weight % |
|-------|----------------------|---------|-----------|----------------|-----------------|
| Cisneros (2010) [41] | 8 30 | 8 23 | 0.77 (0.34, 1.73) | 21.5 | 23.5 |
| Litzelman et al (1993) [44] | 7 191 | 16 205 | 0.47 (0.20, 1.11) | 19.1 | 21.2 |
| McCabe et al (1998) [45] | 24 997 | 35 1000 | 0.69 (0.42, 1.14) | 54.5 | 49.2 |
| Liang et al (2012) [43] | 0 31 | 7 31 | 0.07 (0.01, 1.11) | 1.8 | 2.3 |
| LeMaster et al (2008) [42] | 1 41 | 5 38 | 0.19 (0.03, 1.51) | 3.3 | 4.1 |
| **Total** | **1290** | **1297** | | | |

Heterogeneity: $I^2$ 10%, $p = 0.347$

### d

| Study | Custom footwear, off loading | Control | RR 95% CI | Fixed weight % | Random weight % |
|-------|-----------------------------|---------|-----------|----------------|-----------------|
| Bus et al (2013) [46] | 33 85 | 38 86 | 0.88 (0.61, 1.26) | 32.3 | 21 |
| Reiber et al (2002) [47] | 57 240 | 38 160 | 1 (0.69, 1.44) | 32.1 | 21 |
| Uccolo et al (1995) [51] | 9 33 | 21 36 | 0.47 (0.25, 0.88) | 10.7 | 17 |
| Ulbrecht et al (2014) [50] | 6 79 | 16 71 | 0.34 (0.13, 0.82) | 5.3 | 13.2 |
| Rizzo et al (2012) [48] | 17 148 | 58 150 | 0.3 (0.18, 0.49) | 17.2 | 19.1 |
| Lavery et al (2012) [49] | 3 149 | 10 150 | 0.31 (0.08, 1.08) | 2.6 | 9 |
| **Total** | **734** | **653** | | | |

Heterogeneity: $I^2$ 78%, $p = 4 \times 10^{-5}$
interventions and (insoles [46–51]. Six RCTs evaluated custom-made footwear and offloading insoles (RR 0.59 [95% CI 0.33, 0.85]; Fig. 2d) for outcomes collected at 12–24 months in 1387 people, of whom 464 had no history of foot ulceration. There was evidence of considerable statistical heterogeneity (I² = 78%), which we explored using baseline risk of ulceration in a subgroup analysis (Fig. 3). This pooled analysis of four trials [46, 47, 50, 51], all of which excluded people with no history of foot ulceration, failed to detect a statistically significant difference (RR 0.71 [95% CI 0.47, 1.06]). The six trials were of variable quality, with only two [46, 50] having a low risk of bias across all five domains.

Secondary outcomes Adherence [46, 48, 49] and/or cost [48] data were reported in four trials. One trial measured adherence using a temperature-based monitor placed inside the shoe, and found that 35/85 participants in the intervention group and 42/86 in the control group adhered to wearing their allocated footwear [46]. The trial authors conducted a subgroup analysis in participants who wore their allocated footwear, which showed a statistically greater reduction in ulcer recurrence in the intervention group; however, the analysis using data from the entire trial population failed to detect a beneficial association. A second trial of custom-made footwear and offloading insoles measured adherence using a self-reported physical activity questionnaire, and found that footwear and insole use was high in the groups who received cork inserts (83%) and prefabricated insoles (86%) [47]. A third trial measured participant compliance with footwear using self-reports of the number of hours per day that the shoes were worn. There were no statistically significant differences between each group in the number of people who wore the shoes for less than 4 h per day (23/149 vs 16/150), 4–8 h (77/149 vs 83/150), 8–12 h (38/149 vs 46/150) and 12–16 h (10/149 vs 6/150) [49].

Cost data collected in one trial published in 2012 found the cost of supplying footwear and insoles to be €675 per person per year [48].

Digital silicone devices

In one RCT of digital silicone devices [32], 167 participants with peripheral neuropathy, as defined by a vibration perception threshold of >25 V measured using a biothesiometer, and toe deformities (clawed toes, hallux valgus, interdigital lesions) were randomised to receive a bespoke silicone digital orthotic (n = 89) or standard care (n = 78). The number of ulcers was statistically significantly lower in the intervention group (RR 0.07 [95% CI 0.01, 0.55]) at 3 month follow-up. This trial had a low risk of bias in all domains except for allocation concealment, which was unclear.

Antifungal treatment

In a trial of antifungal nail lacquer, participants in the intervention group (n = 34) received advice to inspect their feet daily and apply ciclopirox 8% to their toenails [30]. The control group (n = 36) received advice about daily foot inspections. A history of foot ulcers was reported by 57% of participants. After 12 months there were two ulcerations in each
group (RR 1.06 [95% CI 0.19, 5.76]). The risk of bias was unclear in two domains: allocation concealment and blinding of the outcome assessor.

**Elastic compression stockings**

An RCT of elastic stockings randomly allocated 160 people with no history of foot ulceration to either knee-length elastic stockings worn for 6 h/day or standard care [31]. There were three ulcers in the intervention group and ten in the control group, a difference that was not statistically significant (RR 0.37 [95% CI 0.11, 1.02]). The trial had a high or unclear risk of bias in the domains of sequence generation, allocation concealment and assessor blinding.

**Secondary outcomes** Thirteen limbs were reported as lost during the 48 month trial; 3/74 in the intervention arm and 10/75 in the control arm.

**Podiatric care**

One trial compared free chiropody care (n = 47) with no chiropody care (n = 44) for people all at high risk of foot ulceration [33]. Those receiving free chiropody were recommended to seek care at least once per month. The control group could seek chiropody if they were willing to pay for it, and their standard care included advice on the possible benefits of regular chiropody. There was no statistically significant difference in the number of ulcerations in the two groups (RR 0.67 [95% CI 0.43, 1.05]). This trial had a low risk of bias in all domains except assessor blinding to outcome data, which was unclear.

**Secondary outcomes** There were 2/47 amputations in the intervention arm vs 1/44 in the control arm. Deaths were recorded as 2/47 in the intervention arm vs 4/44 in the control arm [33].

Data for other secondary outcomes of interest, such as gangrene, self-care, hospital admissions, timing of screening and adverse events or harms, were absent from the trial reports.

**Ongoing trials**

The search for ongoing trials of foot ulcer prevention in diabetes from the ClinicalTrials.gov website found 24 studies being conducted worldwide. The stated interventions in these studies are: physiotherapy (n = 1), skin temperature (n = 6), hygiene (n = 1), offloading insoles (n = 10), risk stratification (n = 2), PET-CT (n = 1), amniotic tissue (n = 1) and unclear (n = 2). The list of these studies can be obtained from the corresponding author.

**Discussion**

The purpose of this systematic review was to evaluate the evidence base and obtain summary statistics for preventative interventions for foot ulceration in diabetes to create a cost-effective, evidence-based care pathway. The meta-analyses of dermal infrared thermometry, complex interventions and therapeutic footwear with offloading insoles suggest that these interventions can help prevent foot ulceration in people with diabetes.

The meta-analysis of data from RCTs of dermal infrared thermometry in people with a history of foot ulceration and a
moderate to high risk of ulceration indicates that this is a promising intervention deserving of further evaluation in randomised trials with larger participant samples, and we note from our search of the ClinicalTrials.gov trial registry that new trials are currently underway. If foot ulcer prevention can be confirmed in large, well-conducted trials, this form of self-monitoring could relieve pressure on healthcare systems. However, advising individuals to abstain from all weight-bearing activities when foot temperatures rise by more than 4°C may prove challenging, and poor adherence might diminish any benefit in a real-world context outside of a trial setting.

Specialist foot care, of the type evaluated in the included trials of complex interventions, is considered a marker of good-quality diabetes service delivery and it is intuitively correct to suppose it leads to improved outcomes. While a statistically significant reduction in foot ulcers was apparent in our meta-analysis, such an effect was not evident in any single trial. This does support the suggestion of others that very large sample sizes may be needed for trials of this nature [53]. Surprisingly, there was a low level of statistical heterogeneity in the pooled data, despite quite marked differences in the clinical care provided in the intervention arms of the trials and the participation of people with three different levels of ulcer risk.

Our review did not identify any trials of complex interventions that reflect the composition of multidisciplinary foot services as recommended in clinical guidelines [54–56]. These influential documents advise the involvement of diabetologists, podiatrists, vascular surgeons, diabetes specialist nurses and orthotists as the core team in a diabetes foot care service, but patient outcomes from such healthcare service arrangements have not been evaluated in RCTs. An evaluation of outcomes from people at different levels of ulceration risk who receive care in specialist foot care settings would be worthwhile.

The true value of therapeutic footwear and offloading insoles in preventing foot ulcers has been obscured by contradictory trial results and poor interpretation of data in systematic reviews; two larger trials involving only those with a history of foot ulcers both failed to detect evidence of effectiveness [46, 47], and visual inspection of our analyses of pooled data from all six trials shows greatest beneficial effect in those where the majority of participants were considered to be at high or moderate risk but had not experienced a foot ulcer [48, 49], albeit only one reached statistical significance [48]. Our subgroup analysis of data from four trials of participants with a history of foot ulceration found no statistically significant difference in the number of recurrent ulcers between the custom footwear and control groups.

This observation calls into question the conclusions of other systematic reviews evaluating footwear and insoles in the prevention of foot ulcers [6, 17, 24]. The most recent included randomised and non-randomised data and adopted a consensus approach to the analysis. The reviewers concluded that: “The evidence base to support the use of specific self-management and footwear interventions for the prevention of recurrent plantar foot ulcers is quite strong, but...is practically non-existent for the prevention of a first foot ulcer and non-plantar foot ulcer” [24]. An individual participant data analysis using data from these six trials together with data from the ten ongoing studies of offloading insoles identified by our search of the ClinicalTrials.gov database could permit subgroup analyses to explore the value of footwear and offloading insoles in people with different baseline risks, and potentially resolve these ongoing uncertainties.

The marked reduction in ulcerations reported with the use of a dermal silicone device by individuals at high risk of ulceration is encouraging [32]. These devices are simple to make at the chair-side and easy for wearers to keep clean. Although they are a type of offloading intervention, we did not include these data in the meta-analysis of footwear and offloading insoles because they differ substantially in that they are only worn around the toes.

Three separate small trials [30, 31, 33] evaluating, respectively, the effects of a daily application of a fungal nail lacquer (ciclopirox 8%) with daily foot inspections, the use of elastic compression stockings and podiatry all failed to show a reduction in foot ulcers, possibly as a result of small sample sizes.

Strengths and limitations of this review. We have comprehensively reviewed a body of evidence from RCTs and made the fullest use of the data currently available to derive best estimates of treatment effects to inform a wider piece of work. In so doing we have highlighted uncertainties, gaps and limitations in the existing evidence base to inform practice, generated new research hypotheses and added value to this area of research.

The weaknesses of this review arise from the potential biases identified in many of the trial reports, especially for complex interventions, which may have produced unreliable results. Previous authors of systematic reviews have cited a lack of similarity between studies [13], lack of standardisation in terminology, prescription, manufacture and material properties of interventions [16], heterogeneity in study designs, methodology and participant populations [18], and differences in participant demographics [22] as reasons for not conducting meta-analyses, and we are aware of the potential limitations in the pooled analyses that we present here, both in the number and quality of trials. We have tried to produce conservative, less biased summary measures by adopting an intention-to-treat approach and a random-effects model. We acknowledge criticisms about the use of the latter [57], but believe the insights gleaned and the generation of new research hypotheses justifies our decision to pool data [58].

Conclusions Our analyses found evidence of beneficial effects for four types of interventions used to prevent foot ulcers in
people with diabetes, but considerable uncertainty remains about what works and who is most likely to benefit. Attention should be given to recommendations for the conduct of trials of interventions for the foot in diabetes, and researchers conducting future trials should endeavour to complete the trial to target recruitment as informed by an a priori sample size calculation [29, 59].

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Data availability A copy of the extracted dataset can be obtained from the corresponding author.

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