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Blood flow restriction training compared to conventional training in people with knee pain: a systematic review with meta-analysis

Camilla Zeitlin [a], Matthew Shepherd [a], Simon David Lack [b,c], Bradley Stephen Neal [a,b,*]

[a] School of Sport, Rehabilitation and Exercise Science, University of Essex, Wivenhoe Park, Colchester, Essex, CO4 3WA, UK
[b] Sports and Exercise Medicine, Queen Mary University of London, Mile End Hospital, Bancroft Road, London, E1 4DG, UK
[c] Pure Sports Medicine, Point West Building, 116 Cromwell Road, London, SW7 4XR, UK

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ABSTRACT

Objective: Evaluate the efficacy of blood flow restriction training (BFRT) in people with knee conditions.
Methods: We searched Medline, Web of Science, and Sport DISCUS from inception until October 2023, seeking randomised controlled trials (RCTs) involving participants with any knee condition and BFRT in at least one intervention arm. We used a random-effects model meta-analysis to pool methodologically homogeneous data and the Grading of Recommendations, Assessment, Development, and Evaluations approach to categorise certainty of evidence.
Results: 15 RCTs involving 418 participants were eligible, investigating people post-anterior cruciate ligament reconstruction (n = 7) and cartilage surgery (n = 2), or with knee osteoarthritis (n = 3) and patellofemoral pain (n = 3). There is very low certainty evidence that adding BFRT to resistance training is superior to resistance training for pain outcomes (small SMD 0.47, 95 % CI 0.09, 0.85). There is very low certainty evidence that adding BFRT to resistance training is equivalent to resistance training for function and strength outcomes.
Conclusions: BFRT offers a significant effect on short-term pain that is of questionable clinical relevance, and no significant effects on function or quadriceps strength. Future high-quality RCTs are required to appropriately explore clinical efficacy, and clinicians should exercise caution in offering BFRT to people with knee conditions.

1. Introduction

The knee is the second most common site for musculoskeletal pain in the human body, affecting athletes and non-athletes in a comparable manner (van Middelkoop et al., 2008). Knee osteoarthritis has a pooled global prevalence of 16 % that increases exponentially with age (Cui et al., 2020) and patellofemoral pain (PFP) has an annual prevalence of 23 % in the general population (Smith et al., 2018). Rupture of the anterior cruciate ligament (ACL) is a common orthopaedic problem, with an age- and sex-adjusted incidence of 67 per 100,000 person years (Sanders et al., 2016). Regardless of the specific diagnosis, symptoms of knee pain limit peoples' activity of daily living and impairs their quality of life (van Middelkoop et al., 2008). Gradual progression of knee joint loading via exercise-based rehabilitation is a frequent element of recovery from knee pain (van Rossom et al., 2018).

Blood flow Restriction Training (BFRT), also known as Kaatsu training (Patterson et al., 2019), involves restricting blood flow at the most proximal part of the limb being trained, using an inflatable cuff or strap (Patterson et al., 2019). An applied pressure whereby modest arterial flow is maintained but venous return is occluded creates a hypoxic environment within the targeted tissues (Pearson & Hussain, 2015). BFRT combined with low load resistance exercise is reported to be as effective as high load resistance exercise in stimulating hypertrophy in healthy people, via a probable mechanism of increased metabolic stress (Pearson & Hussain, 2015) (Lixandrao et al., 2018). BFRT is gaining traction as a therapeutic option for people with musculoskeletal conditions who cannot participate in traditional high load resistance exercise (e.g., people with knee osteoarthritis) (Hughes et al., 2017).

Whilst BFRT is reported to be safe for people with musculoskeletal conditions (Minniti et al., 2020), its efficacy is uncertain. Alvarez et al., (Bobes Alvarez et al., 2020) systematically reviewed the evidence for BFRT in people either post-ACL reconstruction or with knee osteoarthritis up to 2020, describing significant improvements in pain from four randomised controlled trials (RCTs), but did not conduct meta-analyses to estimate treatment effect sizes. Whilst Li et al., (Li et al., 2021) report significant improvements in both pain and strength in people with knee

* Corresponding author. School of Sport, Rehabilitation and Exercise Sciences, University of Essex, Wivenhoe Park, Colchester, Essex, CO4 3SQ, UK.
E-mail address: b.neal@essex.ac.uk (B.S. Neal).

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pain following BFRT, they inappropriately pooled point follow up data using a fixed effects meta-analysis model. A further systematic review with meta-analysis in people with knee osteoarthritis published in 2021 was subsequently retracted due to statistical errors (Ferlito et al., 2020). Other recent systematic reviews with meta-analyses in people post-knee surgery focus primarily on muscle strength and morphology as opposed to patient-reported pain and function outcomes (Wengle et al., 2022) (Colapietro et al., 2023), with calculated effect sizes of questionable clinical importance.

We therefore aimed to evaluate the efficacy of BFRT for pain, function, and strength outcomes in people with knee conditions by pooling data using appropriate meta-analysis methods from available RCTs.

2. Materials and methods

We registered this systematic review with meta-analysis with PROSPERO *a priori* (CRD42022352944) and conducted it with no deviations from protocol. We have reported this systematic review in accordance with the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009).

2.1. Search strategy

We searched Medline, Web of Science, and Sport DISCUS from inception until October 2023 using the following search terms: (a) Blood Flow Restriction Training or BFR or Kaatsu or Occlu* and (b) Knee or Patella or Patello* or ACL or Cruciate or MCL or PFP or LCL or Menis* or knee injury or anterior knee pain or osteoarth*. Our search was limited to papers involving human participants and published in the English language. We also examined the reference lists of included studies and conducted a cited reference search using Google Scholar.

2.2. Inclusion criteria and study selection

One investigator (BSN) imported all identified studies into Covidence (https://www.covidence.org/). We included studies that met the following inclusion criteria: (a) randomised controlled trial design; (b) population: participants aged ≥18 years with any type of knee condition; (c) intervention: BFRT; (d) control: non-BFRT; (e) outcomes: pain, function, or strength measures. We considered a BFR intervention to equate to any level of vascular occlusion during resistance exercise and conventional training as any form of resistance exercise without vascular occlusion. Two independent investigators (MS and CZ) screened titles and abstracts, followed by full text articles, to reach consensus on eligibility. Input from a third investigator (BSN) was available but not required.

2.3. Risk of bias (RoB)

We used the Cochrane RoB2 tool (Sterne et al., 2019) to categorise eligible RCTs as (i) high risk of bias, (ii) some concerns of bias, or (iii) low risk of bias. Two independent investigators (MS and CZ) applied the RoB2 tool before reaching consensus on RoB categorisation. Input from a third investigator (BSN) was available but not required.

2.4. Data extraction

Descriptive data were extracted from all eligible RCTs by a single investigator (CZ) and then checked for accuracy by a second (BSN). This included details of the BFRT intervention and control, sample size and sex, participant age, body mass index (BMI), and symptom duration. We subsequently sought to extract within-group mean change and the associated SD for the reported pain (e.g., numerical pain rating scale), function (e.g., lower extremity function scale), and strength (e.g., peak torque) outcomes. We extracted the smallest within-group effect where RCTs presented more than one pain, function, or strength outcome to reduce the risk of type I error. We contacted corresponding authors up to three times where data were not reported in the required format.

2.5. Statistical analysis

All statistical analyses were performed by a single investigator (BSN) using Review manager 5.4 (Cochrane Collaboration, Copenhagen, Denmark). We used within-group mean change and SD to calculate standardized mean differences (SMDs) with 95 % CIs that were classified as small (≤0.59), medium (0.60–1.19), and large (≥1.20) as modified by Hopkins and described by Hume et al., (Hume et al., 2008). We used the Cochrane guidelines to convert variances expressed as either 95 % confidence interval (CI) or standard error (SE) to SD if required (Higgins et al., 2024). We used a random-effects model to pool methodologically homogeneous data using meta-analysis (Borenstein et al., 2010), defined as resistance training with BFRT compared to resistance training in isolation. Statistical homogeneity for pooled data was determined using the I^2 statistic, defined as I^2>50 %, $p < .05$. Data were pooled relative to follow-up from commencement of treatment, defined as short- (≤3 months), medium- (>3 but <12 months), and long-term (≥12 months). The latest data point was extracted when RCTs provided multiple data points within one follow-up period (e.g., 4 and 8 weeks).

2.6. Certainty of evidence

We used the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) approach to categorise certainty of evidence for all outcomes (high, moderate, low, very low) (Guyatt et al., 2011a). Certainty of evidence started as high as all outcomes come from RCTs, before being adjusted according to specific criteria. We applied a ceiling of moderate certainty for outcomes from single RCTs (Neal, Bartholomew, et al., 2022). We used risk of bias to rate down one level if serious (50–75 % of pooled data coming from RCTs with high or some concern of RoB, or a single RCT with some concern of RoB) or two levels if very serious (>75 % of pooled data coming from RCTs with high or some concern of RoB, or a single RCT with high RoB) (Guyatt et al., 2011b). We rated down one level for inconsistency if I^2 >50 % or where data pooling was not possible (Guyatt et al., 2011c). We rated down one or two levels for imprecision if either 95 % CI crossed one or two effect size thresholds (Guyatt et al., 2011d). We rated up one or two levels for effect size if medium or large respectively (Guyatt et al., 2011a). Publication bias was not considered as no outcome involved pooling data from >10 RCTs (Ioannidis & Trikalinos, 2007).

3. Results

3.1. Study selection

4839 articles were identified by our systematic search, with 3363 remaining after removing duplicates. 3315 articles were excluded based on title and abstract screening, leaving 48 full texts for review, of which 15 were eligible for inclusion (Bryk et al., 2016; Constantinou et al., 2022; Curran et al., 2020; De Melo et al., 2022; Ferraz et al., 2018; Giles et al., 2017; Girardi & Guenka, 2022; Hughes et al., 2018a, 2019a, 2019b; Ke et al., 2022; Khalil et al., 2023; Mason et al., 2022; Segal et al., 2015; Tramer et al., 2023), with one RCT including a duplicate dataset (Hughes, Patterson, et al., 2019). One RCT was identified via citing reference searching in Google scholar (Girardi & Guenka, 2022). The stages of our systematic search process are illustrated in Fig. 1.

3.2. Study characteristics

Of the 15 eligible RCTs, seven included participants post-ACL reconstruction (Curran et al., 2020; De Melo et al., 2022; Hughes et al., 2018a, 2019a, 2019b; Khalil et al., 2023; Tramer et al., 2023), three included participants with knee osteoarthritis (Bryk et al., 2016;

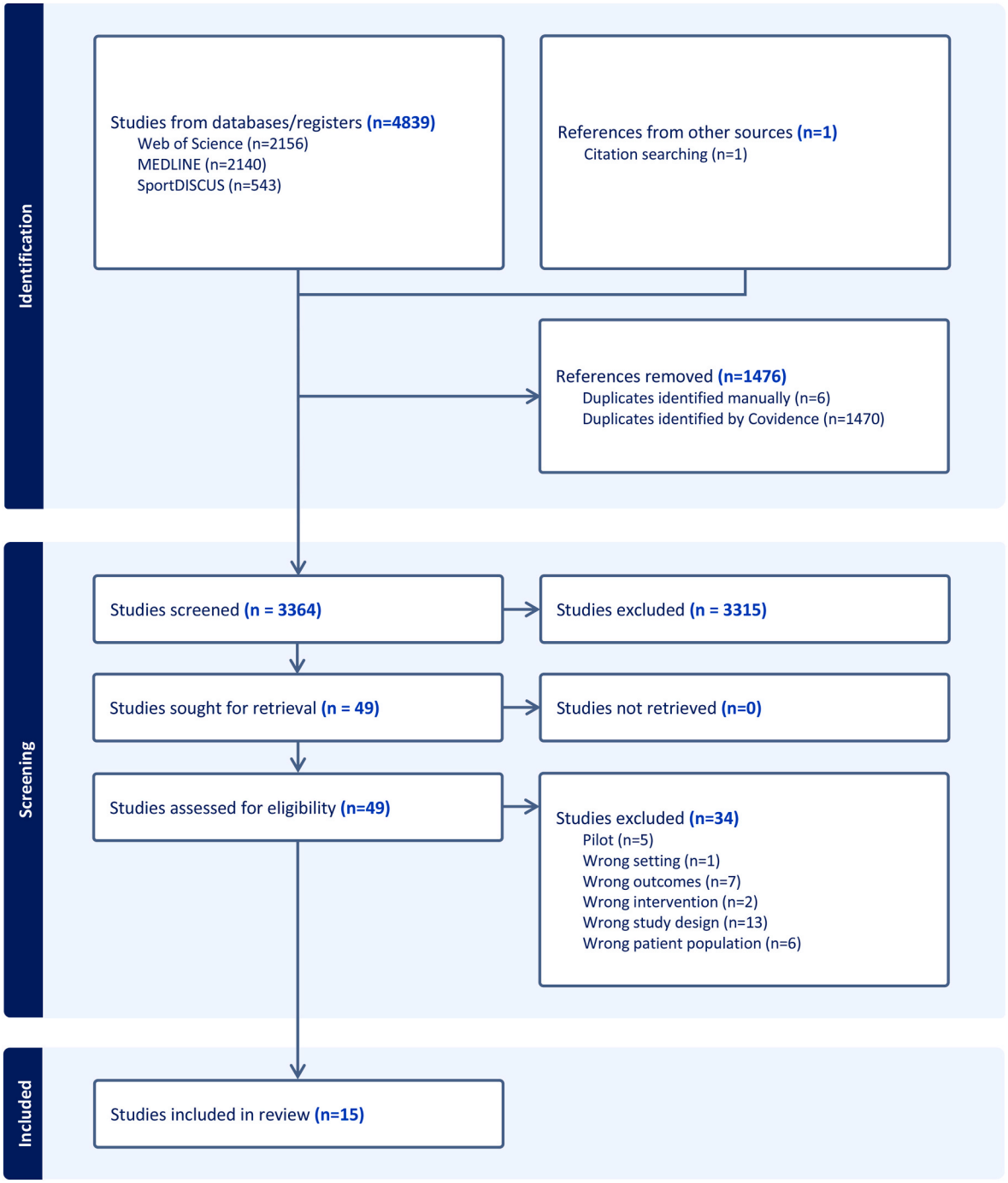

Fig. 1. PRISMA flow diagram.

Ferraz et al., 2018; Segal et al., 2015), three included participants with PFP (Constantinou et al., 2022; Girardi & Guenka, 2022; Giles et al., 2017), and two included participants post-cartilage surgery (Ke et al., 2022; Mason et al., 2022). A total of 418 participants were included in the eligible RCTs, and 11 RCTs included data suitable for pooling using meta-analysis (Constantinou et al., 2022; Curran et al., 2020; De Melo et al., 2022; Bryk et al., 2016; Ferraz et al., 2018; Hughes, Rosenblatt, et al., 2019; Khalil et al., 2023; Segal et al., 2015; Tramer et al., 2023; Mason et al., 2022; Girardi & Guenka, 2022). A summary of the participant characteristics and BFRT/control interventions from the 15 eligible studies is presented in Table 1.

3.2.1. *Data handling*

We were able to pool pain data from three ACL trials (De Melo et al., 2022) (Hughes, Rosenblatt, et al., 2019) (Khalil et al., 2023), two OA trials (Bryk et al., 2016) (Segal et al., 2015), and two PFP trials (Constantinou et al., 2022) (Girardi & Guenka, 2022); with data extracted directly from five trials (Constantinou et al., 2022) (De Melo et al., 2022) (Hughes, Rosenblatt, et al., 2019) (Bryk et al., 2016) (Segal et al., 2015) and raw data provided by two trials (Khalil et al., 2023) (Girardi & Guenka, 2022). We were able to pool function data from three ACL trials (De Melo et al., 2022) (Curran et al., 2020) (Hughes, Rosenblatt, et al., 2019), two OA trials (Bryk et al., 2016) (Ferraz et al., 2018), two PFP trials (Constantinou et al., 2022) (Girardi & Guenka, 2022), and one cartilage surgery trial (Mason et al., 2022); with data

Table 1
Study characteristics.

	Sample size (F:M) Age in years BMI in kg/m2 Symptom duration Follow up length	Sets Repetitions Frequency Duration Load BFRT application	Sample size (F:M) Age in years BMI in kg/m2 Symptom duration Follow up length	Sets Repetitions Frequency Duration Load	Pain outcome Function outcome Strength outcome
	BFRT		Control		
ACL trials					
Curran 2020 (Curran et al., 2020)	9 (4:5) 15.3 ± 0.9 NR NR 8-weeks	5 10 Twice weekly 8-weeks 70 % RM 80 % LOP	18 (10:8) 15.7 ± 1.3 NR NR 8-weeks	5 10 Twice weekly 8-weeks 70 % RM	NR NR IKD
De Melo 2022 (De Melo et al., 2022)	12 (4:8) 41.1 ± 9.8 24.2 ± 3.0 NR 4-weeks	4 30/15/15/15 Twice weekly 4-weeks 30 % RM 80 % LOP	12 (3:9) 39.6 ± 10.8 23.6 ± 2.4 NR 4-weeks	3 10 Twice weekly 4-weeks 70 % RM	PRS IKDC NR
Hughes 2018 (Hughes, Paton, et al., 2018)	10 (6:4) 29 ± 5 25.7 ± 4.2 NR 24-h	4 30/15/15/15 Once Single session 30 % RM 80 % LOP	10 (3:7) 31 ± 7 23.5 ± 3.4 NR 24-h	3 10 Once Single session 70 % RM	PRS NR NR
Hughes 2019a (Hughes, Rosenblatt, et al., 2019)	14 (5:5) 29 ± 7 25.4 ± 3.9 NR 8-weeks	4 30/15/15/15 Twice weekly 8-weeks 30 % RM 80 % LOP	14 (2:10) 29 ± 7 26.4 ± 4.4 NR 8-weeks	3 10 Twice weekly 8-weeks 70 % RM	KOOS KOOS 10RM
Hughes 2019b (Hughes, Patterson, et al., 2019)	Duplicate data set				
Khalil 2023 (Khalil et al., 2023)	18 (3:15) 23.8 ± 3.9 25.4 ± 2.1 NR 12-weeks	3 10 NR NR NR 80 % LOP	18 (2:16) 25.2 ± 4.8 26.2 ± 3.9 NR 12-weeks	3 10 NR NR NR	VAS NR NR
Tramer 2023 (Tramer et al., 2023)	23 (12:11) 26.5 ± 12.0 25.3 ± 3.2 NR 2-weeks	NR 30/15/15/15 5 times weekly 2-weeks NR 80 % LOP	22 (8:14) 27.0 ± 11.0 26.8 ± 4.9 NR 2-weeks	NR 30/15/15/15 5 times weekly 2-weeks NR	NR NR IKD
Knee osteoarthritis trials					
Bryk 2016 (Bryk et al., 2016)	17 (NR) 62.3 ± 7.0 28.9 ± 3.7 NR 6-weeks	3 10 3 times weekly 6-weeks 30 % RM 200 mmHG	17 (NR) 60.4 ± 6.7 30.8 ± 3.7 NR 6-weeks	3 10 3 times weekly 6-weeks 70 % RM	NPRS Lequesne HHD
Ferraz et al., 2018 (Ferraz et al., 2018)	16 (NR) 60.3 ± 3 30.2 ± 3 56.4 ± 36 months 12-weeks	4–5 15 Twice weekly 12-weeks 30 % RM 70 % LOP	16 (NR) 60.7 ± 4 29.9 ± 3 56.4 ± 36 months 12-weeks	4–5 15 Twice weekly 12-weeks 30 % RM	WOMAC WOMAC 1RM
Segal 2015 (Segal et al., 2015)	19 (19:0) 56.1 ± 5.9 28.7 ± 4.4 NR 4-weeks	4 30/15/15/15 3 times weekly 4-weeks 30 % RM 160–200 mmHg	21 (21:0) 54. 6 ± 6.9 32.1 ± 5.2 NR 4-weeks	4 30/15/15/15 3 times weekly 4-weeks 30 % RM	KOOS KOOS IKD
PFP trials					
Constantinou 2022 (Constantinou et al., 2022)	30 (14:16) 30.5 ±NR 24.7 ± 4.3 11 ±NR months 8-weeks	3 10 3 times weekly 4-weeks 30 % RM	30 (13:17) 25.5 ±NR 24.6 ± 3.0 14 ±NR months 8-weeks	3 10 3 times weekly 4-weeks 70 % RM	VAS AKPS NR

(*continued on next page*)

Table 1 (*continued*)

	Sample size (F:M) Age in years BMI in kg/m2 Symptom duration Follow up length	Sets Repetitions Frequency Duration Load BFRT application	Sample size (F:M) Age in years BMI in kg/m2 Symptom duration Follow up length	Sets Repetitions Frequency Duration Load	Pain outcome Function outcome Strength outcome
	BFRT		Control		
Giles 2017 (Giles et al., 2017)	40 (24:16) 28.5 ± 5.2 NR 31.6 ± 40.9 months 24-weeks	70 % LOP 3 30/15/15/15 3 times weekly 8-weeks 30 % RM	39 (19:20) 26.7 ± 5.5 NR 37.8 ± 55.5 months 24-weeks	3 7–10 3 times weekly 8-weeks 70 % RM	VAS AKPS IKD
Girardi 2022 (Girardi & Guenka, 2022)	8 (8:0) 23.2 ± 2.0 22.0 ± 2.1 NR 6-weeks	60 % AOP 4 30/15/15/15 3 times weekly 6-weeks 20 % RM	7 (7:0) 28.5 ± 3.9 23.7 ± 4.7 NR 6-weeks	4 30/15/15/15 3-times weekly 6-weeks 20 % RM	NPRS AKPS 1RM
Cartilage surgery trials		~140 mmHg			
Ke 2022 (Ke et al., 2022)	19 (7:12) 37.6 ± 11.4 24.2 ± 2.7 7.1 ± 7.2 months 8-weeks	3 10 Twice weekly 8-weeks 30 % RM	19 (10:9) 37.7 ± 11.3 23.1 ± 3.2 8.2 ± 8.6 months 8-weeks	3 10 Twice weekly 8-weeks 30 % RM	VAS Lysholm IKD
Mason 2022 (Mason et al., 2022)	8 (0:8) 23 ± 3 NR NR 24-weeks	80 % LOP 4 30/15/15/15 2-3 times weekly 12-weeks NR	9 (1:9) 23 ± 4 NR NR 24-weeks	4 30/15/15/15 2-3 times weekly 12-weeks NR	NR LEFS IKD
		80 % LOP			

Key: BFRT – blood flow restriction training; BMI – body mass index; NR; not reported; RM – repetition maximum; LOP – limb occlusion pressure; AOP; arterial occlusion pressure; PRS – pain rating scale; VAS – visual analogue scale; IKD – isokinetic dynamometry; KOOS – knee injury and osteoarthritis outcome score; RM – repetition maximum; NPRS – numerical pain rating scale; HHD – handheld dynamometry; AKPS – anterior knee pain scale; lower extremity functional scale.

extracted directly from six trials (Constantinou et al., 2022; Curran et al., 2020; De Melo et al., 2022) (Hughes, Rosenblatt, et al., 2019) (Bryk et al., 2016) (Mason et al., 2022) and raw data provided by two trials (Ferraz et al., 2018) (Girardi & Guenka, 2022). We were able to pool strength data from two ACL trials (Curran et al., 2020) (Tramer et al., 2023) and two OA trials (Bryk et al., 2016) (Segal et al., 2015); with data extracted directly from all four trials. No variance conversion was necessary for any extracted or provided data. Three eligible RCTs presented their data in a manner that did not allow for meta-analysis and these authors did not respond to raw data requests (Hughes, Paton, et al.,

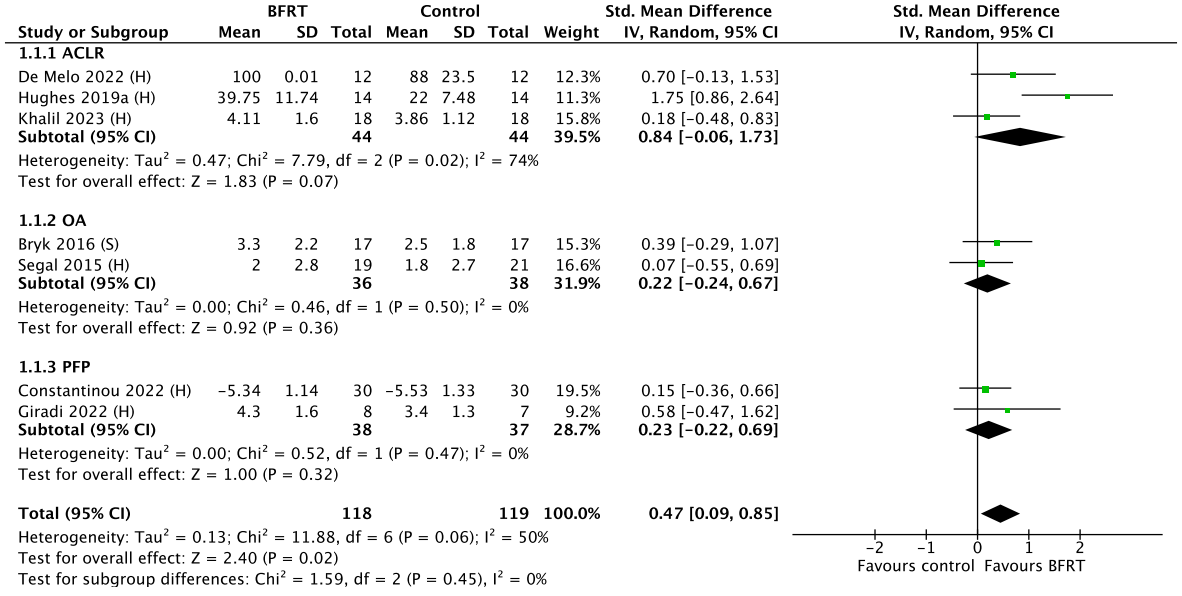

Fig. 2. Forest plot for short-term pain outcomes.

2018) (Ke et al., 2022) (Giles et al., 2017).

3.3. Risk of bias

After applying the RoB2 tool to the 15 eligible RCTs, one was categorised as having a low RoB, three were one was categorised as having some RoB, and eleven were categorised as having a high risk of bias. RoB outcomes for the included trials are summarised in Fig. S1.

3.4. Short-term effects of BFRT on pain (Fig. 2)

There is very low certainty evidence from seven RCTs (Constantinou et al., 2022) (De Melo et al., 2022) (Hughes, Rosenblatt, et al., 2019) (Khalil et al., 2023) (Bryk et al., 2016) (Segal et al., 2015) (Girardi & Guenka, 2022) that adding BFRT to resistance training is *superior* to resistance training without BFRT (small significant SMD 0.47, 95 % CI 0.09, 0.85).

3.4.1. ACLR

There is very low certainty evidence from three RCTs (De Melo et al., 2022) (Hughes, Rosenblatt, et al., 2019) (Khalil et al., 2023) that adding BFRT to resistance training is *equivalent* to resistance training without BFRT (non-significant SMD 0.84, 95 % CI -0.06, 1.73).

3.4.2. Osteoarthritis

There is very low certainty evidence from two RCTs (Bryk et al., 2016) (Segal et al., 2015) that adding BFRT to resistance training is *equivalent* to resistance training without BFRT (non-significant SMD 0.22, 95 % CI -0.24, 0.67).

3.4.3. PFP

There is very low certainty evidence from two RCTs (Constantinou et al., 2022) (Girardi & Guenka, 2022) that adding BFRT to resistance training is *equivalent* to resistance training without BFRT (non-significant SMD 0.23, 95 % CI -0.22, 0.69).

3.5. Short-term effects of BFRT on patient-reported function (Fig. 3)

There is very low certainty evidence from eight RCTs (Constantinou et al., 2022) (De Melo et al., 2022) (Hughes, Rosenblatt, et al., 2019) (Khalil et al., 2023) (Bryk et al., 2016) (Segal et al., 2015) (Mason et al., 2022) (Girardi & Guenka, 2022) that adding BFRT to resistance training is *equivalent* to resistance training without BFR (non-significant SMD 0.75, 95 % CI -0.07, 1.58).

3.5.1. ACLR

There is very low certainty evidence from three RCTs (De Melo et al., 2022) (Curran et al., 2020) (Hughes, Rosenblatt, et al., 2019) that adding BFRT to resistance training is *equivalent* to resistance training without BFR (non-significant SMD 3.40, 95 % CI -0.06, 6.85).

3.5.2. Osteoarthritis

There is very low certainty evidence from two RCTs (Bryk et al., 2016) (Ferraz et al., 2018) that adding BFRT to resistance training is *equivalent* to resistance training without BFR (non-significant SMD -0.01, 95 % CI -0.53, 0.51).

3.5.3. PFP

There is very low certainty evidence from two RCTs (Constantinou et al., 2022) (Girardi & Guenka, 2022) that adding BFRT to resistance training is *equivalent* to resistance training without BFR (non-significant SMD 0.23, 95 % CI -0.23, 0.68).

3.5.4. Cartilage surgery

There is very low certainty evidence from one RCT (Mason et al., 2022) that adding BFRT to resistance training is *equivalent* to resistance training without BFR (non-significant SMD 0.78, 95 % CI -0.07, 1.58).

3.6. Short-term effects of BFRT on quadriceps strength (Fig. 4)

There is very low certainty evidence from four RCTs (Curran et al., 2020) (Tramer et al., 2023) (Bryk et al., 2016) (Segal et al., 2015) that adding BFRT to resistance training is *equivalent* to resistance training

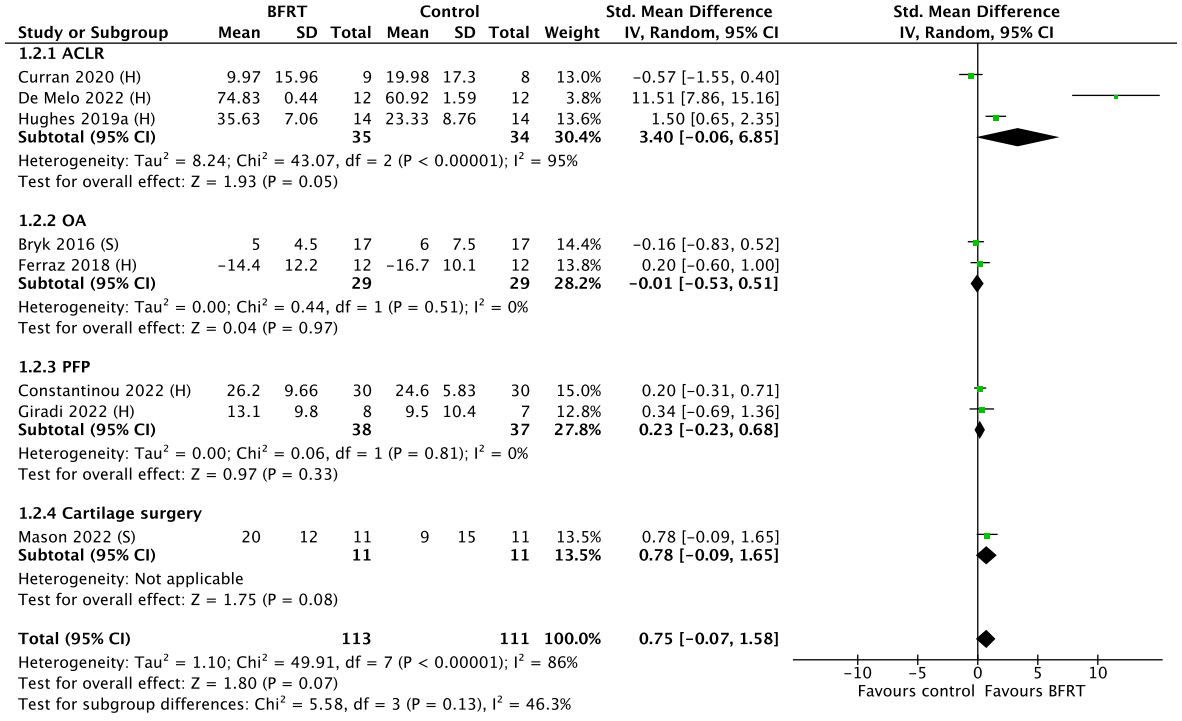

Fig. 3. Forest plot for short-term function outcomes.

without BFRT (non-significant SMD 1.14, 95 % CI -0.33, 2.61).

3.6.1. ACLR

There is very low certainty evidence from two RCTs (Curran et al., 2020) (Tramer et al., 2023) that adding BFRT to resistance training is *equivalent* to resistance training without BFRT (non-significant SMD 0.01, 95 % CI -0.49, 0.50).

3.6.2. Osteoarthritis

There is very low certainty evidence from two RCTs (Bryk et al., 2016; Ferraz et al., 2018; Segal et al., 2015) that adding BFRT to resistance training is *equivalent* to resistance training without BFRT (non-significant SMD 2.32, 95 % CI -0.77, 5.40).

3.7. Medium-term effects of BFRT on function (Fig. 5)

There is very low certainty evidence from one RCT (Mason et al., 2022) involving people post-cartilage surgery that adding BFRT to resistance training is equivalent to resistance training without BFR (non-significant SMD 0.06, 95 % CI -0.77, 0.90).

4. Discussion

After pooling data from 11/15 eligible RCTs, we identified that adding BFRT to resistance training achieved superior reductions in knee pain at short-term follow up. This outcome was influenced significantly by a single RCT (Hughes, Rosenblatt, et al., 2019). No significant effects were identified for either patient-reported function or quadriceps strength in the short-term, or patient-reported function in the medium-term. All subgroup analyses for specific knee pain diagnoses were non-significant. These findings need to be interpreted with caution as we were able to pool data from a limited number of trials, all trials included have small participant numbers, and 14/15 trials had at least some risk of bias.

Our finding that adding BFRT to resistance training is superior to resistance training in reducing knee pain at short-term follow up was influenced significantly by a single RCT (Hughes, Rosenblatt, et al., 2019). This was the only RCT with 95 % confidence intervals that did not cross zero and a sensitivity analysis revealed a non-significant outcome when these trial data were removed. The superior effects reported by Hughes et al., (Hughes, Rosenblatt, et al., 2019) are unlikely to be explained by variability in BFRT delivery, as all trials in this data pool used either 70–80 % limb occlusion pressure (Constantinou et al., 2022) (De Melo et al., 2022) (Hughes, Rosenblatt, et al., 2019) (Khalil et al., 2023) or an occlusion pressure of 200 mmHg (Bryk et al., 2016) (Segal et al., 2015), likely to reflect comparable limb occlusion pressures (Hughes, Jeffries, et al., 2018) (Neal et al., 2023). Girardi et al., (Girardi & Guenka, 2022) used a significantly lower cuff pressure of 140 mmHg but the individual SMD from this RCT still favours the BFRT added to resistance training group. Four of seven RCTs in this data pool also compared low load resistance training with BFRT (30 % one-repetition maximum) to high load resistance training (70 % one-repetition maximum) (De Melo et al., 2022) (Hughes, Rosenblatt, et al., 2019) (Khalil et al., 2023) (Bryk et al., 2016), whilst two RCTs used low load resistance training with BFRT (20–30 % one-repetition maximum) in both arms (Segal et al., 2015) (Girardi & Guenka, 2022). Whilst all the individual SMDs favour BFRT added to resistance training, the wide 95 % CIs reflect the small sample sizes and thus high variability in response. More robustly designed trials with larger samples and reduced risk of bias are required to fully investigate the clinical effects of BFRT on pain measures in people with knee conditions.

Our finding that adding BFRT to resistance training is not superior to resistance training at improving patient-reported knee-function in the short-term is unsurprising for some of the specific diagnoses involved. Length of follow up in the trials pooled ranged from 4- to 12-weeks and it is unrealistic to expect people post-ACL reconstruction or cartilage surgery to report significantly improved function within these time-frames (Neal, Miller, et al., 2022). Whilst data from one RCT identified no significant improvement in patient-reported knee-function in the medium-term, more robustly designed trials with larger samples and reduced risk of bias are required to fully investigate the effects of BFRT on patient-reported knee-function beyond the short-term.

Unlike people post-ACLR or cartilage surgery, significant short-term effects on patient-reported knee-function would be expected in people with PFP (Neal, Bartholomew, et al., 2022) and osteoarthritis (Holden et al., 2023) following exercise therapy. No significant effects of adding BFRT to resistance training on patient-reported knee-function were identified by this review in either of these diagnostic subgroups. When combined with the absence of BFR from the recently published best practice guide (Neal et al., 2024) that includes patient preferences and expert reasoning, the current available evidence suggests BFRT may not be a useful adjunct in people with either PFP or osteoarthritis diagnoses.

Despite one of the proposed mechanisms of BFRT being a hypoxic environment within the targeted tissues stimulating hypertrophy via increased metabolic stress (Pearson & Hussain, 2015), we were able to pool quadriceps strength data from just four RCTs (Curran et al., 2020) (Tramer et al., 2023) (Bryk et al., 2016) (Segal et al., 2015). No significant increase in quadriceps strength was identified when adding BFRT to resistance training. This conflicts with the review conducted by Li et al., (Li et al., 2021), most likely explained by the choice of both a fixed effects model and the decision to pool point follow up rather than mean change data. A recent sham controlled RCT conducted by Erickson et al., (Erickson et al., 2024) also reports no significant improvement in quadriceps muscle strength, cross-sectional area, or fibre physiology in

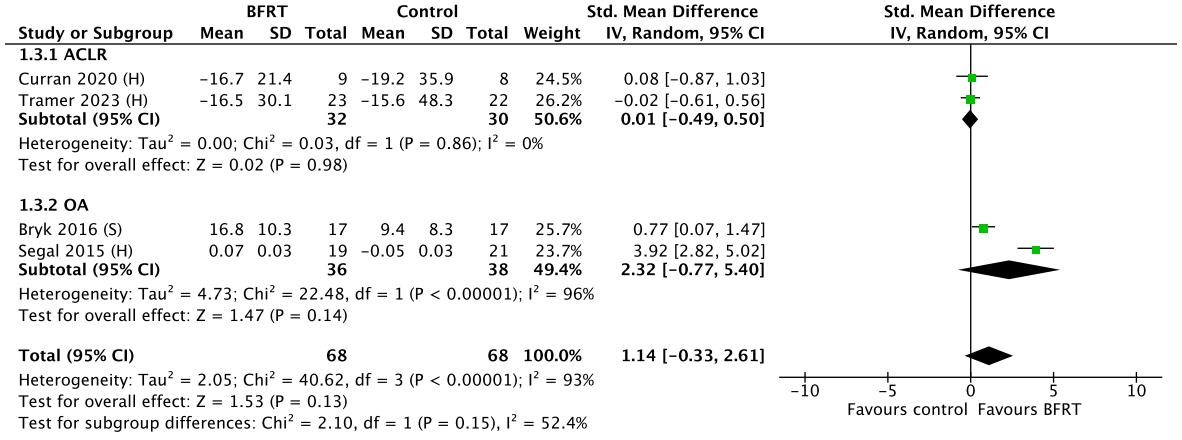

Fig. 4. Forest plot for short-term strength outcomes.

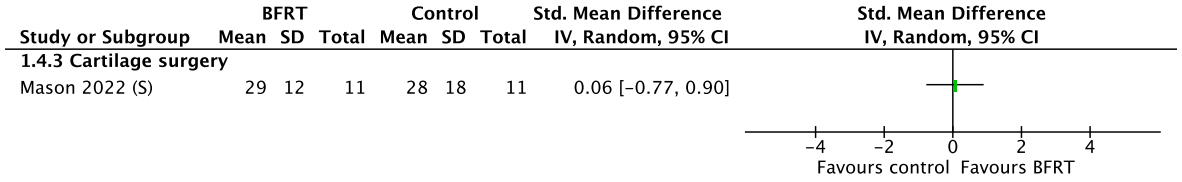

Fig. 5. Forest plot for medium-term function outcomes.

people post-ACLR at medium-term follow up following BFRT. These outcomes challenge the notion that adding BFRT to resistance training will result in superior muscle strength gains in people with knee pain, despite this having been reported consistently in healthy people (Pearson & Hussain, 2015) (Lixandrao et al., 2018).

4.1. Limitations and strengths

We limited our search to three databases and studies published in the English language but are confident that no eligible trials have been omitted given our cited reference search and hand searching the reference lists of eligible studies. We were unable to pool data from three eligible RCTs owing to authors failing to respond to raw data requests, and the inclusion of these additional data may have altered the results. Our decision to pool within-group mean change data as opposed to point observational data at follow up reduces the potential for error. We made pairwise comparisons between resistance training with BFRT and resistance training in isolation, but did not subgroup by prescription parameters (e.g., overall training volume, load magnitude, or occlusion pressures) given the low number of included RCTs. Future work should continue to explore if manipulating specific prescription parameters leads to superior outcomes when delivering BFRT.

5. Conclusions

Whilst adding BFRT to resistance training appears to offer significant effects on short-term pain outcomes, this is of questionable clinical relevance, and no significant effects on patient-reported function or quadriceps strength were identified. RCTs in this field are typically small, with a high risk of bias and short-term follow up, with future higher quality RCTs required to fully explore clinical efficacy. Clinicians should exercise caution in offering BFRT to people with knee conditions considering our results.

CRediT authorship contribution statement

Camilla Zeitlin: Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Matthew Shepherd:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Data curation. **Simon David Lack:** Writing – review & editing, Writing – original draft, Validation. **Bradley Stephen Neal:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Formal analysis, Data curation, Conceptualization.

Ethics

No ethical approval was required for the systematic review with meta-analysis design.

Funding information

This project was unfunded.

Declaration of competing interest

Dr Bradley Neal is an editorial advisor and social media editor at Physical Therapy in Sport.

All other authors have no competing interests to declare.

Appendix

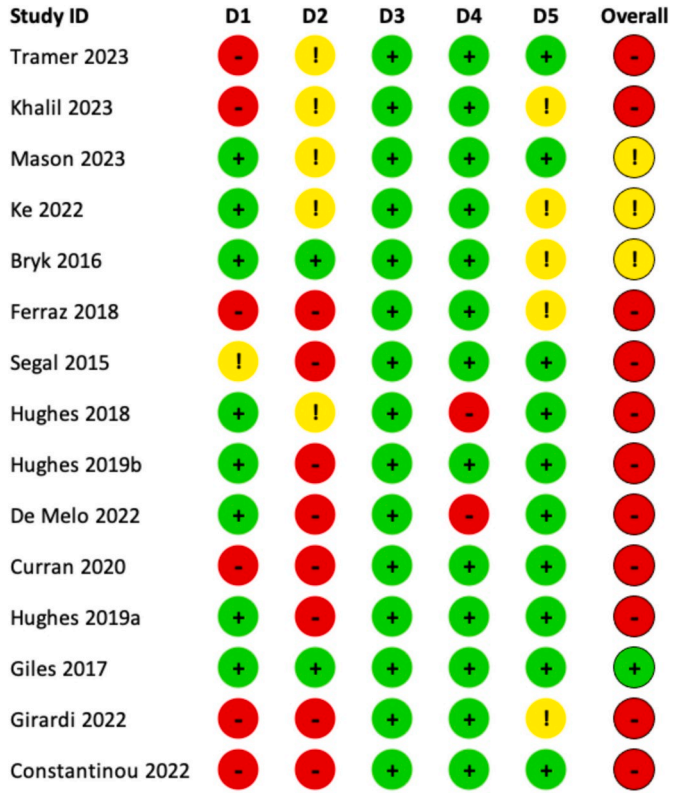

Fig. S1. Risk of bias scores for the included trials.

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