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PLEASE CITE THE PUBLISHED VERSION

<https://doi.org/10.1016/j.jdiacomp.2020.107815>

PUBLISHER

Elsevier BV

VERSION

AM (Accepted Manuscript)

PUBLISHER STATEMENT

This paper was accepted for publication in the journal Journal of Diabetes and its Complications and the definitive published version is available at <https://doi.org/10.1016/j.jdiacomp.2020.107815>

LICENCE

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REPOSITORY RECORD

Jones, Petra, Melanie J Davies, Kamlesh Khunti, Daniel Fong, and David Webb. 2020. "In-shoe Pressure Thresholds for People with Diabetes and Neuropathy at Risk of Ulceration: A Systematic Review". Loughborough University. <https://hdl.handle.net/2134/13340852.v1>.

<https://doi.org/10.1016/j.jdiacomp.2020.107815> Link to formal publication

REVIEW ARTICLE

In-shoe Pressure Thresholds for People with Diabetes and Neuropathy at Risk of Ulceration: A Systematic Review

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Introduction

In-shoe pressure thresholds play an increasingly important role in the prevention of diabetes-related foot ulceration (DFU). The evidence of their effectiveness, methodological consistency and scope for refinement are the subject of this review.

Methods

1,107 records were identified (after duplicate removal) based on a search of five databases for studies which applied a specific in-shoe pressure threshold to reduce the risk of ulceration. 37 full text studies were assessed for eligibility of which 21 were included.

Results

Five in-shoe pressure thresholds were identified, which are employed to reduce the risk of diabetes-related foot ulceration: a mean peak pressure threshold of 200 kPa used in conjunction with a 25% baseline reduction target; a sustained pressure threshold of 35 mmHG, a threshold matrix based on risk, shoe size and foot region, and a 40-80% baseline pressure reduction target. The effectiveness of the latter two thresholds have not been assessed yet and the evidence for the effectiveness of the other in-shoe pressure thresholds is limited, based only on two RCTs and two cohort studies.

Conclusions

The heterogeneity of current measures precludes meta-analysis and further research and methodological standardisation is required to facilitate ready comparison and the further development of these pressure thresholds.

KEYWORDS

diabetes, foot, neuropathy, in-shoe, pressure, threshold

Abbreviations

BMI, Body mass index; CG, Control group, without diabetes; D, Diabetes without neuropathy; DFU, Diabetes-related foot ulcer; DN, Diabetes and neuropathy; DN+HU, Diabetes, neuropathy and a history of foot ulceration; kPa, Kilopascals, a measurement unit of pressure; mmHG, Millimetres of Mercury, an alternative measurement unit of pressure; LOPS, Loss of protective sensation associated with neuropathy; MTH, Metatarsal heads; MTP, Metatarsophalangeal joint; N/cm², Newtons, an alternative measurement unit of pressure for a defined area in centimetres; SD, Standard deviation; VPT, Vibration perception threshold.

1. Introduction

Globally 463 million adults are currently living with diabetes which is predicted to rise to 700 million by 2045 [1]. Among these, 15%-25% [2, 3] are likely to develop a foot ulcer within their lifetime. The financial burden of diabetes-related foot ulceration (DFU) is immense: an estimated \$9-13 billion [4] and up to £1.13 billion per year [5] is spent on treatment in the United States and UK alone. DFU is also associated with an increased risk of cardiovascular mortality [6] and amputation [7]. An estimated 40% of ulcers will reoccur within a year after healing, which increases to almost 60% within three years [8].

Predicting ulceration events remains problematic given their multi-factorial nature [9] where the degree of peripheral vascular disease and neuropathy, foot shape and deformity, altered Achilles reflex and footwear may all be implicated. Development of a threshold or set of thresholds to either predict or at least minimise the risks of DFU is important given five-year mortality rates after new-onset diabetic ulceration ranging between 43% and 55% [10]. As many as one-in-three individuals with neuropathic DFU will have an amputation [11].

A particularly active area of research concerns ulcer prevention through assessment of in-shoe plantar pressures, given that people with diabetes and neuropathy have increased mean plantar pressures [12-17] in comparison with those with healthy feet (see Supplemental Table 1). These pressures are elevated further in those with a history of ulceration as well as diabetes and neuropathy [16, 18-19]. Elevated plantar pressures may be linked to a variety of factors including deformity [20], limited joint mobility [21] and ankle equinus [22], soft tissue glycation [23], shortening of the Achilles tendon [24] or disorganisation of its tendon fibres [25-26] and a reduction in cross-sectional muscle area [27].

A review of pressure thresholds is also important because peripheral neuropathy limits the ability to detect abnormal high pressures within footwear. In-shoe pressure monitoring technology offers potential both to determine thresholds associated with an increased risk of ulceration and a means of alerting individuals with neuropathy to their presence. In-shoe pressure analysis is also playing a growing role in footwear, insole and orthotic design and may also come have a future role to play in fit, having been used to evaluate the role toe box shape [28]. There are no systematic reviews on

this topic as yet as previous reviews are narrative [29] and the range of available wearable devices is growing with a corresponding expanding literature that requires synthesis.

In this systematic review, we examine the literature around specific in-shoe pressure thresholds to prevent diabetes-related foot ulceration.

2. Methods

2.1 Search strategy

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used to perform this systematic review. [30] This involved defining the population of interest, which includes people with diabetes mellitus (type 1 or type 2) with neuropathy and either a history of foot ulceration or those at risk of ulceration. By risk of ulceration, we refer to the International Working Group on the Diabetic Foot (IWGDF) definition of an at-risk person as a 'person with diabetes who does not have an active foot ulcer, but who has peripheral neuropathy, with or without the presence of foot deformity or peripheral artery disease, or a history of foot ulcer(s) or amputation of (a part of) the foot or leg' [31].

We searched Medline/Pubmed, Scopus, Google Scholar and Web of Science databases for all studies ever published until 1 September 2020 using the search criteria "pressure" AND "foot" AND "in-shoe" AND "diabetes" AND "threshold" across all databases. In addition, a further search was carried out on all these databases with no start date specified through to 3 September 2020 which used the search terms "plantar" AND "pressure" AND "foot" AND "in-shoe" AND "diabetes" AND "threshold".

2.2 Inclusion Criteria

Studies were included if they fulfilled the following selection criteria: (i) Studies which a priori involved the application of specific *in-shoe* plantar pressure thresholds in an intervention intended to prevent DFU; (ii) Type of study: RCT, cohort, or case-control studies published within peer-reviewed journals; (iii) Results: studies which evaluated pressure reduction through an intervention related to the use of in-shoe pressure thresholds and DFU; and (iv) published in the English language. We concentrated on in-shoe rather than barefoot pressure thresholds given people with diabetes and neuropathy spend most of their time wearing footwear and engaging in physical activity during which foot inflammation, calluses or trauma may arise. Poor footwear fit is considered a risk factor for foot injury and ulceration, notably at the toes, or metatarsals [32]. The review does not include thresholds for healed Charcot foot, amputation or post-surgery.

2.3 Data extraction

Data extracted was performed by PJ. This included (i) Article identification: title, authors and publication year; (ii) Methods: sample size and demographic (e.g. history of ulceration, neuropathy), loss of protective sensation testing to establish neuropathy, in-shoe pressure monitoring methodology including pace, number of steps, sensor type and standardisation of footwear and socks, plantar region of interest and pressure threshold criteria; (iii) Outcome: objective and type of intervention; (iv) Results: methods of statistical analysis and degree of statistical significance (Tables 1–3). DW checked the extracted data and was consulted regarding queries on whether to include or exclude particular studies with MJD available to resolve any disagreements.

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Figure 1 PRISMA flow diagram of article selection process through the systematic review

3. Results

A total of 2,370 references were identified during the combined database searches, of which 1,267 were duplicates. 1,108 studies were screened (including 5 papers found through citations) based on an assessment of title and abstract of which 1,071 were discarded, including studies unconnected with diabetes or neuropathy, studies focused on the pressure sensing technology itself or pressure monitoring without any attempt to derive or apply in-shoe thresholds. Overall, 37 studies full text articles were reviewed from which 21 peer-reviewed research articles were selected for inclusion in accordance with the eligibility criteria (see Figure 1 above).

3.1 Demographics

All 21 studies were completed within the last 11 years, ranging from 2009 to 2019 including numbers of participants from 10 [33] to 171 [34, 42, 48]. Age, where provided for the whole cohort, varies between 57.0 ± 9.0 [35] – 68.0 ± 9.0 [36], with the percentage of male participants ranging from 38.5% [36] – 89.0% [37] (Table 1). A breakdown of type 1 and type 2 diabetes participants is available in 9 studies ranging between 28.6% type 1 [38] to 41.0% [39] (Table 1). Duration of diabetes (reported in 12 studies) ranges between 12.6 ± 7.6 [36] – 22.0 ± 15.9 [40].

3.2 Current In-shoe Pressure Thresholds

3.2.1 200 kPa in-shoe pressure threshold

Five in-shoe pressure thresholds were found and summarised (Table 2). Among these five thresholds, the most frequently applied was a ‘mean peak pressure’ of 200 kPa. This referred initially to the mean average of the maximum (peak) in-shoe plantar pressures at the previous ulcer location (region of interest) during 30 steps of walking [41] and later to the mean average of the maximum (peak) in-shoe plantar pressure at the specified regions of interest during a specified number of steps whilst walking (see regions of interest and no. of steps in Table 2). This 200 kPa threshold was used primarily as a benchmark in the design and modification of footwear (n=9) [34, 35, 39, 40-44, 50], insoles (n=3) [36, 45, 46] and orthoses (n=1) [47] but also in the analysis of equinus (n=1) [22] and real-time modification of gait to reduce pressure (“biofeedback”) (n=2) [34, 51]. One study was unique in using a 450 kPa barefoot pressure threshold in the initial selection of regions of interest for optimised insole designs later assessed using the 200 kPa threshold [46].

3.2.2 25% baseline in-shoe pressure reduction target

Some studies aimed to *either* reduce in-shoe pressure below 200 kPa or by 25% (n=4) [34, 44, 39-40]. A footwear offloading target of 25% was chosen to represent a “significant, probably clinically relevant reduction in plantar pressure” [44]. In another study, only 16 of 50 previous ulcer locations had pressures above 200 kPa [40] which may also have been a factor in developing this alternate 25% reduction target for footwear modification.

3.2.3 40-80% baseline in-shoe pressure reduction target

An alternate in-shoe pressure reduction target of 40-80% of baseline at the area of highest peak plantar pressure has been used in biofeedback, the process of adjusting walking strategy/gait to reduce in-shoe pressures. The aim was to assess the feasibility of achieving this reduction for a minimum of seven steps out of each ten during three trials of walking in habitual footwear during

both the learning phase and during ten-day follow-up [38, 51] or two week and six week follow-up [52]. This large threshold target range appears to be based on its potential achievability following a short review of studies of reductions within healthy volunteers, and to facilitate ease of learning [51].

3.2.4 *Low sustained in-shoe pressure threshold of 32-35 mmHG*

A low sustained pressure in-shoe threshold of 32 mmHG (millimetre of mercury, a pressure measure equivalent to 4.3 kPa) for a fifteen-minute period was suggested in Ferber et al. [33] based on the minimum pressure reported to cause bed sores. However, the study was limited to ten healthy participants, and intended simply to evaluate the SurroSense pressure monitoring insole against a gold standard. A subsequent RCT by Abbott et al. [37] evaluated a similar threshold of a sustained pressure exceeding 35 mmHG in-shoe for 95% of the preceding 15 minutes against DFU outcomes in 58 participants with diabetes and neuropathy. Real-time biofeedback alerts suggested wearers should modify their stance or position, or rest.

3.2.5 *Risk, shoe size and foot region threshold matrix*

Giacomozzi proposed a matrix of thresholds depending on (1) the regions of the foot (toes, forefoot, midfoot or rearfoot); (2) the level of risk (level 0 = no neuropathy, history of ulceration or foot deformity, 1 = neuropathy but no deformity or history of ulceration; 2 = neuropathy and deformity but no history of ulceration or 3 = neuropathy, deformity and a history of ulceration) and (3) individual shoe size [49]. The suggested thresholds were based on reference in-shoe pressures obtained during walking in semi-rigid Terapes shoes with Pedar-X insoles for 20 healthy volunteers and 11 participants with diabetes and neuropathy.

3.3 *Outcomes*

The evidence of the effectiveness of these in-shoe pressure threshold is limited to just four studies [34, 37, 41, 48], consisting of two non-RCT cohort studies [41, 48] and one RCT [34] relating to the 200 kPa threshold and one RCT relating to the 35 mmHG threshold [37]. The majority of these studies are non-RCT (n=17) [22, 33, 35, 36, 38-46, 48-51] concerned with the feasibility of various mechanisms of pressure reduction within the threshold target or as a benchmark for evaluating multiple interventions e.g. rival insoles or footwear designs. The only other RCT is concerned with pressure reduction outcomes in relation to cost and supply chain analysis [47] (Table 1).

This 200 kPa threshold is derived from Owings et al. (2009) [41] a small non-RCT where Pedar-X brand insole sensors were placed within prescription extra depth footwear with custom insoles to measure average in-shoe pressures of 49 people with diabetes and neuropathy who had been in remission from DFU for at least 90 days (average remission 3.6 years). The participants' mean in-shoe pressure of 207 kPa whilst walking 30 steps, was rounded down to 200 kPa to provide a target mean in-shoe peak pressure. Participants were typically wearing an extra-depth shoe with custom-moulded insoles and a custom-moulded sandal for indoor use.

In a cohort study of 171 people with diabetes, neuropathy and a recently healed ulcer, wearing prescription footwear that reduced in-shoe pressure below this 200 kPa threshold (n=171) for more than 80% of daylight hours led to a decreased risk of ulcer recurrence (odds ratio 0.43 [0.20-0.94]) [48].

The main evidence for this threshold comes from an RCT of 171 people with diabetes, neuropathy and a recently healed ulcer. The intervention group wore footwear which reduced pressures either below the 200 kPa threshold or by 25% of baseline, which were evaluated at three monthly follow-ups for up to 18 months and succeeded in decreased re-ulceration by 46% (odds ratio 0.38 [0.15-0.99], $p=0.045$) [34]. The 25% improvement in in-shoe pressure led to a non-significant relative risk reduction of 11% insufficient to significantly reduce ulcer recurrence risk [34] unless accompanied by sufficient adherence (80% of all steps taken in custom made footwear). The other studies (non-RCT) which used a target 25% pressure reduction did not evaluate the effect on ulceration rates, given their alternative aims of evaluating feasibility, optimisation and the number of rounds of modifications required to achieve this target [39-40, 44].

Abbott et al. [37] is a RCT which evaluated a sustained pressure threshold exceeding 35 mmHG in-shoe for 95% of the preceding 15 minutes against DFU outcomes in 58 participants with diabetes and neuropathy. Real-time biofeedback alerts suggested wearers should modify their stance or position, or rest. A 71% reduction in the cumulative number of ulcer sites over total person days was achieved in the intervention group as compared with the control group (incident rate ratio 0.29, 95% CI, 0.09-0.93, $p=0.037$) in footwear worn on average 6.1 hours per day. Numbers of patients who ulcerated were 6 of 26 in the control group versus 4 of 32 in the intervention group.

The impact of a 40-80% reduction in baseline in-shoe pressure through biofeedback-based walking strategies on ulceration rates has yet to be evaluated [38, 51, 52]. To date, only one study has evaluated retention of these walking strategies beyond ten days, where only 50% achieved the required maximum pressure threshold in a small non-RCT cohort with just 11 participants [52].

Equally the suggested approach of a matrix of different thresholds providing thresholds for four regions (toes, forefoot, midfoot and rearfoot) based on both an individual's risk level and shoe size [49] has yet to be formally assessed against ulceration rates or days spent in remission. This protocol was derived from a validation session of only 11 participants with diabetes and neuropathy who were provided with modified prescription footwear and followed for only four months. The Terapes shoe with which reference data was also obtained has a very small heel and appears to be open-toed [49].

3.4 Population within In-Shoe Pressure Threshold Studies

Both the 200 kPa and 35 mmHG in-shoe pressure thresholds have been applied to prevent re-ulceration in those with diabetes, neuropathy and a history of ulceration ($n=11$) [34, 36, 37, 39-44, 47, 48]. The 200 kPa threshold was originally intended to prevent re-ulceration, but has since been applied to those with diabetes, neuropathy and no history of ulceration ($n=2$) [35, 45] or mixed groups of both ($n=3$) [36, 44, 47], or with diabetes without neuropathy ($n=2$) [35, 50]. Most studies aim to prevent re-ulceration in those with a "recently healed ulcer" ($n=8$) [34, 37, 41-44, 39-40, 48] meaning an ulcer that healed within the 18 months prior to the study ($n=6$) [34, 42-43, 39-40, 48] or which has been healed for more than 90 days ($n=1$) with a mean of 3.6 years [41] or where the length of time since the ulcer healed is unspecified ($n=2$) [44, 37].

TABLE 1 In-shoe Pressure Threshold Study Demographics

Paper, Year	Study Type	Size	Cohort	Recently Healed	DM1	DM2	Age	M / F (%)	Weight	Duration (Diabetes)
Abbott, 2019 [37]	RCT (multicentre)	26 32	DN+HU DN+HU	“recent history” (not specified)	58		67.1 ± 9.6 59.1 ± 8.5	89.0 / 11.0 88.0 / 12.0	95.7 ± 16.8 102.1 ± 18.9	21.2 ± 10.7 22.2 ± 14.3
Arts, 2012 [42]	Non-RCT. Cohort study	171	DN+HU	< 18 months	49	122	62.8 ± 10.2	81.9 / 18.1	--	14.0 ± 10.0 - 27.5~
Arts, 2015 [43]	Non-RCT. Cohort study. (From Bus 2013 below)	85	DN+HU	< 18 months	28	57	62.6 ± 10.2	82.4 / 17.6	--	19.9 ± 15.1
Bus, 2011 [44]	Noninterventional study	18 5	DN+HU DN	Length of time not specified	8	15	59.1 ± 12.6	73.9 / 26.1	--	13.8 ± 10.1
Bus, 2013* [34]	RCT. (With/without pressure relief)	171	DN+HU	< 18 months	49	122	63.3 ± 10.2	81.9 / 18.1	--	19.9 ± 15.1
Chapman, 2014 [50]	Non-RCT Factorial design (2-way ANOVA)	87	D	--	--	--	--	--	--	--
De León Rodriguez, 2013 [38]	Non-RCT. Cohort study. (new walking strategy)	21	DN	--	6	15	57.8 ± 2.9	57.1 / 42.9	85.8 ± 3.6	17.3 ± 2.1
Ferber, 2013 [33]	Non-RCT. Prototype sensor validation	10	CG	--	--	--	27.9 ± 6.7	70.0 / 30.0	78.6 ± 11.1	--
Giacomozzi, 2013 ** [49]	Protocol + preliminary validation	20 11	CG DN	--	-- --	-- --	67.0 ± 7.9 70.2 ± 6.7	-- --	75.0 ± 8.1 79.0 ± 11.5	-- --
Lin, 2013 [36]	Non-RCT. Cohort study. (plug removal insole)	26 (3)	DN DN+HU	--	0	26	68.0 ± 9.0	38.5 / 61.5	64.6 ± 9.6	12.6 ± 7.6
Martinez-Santos, 2019 [45]	Non-RCT. Cohort study (9 insole variants)	60	DN	Excluded DN+HU	60		67.3 ± 13.0	66.6 / 33.4	--	--
Owings, 2009 [41]	Non-RCT. Cohort study.	49	DN+HU	>90 days Median 3 years since healing	--	--	62.9 ± 10.3	77.6 / 22.4	88.1 ± 17.5	
Parker, 2019 [47]	RCT (pressure reduction outcomes + cost analysis)	57 (23)	DN DN+HU	>2 years since HU	57		61.4 ± 10.0 66.3 ± 10.5	88.5 / 11.5 84.6 / 15.4	--	--
Pataky, 2010 [51]	Non-RCT. Cohort study.	13	DN	--	13		60.8 ± 12.3	46.2 / 53.8	82.9 ± 14.1	16.0 ± 10.6
Preece, 2017 [35]	Non-RCT. Cohort study (rocker sole design evaluation).	102 (17) 66	D (DN) CG	Excluded DN+HU	102		57.0 ± 9.0	51.0 / 49.0	87.0 ± 18.0	--
Searle, 2018 [22]	Non-RCT. Cohort study (equinus within diabetes)	71 65	D DN	--	--	--	--	--	--	--

Telfer, 2017 [46]	Randomised crossover (insole optimisation)	18	DN	--	0	18	64.4 ± 9.2	75.0 / 25.0	87.8 ± 16.1	17.5 ± 12.3
Van, 2017 [52]	Non-RCT. Cohort study.	11	DN	--	--	--	--	--	--	--
Waaijman, 2011 [40]	Non-RCT. Cohort study.	58	DN+HU	< 18 months	--	--	62.6 ± 10.3	--	--	22.0 ± 15.9
Waaijman, 2012 [39]	Non-RCT. Cohort study.	117	DN+HU	< 18 months	34	83	63.3 ± 10.1	--	--	17.7 ± 14.1
Waaijman, 2014 [48]	Non-RCT. Cohort study.	171	DN+HU	< 18 months Mean 5.5 months ± 5.5	49	122	63.3 ± 10.1	81.9 / 18.1	--	17.3 ± 13.5

Key

Participant Cohort: CG = Control group, without diabetes. D = people with diabetes. DN = people with both diabetes and neuropathy. DN+HU = people with diabetes, neuropathy and a history of ulceration, usually a recently healed plantar foot ulcer. Brackets indicate a subgroup of the main cohort included within the total.

All demographics: mean ± standard deviation unless ~ indicating interquartile range. -- means data unavailable.

*Numbers with DM1/2 calculated from percentages in Table 1, p4111. Weighted mean calculation performed to obtain age mean and standard deviation.

** DNU implied from participants being 'high risk', having neuropathy and prescription footwear.

TABLE 2 In-shoe Pressure Thresholds and Measurement

Paper, Year	Threshold Criteria	Region of Interest	Sensor Type	No. Sub Regions	No. Steps	Footwear Type	Pace	Study Duration	Purpose
Abbott, 2019 [37]	95-100% readings over past 15 mins $\geq$ 35 mmHG * trigger audio-visual and vibratory alerts to offload	Entire foot	Surro Sense	8 sensors	N/A	Prescription (Customised)	Free Living	18 months	Biofeedback
Arts, 2012 [42]	Offloading target of in-shoe pressure < 200 kPa at previous ulcer location and up to two other locations of highest barefoot pressure attributable to deformity	Entire foot	Pedar X	10 regions	12 steps per ft	Fully ¹ /Semi ² Custom 85.4%/14.6%	Self - Select 1 m/s	Single session	Footwear Offloading Deformity
Arts, 2015 [43]	Footwear modified at any location distal to the heel $\geq$ 200 kPa including previous ulcer location or site of deformity and up to two other locations	Forefoot +midfoot	Pedar X	8 regions	12 steps per ft	Fully Custom ¹ 100%	Self - Select	15 months	Evaluate Footwear Modification
Bus, 2011 [44]	Footwear modified where previous ulcer location or location of deformity or pre-ulcerative signs > 200 kPa or where two other peak pressure locations > 300 kPa. Modification successful if < 200 kPa or in-shoe pressure reduced by 25%	Entire foot	Pedar X	10 regions	15 steps	Fully Custom ¹ 100%	Self - Select	Single session (multi tests)	Evaluate Footwear Modification
Bus, 2013 [34]	Footwear designed to reduce in-shoe pressure at previous ulcer location or two other locations < 200 kPa or reduction by 25% baseline. Effect on ulceration with and without > 85% adherence	Forefoot +midfoot	Pedar X	--	15 steps	Fully ¹ /Semi ² Custom 85.4%/14.6%	Self - Select	18 months	Footwear & ulceration study
Chapman, 2014 [50]	Threshold of 200 kPa used to evaluate rocker shoes	--	--	--	--	Fully Custom (Rocker shoe)	1 m/s	Single session	Evaluate Footwear
De León Rodriguez, 2013 [38]	Developing a pressure-reduction walking strategy based on 40-80% baseline in-shoe pressures for 70% of totality of steps	Entire foot	Pedar X	11 regions	10 steps	Everyday shoes	N/A	10 days	Biofeedback
Ferber 2013 [33]	Comparison of SurroSense device sensors with Pedar-X. Bed sore pressure threshold of $\geq$ 32 mmHG suggested for use in diabetic foot ulceration without detailed discussion	Entire foot	Surro Sense	8 sensors	N/A	Retail shoes	Self - Select	Single session	Sensor Test Biofeedback
Giacomozzi 2013 [49]	Matrix of target pressures for four regions (toes, forefoot, midfoot, rearfoot) stratified by risk level and shoe size proposed to minimise ulceration	Entire foot	Pedar X	4 regions	20 steps per ft	Post-surgery semi-rigid (12 mths old)	Self - Select	4 months	Suggest Threshold
Lin 2013 [36]	Site of highest mean forefoot pressure is region of interest. Target of 200 kPa used to evaluate insole	Forefoot	Pedar X	5 regions	30 steps	Extra depth shoes	Self - Select	Single session	Evaluate Insole
Martinez-Santos 2019 [45]	Target of mean forefoot pressure < 200 kPa used to evaluate nine alternative insole designs	Forefoot	Pedar X	5 regions	20 steps	Retail shoes (Standard)	Self - Select	Single session	Evaluate Insoles

TABLE 2 In-shoe Pressure Thresholds and Measurement (Continued)

Paper, Year	Threshold Criteria	Location	Sensor Type	No. Regions	No. Steps	Footwear Type	Pace	Study Duration	Purpose
Owings 2009 [41]	200 kPa target established to prevent re-ulceration	Prior ulcer site (Hallux + MTHs)	Pedar	3 regions	30 steps	Prescription Extra depth shoes	Self - Select	Single session	Suggest Threshold
Parker, 2019 [47]	Evaluation of orthoses and secondary aim of reducing pressures at site of highest pressure and up to three regions at risk which are > 200 kPa	Hallux + MTHs	Pedar	3 regions	30 steps per ft	Everyday shoes	Self - Select	6 months	Evaluate Orthoses
Pataky, 2010 [51]	Minimum of seven steps reduced to within 40-80% baseline pressure at highest pressure regions through biofeedback / walking strategies	Highest pressure region	Pedar	--	10 steps	Everyday shoes	Self - Select	Baseline, @ 1, 5, 10 days	Biofeedback
Preece, 2017 [35]	Target of < 200 kPa used to evaluate footwear intended to prevent first-ulceration	Hallux, MTHs, MTP	Pedar X	3 regions	25 steps per ft	Group optimised shoes	Pace 1 m/s	Single session	Evaluate Footwear
Searle, 2018 [22]	Analysis of relationship between equinus and high pressure defined as ≥ 200 kPa and low pressure < 200 kPa	Entire foot	Pedar X	5 regions	12 steps per ft*	Everyday shoes (trainer)	Self - Select	Single session	Evaluate equinus & pressure
Telfer, 2017 [46]	Hybrid: Owings barefoot pressure threshold of 450 kPa used to select regions of interest Owings 200 kPa target used to assess insoles and determine how much insole material to remove	MTHs	Pedar X	3 regions	12 steps per ft	Extra depth shoes	Self - Select	Single session	Evaluate Insoles
Van, 2017 [52]	40-80% reduction in baseline in-shoe peak pressures for 70% of the totality of steps	Entire foot	Feetme	--	20 steps	--	Self - Select	Baseline, @ 2, 6 weeks	Biofeedback
Waaijman, 2011 [40]	Footwear modification regions of interest based on previous ulcer location and highest two pressure areas > 200 kPa Target: <200 kPa or 25% reduction in pressure	--	Pedar X	--	--	Fully ¹ /Semi ² Custom	--	--	Evaluate Footwear Modification
Waaijman, 2012 [39]	Footwear modification regions of interest based on previous ulcer location and highest two pressure areas > 200 kPa (midfoot or forefoot) Target: <200 kPa or 25% reduction in pressure	Entire foot	Pedar X	10 regions	20 steps	Fully ¹ /Semi ² Custom 81.2%/18.8 %	Self - Select	12 months	Evaluate Footwear Modification
Waaijman, 2014 [48]	In-shoe pressure monitored in custom-made shoes every 3 months for 18 months or until ulceration. Previous ulcer location or plantar area > 200 kPa	Entire foot	Pedar X	10 regions	12 steps per ft	Fully ¹ /Semi ² Custom	Self - Select	18 months	Pressure & Ulceration Study

	used to classification participants into groups above/below threshold					85.4%/14.6 %			
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Key

No. Steps: Numbers of midgait steps over which the mean in-shoe pressure is measured. "Per ft" indicates steps per foot, rather than the total. *Where 12 midgait steps are based on two walking trials, each consisting of six mid-gait steps.

Footwear: ¹ Both custom insoles and custom-made shoes; ² Custom insoles and extra depth shoes. -- indicates no information provided.

3.5 *Degree of neuropathy and loss of protective sensation (LOPS)*

The most common approach for testing loss of protective sensation is a 10g monofilament (n=11) applied to the hallux (n=8), first and fifth metatarsals (n=8) although there was considerable variation both in number and location of sites tested, and the combination of tests applied (see Supplemental Table 4 for details) rendering meta-analysis impossible. There was no in-depth analysis on the impact of either severity of neuropathy or peripheral vascular disease in relation to ulceration within these studies.

3.6 *Sensor Types and Region of Interest*

Most of the studies used Pedar-X insoles to measure laboratory-based in-shoe peak pressures (n=17) whereas the SurroSense insole system provided alerts which flagged sustained low pressures in free living (n=2) [33, 37]. The SurroSense insole measures in-shoe pressure using 8 sensors (five located at the forefoot, one at the midfoot and two at the heel) whereas the Pedar-X system employs 99 sensors across the plantar region which can be sub-divided into regions of interest (ROI). A FeetMe insole to measure max peak pressure reduction was also used in a biofeedback walking strategy study although details of the number and location of sensors is not provided [52]. The 200 kPa threshold was intended to prevent forefoot re-ulceration (primarily hallux and metatarsals regions) and has since been applied to the entire plantar region (n=4) [22, 39, 42, 44], forefoot and midfoot (n=2) [34, 43], forefoot (n=2) [36, 45], hallux, metatarsals and metatarsophalangeal joint [35], hallux and metatarsals (n=1) [47] and metatarsals (n=1) [46]. When reporting pressures by region, subdivision of the plantar region varies from 4 regions [49] to 11 (Table 1) [38]. Within these 200 kPa threshold studies, the maximum number of target regions for pressure reduction varied between 1 (usually to test mean in-shoe pressure to evaluate footwear, insoles or orthoses) [36, 45, 49] - 4 [47] where the most common approach targeted the previous ulcer location (see Supplemental Table 2) and the two highest pressure locations (n=5) [39-40, 42, 44] (Table 2).

3.7 *Number of steps required to calculate mean in-shoe pressure*

The target mean in-shoe peak pressure of 200 kPa developed in Owings [41] was based on approximately 30 steps i.e. the mean average peak pressure detected at the previous ulcer location during those 30 steps. Similarly, mean peak pressure is applied in other studies [22, 34-36, 39-45, 47, 48, 50]. However, in studies which subsequently applied this threshold this varies between 12 steps [42, 43] and 30 steps per foot [47].

3.8 *Length of study and frequency of pressure measurement*

The length of these studies and therefore the number of times in-shoe pressure is measured also varied: in 200 kPa studies to evaluate footwear, insole and orthoses designs, these ranged from a single measurement to evaluation over a six month period [47], or at three month intervals when evaluating footwear modifications from 12 [39] to 18 months (n=2) [34, 48]. Biofeedback studies ranged from 10 days (200 kPa) [38, 51] with three sets of laboratory in-shoe pressure measurements to 18 months (35 mmHG) in free-living [37].

3.9 *Footwear worn during in-shoe pressure measurement*

Footwear customised to the individual were often used (n=10 [34, 37, 39-44, 48, 50]), or off-the-

shelf retail or everyday footwear (n=6) [22, 33, 38, 45, 47, 51], and standardised footwear in the form of either extra depth (n=2) [36, 46], semi-rigid footwear intended for post-surgery use [49] or group-optimised footwear [35] (Table 2) or unspecified [52]. Studies measuring in-shoe pressures within customised footwear either involved all participants wearing prescription (n=1) [37] or ‘fully-customised’ footwear (i.e. both a custom insole and custom shoe) (n=2) [43-44] or a mixture of fully and semi-customised footwear consisting of extra-depth shoes with a custom insole (n=7) [34, 39, 40-42, 48, 50] (Table 2). Only 4 studies explicitly mention standardisation of socks (Supplemental Table 3) [36, 39, 42-43].

4. Discussion

The relative contribution of peak pressure versus sustained low pressures within shoes to diabetes-related ulceration remains unknown. We suspect that increased risk arises through a combination of both forms of in-shoe pressure combined with step count, type and intensity of physical activity or changes in lifestyle but RCT-based evidence for this hypothesis remains scarce. Technological barriers have prevented us thus far from capturing the complete picture: physical activity, peak and sustained low in-shoe pressures during in the run-up prior to ulceration. We need this to answer fundamental questions like ‘Are dynamic peak pressures during walking more damaging to diabetic foot skin and tissue than sustained static pressures during standing or driving?’ Suggested biofeedback interventions have developed around both a reduction in peak and sustained low pressures but have yet to be compared or combined within randomised controlled trials which assess ulceration rates and days spent in remission.

The evidence for both these in-shoe pressure thresholds is itself limited to one RCT for the 35mmHG sustained pressure threshold (n=58) [37] and one RCT (n=171) [34], and two cohort studies (n=49 [41], n=171 [48]) for the 200 kPa peak pressure threshold. These studies are all focused on the prevention of re-ulceration. A separate threshold for first ulceration for those with diabetes and neuropathy or PVD has yet to be evaluated (7 studies focus on recently healed ulcers – Table 1). The remaining suggested thresholds of 40-80% reduction in baseline pressure [38, 51] and shoe size and foot region threshold matrix [49] have yet to be assessed against ulceration rates or days spent in remission.

Our review has revealed considerable variation in the number of regions analysed, the subdivision of those forefoot or plantar region analysed, or the number of steps over which the 200 KPA threshold is assessed – all required some standardisation for facilitate ready comparison. Arts and Bus recommend a minimum number of twelve steps per foot (24 in total) [53] necessary for statistically reliable data. In research analysing in-shoe pressures and ulceration outcomes, assessment of footwear fit is another important element (the International Working Group on Diabetic Foot [54] guidelines recommended a 1-2 cm toe gap) given its potential impact on in-shoe pressure [55].

Obstacles to meta-analysis have included varying methods of assessing loss of protective sensation, and a lack of sub-group analysis around severity of neuropathy and peripheral vascular disease. A possible approach might be to employ a system of ranges either around neuropathy disability score as in Caselli [56] : 0 as “absent”, 1–5 as “mild”, 6 –16 as “moderate” and 17+ as “severe” or alternatively based around VPT as in Mondal et al. [57] consisting of 25-35V as “mild”; 36-50 as “moderate” and > 50V as “severe”. Similarly with PVD, Society for Vascular Surgery Wifl (wound, ischemia, foot infection) classification might be employed [58], ankle brachial index of ≥ 0.80 as

“Grade 0”, 0.6–0.79 as “Grade 1”, 0.4–0.59 as “Grade 2”, and ≤ 0.39 as “Grade 3” or a similar classification system [59]. Together with past ulcer history, this may assist us to develop separate in-shoe pressure thresholds for those with a history of ulceration versus recommended thresholds for those at risk of a first ulcer, stratified by these risk factors.

A range of commercial in-shoe pressure systems exist each with a differing number of sensors, sensor mechanism, measurement range, insole thickness and sampling rate [60]. This means that measurements taken with one system may not readily facilitate comparison with another as each works differently. For instance, in Owings [41] Pliance sensors were also used, taped to the previous ulcer location, and produced values which were larger than those produced using the Pedar system which was attributed to a smaller sensor size [41]. The relative merits of each system and their performance are beyond the scope of this review [60].

A limitation of this review is that the data extraction, assessment and extraction were performed by one reviewer (PJ). Our review was also limited to the use of in-shoe pressure thresholds in the prevention of diabetes-related foot ulceration – another useful review might address their use in assisting active ulcer healing [61] or Charcot remission. A previous narrative analysis [29] covered both barefoot and in-shoe pressure analysis but we attempted a more comprehensive treatment of specific in-shoe pressure thresholds through a formal systematic review to reveal both the multiple ways in which thresholds are currently employed and the wide variation in their usage.

This systematic review is focused on in-shoe plantar pressure in isolation, but pressure is just one aspect of foot microclimate monitoring that potentially includes temperature and humidity [62] not to mention growing research around wearables such as accelerometers which can measure physical activity type and intensity. In-shoe pressure thresholds may become part of multi-factorial prognostic models.

5. Conclusion

Five in-shoe pressure thresholds were identified, which are employed to reduce the risk of diabetes-related foot ulceration: a mean peak pressure threshold of 200 kPa used in conjunction with a 25% baseline reduction target; a sustained pressure threshold of 35 mmHG, a threshold matrix based on risk, shoe size and foot region, and a 40-80% baseline pressure reduction target. The effectiveness of the latter two thresholds have not been assessed yet and the evidence for the effectiveness of the other in-shoe pressure thresholds is limited, based only on two RCTs and two cohort studies. The contribution of peak in-shoe pressures to foot ulceration as opposed to sustained low pressures remains as is their potential impact on ulceration rates and days spent in remission if they were combined. Divergence in methodological approaches around footwear, insole and socks, region of interest, loss of protective sensation preclude meta-analysis and standardisation is needed. Further research is needed as described below.

Summary Recommendations

Further randomised controlled trials are needed to assess the efficacy of footwear interventions based around in-shoe pressure threshold on ulceration rates and days spent in remission which:

- (i) Track both step count and physical activity type and intensity whilst wearing pressure minimising

footwear (necessitating pedometer, accelerometer and adherence data capture)
(ii) In-shoe peak pressure measurements are recorded every 3-months (based on a standardised 12 steps) and the number of days elapsed between measurement and any subsequent ulceration event recorded
(iii) Sustained low pressures (35 mmHg) during daily living should also be monitored to provide useful data regarding the impact of both thresholds upon ulceration
(iv) Standardise socks, insole and footwear (prescription extra depth)
(v) Research should prioritise people with diabetes at high risk of ulceration i.e. category 2 of the risk classification system of the International Working Group on the Diabetic Foot (IWGDF) with either a diagnosis of neuropathy or peripheral artery disease (PAD) and a history of ulceration. We suggest standardising loss of protective sensation testing to a 10g monofilament applied to the hallux, first and fifth metatarsals and VPT $\geq$ 25V (the most common approach found in these studies – see Supplemental Table 4). Severity of neuropathy and PVD should also be graded by VPT and ankle brachial index response.

The heterogeneity of current measures precludes us from conducting meta-analysis. Our review has revealed the importance of consistent application and minimal methodological variation in studies applying in-shoe pressure thresholds. Standardised methods enable us to conduct meta-analyses and readily draw comparisons through which we may build on past research to derive location-specific thresholds or formulate multi-factorial pressure thresholds for use in diabetes-related ulcer prevention.

CONFLICT OF INTERESTS

The authors declare that they have no conflict interests.

AUTHORS' CONTRIBUTION

PJ conceived and designed the study, performed the literature search, assessed the literature, extracted data and drew conclusions. PJ and DW wrote the manuscript. DW, MJD, KK, RB, and PC critically reviewed and edited the manuscript. All authors have read and approved the final manuscript.

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ACKNOWLEDGEMENTS

The authors would like to thank UHL Libraries and Information Services for their ongoing and invaluable assistance and the ongoing support of NIHR Leicester Biomedical Research Centre with this area of research.

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SUPPLEMENTAL TABLE 1 Studies Comparing Plantar Pressure in People with Diabetes and Neuropathy (DN) with Healthy Controls (CG)

		Participant Cohort						Pressure (Mean kPa for Region and Standard Deviation)				
Paper	Year	CG	D	DN	DNU	DNA	Region	CG	D	DN	DNU	DNA
Bacarin [16]	2008	20	--	17	10	--	Mid-foot	139.4 ± 76.4	--	205.3 ± 118.6	290.7 ± 151.5	--
Fawzy [17]	2014	--	37	33	--	30	Forefoot	--	292.8 ± 83.9	318.2 ± 58.8	--	348.6 ± 43.0
Halawa [14]	2018	30	30	20	--	--	Mid-foot (right) Mid-foot (left)	82.1 ± 30.8 79.5 ± 27.5	104.9 ± 40.9 106.2 ± 46.3	138.2 ± 76.3 117.1 ± 64.0	--	--
Sawacha[13]	2011	12	--	12	--	--	Mid-foot	312.3	--	515.6	--	--
Pataky [15]	2005	15	--	15	--	--	Hallux (right) Hallux (left) MTS5 (right) MTS5 (left)	101 ± 94 104 ± 43 97 ± 32 91 ± 42	--	205 ± 94 165 ± 61 160 ± 68 174 ± 65	--	--
Paper	Year	CG	D	DN	DNU	DNA	Region	Pressure (Mean N/cm ² for Region and Standard Deviation)				
Stess [12]	1997	--	34	14	49	33*	Forefoot	--	40.7 ± 1.7	40.5 ± 2.8	48.0 ± 1.8	--

Key

Participant Cohort: CG = Control group; D = Diabetes without neuropathy or history of ulceration; DN = Diabetes and neuropathy; DNU = Diabetes, neuropathy and a history of ulceration; DNA = Diabetes, neuropathy and an active ulcer where in Bacarin, DNA=33 is a subset of DNU=49.

Region: ~ Only the mid-foot peak plantar pressure was found to be statistically significant – see Bacarin’s table 2 and Sawacha’s table 3

Pressure: kPa = Kilopascals. N/cm² = Newtons for a defined area in squared centimetres

SUPPLEMENTAL TABLE 2 Previous ulcer locations (where known) within in-shoe pressure studies

Paper	Year	Total	Hallux	Toes 2/3	Toes 4/5	MTH 1	MTH 2/3	MTH 4/5	Medial Midfoot	Lateral Midfoot	MTH Base	Heel
Arts	2012	147	(34) 23.1%	(23) 15.6%	(2) 1.4%	(39) 26.5%	(20) 13.6%	(17) 11.6%	(5) 3.4%	(2) 1.4%	(4) 2.7%	(1) 0.7%
Arts	2015	139	38.1%	2.9%	--	28.1%	19.4%	10.8%	0.7%	--	--	--
Bus	2011	18	(3) 16.7%	(1) 5.5%		(11) 61.1%			(3) 16.7%		--	--
Bus	2013	IF UC	17.6% 30.2%	22.4% 17.4%		25.9% 25.6%	31.8% 19.8%		2.4% 7.0%		--	--
Owings	2009	--	x	--	--	x	--	--	--	--		
Waaijman	2012	85	(15) 17.6%	(17) 20.0%	(2) 2.4%	(23) 27.1%	(15) 17.6%	(11) 12.9%	(1) 1.2%	(1) 1.2%	--	--
Waaijman*	2014	147	(34) 23.1%	(23) 15.6%	(2) 1.4%	(39) 26.5%	(20) 13.6%	(17) 11.6%	(5) 3.4%	(2) 1.4%	(4) 2.7%	(1) 0.7%

Numbers of ulcers at each location shown in brackets; and percentages of ulcers at each location. Where the number or percentage of ulcers at each location is not known, a marker is provided to indicate the locations where ulcers are known to have occurred.

Where these figures are split into sub-totals, IF = Improved Footwear, UC = Usual Care.

*171 people with healed ulcers but only 147 ulcer locations given amputations.

Abbott missing given split into both intervention group/control group and left/right feet.

SUPPLEMENTAL TABLE 3 In-shoe Pressure Threshold Study Demographics

Paper	Year	Standardisation		Sensor	Pressure Measurement	
		Socks	Insoles		Sampling Rate	Intervention
Abbott	2019	×	×	SurroSense	8 Hz	Biofeedback (Real-time)
Arts	2012	✓	✓	Pedar-X	50 Hz	Footwear evaluation
Arts	2015	✓	✓	Pedar-X	50 Hz	Footwear evaluation
Bus	2011	×	✓	Pedar-X	50 Hz	Footwear evaluation
Bus	2013	×	✓	Pedar-X	50 Hz	Outcomes from Threshold
Chapman	2014	--	--	--	--	Footwear evaluation
De León Rodriguez	2013	×	×	Pedar-X	50 Hz	Biofeedback
Giacomozzi	2013	×	✓	Pedar-X	50 Hz	Footwear evaluation
Lin	2013	✓	⊖	Pedar-X	50 Hz	Insole evaluation / arch support
Martinez-Santos	2019	×	⊖	Pedar-X	50 Hz	Insole evaluation
Owings	2009	×	×	Pedar	--	Pressures in Remission
Parker	2019	×	✓	Pedar	--	Orthoses evaluation
Pataky	2010	--	--	Pedar	100 Hz	Biofeedback
Preece	2017	×	×	Pedar-X	50 Hz	Footwear evaluation
Searle	2018	✓	--	Pedar-X	100 Hz	Equinus & pressure analysis
Van	2017	--	--	Feetme	--	Biofeedback
Waaijman	2011	×	✓	Pedar-X	--	Footwear evaluation
Waaijman	2012	✓	✓	Pedar-X	50 Hz	Footwear evaluation
Waaijman	2014	×	✓	Pedar-X	50 Hz	Risk factor evaluation

Key

⊖ = The subject of evaluation e.g. footwear, insole etc. × = Not standardised. ✓ = Standardised -- = unspecified.

SUPPLEMENTAL TABLE 4 Neuropathy Testing in Pressure Threshold Studies

Paper and year	Test Method 1	No. Sites	Prior ulcer	Hallux	Mth 1	Mth 2	Mth 3	Mth 4	Mth 5	Malleoli	Midfoot	Heel	Toe 5	Styloid p.	Cond	Test Method 2	No. Sites	Hallux	Patella	Ankle	Other
Abbott 2019 [37]	M / 10g	1 of 3			x		x		x												
Arts 2012 [42]	M / 10g	1 of 3		x	x				x						OR	V / ≥25V	1 of 1	x			
Arts 2015 [43]	M / 10g	1 of 3		x	x				x						OR	V / ≥25V	1 of 1	x			
Bus 2011 [44]	M / 10g	1 of 6		x	x		x		x		x	x									
Bus 2013 [34]	M / 10g	1 of 3		x	x				x						OR	V / ≥25V	1 of 1	x			
Chapman, 2014 [50]	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
De León Rodriguez 2013 [38]	TF / 128 Hz	4 of 8		x						x					AND	P / absence ¹			x	x	
Ferber, 2013 [33]			Healthy participants. People with neuropathy excluded																		
Giacomozzi ² 2013 [49]	NDS 6/10	N/A	Neuropathy disability score > 6/10												AND	V / ≥25V + >20V	2 of 2	x			
Lin 2013 [36]	M / 10g	1 of 6		x	x	x	x	x	x						AND	TF / 128 Hz	2 of 6	Unclear ³			
Martinez-Santos 2019 [45]	M / 10g	1 of 10	Hallux, toes 3+5, MTH 1+3+5, medial & lateral arches, heel and dorsum between toes 1 & 2												OR	TF / 128 Hz	1 of 4	Hallux, MTH1+5, malleoli			
Owings 2009 [41]	M / 10g	1 of 1	x																		
Parker 2019 [47]	M / 10g	3 of 10	Sites at foot and ankle unspecified																		
Pataky, 2010 [51]	TF / 128 Hz	≤4 of 8		x						x					AND	Absence of reflexes	--		x	x	
Preece, 2017 [35]	M / 10g	--		x	x				x				x	x							
Searle, 2018 [22]	M / 10g	1 of 4		x	x		x		x						OR	V / >25V	1 of 1	x			
Telfer 2017 [46]	M / 10g	≥ 1	Sites / No. of sites unspecified																		
Van, 2017 [52]	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
Waijman, 2011 [40]	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
Waijman 2012 [39]	M / 10g	1 of 3		x	x				x						OR	V / >25V	1 of 1	x			
Waijman 2014 [48]	M / 10g	1 of 1		x											OR	V / Mean >25V	3	x			x

Key

Method: M (Monofilament), V (Vibration perception threshold), TF (Tuning fork), P (patella and ankle reflexes); NDS (Neuropathy disability score), -- method used is

unspecified.

¹ Neuropathy is determined from patellar and ankle reflexes and a tuning fork used at the hallux and malleoli of both feet.

² Vibration perception threshold measured at the hallux of both feet, with two thresholds: 25V for the first foot and 20V for the second.

³ Lin: Possibly the same six sites as with the monofilament although methodology cited involves dorsum of the first toe and dorsal aspect of the distal phalanx tested twice on each toe.

⁴ Various = Toes 1,3,5; Metatarsal heads 1,3,5, medial and lateral arches, heel and dorsum between toes 1 and 2.

SUPPLEMENTAL TABLE 5 PVD and re-ulceration within in-shoe pressure studies

Paper	Year	PVD related data
Abbott	2019	<p>This study excluded severe vascular disease. No ABI. Peripheral arterial status was assessed by palpating the dorsalis pedis and posterior tibial pulses on both feet:</p> <p><i>Palpable dorsalis pedis pulse</i> Left 89% control group; 87% intervention group Right 83% control group; 79% intervention group</p> <p><i>Palpable dorsalis posterior tibial pulse</i> Left 83% control group; 70% intervention group Right 83% control group; 69% intervention group</p> <p>No further analysis on impact of presence of PVD on re-ulceration.</p>
Bus	2013	<p>Peripheral arterial status was assessed according to the PEDIS (perfusion, extent/size, depth/tissue loss, infection, sensation) classification. Peripheral arterial disease was confirmed present when pedal pulses were nonpalpable and the ankle-brachial index was 0.9 in the foot with the most recent episode of ulceration according to the PEDIS classification. In five patients, peripheral arterial disease could not be assessed, and in six, data were missing (n=160/171).</p> <p>Peripheral artery disease:</p>

		<p>Improved footwear 28.8%</p> <p>Usual care 37.5%</p> <p>No further analysis on impact of presence of PVD on re-ulceration.</p>
Owings	2009	<p>Exclusion criteria included major vascular disease.</p> <p>“Only patients aged 30-80 years with ulcers that were of predominantly neuropathic aetiology and who had remained healed for at least 90 days were included.”</p>
Waaijman	2014	<p>Grade II peripheral arterial disease (%):</p> <p>Presence of peripheral arterial disease (grade I = no; grade II = yes) was assessed using the Perfusion Extent Depth Infection Sensation (PEDIS) classification.</p> <p>All patients: 35.2</p> <p><i>All ulcer recurrences (model 1):</i></p> <p>Patients with no ulcer 38.5</p> <p>Patients with ulcer 30.4</p> <p><i>Ulcer recurrences from unrecognized repetitive trauma (model 2):</i></p> <p>Patients with no ulcer 36.5</p> <p>Patients with ulcer 30.8</p> <p><i>Univariate model (All ulcer recurrences model 1):</i></p> <p>Peripheral arterial disease, grade II (vs. grade I)[†]</p> <p>OR: 0.78 (0.53–1.15) (95% CI) P: 0.206</p> <p><i>Univariate model (Ulcer recurrences from unrecognized repetitive trauma (model 2))</i></p> <p>OR: 0.79 (0.37–1.68) (95% CI) P: 0.540</p> <p>“The inclusion of a selected group of only high-risk patients may also</p>

		have been the reason that other parameters such as peripheral vascular disease and diabetes control were not associated with ulcer recurrence.” No further analysis on impact of presence of PVD on re-ulceration.
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SUPPLEMENTAL TABLE 6 Severity of neuropathy and re-ulceration within in-shoe pressure studies

Paper	Year	Severity of neuropathy related data
Abbott	2019	<p><i>Severe (Neuropathy Disability Score: NDS 9 or 10):</i> Control group 46% Intervention group 44%</p> <p><i>10g Semmes-Weinstein monofilament, abnormal test:</i> Left foot: control group 76%; intervention group 91% Right foot: control group 68%; intervention group 97%</p> <p><i>Neuropad, abnormal test:</i> Control group: 96% Intervention group: 92%</p> <p>No further analysis on impact of presence of severe neuropathy on re-ulceration.</p>
Bus	2013	<p>Inclusion criteria included participants with loss of protective foot sensation as a result of peripheral neuropathy.</p> <p>Loss of protective sensation based on vibration perception threshold > 25 volts Improved footwear: 85.2%; Usual care: 85.9% Vibration perception threshold (volts): Improved footwear: 50.0 mean (11.1 SD); Usual care: 50.0 mean (9.0 SD)</p>
Owings	2009	No apparent discussion of severity of neuropathy within cohort.

Waijman	2014	<p><i>Univariate model (All ulcer recurrences model 1):</i></p> <p>Vibration perception threshold (volt) OR: 0.98 (0.95–1.01 CI) P: 0.267</p> <p><i>Ulcer recurrences from unrecognized repetitive trauma (model 2):</i></p> <p>Vibration perception threshold (volt) OR: 0.99 (0.96–1.03 CI) P: 0.662</p> <p>“All patients had neuropathy and as a result already a high vibration perception threshold, which limits its potential to discriminate in logistic regression analysis”.</p>
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Supplemental Figure 1**Examples of algorithms utilising the 200 kPa threshold in offloading** **Appendix A Search strings**

"pressure" AND "foot" AND "in-shoe" AND "diabetes" AND "threshold"

"plantar" AND "pressure" AND "foot" AND "in-shoe" AND "diabetes" AND "threshold"