Review Article

Effects of Special Therapeutic Footwear on the Prevention of Diabetic Foot Ulcers: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Bo Luo,1 Yuying Cai,2 Dawei Chen,1 Chun Wang,1 Hui Huang,1 Lihong Chen,1 Yun Gao, and Xingwu Ran1

1Innovation Center for Wound Repair, Diabetic Foot Care Center, Department of Endocrinology and Metabolism, West China Hospital, Sichuan University, Chengdu, 610041 Sichuan, China
2West China Medical School, Sichuan University, Chengdu, 610041 Sichuan, China

Correspondence should be addressed to Yun Gao; gaoyun@wchscu.cn and Xingwu Ran; ranxingwu@163.com

Received 4 October 2021; Revised 9 August 2022; Accepted 3 September 2022; Published 26 September 2022

Academic Editor: Vincenza Spallone

Copyright © 2022 Bo Luo et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Objective. To reduce diabetic foot ulcer (DFU) occurrence or recurrence, diabetic therapeutic footwear is widely recommended in clinical practice for at-risk patients. However, the effectiveness of therapeutic footwear is controversial. Thus, we performed a systematic review and meta-analysis of randomized controlled trials (RCTs) to examine whether special therapeutic footwear could reduce the incidence of DFU. Method. We systematically searched multiple electronic databases (Medline, EMBASE, and EMB databases) to identify eligible studies published from inception to June 11, 2021. The database search, quality assessment, and data extraction were independently performed by two reviewers. Efficacy (i.e., incidence of DFU) was explored using the R’meta’ package (version 4.15-1). To obtain more robust results, the random-effects model and the Hartung-Knapp-Sidik-Jonkman method were selected to assess pooled data. Meta-regression analysis and sensitivity analysis were performed to explore heterogeneity, and publication bias was assessed by a visual inspection of funnel plots and the AS-Thompson test. Results. Eight RCTs with a total of 1,587 participants were identified from the search strategy. Compared with conventional footwear, special therapeutic footwear significantly reduced the incidence of DFU (RR 0.49; 95% CI, 0.28-0.84), with no evidence of publication bias (P = 0.69). Unexpectedly, the effectiveness of special therapeutic footwear had a reverse correlation with the intervention time (coefficient = 0.085, P < 0.05) in the metaregression analysis. Conclusion. Special therapeutic footwear with offloading properties is effective in reducing the incidence of DFU. However, the effect may decrease gradually over time. Despite undefined reasons, the optimal utility time and renewal frequency of special therapeutic footwear should be considered.

1. Introduction

Diabetic foot ulcer (DFU), a major complication of diabetes mellitus (DM), is not uncommon and is linked to high-normal levels of morbidity and mortality as well as enormous economic costs. The lifetime risk for the development of a foot ulcer in a patient with DM is estimated to be 19-34% [1]. Diabetes-related foot ulcers precede at least 60% of all non-traumatic lower limb amputations [2]. Moreover, even after the resolution of a foot ulcer, recurrence is also common [1]. The annual incidence of DFU increases by 31.6% in the presence of a history of foot ulceration [3]. Therefore, the prevention of ulcer occurrence or recurrence is of prime importance in the current approach to DFU.

Abnormal biomechanical stress, including elevated vertical pressure and horizontal shear pressure, accounts for the development of a foot ulcer, especially acting on the foot during ambulation. High levels of mechanical pressure contribute to approximately 50% of DFUs during repetitive weight-bearing activity [1, 4–6]. Thus, foot ulceration is probably the most
preventable of all the complications of diabetes [7]. Offloading, namely, reducing supranormal mechanical pressure, is considered the cornerstone of preventing foot ulcer occurrence or recurrence [8–12].

To prevent diabetic foot ulcers, various offloading interventions (e.g., offloading devices, special therapeutic footwear, surgery, and other offloading interventions) are utilized in clinical practice worldwide [11–16]. Among these offloading methods, special therapeutic footwear, recommended by the International Working Group on the Diabetic Foot (IWGDF) for persons at risk for foot ulceration (IWGDF risk 2–3) [8], was demonstrated to be capable of redistributing the pathological mechanical pressure and relieving the abnormal load on the plantar foot surface (i.e., the weight-bearing surface of the foot) [8, 17–19] and could be routinely worn at all times, both indoors and outdoors [8].

Unfortunately, few studies provide strong evidence on the efficacy of special therapeutic footwear. Thus, the quality of evidence for the recommendation of special therapeutic footwear to prevent DFU remains low [8]. Therefore, the aims of this paper were to systematically review published randomized controlled trials (RCTs) and conduct a comprehensive meta-analysis to evaluate the efficacy of reducing foot ulcer occurrence or recurrence in the presence of special therapeutic footwear to provide powerful evidence supporting the rational prescription of special therapeutic footwear in clinical practice.

2. Materials and Methods

The systematic search was performed according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) [20].

2.1. Search Strategy. Two authors (BL and YYC), trained in health research methods, performed a systematic literature search of Medline via OVID, Embase via OVID, and all EBM databases via OVID from inception to June 11, 2021. MeSH combined with free word terms about “Diabetic Foot”, “Foot Ulcer”, “walking”, “walkers”, “shoe”, and “orthotic Devices” were used to identify relevant articles. We also screened the reference lists of published reviews to identify additional relevant studies. A full overview of the specific searches per database is provided in Appendix 1.

2.2. Inclusion and Exclusion Criteria. We included randomized controlled trials (RCTs) that compared special therapeutic footwear against conventional footwear in an at-risk adult population with DM. The special therapeutic footwear, including extra-depth shoes, custom-made shoes, custom-made insoles, or toe orthoses, was defined based on IWGDF guidelines on the prevention and management of diabetic foot disease [8]. Exclusion criteria included (1) all case reports, case series, cross-sectional, letters to the editor, opinion pieces, conference proceedings, and editorials and animal studies, (2) patients with Charcot foot or patients with current (active or healed) foot ulceration and requiring treatment, and (3) combined offloading measures as intervention.

If multiple published reports from the same study were available, we included only the one with the most detailed information for both intervention and outcome. No language restriction was applied.

2.3. Study Screening and Data Extraction. After the removal of duplicates, two authors (BL and YYC) independently screened the titles/abstracts to identify all potentially eligible articles. Both authors then read the full texts of these articles and discussed the final list of included articles to reach consensus. Any discrepancy was resolved in consultation with a third reviewer (YG). Data were extracted by one author (BL) and supervised by a second author (YYC). The primary extracted data included (1) authors; (2) year of publication; (3) study design; (4) sample size; (5) length of follow-up; (6) follow-up rate; (7) sex, age, body mass index (BMI), glycosylated hemoglobin (HbA1c), and duration of diabetes; and (8) the intervention and outcomes of interest. In the present study, the main outcome of interest was the risk of DFU.

2.4. Risk of Bias Assessment. The methodological quality of the included studies was assessed with a modified version of the Cochrane Collaboration tool [21]. This tool was designed to evaluate the risk of bias for randomized studies and includes six domains: randomization, blinding, allocation concealment, incomplete outcome data, selective outcome reporting, and sample size estimate.

The quality of evidence was evaluated using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) working group classification [22, 23]. The GRADE approach categorized evidence from the included studies into high, moderate, low, or very low quality.

2.5. Statistical Analysis. The meta-analysis was conducted using R’ (version 4.0.3), meta’ package (version 4.15-1), metafor’ package (version 2.4-0), and dmetar’ package (https://dmetar .protectlab.org/). The results are presented with 95% confidence intervals (CIs). Estimates for dichotomous outcomes (e.g., foot ulceration: yes or no) were reported as relative risk (RR). The overall relative risk (RR) and 95% CI were calculated by pooling RRs between the intervention group and the control group provided by the original studies using a random-effect model. The Hartung-Knapp-Sidik-Jonkman method was performed to reduce type I error [24].

Statistical heterogeneity between studies was measured using the Q-statistic, Tau²-statistic, H-statistic, and I²-statistic. I² was interpreted based on a “rule of thumb” (I² = 25%: low heterogeneity; I² = 50%: moderate heterogeneity; I² = 75%: substantial heterogeneity) [24]. Between-study heterogeneity was explored by searching for outliers. A study was defined as an outlier when its effect size estimate was so extreme that we have high certainty that the study cannot be part of the “population” of effect sizes we actually pooled in our meta-analysis (i.e., the individual study differs significantly from the overall effect). Additionally, to assess whether studies might exert a very high influence on our overall results and then distort our pooled effect, an influence analysis was performed using the leave-one-out method.
A metaregression analysis was performed to explore the possible source of heterogeneity. At the beginning of the metaregression analysis, multimodel inference was used to comprehensively identify possible predictor combinations that provided the best fit for the metaregression model, and the mixed-effects model was finally employed in the metaregression analysis. Before reporting the results, we tested the robustness of the metaregression model using a permutation test [25].

Publication bias was detected by visually examining the symmetry of the funnel plot and the AS-Thompson test [26].

3. Results

3.1. Search Results. As shown in Figures 1, 906 records were retrieved by the literature search. After study assessment, we identified 8 RCTs [6, 27–33] that met our inclusion criteria.

3.2. Characteristics of Included Studies. The characteristics of the 8 included trials with 1587 participants are summarized in Table 1. Overall, the included studies were conducted in 4 different countries: 3 in Italy, 3 in the USA, 1 in Brazil, and 1 in the Netherlands. These studies enrolled 53–400 patients (mean age range of 56–70, mean baseline HbA1c range of 7.6–8.7%, and mean duration of diabetes range of 12 to 18 years). The duration of follow-up ranged from 3 to 24 months. Of the included studies, a total of 923 (58.2%) participants had a history of foot ulcers. Based on the Risk Classification System of IWGDF [8], more than 96% of the included patients had a moderate or high ulcer risk (IWGDF risk 2-3).

3.3. Risk of Bias Assessment. Table 2 summarizes the methodological quality of the included studies. Of the 8 RCTs, 6 (75%) [6, 28–30, 32, 33] reported adequate random sequence generation, and 2 (25%) [27, 31] were probably adequately generated random sequences; 2 (25%) [6, 32] definitely blinded patients and 5 (62.5%) [6, 27, 28, 30, 33] definitely blinded outcome assessors. Three RCTs (37.5%) [27, 28, 33] definitely conducted sample size estimates. All 8 RCTs (100%) reported complete outcome data and were free from selective reporting.

3.4. Special Therapeutic Footwear and the Incidence of Foot Ulcers. The incidence of DFU was reported in all 8 RCTs [6, 27–33]. Compared with conventional footwear, special therapeutic footwear significantly reduced foot ulceration or ulceration (RR 0.49, 95% CI, 0.28 to 0.84; Figure 2). Moderate heterogeneity existed in the overall analysis ($I^2 = 68\%$, $P < 0.01$).

3.5. The Efficacy of Special Therapeutic Footwear and Intervention Time (Duration of Follow-Up). In the metaregression analysis, which was used to explore the possible source of heterogeneity, the multimodel influence showed that intervention time as the predictor was the best fitting model for further analysis. Subsequently, the metaregression model with intervention time as the predictor indicated that the effect of special therapeutic footwear gradually decreased as the intervention time period was extended (coefficient = 0.085, $P = 0.015$; Figure 3).

3.6. Publication Bias. As shown in Figure 4, an asymmetric funnel plot suggested possible publication bias. To further define whether publication bias existed, the AS-Thompson test was performed. However, the AS-Thompson test did not show statistical significance ($P = 0.69$), which suggested that no evidence of publication bias existed.

4. Discussion

In this study, we extracted data from all RCTs published in the field of special therapeutic footwear to comprehensively evaluate their effectiveness in preventing foot ulcers in populations with diabetes. The results demonstrated that special therapeutic footwear provided a clear benefit in preventing ulcer occurrence or recurrence compared with conventional footwear.

Unlike previous systematic reviews, the present study only included RCTs comparing special therapeutic footwear and conventional footwear, which could provide consistent outcomes to explore the overall effect and obtain high-quality evidence. In a recent systematic review, Ahmed et al. summarized and evaluated the evidence for footwear and insole features for reducing the occurrence of diabetic neuropathy ulceration. However, this review was only a descriptive summary of outcome measures from twenty-five studies with five different study designs, instead of combining results in a statistically sound manner. Similarly, the other five earlier systematic reviews were also limited to conducting a structured literature review.
Table 1: Characteristics of included studies.

(a)

| Author/year | Country | Prevention target | Group | Number of participants | Age (years) | Male (%) | History of foot ulcer (%) | Intervention time (months) | HbA1c (%) at baseline | VPT (V) | BMI (kg/m²) | Duration of diabetes (years) | Incidence of foot ulcers |
|-------------|---------|-------------------|-------|------------------------|-------------|---------|---------------------------|--------------------------|----------------------|---------|------------|----------------------------|--------------------------|
| Bus et al., [6] | Netherlands | Secondary prevention | Intervention | 85 | 62.6 ± 10.2 | 82 | 100 | 18 | 7.5 ± 1.4 | 50.0 ± 11.1 | 30.9 ± 6.4 | 19.9 ± 15.1 | 33 |
| | | | Control | 86 | 63.9 ± 10.1 | 83 | 100 | 18 | 7.6 ± 1.5 | 50.0 ± 9.0 | 30.4 ± 4.9 | 14.7 ± 11.2 | 38 |
| Lavery et al., [27] | USA | Primary and secondary prevention | Intervention | 149 | 69.4 ± 10.0 | 69 | 27.5 | 18 | NR | 29.8 ± 16.1 | NR | 13.0 ± 8.7 | 3 |
| | | | Control | 150 | 71.5 ± 7.9 | 67 | 25.3 | 18 | NR | 29.0 ± 15.1 | NR | 12.0 ± 4.9 | 10 |
| Reiber et al., [28] * | USA | Secondary prevention | Intervention 1 | 121 | 61.0 ± 10.1 | 78 | 100 | 24 | NR | NR | 33.0 ± 6.8 | NR | 18 |
| | | | Intervention 2 | 119 | 62.0 ± 10.1 | 77 | 100 | 24 | NR | NR | 32.0 ± 6.9 | NR | 17 |
| | | | Control | 160 | 63.0 ± 10.0 | 77 | 100 | 24 | NR | NR | 33.0 ± 7.2 | NR | 27 |
| Rizzo et al., [29]** | Italy | Primary and secondary prevention | Intervention | 148 | 68.1 ± 14.1 | 68 | NR | 12 | 8.6 ± 1.4 | 26.1 ± 5.2 | 68.1 ± 14.1 | 17.4 ± 10.9 | 17 |
| | | | Control | 150 | 66.2 ± 9.4 | 66 | NR | 12 | 8.7 ± 1.1 | 27.6 ± 6.1 | 66.2 ± 9.4 | 18.1 ± 12.1 | 58 |
| Scire et al., [30] | Italy | Primary prevention | Intervention | 89 | 58.2 ± 17.1 | NR | 0 | 3 | 8.2 ± 1.7 | 37.4 ± 10.2 | 58.2 ± 17.1 | 15.2 ± 8.9 | 1 |
| | | | Control | 78 | 54.9 ± 18.2 | NR | 0 | 3 | 7.9 ± 0.9 | 34.1 ± 9.9 | 54.9 ± 18.2 | 16.4 ± 9.4 | 12 |
| Uccioi et al., [31] | Italy | Secondary prevention | Intervention | 33 | 59.6 ± 11.0 | 61 | 100 | 12 | NR | 33.0 ± 9.0 | NR | 16.8 ± 12.7 | 9 |
| | | | Control | 36 | 60.2 ± 8.2 | 64 | 100 | 12 | NR | 31.0 ± 12.0 | NR | 17.5 ± 8.0 | 21 |
| Cisneros et al., [32] | Brazil | Primary and secondary prevention | Intervention | 30 | 64.4 ± 9.2 | 63 | 26.7 | 24 | NR | NR | NR | 14.0 ± 10.0 | 8 |
| | | | Control | 23 | 59.8 ± 9.0 | 36 | 34.8 | 24 | NR | NR | NR | 15.0 ± 10.5 | 8 |
| Ubcricht et al., [33] | USA | Secondary prevention | Intervention | 66 | 60.5 ± 10.1 | 76 | 100 | 15 | NR | NR | 32.3 ± 7.1 | NR | 6 |
| | | | Control | 64 | 58.5 ± 10.7 | 81 | 100 | 15 | NR | NR | 31.4 ± 5.5 | NR | 16 |

(b)

| Author/year | Country | Group | Number of participants | Adherence (%) | Insensate to monofilament (%) | Peripheral artery disease (%) | Foot deformity (%) | History of minor amputation (%) |
|-------------|---------|-------|------------------------|---------------|-----------------------------|---------------------------|----------------------|-------------------------------|
| Bus et al., [6] | Netherlands | Intervention | 85 | 41.2 | 94.1 | 28.8 | 95.3 | 0 |
| | | Control | 86 | 51.2 | 91.9 | 37.5 | 97.7 | 0 |
| Lavery et al., [27] | USA | Intervention | 149 | NR | 0 | NR | NR | 12.1 |
| Author/year | Country | Group | Number of participants | Adherence (%) | Insensate to monofilament (%) | Peripheral artery disease (%) | Foot deformity (%) | History of minor amputation (%) |
|-------------|---------|-------|------------------------|--------------|-------------------------------|-------------------------------|-------------------|-------------------------------|
| Reiber et al., [28]* | USA | Intervention 1 | 121 | 83.0 | 59 | NR | NR | 36 | 0 |
| | | Intervention 2 | 119 | 86.0 | 66 | NR | NR | 22 | 0 |
| | | Control | 160 | NR | 52 | NR | NR | 35 | 0 |
| Rizzo et al., [29]** | Italy | Intervention | 148 | NR | NR | NR | NR | NR | 0 |
| | | Control | 150 | NR | NR | NR | NR | NR | 0 |
| Scire et al., [30] | Italy | Intervention | 89 | NR | NR | 0 | 6 | NR | 0 |
| | | Control | 78 | NR | NR | 0 | 8 | NR | 0 |
| Uccioli et al., [31] | Italy | Intervention | 33 | 100 | NR | NR | NR | 0 | 0 |
| | | Control | 36 | NR | NR | NR | NR | 0 | 0 |
| Cisneros et al., [32] | Brazil | Intervention | 30 | ≤6 h/d: 34.5 | NR | NR | NR | 50.0 | NR |
| | | Control | 23 | NR | NR | NR | NR | 30.4 | NR |
| Uhlbrecht et al., [33] | USA | Intervention | 66 | NR | NR | NR | NR | 31.8 | NR |
| | | Control | 64 | NR | NR | NR | NR | 37.5 | NR |

Data are shown as numbers, mean ± SD or %. NR, not reported; BMI, body mass index; VPT, vibration perception threshold; HbA1c, glycosylated hemoglobin. * This study had two intervention groups (intervention 1: custom cork-insert group; intervention 2: polyurethane insert group). For the meta-analyses the intervention 1 group and intervention 2 were incorporated into a single intervention group to compare with control group. ** This study reported only the overall proportions of patients with foot deformities (46%), history of foot ulcer (20%), and history of minor amputation (25%) among all participants.
ally decreased as the intervention time increased. This was rarely noticed in previous relevant studies. The potential mechanisms may include the following: (1) the gradual decreasing of education activities [38]. However, studies that can provide direct evidence are needed to confirm this correlation and identify potential causes in the future. (2) Alternatively, the wear and aging of special therapeutic footwear during intervention may be responsible. Empirical evidence supports the important role of the ruggedness of special therapeutic footwear in the effectiveness of preventing foot ulcers. However, the correlation between these factors has not yet been explored due to the considerable differences in footwear materials, design features, and patients’ habits of walking and usage. Therefore, the optimal utility time and renewal frequency for one pair of special therapeutic footwear have not yet been established. More related RCTs or observational studies should focus on the correlation between the ruggedness of special therapeutic footwear and the effectiveness of preventing foot ulcers in the future.

| Author/year      | Adequate randomization sequence generation | Adequate blinding of participants | Adequate blinding of assessors | Adequate allocation concealment | Free from incomplete outcome data | Free from selective reporting | Sample size estimate | Total risk of bias |
|------------------|-------------------------------------------|----------------------------------|-------------------------------|--------------------------------|----------------------------------|---------------------------|---------------------|-------------------|
| Bus et al., [6]  | Definitely yes                            | Definitely yes                    | Definitely yes                 | Definitely yes                 | Definitely yes                    | Definitely yes           | Probable yes        | Low risk          |
| Lavery et al., [27] | Probably yes                              | Definitely no                     | Definitely yes                 | Definitely yes                 | Definitely yes                    | Definitely yes           | Definitely yes      | High risk         |
| Reiber et al., [28] | Definitely yes                            | Definitely yes                    | Definitely yes                 | Definitely yes                 | Definitely yes                    | Definitely yes           | Definitely yes      | Low risk          |
| Rizzo et al., [29] | Definitely yes                            | Definitely yes                    | Definitely yes                 | Definitely yes                 | Definitely yes                    | Definitely yes           | Definitely yes      | High risk         |
| Scire et al., [30] | Definitely yes                            | Definitely yes                    | Definitely yes                 | Definitely yes                 | Definitely yes                    | Definitely yes           | Definitely yes      | Low risk          |
| Uccioli et al., [31] | Definitely yes                            | Definitely yes                    | Definitely yes                 | Definitely yes                 | Definitely yes                    | Definitely yes           | Definitely yes      | High risk         |
| Cisneros et al., [32] | Definitely yes                            | Definitely yes                    | Definitely yes                 | Definitely yes                 | Definitely yes                    | Definitely yes           | Definitely yes      | Low risk          |
| Ulbrecht et al., [33] | Definitely yes                            | Definitely no                     | Definitely yes                 | Definitely yes                 | Definitely yes                    | Definitely yes           | Definitely yes      | High risk         |

Table 2: Risk of bias of included studies.

| Study          | Experimental Events | Control Events | Risk ratio | RR | 95%–CI | Weight |
|----------------|---------------------|----------------|------------|----|--------|--------|
| Lavery2012     | 3                   | 149            | 10         | 150| 0.30   | [0.08; 1.08] | 8.4%    |
| Reiber2002     | 35                  | 240            | 27         | 160| 0.86   | [0.55; 1.37] | 15.9%   |
| Rizzo2012      | 17                  | 148            | 58         | 150| 0.30   | [0.18; 0.49] | 15.6%   |
| Scire2009      | 1                   | 89             | 12         | 78 | 0.07   | [0.01; 0.55] | 4.6%    |
| Uccioli1995    | 9                   | 33             | 21         | 36 | 0.47   | [0.25; 0.87] | 14.3%   |
| Bus2013        | 33                  | 85             | 38         | 86 | 0.88   | [0.61; 1.26] | 16.8%   |
| Cisneros2010   | 8                   | 30             | 8          | 23 | 0.77   | [0.34; 1.73] | 12.4%   |
| Ulbrecht2014   | 6                   | 66             | 16         | 64 | 0.36   | [0.15; 0.87] | 11.8%   |

Random effects model: 840
Heterogeneity: $I^2 = 68\%$, $r^2 = 0.3558$, $p < 0.01$

Figure 2: Forest plot of the effect of special therapeutic footwear in reducing the incidence of diabetes-related foot ulcers in 8 RCT studies including 1,587 participants and 302 events. Results are expressed as relative risk (RR) and 95% confidence intervals (95% CI). Pooled analysis $P < 0.05$; heterogeneity test: $I^2 = 68\%$, $p < 0.01$. Due to the different study designs and diverse results of the included studies, their structured literature review did not yield consistent and strong evidence to support the clinical benefits of special therapeutic footwear in preventing foot ulcer occurrence. In contrast, the present meta-analysis employed rigorous statistical methods to merge consistent outcomes from the included RCTs and then yielded a robust conclusion.

Interestingly, we observed in the metaregression analysis that the protective effect of special therapeutic footwear gradually decreased as the intervention time increased. This finding suggests that the efficacy of specialized therapeutic footwear in preventing foot ulcers might diminish over time, which was rarely noticed in previous relevant studies. The potential mechanisms underlying this finding are not fully understood. Causative mechanisms may include the following: (1) the gradual declining compliance of the patients may be responsible. Several studies have suggested that adherence to wearing special therapeutic footwear is paramount for the effectiveness of preventing foot ulcers [6, 18, 19]. Regrettably, few studies have explored the association between intervention time and adherence. In a small-sample study of the Dutch population, Keukenkamp et al. explored the effect of using motivational interviewing to improve footwear adherence in individuals with diabetes who were at high risk for foot ulceration and had low footwear adherence. This study showed that median footwear adherence at home was 67% at baseline, 90% at one week, and 56% at 3 months in the motivational interviewing group and 35%, 33%, and 31%, respectively, in the standard education group. These data indirectly indicated that footwear adherence was inclined to worsen with increasing intervention time, despite the intensity of education activities [38]. However, studies that can provide direct evidence are needed to confirm this correlation and identify potential causes in the future.
A recent meta-analysis partially explored individuals who are most likely to benefit. In this study, Crawford et al. performed a subgroup analysis based on whether the subjects of the included trials had a history of foot ulceration. In the subgroup with a history of foot ulcers, special therapeutic footwear did not significantly reduce foot ulcer occurrence (RR 0.71; 95% CI, 0.47-1.06). However, opposite results were observed in the subgroup without a history of foot ulcers (data not shown). They concluded that special therapeutic footwear might be more beneficial to patients without a history of foot ulcers [39]. However, when the subjects included in our meta-analysis were stratified according to the presence or absence of healed DFUs, we did not find a significant correlation between the effectiveness of special therapeutic footwear and a history of DFUs in the metaregression analysis (P = 0.64). In other words, the patients who had no history of DFU did not receive a greater benefit from special therapeutic footwear than those who had a history of DFU. We also performed a subgroup analysis in four RCTs [6, 28, 31, 33] in which all participants had a history of DFU. The results showed that special footwear tended to decrease the risk of foot ulcer recurrence, but this correlation did not reach statistical significance (RR 0.66 [95% CI, 0.34-1.28], P = 0.140) (shown in Appendix 3). This controversy might be attributed to the fact that the performance of subgroup analysis under the condition of a limited number of included studies may lead to unstable results. Thus, more carefully designed and adequately powered studies (both RCTs and observational studies) are warranted to examine whether the effect of special therapeutic footwear differs among patients with or without a history of DFU. From a physiopathological point of view, elevated mechanical stress in the presence of a loss of protective sensation (LOPS) is one of the most common causes of DFU [1]. Peripheral neuropathy can also cause further changes in gait, foot deformity, and soft tissue, all of which can further increase mechanical stress [40]. Thus, the combination of LOPS and elevated mechanical stress leads to tissue damage and DFU [1, 13]. The use of special therapeutic footwear is only intended to help relieve excessive mechanical stress at the plantar and dorsal surfaces of the foot. As foot deformity is one of the common reasons for increased mechanical stress [8], patients with LOPS-foot deformity should benefit more from the use of special therapeutic footwear. For patients with peripheral artery disease (PAD), the severity of PAD may influence the benefits. In patients with severe PAD (e.g., interstitial claudication or rest pain), the main reason for foot ulcers may be tissue ischemia and dysfunction instead of increased mechanical stress [41]. Thus, patients with severe PAD may have fewer benefits from the use of special therapeutic footwear. However, if PAD is mild and does not severely impair blood supply to the feet, patients with mild PAD+foot deformity may also benefit more from the use of special therapeutic footwear. Additionally, most patients with a history of DFU often have elevated mechanical stress at the plantar and dorsal surfaces of the foot, and patients with a minor lower-extremity amputation usually develop foot deformities [42]. Thus, among patients with an IWGDF risk 3, those with LOPS or mild PAD followed by a history of a foot ulcer or minor lower-extremity amputation would probably benefit from the use of special therapeutic footwear. Therefore, despite the second or third class of risk of DFU according to IWGDF classification, a person with diabetes and LOPS or mild PAD would more likely benefit from the use of special therapeutic footwear as long as excessive mechanical stress occurs at the plantar and dorsal surfaces of feet, which may become the main reason for a potential foot ulcer.

Our study has several strengths: (1) in the present meta-analysis, the updated pooled results regarding the efficacy of special therapeutic footwear in preventing foot ulcers were from data from RCTs, which would contribute to producing more convincing evidence. Based on the definition of special
therapeutic footwear in the latest IWGDF Practical Guidelines (2019), we collected data from all eligible RCTs on special footwear and obtained powerful evidence that further supported the recommendation on special footwear in the aforementioned guidelines. (2) In the overall analysis of the main outcome, we selected the random-effect model and the Hartung-Knapp-Sidik-Jonkman method, which could reduce type I error and generate more robust results, particularly in the presence of substantial heterogeneity and a limited number of enrolled studies [43]. (3) Based on the data from all relevant RCTs, we first found that longer intervention time period worsened the efficacy of special therapeutic footwear in preventing diabetes-related foot ulcers, which suggested that more attention should be given to the relationship between patients’ compliance with special therapeutic footwear or special therapeutic footwear durability and the effect of therapeutic footwear. However, our findings should be interpreted cautiously due to some limitations. First, some included trials lacked a rigorous approach and complete reporting, such as sample size estimates, allocation concealment, blinding of assessors, or drop-out rates. Thus, the quality of these individual trials was variable and usually unclear, which might result in a high risk of bias in the current meta-analysis. Second, the diverse materials and design features of special therapeutic footwear as well as the different intervention times of the included trials might contribute to significant heterogeneity in our study. Third, reductions in peak pressure and footwear adherence are important factors that have the potential to significantly impact whether special therapeutic footwear produces improvement in plantar foot ulcer occurrence or recurrence. However, in this study, we were unable to perform statistical pooling for these key parameters because most of the included studies did not collect the relevant data or report them. Fourth, the severity of neuropathy, deformities, vascular status, and history of amputation may also influence DFU occurrence or recurrence. We extracted data, such as insensitivity to monofilament, VPT, foot deformities, peripheral artery disease, and a history of amputation. However, we were unable to obtain the respective incidence of DFU occurrence or recurrence among patients with different severities of neuropathy, foot deformities, peripheral artery disease, or a history of amputation. Thus, we were also unable to explore the influence of these potential factors on DFU occurrence or recurrence.

5. Conclusion

In conclusion, our analyses provide robust evidence that special therapeutic footwear with offloading properties significantly reduces the incidence of DFU. However, the effect may decrease gradually over time. Despite undefined reasons, the optimal utility time and renewal frequency of special therapeutic footwear should be considered.

Data Availability

The data supporting this meta-analysis are from previously reported studies and datasets, which have been cited.

Conflicts of Interest

The authors declare no conflict of interest.

Acknowledgments

This study was supported by the 1.3.5 Project for Disciplines of Excellence, West China Hospital, Sichuan University (Grant No. ZYGID18025), the Science and Technology Bureau of Sichuan Province (Grant No. 2022YSF0308, 2021YSF0014, 2021JDKP0044, 2020YSF0193), the Science and Technology Bureau of Chengdu City (Grant No. 2017-CY02-00028-GX), and the National Youth Science Fund Project of National Natural Science Foundation of China (Grant No. 81700087).

Supplementary Materials

Supplementary 1. Appendix 1: Search strategy. Supplementary 2. Appendix 2: PRISMA checklist. Supplementary 3. Appendix 3: Subgroup analysis for patients with a history of foot ulceration.

References

[1] D. G. Armstrong, A. J. Boulton, and S. A. Bus, "Diabetic foot ulcers and their recurrence," The New England Journal of Medicine, vol. 376, no. 24, pp. 2367–2375, 2017.
[2] D. G. Armstrong, T. K. Fisher, B. Lepow, M. L. White, and J. L. Mills, "Pathophysiology and principles of management of the diabetic foot," in Mechanisms of Vascular Disease: A Reference Book for Vascular Specialists, R. Fitridge and M. Thompson, Eds., pp. 475–496, University of Adelaide Press, Adelaide, AU, Australia, 2011.
[3] Y. Jiang, X. Wang, L. Xia et al., "A cohort study of diabetic patients and diabetic foot ulceration patients in China," Wound Repair and Regeneration, vol. 23, no. 2, pp. 222–230, 2015.
[4] M. Monteiro-Soares, E. J. Boyko, J. Ribeiro, I. Ribeiro, and M. Dinis-Ribeiro, "Predictive factors for diabetic foot ulceration: a systematic review," Diabetes/Metabolism Research and Reviews, vol. 28, no. 7, pp. 574–600, 2012.
[5] F. Crawford, G. Cezard, F. M. Chappell et al., "A systematic review and individual patient data meta-analysis of prognostic factors for foot ulceration in people with diabetes: the international research collaboration for the prediction of diabetic foot ulcerations (PODUS)," Health Technology Assessment, vol. 19, no. 57, pp. 1–210, 2015.
[6] S. A. Bus, R. Waaijman, M. Arts et al., "Effect of custom-made footwear on foot ulcer recurrence in diabetes: a multicenter randomized controlled trial," Diabetes Care, vol. 36, no. 12, pp. 4109–4116, 2013.
[7] M. Brownlee, L. P. Aiello, M. E. Cooper, A. I. Vinik, J. Plutzky, and A. J. M. Boulton, "Complications of diabetes mellitus," in William's textbook of endocrinology, p. 1558, Elsevier, Philadelphia, PA, USA, 13th edition, 2016.
[8] N. C. Schaper, J. J. van Netten, J. Apelqvist et al., "Practical guidelines on the prevention and management of diabetic foot disease (IWGDF 2019 update)," Diabetes/Metabolism Research and Reviews, vol. 36, no. S1, article e3266, 2020.
[9] S. A. Bus, “Priorities in offloading the diabetic foot,” *Diabetes/Metabolism Research and Reviews*, vol. 28, pp. 54–59, 2012.

[10] W. J. Jeffcoate and K. G. Harding, “Diabetic foot ulcers,” *The Lancet*, vol. 361, no. 9368, pp. 1545–1551, 2003.

[11] M. L. Maciejewski, G. E. Reiber, D. G. Smith, C. Wallace, S. Hayes, and E. J. Boyko, “Effectiveness of diabetic therapeutic footwear in preventing ulceration,” *Diabetes Care*, vol. 27, no. 7, pp. 1774–1782, 2004.

[12] S. Spencer, “Pressure relieving interventions for preventing and treating diabetic foot ulcers,” *Cochrane Database of Systematic Reviews*, vol. 3, article CD002302, 2000.

[13] S. A. Bus, G. D. Valk, R. W. van Deursen et al., “The effectiveness of footwear and offloading interventions to prevent and heal foot ulcers and reduce plantar pressure in diabetes: a systematic review,” *Diabetes/Metabolism Research and Reviews*, vol. 24, Supplement 1, pp. S162–S180, 2008.

[14] A. J. Dorrsteijn, D. M. Kriegsman, and G. D. Valk, “Complex interventions for preventing diabetic foot ulceration,” *Cochrane Database of Systematic Reviews*, vol. 1, article CD007610, 2010.

[15] R. J. Hinchcliffe, G. D. Valk, J. Apelqvist et al., “A systematic review of the effectiveness of interventions to enhance the healing of chronic ulcers of the foot in diabetes,” *Diabetes/Metabolism Research and Reviews*, vol. 24, Supplement 1, pp. S119–S144, 2008.

[16] J. Mason, C. O’Keeffe, A. McIntosh, A. Hutchinson, A. Booth, and R. J. Young, “A systematic review of foot ulcer in patients with type 2 diabetes mellitus: I. prevention,” *Diabetic Medicine*, vol. 16, no. 10, pp. 801–812, 1999.

[17] J. J. van Netten, P. A. Lazzarini, D. G. Armstrong et al., “Diabetic foot Australia guideline on footwear for people with diabetes,” *Journal of Foot and Ankle Research*, vol. 11, no. 1, p. 2, 2018.

[18] S. Ahmed, A. Barwick, P. Butterworth, and S. Nancarrow, “Footwear and insole design features that reduce neuropathic plantar foot ulcer risk in people with diabetes: a systematic literature review,” *Journal of Foot and Ankle Research*, vol. 13, no. 1, p. 30, 2020.

[19] M. López-Moral, J. L. Lázaro-Martínez, E. García-Morales, Y. García-Alvarez, F. J. Álvaro-Afonso, and R. J. Molines-Barroso, “Clinical efficacy of therapeutic footwear with a rigid rocker sole in the prevention of recurrence in patients with diabetes mellitus and diabetic polyneuropathy: a randomized clinical trial,” *PLoS One*, vol. 14, no. 7, article e0219537, 2019.

[20] D. Moher, A. Liberati, J. Tetzlaff, D. G. Altman, and The PRISMA Group, “Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement,” *PLOS Medicine*, vol. 6, no. 7, article e1000697, 2009.

[21] J. P. T. Higgins, D. G. Altman, P. C. Gøtzsche et al., “The Cochrane collaboration’s tool for assessing risk of bias in randomised trials,” *BMJ*, vol. 343, article d5928, 2011.

[22] M. H. Murad, V. M. Montori, A. N. Sidawy et al., “Guideline methodology of the society for vascular surgery including the experience with the GRADE framework,” *Journal of Vascular Surgery*, vol. 53, no. 5, pp. 1375–1380, 2011.

[23] M. H. Murad, B. A. Swiglo, A. N. Sidawy, E. Ascher, and V. M. Montori, “Methodology for clinical practice guidelines for the management of arteriovenous access,” *Journal of Vascular Surgery*, vol. 48, no. 5, pp. 526–530, 2008.

[24] J. P. Higgins, S. G. Thompson, J. J. Deeks, and D. G. Altman, “Measuring inconsistency in meta-analyses,” *BMJ*, vol. 327, no. 7414, pp. 557–560, 2003.

[25] J. P. Higgins and S. G. Thompson, “Controlling the risk of spurious findings from meta-regression,” *Statistics in Medicine*, vol. 23, no. 11, pp. 1663–1682, 2004.

[26] G. Rücker, G. Schwarzer, and J. Carpenter, “Arcsin test for publication bias in meta-analyses with binary outcomes,” *Statistics in Medicine*, vol. 27, no. 5, pp. 746–763, 2008.

[27] L. A. Lavery, J. LaFontaine, K. R. Higgins, D. R. Lancot, and G. Constantinides, “Shear-reducing insoles to prevent foot ulceration in high-risk diabetic patients,” *Advances in Skin & Wound Care*, vol. 25, no. 11, pp. 519–524, 2012.

[28] G. E. Reiber, D. G. Smith, C. Wallace et al., “Effect of therapeutic footwear on foot ulceration in patients with diabetes: a randomized controlled trial,” *JAMA*, vol. 287, no. 19, pp. 2552–2558, 2002.

[29] L. Rizzo, A. Tedeschi, E. Fallani et al., “Custom-made orthosis and shoes in a structured follow-up program reduces the incidence of neuropathic ulcers in high-risk diabetic foot patients,” *The International Journal of Lower Extremity Wounds*, vol. 11, no. 1, pp. 59–64, 2012.

[30] V. Sciri, E. Leporati, I. Teobaldi, L. A. Nobili, L. Rizzo, and A. Piaggesi, “Effectiveness and safety of using Podikon digital silicone padding in the primary prevention of neuropathic lesions in the forefront of diabetic patients,” *Journal of the American Podiatric Medical Association*, vol. 99, no. 1, pp. 28–34, 2009.

[31] L. Uccioli, E. Faglia, G. Monticone et al., “Manufactured shoes in the prevention of diabetic foot ulcers,” *Diabetes Care*, vol. 18, no. 10, pp. 1376–1378, 1995.

[32] L. L. Cisneros, “Avaliação de um programa para prevenção de úlceras neuropáticas em portadores de diabetes,” *Revista Brasileira de Fisioterapia*, vol. 14, no. 1, pp. 31–37, 2010.

[33] J. S. Ulbrecht, T. Hurley, D. T. Mauger, and P. R. Cavanagh, “Prevention of recurrent foot ulcers with plantar pressure-based in-shoe orthoses: the CareFUL prevention multicenter randomized controlled trial,” *Diabetes Care*, vol. 37, no. 7, pp. 1982–1989, 2014.

[34] N. Singh, D. G. Armstrong, and B. A. Lipsky, “Preventing foot ulcers in patients with diabetes,” *JAMA*, vol. 293, no. 2, pp. 217–228, 2005.

[35] J. Paton, G. Bruce, R. Jones, and E. Stenhouse, “Effectiveness of insoles used for the prevention of ulceration in the neuropathic diabetic foot: a systematic review,” *Journal of Diabetes and its Complications*, vol. 25, no. 1, pp. 52–62, 2011.

[36] A. Healy, R. Naemi, and N. Chockalingam, “The effectiveness of footwear as an intervention to prevent or to reduce biomechanical risk factors associated with diabetic foot ulceration: a systematic review,” *Journal of Diabetes and its Complications*, vol. 27, no. 4, pp. 391–400, 2013.

[37] P. R. Cavanagh and S. A. Bus, “Off-loading the diabetic foot for ulcer prevention and healing,” *Plastic and Reconstructive Surgery*, vol. 127, Supplement 1, pp. 2485–256S, 2011.

[38] R. Keukenkamp, M. J. Merkx, T. E. Busch-Westbroek, and S. A. Bus, “An explorative study on the efficacy and feasibility of the use of motivational interviewing to improve footwear adherence in persons with diabetes at high risk for foot ulceration,” *Journal of the American Podiatric Medical Association*, vol. 108, no. 2, pp. 90–99, 2018.

[39] F. Crawford, D. J. Nicolson, A. E. Amanna et al., “Preventing foot ulceration in diabetes: systematic review and meta-analyses ofRCT data,” *Diabetologia*, vol. 63, no. 1, pp. 49–64, 2020.
[40] M. Fernando, R. Crowther, P. Lazzarini et al., “Biomechanical characteristics of peripheral diabetic neuropathy: a systematic review and meta-analysis of findings from the gait cycle, muscle activity and dynamic barefoot plantar pressure,” *Clinical Biomechanics*, vol. 28, no. 8, pp. 831–845, 2013.

[41] M. E. Edmonds and A. V. M. Foster, *Managing the Diabetic Foot*, John Wiley & Sons, Ltd, Chichester, UK, 3rd edition, 2014.

[42] R. J. Hinchliffe, R. O. Forsythe, J. Apelqvist et al., “Guidelines on diagnosis, prognosis, and management of peripheral artery disease in patients with foot ulcers and diabetes (IWGDF 2019 update),” *Diabetes/Metabolism Research and Reviews*, vol. 36, article e3276, Supplement 1, 2020.

[43] J. IntHout, J. P. Ioannidis, and G. F. Borm, “The Hartung-Knapp-Sidik-Jonkman method for random effects meta-analysis is straightforward and considerably outperforms the standard DerSimonian-Laird method,” *BMC Medical Research Methodology*, vol. 14, no. 1, p. 25, 2014.