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SUPPLEMENT ARTICLE

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Prevention of foot ulcers in the at-risk patient with diabetes: a systematic review

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Abstract

Prevention of foot ulcers in patients with diabetes is important to help reduce the substantial burden on both patient and health resources. A comprehensive analysis of reported interventions is needed to better inform healthcare professionals about effective prevention. The aim of this systematic review is to investigate the effectiveness of interventions to help prevent both first and recurrent foot ulcers in persons with diabetes who are at risk for this complication. We searched the available medical scientific literature in PubMed, EMBASE, CINAHL, and the Cochrane databases for original research studies on preventative interventions. We screened trial registries for additional studies not found in our search and unpublished trials. Two independent reviewers assessed data from controlled studies for methodological quality, and extracted and presented this in evidence and risk of bias tables. From the 13,490 records screened, 35 controlled studies and 46 non-controlled studies were included. Few controlled studies, which were of generally low to moderate quality, were identified on the prevention of a first foot ulcer. For the prevention of recurrent plantar foot ulcers, there is benefit for the use of daily foot skin temperature measurements, and for therapeutic footwear with demonstrated plantar pressure relief, provided it is consistently worn by the patient. For prevention of ulcer recurrence, there is some evidence for providing integrated foot care, and no evidence for a single session of education.Surgical interventions have been shown effective in selected patients, but the evidence base is small. Foot-related exercises do not appear to prevent a first

Abbreviations: IWGDF, International Working Group on the Diabetic Foot; LOPS, loss of protective sensation; PAD, peripheral artery disease; PICOs, population, intervention, control, outcomes; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, randomized controlled trial; SIGN, Scottish Intercollegiate Guidelines Network.

foot ulcer. A small increase in the level of weight-bearing daily activities does not seem to increase the risk for foot ulceration. 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. The evidence is weak for the use of other, sometimes widely applied, interventions, and is practically non-existent for the prevention of a first foot ulcer and non-plantar foot ulcer.

KEYWORDS

diabetes mellitus, diabetic foot, foot ulcer, home monitoring, podiatry, prevention, self-management, shoes, surgery, systematic review

1 | INTRODUCTION

Foot ulcers are a major complication of diabetes mellitus, with high morbidity, mortality, and resource utilization.[1-3] Yearly incidence is estimated to be around 2%, and lifetime incidence lies between 19% and 34%.[4] Treatment of these foot ulcers is challenging because of their multifactorial aetiology, and it 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 of paramount importance 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), or 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. Various classification and stratification systems based on these risk factors show similar diagnostic/prognostic results (such as sensitivity, specificity, predictive values, and likelihood ratios) in predicting ulceration.[7] Despite the popularity and common use of these systems, the evidence base for their use is limited, with little validation of their predictive ability.[7]

There are numerous interventions to prevent foot ulcers that are used in routine clinical practice and that have been scientifically evaluated. The effectiveness of some of these interventions has been systematically reviewed, that is, on complex interventions,[8] patient education,[9] interventions studied in randomized controlled trials (RCTs),[10] population-based screening,[11] podiatry,[12] therapeutic footwear,[13] footwear and offloading interventions,[14] insoles,[15] flexor tenotomy,[16] and cost-effectiveness.[17] However, each of these reviews has used different inclusion criteria for their study selection, different patient populations, and a variety of outcomes, which limit comparisons. Further, foot- and mobility-related exercises to improve foot, ankle, and lower-extremity function characteristics have not been included in any review, despite their increased clinical use (eg, Sartor et al,[18] Melai et al,[19] and Mueller et al[20]) and despite the importance of weight-bearing activity for general health.[21] Finally, none of these reviews conducted a comprehensive analysis of all reported preventative interventions. Such an analysis is needed to properly inform caregivers about effective preventative treatment.

The aim of this systematic review is to investigate the effectiveness of interventions to prevent first and recurrent foot ulcers in persons with diabetes who are at risk for ulceration and do not have a current foot ulcer. This systematic review is an update of our review published in 2016.[22] This systematic review forms the basis for developing the IWGDF guideline on prevention of foot ulcers in at-risk patients with diabetes.[23]

2 | METHODS

The systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[24] and was in line with the consensus and checklist on updating systematic reviews.[25] The systematic review was prospectively registered in the PROSPERO database for systematic reviews in 2014, and this update was prospectively registered under the same number (CRD42014012964).

As a start, the population of interest (P), interventions (I), and outcomes (O) were defined, and clinical questions (PICOs) were formulated accordingly. These definitions and PICOs were reviewed for their clinical relevance by the IWGDF Editorial Board and 14 external experts worldwide, from various geographical regions. The final definitions and PICOs are integrated within this article.

2.1 | Population

The population of interest for this systematic review was people at risk of foot ulceration, defined according to the 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 a LOPS in the feet, ie, the inability to perceive light pressure or vibration, eg, as applied with a 10-g Semmes-Weinstein monofilament, tuning fork, or a biothesiometer. 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.

2.2 | Interventions

We included eight interventions with the goal of preventing a first-ever or recurrent foot ulcer:

1. Foot self-care: consisting of, but not limited to footwear inspection, washing of feet, careful drying between the toes, proper nail cutting, using emollients to lubricate skin, foot inspection, avoiding chemical agents or plasters to remove callus, not walking barefoot or with only socks or in shoes with holes, not wearing tight socks, and avoiding foot exposure to excessive cold or heat.
2. Structured education about foot 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, computer software, quizzes, or pictorial education via animated drawing or descriptive images.
3. Foot self-management: interventions consisting of, but not limited to home monitoring systems, lifestyle interventions, telemedicine, technological applications, and peer support programmes.
4. Treatment of risk factors or pre-ulcerative signs on the foot: for example, removing callus and treating haemorrhagic callus, protecting blisters and draining when necessary, or treating dry skin fissures and cracks not extending into the dermis.
5. Orthotic interventions: including therapeutic footwear (eg, shoes, insoles and orthoses) and walking aids (eg, crutches or stick). We defined this as any footwear or insole designed with the intention of offloading pressure from a foot site, 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. Surgical interventions: eg, Achilles tendon lengthening, tendon flexor tenotomy, single or pan-metatarsal head resection, metatarsophalangeal joint arthroplasty, or nerve decompression.
7. Foot-related exercises: any physical exercise specifically targeting any part of the lower extremity with the aim of changing foot function parameters (eg, strength or mobility).
8. Integrated foot care: care given by one or multiple collaborating professionals treating patients on multiple occasions, possibly at multiple locations, with multiple interventions, also including referrals between different levels of health care.

2.3 | Outcomes

Critically important outcomes were first-ever diabetic foot ulcer and recurrent diabetic foot ulcer. We defined a diabetic foot ulcer as a "full thickness lesion of the skin distal to the malleoli in a person with diabetes mellitus."[5] We defined "first-ever ulcer" as the first-ever recorded diabetic foot ulcer in a patient and "Recurrent ulcer" as a new ulcer in a patient with a previous diabetic foot ulcer, irrespective of its location and time. We have reported these separately, because patients with a previous ulcer are at higher risk than are those without,[6] thus requiring more preventative foot care. If a study included both patients with and without a previous ulcer but did not present data separately for these patients, the primary outcome was classified based on the majority of included patients. If a study did not specify ulcer history, it was included as "first-ever/recurrent ulcer."

The following outcomes were considered important but not critical: lower-extremity amputation, ulcer severity (based on depth, ischemia or infection), ulcer-free survival days, health-related quality of life, and financial costs. While lower-extremity amputations are important, they are not the primary aim of a preventative intervention, as that will be focused on ulcer prevention. No ulcer will generally mean no amputation. Moreover, when an ulcer develops, the need for and decision to amputate is greatly affected by the care provided for the ulcer.[5] We therefore include this outcome as "important, but not critical."

2.4 | Inclusion and exclusion criteria

We included original studies that reported on the population of interest, at least one of the predefined interventions, and a critically important outcome. We excluded studies on healthy subjects, on persons with other diseases but no diabetes, or on persons with diabetes who were not at risk for foot ulceration. We only included studies enrolling persons with an active ulcer if they reported outcomes on ulcer recurrence after healing of the active ulcer. We excluded studies reporting on interventions with outcomes indirectly related to ulcer prevention, but not reporting any of the critically important outcomes relevant to this review, eg, studies with results on foot care behaviour, knowledge and awareness, quality of life, pre-ulcerative lesions, or plantar pressure, as these were included in a separate systematic review (Prospero registry: CRD42018105073). We included systematic reviews and meta-analyses, 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 but 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 24 July 2018 and covered publications in all languages. See Appendix S1 for a detailed

description of the search strings. 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.

To further assess for possible publication bias or selective reporting of results, the WHO-ICTRP trial registry (http://apps.who.int/trialsearch/default.aspx) search was updated, limited from the previous search date (30 July 2014) to 25 July 2018. The Clinicaltrials.gov registry was also searched separately (https://clinicaltrials.gov), limited from 2014 to 25 July 2018 (Appendix S1). Two reviewers independently assessed identified trials for eligibility on the basis of three criteria: patient group, outcomes, and intervention. Reviewers obtained status of eligible trials ("completed," "ongoing," or "not yet started") from the databases. Cohen kappa was calculated for agreement. Reviewers solved disagreement concerning eligibility by discussion until consensus was reached. Any relevant publication related to a completed trial was searched for in the same databases as for the literature search. If no publications were identified, the principal investigator of the trial was contacted once for more information.

2.6 | Eligibility assessment

Per intervention, teams of two members of the working group 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 for eligibility assessment.[26] Cohen kappa was calculated for agreement between reviewers. 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 after 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 authors once for more information, to assess for any possible publication bias or selective reporting of results.

2.7 | Assessment of included publications

We used the Scottish Intercollegiate Guidelines Network (SIGN) algorithm for classifying study design for questions of effectiveness (http://www.sign.ac.uk/pdf/studydesign.pdf). The same two reviewers per intervention 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 21-item score for reporting standards of studies and papers on the prevention and management of foot ulcers in diabetes.[27] 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 was determined for each study as very low when scoring ≥8/10, low when scoring 6-7/10, 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). Level 1 refers to systematic reviews or RCTs, and level 2 refers to case-control, cohort, controlled before-and-after designs, or interrupted time series. Data were extracted from each included publication with a controlled study design and summarized in the evidence tables. This included patient 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 this for content and presentation. All members of the working group thoroughly discussed the evidence tables. To prevent any conflict of interest, reviewers did not participate in the assessment and data extraction of publications of which they were a co-author.

2.8 | Evidence statements

Finally, the two reviewers per intervention drew conclusions based on the strength of the available evidence, formulated as evidence statements and accompanying assessment of the quality of the evidence (QoE), according to GRADE.[28] The authors rated the QoE for each formulated evidence statement as "high," "moderate" or "low." 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."[28] 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.[28] All members of the working group discussed these evidence statements until consensus was reached.

3 | RESULTS

In total, 91 publications were included (see for details the PRISMA flowchart in Figure 1). We will describe the results for each intervention with the concluding evidence statements (Table 1). Risk of bias assessment scores of controlled studies can be found in Table 2. All results per included controlled study are described in the evidence table (Appendix S2).

3.1 | Foot self-care

PICO: In people with diabetes at risk for foot ulceration, can foot self-care, compared with no self-care, help prevent a first-ever or recurrent diabetic foot ulcer?

Summary of the literature: We found two noncontrolled studies.[29,30] In a noncontrolled study of 318 neuropathic patients, who underwent four 90- to 120-minute foot educational sessions held during 1 week and

were followed up for at least 3 years, those adherent to the foot care habits taught in the educational session presented with a significantly lower percentage of ulceration: 3.1% vs 31.6%; $P < .001$.[29] Another non-controlled study included 3245 participants with diabetic neuropathy who were educated regarding diabetic foot disease and its complications. At 18-month follow-up, they found a combined ulcer or foot infection (with or without ulceration) incidence of 5.8%; those adherent to the advice for at least 5 days a week presented with a lower incidence than did those who did not (5% vs 26%; $P < .0001$; Viswanathan et al[30]).

Evidence statement: In people with diabetes at risk of foot ulceration, adherence to foot self-care might reduce the risk of developing a foot ulcer.

Quality of the evidence: Low. Based only on noncontrolled studies.

3.2 | Structured education about foot self-care

PICO: In people with diabetes at risk for foot ulceration, can providing structured education about foot specific self-care, compared with not providing it, help prevent a first-ever or recurrent diabetic foot ulcer?

Summary of the literature: We found two systematic reviews with meta-analyses,[9,31] including six RCTs of which three met our inclusion criteria[32-34] and three did not,[35-37] as well as one additional RCT.[38] While some RCTs in these meta-analyses included participants without neuropathy, thereby not meeting our inclusion criteria of "only at-risk patients," we decided to include a description of both meta-analyses, as three of the six included RCTs did meet our inclusion criteria. As neither meta-analysis differentiated between first-ever and recurrent foot ulcer, we combined these outcomes.

Adiewere and colleagues[31] performed a systematic review with meta-analyses with low risk of bias, including six RCTs of which five were with high risk of bias[32,34-37] and one with low risk of bias.[33] In a combined random effect model comparing education about foot self-care with usual care, meta-analyses over a total of 1349 participants (680 intervention and 669 control) resulted in a risk ratio (RR) of 0.52 (95% CI, 0.23-1.15; $P = .11$; I^2: 90%) for ulcer prevention. A sub-analysis on four RCTs[33-35,37] for intensive vs brief education (of which two met our inclusion criteria[33,34]) resulted in an RR of 0.37 (95% CI, 0.14-1.01; $P = .05$; I^2: 91%) for ulcer prevention. Based on two RCTs,[33,35] an RR of 0.57 (95% CI, 0.20-1.63; $P = .29$; I^2: 69%) for amputation prevention was found. Dorresteijn and colleagues performed a systematic review with meta-analyses,[9] but since the four

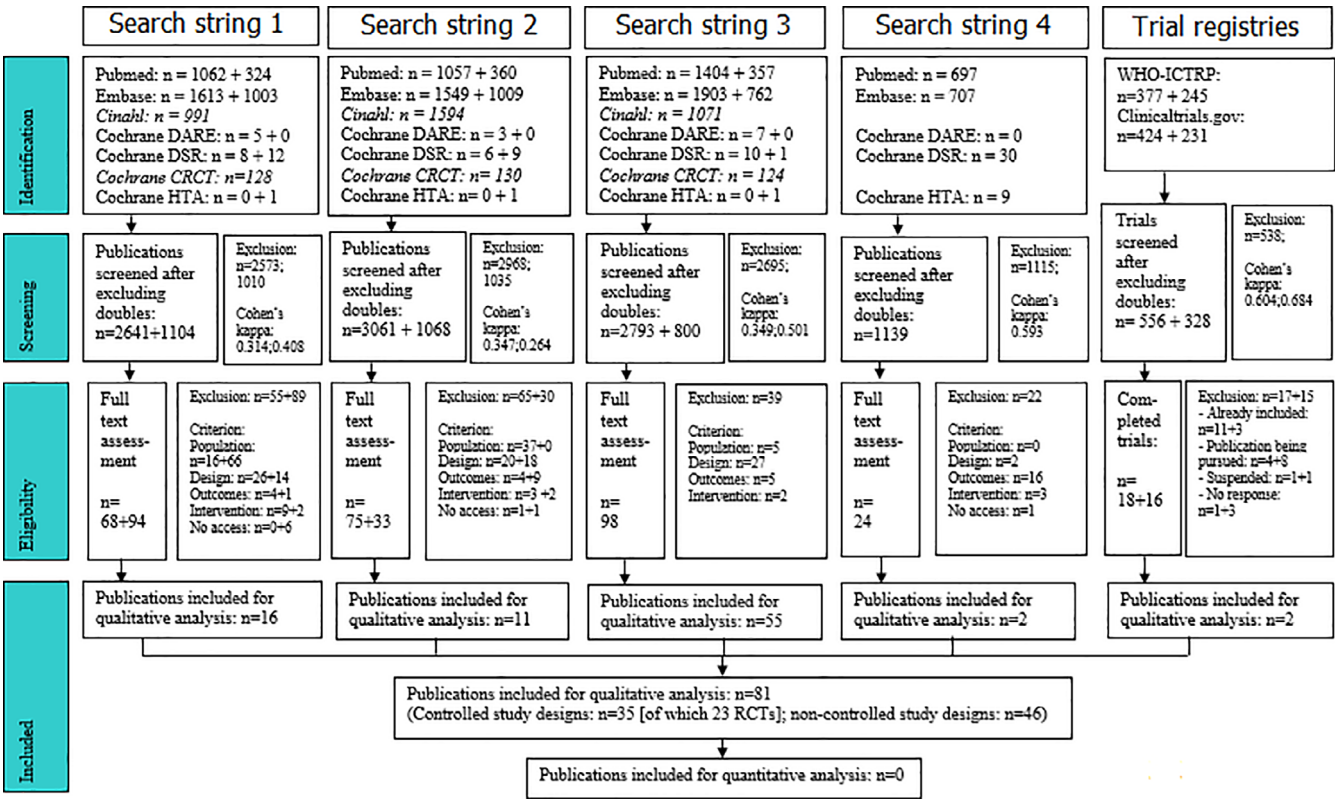


FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram. Note: Numbers are given for the 2014 and 2018 literature searches separately, for search strings 1, 2, and 3, and the trial registries. Search string 4 was only done in 2018. Search string 1 included interventions foot self-care, education, and self-management; search string 2 included treatment of risk factors or pre-ulcerative signs on the foot and integrated foot care; search string included orthotic and surgical interventions; search string 4 included foot-related exercises. Cochrane CRCT and Cinahl were not searched in 2018. CRCT, Central Register of Controlled Trials; DARE, Database of Abstracts of Reviews of Effects; DSR, Database of Systematic Reviews; HTA, Health Technology Assessment; WHO-ICTRP, World Health Organization International Clinical Trials Registry Platform

TABLE 1 Evidence statements per intervention category for the prevention of a first-ever or recurrent diabetic foot ulcer

Intervention	Evidence Statement	QoE	References
Foot self-care	In people with diabetes at risk of foot ulceration, adherence to foot self-care might reduce the risk of developing a foot ulcer.	Low	Viswanathan et al 2005[30]; Calle-Pascual et al 2001[29]
Structured education about foot self-care	In people with diabetes at risk for foot ulceration, there is insufficient robust evidence that limited structured education alone is effective in achieving clinically relevant reductions in foot ulcer risk.	Low	Adiewere et al 2018[31]; Dorresteijn et al 2014 [9]; Gershater et al 2011[32]; Lincoln et al 2008[33]; Monami et al 2015[34]; Liang et al 2012[35]
Foot self-management	In people with diabetes at risk for foot ulceration, applying daily antifungal nail lacquer as a way to increase frequency of foot self-inspection does not seem to help prevent a recurrent diabetic foot ulcer.	Low	Armstrong et al 2005[40]
	In people with diabetes at risk for foot ulceration, monitoring foot skin temperature at home, combined with patients contacting a research nurse and dosing their activity when abnormal left to right temperature differences were measured, can help prevent a recurrent plantar diabetic foot ulcer.	Moderate	Armstrong et al 2007[43]; Lavery et al 2004[41]; Lavery et al 2007[42]; Skafjeld et al 2015[44]
Treatment of risk factors or pre-ulcerative signs on the foot	We did not find any published evidence.		
Orthotic interventions	In people with diabetes with moderately increased risk for foot ulceration (IWGDF risk 2), therapeutic footwear, including shoes, insoles or orthoses, may reduce the risk of a first-ever foot ulcer.	Low	Rizzo et al 2012[47]; Lavery et al 2012[46]; Scire et al 2009[45]
	In people with diabetes at high risk for foot ulceration (IWGDF risk 3), therapeutic footwear, including custom-made shoes or insoles with a demonstrated plantar pressure–reducing effect on the plantar surface of the foot during walking, and that the patient actually wears, reduces the risk of a recurrent plantar diabetic foot ulcer.	Moderate	Bus et al 2013[49]; Ulbrecht et al 2014[48]; Uccioli et al 1995[51]; Reiber et al 2002[50]; Viswanathan et al 2004[52]; Busch et al 2003[53]; and Reike et al 1997[54]
Surgical interventions	In selected patients with diabetes and a nonhealing plantar forefoot ulcer, Achilles tendon lengthening, single or pan-metatarsal head resection, and metatarsophalangeal joint arthroplasty may reduce the risk of a recurrent plantar foot ulcer after healing of their current ulcer, when compared with nonsurgical treatment.	Low	Mueller et al 2003[67]; Piaggesi et al 1998[68]; Armstrong et al 2003[72], 2005[71], 2012[70]; Giurini et al 1993[86]; Hamilton et al 2005[88]; Petrov et al 1996[87]; Molines-Barroso et al 2013[89]; Griffiths et al 1990[85]
	In selected patients with diabetes and a nonhealing plantar foot ulcer, osteotomy may reduce the risk of a recurrent plantar foot ulcer after healing of their current ulcer, but it is not clear in comparison with what form of standard care.	Low	Lin et al., 2000[84]; Downs et al 1982[83]
	In selected patients with diabetes and a nonhealing toe ulcer, digital flexor tendon tenotomy may reduce the risk of a recurrent toe ulcer after healing of their current ulcer, when compared with nonsurgical treatment.	Low	Tamir et al 2014[91]; Rasmussen et al 2013[93]; van Netten et al, 2013[94]; Kearney et al 2010[95]; Schepers et al 2010[96]; Tamir et al 2008[92]; Laborde et al 2007[97];
	In patients with diabetes at high risk for ulceration (IWGDF risk 3), and with abundant	Low	Rasmussen et al 2013[93]; Van Netten et al, 2013[94]; Tamir et al 2008[92]

(Continues)

TABLE 1 (Continued)

Intervention	Evidence Statement	QoE	References
	callus on the tip of their toe, a hammertoe or with thickened nails, flexor tenotomy may reduce the risk of developing an ulcer.		
	In people with diabetes at risk of foot ulceration, there is no convincing evidence to support an ulcer prevention effect of nerve decompression surgery over good standard of care.	Low	Aszmann et al, 2004[74]; Nickerson and Rader, 2014[75]; Nickerson, 2010[100]; Dellon et al, 2012[101]; Nickerson and Rader, 2013[102]
Foot-related exercises	In people with low or high risk for foot ulceration (IWGDF risk 1 or 3), foot-related exercises do not appear to help prevent a diabetic foot ulcer.	Low	LeMaster et al, 2010[103]; Mueller et al, 2013[20]
	In people with low or high risk for foot ulceration (IWGDF risk 1 or 3), a small increase in the level of weight-bearing daily activities (1000 steps/d, 20% increase) does not seem to increase the risk for first-ever or recurrent diabetic foot ulcer.	Low	LeMaster et al, 2010[103]; Mueller et al, 2013[20]
Integrated foot care	In people with diabetes at low or moderate risk for foot ulceration (IWGDF risk 1 or 2), integrated foot care does not seem to reduce the risk of a first foot ulcer, although it may prove beneficial in specific populations or in reduction of more complicated ulcers.	Low	Van Putten et al, unpublished[104]; Cisneros et al 2010[105]; Hamonet et al 2010[107]; Calle-Pascual et al 2002[108]
	In people with diabetes at high risk for foot ulceration (IWGDF risk 3), integrated foot care may reduce the risk of a recurrent foot ulcer.	Low	Plank et al 2003[106]; Dargis et al 1999[39]; Jimenez et al 2018[109]; Fujiwara et al 2011[110]; Hamonet et al 2010[107]; Armstrong and Harkless 1998[111]; Marcinia et al 1998[112]; Abbas et al 2011[113]

Abbreviations: IWGDF, International Working Group on the Diabetic Foot; QoE, Quality of the Evidence determined following GRADE methodology (see Section 2 for more details).

included RCTs were also part of the six RCTs included in the review by Adiewere and colleagues, we excluded this article from further assessment. They did include one additional study, but it investigated education as part of integrated foot care and is included in our review under that specific intervention.[39]

Three RCTs included in both meta-analyses did meet our inclusion criteria. In an RCT with high risk of bias, Gershater and colleagues found in 131 patients no reduction in ulcer recurrence after 6 months of one participant-driven 60-minute patient education group session in addition to standard care, compared with standard care alone: 48% vs 38%; $P > 0.05$.[32] Lincoln and colleagues, in an RCT with low risk of bias, found in 172 patients that in addition to standard care, a single 1-hour education session, followed by a single phone call 4 weeks later, did not significantly reduce ulcer recurrence at 12 months than did standard care alone: 41.4% vs 41.2%.[33] Monami and colleagues prematurely terminated an RCT with high risk of bias after inclusion of 121 patients at high risk of ulceration because an unplanned interim analysis found six ulcers during the 6-month follow-up in the control group and none in the intervention group (10% vs 0%; $P = .012$).[34] The educational intervention consisted of a 2-hour programme for five to seven patients, including face-to-face lessons and interactive sessions with preventative self-care exercises.

We identified one additional RCT with high risk of bias conducted in a Chinese minority group by Liang and colleagues, in 59 participants without a previous ulcer.[38] They found a significantly lower percentage of recurrent ulcers after 2 years in those provided with a foot care kit and education to patients and caregivers on how to use it, in addition to standard care provided by an endocrinologist and diabetes nurse, compared with standard care alone (ie, 2 h of diabetes education): 0% vs 24.1%; $P = .014$. While the study investigated an educational programme, giving the foot care kit to patients might have improved their adherence to foot self-care habits and reduced ulcer outcomes.

Evidence statement: In people with diabetes at risk for foot ulceration, there is insufficient robust evidence that limited structured education alone is effective in achieving clinically relevant reductions in foot ulcer risk.

Quality of the evidence: Low. Based on one systematic review with meta-analyses and four RCTs. There was no publication bias, but we downgraded the strength of the recommendation because of the

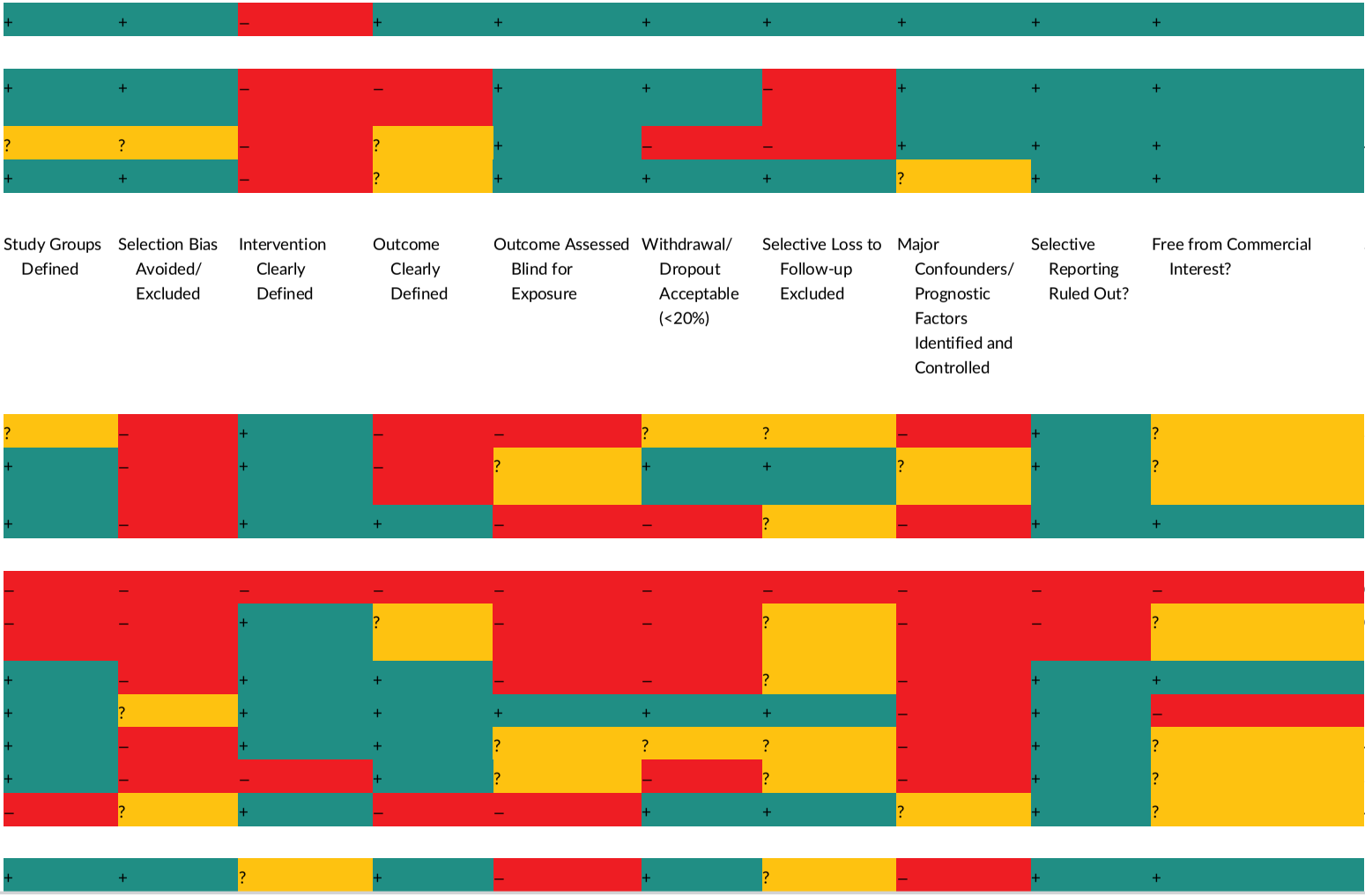
TABLE 2 Risk of bias of included publications

Systematic Reviews *Intervention*, reference	Cleary Defined Research Question	>1 Person Select Studies + Extract Data	Comprehensive Literature Search	States If and How Limit by Publication Type	Review Lists Included + Excluded Articles	Characteristic Included Studies Provided	Scientific Quality Assessed + Documented	Scientific Quality Assessed Appropriately	Appropriate Methods to Combine Study Results	Publication Bias Assessed	Conflicts of Interest	Score
Structured education												
Adiewere et al, 2018	+	?	+	+	–	+	+	+	+	–	+	8/11

RCTs *Intervention*, reference	Randomization	Independent Assignment	Patient/Care Provider Blinded	Outcome Assessor Blinded	Similarity Groups	Withdrawal/ Dropout Acceptable (<20%)	Intention to Treat	Patients Treated Equally Except for Intervention	Selective Reporting Ruled out	Free from Commercial Interest	Score
Structured education											
Gershater et al, 2011	+	+	–	–	+	–	–	+	+	+	6/10
Lincoln et al, 2008	+	+	–	?	+	+	+	+	+	+	8/10
Monami et al, 2015	+	+	–	?	+	+	–	?	+	+	6/10
Liang et al, 2012	?	?	–	?	+	+	–	+	+	+	5/10
Self-management											
Armstrong et al, 2005	+	+	–	?	+	?	+	+	+	?	6/10
Armstrong et al, 2007	+	+	–	–	+	–	–	+	+	+	7/10
Lavery et al, 2004	?	?	–	?	+	+	+	+	+	+	6/10
Lavery et al, 2007	+	+	–	?	+	+	–	+	+	+	8/10
Skafjeld et al, 2015	+	?	–	?	+	+	–	+	+	+	5/10
Orthotic interventions											
Scire et al, 2009	+	?	–	?	+	?	+	+	+	+	8/10
Lavery et al, 2012	?	?	–	–	+	–	+	+	+	+	5/10
Rizzo et al, 2012	+	?	–	–	+	–	–	+	+	+	5/10
Ulbrecht et al, 2014	+	+	–	+	+	–	+	+	+	+	8/10
Bus et al, 2013	+	+	–	+	+	+	+	+	+	+	9/10
Reiber et al, 2002	+	?	–	+	+	+	?	+	+	+	7/10
Uccioli et al, 1995	+	?	–	–	+	?	?	+	?	–	3/10
Surgical interventions											
Mueller et al, 2003	+	+	–	?	+	+	–	+	+	+	7/10
Piaggesi et al, 1998	+	?	–	–	+	+	+	+	+	–	6/10
Foot-related exercises											
LeMaster et al, 2010	+	+	–	+	+	+	+	+	+	+	9/10

(Continues)

TABLE 2 (Continued)



risk of bias in the included studies that make up the meta-analyses and inconsistency in findings.

3.3 | Foot self-management

PICO: In people with diabetes at risk for foot ulceration, can foot self-management, compared with no self-management, help prevent a first-ever or recurrent diabetic foot ulcer?

Summary of the literature: We identified five RCTs on this topic, all concerning recurrent foot ulcers.[40-44]

One RCT with low risk of bias by Armstrong and colleagues included 70 participants (34 intervention and 36 control). They instructed patients in the intervention group to apply on a daily basis topical antifungal nail lacquer as a way to increase frequency of foot self-inspection, but they found no benefit after 12 months compared with standard care (5.9% vs 5.6% ulcer incidence; $P = .9$).[40]

Evidence statement: In people with diabetes at risk for foot ulceration, applying daily antifungal nail lacquer as a way to increase frequency of foot self-inspection does not seem to help prevent a recurrent diabetic foot ulcer.

Quality of the evidence: Low, based on one RCT only.

Three RCTs with low risk of bias and one RCT with high risk of bias assessed the preventative effect of daily foot skin temperature measurements, combined with patients contacting a research nurse and dosing their activity when abnormal left to right temperature differences were measured.[41-44] Two low-risk-of-bias RCTs compared the intervention with standard care alone, in 225 and 85 patients. Both found significantly fewer ulcers in the intervention group: Lavery and colleagues after 6 months (2.4% vs 16.0%; $P < .05$)[41] and Armstrong and colleagues after 18 months (4.7% vs 12.2%; $P = .038$).[43] In the third low-risk-of-bias RCT, the same intervention was compared with either standard care plus instructions to perform daily foot inspection or with standard care alone.[42] In 173 patients, Lavery and colleagues showed significantly fewer recurrent ulcers after 15 months in the intervention group (8.5%) compared with each of the other conditions (30.4%, $P = .0061$, and 29.3%, $P = .008$, respectively). Additionally, patients who were less adherent to daily foot skin temperature measurements had substantially higher ulcer recurrence risk (OR 50.0; $P < .001$). Finally, in a high-risk-of-bias RCT with 41 patients, Skafjeld and colleagues found no effect on either ulcer recurrence or time to recurrence when comparing this intervention with standard care (39% vs 50% recurrence after 12 mo; $P = .532$).[44] However, post hoc power analysis showed the study was underpowered and that the mean value of some key characteristics was different between groups at baseline (such as the number of patients with multiple ulcer history).

Evidence statement: In people with diabetes at risk for foot ulceration, monitoring foot skin temperature at home, combined with patients contacting a research nurse and dosing their activity when abnormal left to right temperature differences were measured, can help prevent a recurrent plantar diabetic foot ulcer.

Quality of the evidence: Moderate. Based on four RCTs, with consistent results between the three RCTs at low risk of bias but downgraded because one additional RCT with high risk of bias gives inconsistent results. No publication bias.

3.4 | Treatment of risk factors or pre-ulcerative signs on the foot

PICO: In people with diabetes at risk for foot ulceration, can treating risk factors or pre-ulcerative signs on the foot, compared with not treating them, help prevent a first-ever or recurrent diabetic foot ulcer?

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

3.5 | Orthotic interventions

PICO: In people with diabetes at risk for foot ulceration, can one orthotic intervention, including therapeutic footwear (eg, shoes or insoles) and walking aids, compared with another or no form of orthotic intervention, help prevent a first-ever or recurrent diabetic foot ulcer?

Summary of the literature: We found seven RCTs,[45-51] three cohort studies,[52-54] and nine noncontrolled studies.[55-63] Given the relatively large number of controlled studies, we decided not to discuss the noncontrolled studies.

First-ever foot ulcer: In an RCT with low risk of bias in 167 patients, Scire and colleagues showed significantly fewer ulcers (1.1% vs 15.4%, $P < .001$) and hyperkeratotic lesions (41% vs 84%, $P = .002$) at 3 months, after the use of one of three types of custom-made digital silicon orthoses in addition to standard care, compared with standard care alone (ie, sharp debridement, a "soft" accommodating insole, and extra-depth footwear).[45]

An RCT with high risk of bias by Lavery and colleagues found that in 299 patients, of whom 26% had a prior ulcer, insoles designed to reduce shear stress and were worn in extra-depth therapeutic shoes did not significantly reduce ulcer incidence in 18 months, compared with standard insoles (2.0% vs 6.7%, $P = .08$).[46]

Another RCT with high risk of bias from Rizzo and colleagues[47] involved the initial randomization of 298 patients, 20% with previous foot ulceration, to intensive footwear therapy based on a prescription algorithm[64] or standard care consisting of footwear advice but no footwear prescription. Ulcer incidence at 1, 3, and 5 years after the intervention was significantly lower in the intensive footwear group (11.5%, 17.6%, and 23.5%, respectively) compared with standard care (38.6%, 61%, and 72%, respectively, $P < .0001$ at each time point), but there was a large attrition after 1 year. Some aspects of the methodology of this study are not clear (see evidence table).

Evidence statement: In people with diabetes with moderately increased risk for foot ulceration (IWGDF risk 2), therapeutic footwear, including shoes, insoles, or orthoses, may reduce the risk of a first-ever foot ulcer.

Quality of evidence: Low. We reduced the quality of evidence from high to low because we found a high risk of bias (5/10, 5/10, and 6/10) in the published papers, no publication bias, but large effect sizes (see evidence table), and large confidence intervals around the effect.

Recurrent plantar foot ulcer: An RCT with very low risk of bias by Ulbrecht and colleagues randomized 130 patients with metatarsal head ulcer history (intervention 66 and control 64).[48] Both the intervention and control groups received custom-made insoles based on a patient's foot shape and were worn in extra-depth diabetic shoes; the difference was that the insoles in the intervention group were further optimized based on barefoot plantar pressure measurements. While no difference was found between these groups after 15-month follow-up for a composite outcome of plantar pre-ulcerative lesions and recurrent foot ulcer (37.9% vs 45.3%; P = .13), the shape and pressure-based insoles were associated with a significantly lower rate of recurrent plantar foot ulcer than the shape-based insoles only (9.1% vs 25.0%, P = .007).

An RCT with very low risk of bias by Bus and colleagues randomized 171 patients with plantar foot ulcer history (intervention 85 and control 86). The intervention group received custom-made footwear with improved pressure-relieving properties guided by in-shoe pressure measurement, and the control group received custom-made footwear that did not undergo such improvement.[49] Overall, there was no significant difference in plantar foot ulcer recurrence after 18-month follow-up between the groups (38.8% vs 44.2%, P = .48), but a post hoc analysis of the 79 patients (intervention 35 and control 44) who wore their footwear for at least 80% of their measured activity showed that they had a significantly lower ulcer recurrence incidence with wearing pressure-improved footwear (25.7% vs 47.8%, P = .045).

An RCT with low risk of bias by Reiber and colleagues randomized 400 patients to therapeutic shoes with customized inserts, therapeutic shoes with prefabricated inserts, or the patient's own footwear.[50] They found no significant difference in proportion of persons with recurrent ulcer over a 2-year period among the three groups (15%, 14%, and 17%; no P value given). Despite having a low risk of bias, methodological aspects of this study that were not included in the Cochrane assessment forms have been debated, including the population (half did not have LOPS, and "ulcer history" in these patients could also include minor abrasions or nonplantar lesions), and the outcome (for an ulcer to be scored, it needed to be present for at least 30 days).[65,66]

An RCT with high risk of bias by Uccioli and colleagues in 69 patients found a significantly lower proportion of patients with a foot ulcer over a 1-year period in those who had worn therapeutic shoes compared with those who continued to use their own shoes (27.7% vs 58.3%, P = .009).[51]

A cohort study with high risk of bias by Viswanathan and colleagues found among 241 patients there were significantly fewer recurrent ulcers after 9 months in patients using therapeutic sandals compared with those using sandals with a hard leather board insole.[52] Another cohort study with high risk of bias by Busch and Chantelau found a 15% ulcer recurrence rate over 12 months in 62 patients who were beneficiaries of prescribed diabetic footwear compared with 60% in 30 patients who were not reimbursed and therefore wore their own footwear (P < .001).[53] Reike and colleagues, in a small cohort study with high risk of bias, found no benefit in ulcer recurrence at 2 years between patients who accepted a prescription of orthopaedic footwear and those who did not and wore their own shoes.[54] In all three cohort studies, we could not rule out selection bias, which may have been an important determinant of outcome.

Evidence statement: In people with diabetes at high risk for foot ulceration (IWGDF risk 3), therapeutic footwear, including custom-made shoes or insoles with a demonstrated plantar pressure–reducing effect on the plantar surface of the foot during walking, and that the patient actually wears, reduces the risk of a recurrent plantar diabetic foot ulcer.

Quality of evidence: Moderate. We reduced the quality of evidence for this evidence statement from high to moderate because we found an overall low risk of bias (9/10, 8/10, 3/10, and 7/10), no publication bias, and a large effect size, but the findings between the RCTs were inconsistent (CIs cross the 0-line), and there were large confidence intervals around the effect found (imprecision).

3.6 | Surgical interventions

PICO: In people with diabetes at risk for foot ulceration, can surgical interventions, in comparison with no surgery, help prevent a first-ever or recurrent diabetic foot ulcer?

Summary of the literature: We found two RCTs,[67,68] seven cohort studies,[69-75] and 27 noncontrolled studies.[76-102] We will describe the results per the specific surgical intervention.

Achilles tendon lengthening: An RCT with low risk of bias from Mueller and colleagues included 63 patients (intervention 30 and control 33). They found that patients who were treated with Achilles tendon lengthening, in addition to total contact casting to heal an active forefoot ulcer, had a significantly lower recurrence rate at 7-month follow-up than had those treated with total contact casting alone (15% vs 59%, P = .001).[67] This difference persisted at 2-year follow-up (38% vs 81%, P = .002).

One noncontrolled retrospective study found that 138 patients treated with Achilles tendon lengthening, compared with a historic cohort of 149 patients treated with wound closure surgery for ulcer healing, had, at a mean 3-year follow-up, significantly fewer recurrences (2% vs 25%, P < .001) but significantly more transfer lesions (12% vs 4%, P = .001).[76] Several other noncontrolled studies reported that there were fewer recurrent ulcers (0-20%) during 17-48-month follow-up after successful healing of a neuropathic ulcer with Achilles tendon lengthening.[77-82]

Single or pan-metatarsal head resection: An RCT with low risk of bias by Piaggesi and colleagues[68] included 41 patients with a diabetic foot ulcer (21 intervention and 20 control). They compared patients who were treated for ulcer healing with removal of bone segments underlying the lesion compared with conservative (nonsurgical) treatment. They found at 6-month follow-up significantly fewer recurrent

ulcers in the surgical group: 14% vs 41%, $P < .01$. In a retrospective cohort study with high risk of bias, Faglia and colleagues found in 207 patients no significant differences in ulcer recurrence rates after a mean 40.6-month follow-up between those patients treated with surgical bone removal of the toe (n = 110) vs metatarsal head resection or minor amputation of the toe or ray (n = 97): 15.5% vs 17.3%; $P = .851$.[69] A retrospective cohort study from Armstrong and colleagues, with low risk of bias, found among 92 patients (46 cases and 46 controls) that there were fewer recurrent ulcers at 1 year in those treated with pan-metatarsal head resection compared to those treated nonsurgically for their plantar forefoot ulcers (15.2% vs 39.1%, $P = .02$).[70] In addition, there were fewer foot infections in the surgical group (35.5% vs 64.5%, $P = .047$). Another retrospective cohort study from Armstrong and colleagues, with high risk of bias, found significantly lower recurrence rates at 6-month follow-up after healing in the 22 patients treated with single metatarsal head resection compared with the 18 who received conservative offloading (5% vs 28%, $P = .04$).[71] One prospective and four retrospective noncontrolled studies, including between 10 and 119 patients, on the effects of pan-metatarsal head resection reported recurrent ulcer rates between 0% and 41% after a mean 13.1 to 74 months of follow-up.[85-89]

Metatarsophalangeal joint arthroplasty: One retrospective cohort study by Armstrong and colleagues with high risk of bias in 41 patients (intervention 21 and control 20) found that for primary treatment of a plantar foot ulcer, those undergoing metatarsophalangeal joint arthroplasty of the great toe had significantly fewer recurrent ulcers at 6-month follow-up than those receiving total contact casting (5% vs 35%, $P = .02$).[72]

Two small noncontrolled studies of patients who underwent either inter-phalangeal joint arthroplasty or resection of the proximal phalanx of the great toe found no recurrent ulcers at either 26 months or 2 to 5 years of follow-up after primary healing.[83,84]

Evidence statement: In selected patients with diabetes and a nonhealing plantar forefoot ulcer, Achilles tendon lengthening, single or pan-metatarsal head resection, and metatarsophalangeal joint arthroplasty may reduce the risk of a recurrent plantar foot ulcer after healing of their current ulcer, when compared with nonsurgical treatment.

Quality of evidence: Low. Nearly all controlled studies on the topic are observational studies, and there are more noncontrolled than controlled studies. The effect size in reducing risk of recurrence is large for some surgical interventions, but the inconsistency between studies and confidence interval around the effect size are large (imprecision).

Osteotomy: A retrospective cohort study with high risk of bias by Vanlerberghe and colleagues included 76 patients (intervention 22 and control 54). They found that osteotomy plus arthrodesis, primarily undertaken to heal metatarsal head ulcers, resulted in a significantly lower rate of combined recurrence and amputation when compared with conservative treatment (7.5% vs 35.5%, $P = .0013$), although data on recurrent ulcers alone were not significantly different between groups (7.5% vs 18%, $P = .14$).[73] One noncontrolled study presented no recurrent ulcers during 13-month follow-up in 21 patients who underwent osteotomy for healing of forefoot ulcers.[90]

Evidence statement: In selected patients with diabetes and a nonhealing plantar foot ulcer, osteotomy may reduce the risk of a recurrent plantar foot ulcer after healing of their current ulcer, but it is not clear in comparison with what form of standard care.

Quality of evidence: Low. Based on one controlled study with high risk of bias and one noncontrolled study only.

Digital flexor tendon tenotomy: Seven retrospective case series of percutaneous digital flexor tendon tenotomies performed in patients to heal apex toe ulcers included a total 231 treated patients.[91-97] They found recurrence rates between 0% and 20% over a mean follow-up between 11 and 36 months. Three of the seven studies assessed effects of digital flexor tendon tenotomy of a toe that had no ulcer at the time of the procedure but an impending ulcer (ie, abundant callus on tip of the toe or thickened nails). They found in a total 58 treated patients (all IWGDF risk 3) no ulcer in a mean of 11 to 31 months of follow-up.[92-94]

Tendon transfer and fascia release: Two noncontrolled studies from the same research group, one on the effects of plantar fascia release in 60 patients with a forefoot ulcer and one on the effect of flexor hallucis longus tendon transfer in nine patients with a plantar heel ulcer, found no ulcer recurrence after 24-month follow-up.[98,99]

Evidence statement: In selected patients with diabetes and a nonhealing toe ulcer, digital flexor tendon tenotomy may reduce the risk of a recurrent toe ulcer after healing of their current ulcer, when compared with nonsurgical treatment.

Evidence statement: In patients with diabetes at high risk for ulceration (IWGDF risk 3), and with abundant callus on the tip of their toe, a hammertoe or with thickened nails, flexor tenotomy may reduce the risk of developing an ulcer.

Quality of evidence: Low. Based on noncontrolled studies only.

Nerve decompression: One retrospective cohort study by Aszmann and colleagues, with high risk of bias, found that among 50 patients with neuropathic pain without a previous ulcer, there was a significantly lower ulcer and amputation incidence over a mean of 4.6-year follow-up in the affected leg treated with decompression of the peroneal nerve than the contralateral (control) leg (0 vs 15 events [12 ulcers and 3 amputations]; $P < .001$).[74] A retrospective cohort study, with high risk of bias, by Nickerson and Rader, assessed 42 patients with painful neuropathy and failed pharmacologic treatment for effect of nerve decompression in the previously ulcerated foot; they found that over a mean of 35.8-month follow-up ulcer recurrence was significantly lower in the operated limb compared with the nonoperated limb (1.6% vs 7% per patient per year; $P = .048$).[75] One retrospective and two prospective noncontrolled studies presented low percentages of recurrent ulcers (2.6%-4.3% per patient year) after 1 to 5.5 years of follow-up with decompression of the peroneal and tibial nerves in diabetic patients with (symptomatic) peripheral neuropathy and a previous ulcer.[100-102]

Evidence statement: In people with diabetes at risk of foot ulceration, there is no convincing evidence to support an ulcer prevention effect of nerve decompression surgery over good standard of care.

Quality of evidence: Low. Observational studies only, with high risk of bias and lacking comparison with standard of care conservative treatment.

3.7 | Foot-related exercises

PICO: In people with diabetes at risk for foot ulceration, can foot-related exercises, compared with no foot-related exercises, help prevent a first-ever or recurrent diabetic foot ulcer?

PICO: In people with diabetes at risk for foot ulceration, can the level of weight-bearing daily activities be safely increased without increasing risk for a first-ever or recurrent diabetic foot ulcer?

Summary of the literature: We found two RCTs,[20,103] both with a mixed group of participants who were either at risk (IWGDF risk 1) or at high-risk (IWGDF risk 3) for ulceration. Neither study was powered to detect differences in ulcers between groups.

An RCT by LeMaster and colleagues,[103] with low risk of bias, included 79 participants with diabetes and neuropathy (IWGDF risk 1 [58%] or IWGDF risk 3 [42%]). The intervention group (n = 41) undertook foot-related exercises administered by a physical therapist for an initial 3 months (ie, leg strengthening and balance exercises), and a self-monitored walking programme, motivational calls (ie, 10-min call from a nurse) for the subsequent 9 months, diabetic foot care education, and regular foot care, while the control group (n = 38) received foot care education and foot care alone. There were no differences between groups in total ulcer incidence (n = 9 in both groups; 22% and 24% in intervention and control group, respectively) or ulcer duration (74 vs 51.5 d, respectively), or in the incidence rate of weight-bearing ulcers (0.02 vs 0.12 ulcers/person-year-at-risk, respectively) at 12-month follow-up. Total daily step count decreased in both groups between baseline and 12 months nonsignificantly in the intervention group (from 3335 to 3183 steps), while the reduction in the control group was significant (from 3.350 to 2.921; $P < .05$). Between baseline and 6 months, steps taken during 30-minute exercise bouts significantly increased in the intervention group (from 482 to 548 steps; $P < .05$) and decreased nonsignificantly in the control group (from 495 to 465 steps). The difference at 6 months between both groups was statistically significant ($P < .01$). At 12 months, however, the difference was no longer significant (510 vs 477 steps). In the 23 (29%) participants with an increase in steps (either total steps, or during 30-min exercise bouts), the median increase was 898 total daily steps.

An RCT by Mueller and colleagues,[20] with low risk of bias, included 29 participants (IWGDF risk 1 [86%] and IWGDF risk 3 [14%]). The weight-bearing intervention group (n = 15) participated in 12 weeks of foot-related exercises provided by a physical therapist (ie, stretching and strengthening foot and ankle exercises, and weight-bearing aerobic exercise—walking) and was compared with a non–weight-bearing group (n = 14) undergoing the same stretching and strengthening exercises but non–weight-bearing aerobic exercise (stationary bike). They also found no difference between groups in the incidence of ulceration (1 vs 3 ulcers in 1 vs 2 participants; 7% vs 14%, respectively) or formation of lesions (7 vs 6 in 7 vs 5 participants; 47% vs 36%) during the 12 weeks of the study. In comparing the weight-bearing group with the non–weight-bearing group, there was a statistically significant increase of 29 m for the 6-minute-walking test (95% CI, 6-51; $P = .014$) and 1178 steps for the daily number of steps (95% CI, 150-2205; $P = .026$) in the weight-bearing group.

Evidence statement: In people with low or high risk for foot ulceration (IWGDF risk 1 or 3), foot-related exercises do not appear to help prevent a diabetic foot ulcer.

Evidence statement: In people with low or high risk for foot ulceration (IWGDF risk 1 or 3), a small increase in the level of weight-bearing daily activities (1000 steps/day, 20% increase) does not seem to increase the risk for first-ever or recurrent diabetic foot ulcer.

Quality of evidence: Low. Based on two RCTs with very low risk of bias (9/10, 9/10); there was no publication bias or inconsistency of results across studies, but neither study was powered for the outcome of ulcer prevention.

3.8 | Integrated foot care

PICO: In people with diabetes at risk for foot ulceration, can providing integrated foot care, compared with not providing integrated foot care, help prevent a first-ever or recurrent diabetic foot ulcer?

Summary of the evidence: We found three RCTs,[104-106] one cohort study,[39] and seven noncontrolled studies.[107-113]

First-ever ulcer: An unpublished RCT with low risk of bias by Van Putten and colleagues enrolled 569 neuropathic patients without a foot ulcer in the previous 12 months.[104] They found that integrated foot care, consisting of podiatric treatment given at least twice a year in addition to standard care, did not significantly reduce ulcer incidence in 3 years over standard care alone (10% vs 11%; $P = .89$). However, the participants in the integrated foot care group had significantly fewer infected or deep ulcers (11% vs 37%; $P \leq 0.03$).

Cisneros and colleagues, in an RCT with high risk of bias in 53 patients, found after 24 months of integrated foot care a lower but not significantly reduced ulcer incidence compared with standard care (38.1% [8/30] vs 57.1% [8/23]; $P = .317$).[105]

In a noncontrolled study of 24 patients who visited a multidisciplinary foot clinic for preventative care, patients did not present with any ulcers in a 20-month retrospective analysis (3.46 consultations per patient), but an ulcer was found in 16.7% of patients in a 20-month prospective analysis (0.23 consultations per patient).[107] Another noncontrolled study of 308 patients who were followed up for a mean 4.6 years found a significantly lower ulcer incidence for those patients who were adherent to integrated foot care compared with those who were not adherent (0.2% vs 4.4% [$P < .01$] in a lower-risk category and 0.5% vs 4.3% [$P < .01$] in a higher-risk category of patients).[108]

Evidence statement: In people with diabetes at low or moderate risk for foot ulceration (IWGDF risk 1 or 2), integrated foot care does not seem to reduce the risk of a first foot ulcer, although it may prove beneficial in specific populations or in reduction of more complicated ulcers.

Quality of evidence: Low. Because the evidence statement is based on two RCTs, one with high risk and one with low risk of bias,

with inconsistent results, we downgraded the quality of evidence from high to low.

For a recurrent ulcer: In an RCT with low risk of bias, Plank and colleagues included 93 patients (intervention 47 and control 44).[106] They compared integrated foot care (4-weekly chiropody treatment visits free of charge in addition to standard care) with standard care alone. After 2 years, they found no significant difference in ulcer incidence between groups in the "per patient" analysis (38% vs 57%; $P = .09$), but the incidence of ulcers was significantly lower in the chiropody group in the "per foot" analysis (22% vs 38%; $P = .03$).

In a prospective cohort study with high risk of bias in 145 neuropathic patients (intervention 56 and control 89), Dargis and colleagues found that multidisciplinary foot care given at least once every 3 months resulted in significantly fewer ulcers than standard foot care after 2 years: 30.4% vs 58.4%; OR: 0.31, $P < .01$.[39]

In a noncontrolled study, a comparison was made of ulcer recurrence rates in a period before and after introduction of integrated foot care at one centre in Spain.[109] In the period 2008-2010, 77 out of 130 patients (59%) had ulcer recurrence, while in 2010-2014, this was 49 out of 150 (33%); the multivariate hazard ratio between these two periods of 0.60 was statistically significant ($P = .007$). In another noncontrolled study, 88 patients with varying risk grades received integrated nursing care consisting of foot care, treatment of preulcerative signs, and education.[110] Of the 26 patients with a previous ulcer (IWGDF risk 3), none of them had ulcer recurrence during 2-year follow-up. In a 20-month prospective noncontrolled study, higher adherence to multidisciplinary care was associated with a 2.5-fold reduced ulcer recurrence rate.[107] In another noncontrolled study, patients who were adherent to once every 1 to 2 months of preventative care in a multidisciplinary diabetes clinic for 3 years had a lower ulcer recurrence rate than had nonadherent patients (5.4% vs 81.8%, $P < .0001$).[111] A case series of patients who received integrated foot care by a trained diabetes nurse reported an 8% ulcer recurrence per year.[112] Finally, the implementation of the IWGDF "Step by Step" programme, aimed at ulcer prevention in lower income countries, demonstrated in one noncontrolled study a lower ulcer incidence in one centre when compared with preimplementation data.[113]

Evidence statement: In people with diabetes at high risk for foot ulceration (IWGDF risk 3), integrated foot care may reduce the risk of a recurrent foot ulcer.

Quality of evidence: Low. The evidence statement is based on one RCT and one cohort study, both with low risk of bias, and six noncontrolled studies. Although the results are relatively consistent, they are based on studies of small numbers of patients, and they showed only small effect sizes, so we downgraded the quality of evidence from high to low.

4 | DISCUSSION

In this systematic review, we updated our search of the literature for publications on interventions to prevent first and recurrent foot ulcers in persons with diabetes who are at risk for ulceration.[22] Overall, we included 35 controlled studies, including 23 RCTs, and described a further 46 noncontrolled studies. Of these publications, only three controlled and two noncontrolled studies were identified in the updated search. The evidence base to support some interventions is quite strong and based on several high-quality RCTs, whereas more high-quality controlled studies are required for other interventions.

4.1 | Foot self-care

Unlike the first version of this systematic review,[22] we now define "foot self-care" as a separate intervention category, different from foot self-management. Specifically, foot self-care constitutes a variety of activities designed to reduce the risk of foot complications associated with diabetes that a patient can perform at home, either alone or with the support of other non-professional carers. These aspects of foot self-care are mostly considered basic information provided to people with diabetes. However, evidence supporting the preventative effect of these interventions in preventing foot ulceration is limited. We found only two noncontrolled studies on this topic; these studies suggest that adherence to foot self-care might help prevent foot ulceration.[29,30] This lack of evidence might be the result of this care being considered basic or standard, and clinicians and researchers may therefore not see the need to investigate this. However, future studies are needed to further investigate the outcomes associated with adherence to foot self-care and to develop a better evidence base for supporting these foot self-care activities or not.

4.2 | Structured education about foot self-care

There is insufficient robust evidence that limited patient education alone is effective in achieving clinically relevant reductions in risk of a foot ulcer.[31-34,38] Structured education can have many forms, with different methods, at various intervals, of different lengths, and with different educators. Finding what type of structured education is most beneficial in foot ulcer prevention will require further investigations. Furthermore, many educational interventions focus primarily on improving foot self-care knowledge or adherence to the foot self-care.[9] This may be beneficial in itself for people with diabetic foot disease, but we did not fully consider this to be within the scope of ulcer prevention for the current review. More evidence from well-designed studies is needed on this topic. Rather than focusing solely on education, these studies should take a broader behavioural perspective and include different forms of structured education, account for adherence to changes in behaviour, and take patient preferences into account. An example of such an intervention has recently been published.[114]

4.3 | Foot self-management

Self-management is important in prevention as foot ulcers nearly always develop outside the clinical setting. We consider foot self-management

to differ from foot self-care by targeting prevention of diabetic foot ulceration through the additional use of materials such as via home monitoring systems or other technological applications. We found no support for the daily use of antifungal nail lacquer as a surrogate to help improve frequency of foot inspection and early recognition of foot problems to prevent foot ulcers.[40] In contrast, we found strong support for the use of home monitoring of foot skin temperature, to inform subsequent preventative actions taken when abnormal temperatures are recorded, so as to prevent a recurrent foot ulcer. This is based on the results of three high-quality RCTs from a single research group that were conducted in three different clinical settings.[41-43] Foot temperature monitoring provides instantaneous and clinically meaningful feedback on the risk of ulceration. Patient adherence to the daily measurement of foot temperature proved to be an important component in clinical outcome,[42] and therefore, this should be monitored in any future studies. An additional RCT on the outcomes of this intervention was recently published reporting no effect of the intervention, but it was underpowered.[44] The positive findings from the above-mentioned studies, all with low risk of bias, led us to an overall assessment that monitoring foot skin temperature at home can help prevent a recurrent plantar diabetic foot ulcer. The published positive findings do require confirmation in well-designed studies by other research groups in other regions of the world, in which cost-effectiveness and feasibility of implementation should be addressed, as this procedure is currently not implemented in routine clinical practice. Technological advancements in the monitoring of foot temperature that reduce the user burden, such as with automatic detection of impending problems[115] or thermal cameras for the smartphone,[116] may improve the usability of this approach.

4.4 | Treatment of risk factors or pre-ulcerative signs on the foot

It is widely considered standard clinical practice to treat risk factors or pre-ulcerative signs on the foot, such as removing callus or treating fissures. However, we found no evidence that such treatments prevent foot ulcers. Some evidence supports treatment of surrogate outcomes, such as callus removal to reduce plantar pressure.[117,118] However, all pre-ulcerative treatments are subject to clinical variations, such as in skills of practitioners, frequency of treatment, and duration of treatment. Thus, we need controlled trials on these interventions in relation to foot ulcer prevention to better understand the potential effects of such variations and to define optimal treatment of pre-ulcerative signs.

4.5 | Orthotic interventions

For this intervention, controlled studies on the prevention of a first ulcer have considered both orthoses and footwear, while all controlled studies on the prevention of a recurrent ulcer have considered therapeutic footwear.

For first-ulcer prevention, one RCT found that prescribing footwear according to a structured consensus-based algorithm resulted in fewer ulcers than not prescribing footwear.[47] While this may seem obvious, it is useful to have evidence to support this basic tenet of foot care. Further, one trial on custom-made orthoses showed a reduction of ulcer risk,[45] while a trial on shear reducing insoles did not find significant differences between the groups.[46] We therefore conclude that therapeutic footwear, including shoes, insoles, or orthoses, may reduce the risk of a first-ever foot ulcer in someone with a moderately increased risk for foot ulceration; however, further research in this population is urgently needed.

For recurrent ulceration, two high-quality RCTs found that directly measuring the plantar pressure on the plantar surface of the foot can help improve the design and pressure-reducing capacity of the provided footwear, and this resulted in reduced ulcer risks when patients wear their footwear.[48,49] This suggests some underlying principles that can guide footwear prescription, to move towards a more data-driven and scientific approach.[119,120] We therefore conclude that therapeutic footwear for ulcer prevention needs to have a demonstrated plantar pressure–reducing effect. Further, adherence to wearing the footwear is crucial.[49] However, achieving better adherence is a challenge. Observational studies suggest that a perceived benefit is associated with better adherence,[121,122] but a first attempt to improve adherence via this pathway, a pilot RCT using motivational interviewing, found only somewhat improved adherence, and only at the short-term.[123] More research on this topic is needed, to better understand how adherence to wearing therapeutic footwear can be improved. In these studies, adherence should be quantitatively monitored.[124,125]

4.6 | Surgical interventions

With only few exceptions, surgical interventions are primarily studied in the context of ulcer treatment. However, because surgery most often changes foot structure, it may have an enduring preventative effect after healing. From the limited number of controlled studies, Achilles tendon lengthening, single or pan-metatarsal head resection, and metatarsophalangeal joint arthroplasty appear to reduce ulcer recurrence risk in selected patients with nonhealing ulcers when compared with nonsurgical treatment.[67,68,70-72,83-89] Several other surgical offloading procedures, such as osteotomy and digital flexor tendon tenotomy, are promising for helping prevent ulcer recurrence.[73,90-99] Based on the results of a few case series, flexor tenotomy may even have value in preventing a first-ever foot ulcer in patients with abundant callus on the tip of their toes or thickened nails.[92-94] These outcomes require confirmation in well-designed studies.

As a separate group of surgical interventions, studies on nerve decompression have found low ulcer incidence rates over extended follow-up periods in patients both with or without a prior foot ulcer who are experiencing neuropathic pain.[74,75,100-102] However, risk of bias in these studies was high, and study design was not always appropriate, often lacking comparison with standard care. Efficacy has

not yet been assessed within an RCT design, and most of the studies performed have been done by the same research group. Therefore, there is no convincing evidence to support an ulcer prevention effect of nerve decompression over good standard of care.

We realize that studies on surgical interventions with the appropriate design are not always easy or ethical to perform, as surgery is sometimes a last-resort approach after failed conservative treatment, usually does not allow randomization of patients, and benefits should be considered with respect to the possible harms. For example, Achilles tendon lengthening can negatively influence locomotion and may, as other procedures do, increase risk of transfer ulcers.[67,126] Nevertheless, more controlled, high-quality studies, such as one ongoing trial,[127] are needed before we can make evidence-based statements about the safety and efficacy of surgical interventions to prevent ulcer recurrence.

4.7 | Foot-related exercises

Foot- and mobility-related exercises have not been studied as an intervention aiming for ulcer prevention. However, we found two RCTs investigating the effects of a combination of foot-related exercises and a walking programme that did report ulcer outcomes.[20,103] Both trials were not powered to detect a difference in this outcome nor to prove equivalence. Despite this shortcoming, the differences between both groups were very small (9 ulcers in both groups in one trial; 1 vs 3 ulcers in the other trial), while patients in the intervention arm increased their weight-bearing activity. We therefore conclude that while foot- and mobility-related exercises do not appear to help prevent foot ulcers, they can be considered safe to increase a patient's level of weight-bearing activity without increasing the risk for ulceration. Other studies on this topic primarily aimed to reduce risk factors for ulceration, such as plantar pressure reduction or redistribution, but did not report ulcer outcomes.[128-131] Considering the health advantages resulting from specific foot-related exercises,[128-131] or from general weight-bearing activity,[21] these interventions can be considered for this population. However, no definitive conclusions can yet be drawn because of the limited evidence available, and further research is strongly advised.

4.8 | Integrated foot care

In most studied integrated foot care programmes, the key responsible professional was a podiatrist or chiropodist, who worked alone or in a multidisciplinary setting.[39,104-113] Integrated foot care differed between studies but always included foot treatment by an adequately trained professional, structured education, and prescription of appropriate footwear, with a regular examination of the patient and their feet. Frequency of foot treatment varied from once per month to once per 6 months.

No evidence was found to support integrated foot care to prevent a first-ever foot ulcer.[104,105] To prevent a recurrent ulcer, we found evidence suggesting that integrated foot care may reduce the risk of a recurrent foot ulcer.[39,106,107,109-113] All reported integrated foot care programmes lacked sufficient detail on the treatment given, which limits reproducibility of the study findings, translation to settings other than those studied, and analysis of the part(s) of the care that drive the outcomes. Additionally, limited description of the education given and footwear prescribed hinders comparison with studies on these specific topics. Future studies should describe integrated foot care in more detail.

4.9 | Other considerations and limitations

Readers should consider several issues related to this systematic review.

First, the population of interest of our review was limited to persons with diabetes at risk for foot ulceration, since these patients are expected to benefit more from preventative interventions than patients who are not at risk.[6] Studies were excluded if information on clinical presentation to define "at risk" was insufficient or if the "at risk" population was not specifically analysed. For example, the paper on education by Malone and colleagues[35] provided no information on ulcer healing in their study population of patients with an active foot ulcer, yet this information is essential to adequately assess ulcer recurrence. Another example is the study on foot screening and treatment by McCabe and colleagues,[132] which provides no information on the number of high-risk patients in the control group, and outcomes are not presented specifically for persons at risk. Other studies focused on a population with specific comorbidities, such as chronic kidney disease requiring dialysis treatment.[133,134] Even though foot ulcer risk is high in this population,[135-137] the lack of specific reporting of findings for the patients at risk limits assessment of effectiveness of an intervention for at-risk patients. For similar reasons, we did not assess the efficacy of lifestyle interventions or intensified glucose treatment,[138] as they target a general population of patients with diabetes mellitus. We made one exception, by including the systematic review and meta-analysis by Adiewere and colleagues, even though this was partly based on studies that included patients who were not at risk.[31] However, because the majority of patients in the meta-analysis was at risk, we decided to include these outcomes. Overall, we strongly advocate for the reporting of results in intervention studies that are specific for the population at risk, with risk reported according to a validated stratification system (eg, [23]), and with each item of such a system reported separately for the population included as well (eg, neuropathy, foot deformities, ulcer, and amputation history).

Second, in this systematic review on interventions, we did not analyse or describe risk factors for ulcer development and ulcer risk classification systems. Despite the importance of this topic, ulcer risk classification is only considered an intervention when a classification is linked directly to a strategy based on referral of patients for treatment.[139] No such studies were identified. It remains crucial to better understand if the way in which we stratify risk is effective for ulcer prevention.

Third, we lacked clear definitions and assessment methods for our primary outcome "first or recurrent ulcer" in many studies. The use and reporting of a standardized definition for diabetic foot ulcers, together with a clear description of methods for assessing outcomes, are a key recommendation in the reporting standards for studies on diabetic foot disease by Jeffcoate and colleagues.[27] Furthermore, we did not consider amputation as a primary outcome in this systematic review, because it depends largely on ulcer treatment and is therefore not a specific outcome for prevention in the nonulcerated foot. Also, amputation is an elective procedure and not a natural outcome from an intervention. As a consequence, we did not consider the existing population-based studies only reporting on amputation prevention (eg, Krishnan et al[140] and Larsson et al[141]).

Fourth, a key aspect of prevention that plays a critical role in outcome is treatment adherence.[4,142] Studies on different interventions assessed for in this systematic review consistently report that those patients who do not adhere to an intervention present with significantly worse outcomes.[29,30,42,49,107,108,111] Future studies on ulcer prevention should incorporate a measure of treatment adherence, preferably one that is objective, and investigate and implement strategies to improve adherence.

Fifth, the overall quality of studies on interventions to prevent a foot ulcer in at-risk patients with diabetes should further improve, so that stronger recommendations for clinical practice can be made. Studies should conduct a power analysis, ensure adequate blinding whenever possible, use intention-to-treat analysis, and follow the reporting standards for studies on diabetic foot disease.[27] More clarity is required in the description of study populations, interventions, outcomes, and outcome assessment. In addition, more focus should be put on cost-effectiveness studies, to inform those responsible for allocating health-care resources.

Sixth, this update of our systematic review resulted in only five newly included studies. Four years ago, we concluded that there is an urgent need for properly executed controlled studies on ulcer prevention.[22] Apparently, the paucity of studies in this field remains. However, with some protocols for RCTs or descriptions of interventions published recently,[114,127,143,144] and some other ongoing RCTs identified in our registry search, we hope that our next update will result in more included studies of high-quality.

Seventh, we operated in five different twosomes in our search of the literature, which can be considered a strength but also a limitation. This means that no single author has assessed all records identified in our search. We did not formally test inter-assessor variability, and it is 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 team meeting was held to discuss potential differences in assessment before choices were finalized. Finally, one assessor (J.v.N.) had access to all assessments and did some informal consistency checks that did not result in different outcomes of excluded papers. We therefore think that this division of tasks did not affect inclusion of publications. The advantage of this approach was a better division of the work over the assessors and avoiding authors having to assess publications they (co-) authored, thereby minimizing bias.

5 | CONCLUSIONS

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. The evidence is weak for the use of other, sometimes widely applied, interventions and is practically nonexistent for the prevention of a first foot ulcer and nonplantar foot ulcer. More controlled studies of high quality are needed in these areas, so as to better inform health-care professionals about effective preventative treatment in diabetic foot disease.

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CONFLICT OF INTEREST

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Full conflict of interest statements of all authors can be found online at www.iwgdfguidelines.org.

AUTHOR CONTRIBUTIONS

J.v.N. designed the search strings, performed the literature search, assessed the literature, extracted data, and drew conclusions within "interventions 4 & 8" and "trial registries"; checked and completed the evidence and risk of bias tables; and wrote the manuscript. AnitaR.

assessed the literature, extracted data, and drew conclusions within "interventions 1-3 & 7" and critically reviewed and edited the manuscript. L.L. assessed the literature, extracted data, and drew conclusions within "interventions 4 & 8" and critically reviewed the manuscript. MMS assessed the literature, extracted data, and drew conclusions within "interventions 1-3" and critically reviewed the manuscript. AnneR. assessed the literature, extracted data, and drew conclusions within "interventions 5 & 6" and "trial registries" and critically reviewed the manuscript. I.S. assessed the literature, extracted data, and drew conclusions within "interventions 5-7" and critically reviewed the manuscript. SB designed the search strings, assessed the literature, extracted data, and drew conclusions within "interventions 5 & 6" and co-authored the manuscript. J.v.N. acted as the secretary of the working group and S.B. as the chair of the working group. J.v.N. takes 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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