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RESEARCH ARTICLE

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Clinical and biomechanical effectiveness of foot-ankle exercise programs and weight-bearing activity in people with diabetes and neuropathy: A systematic review and meta-analysis

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Abstract

Background: Most interventions to prevent foot ulcers in people with diabetes do not seek to reverse the foot abnormalities that led to the ulcer. Foot-ankle exercise programs target these clinical and biomechanical factors, such as protective sensation and mechanical stress. Multiple RCTs exist investigating the effectiveness of such programs, but these have never been summarised in a systematic review and meta-analysis.

Methods: We searched the available scientific literature in PubMed, EMBASE, CINAHL, Cochrane databases and trial registries for original research studies on foot-ankle exercise programs for people with diabetes at risk of foot ulceration. Both controlled and non-controlled studies were eligible for selection. Two independent reviewers assessed the risk of bias of controlled studies and extracted data. Meta-analysis (using Mantel-Haenszel's statistical method and random effect models) was performed when >2 RCTs were available that met our criteria. Evidence statements, including the certainty of evidence, were formulated according to GRADE.

Results: We included a total of 29 studies, of which 16 were RCTs. A foot-ankle exercise programme of 8–12 weeks duration for people at risk of foot ulceration results in: (a) no increase or decrease risk of foot ulceration or pre-ulcerative lesion (Risk Ratio (RR): 0.56 (95% CI: 0.20–1.57)); (b) no increase or decrease risk of adverse events (RR: 1.04 (95% CI: 0.65–1.67)); (c) not increase or decrease barefoot peak plantar pressure during walking (Mean Difference (MD): −6.28 kPa (95% CI: −69.90–57.34)); (d) no increase or decrease health-related quality of life (no meta-

Abbreviations: GRADE, grading of recommendations assessment development and evaluation; IWGDF, international working group on the diabetic foot; 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 grouping network.

analysis possible). Likely results in increases in ankle joint and first metatarsalphalangeal joint range of motion (MD: 1.49° (95% CI: −0.28–3.26)) may result in improvements in neuropathy signs and symptoms (MD: −1.42 (95% CI: −2.95-0.12)), may result in a small increase in daily steps in some people (MD: 131 steps (95% CI: -492-754)), and may not increase or decrease foot and ankle muscle strength and function (no meta-analysis was possible).

Conclusions: In people at risk of foot ulceration, a foot-ankle exercise programme of 8–12 weeks duration may not prevent or cause diabetes-related foot ulceration. However, such a programme likely improves the ankle joint and first metatarsalphalangeal joint range of motion and neuropathy signs and symptoms. Further research is needed to strengthen the evidence base, and should also focus on the effects of specific components of foot-ankle exercise programs.

KEYWORDS
diabetes mellitus, diabetic foot, diabetic neuropathies, exercise, foot ulcer, prevention

1 | INTRODUCTION

Diabetes-related peripheral neuropathy is a key predisposing factor for foot ulcers.[1] These ulcers are frequent, with a lifetime incidence in people with diabetes of 19%–34%, and are the main cause of amputation and reduced quality of life.[1] The common pathway from peripheral neuropathy to foot ulceration includes a combination of sensory neuropathy (resulting in loss of protective sensation), motor neuropathy (resulting in biomechanical abnormalities) and autonomic neuropathy (resulting in skin changes).[1] Collectively, these peripheral neuropathy-related changes alter foot form and function, including a reduced range of motion, development and progression of foot deformities, reduced strength and function of the distal muscles, and alterations in foot rollover while performing locomotor activities. These abnormalities increase the mechanical stress on the plantar surface and contribute to the increased the risk of foot ulceration in people with diabetes-related neuropathy.[1]

Traditionally, interventions that aim to prevent diabetes-related foot ulcers, such as footwear and insoles, podiatric care and self-management,[2] do not seek to reverse the foot alterations that have led to the ulcer. These interventions help prevent foot ulcers; however, they do not work by mitigating the factors that cause these ulcers, such as protective sensation, mechanical stress, range of motion and foot strength and function. An intervention that targets these factors is a foot-ankle exercise programme. Foot-ankle exercise programs may vary in the prescription, but they typically include components of strengthening, stretching and functional exercises of the foot or lower leg, performed under the supervision of a skilled professional (e.g. physical therapist) or by people with diabetes independently. Examples of such exercises are one-legged standing, one-footed toe raises, sitting or standing heel raises, cycling motion of foot small joints (with and without rubber bands as resistance), alternating dorsal and plantar flexion, eversion and inversion (with or without an elastic band as resistance), or (brisk) walking. These exercises differ from other, more general exercises, such as squats, leg presses, chest presses, or stationary cycling, by primarily targeting the foot or the lower leg. Given the potential effects of foot-ankle exercise programs on ulcer risk factors, interest and research in this field has been growing in the past decade, with multiple RCTs published on the clinical and biomechanical effectiveness of foot-ankle exercise programs (e.g. on neuropathy, plantar pressure or range of motion[3–5]). While our previous systematic review of some of these outcomes is available,[6] and with some studies incorporated in systematic reviews that focus more generally on any type of exercise,[7,8] there is a gap in that a systematic review encompassing all relevant clinical and biomechanical outcomes following specific foot-ankle exercise programs, and accompanying meta-analyses is lacking. With mixed outcomes reported in the various RCTs,[6] and new RCTs published since our previous systematic review (e.g.,[9,10]), a systematic review and meta-analysis of all studies and outcomes published to date is required to advance our understanding of the clinical and biomechanical effectiveness of foot-ankle exercise programs in people with diabetes-related neuropathy.

Very specific types of foot-ankle exercise programs concern programs focused on increasing weight-bearing activity. The primary weight-bearing activity is walking, but also other forms such as standing, shuffling or running require energy expenditure from the foot and ankle. Increasing weight-bearing activity has long been discouraged in people with diabetes-related neuropathy as the increase in cumulative plantar stress on the foot was thought to increase ulcer risk.[11,12] However, increasing this activity may improve foot-ankle range of motion and strength.[6] In our previous systematic review, we concluded, based on two seminal RCTs,[5,13] that weight-bearing activity can be increased safely in this population.[2] With new studies published on this topic,[10,14] however, an update is required to incorporate newer evidence.

Therefore, the aim of this study was to perform a systematic review and meta-analysis of peer-reviewed publications, investigating the clinical and biomechanical effectiveness of foot-ankle exercise programs and weight-bearing activity in people with diabetes and neuropathy. This systematic review is an update and an extension of our previous systematic reviews including this intervention.[2,6] This systematic review forms one of the bases for developing the International Working Group on the Diabetic Foot (IWGDF) Guideline on the prevention of foot ulcers in people with diabetes.[12]

2 | METHODS

A systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines,[15] and prospectively registered in the PROSPERO database for systematic reviews in (CRD42022313323). First, the population of interest (P), interventions (I) and outcomes (O) were defined, and clinical questions were formulated accordingly by the assessors (i.e. the authors of this paper). These definitions and PICOs were reviewed for clinical relevance by the IWGDF Editorial Board and 16 external experts (including two persons with diabetes) from various geographical regions (see acknowledgements for their names and countries). Aligned to these final definitions, the clinical questions focusing on foot- and ankle exercises are answered in this systematic review. The clinical questions focusing on ulcer preventative treatments are answered in our other systematic review.[2]

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.[16] This includes patients with diabetes mellitus type 1 or 2, peripheral neuropathy and/or peripheral artery disease (PAD), with or without foot deformities, a history of foot ulceration or lower extremity amputation and/or end-stage renal disease. Peripheral neuropathy was defined as “the presence of symptoms or signs of peripheral nerve dysfunction, after the exclusion of other causes”. This includes a loss of protective sensation in the feet, that is, the inability to perceive light pressure or vibration, for example, as applied with a 10 g Semmes-Weinstein monofilament, biothesiometer or a tuning fork.

For each included publication, the population was—where possible based on the data provided—grouped according to the IWGDF risk stratification scheme.[12] In the final evidence statements and conclusions, the population was specified. This was dependent on the populations included, as we did not draw conclusions for IWGDF risk groups not included in the studies underlying each specific evidence statement or conclusion.

2.2 | Intervention

The intervention studied was foot-ankle exercise programs. We defined this as any physical activity specifically targeting any part of the foot, ankle or lower leg that is delivered in a predefined and structured programme with specified time, content and supervision, and with the aim of changing foot function (e.g. strength or mobility).

Within this definition, we define the physical activity in accordance with the World Health Organization as “any bodily movement produced by skeletal muscles that require energy expenditure”.[17] A programme could consist of one or multiple forms of physical activity, for example, stretching, strengthening, functional exercises, or walking. The form(s) of physical activity did have to target the specified anatomical locations in our definition above. This means we excluded exercise programs if these targeted other parts of the body (e.g. upper leg, upper body), operationalised as >50% of the foot-ankle exercise programme targeting other parts of the body.

Foot-ankle exercise programs could differ in multiple ways. For example, the type of exercises, the intensity of the exercises, the frequency of the exercises, the duration of the programme, the group size within the programme (e.g. delivered to an individual alone or in a group session), the involvement of skilled professionals (e.g. recurring in-person and face-to-face or no supervisory involvement), etc., could all differ. Subgroup analyses were performed based on the most frequently occurring differences in interventions. These were not defined a priori, but based on the findings. Descriptions of all exercise programs were collected as outcomes, and presented in the results section.

2.3 | Outcomes

Outcomes were selected by the assessors following the GRADE process.[18,19] These were rated on importance by the 16 external experts, with a score of 1 (not important), 2 (of some importance), or 3 (very important). Subsequently, each assessor independently rated the outcomes according to GRADE as ‘not important for decision-making’ (score 1–3), ‘important but not critical for decision-making’ (score 4–6), ‘critically important for decision-making’ (score 7–9). Group means and medians were calculated and discussed in a meeting with all assessors until consensus was reached. Table 1 lists the outcomes included for the interventions included in this systematic review, their rating and their definition.

2.4 | Inclusion and exclusion criteria

Original studies including the population of interest and reporting on one of the 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 randomized controlled trials, non-randomized controlled trials, case-control studies, cohort studies, (controlled) before-and-after studies,

TABLE 1 Outcomes included in the current systematic review.

Outcome	Rating[a]	Definition
Diabetic foot ulcer	9	Full thickness lesion of the skin of the foot in a person with diabetes
First-ever diabetic foot ulcer	9	First-ever recorded diabetic foot ulcer in a patient
Recurrent diabetic foot ulcer	9	New ulcer in a patient with a diabetic foot ulcer in their history, irrespective of location and time since previous ulcer
Ulcer severity	6.5	Severity of an ulcer, based on ulcer size, or depth, or grade of infection
Pre-ulcerative lesion	9	Foot lesion that has a high risk of developing into a foot ulcer (e.g. subcutaneous haemorrhage or blister)
Ulcer-free survival days	6.5	Days that a person is alive and without a foot ulcer
Health-related quality of life	7	A person's perceived physical and mental health
Costs	8	Monetary costs resulting from foot ulceration or foot care
Mortality	6.5	Percentage of persons not alive at the end of the study
Foot-related mechanical stress	7	The accumulation of all mechanical stresses on an area of the foot from weight-bearing activity or from the orthosis worn, including pressure and shear
Weight-bearing daily activity	6	Activity during which the foot is loaded by supporting the body weight of the person
Foot and ankle range of motion	6.5	The extent to which foot or ankle joints can move or stretch
Foot and ankle muscle strength/function	5	The muscle strength or function of the foot and ankle, as objectively measured
Neuropathy signs and symptoms	6.5	Any sign or symptom of peripheral neuropathy, such as loss of protective sensation, excluding painful neuropathy
Adverse events	8	An event, preventable or non-preventable, that caused harm to a person as a result of medical care

[a]Ratings could range from 1 to 9 as described in the methods, with scores of 7-9 meaning the outcome is critically important for decision-making; median ratings are provided.

interrupted time series, prospective and retrospective non-controlled studies, cross-sectional studies, and case series, and excluded systematic reviews, meta-analyses and case reports. If systematic reviews were identified, reference checking of the papers identified in that publication was performed, but the systematic review itself was excluded.

2.5 | Search strategy

The literature search was performed on 9 March 2022, 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 and Excerpta Medica Database (EMBASE) via Ovid SP. The Cochrane databases (Cochrane Database of Systematic Reviews, Cochrane Database of Abstracts of Reviews of Effect and Cochrane Health Technology Assessment) were searched until 24 July 2018, but this could not be updated given Cochrane's decision to stop supporting these databases.

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 (25 July 2018) to 6 January 2023. The Clinicaltrials.gov registry was also searched separately (https://clinicaltrials.gov), limited from 2018 to 6 January 2023 (Appendix 1). Two assessors independently assessed identified trials for eligibility based on three criteria: target population, outcomes, and intervention. Assessors obtained the status of eligible trials ('completed', 'ongoing', or 'not yet started') from the databases. Cohen's kappa was calculated for agreement. Assessors resolved disagreements concerning eligibility by discussion until a 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

Two assessors (IS and JvN) 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.[20] They discussed and reached a consensus on any disagreement on the inclusion of publications. Subsequently, they independently assessed full-paper copies of included publications on the same four criteria for final eligibility. Conference proceedings, if included during the 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. If no full-paper was available, the study was excluded.

2.7 | Assessment of included publications

The same two assessors independently assessed included publications with a controlled study design for methodological quality (i.e. 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[21] (Appendix 1). Assessors did not participate in the assessment, data extraction and discussion of publications of which they were co-authors to prevent any conflict of interest; in those situations, another author (AR or JP) was involved as a second assessor. The authors resolved disagreement regarding the 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, the risk of bias for each study was very low when scoring ≥8/10, low when scoring 6–7/10, or high when scoring ≤5/10. The score could be downgraded if the 21-item list identified specific topics that could raise concern regarding topic-specific risk of bias.[22] 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 randomized controlled trials (RCT) 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 summarised 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 authors extracted the data and the other author checked the data for content. All authors thoroughly discussed the evidence tables.

2.8 | Meta-analysis

A meta-analysis was done when three or more RCTs were available that included the same or a similar intervention, the same or a similar comparator, and the same outcome. Subgroup analyses were conducted, with groups separated based on whether the study included an intervention that was predominantly in-person face-to-face (direct contact between participant and health professional) or an intervention programme that was predominantly performed by participants independently. We followed the methodology as outlined in the Cochrane handbook. The aim of the meta-analysis was to generate a pooled effect estimate. For dichotomous outcomes, all meta-analyses were performed using Mantel-Haenszel's statistical method and random effect models anticipating substantial heterogeneity. The results were reported as relative risks and 95% confidence intervals (95% CI). For continuous outcomes, meta-analyses were performed using the inverse variance method and random effect models anticipating substantial heterogeneity. Mean difference was reported as effect measure, with 95% CI. For statistical analyses, two-side tests with alpha set at 0.05 were used. Heterogeneity was assessed using the I^2 statistic and interpreted as low (0%–49%), moderate (50%–74%) or high (75%–100%). A Forest plot was made to visualise outcomes, and a funnel plot was made to assess potential publication bias. Meta-analysis was conducted using RevMan 5, version 5.4 (The Cochrane Collaboration, Nordic Cochrane Centre).

2.9 | Evidence statements

Finally, two authors (IS and JvN) drew conclusions for each intervention based on the strength of the available evidence, which were formulated as evidence statements and accompanying assessment of the certainty of the evidence, according to GRADE.[23] The authors rated the certainty of the evidence (QoE) for each formulated evidence statement as "high", "moderate", "low", or "very low".[23] GRADE defines "high" as "We are very confident that the true effect lies close to that of the estimate of the effect"; "moderate" as "We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different"; "low" as "Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect", and "very low" as "We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect".[23] The rating was determined based on the level of evidence, the risk of bias, (in)consistency of results, (im)precision, (in)directness, publication bias, effect size and evidence of dose-response relation.[23] Each evidence statement was phrased in accordance with the methods described by GRADE. When the certainty of evidence was rated as moderate, the evidence statement was generated using the words "likely results in …"; likewise, when rated with a low certainty of effect, the statement contained "may result in …"; for evidence rated as having a very low certainty of effect, the statement contained "(very) uncertain"; when the effect or effect size could not be estimated, no evidence statement was provided. All authors discussed these evidence statements until consensus was reached.

3 | RESULTS

Of a total 2150 records screened, we included 16 RCTs and 13 non-controlled studies (including 3 RCTs that have at this moment only reported outcomes for the intervention group, and of which publication of full trial results are awaited), see for details the PRISMA flowchart in Figure 1. The foot-ankle exercise programs of the included RCTs most often consisted of foot-ankle muscles strengthening (69%; *n* = 11) and stretching (56%; *n* = 9) exercises, and functional exercises (e.g. balance; 53%; *n* = 8), with walking programs (19%; *n* = 3) and gait retraining (13%; *n* = 2) less frequent (see Table 2 and Appendix 3 for more details).

Components of the foot-ankle exercise programs of the included RCTs differed in various aspects (Table 2). Firstly, most intervention programs were individual (75%; *n* = 12), while the others were group-based (25%; *n* = 4). Secondly, most intervention programs included a weekly in-person component with a health professional (63%; *n* = 10). Of these, half (*n* = 5) included additional exercises to be performed without in-person supervision, while the other half (*n* = 5) did not ask participants to perform additional exercises at home. The remaining 6 RCTs (38%) did not include an in-person component during the intervention, instead participants performed all exercises independently guided by booklets or videos. Thirdly, the duration of the intervention ranged from 1 to 24 weeks. Most interventions had a duration of 8 weeks (44%; *n* = 7) or 12 weeks (38%; *n* = 6). Fourthly, weekly dose differed, ranging from daily to once weekly (Table 2).

The risk of bias was very low in 5, low in 6, and high in 5 RCTs (Table 3). Details (e.g. participant characteristics, intervention, study outcomes, and comments) for each included study (both controlled and non-controlled) are provided in the evidence table (Appendix 3). In the next sections, all results are described for each outcome separately, with a meta-analysis if pertinent, and concluded with an evidence statement. No results were found on the following outcomes of interest: ulcer severity, ulcer-free survival days, costs, and mortality.

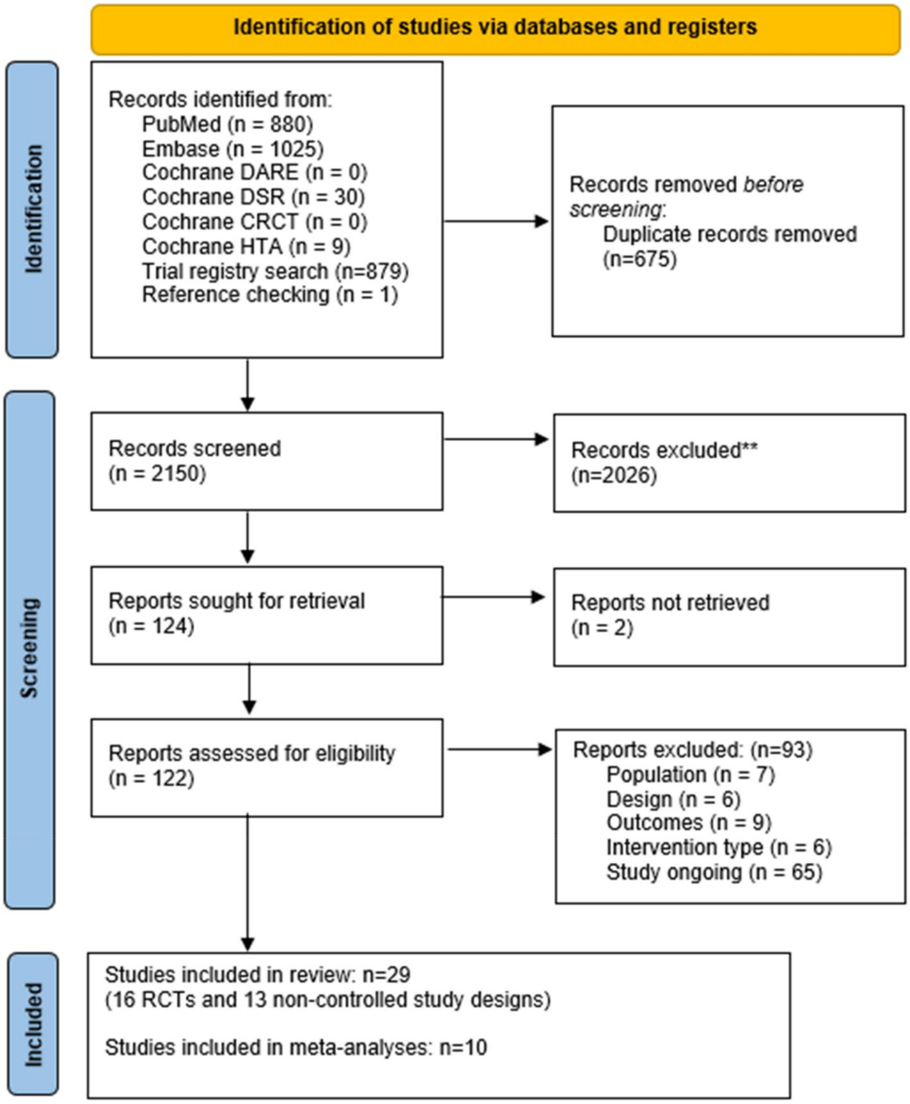

FIGURE 1 PRISMA flowchart. CRCT, Central Register of Controlled Trials; DARE, Database of Abstracts of Reviews of Effects; DSR, Database of Systematic Reviews; HTA, Health Technology Assessment. * Reference lists of included articles were checked; see Appendix 1 with the search strategy for further details.

TABLE 2 Descriptions of foot-ankle exercise programs of included RCTs.

			Intervention components					
Reference	RoB	Participants	Group or individual	In-person supervision or independent	Duration (weeks)	Dose (per week)	Content of the intervention	Outcomes
Goldsmith et al. (2002)	High	*N* = 21 I: 11; C: 10	Individual	Independent	4	3 times a day	Passive and active stretching exercises and soft tissue manipulation of the foot and ankle	Pressure
LeMaster et al. (2008)	Very low	*N* = 79 I: 41; C: 38	Individual	Both	8	Part 1: 3 times[a] Part 2: individualised	Part 1 (3 months): Leg strengthening and balance exercises; Part 2 (9 months): Graded self-monitored walking programme	(Pre-)ulcer; Adverse events; Activity
York et al. (2009)	High	*N* = 29 I: ?; C: ?	Individual	In-person	1[b]	2 days (total)	Gait training practice with visual and verbal feedback	Pressure
Kruse et al. (2010)	Very low	*N* = 79 I:41; C:38	Individual	Both[c]	8	Group weekly; At-home daily	Group strengthening and balance exercises; At-home strengthening and balance exercises	Adverse events; Strength
Allet et al. (2010)	Very low	*N* = 71 I: 35; C: 36	Group	In-person	12	2 times	Gait and balance exercises with function-orientated strengthening and resistance exercises	ROM
Melai et al. (2013)	Low	*N* = 92 I: 48; C: 46	Group	Both[c]	24	Group weekly; At-home daily	Group strength training and functional tasks; At-home strength exercises	Pressure
Mueller et al. (2013)	Very low	*N* = 29[d] I: 15; C: 14	Group	In-person	12	3 times, for 1 h	Flexibility and stretching exercises, strengthening exercises, weight bearing aerobic exercise (walking)	(Pre-)ulcer; Adverse events; ROM; Activity; Strength
Sartor et al. (2014)	Low	*N* = 55 I: 26; C: 29	Individual	Both	12	2 times, for 40–60 min	Strength and functional performance plus walking skills	Adverse events; Pressure; ROM; Neuropathy; Strength
Fayed et al. (2016)	High	*N* = 40 I: 20; C: 20	Individual	In-person	8	3 times, for 1 h	Stretching and strengthening exercises for foot and ankle, balance and gait training	Pressure
Kanchanasamut et al. (2017)	Low	*N* = 21 I: 11; C: 10	Individual	Independent[e]	8	5 times	Foot-ankle exercises with four levels of progression, using the mini-trampoline	Range of motion
Win et al. (2018)	High	*N* = 104 I: 51; C:53	Individual	Independent[e]	8	2–3 times, 10 min	Foot tapping, V-shape making, ankle rotating, and tennis ball rolling	Neuropathy
Venkataraman et al. (2019)	Low	*N* = 143 I: 70; C: 73	Individual	Independent	8	3 times	Foot strengthening, stretching and balance retraining	Adverse events; HRQoL; ROM; Neuropathy; Strength

(Continues)

TABLE 2 (Continued)

Reference	RoB	Participants	Intervention components					Outcomes
			Group or individual	In-person supervision or independent	Duration (weeks)	Dose (per week)	Content of the intervention	
Ahmad et al. (2020)	Low	$N = 38$ I: 21; C: 17	Individual	In-person	8	3 times	Sensorimotor and gait training	Neuropathy
Suryani et al. (2021)	High[f]	$N = 50$ I: 25; C: 25	Individual	Independent	12	3 times	Foot-ankle flexibility and resistance exercise	(Pre-)ulcer; Adverse events; Neuropathy
Monteiro et al. (2020) and (2022)	Very low	$N = 88$ I: 39; C: 39	Group	Both	12	Group: 2 times; At-home: 2 times	Strengthening and functional (balance and gait) exercises; individualised intensity, repetitions and sets (At-home with remote software supervision)	(Pre-)ulcer; Pressure; HRQoL; ROM; Neuropathy; Activity; Strength
Vratna et al. (2022)	Low	$N = 38$ I: 19; C: 19	Individual	Independent	12	Training 1: 4 times Training 2: 3 times	Training 1: Stabilisation and toning exercises (mainly of the greater joints); Training 2: Mobilisation and cyclic aerobic activity (walking)	(Pre-)ulcer; Activity; Strength

Abbreviations: C, control; HRQoL, Health-related quality of life; I, intervention; RoB, Risk of Bias; ROM, Range of Motion.

[a]Also included a total of 8 supervised sessions during the 3-month period.

[b]Programme lasted 2 days in a one-week period.

[c]Part 1 included In-person supervision, part 2 was Independent.

[d]Intervention consisted of weight-bearing exercises and control of non-weight-bearing exercises.

[e]Included a booklet as a guide for the programme.

[f]Downgraded from low to high based on 21-item list score (see Appendix 3).

3.1 | Foot ulcers and pre-ulcerative lesions

PICO: In people with diabetes at risk of foot ulceration, does a foot-ankle exercise programme, compared to no foot-ankle exercise programme, help prevent a first-ever or recurrent diabetic foot ulcer?

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

Summary of the literature: We identified 5 RCTs with a combined total of 274 participants (Figure 2) reporting ulcer incidence during a foot-ankle exercise programme that met the criteria for meta-analysis.[5,10,13,14,24] In the meta-analysis (Figure 2), the relative risk of ulceration was 0.63 (95% CI: 0.28–1.42), a statistically non-significant difference in favour of the intervention, with low heterogeneity (I^2: 41%). In subgroup analyses, the 2 interventions without in-person component showed a reduced ulcer risk (RR: 0.43), albeit

TABLE 3 Risk of bias of included RCTs.

Reference	Randomization	Independent assignment	Outcome assessor blinded	Patient / Care provider blinded	Similarity groups	Drop-out acceptable (<20%)	Intention-to-treat	Patients treated equally except for intervention	Selective reporting ruled out?	Free from commercial interest ?	Score	Final RoB assessment*
Goldsmith et al, 2002	+	-	-	-	+	-	-	?	+	+	4/10	High
LeMaster et al, 2008	+	+	+	-	+	+	+	+	+	+	9/10	Very low
York et al, 2009	+	?	-	-	-	?	-	+	+	+	4/10	High
Kruse et al, 2010	+	+	+	-	+	+	+	+	+	+	9/10	Very low
Allet et al, 2010	+	+	+	-	+	+	+	+	+	+	9/10	Very low
Melai et al, 2013	+	+	-	-	+	-	+	?	+	+	6/10	Low
Mueller et al, 2013	+	+	+	-	+	+	+	+	+	+	9/10	Very low
Sartor et al, 2014	+	+	?	-	+	-	+	+	+	+	7/10	Low
Fayed et al, 2016	-	-	?	-	+	+	-	+	+	+	5/10	High
Kanchanasamut et al, 2017	-	-	+	-	+	+	-	+	+	+	6/10	Low
Win et al, 2018	+	?	-	-	+	-	-	?	-	+	3/10	High
Venkataraman et al, 2019	+	+	+	-	+	+	?	?	+	+	7/10	Low
Ahmad et al, 2020	+	+	?	-	+	+	-	?	+	+	6/10	Low
Suryani et al, 2021	+	?	+	-	+	+	+	?	-	+	6/10	High
Monteiro et al, 2022	+	+	+	-	+	-	+	+	+	+	8/10	Very low
Vratna et al, 2022	+	-	+	-	+	+	-	?	-	+	5/10	High

Note: *RoB, Risk of Bias – final assessment was based on score as shown in the table and score on the 21-item list (Appendix 2).

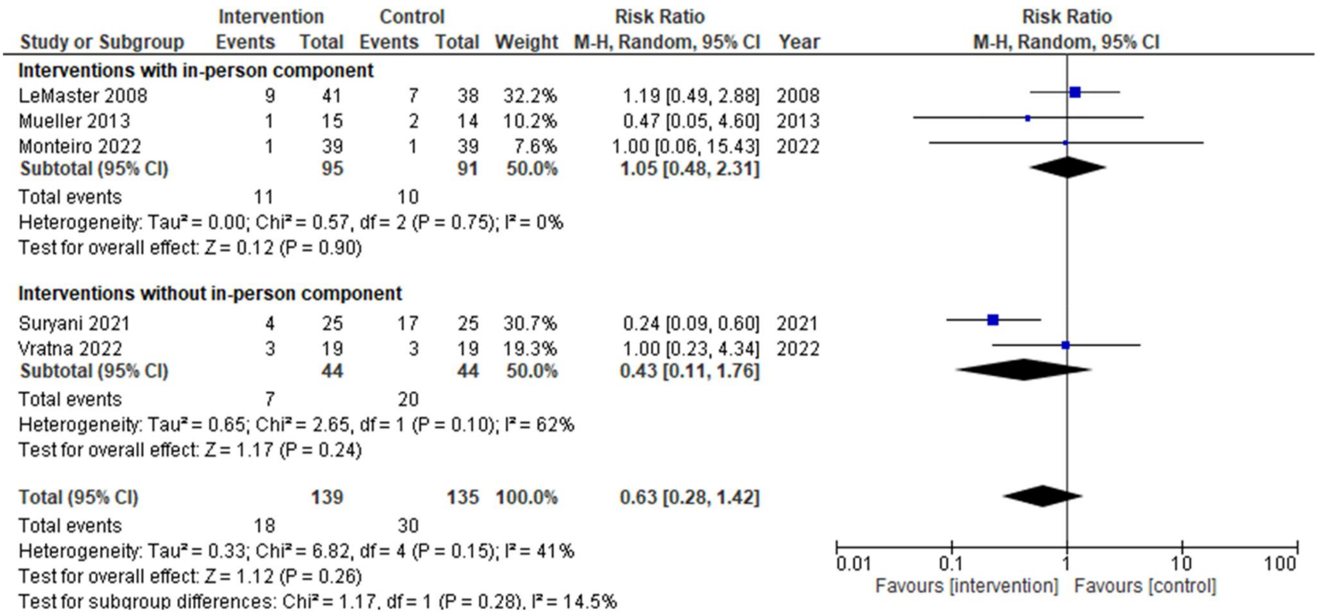

FIGURE 2 Meta-analysis of ulcer incidence during foot-ankle exercise programs.

statistically non-significant, while the three interventions with in-person component did not show an effect (Figure 2). However, this effect was driven by an RCT at high risk of bias, with unusually high ulcer recurrence in usual care, while usual care did not reflect current standard practice because adequate footwear was not provided for IWGDF risk 3 patients. The interventions with in-person component were all RCTs with very low ($n = 3$) risk of bias (Tables 2 and 3).

Two RCTs were reported on pre-ulcerative lesions. During 1 year follow-up, LeMaster et al found 26 patients (0.61/year) with a total of 27 lesions in the intervention group, compared to 19 patients (0.46/year) with a total of 21 lesions in the control group (rate ratio (95% CI): 1.24 (0.70–2.19)).[13] During 12-week follow-up, Mueller et al found 7 versus 6 total lesions in 7 versus 5 participants.[5]

In the RCTs of LeMaster et al,[13] Mueller et al,[5] and Monteiro et al,[10] an increase in weight-bearing activity of around 1000 steps was seen in the intervention group (898, 1178 and 914 respectively), with no difference in ulcer incidence compared to the control group (Figure 6). In the RCT from Vratna et al,[24] more high-intensity and moderate-intensity physical activity was seen in the intervention group as measured using a questionnaire; however, the increase in the weight-bearing activity was not quantified (Appendix 3).

Evidence statement: A foot-ankle exercise programme of 8–12 weeks duration may not increase or decrease the risk of foot ulceration or pre-ulcerative lesion formation in people at risk of foot ulceration (IWGDF risk 1, 2 or 3).

Certainty of the evidence: Low. Downgraded for risk of bias (effect in meta-analysis primarily driven by high risk of bias study) and imprecision (large confidence intervals in meta-analysis).

Evidence statement: A small increase in the level of weight-bearing daily activity (1000 steps/day, 20% increase) may not increase or decrease the risk of foot ulceration in people at risk of foot ulceration (IWGDF 1, 2 or 3).

Certainty of the evidence: Low. Downgraded for risk of bias (none of the RCTs were powered to detect such an effect) and imprecision (large confidence intervals in meta-analysis).

3.2 | Adverse events

PICO: In people with diabetes at risk for foot ulceration, does a foot-ankle exercise programme compared to no foot-ankle exercise programme increase adverse events?

Summary of the literature: Adverse events (excluding foot ulceration, as these are included in the PICO above) were reported in 6 RCTs. In the remaining 10 RCTs, adverse events were not reported. The RCT that reported the highest number of adverse events found 16 persons with 1 or multiple falls during follow-up in both intervention and control groups (39% and 42% of participants, respectively; $p = 0.97$).[25] The other RCTs reported an aggregate 4 adverse events potentially related to the intervention (1 fractured toe,[13] 1 calf strain[5], 2 falls[9]), 5 adverse events not related to the intervention (2 unspecified emergency conditions,[14] and 3 medical conditions[3]), and 5 adverse events in the control groups (3 falls[9] and 2 medical conditions[3]). In the meta-analysis (Figure 3), the relative risk of adverse events in the intervention was 1.04 (95% CI: 0.21–1.67), a statistically non-significant difference, with low heterogeneity (I^2: 0%).

Evidence statement: A foot-ankle exercise programme of 8–12 weeks duration may not increase or decrease the risk of adverse events in people at risk of a foot ulcer (IWGDF risk 1, 2 or 3).

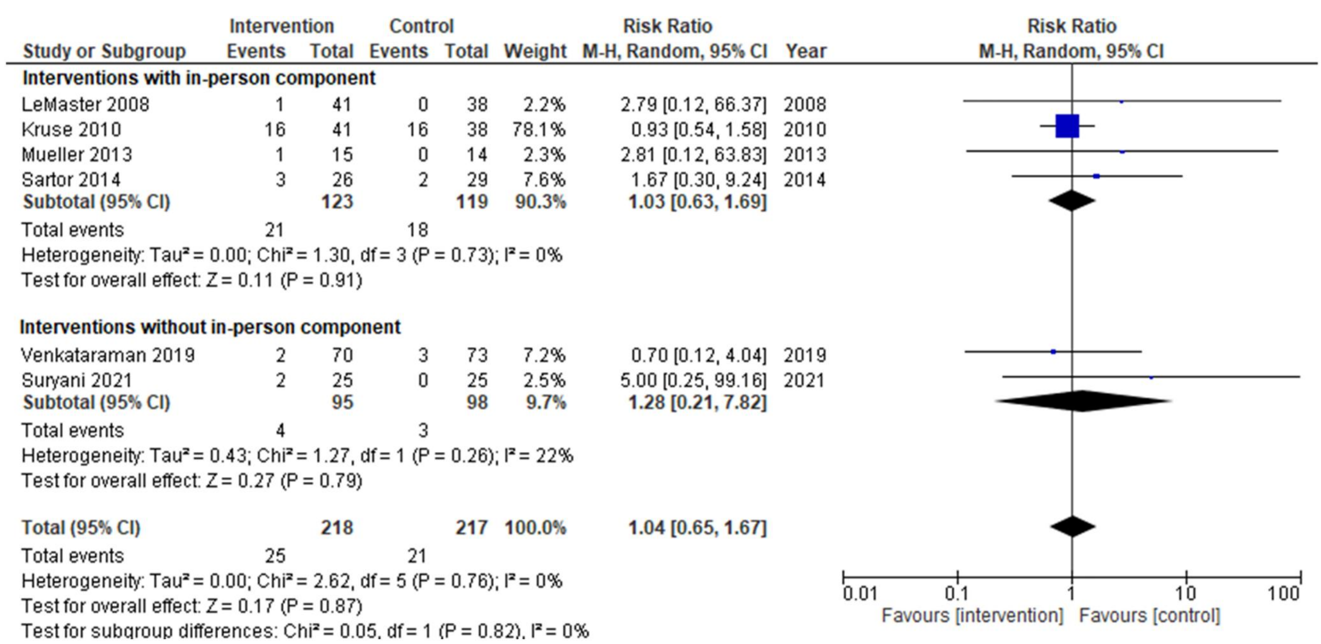

FIGURE 3 Meta-analysis on adverse events during foot-ankle exercise programs.

Certainty of the evidence: Low. Downgraded because of imprecision and publication bias (with the majority of RCTs not reporting adverse events).

3.3 | Foot-related mechanical stress

PICO: In people with diabetes at risk for foot ulceration, does a foot-ankle exercise programme compared to a no foot-ankle exercise programme reduce foot-related mechanical stress/pressure?

Summary of the literature: We identified 8 RCTs and 7 non-controlled studies. Five RCTs met the inclusion criteria for meta-analyses, as they all reported barefoot peak plantar pressure at the medial forefoot.[3,4,26–28] Of these, Goldsmith et al[27] and Melai et al[4] only provided figures with outcomes, but not the exact means and SDs. As such, these could not be included in the meta-analysis; authors replied on requests for information that the raw data was no longer available. In the meta-analysis of the remaining 3 RCTs (Figure 4), we found a statistically non-significant mean pressure reduction of 6.28 kPa (95% CI: −69.90, 57.34) favouring the intervention with high heterogeneity (I^2: 81%). The effect was similar in both subgroups (Figure 4).

In the RCTs not included in the meta-analysis, Goldsmith et al[27] found in the intervention group a significantly lower average barefoot peak plantar pressure during gait of 4.2% compared to baseline, while pressure increased by 4.4% in the control group (no values given). Melai et al[4] found lower barefoot peak plantar pressure changes during gait between the intervention and control groups at baseline, 12, 24 or 52 weeks ($p < 0.05$; only figures provided, no quantification of differences given), but given the existing differences at baseline, no time effect was found and it was concluded that the intervention did not improve plantar pressures compared to control. Of the 7 non-controlled studies, 2 reported an increase in plantar pressure,[29,30] 4 reported a reduction,[31–34] and 1 reported a reduction in some but no change in most measured locations[35] (Appendix 3).

Only 1 RCT measured pressure in shod conditions.[36] York et al found in the intervention group a significant reduction in in-shoe peak plantar pressure at the first metatarsal area after 1 day (p = 0.01, no numbers given) but not at one-week follow-up, while the control group showed no change. No significant changes were found in other regions, neither after 1 day nor 1 week.

Evidence statement: A foot-ankle exercise programme of 8–12 weeks duration may not increase or decrease barefoot peak plantar pressure during walking in people with a low or moderate risk of foot ulceration (IWGDF risk 1 or 2).

Certainty of the evidence: Low. Downgraded because of imprecision (large confidence intervals, small mean difference) and inconsistency (some studies showing a positive effect, some studies a negative effect).

3.4 | Health-related quality of life

PICO: In people with diabetes at risk for foot ulceration, does a foot-ankle exercise programme compared with no foot-ankle exercise programme improve health-related quality of life?

Summary of the literature: We identified two RCTs and one non-controlled study reporting health-related quality of life after a foot-related exercise intervention. Venkataraman and colleagues found a non-significant mean difference of 0.02 (95% CI: −0.01–0.06; p = 0.175) on the EQ5D in favour of the intervention.[9] Monteiro and colleagues found no difference in EQ5D scores at 6, 12 and 52 weeks, but higher scores at 24 weeks in the intervention group in comparison with the control group.[10] One non-controlled study found improvements in perceived foot health.[37]

Evidence statement: A foot-ankle exercise programme may not increase or decrease health-related quality of life in people at risk of foot ulceration (IWGDF risk 1, 2 or 3).

Certainty of the evidence: Low. Downgraded because of imprecision and inconsistency.

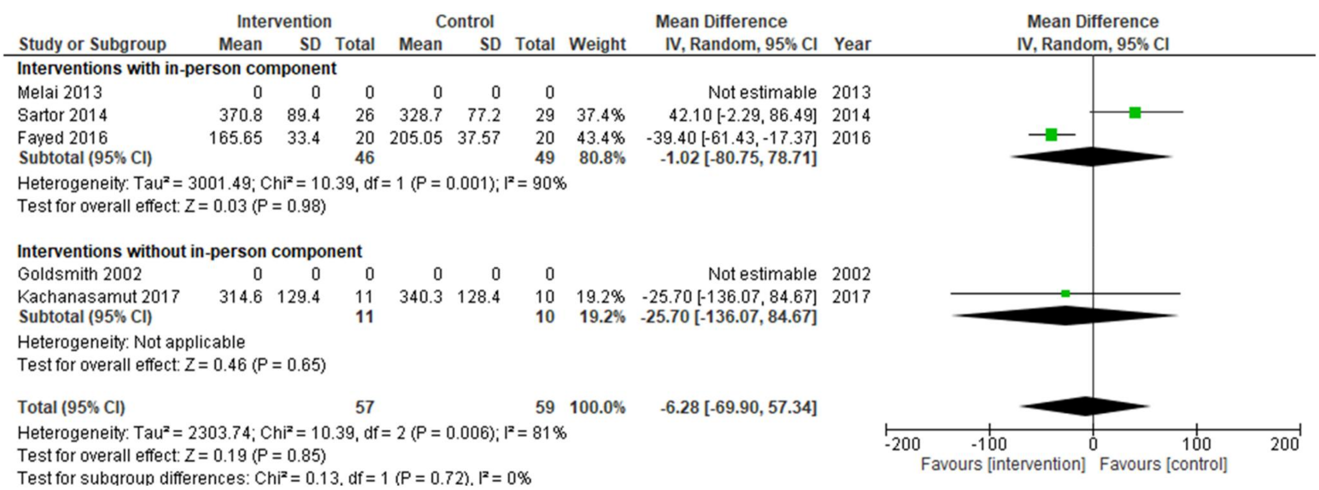

FIGURE 4 Meta-analysis of barefoot peak plantar pressure at the medial forefoot (kPa) at final follow-up following foot-ankle exercise programs.

3.5 | Foot and ankle range of motion

PICO: In people with diabetes at risk for foot ulceration, does a foot-ankle exercise programme compared to a no foot-ankle exercise programme improve limited foot and ankle range of motion (ROM)?

Summary of the literature: We identified 7 RCTs and 6 non-controlled studies. Five RCTs met the inclusion criteria for meta-analyses, as they all reported changes in ankle passive, active, or dynamic (gait) ROM after the intervention.[3,5,9,10,38] In the meta-analysis (Figure 5), we found a mean difference of 1.49° (95% CI: −0.28–3.26) range of motion increase, a statistically non-significant difference favouring the intervention, with high heterogeneity (I^2: 62%). The effect was higher and statistically significant in interventions that included an in-person component, where heterogeneity was lower (I^2: 0%; Figure 5).

In the 2 other RCTs, Kanchanasamut and Pensri[28] found flexion and extension ROM at the first metatarsophalangeal joint of both left and right feet increased in the intervention group, after 8 and 20 weeks, with a significant interaction effect for time and intervention (p-values range 0.002 to 0.040). Goldsmith et al[27] found no differences in joint stiffness in the ankle and the first metatarsophalangeal joint. All 6 non-controlled studies observed increases in the ROM of foot-ankle-related joints[29,31,35,39–41] (Appendix 3).

Evidence statement: A foot-ankle exercise programme of 8–12 weeks duration that includes a weekly or twice-weekly in-person component with an adequately trained health professional likely results in increases in ankle joint and first metatarsalphalangeal joint range of motion in people at risk of foot ulceration (IWGDF risk 1, 2 or 3).

Certainty of the evidence: Moderate. Downgraded because of imprecision (large confidence intervals around the effects found in the meta-analysis).

3.6 | Neuropathy signs and symptoms

PICO: In people with diabetes at risk for foot ulceration, does a foot-ankle exercise programme compared with no foot-ankle exercise programme improve neuropathy signs and symptoms?

Summary of the literature: We identified 6 RCTs and 5 non-controlled studies. Four RCTs reported changes in neuropathy symptoms using a similar or identical and validated questionnaire and thus met the inclusion criteria for meta-analyses.[3,10,14,28] In the meta-analysis (Figure 6), we found a statistically non-significant mean difference of 1.42 points (95% CI: −2.95, 0.12), representing a reduction in neuropathy signs and symptoms, favouring the intervention, with high heterogeneity (I^2: 89%). The effect was similar in both subgroups (Figure 6).

In the other 2 RCTs, Win et al[42] found no difference in neuropathy severity scores at the final follow-up. Ahmad et al[43] tested latency, amplitude, duration and conduction velocity in both the peroneal and tibial nerves and found a statistically significant increase in conduction velocity of the peroneal nerve and a reduction in the latency of the tibial nerve, but no difference for the other six outcomes.

In addition to the results included in the meta-analyses, Kanchanasamut and Pensri[28] found a lower absolute number of participants with neuropathy symptoms in the intervention group during the follow-up, while this was the same at baseline (Appendix 3). Monteiro et al[10] found no changes in tactile sensitivity ($p > 0.05$), but an improvement in vibration perception ($p = 0.03$). From the 5 non-controlled studies, 4 observed improvements in neuropathy signs and symptoms,[37,39,44,45] 1 did not find any changes[29] (Appendix 3).

Evidence statement: A foot-ankle exercise programme of 8–12 weeks duration may result in improvements in neuropathy signs and symptoms in people at risk of foot ulceration (IWGDF risk 1, 2 or 3).

Certainty of the evidence: Low. Due to inconsistency (not all studies showing a consistent positive effect) and imprecision of results (small effect sizes and large confidence intervals around the effect).

3.7 | Weight-bearing activity

PICO: In people with diabetes at risk for foot ulceration, does a foot-ankle exercise programme compared with no foot-ankle exercise programme increase weight-bearing activity?

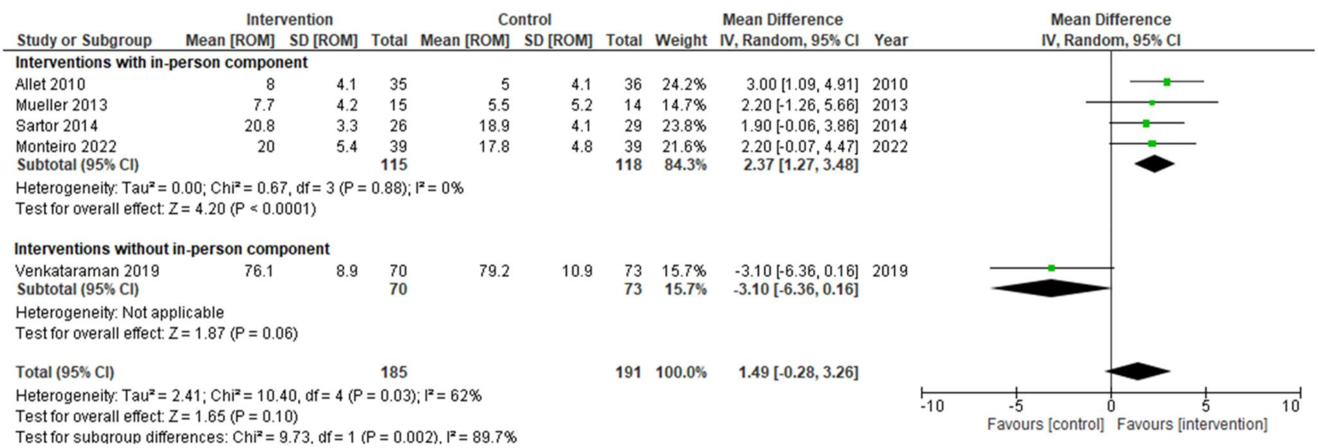

FIGURE 5 Meta-analysis of ankle range of motion (in degrees) at final follow-up following foot-ankle exercise programs.

Summary of the literature: We identified 4 RCTS, of which 3 measured daily steps and met the criteria for meta-analysis.[5,10,13] In the meta-analysis (Figure 7), we found on average a higher number of daily steps in the intervention (mean 131 more daily steps; 95% CI: −492, 754), non-significantly favouring the intervention, with low heterogeneity (I^2: 0%). Subgroup analysis was not performed.

In 1 other RCT, physical activity was measured using a questionnaire.[24] Vratna et al found a statistically significantly larger increase in high- and moderate-intensity physical activity in the intervention group, compared to the control group.[24]

In secondary analyses, LeMaster et al[13] found in the 23 (29%) participants with an increase in steps (either total steps, or during 30-min exercise bouts) that the median increase at 12 months was 898 total daily steps. Mueller et al[5] found the difference between baseline and post-intervention (at 12 weeks) to be a mean 1178 steps higher in the weight-bearing intervention group (increase of 685 in weight-bearing intervention group, decrease of 493 in the non-weight bearing intervention group; $p = 0.026$). Monteiro et al[10] found the difference between baseline and post-intervention (at 12 weeks) to be mean 531 steps higher in the intervention group (increase of 366 daily steps in the intervention, and a decrease of 256 in the control group); at 12 months, this was 914 steps higher in the intervention group.

In other outcomes related to weight-bearing activity, LeMaster et al[13] found that the mean number of steps taken during 30-min exercise bouts significantly increased in the intervention group (from 482 to 548 steps) and decreased in the control group (from 495 to 465 steps). The difference at 6 months between both groups was statistically significant ($p < 0.01$). At 12 months, however, the difference was not statistically significant (510 vs. 477 steps). Mueller et al[5] found a statistically significant mean increase of 29 m for the 6-minutes-walking test (95% CI: 6–51; $p = 0.014$). Monteiro et al[10] found an increase in fast gait speed but not in self-selected gait speed.

Evidence statement: A foot-ankle exercise programme of 8–12 weeks duration may result in a small increase in daily steps in some people at risk of foot ulceration (IWGDF risk 1, 2 or 3).

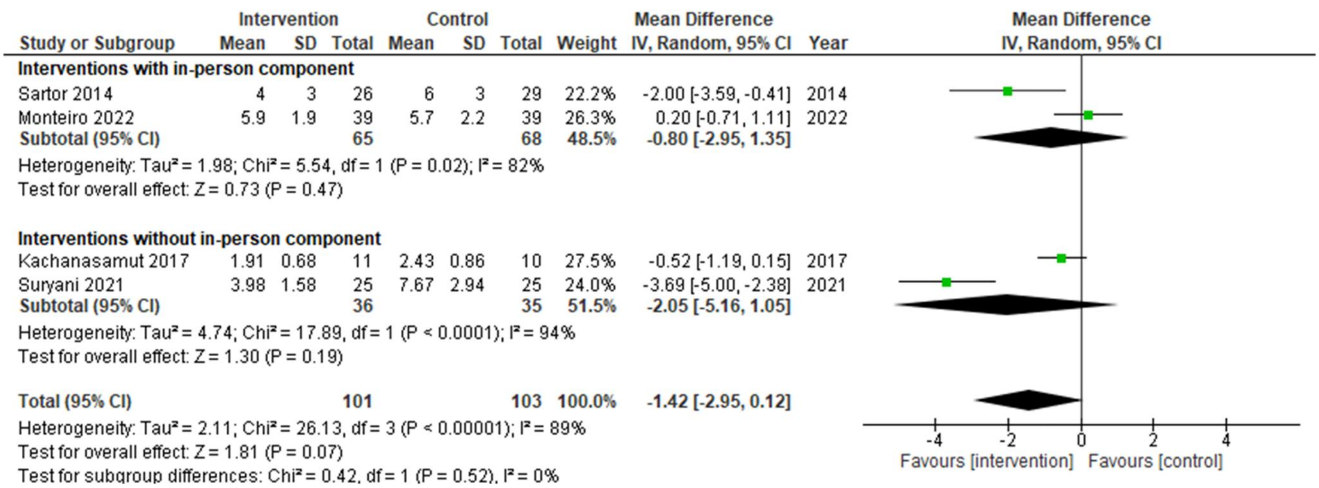

FIGURE 6 Meta-analysis of neuropathy signs and symptoms as measured using a questionnaire at final follow-up following foot-ankle exercise programs.

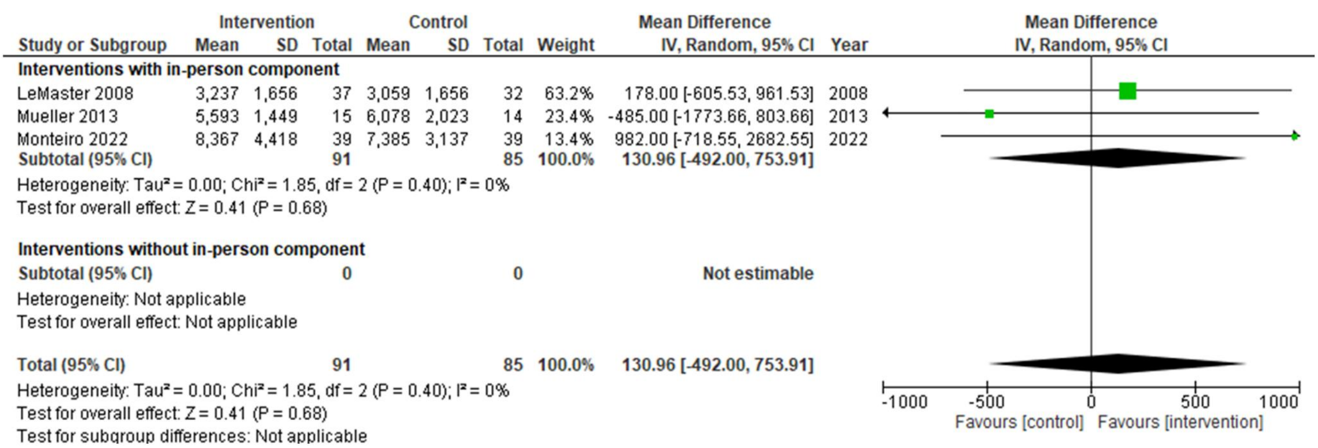

FIGURE 7 Meta-analysis of weight-bearing activity at final follow-up following foot-ankle exercise programs.

Certainty of the evidence: Low. Downgraded because of imprecision (large confidence intervals in the meta-analysis) and inconsistency (studies showing differing effects).

3.8 | Foot and ankle muscle strength and function

PICO: In people with diabetes at risk for foot ulceration, can a foot-ankle exercise programme compared to a no foot-ankle exercise programme improve foot strength or foot function?

Summary of the literature: We identified 5 RCTs and 2 non-controlled studies. Given the differences in methods to quantify muscle strength between these studies, a meta-analysis was not possible. Allet et al[38] found a significant increase in the ankle plantarflexor muscle strength (I: 233–268N; C: 246 to 243N; $p < 0.05$) and dorsiflexor muscle strength (I: 202–238N; C: 202–212N; $p < 0.05$). The improvements obtained did not last for the 6-month follow-up period. Kruse et al[25] found no statistically significant differences in ankle joint dorsiflexion strength between the intervention and control groups after 6 months (C: 23.8 vs. I: 24.3 kg; $p = 0.11$) or 12 months (C: 20.4 vs. I: 22.0 kg; $p = 0.22$). Sartor et al[3] found at 12 weeks significant ($p < 0.05$) increases for the intervention compared to the control group in muscle strength of flexor digitorum brevis (4.0 vs. 5.0), interosseous (3.0 vs. 4.0) and tibialis anterior (4.0 vs. 5.0) but not for muscle strength of extensor digitorum and hallucis, flexor hallucis, lumbrical and triceps surae ($p > 0.05$). Venkataraman et al[9] found at 8 weeks more muscle strength in the intervention group (mean difference: 4.18 (95% CI: 0.4–7.92)), in addition to improvements in tests that infer function, such as timed up-and-go and five times sit-to-stand. Vratna et al[24] found at 12 weeks a significant ($p = 0.03$ and $p = 0.043$ for left and right leg, respectively) improvement in isometric plantarflexor muscle strength in the intervention group (I: 97; C: 12; units not defined). From the 2 non-controlled studies, 1 observed an increase in isometric muscle strength,[41] the other did not[29] (Appendix 3).

Evidence statement: A foot-ankle exercise programme of 8–12 weeks duration may not increase or decrease foot and ankle muscle strength and function in people with a low or moderate risk of foot ulceration (IWGDF risk 1 or 2).

Certainty of the evidence: Low. Due to inconsistency (some studies show an effect, others not) and imprecision (large confidence intervals reported in studies) of results.

4 | DISCUSSION

In this systematic review and meta-analysis, we found 29 studies (including 16 RCTs) investigating the effects of foot-ankle exercise programs and weight-bearing activities in people with diabetes-related neuropathy. We first defined a set of 15 outcomes considered (critically) important for clinical decision-making, based on consensus within the author group and with extensive external feedback. This included desirable (e.g. improved health) and undesirable outcomes (e.g. adverse outcomes). For the primary outcome from a clinical perspective (foot ulcer incidence), we found that in people with diabetes at risk for foot ulceration, a foot-ankle exercise programme may not prevent or cause diabetes-related foot ulceration. For desirable outcomes, we found that such a programme likely increases foot and ankle joint range of motion and may result in improvements in neuropathy signs and symptoms, and to a small increase in daily steps in some people. Such a programme does not increase or decrease barefoot plantar pressure, health-related quality of life, or foot and ankle muscle strength and function. For the undesirable outcomes, we found that a foot-ankle exercise programme seems like not to increase or decrease the risk of adverse events. Also, a small increase in the level of weight-bearing daily activity (1000 steps/day, 20% increase) does not seem to increase or decrease the risk of a first-ever or recurrent diabetic foot ulcer. Collectively, this most extensive overview of outcomes of foot-ankle exercise programs in people with diabetes-related neuropathy to date suggests that these programs may have beneficial effects in this population, without increasing foot ulcer risk; however, more research remains required.

4.1 | Components of the foot-ankle exercise programs

Foot-ankle exercise programs consist of multiple components. Variations were seen in the included programs in relation to the type, frequency and intensity of the exercises, the organisation of the programme in terms of the number of people attending to the intervention (individual or group-based), the involvement of appropriately trained healthcare professionals, the duration of the programs and the timing of follow-up measurements (Table 2). These large variations between trials might be an explanation for the differences in the outcomes found in these studies. In our meta-analyses, separation was possible based on one component. We chose the in-person component in the programme as a key differentiating criterion because we think that involving an appropriately trained health professional with regular in-person encounters increases adherence and satisfaction of patients, while it also facilitates correct performance of the exercises.[46] In people with diabetes, the treatment burden is high. People already have to adhere to multiple diabetes-related self-care and self-management strategies. Professional in-person support is likely to help encourage and motivate patients to carry on with the exercise: the few RCTs that did report on adherence found higher adherence when professional support was provided (mean > 80% adherence in 2 RCTs with a professional,[10,38] and only 45% adherence in 1 RCT without professional support[42]; see Appendix 3). Home-based and technology-based interventions do have advantages, enabling care from a distance (especially relevant during the COVID-19 pandemic), mitigating against long waiting lists, resource constraints and therapist availability at rehabilitation services, and it is person-centred so people can choose the time and place to exercise. The extent to which home-based and technology-based interventions fulfil these expectations remains to be investigated. We also noted a difference in the duration of the programs, with most programs with an in-person component lasting 12 weeks, while those without lasting mostly 8 weeks. It is unclear why this difference exists, perhaps it is purposively designed because of lower expected adherence, and it is unclear how that interferes with the (small) differences in outcomes. More studies are needed to better clarify the specific effect of the involvement of a health professional, as well as the effects of the other foot-ankle exercise programme components.

4.2 | Outcomes

Almost all foot-ankle exercise programs targeted multiple desirable outcomes, with some programs specifically targeting one or two outcomes, while other programs targeted almost all. We found evidence for nine of our predefined outcomes (ulceration, pre-ulcerative signs, adverse events, health-related quality of life, mechanical stress, range of motion, neuropathy signs and symptoms, foot strength and function, and weight-bearing activity), with positive outcomes for some, and little to no effect for others. Evidence for foot ulcer prevention, adverse events, health-related quality of life, and foot strength and function is very limited and requires further research. We strongly recommend for all RCTs to accurately report adverse events, in line with general recommendations,[22] as these were often not reported in the included publications.

4.2.1 | Foot ulceration and pre-ulcerative signs

With 5 RCTs reporting on foot ulceration, the evidence base is increasing. The 4 RCTs at low or very low risk of bias showed no effect of foot-ankle exercise programs on foot ulceration,[5,10,13,24] but none of these RCTs was powered for equivalence. One other RCT[14] demonstrated conflicting results, and suggested that foot-ankle exercise programs prevent foot ulcers. However, when the data from this and the other RCTs were merged in the meta-analysis, the conclusion drawn is that foot-ankle exercises do not seem to help prevent foot ulcers but can be considered safe. The large positive effect seen in the opposing RCT seemed largely driven by an uncharacteristically high percentage of ulcers in the control group. This could be explained by the absence of appropriate footwear offered as part of the standard care provided to participants categorised as IWGDF risk three in the control group. These findings should therefore not be generalised to settings where appropriate footwear is available. However, this might suggest that foot-ankle exercise programs could be an alternate solution in low-resource settings where adequate footwear is unavailable. More research from such settings is needed to investigate this hypothesis.

4.2.2 | Mechanical stress

With regard to mechanical stress, we only considered peak plantar pressure and found little or no effect. This variable is a key risk factor for ulceration,[1] and the primary outcome in interventions targeting plantar pressure. 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 plantar loads, and are only effective when worn.[2] Foot-ankle exercises have the potential benefit of intrinsically changing foot mobility, strength and functionality during gait. This biomechanical effect might be achieved by promoting changes in the absorption and transmission of loads, following the recovery of muscle function and joint mobility.[47] Although we found that there is little to no effect from foot-ankle exercise programs on peak plantar pressure, changes in other aspects of plantar pressure distribution and reduction were found, including time to peak pressure, centre of pressure trajectory, and pressure-time integral.[3] We did not discuss these in our systematic review because these are not proven risk factors for ulceration. However, these changes may indicate improvements in foot function, which may be linked to other long-term patient benefits such as the level of daily physical activity or pressure patterns.[47] One limitation of peak pressure is that it only represents vertical loading in a very short time of the stance phase. Deeper investigation of the whole process of foot roll-over, based on different outcomes and using different statistical techniques, such as parametric mapping of pressures,[48,49] is needed. This would facilitate a deeper understanding of the effect of foot-ankle exercise on plantar pressure distribution and associated foot ulcer risk. With this understanding, we can progress ulcer prevention in people with peripheral neuropathy beyond merely reducing peak pressures.

4.2.3 | Range of motion

For joint mobility, the changes in joint range of motion were often small (2–5°), and mostly seen in the ankle joint. Although these changes were statistically significant in the meta-analysis, it is unclear if these changes are clinically meaningful. Although an association between reduction in ankle rom and elevated PP has been shown (e.g.[50,51]), limited joint mobility is only a proven risk factor for ulceration when present in the subtalar and first metatarsophalangeal joints.[52,53] In these joints, small differences (2–4°) were seen between patients who ulcerated and those who did not, in line with the differences found after a foot-ankle exercise programme. While there is debate about the reliability and validity of limited joint mobility measurements used in the included studies,[54,55] especially when changes in range of motion are small, outcome assessment was blinded for the group allocation and done by a single assessor in most studies, so 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 who do not show adequate physiological motion in their daily living activities. We conclude that foot-ankle exercise programs likely improve joint range of motion, with moderate certainty. We recommend that future studies always include assessment of subtalar and metatarsophalangeal joint mobility, either active, passive, or dynamically (gait), as long as it is clearly stated, and that these studies minimise potential errors in joint mobility assessment and quantify the findings and the error margins in joint motion for statistical and clinical significance.

4.2.4 | Neuropathy signs and symptoms

The meta-analysis showed an improvement in neuropathy signs and symptoms measured by questionnaires, favouring the intervention, regardless of whether the in-person component was present in the exercise programme. Although the changes in the questionnaire's absolute scores were small (mean difference of 1.49 points), it might represent an important improvement for patients who experience the uncomfortable neuropathy symptoms and somatosensory losses that interfere in their daily living activities. These RCTs also identified improvements in other neuropathy signs and symptoms outcomes, such as pressure and vibration perceptions[10,14,28] and nerve conduction velocity and latency.[43] Such improvements might be associated with nerve regeneration mechanisms following exercise, such as increased endoneural blood flow, improved oxygen perfusion, decreased nitric oxide, and decreased oxidative stress.[7,8,56–60] Sensitivity loss is a well-known risk factor for diabetic foot ulceration and any enhancement in the perception of sensorial stimulation might heighten the patients' awareness and thus their ability to avoid potentially dangerous levels of mechanical stress. Although these hypothesis-driven mechanisms are yet to be confirmed, we conclude that a foot-ankle exercise programme may improve neuropathy signs and symptoms. Further studies should be conducted to add to the evidence-base, and also to investigate if these changes remain over the longer-term.

4.3 | Study limitations

A limitation of this systematic review was the great variation in the components of the foot-ankle exercise programs, that is, duration, type, frequency and intensity of the exercises, the organisation of the programme (individual or group-based), and the differences between programs with an in-person component or independent programs. We decided to take a broad approach to foot-ankle exercise programs, including any exercise programme that aimed to improve foot and ankle functionality. This also included gait retraining as this does involve exercising the mobility of the lower extremity. However, we could only specifically compare programs with an in-person component versus those without (home-based programs). No further specific conclusions per intervention type could be drawn given the small number of studies per outcome category. Furthermore, as foot-ankle exercise programs are often tailored to groups of patients, drawing specific conclusions about specific interventions was not feasible within the current systematic review.

We were also limited by differences in exercise intensity. Exercise intensity is usually controlled by manipulating the parameters of the training programme according to the individual's effort, such as the number of repetitions and sets. However, the exact volume and intensity progression were mostly not described, making it difficult to conclude if the heterogeneity among the studies' results could be attributed to the uncontrolled intensity of the programs. Further investigations with increased exercise intensity, longer programme durations, and combinations of different training modalities (independent, group-based, and supervised exercise) are needed to substantially improve the quality of the evidence.

Furthermore, we limited this systematic review to a predefined set of outcomes, thereby excluding additional benefits of foot-ankle exercise programs, such as glucose control or BMI (e.g.[24,42]). The predefined set of outcomes used in this systematic review was also a methodological strength. We used an extensive strategy to determine the most relevant set of outcomes, achieving consensus within the authors, and with input from a diverse group of external experts. Also, most systematic reviews in the field of diabetes-related foot disease focus on only one or two outcomes. Our large set of outcomes makes this a more comprehensive overview.

Regarding the risk of bias assessment, a limitation was using a composite score. Based on this score, a final assessment of high, low, or very low risk of bias was provided per study. Such a composite score has disadvantages, as it weighs all items in the risk of bias assessment equally. For example, not blinding outcome assessors can be considered to pose a more serious bias risk than not having a similarity of groups at baseline. However, where the risk of bias was used in the interpretation (e.g. in rating the certainty of the evidence), we looked beyond the composite score and took the assessment of the individual items into account. The composite scores should therefore only be viewed as an indication, and we urge readers to take the assessment of the individual assessment into account.

5 | CONCLUSIONS

We conclude that, in people at risk of foot ulceration, a foot-ankle exercise programme of 8–12 weeks duration may not prevent or cause diabetes-related foot ulceration. However, such a programme likely improves the ankle joint and first metatarsalphalangeal joint range of motion and neuropathy signs and symptoms. Future research is needed to strengthen the evidence base, and should also focus on the effects of specific components of foot-ankle exercise programs.

AUTHOR CONTRIBUTIONS

Jaap J. van Netten designed the search strings, performed the literature search, assessed the literature, extracted data, performed the meta-analysis and drew conclusions, checked and completed the evidence and risk of bias tables, and wrote the manuscript. Isabel C. N. Sacco assessed the literature, extracted data and drew conclusions, and co-authored reviewed the manuscript. All authors were responsible for developing the clinical questions, selecting the outcomes, formulating the PICOS, and all authors critically reviewed the conclusions and the manuscript. Jaap J. van Netten acted as the secretary of the working group and Sicco A. Bus as the chair of the working group. Jaap J. van Netten and Sicco A. Bus take full responsibility for the content of the publication.

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CONFLICT OF INTEREST STATEMENT

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ETHICS STATEMENT

Not applicable.

DATA AVAILABILITY STATEMENT

All data are from publicly accessible sources, or included in the manuscripts and supporting information.

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SUPPORTING INFORMATION

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

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