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SUPPLEMENT ARTICLE

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Treatment of modifiable risk factors for foot ulceration in persons with diabetes: a systematic review

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Abstract

Background: Prevention of diabetic foot ulcers is important. Preventative treatment mostly targets and aims to improve modifiable risk factors of foot ulceration. While effectiveness of interventions in ulcer prevention has been systematically reviewed, their effectiveness in improving modifiable risk factors is unknown.

Methods: The available medical scientific literature in PubMed, Excerpta Medica Database, and the Cochrane database was searched for original research studies on six interventions to treat modifiable risk factors for diabetic foot ulceration (ie, education for patients; education for professionals; self-management; pre-ulcer treatment; orthotic interventions; and foot- and mobility-related exercises). We assessed interventions for eight outcomes (ie, patients' knowledge; treatment adherence; professionals' knowledge; pre-ulcers; mechanical stress; neuropathy symptoms; foot/ankle joint mobility; and foot function). Both controlled and noncontrolled studies were selected. Data from controlled studies were assessed for methodological quality by two independent reviewers and extracted and presented in evidence and risk of bias tables.

Results: We included 72 publications (26 with a controlled study design and 46 non-controlled). We found that structured education may improve foot self-care behaviour of patients, yearly foot examinations, and foot disease knowledge of health care professionals. Callus removal reduces peak plantar pressure. Custom-made therapeutic footwear can be effective in reducing plantar pressure and may reduce callus. Foot- and mobility-related exercises may improve neuropathy symptoms and foot

Abbreviations: IWGDF, International Working Group on the Diabetic Foot; PICOs, Population Intervention Control Outcomes; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, randomized controlled trial; SIGN, Scottish Intercollegiate Grouping Network.

and ankle joint range of motion, while they do not seem to reduce peak plantar pressure; evidence for their effect on foot strength is conflicting.

Conclusions: Structured education for patients and health care professionals, callus removal, custom-made therapeutic footwear, and foot- and mobility-related exercises may be beneficial for improving modifiable risk factors for foot ulceration. However, we generally found low quality of evidence for interventions targeting modifiable risk factors for ulceration in persons with diabetes, with frequently inconsistent or limited results available per intervention and outcome.

KEYWORDS

callus, diabetes mellitus, diabetic foot, exercise, foot ulcer, footwear, pressure, prevention, risk factors, self-management, shoes, systematic review

1 | INTRODUCTION

Foot ulcers are a major complication of diabetes mellitus, with high morbidity, mortality, and resource utilization.[1-3] Yearly incidence in people with diabetes is estimated to be around 2%, and lifetime incidence lies between 19% and 34%.[4] Treatment of these foot ulcers is challenging due to their multifactorial aetiology and places a high burden on patients, health care systems, and society.[5] Even when an ulcer is successfully healed, risk for recurrence is high, with reported recurrence rates of 40% in the first year, and 65% in the first 3 years, after healing.[4] Therefore, prevention of foot ulcers is important and has long been recognized as a priority by the International Working Group on the Diabetic Foot (IWGDF).

Not all patients with diabetes are at risk for foot ulceration. Key risk factors include a loss of protective sensation (LOPS), foot deformity, peripheral artery disease (PAD), and a history of foot ulceration or any level of lower extremity amputation.[4,6] In general, patients without any of these risk factors are considered not to be at risk for ulceration. Other risk factors include presence of pre-ulcerative lesions, elevated mechanical stress on the foot, and limited foot and ankle joint mobility.[4,7]

Various interventions to prevent foot ulcers in at-risk people with diabetes exist, such as therapeutic footwear, home temperature monitoring, corrective surgery, and integrated foot care.[8] These interventions target modifiable risk factors, which are foot- or person-related characteristics that can be changed to reduce someone's risk of ulceration. These modifiable risk factors include for example pre-ulcerative lesions, foot deformities, plantar pressures, neuropathy symptoms, or joint range of motion. The working mechanism of these interventions is to target and improve risk factors, thereby helping to prevent foot ulcers. Evidence for the effectiveness of these interventions in ulcer prevention is provided in our systematic review of the literature.[8]

However, evidence for an intervention to be effective in ulcer prevention requires studies with a controlled study design and long-term follow-up (at least 1 year). Probably as a result of this, several interventions that target modifiable risk factors have not (yet) been studied for effectiveness in ulcer prevention. For example, specific types of therapeutic footwear to reduce plantar pressure,[9,10] or foot- and mobility-related exercises to reduce neuropathy symptoms.[11,12] If such interventions indeed successfully improve modifiable risk factors for ulceration, they could provide important avenues for future research on ulcer prevention and for interventions clinicians may add to their armamentarium to help prevent foot ulcers. However, the efficacy of these interventions in improving modifiable ulcer risk factors in persons with diabetes is unknown.

The aim of this systematic review is to investigate the effectiveness of interventions targeting modifiable risk factors for foot ulceration in persons with diabetes who are at risk for ulceration and do not have a current foot ulcer, with improvements in these risk factors as primary outcome. Together with our systematic review that investigates ulcer prevention as primary outcome,[8] the current systematic review forms the basis for developing the IWGDF guideline on prevention of foot ulcers in persons with diabetes.[13]

2 | METHODS

A systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[14] and prospectively registered in the PROSPERO database for systematic reviews in 2018 (CRD42018105073).

As a start, the population of interest, interventions, and outcomes (PICOs) were defined, and clinical questions were formulated accordingly. These definitions and PICOs were reviewed for their clinical relevance by the IWGDF Editorial Board and 13 external experts from various geographical regions (see acknowledgements for their names and countries). We integrated the final definitions and PICOs within this paper.

2.1 | Population

The population of interest for this systematic review was people at risk of foot ulceration, as ulcer incidence is very low in people not at risk.[15,16] At risk was defined according to the 2015 IWGDF risk stratification as "people with diabetes mellitus and peripheral neuropathy."[5] Peripheral neuropathy was defined as "the presence of symptoms or signs of peripheral nerve dysfunction, after exclusion of other causes."[5] This includes an LOPS in the feet, ie, the inability to perceive light pressure or vibration, eg, as applied with a 10-g Semmes-Weinstein monofilament or a tuning fork. This population includes people with or without foot deformities, PAD or lower-extremity amputation, and both people in remission from foot ulceration and those with no foot ulcer history. For intervention 2 (see below), the population of interest was health care professionals treating people who are at risk of foot ulceration.

2.2 | Interventions

Interventions were selected by the authors based on their knowledge of the literature and clinical experience, and the selection was reviewed and approved by the IWGDF Editorial Board and the 13 external experts (see acknowledgements). We only included interventions directly targeting the foot or the lower extremity. The following interventions with the goal of modifying risk factors for diabetic foot ulceration were included:

1. Structured education about foot specific self-care: any educational modality that is provided to patients in a structured way. This may include, but is not limited to, one-to-one verbal education, motivational interviewing, educational group sessions, video education, booklets, software, quizzes, or pictorial education via animated drawing or descriptive images.
2. Structured education aimed at health care professionals: any educational modality that is provided in a structured way to health care professionals treating people with diabetes.
3. Foot self-management: interventions consisting of, but not limited to, home foot-monitoring systems, lifestyle interventions, telemedicine, technological applications, and peer support programmes.
4. Treatment of pre-ulcerative or other clinical signs on the foot: for example, removing callus, protecting blisters and draining when necessary, treating dry skin and cracks, treating ingrown or thickened toe nails, treating haemorrhage when necessary, and prescribing antifungal treatment for fungal infections and providing first aid to abrasions, cuts, and scratches.
5. Orthotic interventions: including therapeutic footwear (eg, shoes or insoles) and walking aids (eg, crutches or stick). We defined this as any footwear or insole designed with the intention to offload a region of interest in the foot, for example, with custom-made shoes, prefabricated extra depth shoes, custom-made orthotics/insoles, prefabricated orthotics/insoles, or shoe modifications such as rocker-bottom sole, metatarsal bar, or felted foam.
6. Foot- and mobility-related exercises: any physical exercise specifically targeting the foot or lower extremity with the aim of changing foot function parameters such as foot or ankle joint mobility or muscle strength.

2.3 | Outcomes

Outcomes for study were selected by the authors and reviewed and approved by the IWGDF Editorial Board and the 13 external experts (see acknowledgements). Outcomes related to PAD are considered by the IWGDF PAD working group and were therefore not included.[17]

We included the following outcomes, all modifiable risk factors for ulceration:

- Patient's knowledge about foot disease and foot self-care;
- Adherence to preventative treatment interventions (eg, therapeutic footwear);
- Health care professionals' knowledge about foot disease or their frequency of foot screening;
- Presence of risk factors or pre-ulcerative lesions on the foot, such as abundant callus, blisters, haemorrhage, ingrown or thickened toe nails, and fungal infections;
- Foot-related mechanical stress/pressure;
- Neuropathy symptoms (in persons with existing peripheral neuropathy, excluding painful neuropathy);
- Foot or ankle joint mobility;
- Foot or ankle muscle strength and function, as assessed by functional testing (eg, muscle function test gradation).

2.4 | Inclusion and exclusion criteria

Original studies including the population of interest and reporting on one of the predefined interventions and outcomes were included. We excluded studies on healthy subjects or on persons with diseases other than diabetes. Studies on persons with diabetes who were not at risk for foot ulceration were excluded if >50% of subjects were not at risk. If ≤50% of subjects were not at risk or if separate analyses for those at risk were reported, studies were included. We included systematic reviews and meta-analyses, randomized controlled trials (RCTs), nonrandomized controlled trials, case-control studies, cohort studies, (controlled) before-and-after studies, interrupted time series, prospective and retrospective non-controlled studies, cross-sectional studies, and case series, and excluded case reports. Systematic reviews were only included when all publications identified in the systematic review met our inclusion criteria or when a meta-analysis was presented based on publications meeting our inclusion criteria. If not, reference checking of the papers identified in the systematic review was performed, but the systematic review itself was excluded.

2.5 | Search strategy

The literature search was performed on July 24, 2018, and covered publications in all languages. See Appendix 1 for a detailed description of the search strings. We also checked the references of all included publications to identify additional publications to be included for assessment. The following databases were searched: PubMed, Excerpta Medica Database (EMBASE) via Ovid SP, Cochrane Database of Systematic Reviews, Cochrane Database of Abstracts of Reviews of Effect, and Cochrane Health Technology Assessment.

2.6 | Eligibility assessment

For each intervention group, teams of two members of the working group (ie, the authors) independently reviewed publications by title and abstract for eligibility to be included in the analysis, based on four criteria: population; study design; intervention; and outcomes. We used the online application Rayyan QCRI for eligibility assessment.[18] Reviewers discussed and reached consensus on any disagreement on inclusion of publications. Subsequently, the same two reviewers independently assessed full-paper copies of included publications on the same four criteria for final eligibility. Conference proceedings, if included during assessment of title and abstract, were used to search for full-paper publications. If no full-paper copy of the study was found, we contacted the corresponding author for more information, to assess for any possible publication bias or selective reporting of results.

2.7 | Assessment of included publications

The same two reviewers per intervention group independently assessed included publications with a controlled study design for methodological quality (ie, risk of bias), using scoring sheets developed by the Dutch Cochrane Centre (www.cochrane.nl) and the IWGDF 21-item score for reporting standards of studies and papers on the prevention and management of foot ulcers in diabetes.[19] Reviewers resolved disagreement regarding risk of bias by discussion until consensus was reached. Depending on the number of questions answered with "yes" on the 10 items of the Cochrane scoring sheet, risk of bias for each study was very low when scoring ≥8/10, low when scoring 6 to 7/10 or high when scoring ≤5/10. The SIGN level of evidence was determined for each publication (https://www.sign.ac.uk/assets/study_design.pdf) and combined with the risk of bias score. Level 1 refers to systematic reviews or RCTs and level 2 refers to case-control and cohort studies, controlled before-and-after designs, or interrupted time series.

Data were extracted from each included publication with a controlled study design and summarized in evidence tables. These data included participant and study characteristics, characteristics of the intervention and control conditions, and primary and secondary outcomes. One of the reviewers extracted the data, and the other reviewer checked data for content. All members of the working group thoroughly discussed the evidence tables. Reviewers did not participate in the assessment, data extraction, and discussion of publications of which they were a co-author to prevent any conflict of interest.

2.8 | Evidence statements

Finally, the two reviewers per intervention group drew conclusions for each intervention based on the strength of the available evidence, which were formulated as evidence statements and accompanying assessment of the quality of the evidence (QoE), according to GRADE.[20] The authors rated the QoE for each formulated evidence statement as "high," "moderate," or "low".[20] GRADE defines "high" as "further research is unlikely to change our confidence in our evidence statement"; "moderate" as "further research is likely to have an impact on our confidence in our evidence statement"; and "low" as "further research is very likely to have an impact on our confidence in our evidence statement."[20] The rating was determined based on the level of evidence, risk of bias, consistency of results, publication bias, effect size, and evidence of dose-response relation.[20] All members of the working group discussed these evidence statements until consensus was reached.

3 | RESULTS

In total, we included 72 publications (see for details the PRISMA flowchart in Figure 1). We will describe the results for each intervention group and conclude with an evidence statement (Table 1). Risk of bias assessment of controlled studies can be found in Table 2. Results per included controlled study are described in the evidence table (Appendix 2).

4 | STRUCTURED EDUCATION ABOUT FOOT SPECIFIC SELF-CARE

PICO: In people with diabetes at risk for foot ulceration, can structured education about foot specific self-care compared with no such education improve knowledge about foot disease and foot self-care?

Summary of the literature: We did not find any published evidence to answer this PICO.

PICO: In people with diabetes at risk for foot ulceration, can structured education about foot specific self-care compared with no such education improve adherence to preventative treatment interventions?

Summary of the literature: We found three RCTs. In one RCT with low risk of bias, Lincoln and colleagues[21] included 172 patients (87 in intervention group and 85 in the control group) with a recently healed foot ulcer. They assessed the impact of a single 1-hour education session in the participants' own homes plus single phone call with semistructured format in addition to standard care, vs standard care alone, on improving foot care behaviour measured through the NAFF (Nottingham Assessment of Functional Footcare) checklist. At 12 months follow-up, the intervention group engaged in significantly more foot care behaviours compared to the control group (42.0 vs 38.7 points, $P = .03$).

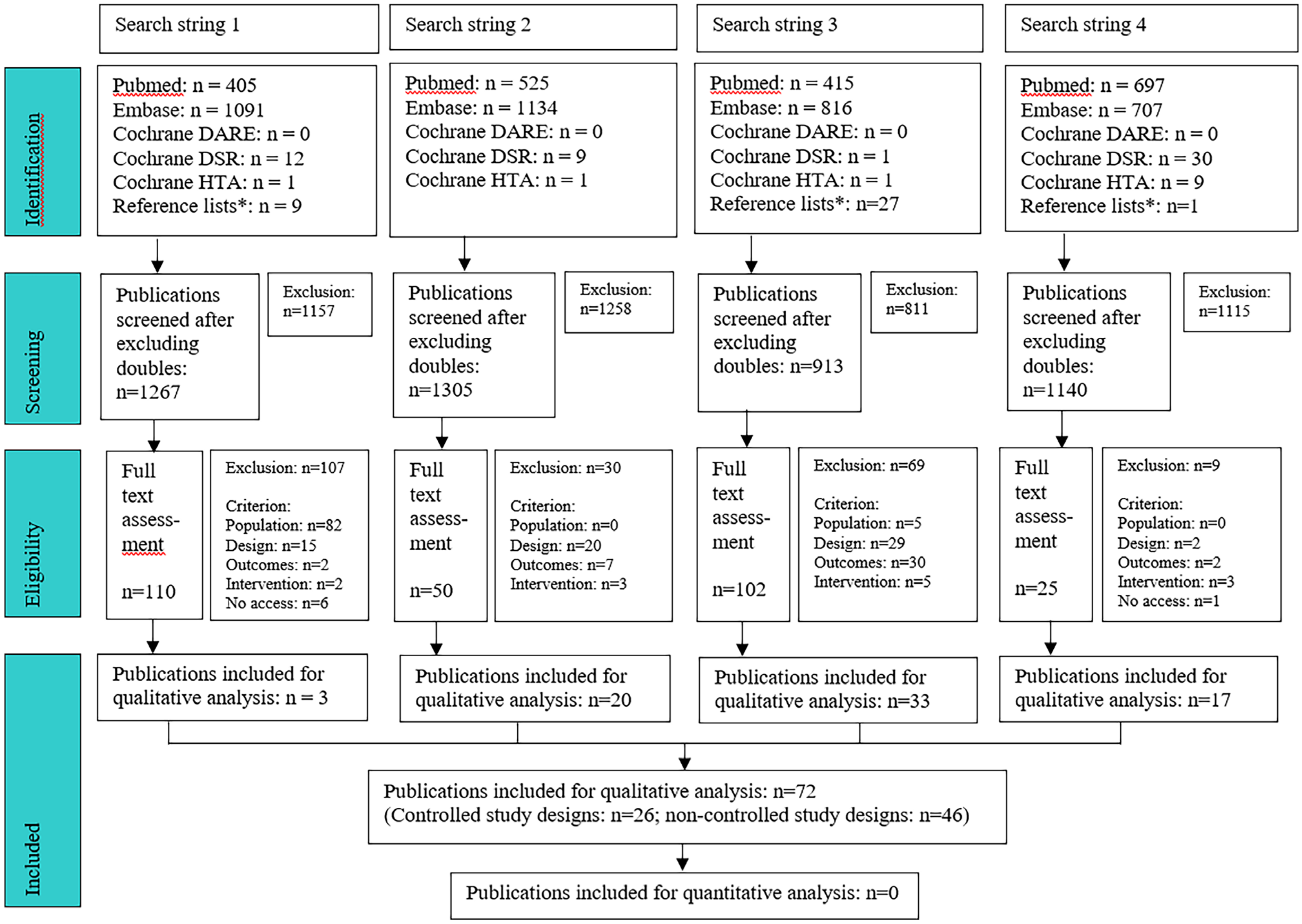

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram. DARE, Database of Abstracts of Reviews of Effects; DSR, Database of Systematic Reviews; CRCT, Central Register of Controlled Trials; HTA, Health Technology Assessment. *Reference lists of included articles were checked, see Appendix 1 with the search strategy for further details

Liang and colleagues,[22] in an RCT with high risk of bias in a Chinese minority, included 59 participants without a previous ulcer. They evaluated if giving a foot care kit and education to patients and caregivers, in addition to standard care, would improve foot care behaviour (measured by a self-developed checklist). While the study was not powered for this outcome, the authors reported a higher value (representing more foot care behaviour) for the intervention group (n = 30) when compared with the control group (n = 29) by the end of the first year (86.35 vs 75.86 points, $P < .05$), that was maintained by the second year (87.24 vs 71.43 points, $P < .01$).

Keukenkamp and colleagues,[23] in a pilot RCT with high risk of bias, studied 13 patients to assess if providing motivational interviewing in addition to and compared with standard care (consisting of written and verbal information at footwear delivery on the proper use of footwear and importance of wearing it), would increase footwear adherence. No significant association was reported for adherence overall, with median percentages at baseline, 1 week and 3 months being 67%, 90%, and 56%, respectively, for the intervention group, and 45%, 47%, and 59%, respectively, for the control group. Nonsignificant associations were also reported for adherence at home or away from home. This study was underpowered with only five participants per study group assessed.

Evidence statement: In people with diabetes at risk for foot ulceration, structured education about foot specific self-care may improve foot specific self-care behaviour.

QoE: Low. Based on three RCTs, of which two with consistent results, and two with high risk of bias.

5 | STRUCTURED EDUCATION AIMED AT HEALTH CARE PROFESSIONALS

PICO: For health care professionals treating people with diabetes at risk for foot ulceration, does structured education about foot-specific care compared with no such education, improve health professionals' knowledge about foot disease?

Summary of the literature: We found three RCTs, three cohort studies, and nine noncontrolled studies on health care professionals' knowledge about foot disease and treatment of pre-ulceration. Jones and Gorman performed an RCT at high risk of bias.[24] A total of

TABLE 1 Evidence statements per intervention category for the treatment of modifiable risk factors for foot ulceration

Intervention	Evidence Statement	QoE	References
Structured education about foot self-care	In people with diabetes at risk for foot ulceration, structured education about foot specific self-care may improve foot specific self-care behaviour.	Low	Lincoln et al, 2008[21]; Liang et al, 2012[22]; Keukenkamp et al, 2018.[23]
Structured education aimed at health care professionals	There is some evidence to suggest that educational interventions may improve percentage of yearly foot examinations performed and knowledge on foot disease of health care providers.	Low	Jones and Gorman, 2004[24]; Donohoe et al, 2000[25]; Kiefe et al, 2001[26]; Holmboe et al, 1999[27]; Harris et al, 2004[28]; Vidal-Pardo et al, 2013[29]; Allen et al 2016[30]; Herring et al 2013[31]; O'Brien et al 2003[32]; Szpunar et al 2014[33]; Bruckner et al 1999[34]; Brand et al 2016[35]; Schoen et al 2016[36]; Tewary et al 2014[37]; Leese et al 2008.[38]
Treatment of risk factors or pre-ulcerative signs	Silicone injections do not reduce the amount of callus, but may increase tissue thickness. Clinical follow-up frequency does not seem to affect the amount of callus removed.	Low	Van Schie et al, 2000[39]; Pitei et al, 1999.[40]
	Callus removal is effective in reducing in-shoe peak plantar pressure immediately following treatment. The effects of silicone injections underneath the metatarsal heads on barefoot peak plantar pressure are variable over time.	Low	Van Schie et al, 2000[39]; Young et al, 1992[41]; Pitei et al, 1999.[40]
Orthotic interventions	Therapeutic footwear, including custom-made shoes and/or insoles, are effective in reducing foot-related mechanical pressure high pressure areas during walking in persons at risk of a foot ulcer.	Moderate	Paton et al 2012[42]; Hellstrand Tang et al. 2014[43]; Ramzy et al. 2015[44]; + 27 non-controlled studies (refs 9, 10, 45-69.
	Orthotic interventions, such as silicone or rigid orthoses, may reduce callus, if used on a daily basis.	Low	Colagiuri et al. 1995[70]; Scire et al. 2009[71]; Ulbrecht et al. 2014.[72]
Foot- and mobility-related exercises	Foot- and mobility-related exercises do not seem to reduce peak plantar pressure during walking in patients with a low or moderate risk of foot ulceration (IWGDF 1 or 2).	Low	Cerrahoglu 2016[73]; Goldsmith et al. 2002[12]; Kanchanasamut & Pensrial 2017[74]; York et al. 2009[75]; Sartor et al. 2014[11]; Fayed et al. 2016[76]; Melai et al. 2013[77]; Mueller et al 1994[78]; Pataky et al. 2010,[79] Rodriguez et al. 2013 (2013), Iunes et al. 2014.[80]
	Foot- and mobility-related exercises may improve neuropathy symptoms in patients with a low or moderate risk of foot ulceration (IWGDF 1 or 2).	Low	Sartor et al. 2014[11]; Kanchanasamut & Pensrial 2017[74]; Iunes et al. 2014,[80] Chang et al. 2015.[81]
	Foot- and mobility-related exercises may increase ankle joint and first metatarsalphalangeal joint range of motion in patients with a low or moderate risk of foot ulceration (IWGDF risk 1 or 2).	Low	Mueller et al. 2013,[82] Kanchanasamut & Pensrial 2017[74] Allet et al. 2010,[83] Cerrahoglu et al. 2016,[73] Goldsmith et al. 2002,[12] Sartor et al. 2014,[11] Dijs et al. 2000,[84] Iunes et al 2014,[80] Francia et al. 2014.[85]
	It is unclear if foot-related exercises improve foot and ankle muscle strength and function in patients with a low or moderate risk of foot ulceration (IWGDF 1 or 2).	Low	Allet et al. 2010,[83] Kruse et al. 2010,[86] Sartor et al. 2014,[11] Francia et al. 2015,[85] Iunes et al. 2014.[80]

Note: QoE, quality of the evidence, determined following GRADE methodology (see methods section for more details); IWGDF, International Working Group on the Diabetic Foot.

TABLE 2 Risk of bias of included publications

Randomized Controlled Trials Intervention Reference	Randomization	Independent Assign-ment	Patient/Care Provider Blinded	Outcome Assessor Blinded	Similarity Groups	Withdrawal/ Drop-out Acceptable (<20%)	Intention to Treat	Patients Treated Equally Except for Intervention	Selective Reporting Ruled Out?	Free from Commercial Interest?	Score
Structured education											
Lincoln et al, 2008	+	+	–	?	+	+	+	+	+	+	8/10
Liang et al, 2012	?	?	–	?	+	+	–	+	+	+	5/10
Keukenkamp et al, 2018	+	+	–	?	–	–	–	+	+	+	5/10
Education of health care professionals											
Jones and Gorman, 2004	+	?	–	?	?	+	+	?	+	+	5/10
Donohoe et al, 2000	+	?	–	?	+	+	+	+	+	+	8/10
Kiefe et al, 2001	+	?	–	+	+	–	+	+	+	+	7/10
Treatment of pre-ulcerative signs											
Van Schie et al, 2000	+	?	?	?	+	?	+	+	+	+	6/10
Orthotic interventions											
Hellstrand et al, 2014	+	?	–	?	?	+	–	+	+	+	5/10
Paton et al, 2012	+	+	–	–	+	+	+	?	?	+	6/10
Ramzy et al, 2015	+	?	?	?	+	–	?	+	+	+	5/10
Colagiuru et al, 1995	+	–	–	+	+	+	–	?	+	?	5/10
Scire et al, 2009	+	?	–	+	+	+	+	+	+	+	8/10
Ulbrecht et al, 2014	+	+	–	+	+	–	+	+	+	+	8/10
Foot-related exercises											
Goldsmith et al, 2002	+	–	–	–	+	–	–	?	+	+	4/10
York et al, 2009	+	?	–	–	–	?	–	+	+	+	4/10
Melai et al, 2013	+	+	–	–	+	–	+	?	+	+	6/10
Sartor et al, 2014	+	+	–	?	+	–	+	+	+	+	7/10
Fayed et al, 2016	–	–	–	?	+	+	–	+	+	+	5/10
Mueller et al, 2013	+	+	–	+	+	+	+	+	+	+	9/10
Kruse et al, 2010	+	+	–	+	+	+	+	+	+	+	9/10
Allet et al, 2010	+	+	–	+	+	+	+	+	+	+	9/10
Kanchanasamut et al, 2017	–	–	–	+	+	+	–	+	+	+	6/10

(Continues)

Cohort Studies Interventions Reference	Study Groups Defined	Selection Bias Avoided/Excluded	Intervention Clearly Defined	Outcome Clearly Defined	Outcome Assessed Blind for Exposure	Withdrawal/Drop-out Acceptable (<20%)	Selective Loss to Follow-up Excluded	Major Confounders/Prognostic Factors Identified and Controlled	Selective Reporting Ruled Out?	Free from Commercial Interest?	Score
Education of health care professionals											
Holmboe et al, 1999	+	−	+	?	+	+	+	+	+	+	8/10
Harris et al, 2004	+	+	+	+	+	+	+	+	+	+	10/10
Vidal et al, 2013	?	+	+	?	?	+	+	+	+	+	7/10

81 participants (56 nurses and 25 podiatrists) were randomized to receive either a foot disease training package consisting of 2 days of training or no training. A self-designed 60-item knowledge test (not validated) was used for assessment. Training resulted in a significant improvement of knowledge (20.1 pretest vs 33.2 post-test; $P < .001$), while knowledge remained similar in the control group (17.1 vs 18.2; $P = .7$).

Donohoe and colleagues performed an RCT with low risk of bias.[25] They compared 10 practices within Devon (UK), including assessment of 1949 patients. In five practices, an integrated health model with complementary educational interventions to clarify diabetic foot management, referral criteria, and professional responsibilities was introduced. The control, applied to the other five practices, consisted of unrelated educational interventions. The intervention resulted in significant improvements in health care professional knowledge (+13.2; $P < .001$), and a significant rise in appropriate referrals, compared with the control group. Patient knowledge and attitudes towards foot care improved in both the intervention and control group.

Kiefe and colleagues performed an RCT with low risk of bias.[26] They included 70 physicians, and half of them received performance feedback based on quality measures. Postintervention, percentage of yearly foot exams improved in both the intervention (46-61%) and control group (32-45%), but this improvement was significantly larger in the intervention group (OR: 1.33; $P = .02$).

Holmboe and colleagues performed a prospective cohort study at low risk of bias.[27] They included 26 internal medicine residents and 107 of their patients. Residents in their second year received the intervention, while those in their third year served as control group. The intervention consisted of a three-part training programme, including a syllabus self-audit and four weekly academic training sessions. No difference was found in the percentage of yearly foot exams performed between both groups (67% vs 60%; not significant), but a monofilament had been used more frequently in the intervention group (26% vs 8%; $P = .02$).

Harris and colleagues performed a retrospective cohort study with very low risk of bias.[28] They included 68 physicians, and 809 of their patients, and investigated the effects of an extensive quality improvement programme on type 2 diabetes management. The programme did not have a significant effect on performing yearly foot exams (48% vs 38% in the control group; $P = .15$).

Vidal-Pardo and colleagues performed a combined retrospective and prospective cohort study with low risk of bias.[29] They included 103 primary care physicians and 5868 of their patients and investigated the effect of an educational intervention on indicators of good clinical practice. Yearly foot examination (including measuring at least peripheral pulses) was significantly more frequently performed postintervention (30.1% intervention group vs 14.0% control group; $P = .023$).

In nine noncontrolled studies with a pre-post design, mixed outcomes were reported. Some found an increase in yearly foot examinations and self-reported knowledge,[30-34] while others reported improvements in some centres/participants only or no differences postintervention.[35-38]

Evidence statement: There is some evidence to suggest that educational interventions may improve percentage of yearly foot examinations performed and knowledge on foot disease of health care providers.

QoE: Low. While based on three RCTs and three cohort studies with mostly low or very low risk of bias, the results are not consistent, the studies have been done in different health care populations, and the effects are small.

5.1 | Foot self-management

PICO: In people with diabetes at risk for foot ulceration, can foot self-care/self-management interventions compared with no such interventions prevent pre-ulcerative lesions?

Summary of the literature: We did not find any published evidence to answer this PICO.

5.2 | Treatment of pre-ulcerative or other clinical signs on the foot

PICO: In people with diabetes at risk for foot ulceration, does treatment of pre-ulcerative or other clinical signs on the foot, compared with no such treatment, heal pre-ulcerative lesions?

PICO: In people with diabetes at risk for foot ulceration, does treatment of pre-ulcerative or other clinical signs on the foot, compared with no such treatment, reduce plantar pressure?

Summary of the literature: We found one RCT and two non-controlled studies. One RCT with low risk of bias by Van Schie and colleagues tested the effect of injections with silicone underneath the metatarsal heads on tissue thickness and presence of callus.[39] In 28 participants (14 in both groups) they found no difference after 12 months between silicone injections vs saline injections on callus based on a self-developed scoring system (0.5 vs 0; $P = .3$). Regarding pre-ulcerative lesions, they found tissue thickness increased significantly more at 3, 6, and 12 months following injections with silicone (1.8, 2.1, and 1.8 mm, respectively) vs injections with saline (0.08, 0.2, and 0.25 mm, respectively; $P < .05$). Regarding plantar pressure, they found after 3, 6, and 12 months a larger median barefoot peak plantar pressure reduction in patients with silicone injections (−232, −182, and − 216 kPa, respectively) vs saline injections (−25, +58, and + 145 kPa, respectively; $P < .05$ at 3 and 12 months; $P = .11$ at 6 months).

In one cross-sectional study, Pitei and colleagues[40] found no difference in the amount of callus removed between patients who, according to clinician assessment, needed treatment every 3 to 4 weeks vs patients who needed treatment every 6 to 8 weeks vs patients who did not visit the clinic before (276.5 vs 467.8 vs 341.5 g respectively; range of P values: .43-.78). They further found in all three study groups a significant difference in peak plantar pressure (measured in standard shoes) following callus removal: six patients with no history of ulceration or callus removal (375 kPa before vs 278 kPa after removal), 10 patients with a history of ulceration and podiatry treatment every 6 to 8 weeks (352 vs 241 kPa), and eight patients with a history of ulceration and podiatry treatment every 3 to 4 weeks (241 vs 176 kPa).

In one cross-sectional study, Young and colleagues[41] studied the effect of callus removal on barefoot peak plantar pressure in 17 patients. They found a mean 26% reduction in peak pressure (from 14.2-10.3 kg/cm^2; $P < .001$).

Evidence statement: Silicone injections do not reduce the amount of callus but may increase tissue thickness. Clinical follow-up frequency does not seem to affect the amount of callus removed.

QoE: Low. Based on one RCT and one noncontrolled study only.

Evidence statement: Callus removal is effective in reducing peak plantar pressure immediately following treatment. The effects of silicone injections underneath the metatarsal heads on barefoot peak plantar pressure are variable over time.

QoE: Low. Based on one RCT and two noncontrolled studies only.

5.3 | Orthotic interventions

PICO: In people with diabetes at risk for foot ulceration, do orthotic interventions (including therapeutic footwear [eg, shoes or insoles] and walking aids), compared with other orthotic interventions, reduce foot-related mechanical stress/pressure?

Summary of the literature: We found three RCTs and 27 predominantly cross-sectional studies investigating a variety of interventions. An RCT by Paton and colleagues,[42] with low risk of bias, randomized 109 patients to either over-the-counter insoles or custom-made insoles that were designed by a single individual according to a defined protocol. There were no significant differences between groups in regional peak pressure either at baseline or at 6 months follow-up.

An RCT at high risk of bias by Hellstrand and colleagues randomized patients with low and moderate risk for ulceration to different insoles.[43] They used custom-made ethylene vinyl acetate (EVA) insoles with two different hardness levels (soft: 35 shore; hard: 55 shore) put in outdoor walking shoes, and as control group, they included a prefabricated insole based on positive plaster mould of the foot. After 6 months of usage, the soft and hard EVA insoles resulted in lower peak pressures and pressure-time integrals when all seven regions of interest were analysed together (EVA soft: 180 kPa; EVA hard: 189 kPa; control: 211 kPa). In mixed model assessment per region, these differences remained statistically significant for the heel, with a difference of 63 kPa (EVA soft) and 72 kPa (EVA hard) compared with the control insoles ($P < .001$). For EVA soft, further differences were found at the first and second metatarsal head (difference with control 41 and 42 kPa, $P = .05$ and $P = .04$, respectively). For EVA hard, a further difference was found at the fifth metatarsal head (difference with control 35 kPa, $P = .02$). There was no difference in patient satisfaction between insoles, neither in footwear adherence.

An RCT with high risk of bias by Ramzy and colleagues randomized patients with low risk for ulceration (IWGDF risk 1) to either gait training using vibratory insoles or no insoles, in addition to the same physical training programme three times/week for 2 months.[44] Vibration insoles were used for the application of subsensory mechanical noise signal to the soles of the feet. There was a significant reduction in the total plantar pressure in the intervention group (11-17%) compared with the control group.

Based on cross-sectional studies, shoes with a rocker-bottom outsole are reported to be effective in reducing forefoot peak pressures.[10,45,46] Also, forefoot offloading shoes effectively offload the forefoot[9] and are more effective than accommodative felt and foam dressings worn in a post-operative sandal or compared with post-operative shoes alone.[47] A shoe with removable insole plugs can provide significantly more pressure relief than a control shoe or the patients' own shoes.[48] Using an insole with removable plugs and an arch support can provide even further pressure relief when compared with just using insoles with removable plugs or basic flat insoles.[49]

A series of studies show that custom-moulded insoles or orthoses more effectively offload the foot than prefabricated insoles.[50-61] Shoes with flat insoles showed to be less effective than shoes with custom-made insoles,[58,62] even though the use of polyurethane foam sheets inside the patients' own shoes can improve offloading compared with wearing standard shoes.[63] Custom-made insoles designed on the basis of foot shape and plantar pressure profile of the patient provide significantly more offloading than custom insoles that are designed on the basis of foot shape alone.[64] With the use of in-shoe plantar pressure measurement as a tool to guide modifications to custom-made insoles and shoes, significantly more offloading can be achieved than compared with not using in-shoe pressure analysis.[65] Metatarsal pads, used either alone or in combination with a medial longitudinal arch support, provide a significant pressure relief compared with not using these elements, but this is critically dependent upon placement; pads may actually increase plantar pressure if placed incorrectly.[61,66,67] Two studies have examined long-term pressure relief provided by insoles.[68,69] Peak pressures with these insoles were found to be higher compared with baseline after the subject took 50 000 steps. Most insole compression occurred during the initial 6 months of wear, and compression did not appear to change between 6 and 12 months.

Evidence statement: Therapeutic footwear, including custom-made shoes and/or insoles, are effective in reducing foot-related mechanical pressure at high pressure areas during walking in persons at risk of a foot ulcer.

QoE: Moderate. Based on three RCTs and 27 non-controlled studies, with low to medium effect size, low risk of bias, and consistent results.

PICO: In people with diabetes at risk for foot ulceration, do orthotic interventions (including therapeutic footwear [eg, shoes or insoles] and walking aids), compared with other orthotic interventions, prevent pre-ulcerative lesions?

Summary of the literature: Three RCTs on prevention of pre-ulcerative lesions were found. A high risk of bias RCT by Colagiuri and colleagues[70] randomized 20 patients with no or low risk for ulceration (IWGDF risk 0 and 1). Participants received either a custom-made rigid orthotic device made from a thermal pliable plastic and worn for at least 7 hours/day (n = 9) or a traditional treatment of callus by a podiatrist (n = 11). They looked for the severity of plantar callosity according to a classification that took into account the thickening of the keratin layer and the presence or absence of other pathology at the site of the callus. They found an improvement in the callus grade in 16 of the 22 calluses, and no change in the other six in the intervention group after 12-months follow-up, vs no improvement in 25 of 32 calluses and deterioration of the other seven in the control group (P = .02). There were no adverse effects and no reported difficulties from wearing the orthotic device.

A low risk of bias RCT by Scire and colleagues[71] randomized 167 patients with moderate risk for ulcer (IWGDF risk 2). Participants received either digital silicone orthoses for offloading toes (corrective, protective, or mixed) plus standard care (n = 89), or standard care alone, including sharp debridement, "soft" accommodating insole, and extra depth shoe aiming to reduce plantar hyperkeratosis (n = 78). After 3 months, the intervention group showed a 41% presence of hyperkeratosis, compared with 84% in the control group (P = .002). There was no information on adherence, but 17% of patients in the intervention group (n = 15) discontinued the use of the orthoses.

A very low risk of bias RCT by Ulbrecht and colleagues[72] randomized 130 patients with LOPS and a recently healed plantar metatarsal head ulcer. Participants received either computer-aided designed insoles based on foot shape and barefoot plantar pressure in a standardized double extra-depth shoes (n = 66) or standard commercial insoles based on foot shape and clinical reasoning in standardized extra-depth shoes (n = 64). The authors observed no significant difference between study groups in the number of nonulcerative lesions (haemorrhage into callus or redness at a site of bony prominence persisting more than 20 minutes after removal of footwear and rest) during 16.5 months follow-up (Kaplan-Meier curve only, no numbers given; P = .76).

Evidence statement: Orthotic interventions, such as silicone or rigid orthoses, may reduce callus, if used on a daily basis.

Quality of the evidence: Low. Based on three RCTs with inconsistent results and small effect sizes.

5.4 | Foot- and mobility-related exercises

We found a total nine RCTs and eight noncontrolled studies that reported on foot- and mobility-related exercises targeting the foot or lower extremity with the aim of changing one or more of the four outcomes of interest (ie, mechanical stress, neuropathy symptoms, limited joint mobility, and foot strength and function). We will first describe the studies here and describe the outcomes of each study following the specific PICO.

In an RCT with high risk of bias by Goldsmith and colleagues, 21 patients (IWGDF 0, 1, or 2—not further specified) were included.[12] They were randomized to either a 4-weeks home-exercise programme up to three times a day, including foot-ankle passive and active stretching exercises and soft tissue manipulation (11 participants; but two lost to follow-up and outcomes reported for nine) or to no intervention (n = 10).

A high risk of bias RCT by York and colleagues enrolled 29 patients with diabetic neuropathy.[75] The intervention consisted of a 2-days gait training with visual and verbal feedback to pull the leg forward from the hip to initiate swing rather than push off the ground with the foot while walking. The patients received feedback regarding in-shoe peak pressures after each practice trial. This was compared with a no feedback control group. In-shoe peak pressure was assessed at baseline, after 1 day and after 1 week.

A very low risk of bias RCT conducted by Allet and colleagues[83] randomized 71 patients at low risk of foot ulceration (IWGDF grade 1) to either a physiotherapeutic training programme (60 minutes) for 12 weeks including gait and balance exercises with function-orientated strengthening and twice weekly resistance foot-ankle exercises (n = 35) or to neither treatment nor specific advice (n = 36).

In a very low risk of bias RCT from Kruse and colleagues,[86] 79 patients at low risk for foot ulceration (IWGDF grade 1) were randomized to a regular foot care education programme in addition to eight physical therapy sessions (foot-ankle strengthening and balance exercises), home strengthening and balance exercises, a walking programme and fortnightly motivational phone calls (n = 41), or to regular foot care education with a physical therapist but no exercises (n = 38).

In a low risk of bias RCT from Melai and colleagues, 92 patients at low risk of foot ulceration (IWGDF risk 1) were included.[77] The intervention group (n = 48) underwent a 24-week group intervention, which included exercises for lower limb strengthening and functional exercises, plus strength exercises at home twice weekly and was compared with a control group undergoing no intervention (n = 46).

A very low risk of bias RCT by Mueller and colleagues,[82] included 29 participants (IWGDF1 [86%] and IWGDF3 [14%]). The weight bearing intervention group (n = 15) participated in three sessions of foot-related exercises per week for 12 weeks. These were provided by a physical therapist and consisted of stretching and strengthening foot and ankle exercises, weight bearing aerobic exercise—walking (eg, sit to stand, stair climbing, treadmill walking, or walking around a hallway). They were compared with a nonweight bearing group (n = 14) undergoing nonweight bearing stretching and strengthening exercises and aerobic exercise on a stationary bike.

In a low risk of bias RCT by Sartor and colleagues, 55 patients at low risk of foot ulceration (IWGDF grade 1) were included.[11] The intervention group (n = 26) participated in 12 weeks of physical therapy of 40 to 60 minutes twice a week, involving foot-ankle stretching and strengthening exercises, functional exercises, and walking skills (eg, foot rollover); the control group (n = 29) received no physical therapy.

A high risk of bias RCT by Fayed and colleagues included 40 women with diabetes at low risk for ulceration (IWGDF risk 1).[76] The intervention group (n = 20) underwent 8 weeks of physiotherapeutic intervention including foot-ankle stretching and strengthening exercises, balance, and gait training (three session/week, 60 minutes each session), while the control group (n = 20) received no intervention besides usual medical treatment.

In an RCT with low risk of bias by Kanchanasamut and Pensri, 21 patients at low risk of foot ulceration (IWGDF risk 1) were enrolled.[74] The intervention group (n = 11) participated in a foot-care education programme (booklet) plus an 8-week home vigorous exercise programme for foot and ankle with four levels of progression, using a minitrampoline and managed by a senior physical therapist; the control group (n = 10) only received foot-care education (booklet).

Eight observational studies were found. Cerrahoglu and colleagues describe an RCT and included 76 patients with either no risk (n = 38) or low risk (n = 38) for foot ulceration (IWGDF risk 0 and 1).[73] Both groups were randomized to either a 4-weeks home-based exercise programme, including weight bearing and nonweight bearing exercises, foot-ankle stretching and strengthening exercises, plus weekly motivational phone calls (n = 19 for both groups), or to no exercise programme and no weekly motivational calls (n = 19 for both groups). However, with only outcomes reported for the intervention group, we have assessed this as a noncontrolled study. Mueller and colleagues taught a group of 13 patients (seven IWGDF risk 3; six age-matched controls without diabetes) to walk using the hip strategy instead of normal walking (ankle strategy) and compared with their self-controlled strategy before training.[78] In two observational studies, Pataky and colleagues[79] and Rodriguez and colleagues[87] investigated an intervention consisting of a learning process including sequences of walking (10 steps), each followed by a subjective estimation of performance and objective feedback using an in-shoe pressure mobile system. The goal was to achieve three consecutive walking cycles of 10 steps, with a minimum of seven steps inside the range of 40% to 80% of the baseline mean peak plantar pressure. The area to be offloaded was determined beforehand as the area with the highest peak plantar pressure. In the fourth noncontrolled study,[80] 97 (of an initially 117 included) participants (IWGDF grade 0: 50%; grade 1: 38%; grade 2: 12%; a total 71.1% had neuropathy, while a total 76.3% had foot deformities) were assessed at the end of a 10-month observation period. Participants had received education about self-care and lower limb home exercises. In another noncontrolled study,[81] 66 patients at moderate risk of foot ulceration (IWGDF grade 2) were enrolled in a two-component exercise programme, including (a) Buerger exercises for 90 minutes a day and a month of a health-promoting programme to change health habits, in individualized sessions; and (b) from the second month till 12-months follow-up, an individualized teaching and counselling programme through home visits and telephone calls. However, only 31 of the 66 participants had completed the programme and were available for outcome assessment. A sixth noncontrolled study, conducted by Francia et al,[85] enrolled 26 patients with low risk for ulceration (IWGDF grade 1) in a supervised plus home exercises physical therapy programme, including stretching, balance, and strengthening foot-ankle exercises. The last noncontrolled study found was by Dijs and colleagues,[84] who enrolled patients with low risk for ulcers (IWGDF grade 1) in a physical therapy programme of passive foot-ankle joint mobilization (manual therapy).

PICO: In people with diabetes at risk for foot ulceration, can foot-related exercises compared with no foot-related exercises reduce foot-related mechanical stress/pressure?

Summary of the literature: We identified six RCTs and five noncontrolled studies. Goldsmith et al[12] found in the intervention group a significantly lower average barefoot peak plantar pressure during gait of 4.2%, while pressure increased 4.4% in the control group (no values given). York et al[75] found in the intervention group a significant reduction in peak plantar pressure at the first metatarsal area after 1 day (P = .01, no numbers given) but not at 1-week follow-up, while the control group showed no changes. No significant changes were found in other regions, neither at 1 day nor 1 week. Melai et al[77] found no differences in barefoot peak plantar pressure changes during gait between the intervention and control group at 12, 24, or 52 weeks (P > .1; only figures provided, no quantification of differences given). Outcomes were only available for participants completing the study, but there was a high drop-out rate in the first 12 weeks (41.7% [n = 20] in the intervention and 23.9% [n = 11] in the control group). Sartor et al[11] found at 12 weeks no significant change in reference to baseline for barefoot peak plantar pressure between intervention or control groups in the six areas measured. Fayed et al[76] found at the end of the training period a significantly reduced peak plantar pressure during gait under the heel and all metatarsal heads in the intervention group (17-26% improvement), while plantar pressure in the control group remained similar (1-4% improvement). Finally, Kanchanasamut and Pensri[74] found at 20-week follow-up for the 10 regions assessed for peak plantar pressure (five per foot), one region with a reduction in the intervention group (left medial forefoot 396 to 315 kPa), and one with an increase (right lateral forefoot: 490 to 582 kPa). No changes were seen in the other eight regions and none in the control group.

In the noncontrolled studies, Mueller et al[78] found that walking with a hip strategy compared with walking without strategy showed a significantly lower peak pressure under the forefoot (from 164 to 120 kPa; P = .003) and higher under the heel (from 141 to 175 kPa; P = .005) immediately after the intervention, with no further follow-up measurements. Pataky et al[79] found peak plantar pressure to be reduced after the learning period (ie, when the target for plantar pressure was achieved) from 262 to 191 kPa; P = .002. The difference between the beginning of learning (262 kPa) and retention tests at 30 minutes (205 kPa), 1 (216 kPa), 5 (209 kPa), and 10 days (210 kPa) persisted; all P values <.05. Rodriguez et al[87] found a significant reduction in the peak pressure at the target area at the end of learning (from 242 kPa to 165 kPa; P < .01) and at 10 days retention test (167 kPa; P = .001). Iunes et al[80] found after the intervention a significant increase in static mean pressure in the left foot (from 29 to 31 kPa; P = .02), while no differences were seen for dynamic plantar pressure. Cerrahoglu et al[73] observed reductions in one out of 12 measured areas for static barefoot peak pressure (right medial forefoot, 13% improvement) and four out of 12 measured areas for dynamic measures (medial forefoot, 12% improvement; lateral forefoot, 24% improvement; midfoot, 29% improvement, heel, 19% improvement) in a comparison of baseline vs 4 weeks after the intervention.

Evidence statement: Foot- and mobility-related exercises do not seem to reduce peak plantar pressure during walking in patients with a low or moderate risk of foot ulceration (IWGDF 1 or 2).

QoE: Low. Because of inconsistent and imprecise results.

PICO: In people with diabetes at risk for foot ulceration, can foot-related exercises compared with no foot-related exercises improve neuropathy symptoms?

Summary of the literature: We identified two RCTs and two noncontrolled studies. Sartor et al[11] found at 12 weeks that neuropathy symptoms (as assessed by the Michigan Neuropathy Screening Instrument [MNSI]) reduced in the intervention group from six (SD: 2) to four (SD: 3), while they remained six (SD: 3) in the control group (P < .05 for before-after differences in intervention group; effect size for difference between intervention and control: 0.52 [medium]). Kanchanasamut and Pensri[74] found at 8- and 20-week follow-up neuropathy symptoms to improve significantly more in the intervention group (P = .013 for pressure perception and P = .04 for vibration perception). Further, NeuroQoL scores decreased significantly in the intervention groups but not in the control group (P = .004); see evidence table for details.

In the noncontrolled studies, Iunes et al[80] found after the intervention no change in the tactile sensitivity as assessed with a 10-g monofilament (27-22%; P = .19). Chang et al[81] found after 12 months that MNSI scores improved from 2.7 (SD: 1.8) to 1.0 (SD: 1.3), P < .001.

Evidence statement: Foot- and mobility-related exercises may improve neuropathy symptoms in patients with a low or moderate risk of foot ulceration (IWGDF 1 or 2).

QoE: Low. Because of inconsistency and imprecision of results, with small effect sizes and large confidence intervals around the effect.

PICO: In people with diabetes at risk for foot ulceration, can foot-related exercises compared with no foot-related exercises improve limited joint mobility?

Summary of the literature: We identified five RCTs and five noncontrolled studies. Allet et al[83] found after a 12-week intervention period that ankle ROM improved for plantar flexion (I: 44 to 47°; C: 42 to 43°; 95% CI = 0.11-6.79), and dorsiflexion (I: 5-8°; C: 6-5°; 95% CI = 0.87-4.12), (P ≤ .05 for group effect—non-Bonferroni corrected alpha value), and this maintained after 6 months for plantar flexion (I: 45 vs C: 41°, 95% CI = 0.34-6.53). Mueller et al[82] found an increase in ankle joint dorsiflexion ROM in both the weight-bearing group (3.6-7.7° [95%CI: 4.1 (1.7-6.5)]) and nonweight bearing group (3.1-5.5° [95%CI: 2.4; −0.1-4.9)]), but the difference between groups was not significant (difference: 1.7° [95%CI: −1.8-5.2]). Kanchanasamut and Pensri[74] found ROM of the first metatarsophalangeal joint to increase in the intervention group for both flexion and extension of the left and the right foot, after 8 and 20 weeks, with a significant interaction effect for time and intervention (P values range .002-.040). Sartor et al[11] found at 12 weeks that more participants had "normal functionality" for ankle flexion, and toe flexion and extension in the intervention compared with the control group, but not for ankle extension (P < .05 between groups). Ankle ROM did not change (I: 20.8-20.8°; C: 22.5-18.9°; P > .05). Goldsmith et al[12] found no differences in joint stiffness in the ankle and the first metatarsophalangeal joint.

From the five noncontrolled studies, four of them observed increases in the ROM of foot-ankle-related joints. Cerrahoglu et al[73] observed an average 5° increase in ROM (<0.001) of the ankle and first metatarsophalangeal joints, for flexion and extension in the left and right foot, when compared with baseline measures. Francia et al[85] found an increase in ankle joint ROM (plantarflexion [from 13 to 20°] and dorsiflexion [from 36 to 46°]; $P < .0001$). Dijs et al[84] reported a significant increase in joint mobility of the tibiotalar joint (flexion-extension), subtalar joint (inversion-eversion), first metatarsophalangeal joint (flexion-extension), and the first ray ($P < .05$). Iunes et al[80] found an improvement of forefoot alignment (right 7.15-6.61°, $P = .04$; left 11.78-8.45°, $P < .01$) and improved foot supination.

Evidence statement: Foot- and mobility-related exercises may increase ankle joint and first metatarsalphalangeal joint range of motion in patients with a low or moderate risk of foot ulceration (IWGDF risk 1 or 2).

QoE: Low. Because inconsistency (not all publications reported positive changes) and imprecision (large confidence intervals around the effects found) of results.

PICO: In people with diabetes at risk for foot ulceration, can foot-related exercises compared with no foot-related exercises improve foot strength or function?

Summary of the literature: We identified three RCTs and two noncontrolled studies. Allet et al[83] found a significant increase in the ankle plantar flexor strength (I: 233-268 N; C: 246-243 N; $P < .05$) and dorsal flexor strength (I: 202-238 N; C: 202-212 N; $P < .05$). The improvements obtained did not last for the 6-month follow-up period. Kruse et al[86] found no statistically significant differences in ankle dorsiflexion strength between the intervention and control groups after 6 months (C: 23.8 vs I: 24.3 kg; $P = .11$) or 12 months (C: 20.4 vs I: 22.0 kg; $P = .22$). Sartor et al[11] found at 12 weeks significant increases in the muscle function test gradation for the flexor digitorum brevis (4.0 vs 5.0), interosseous (3.0 vs 4.0) and tibialis anterior (4.0 vs 5.0), for the intervention compared to the control group ($P < .05$) but not for extensor digitorum and hallucis, flexor hallucis, lumbrical, and triceps surea ($P > .05$).

In the noncontrolled studies, Francia et al[85] found an increase in ankle joint strength (plantarflexion [440-840 N] and dorsiflexion [167-224 N]; $P < .0001$). Iunes et al[80] found no differences in muscle strength of the toe flexor and extensor, hallux extensor and subtalar eversion strength ($P > .05$; no further details given in the paper).

Evidence statement: It is unclear if foot-related exercises improve foot and ankle muscle strength and function in patients with a low or moderate risk of foot ulceration (IWGDF 1 or 2).

QoE: Low. Because of inconsistency and imprecision of results.

6 | DISCUSSION

We systematically reviewed six interventions targeting a total eight modifiable risk factors for foot ulceration in persons with diabetes who are at risk for ulceration and do not have a current foot ulcer. Despite including 22 RCTs, the evidence base for most interventions is still small, because of inconsistencies and imprecision found between studies and also because of there being few RCTs per intervention and outcome category. More high-quality controlled studies targeting modifiable risk factors for foot ulceration are needed, that preferably combine these outcomes with the primary clinical outcome of ulceration.

6.1 | Structured education

Structured education can target two groups: patients or health care professionals. Regarding patients, we included only three RCTs, much less than in a Cochrane review by Dorresteijn and colleagues.[88] They mostly reviewed studies that included participants who were not at risk of ulceration, because they were without peripheral neuropathy or PAD. In our opinion, education as a tool to improve knowledge or adherence to foot care behaviour is mostly useful when targeted at patients at risk—meaning those with at least peripheral neuropathy. With ulcer incidence being low in those patients not at risk,[15,16] it is unlikely that any improvement in knowledge or adherence to foot care behaviour following education in patients not at risk will ultimately have an effect on ulcer prevention.

We found moderate quality evidence for improvements in foot specific self-care behaviour following education. However, structured education can have many forms, with different methods, at various intervals, of different lengths, and with different educators. It is clear that more research to identify the best methods of education for this population is needed.

Diabetic foot disease is described as the “Cinderella” of the diabetic complications,[89,90] or the least-known major health problem,[91,92] reflecting thoughts that knowledge among health care professionals of adequate screening, prevention, and management of diabetic foot disease is suboptimal. Various structured educational programmes to improve this limitation have been studied, either targeting diabetic foot knowledge specifically or targeting yearly foot screening as part of a diabetes care improvement programme. Mixed findings are seen in these programmes, but overall, we conclude that structured education can improve the percentage of yearly foot examinations or professionals' knowledge of diabetic foot disease. In addition to the published programmes, implementation and training programmes such as “train the foot trainer” as started by the IWGDF are available (www.ttft.org), but their effectiveness has not been scientifically evaluated. With the large and increasing global burden of diabetic foot disease,[1] education of health care professionals is important. New programmes should incorporate methods from the studies with positive outcomes,[24-26] while additional research to investigate more advanced methods is needed.

6.2 | Treatment of pre-ulcerative or other clinical signs on the foot

It is widely considered standard clinical practice to treat pre-ulcerative or other clinical signs on the foot, such as removing callus or treating fissures. However, evidence supporting this treatment is limited to one RCT and two noncontrolled studies only. The RCT[39] investigated the effect of silicone injections, and despite some positive findings for plantar pressure reduction, the RCT is old, the only one conducted, and such treatment is not used in clinical practice, probably also reflecting limited implementation opportunities. Both noncontrolled studies clearly showed benefits of callus removal. This is standard clinical practice, and as such, it is unethical to investigate its effectiveness when comparing against no callus removal. However, such treatment is still subject to clinical variations, such as the skills of practitioners, frequency of treatment, and duration of treatment. This also applies to other treatments in this category, for which no evidence was available. Therefore, new controlled trials on callus removal and other interventions to treat pre-ulcerative or other clinical signs on the foot are important.

6.3 | Orthotic interventions

Moderate quality of evidence was available on the effect of therapeutic footwear, including custom-made shoes and/or insoles, on modifiable risk factors. We conclude that these are effective in reducing mechanical pressure, particularly if they are data-driven custom-made designs using plantar pressure measurements. The majority of the evidence does come from noncontrolled studies (n = 27), with only three controlled studies on this topic found. However, that is logical from the point of view that effects of footwear interventions on plantar pressure are immediate, and studies do not necessarily require a prospective randomized design, although follow-up to assess changes in pressure over time can be informative. We did identify multiple RCTs on this topic in our systematic review on ulcer prevention,[8] showing also positive outcomes in ulcer prevention. Together, this suggests some underlying principles that can guide footwear prescription, moving from experienced and skill-based towards data-driven footwear prescription.[93,94] However, additional detailed information on which specific footwear design or protocol best reduces plantar pressure is needed to better inform health care professionals on these principles.

6.4 | Foot- and mobility-related exercises

With nine RCTs and another eight noncontrolled studies, and most of them published in the last 5 years, foot- and mobility-related exercises were the most widely studied intervention targeting modifiable risk factors for foot ulceration. These exercises can target multiple outcomes (plantar pressure, neuropathy symptoms, foot mobility, and foot strength), and further variations were seen in the included trials in relation to the type, frequency, and intensity of the exercises, and in timing of follow-up measurements. These large variations between trials might be an explanation for the differences in outcomes found in these studies. For each of the four outcomes studied, both positive and neutral outcomes were found. This means that the evidence base for foot- and mobility-related exercises is still small, with future research likely to improve confidence in the evidence found.[20] Taken together, the most positive findings were found for improving neuropathy symptoms and increasing joint range of motion in the foot and ankle. No conclusion could be drawn for foot strength, while peak plantar pressure does not seem to reduce following these exercises, although changes in the distribution of plantar pressure were observed after some interventions.

With regard to plantar pressures, we have limited this systematic review to peak plantar pressure. This variable is a key risk factor for ulceration,[4] and it was also the primary outcome in interventions targeting plantar pressure. Based on our findings, it seems more useful to focus on orthotic interventions, rather than foot- and mobility-related exercises, when targeting peak plantar pressure reduction. However, orthotic interventions act as external devices at the interface between the foot and the ground, which passively induce changes in the foot rollover, and in the plantar loads, and are only effective when worn.[8] Foot- and mobility-related exercises have the aim and potential benefit of changing the foot itself. The biomechanical effect might be achieved via promoting changes in the absorption and transmission of loads, following the recovery of muscle function and joint mobility.[11,95] Even though no evidence was found for changes in peak plantar pressure following these exercises, changes in other aspects of plantar pressure distribution and reduction were found, such as in time to peak pressure, centre of pressure trajectory, or pressure-time integral.[11,76] We did not discuss these in our systematic review, because these are not proven risk factors for ulceration. Yet these changes may indicate improvements in, for example, foot rollover, which in the longer term might improve patient outcomes in either level of daily physical activity or pressure patterns.[11,95] A deeper understanding of changes in plantar pressure following foot- and mobility-related exercises that goes beyond investigating peak plantar pressure, as well as its potential associations with ulcer prevention or treatment of risk factors for ulceration, is still needed.

For limited joint mobility, the changes in joint range of motion were often small (2-5°), and mostly seen in the ankle joint. While these changes were statistically significant, it is unclear if these changes are clinically meaningful. Limited joint mobility is only a proven risk factor for ulceration when present in the subtalar and first metatarsophalangeal joints,[7,96,97] with small differences (2-4°) between patients who ulcerated and those who did not. While there is debate about the reliability and validity of limited joint mobility measurements,[98-100] especially when changes in range of motion are small, outcome assessment was blinded for group allocation and done by one assessor only in most studies, so any error margins in assessment can be expected to be similar between intervention and control groups. Finally, a change of 3° in a rather stiff joint could mean an important improvement for patients that do not show adequate physiological motion in their daily living activities. We conclude that foot- and mobility-related exercises improve limited joint mobility. We recommend that future studies always include assessment of subtalar and metatarsophalangeal joint mobility and that these studies minimize potential errors in joint mobility assessment and quantify the findings and the error margins in joint mobility assessment for statistical and clinical significance.

The interventions included in this category varied greatly between studies. We decided to take a broad approach to foot- and mobility-related exercises, including any exercise that aims to affect the foot and ankle. This also included gait retraining, as this does involve exercising mobility of the lower extremity. However, with only few studies per type of exercise, we could not draw specific conclusions. Furthermore, as physical therapy interventions are often tailored to groups of patients, drawing specific conclusions about specific interventions was not feasible within the current systematic review. More research for all interventions included in this category is needed, to better understand if specific foot- and mobility-related exercises may lead to better outcomes than others.

Furthermore, additional benefits of foot- and mobility-related exercises, such as on glucose control (eg, Otterman, et al[101]), were not considered in this systematic review. With the positive findings on some outcomes, and the potential additional benefits on general health-related parameters and quality of life following exercise, we expect foot- and mobility-related exercises to become even more important in this field in the near future, and new trials are already underway (eg, Monteiro et al[102]).

6.5 | Study strengths and limitations

We included six interventions targeting eight specific modifiable risk factors for ulceration. We were limited by not having a predefined core outcome set and had to select outcomes based on input from the authors and external experts. While most of these outcomes have been shown to be a risk factor,[4,7] we also decided to include patient's and health care professionals knowledge and foot strength and function. Even though these are not proven risk factors, based on expert opinion from the authors and the external experts involved, we think these are modifiable outcomes that might be useful targets for ulcer prevention strategies. We did not include foot deformity as an outcome, even though it is a risk factor for ulceration.[4,7] With surgery, foot structure can be changed, and deformity could therefore be seen as a modifiable risk factor. Because surgery also brings risks that need to be balanced with the rewards, we decided that surgery is only relevant when directly aiming for ulcer healing and prevention but not when primarily aiming to reduce a modifiable risk factor.

As also described for our other systematic review,[8] it could be seen as a limitation that we operated in four different twosomes in our assessment of the literature. This means that no single author has assessed all records identified in our search. We did not formally test interassessor variability, and it was therefore not possible to quantify potential differences. However, each record was screened by two authors independently, and if one of those considered it for inclusion, it was included in the next stage. All disagreements in subsequent stages were discussed in person by the two assessors, and they reached consensus. Further, a working group meeting was held to discuss potential differences in assessment before choices were finalized. Finally, one assessor (JvN) had access to all assessments and did informal consistency checks that did not result in different assessment of excluded papers. We therefore think that this division of tasks did not affect inclusion of publications. Rather than a limitation, we argue that this approach was a strength, resulting in a better division of the work over the assessors, avoiding authors having to assess publications they (co-)authored, and ensuring that all authors have contributed to all stages of the systematic review. Taken together, this resulted in a systematic review with significant input from all authors, making use of their multidisciplinary backgrounds.

7 | CONCLUSIONS

We generally found low quality of evidence for the effectiveness of interventions targeting modifiable risk factors for ulceration in at-risk patients with diabetes. We conclude that structured education may improve behaviour of both patients and health care professionals, that callus removal and therapeutic footwear can be effective in reducing mechanical pressure, and that foot- and mobility-related exercises may improve neuropathy symptoms and foot and ankle joint range of motion. However, with frequently inconsistent or limited results per intervention and outcome combination, more high-quality controlled studies targeting modifiable risk factors for foot ulceration are needed to better inform the health care community on effective interventions to improve modifiable risk factors of ulceration in persons with diabetes who are at risk of developing a foot ulcer. The applied value of the findings of this systematic review for clinical practice are to be found in the IWGDF Guideline on Prevention,[13] for which this document formed the basis.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

JvN designed the search strings, performed the literature search, assessed the literature, extracted data, and drew conclusions within category 2, checked and completed the evidence and risk of bias tables, and wrote the manuscript. IS assessed the literature, extracted data, and drew conclusions within category 3 and category 4, and critically reviewed the manuscript. LL assessed the literature, extracted data, and drew conclusions within category 2, and critically reviewed the manuscript. MMS assessed the literature, extracted data, and drew conclusions within category 1, and critically reviewed the manuscript. AnneR assessed the literature, extracted data, and drew conclusions within category 3, and critically reviewed the manuscript. AnitaR assessed the literature, extracted data, and drew conclusions within category 1 and category 4, and critically reviewed and edited the manuscript. SB designed the search strings, assessed the literature, extracted data, and drew conclusions within category 3 and co-authored the manuscript. JvN acted as the secretary of the working group, SB as the chair of the working group. JvN and SB take full responsibility for the content of the publication.

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SUPPORTING INFORMATION

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

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