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Systematic Review or Meta-analysis

Systematic review and meta-analysis of clinical trials examining the effect of hyperbaric oxygen therapy in people with diabetes-related lower limb ulcers

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Abstract

Aim To examine the efficacy of hyperbaric oxygen therapy in healing diabetes-related lower limb ulcers through a meta-analysis of randomized clinical trials.

Methods A literature search was conducted to identify appropriate clinical trials. Inclusion required randomized study design and reporting of the proportion of diabetes-related lower limb ulcers that healed. A meta-analysis was performed to examine the effect of hyperbaric oxygen therapy on ulcer healing. The secondary outcomes were minor and major amputations.

Results Nine randomized trials involving 585 participants were included. People allocated to hyperbaric oxygen therapy were more likely to have complete ulcer healing (relative risk 1.95, 95% CI 1.51–2.52; $P<0.001$), and less likely to require major (relative risk 0.54, 95% CI 0.36–0.81; $P=0.003$) or minor (relative risk 0.68, 95% CI 0.48–0.98; $P=0.040$) amputations than control groups. Sensitivity analyses suggested the findings were dependent on the inclusion of one trial. Adverse events included ear barotrauma and a seizure. Many of the trials were noted to have methodological weaknesses including absence of blinding of outcome assessors, lack of a justifiable sample size calculation and limited follow-up.

Conclusions This meta-analysis suggests hyperbaric oxygen therapy improves the healing of diabetes-related lower limb ulcers and reduces the requirement for amputation. Confidence in these results is limited by significant design weaknesses of previous trials and inconsistent findings. A more rigorous assessment of the efficacy of hyperbaric the efficacy of hyperbaric oxygen therapy is needed.

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Introduction

Diabetes-related lower limb ulcers are a leading cause of global morbidity, mortality and rising healthcare costs [1–3]. Such ulcers often become chronic, are associated with reduced health-related quality of life, and are frequently a prelude to infection, hospital admission and amputation [1–10]. Establishing better ways to treat diabetes-related lower limb ulcers is a global priority [2].

Hyperbaric oxygen therapy (HBOT) is the delivery of 100% oxygen within a pressurized chamber and is proposed to heal lower limb ulcers through improving tissue oxygenation, and promoting angiogenesis and the immune response [11]. Current guidelines suggest that HBOT should be considered for the treatment of lower limb ulcers; however, the findings of previous systematic reviews have been inconsistent [12–18]. A previous Cochrane review reported that HBOT increased the rate of ulcer healing in the short but not the long term [14]. In contrast, a more recent systematic review, which included almost double the number of participants involved in the Cochrane review, reported that HBOT had no significant effect on the proportion of ulcers completely healing, and did not reduce the requirement for major or minor amputation [15]. Furthermore, a recent health technology assessment concluded that the available evidence makes it difficult to draw any definitive conclusions on the clinical benefit and cost-effectiveness of HBOT [16].

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What's new?

- Previous trials and systematic reviews have had conflicting results with regard to the value of hyperbaric oxygen therapy (HBOT) for diabetes-related lower limb ulcers.
- This systematic review examined the efficacy of HBOT in healing diabetes-related lower limb ulcers through a meta-analysis of randomized clinical trials.
- People allocated to HBOT were twice as likely to have complete ulcer healing and half as likely to require a major amputation, but findings were dependent on the inclusion of one highly positive study.
- Included trials frequently lacked key study design features, such as blinding of outcome assessors and strict entry criteria.
- While the overall findings of this meta-analysis support the use of HBOT in the treatment of diabetes-related lower limb ulcers, a high-quality large trial is needed to test the efficacy of this treatment more rigorously.

There is substantial cost associated with HBOT and also potential for complications, such as pneumothorax, visual disturbance and ear barotrauma, and thus its use should be based on firm evidence [14–19]. A number of clinical trials have been published since these prior systematic reviews and have reported contrasting results, with one trial reporting no benefit of HBOT [20] and one reporting that HBOT improved outcomes [21]. Previous trials have all been small, with no individual clinical trial including more than 150 participants [14–16,20.21]. In view of the controversy surrounding the benefit of HBOT and the new evidence from recent randomized controlled trials (RCTs), a further systematic review is needed. The aim of the present systematic review was to meta-analyse data from RCTs on the efficacy of HBOT, in comparison to controls not receiving HBOT, in improving the healing of diabetes-related lower limb ulcers.

Methods

Data sources and searches

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [22]. A comprehensive literature search was performed using multiple databases [Web of Science (via ISI Web of Knowledge; 1965), Scopus (1966), PubMed, the Cochrane Library, CINHAL (1961), and Embase (1980)] to identify RCTs examining the efficacy of HBOT in healing lower limb ulcers. A combination of Medical Subject Heading (MeSH) terms and keywords was used: "((Diabetic Foot[MeSH] OR Foot Ulcer[MeSH] OR Leg Ulcer [MeSH] OR (diabetes OR diabetic)) AND ((ulcer* OR wound*) OR (foot AND ulcer*) OR leg ulcer*)) AND ((Hyperbaric Oxygenation[MeSH] OR (hyperbaric AND oxygen*) OR HBO OR HBOT OR hyperbaric chamber*))". The search was performed in October 2018 and repeated in December 2018, without language restrictions, by two authors (J.G. and T.S.). In addition, reference lists of primary articles and reviews were searched to increase the yield of relevant publications. Titles and abstracts were screened to identify potentially relevant studies. If the suitability of an article was uncertain, the full text was reviewed.

Study selection

For inclusion in this systematic review, studies needed to have assessed the proportion of people whose diabetes-related lower limb ulcer completely healed during at least one time point in participants randomized to HBOT and in a control group. HBOT had to consist of sessions of inhaled 100% oxygen delivered at >1 absolute atmospheres (ATA). Control groups were considered acceptable if they received sessions of sham HBOT in which air only was delivered or received only standard care. Standard care was allowed to include any type of dressing and established therapies for underlying medical conditions including revascularization of limb ischaemia and control of hyperglycaemia. Standard care was not allowed to include experimental treatments which were not established, such as growth factor treatments or similar. Only RCTs were included. Studies were excluded if data on the proportion of participants that had complete healing of the ulcer during at least one time point of follow-up were not reported or available after contacting the corresponding author of the study concerned. Corresponding authors of all studies under consideration for inclusion were contacted regarding this outcome. Studies that included people who did not have diabetes-related ulcers were excluded. Trials investigating administration of topical hyperbaric oxygen to the ulcer were also excluded. The selection of studies for inclusion was performed independently by two authors (J.G. and T.S.) with differences in opinion resolved by discussion.

Data extraction and quality assessment

Data were extracted from included studies independently by the two authors (J.G. and T.S.), with inconsistencies resolved by discussion. The corresponding authors of all studies deemed eligible were contacted on two separate occasions in an attempt to check outcome data and seek additional outcome data. Only two authors responded and this did not result in the addition of any new data. The primary outcome for the meta-analysis was the percentage of participants in whom complete healing of the lower limb ulcers occurred. Secondary outcomes included the percentage of participants requiring minor amputation (defined as any amputation

below the ankle) and the percentage of participants requiring major amputation (defined as any amputation above the ankle). The time point chosen for all outcomes was the latest time of follow-up for which outcome data were reported. In extraction of these outcome data intention-to-treat principles were followed. The way missing data (resulting from participants who were lost to follow-up prior to assessment) for these endpoints were reported varied among trials. To provide consistency, data were extracted using two different standardized approaches to missing values. For the primary analysis, ulcers were assumed to have not healed and major amputation (not minor amputation) to have occurred in participants with missing data as a result of loss to follow-up. A second data extraction related to the primary and secondary outcomes was also performed, assuming the best-case scenario for participants with missing data as a result of loss to follow-up (i.e. ulcer healed and no requirement for major or minor amputation). Summaries of other outcomes reported, such as percentage ulcer reduction, time to ulcer healing, health-related quality of life, cost and adverse events, were also collected, but no attempt was made to meta-analyse these data. The following additional data were collected from included studies: sample sizes for the intervention and control groups; study design; details of HBOT (including methods of delivery, frequency and total number of sessions); details of the management of the controls; information about standard care; risk factors of the included groups (including age, sex, smoking history, prior ulcer, previous amputation and prior revascularization and mean diabetes duration, BMI); characteristics of the ulcer (area, Wagner grade, duration, presence of infection); and measures of limb blood supply (ankle–brachial pressure index, ankle pressure, toe pressure, toe–brachial pressure index, transcutaneous oxygen pressure). Methodological quality and potential bias of included studies were assessed independently by two investigators using the Cochrane collaboration tool for assessing risk of bias [23].

Data synthesis and analyses

Meta-analysis was performed, comparing the percentage of participants with healed ulcers, minor amputation and major amputation that were randomly allocated to HBOT and control groups. All analyses used intention-to-treat principles. For the primary analysis, the data extracted based on the worst-case scenario (that participants with missing outcome data had required major amputation and their ulcer had not healed) was used. A sensitivity analysis was performed using the data extracted based on the best-case scenario. Results were combined using standard Mantel–Haenszel meta-analysis methods, as previously described, and reported as relative risk (RR) and 95% CIs [24,25]. Heterogeneity was assessed using the I^2 statistic. I^2 values of 25%, 50% and 75% were acknowledged to represent low, moderate and high heterogeneity, respectively. Sensitivity analyses were performed for the main analysis to assess the contribution of each study to the pooled estimate by excluding individual studies one at a time and recalculating the pooled estimates for the remaining studies. A sub-analysis was planned to examine results separately for participants with evidence of ischaemic ulcers if at least three suitable trials could be identified. Publication bias was assessed by funnel plots comparing the summary estimate of each study to its precision (1/standard error) for outcomes that were reported in ≥5 studies [26]. Analyses were conducted using STATA version 13.0, 2009 (StataCorp, College Station, TX, USA). All statistical tests were two-sided and a P value of <0.05 was considered significant.

Results

Study selection and description of included studies

Figure 1 shows the selection process for studies included in the present review; ultimately nine clinical trials were included [20,21,27–33]. The nine clinical trials included a total of 585 participants randomly allocated to HBOT or control groups, of whom 31 participants (5.3%) did not complete follow-up assessment of the primary outcome (see Table 1 for details of individual trials) [20,21,27–33]. The trials were performed in Canada [27], China [33], France [32], India [28], the Netherlands [20], Sweden [29], Taiwan [21], Turkey [30], and the UK [31]. The total number of participants randomized to HBOT or control groups in different trials varied from 18 to 120 in the different trials (Table 1). The entry criteria and outcomes varied for the different trials, as shown in Table 1, although all trials reported the proportion of participants with complete ulcer healing as one of the outcomes [20,21,27–33]. Minor and major amputation were more variably reported, with this information only reported in six of the trials (Table 1) [20,21,27–33]. The largest and smallest included trials, in 120 and 19 participants, respectively, only included people with evidence of limb ischaemia based on low ankle or toe pressures or low transcutaneous oxygen pressure (Table 1) [20,31]. Four trials excluded people with large artery ischaemia based on vascular surgeon opinion, ankle–brachial pressure index ≥0.8 or transcutaneous oxygen pressure >30 or 40 mmHg [27,29,32,33], although in one of these trials ischaemia ulcers could be included if no revascularization options were available [29]. Three trials did not report specifically including or excluding ischaemic ulcer [21,28,30]. All trials reported excluded people in whom HBOT is commonly contraindicated, such as people with emphysema with bullae, and those with severe heart failure or ongoing middle ear problems (Table 1).

Assessment of risk of bias of included trials

Table S1 details the findings from the assessment of the risk of bias for the included trials using the Cochrane

collaboration tool. All trials reported random allocation of participants to the intervention and control groups, although the method of random sequence generation was not reported in one trial [28]. Three trials included a sham HBOT in the control group which enabled all personnel and participants (apart from the chamber operator) to be blinded to group allocation [27,29,31]. A clear primary outcome was not reported in three trials [21,30,33]. Blinding of outcome assessors in the assessment of complete ulcer healing was reported in only five of the trials [27,29,31–33]. Only four of the trials reported that sample size calculations had been performed, although the details of the sample size calculation were limited in some cases and the planned sample size was not met in one trial (Table S1) [20,21,27,31]. Four of the trials [20,27,29,31] reported that they used intention-to-treat analysis, but the way missing data (resulting from participants lost to follow-up before endpoint assessment) were handled was not specifically reported in any of the trials.

Intervention and control

The HBOT regimens used were similar in the included trials, involving delivery of 100% oxygen at ~2.5 ATA over sessions lasting up to 90 min, with appropriate decompression (Table 1). Management of the control groups varied between sham HBOT sessions, in which air was delivered rather than 100% oxygen in three trials [27,29,31], to standard care alone in five trials [20,21,30,32,33]. Standard care was also similarly applied to the HBOT groups, except in one trial where the control group received a specific antiseptic dressing regimen, which was not documented to be routinely applied in the HBOT group (Table 1) [28]. The details reported on standard care varied from trial to trial and included wound management regimens, review by a multidisciplinary team, control of blood glucose and consideration of revascularization (Table 1) [20,21,27–33].

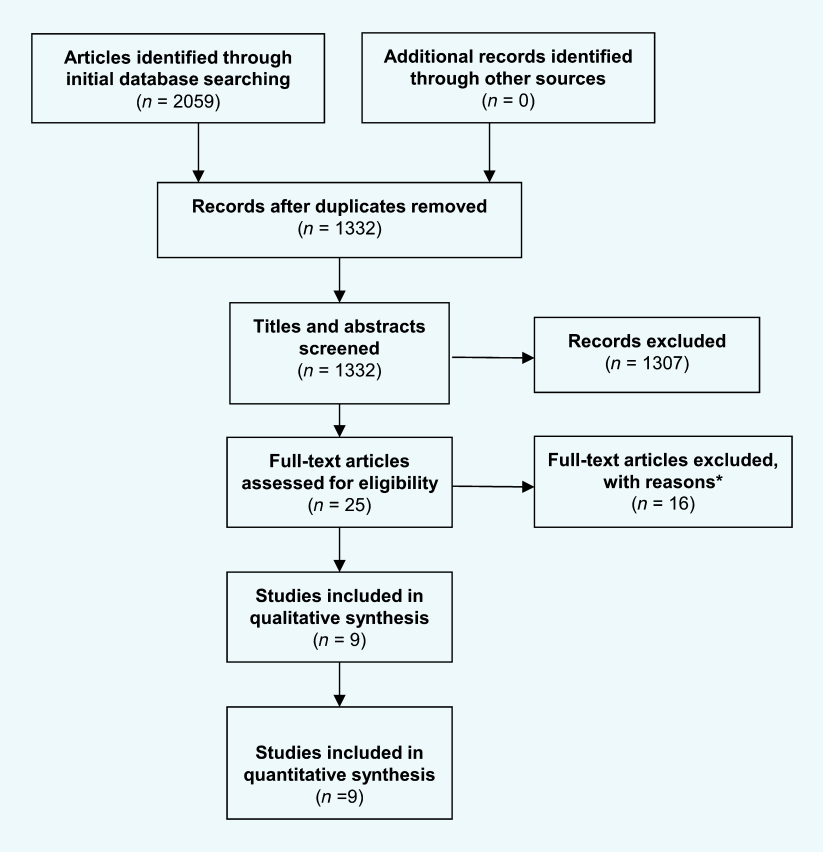

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram describing the identification and selection of the included trials. *Five trials did not report the proportion of participants with complete healing of ulcers at any time during follow-up and this information was not available from the corresponding author; four trials investigated hyperbaric oxygen delivered topically to the wound; two trials included non-randomized allocation to intervention and control groups; two trials included an experimental therapy (growth factor and shockwave therapy) within the control group; two trials investigated patients that did not have diabetes-related ulcers; one trial represented a second report from an already included trial.

Table 1 Entry criteria, intervention and control groups and outcomes for randomized controlled trials assessing HBOT included in this review

Study	Sample size (Screened/ randomized/ completed)	Entry criteria	Intervention	Control	Additional management in both groups (standard care)	Primary outcome	Other outcomes	Follow-up, weeks
Santema *et al.* (2018) [20]	120/115*	Diabetes, lower limb ulcer Wagner grade 2–4, present ≥4 weeks, ischaemia (AP <70 mmHg, TP <50 mmHg or forefoot transcutaneous oxygen pressure <40 mmHg), revascularization already assessed, no prior ipsilateral major amputation, no contraindication to HBOT (COPD GOLD IV, LVEF <20%, external pacemaker, metastatic cancer or pregnancy), no ESRF, no current treatment with immunosuppressant drugs, must be able to complete a questionnaire	Hyperbaric 100% O_2 delivered at a pressure of 2.4 or 2.5 ATA for 75 min with appropriate decompression for 5 days/week, total 40 sessions plus standard care	Standard care alone	Revascularization if applicable, glycaemic control and antibiotics if appropriate, wound management	Major amputation at 52 weeks; time to complete wound healing, complete wound healing at 52 weeks	Minor amputation, revascularization, recurrent ulcers, adverse events, all-cause mortality, quality of life, cost-effectiveness	12, 24 and 52
Chen *et al.* (2017) [21]	43/42/38	Age ≥20 years with diabetes, non-healing foot ulcer that had not healed after ≥2 months and following treatment for ≥1 month, Wagner grades 1–3, appropriate for hospital admission because of skin ulcer and soft-tissue infection, no gangrene, no contraindication for HBOT (untreated pneumothorax, cancer, COPD, pulmonary emphysema with CO_2 retention, no planned revascularization	Hyperbaric 100% O_2 at 2.5 ATA for 120 min with appropriate decompression, 5 days/week for 20 sessions over 1 month	Standard care alone	Topical and systemic therapy for ulcer, glycaemic control, offloading, debridement of necrotic tissue, antibiotic therapyfor management of diabetic foot infection, topical dressings including silver-impregnated dressings (for Wagner 1 and 2) and topical antibiotics (Wagner 2 and 3)	NR	Complete ulcer healing, Serum erythrocyte sedimentation rate and C-reactiveprotein, foot ulcer microbiology and presence of infection, blood flow perfusion, requirement for amputation (not reported if major or minor but assumed to be major) determined by a vascular surgeon based on established criteria, glycaemic control, SF-36	6
Fedorko *et al.* (2016) [27]	157/107/103	Age ≥18 years, diabetes, lower limb wounds (Wagner grade 2–4) for ≥4 weeks, no contra indication to HBOT, no need for urgent	Hyperbaric 100% O_2 delivered at a pressure of 244 kPa for 75 min with appropriate	Hyperbaric air delivered at 125 kPa delivered through an	Weekly wound care by multidisciplinary team, prescription for offloading	The participating blinded vascular surgeon determined *opinion* at 12	Complete ulcer healing, wound surface area and perimeter from digital photographs,	12

Table 1 (*Continued*)

Study	Sample size (Screened/ randomized/ completed)	Entry criteria	Intervention	Control	Additional management in both groups (standard care)	Primary outcome	Other outcomes	Follow-up, weeks
		amputation, exposed calcaneus bone with no prospect of weight bearing, no major large artery occlusions suitable for revascularization, no prior revascularization within 3 months	decompression 5 days/ week, total 30 sessions	identical way to the intervention	devices and wound care dressings	weeks of whether amputation (major or minor) was indicated	manual measured wound width, LAWE, Bates–Jensen wound grading and Wagner grading, adverse events	
Ma *et al.* (2013) [33]	81/36/36	Diabetes, ≥ 1 full-thickness wound below the ankle (Wagner grades 1–3) for >3 months, history of standard care >2 months, no arterial insufficiency, transcutaneous oxygen pressure >30 mmHg at the dorsum of the foot, no X-ray findings suggestive of osteomyelitis, no URTI, no COPD, no previous thoracic surgery, no malignancy, no history of middle ear barotraumas, pregnancy, smoking or abstention <1 month	Hyperbaric 100% O_2 at 2.5 ATA for 90 min with appropriate decompression, 5 days/week for 20 treatments	Standard care alone	Offloading, footwear (with extra depth, arch support, and custom-molded inserts), non-weight-bearing of the affected foot, oral antibiotics based on bacterial culture test results and drug sensitivity test of ulcer tissue, glycaemic control, daily dressings including silver-impregnated dressing when indicated, daily curettage or debridement	NR	Complete ulcer healing, transcutaneous oxygen pressure, ulcer area assessment (ulcer size measured using standardized photographs taken on day 0, day 7, and day 14), malondialdehyde and antioxidant enzyme levels from ulcer tissues	1 and 2
Khandelwal *et al.* (2013) [28]	40/29*	Diabetes-associated foot ulcer ≥8 weeks, lack of vascular insufficiency, age ≥18 years, no uncontrolled diabetes, no gangrene or osteomyelitis or multiple ulcers, no pregnancy, no immune-suppressants, no life-threatening infection, not HIV-positive, no chronic renal insufficiency, no perforated ear drum, no emphysema	Hyperbaric 100% O_2 delivered at 2.5 ATA for 60 min with appropriate decompression, total 30 sessions daily or every other day over 10 weeks, intermittent debridement and saline dressings	Anti-septic dressings: surgical debrided and then treated with Eusol or povidone iodine every 24 hours	Antibiotics based on wound culture	Complete ulcer healing	Healing time and wound contracture	10
Londahl *et al.* (2010) [29]	164/94/90	Diabetes, at least one full thickness wound below the	Hyperbaric 100% O_2 delivered at 244 kPa	Hyperbaric air delivered	Treatment at a multidisciplinary	Complete ulcer healing	Major and minor amputation, death	52

Table 1 (*Continued*)

Study	Sample size (Screened/ randomized/ completed)	Entry criteria	Intervention	Control	Additional management in both groups (standard care)	Primary outcome	Other outcomes	Follow-up, weeks
		ankle for >3 months, previously treated at a diabetes foot clinic for ≥2 months, only if adequate distal perfusion or no revascularization option according to a vascular surgeon, any acute infection resolved, no contraindications to HBOT (severe COPD, malignancy or untreated thyrotoxicosis), no current drug or alcohol abuse, no vascular surgery within the last 2 months, no participation in another study or concern about poor compliance	for 90 min with appropriate decompression, 5 days/week, total 40 sessions	delivered through an identical way to the hyperbaric O_2	clinic focused on treatment of infection, revascularization if indicated, debridement, offloading and control of hyperglycaemia according to international guidelines			
Duzgun *et al.* (2008) [30]	100/100*	Age >18 years, diabetes, foot ulcer for ≥4 weeks despite OMM, no contraindication to HBOT (untreated pneumothorax, COPD, prior ear surgery, URTI, febrile, prior convulsion, hypoglycaemia, current steroids, amphetamine, catecholamines or thyroid hormones)	Hyperbaric 100% O_2 using a volume of 10 m^3 at 2–3 ATA for 90 min with appropriate decompression; 2 or 1 session/ day, alternating for 20–30 days plus standard care	Standard care alone	Daily wound dressings, debridement, antibiotics and amputation if indicated	NR	Complete ulcer healing, graft or flap closure, amputation (distal and proximal), debridement	NR but mean 92
Abidia *et al.* (2003) [31]	25/18/16	Diabetes, ischaemic lower limb ulcers >1 cm and <10 cm, no signs of healing despite OMM for 6 weeks, ABPI <0.8 or TBPI <0.7, HbA_{1c}<8.5%, no revascularization option based on angiogram findings, no planned revascularization	Hyperbaric 100% O_2 at a pressure of 2.4 ATA for 90 min with appropriate decompression, 5 days/week, total 30 sessions	Hyperbaric air, presumably delivered identically to intervention group	All patients regularly attended a multidisciplinary clinic (diabetes physician, vascular surgeon, podiatrist, nurse) for 6 weeks before and during trial, offloading, wound care, aggressive debridement standardized to achieve moist wound	Ulcer surface area (traced onto transparent sheet and photographed prior to digital analysis)	Complete ulcer healing, ulcer depth (not clear how measured), signs of infection, quality of life measured with SF-36, HADS, cost-effectiveness, minor and major amputation	3, 6, 12, 24 and 52

Table 1 (*Continued*)

Study	Sample size (Screened/ randomized/ completed)	Entry criteria	Intervention	Control	Additional management in both groups (standard care)	Primary outcome	Other outcomes	Follow-up, weeks
					environment, antibiotics for clinical signs of infection			
Kessler *et al.* (2003) [32]	64/28/27	Diabetes, chronic foot ulcer (Wagner grades 1–3), ulcer depth <2 mm, not healing over 3 months despite OMM, normal lower limb arterial duplex, transcutaneous oxygen pressure >30 mmHg, no gangrene, no severe sepsis, no exclusion criteria for HBOT (emphysema, proliferative retinopathy, claustrophobia)	Hyperbaric 100% O_2 at 2.5 ATA for 90 min with appropriate decompression, twice daily 5 days/week for 2 weeks total 20 sessions and standard care	Standard care alone	Hospitalized for 2 weeks and 2 weeks outpatient monitoring, Barouk shoe for offloading, optimizing glycaemic control including subcutaneous insulin, antibiotics based on wound culture	Percentage reduction in wound surface area based on analysis of photographs of tracing of wounds	$TCPO_2$, complete ulcer healing	2 and 4

ABPI, ankle–brachial pressure index; AP, ankle systolic blood pressure; ATA, atmospheres absolute; COPD, chronic obstructive pulmonary disease; ESRF, end-stage renal failure; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HADS, Hospital Anxiety and Depression Scale; HBOT, hyperbaric oxygen therapy; LAWE, linear advancement of wound edge; LVEF, left ventricular ejection fraction; NR, not reported; OMM, optimal medical management; SF-12, 12-item short-form quality-of-life questionnaire; SF-36, 36-item short-form quality-of-life questionnaire; TBPI, toe–brachial pressure index; $TCPO_2$, transcutaneous oxygen pressure; TP, toe systolic blood pressure; URTI, upper respiratory tract infection.
*Number screened not reported.

Participant characteristics in the included trials

Participant characteristics in the included trials are provided in Table 2 and Table S2, and generally were poorly reported. Two trials reported significant differences in the distribution of important risk factors between those allocated to the HBOT and control groups, including duration of diabetes, BMI and prevalence of smoking (Table 2) [27,30]. The included characteristics of the ulcers, such as ulcer area, wound grade, duration of ulcer and measures of foot blood supply, were poorly reported, with only one trial reporting wound area, ankle or toe pressure and transcutaneous oxygen pressure (Table S2) [31].

Outcomes of individual trials

Only two of the trials reported that HBOT achieved a significant improvement in the percentage of ulcers completely healed at the completion of the follow-up [29,30]. Duzgun *et al*. [30] reported that the ulcers of 33 of 50 participants (66%) allocated to HBOT healed at an unclear follow-up time compared to none of those within the control group ($P<0.05$). Londahl *et al*. [29] reported that ulcers of 25 of 48 participants (52%) allocated to HBOT compared to 12 of 42 participants (29%) in the control group had healed at 52-week follow-up ($P=0.03$), but this analysis excluded participants lost to follow-up ($n=4$). Likelihood of ulcers healing generally favoured the HBOT group in other trials, although the relative risks varied markedly (Fig. 2).

Five of the trials clearly reported the proportion of participants requiring major and/or minor amputation during follow-up [20,21,27–33]. In one of these trials blinded adjudication of likely requirement for amputation rather than actual amputation was reported [27]. In another trial amputation rates were reported, however, it was not clear if this was minor or major amputation and for the purposes of analysis this was assumed to be major amputation [21]. Investigators of two trials reported a significantly lower major amputation rate in participants allocated to HBOT compared to controls [21,30]. Duzgun *et al*. [30] reported that major amputation was required in 17 of 50 participants (34%) within the control group compared to none of those allocated to HBOT ($P<0.05$). Chen *et al*. [21] also reported a significantly ($P=0.010$) lower amputation rate in participants allocated to HBOT (5%) compared to controls (11%), although it was not possible to replicate their statistical findings. In the other four trials it was reported that the requirement for major amputation was not significantly different between groups [20,21,27–33]. One trial reported that requirement for minor amputation was significantly lower in participants allocated to HBOT than controls (8% vs 48%; $P<0.05$) [30], while the other four trials reported no significant difference between groups [20,27,29,31]. A summary of the other outcomes reported from the trials is provided in Table 3. Three trials [31–33] reported that the percentage reduction in wound size was significantly greater in participants allocated to HBOT than controls during at least one time point, while one trial reported no significant difference in this outcome [27]. Two trials reported that HBOT led to significant improvement in components of the Short-Form-36 health-related quality-of-life tool [21,29].

Adverse events

Five of the trials reported information on adverse events, which is summarized in Table 3 [20,27,29,32,33]. A number of cases of ear barotrauma were reported and one seizure thought to be related to HBOT was reported [20,27,29,32,33].

Quantitative data synthesis

Findings for the main intention-to-treat analysis in which the worst-case scenario was assumed for participants with missing data is shown in Fig. 2. This analysis suggested that HBOT approximately doubled the likelihood of an ulcer healing (RR 1.95, 95% CI 1.51–2.52; $P<0.001$), and approximately halved the risk of major amputation (RR 0.54, 95% CI 0.36–0.81; $P=0.003$) and reduced the likelihood of minor (RR 0.68, 95% 0.48–0.98; $P=0.040$) amputation (Fig. 2). Based on I^2 values of 41% to 70%, heterogeneity for these outcomes was large (Fig. 2). A leave-one-out sensitivity analyses showed that the significance of the findings for the proportion of ulcers completely healed were not dependent on the inclusion of any single study but removal of the trial reported by Duzgun *et al*. [30] led to a marked reduction in the RR to 1.44 [95% CI 1.11, 1.86; $P=0.006$ (Fig. 2)]. Similarly, the findings for major and minor amputation were dependent on the inclusion of the trial reported by Duzgun *et al*. [30] (Fig. 2). Removal of this trial changed the RR for major amputation from 0.54 (95% CI 0.36–0.81) to 0.78 (95% CI 0.50–1.20) and for minor amputation from 0.68 (95% 0.48–0.98) to 1.06 (95% 0.70–1.61). The trial authored by Duzgun *et al*. was not identified to have any unique features compared to other trials, although the reporting of data (such as participant characteristics) in this trial was limited [30].

A further intention-to-treat sensitivity analysis was performed assuming the best-case scenario for participants with missing data (Figs S1–3). The results of this analysis were similar to the main analysis, with HBOT improving ulcer healing (RR 1.79, 95% 1.44–2.22; $P<0.001$), and reducing major (RR 0.46, 95% CI 0.28–0.75; $P=0.002$) and minor (RR 0.68, 95% 0.48–0.98; $P=0.040$) amputations.

Funnel plots are shown in Figs S4–6 for the three different outcomes based on the primary analysis. For the primary outcome of complete ulcer healing, the funnel plot had an asymmetrical distribution of data points, suggesting the possibility of publication bias (Fig. S4). For the outcomes of

Table 2 Characteristics of the included patients in relation to their allocation to hyperbaric oxygen therapy and control groups

Author	Group	Age, years	Male, %	Diabetes, %	BMI, kg/m^2	Current smoking, %	Diabetes duration, years	Prior ulcer	Prior revascularization, %	Prior minor amputation, %	Prior major amputation, %
Santema *et al.* (2018) [20]	HBOT	68 (10)	85	100	28 (6)	22	17 (11)	NR	63	33	0
	Control	71 (11)	77	100	27 (5)	22	19 (15)	NR	55	20	0
Chen *et al.* (2017) [21]	HBOT	64 (13)	50	100	NR	NR	NR	NR	NR	NR	
	Control	61 (7)	61	100	NR	NR	NR	NR	NR	NR	
Fedorko *et al.* (2016) [27]	HBOT	61 (12)	63	100	31 (7)	49	19 (12)†	NR	12	6	
	Control	62 (12)	70	100	30 (5)	56	12 (10)	NR	13	7	
Ma *et al.* (2013) [33]	HBOT	60 (7)	61	100	29 (2)	NR	25(17)	NR	NR	NR	NR
	Control	60 (6)	67	100	29 (1)	NR	23(17)	NR	NR	NR	NR
Khandelwal *et al.* (2013) [28]	HBOT	44 (9)	50	100	NR	NR	NR	NR	NR	NR	NR
	Control	45 (8)	55	100	NR	NR	NR	NR	NR	NR	NR
Londahl *et al.* (2010) [29]	HBOT	69 (37–95)¶	78	100	NR	22	20 (1–63)	NR	57	32	14
	Control	68 (28–86)¶	84	100	NR	29	23 (3–54)	NR	49	47	7
Duzgun *et al.* (2008) [30]	HBOT	58 (11)	74†	100	80%†‡	72†	17 (6)	NR	NR	NR	NR
	Control	63 (9)	54	100	46%‡	40	16 (6)	NR	NR	NR	NR
Abidia *et al.* (2003) [31]	HBOT	72 (13)	67	100	26 (7)	13	13 (10)	38%	25	13	0
	Control	70 (7)	33	100	29 (4)	25	10 (6)	50%	50	25	0
Kessler *et al.* (2003) [32]	HBOT	60 (10)	71	100	30 (3)	NR	18 (13)	NR	NR	NR	NR
	Control	68 (11)	69	100	29 (6)	NR	22 (13)	NR	NR	NR	NR

NR, not reported.
Numbers are mean (SD) or percentage unless otherwise indicated. †P<0.05 compared to control. ‡Reported as proportion of participants with obesity, variably defined as BMI ≥ 24, 25, 30 kg/m2. ¶Median (range). In some cases data were only available for those completing the trials not randomized.

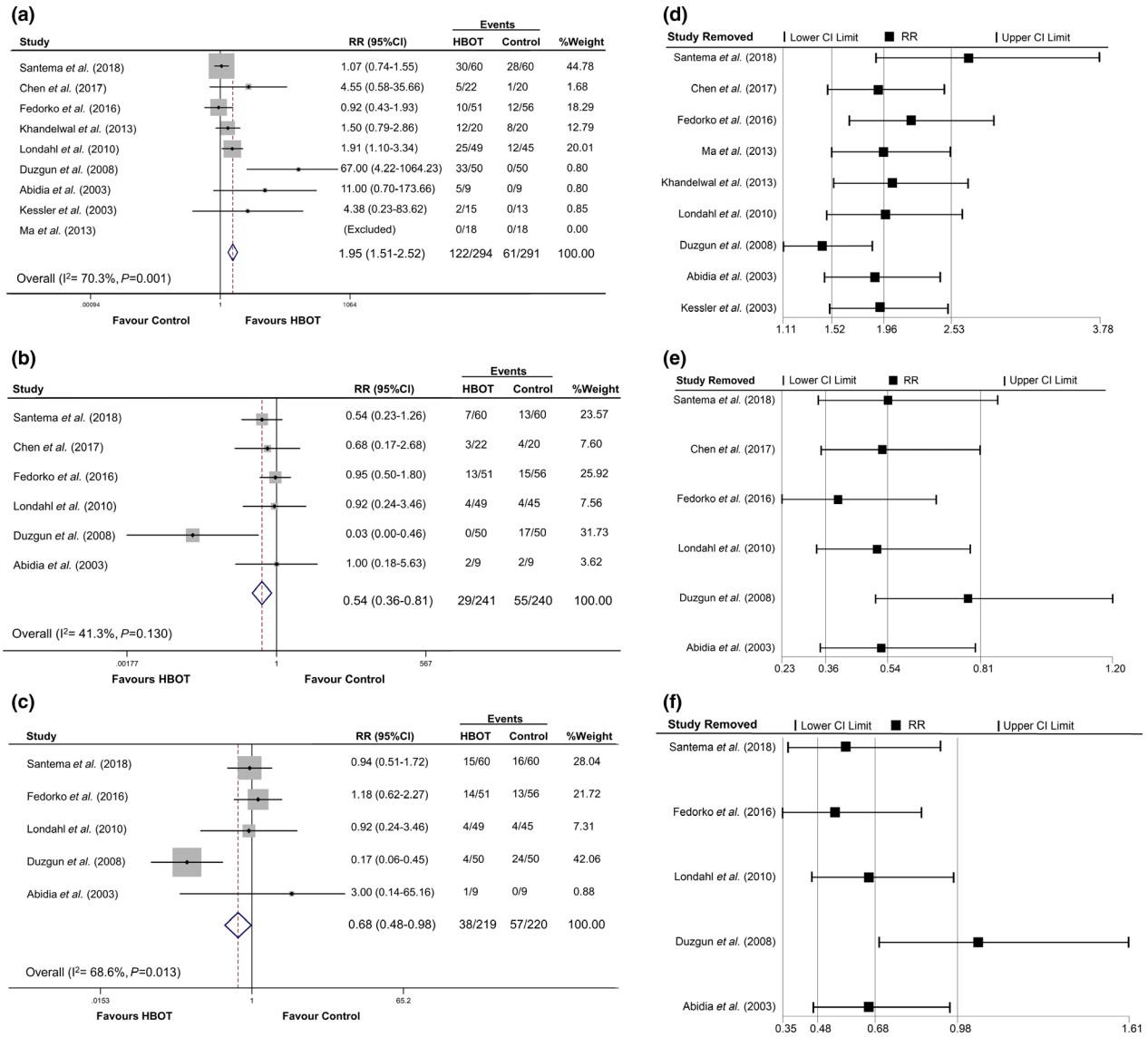

FIGURE 2 Effect of hyperbaric oxygen therapy (HBOT) on proportion of ulcers that completely healed, and requirement for major and minor amputation. Effect of HBOT in achieving ulcer healing (a), and reducing the requirement for major amputation (b) and minor amputation (c), reported as relative risk (RR) and 95% CI for patients randomly allocated to HBOT or control groups. The analyses were performed using intention-to-treat methods and assuming the worst-case scenario for patients with missing data (see methods for further details). Leave one-out sensitivity analyses for ulcer healing (d), major amputation (e) and minor amputation (f). Box areas are inversely proportional to the variance of the RR and horizontal lines illustrate 95% CI. In the trial reported by Chen *et al.* [21] amputation numbers were reported. It was assumed these represented major amputations although it was not possible to confirm this despite contacting the authors.

major and minor amputation, the funnel plots illustrated a more symmetrical distribution of data points (Figs S5 and S6). A sub-analysis focused on ischaemic ulcers was not possible because of the absence of three suitable trials.

Discussion

The main finding of the present meta-analysis was that HBOT improved the healing of diabetes-related lower limb ulcers, evidenced by an approximate doubling in the likelihood of an ulcer healing during follow-up and an approximate halving in the requirement for major amputations. While the findings for the primary outcome of complete ulcer healing still significantly favoured HBOT after removal of any individual study, removal of the trial reported by Duzgun *et al.* [30] substantially reduced the RR. The findings for the secondary outcomes of major and minor amputation were no longer significant after removal of the trial by Duzgun *et al.* [30].

While the present meta-analysis suggests benefit of HBOT, confidence in concluding this is lessened by a number of limitations and potential biases of the included trials. Firstly, the findings of individual trials were quite

Table 3 Tertiary and exploratory outcomes and adverse events for participants involved in the included hyperbaric oxygen therapy trials

Author	Follow-up, weeks	Significant benefits of HBOT compared with control treatment	No significant effect of HBOT compared with control, and AEs
Santema *et al.* (2018) [20]	52		All-cause mortality not different Two AEs related to HBOT (seizure and ruptured ear drum), also three prophylactic grommets
Chen *et al.* (2017) [21]	6	Wound healing score significantly higher; significant improvements in inflammation index, blood flow and health-related quality of life (SF-36) from pre-treatment to 2 weeks after the last therapy; significant improvement in glycaemic control; significant improvement in C-reactive protein; significant improvement in erythrocyte sedimentation rate; significant improvement Doppler blood flow in the limb	AEs not reported
Fedorko *et al.* (2016) [27]	12		Reduction in wound width and surface area, changes in Bates–Jensen wound score, changes in LAWE Incidence of AEs not significantly different between groups.
Ma *et al.* (2013) [33]	1 and 2	Percentage reduction in ulcer size, wound transcutaneous oxygen pressure, malondialdehyde and antioxidant enzyme levels (superoxide dismutase and catalase) from ulcer tissues at 2 weeks	Percentage reduction in ulcer size at 1 week No AEs occurred during follow-up
Khandelwal *et al.* (2013) [28]	10		Time to ulcer healing AEs not reported
Londahl *et al.* (2010) [29]	52	Significant improvement in role emotional and role physical domains of SF-36 in patients allocated HBOT not controls	Other domains of SF-36 no different between groups One case of ear barotrauma, Two cases of myringotomy with tube placement
Duzgun *et al.* (2008) [30]	NR	Less requirement for debridement	AEs not reported
Abidia *et al.* (2003) [31]	6, 24 and 52	Percentage reduction in ulcer size at 6 weeks, mean costs for dressings £1972 vs £7946 (cost saving including cost of HBOT £2960)	Percentage reduction in ulcer size at 24 weeks, HADS and SF-36 no different AEs not reported
Kessler *et al.* (2003) [32]	2 and 4	Percentage reduction in ulcer size at 2 weeks	Percentage reduction in ulcer size at 4 weeks One patient discontinued HBOT as a result of ear barotrauma

AE, adverse event; HADS, Hospital Anxiety and Depression Scale; HBOT, hyperbaric oxygen therapy; LAWE, linear advancement of wound edge; NR, not reported; SF-36, 36-item short-form quality-of-life questionnaire.

variable, illustrated by relatively wide 95% CIs for the RR for all outcomes. Secondly, as noted above, the findings of the meta-analysis were dependent on inclusion of one trial, which was noted to have a substantial risk of bias [30]. That trial reported RRs of ulcer healing, major amputation and minor amputation of 67.00, 0.03 and 0.17, which are results not representative of those of other trials or typically reported as treatment effects [30]. Key elements of trial design, such as blinding of study personnel and outcome assessors, a justifiable sample size calculation and a clear primary outcome measure were not reported for this trial [30]. Thirdly, many of the other included trials had a number of methodological weaknesses, such as absence of a reported blinded outcome assessment in five of the trials [20,21,28,30], and lack of a sample size calculation in five trials [28–30,32,33]. Fourthly, all the included trials were small (the largest included 120 participants) and, while the meta-analysis enabled a total of 585 people to be included for the primary outcome of ulcer healing, the most important outcome of major amputation included a smaller number of participants. It should be also noted that in one of the trials, which included 107 of the total number of participants, this outcome was based on the presumptive requirement of major amputation through adjudication by a blinded vascular surgeon [27]. Also one further trial did not clarify whether minor or major amputations were reported [21]. For the purpose of the present meta-analysis it was assumed the data represented major amputations, although it was not possible to confirm this despite contacting the authors [21]. Finally, the funnel plot for the primary outcome suggested the possibility of publication bias owing to the asymmetrical distribution of data points. It is therefore possible that a number of negative trials remain unreported.

The present meta-analysis included all identified RCTs investigating the benefit of HBOT in the treatment of diabetes-related lower limb ulcer in which complete ulcer healing percentages were reported. Only two studies reported

the specific inclusion of ischaemic ulcers and thus it was not possible to perform sub-analyses to better define whether HBOT may be most effective for these types of ulcers [20,31]. Given the substantial cost of HBOT this should be an important focus for future RCTs. Furthermore, only one previous small trial (which included a total of 18 participants) reported any information on the cost-effectiveness of HBOT [31]. This is another important focus for future trials. Another limitation of the identified trials was that follow-up was limited to 2–12 weeks in five of the trials [21,27,28,32,33], with only four of the trials including follow-up to 1 year [20,29–31].

In conclusion, the present meta-analysis suggests that HBOT has a substantial benefit in healing lower limb ulcers, but a number of methodological weaknesses of prior trials, in addition to the heterogeneity of the findings reported, suggest only moderate confidence in these findings. A large well-designed trial is needed to more rigorously test the efficacy and cost-effectiveness of HBOT for healing lower limb ulcers. Ideally such a trial should be designed to examine the relative efficacy of HBOT for ulcers because of different aetiologies.

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Competing interests

None declared.

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References

1 Armstrong DG, Boulton AJM, Bus SA. Diabetic Foot Ulcers and Their Recurrence. *N Engl J Med* 2017; **376**: 2367–2375.
2 Jeffcoate WJ, Vileikyte L, Boyko EJ, Armstrong DG, Boulton AJM. Current Challenges and Opportunities in the Prevention and Management of Diabetic Foot Ulcers. *Diabetes Care* 2018; **41**: 645–652.
3 Lazzarini PA, Pacella R, Armstrong DG, van Netten JJ. Diabetes-related lower-extremity complications are a leading cause of the global burden of disability. *Diabet Med* 2018; **35**: 1297–1299.
4 Hall J, Buckley HL, Lamb KA, Stubbs N, Saramago P, Dumville JC *et al.* Point prevalence of complex wounds in a defined United Kingdom population. *Wound Repair Regen* 2014; **22**: 694–700.
5 Rigato M, Pizzol D, Tiago A, Putoto G, Avogaro A, Fadini GP. Characteristics, prevalence, and outcomes of diabetic foot ulcers in Africa. A systemic review and meta-analysis. *Diabetes Res Clin Pract* 2018;**142**:63–73.
6 Guest JF, Fuller GW, Vowden P. Diabetic foot ulcer management in clinical practice in the UK: costs and outcomes. *Int Wound J* 2018; **15**: 43–52.
7 Graz H, D'Souza VK, Alderson DEC, Graz M. Diabetes-related amputations create considerable public health burden in the UK. *Diabetes Res Clin Pract* 2018; **135**: 158–165.
8 Mariam TG, Alemayehu A, Tesfaye E, Mequannt W, Temesgen K, Yetwale F, Limenih MA. Prevalence of Diabetic Foot Ulcer and Associated Factors among Adult Diabetic Patients Who Attend the Diabetic Follow-Up Clinic at the University of Gondar Referral Hospital, North West Ethiopia, 2016: Institutional-Based Cross-Sectional Study. *J Diabetes Res* 2017; **2017**: 287–249.
9 Siersma V, Thorsen H, Holstein PE, Kars M, Apelqvist J, Jude EB *et al.* Importance of factors determining the low health-related quality of life in people presenting with a diabetic foot ulcer: the Eurodiale study. *Diabet Med* 2013; **30**: 1382–1387.
10 Hicks CW, Selvarajah S, Mathioudakis N, Sherman RE, Hines KF, Black JH 3rd *et al.* Burden of Infected Diabetic Foot Ulcers on Hospital Admissions and Costs. *Ann Vasc Surg* 2016; **33**: 149–158.
11 Camporesi EM, Bosco G. Mechanisms of action of hyperbaric oxygen therapy. *Undersea Hyperb Med* 2014; **41**: 247–252.
12 Lepäntalo M, Apelqvist J, Setacci C, Ricco JB, de Donato G, Becker F *et al.* Chapter V: Diabetic foot. *Eur J Vasc Endovasc Surg* 2011; **42**: S60–74.
13 Schaper NC, Van Netten JJ, Apelqvist J, Lipsky BA, Bakker K; International Working Group on the Diabetic Foot (IWGDF). Prevention and management of foot problems in diabetes: A Summary Guidance for Daily Practice 2015, based on the IWGDF guidance documents. *Diabetes Res Clin Pract* 2017;**124**:84–92.
14 Kranke P, Bennett MH, Martyn-St James M, Schnabel A, Debus SE, Weibel S. Hyperbaric oxygen therapy for chronic wounds. *Cochrane Database Syst Rev* 2015;CD004123.
15 Zhao D, Luo S, Xu W, Hu J, Lin S, Wang N. Efficacy and Safety of Hyperbaric Oxygen Therapy Used in Patients With Diabetic Foot: A Meta-analysis of Randomized Clinical Trials. *Clin Ther* 2017; **39**: 2088–2094.
16 Health Quality Ontario. Hyperbaric Oxygen Therapy for the Treatment of Diabetic Foot Ulcers: A Health Technology Assessment. *Ont Health Technol Assess Ser* 2017; **17**: 1–142.
17 Chuck AW, Hailey D, Jacobs P, Perry DC. Cost-effectiveness and budget impact of adjunctive hyperbaric oxygen therapy for diabetic foot ulcers. *Int J Technol Assess Health Care* 2008; **24**: 178–183.
18 Elraiyah T, Tsapas A, Prutsky G, Domecq JP, Hasan R, Firwana B *et al.* A systematic review and meta-analysis of adjunctive therapies in diabetic foot ulcers. *J Vasc Surg* 2016; **63**: 46S–58S.
19 Eggert JV, Worth ER, Van Gils CC. Cost and mortality data of a regional limb salvage and hyperbaric medicine program for Wagner Grade 3 or 4 diabetic foot ulcers. *Undersea Hyperb Med* 2016; **43**: 1–8.
20 Santema KTB, Stoekenbroek RM, Koelemay MJW, Reekers JA, van Dortmont LMC, Oomen A *et al.* Hyperbaric Oxygen Therapy in the Treatment of Ischemic Lower- Extremity Ulcers in Patients With Diabetes: Results of the DAMO$_2$CLES Multicenter Randomized Clinical Trial. *Diabetes Care* 2018; **41**: 112–119.

21 Chen CY, Wu RW, Hsu MC, Hsieh CJ, Chou MC. Adjunctive Hyperbaric Oxygen Therapy for Healing of Chronic Diabetic Foot Ulcers: A Randomized Controlled Trial. *J Wound Ostomy Continence Nurs* 2017; **44**: 536–545.
22 Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med* 2009; **339**:b2535.
23 Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD *et al*.; Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomized trials. *BMJ* 2011;**343**:d5928.
24 Higgins JPT, Green S (eds). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. The Cochrane Collaboration, 2011. Available at http://www.handbook.cochrane.orgt. Last accessed 26 April 2019.
25 Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst* 1959; **22**: 719–748.
26 Sterne JA, Gavaghan D, Egger M. Publication and related bias in meta-analysis: power of statistical tests and prevalence in the literature. *J Clin Epidemiol* 2000; **53**: 1119–1129.
27 Fedorko L, Bowen JM, Jones W, Oreopoulos G, Goeree R, Hopkins RB *et al*. Hyperbaric Oxygen Therapy Does Not Reduce Indications for Amputation in Patients With Diabetes With Nonhealing Ulcers of the Lower Limb: A Prospective, Double-Blind. Randomized Controlled Clinical Trial. *Diabetes Care* 2016; **39**: 392–399.
28 Khandelwal S, Chaudhary P, Poddar DD, Saxena N, Singh RA, Biswal UC. Comparative Study of Different Treatment Options of Grade III and IV Diabetic Foot Ulcers to Reduce the Incidence of Amputations. *Clin Pract* 2013; **3**: e9.
29 Löndahl M, Katzman P, Nilsson A, Hammarlund C. Hyperbaric oxygen therapy facilitates healing of chronic foot ulcers in patients with diabetes. *Diabetes Care* 2010; **33**: 998–1003.
30 Duzgun AP, Satir HZ, Ozozan O, Saylam B, Kulah B, Coskun F. Effect of hyperbaric oxygen therapy on healing of diabetic foot ulcers. *J Foot Ankle Surg* 2008; **7**: 515–519.
31 Abidia A, Laden G, Kuhan G, Johnson BF, Wilkinson AR, Renwick PM *et al*. The role of hyperbaric oxygen therapy in ischaemic diabetic lower extremity ulcers: a double-blind randomised-controlled trial. *Eur J Vasc Endovasc Surg* 2003; **25**: 513–518.
32 Kessler L, Bilbault P, Ortéga F, Grasso C, Passemard R, Stephan D *et al*. Hyperbaric oxygenation accelerates the healing rate of nonischemic chronic diabetic foot ulcers: a prospective randomized study. *Diabetes Care* 2003; **26**: 2378–2382.
33 Ma L, Li P, Shi Z, Hou T, Chen X, Du J. A prospective, randomized, controlled study of hyperbaric oxygen therapy: effects on healing and oxidative stress of ulcer tissue in patients with a diabetic foot ulcer. *Ostomy Wound Manage* 2013; **59**: 18–24.

Supporting Information

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

Table S1. Assessment of quality or risk of bias of the included studies

Table S2. Characteristics of the included ulcers and foot perfusion in relation to participants' allocation to HBOT and control groups

Figure S1. Effect of HBOT on proportion of ulcers that completely healed assuming the best-case scenario for participants with missing data.

Figure S2. Effect of HBOT on major amputation assuming the best-case scenario for participants with missing data.

Figure S3. Effect of HBOT on minor amputation assuming the best-case scenario for participants with missing data.

Figure S4. Funnel plot with pseudo 95% CIs of the effect of HBOT on the complete healing of ulcers.

Figure S5. Funnel plot with pseudo 95% CIs of the effect of HBOT on the risk of major amputation.

Figure S6. Funnel plot with pseudo 95% CIs of the effect of HBOT on the risk of minor amputation.