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Review Article

Effect of blood-flow restriction exercise on falls and fall related risk factors in older adults 60 years or above: a systematic review

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Abstract

This systematic review investigated the effect of low-load resistance training combined with blood-flow restriction (LL-BFR) on falls in older adults ≥60 years of age. The databases Embase, Medline, and Cochrane Library were searched from inception to October 1st, 2019 and reference lists of retrieved publications. Main outcomes were fall rates or proportion of fallers. Additional outcomes were physical performance, lower extremity muscle strength or function, and balance. Mean difference ±SD on falls and fall related outcomes were reported and Cochrane Collaboration's risk of bias tool was used to evaluate quality of evidence. Eight RCT-studies met the inclusion criteria. None reported falls data. Assessing physical performance tests (n=12), 8/12 of the LL-BFR groups showed a significant within-group improvement and 5/12 significant between-group effects comparing LL-BFR to respective controls. For muscle strength tests (n=16), 9/16 showed significant positive within-group improvement and 3/16 significant between-group effects. One study reported data on balance with conflicting results. In conclusion, LL-BFR might increase physical performance and muscle strength in older adults ≥60 years of age. None of the included studies investigated the effect on falls. Larger adequately powered studies are required before introducing LL-BFR as an alternative exercise modality to decrease fall risk.

Keywords: Blood-flow Restriction, Falls, Low-Load Resistance Training, Older, Physical Performance

Introduction

The population of older adults above 60 years of age are the fastest growing age group worldwide and the World Health Organisation estimates this group will increase to almost two billion in 2050[1]. Falls are common among older adults with one third of the population aged 65 years and above falling at least once annually[2]. Falls are associated with increased mortality[3], socioeconomic cost[4], decrease in quality of life[5], and morbidity[6]. Furthermore, the incidence of fall-related accidents increases with age[6] and individuals who have fallen once are more likely to experience recurrent falls[7]. With the expected increase in fall prevalence due to the demographic changes the prevention of falls is therefore becoming increasingly important[8].

The risk of falling is associated to several factors including reduced physical performance, lower extremity muscle strength, and postural balance[5,9]. In general, different types of physical training have a positive effect on preventing the risk of falls in older adults[10-12]. One such modality; resistance training, has shown to improve muscle strength, physical performance, and balance in frail older individuals. It is also associated with reduced risk of falls due to the effect on rate of force development and neuromotor adaption[13-15]. This

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exercise modality can be divided into low-load (LL) and high-load (HL) resistance exercise where LL resistance exercise is performed using mass <50% of one repetition maximum (1-RM)[16-18]. HL has shown a trend of greater effect on strength and hypertrophy compared to LL[19] but exercise-mediated pain, injury, and illness may limit the compliance of HL among older adults[20].

Therefore, alternative forms of exercise should be considered to harvest similar benefits to HL, while simultaneously improve compliance for older adults with physical limitations. One such modality could be LL resistance exercise combined with blood-flow restriction (LL-BFR). During LL-BFR inflatable cuffs/tourniquets are applied on this proximal portion of the limb[21]. The training modality induces low mechanical tension compared to traditional high-load resistance exercises[22]. When comparing the effect of LL-BFR to LL, LL-BFR has shown to be more effective than LL alone[23]. Some systematic reviews have compared LL-BFR with no training or effective training modalities, and have reported conflicting results on the outcomes of physical performance and muscle strength[16-18,24,25].

Although recent reviews have investigated different aspects of LL-BFR effects[16-18,24,25], to the best of our knowledge no systematic review has comprehensively investigated the effect of LL-BFR on risk of falls among older adults. This topic is highly important, because of the fast-growing age group and the severe consequences related to falls. Therefore, the objectives of this systematic review were; firstly, to investigate the effect of LL-BFR-exercise on prevention of falls, and secondly to investigate the effect of LL-BFR-exercise on factors associated with falls risk in terms of physical performance, lower extremity muscle strength or function, and balance among adults aged 60 years and above.

Materials and methods

Protocol and registration

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol (PRISMA-P) guideline[26] was used to write the protocol before uploading to Prospective Register of Systematic Reviews (PROSPERO) on September 30th, 2019 (Prospero ID number: 152941). This systematic review followed the guideline provided in the PRISMA statement[27].

Data sources and searches

A systematic search for original publications was conducted in the following electronic databases: Embase, Medline, and Cochrane Library from inception to October 1st, 2019. Additionally, hand searches from the reference lists of the included studies, previous related reviews, and meta-analyses about BFR exercise were performed, to identify additional original publications. The systematic review was performed using the standard PICO method: "P" (Population): Older adults aged 60 years and above; "I" (Intervention): LL resistance training (i.e. <50% of one repetition maximum [1-RM]) with concurrent BFR by occlusion; "C" (Comparison): Clinical trial with a control group or alternative training form; "O" (Outcome): Any of the following: 1) Fall rates or fall risk, 2) physical performance, 3) lower extremity muscle strength or function, or 4) balance. The search string was constructed with assistance from a research librarian and contained two blocks: The first block "P" included synonyms for the population: older people aged 60 years and above and the second block "I" encompassed synonyms for the intervention: LL-BFR training. Both controlled terms (i.e. MeSH or EMTREE terms) and simple phrase terms were used to search the databases when appropriate. The search string did not include filters or restrictions (Appendix 1). To make sure the search was as broad as possible and did not exclude relevant articles, the "C" and "O" were not included in the search string.

Study selection

The articles from the final search were imported into Endnote X9 (Clarivate analytics, Philadelphia, Pennsylvania, USA) to remove duplets. The software Covidence (Covidence systematic review software; Veritas Health Innovation, Melbourne, Australia) was used to administer the selection process. Two independent reviewers (CG and KSC) screened titles and abstracts and evaluated the full-text papers for eligibility. Disagreement among the reviewers was discussed and if agreement could not be reached, conflicts were resolved by a third reviewer (KT). Studies were included if they met the following inclusion criteria: 1) controlled trials with older people aged 60 years or above, 2) the participants in the intervention groups performed LL-BFR for four weeks or more, 3) the BFR could be on either extremity, 4) the control groups performed an alternative training form without BFR or no training continuing their daily activities, and 5) studies reported at least one of the predefined outcomes from the protocol. The main outcomes of interest were fall rates or proportion of fallers. Also, following a consensus discussion among authors this study defined factors associated with falls risk in the following predefined prioritised order: physical performance, lower extremity muscle strength or function, and balance. All outcomes were listed in order of relevance following a consensus process and stated in the PROSPERO protocol before initiation of the search (also see Appendix 2).

Identified studies were excluded if any participants were <60 years of age, were bed-bound or non-ambulatory, had previously performed LL-BFR in the last six months, did not include any of the predefined outcomes, or if the same data was reported in more than one study (double reporting). Furthermore, non-English language publications were excluded.

Data reporting

For all the included studies, data were extracted by two authors (CG and KSC). Information was obtained on study design, description of the population (size, age, and

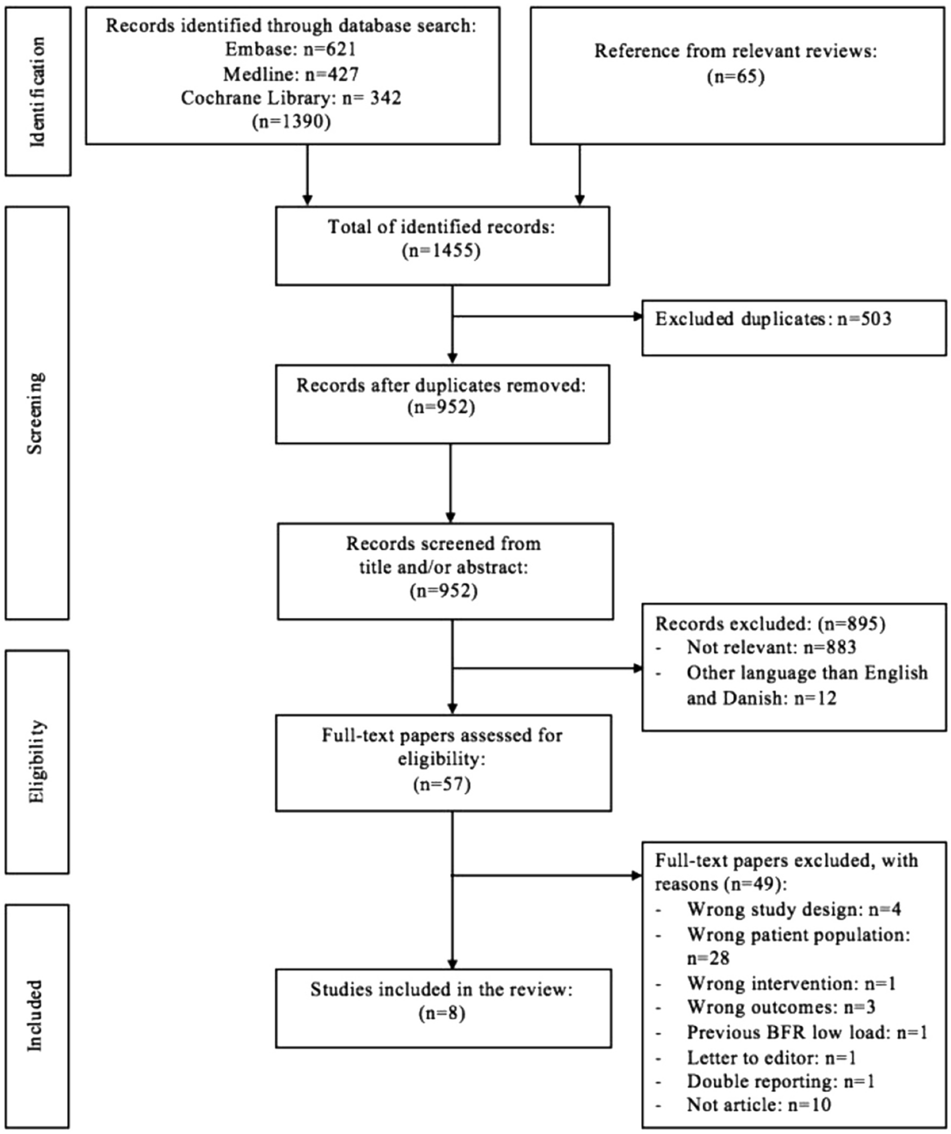

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram presenting the literature searches and the included studies.

characteristics), training protocol (duration, frequency, total training sessions, modality, intensity, and exercises), and description of the BFR (cuff size, location on the body, pressure, and restriction length) for both the intervention and the control groups. The relevant data from the intervention and control groups at baseline and at the last follow-up for the predefined outcomes and authors' conclusion of significance were extracted. If data reporting was incomplete or reported differently, the corresponding authors of the identified studies were contacted to obtain additional data.

Quality assessment

The quality of the included studies was assessed using the Cochrane 'Risk of Bias tool'[28]. The tool covers the following domains: selection, performance, detection, attrition, and reporting bias and each study was rated as having low, high, or unclear risk of bias within each domain. Three reviewers (CG, KSC, and KT) independently assessed the studies and any disagreement was discussed among them. If agreement could not be reached, conflicts were resolved by a fourth reviewer (JR).

Strategy for data synthesis and analysis

The extracted data were used to calculate mean difference with SD when possible. If data reporting was incomplete, the corresponding author was contacted. The mean differences were calculated by subtracting follow-up means from baseline means. The following formula was used to calculate

Table 1. Description of the included studies.

Author/Year reference (Country)	Study information			Intervention group		Control group(s)		Outcomes		
	Design	Population	Duration (D) Frequency (F) Total training sessions (TTS)	N	Modality (M) Intensity (I) Exercises (E) Cuff (C) Placement (Pl) Pressure (Pr) Restriction (R)	N	Modality (M) Intensity (I) Exercise (E)	Physical performance	Lower extremity muscle strength or function	Balance
Abe et al./2010[29] (Japan)	RCT	Healthy, physical active men and women; 60-78 years	D: 6 weeks F: 5 sessions per week TTS: 30	11	M: LL-BFR I: 45% HRR E: Walking C: NA Pl: Each leg Pr: 160-200 mmHg R: 3 min warmup + 20 min walking	8	M: No-training I: NA E: Continue daily physical activity	30STS TUG	MVC (isokinetic, knee, flexion/extension, 30-90-180°/s) MVC (isometric, knee, extension, 75°)	
Clarkson et al./2017[30] (Australia)	RCT	Healthy, physical inactive men and women; 60-80 years BFR: 69±6 years CON: 70±7 years	D: 6 weeks F: 4 sessions per week TTS: 24	10	M: LL-BFR I: 4 km·h-1 E: Walking C: 10.5 cm wide Pl: Each leg Pr: 60% of LOP R: 10 min walking	9	M: LL I: 4 km·h^{-1} E: 10 min walking	30STS TUG 6MWT		
Cook et al./2017[31] (USA)	RCT	Healthy men and women; ≥65 years Total: 75.6 (95%CI: 73.4;78.5)	D: 12 weeks F: 2 sessions per week TTS: 24	12	M: LL-BFR I: 30-50 % of 1-RM E: 3 sets to volitional failure of LE, LC, and LP C: 6 cm wide Pl: Each leg Pr: 184 ± 25 mmHg R: Approx. 5 min per exercise	(A)12 (B) 12	(A) M: HL I: 70% 1-RM E: 3 sets to volitional failure of LE, LC, and LP (B) M: LL I: Light E: 3 sets of upper extremities exercises	SPPB 400-m walk	MVC (isometric, knee, extension, 60°) LP 1-RM KE 1-RM	
Harper et al./2019[32] (USA)	Pilot RCT	Men and women with knee osteo-arthritis; ≥60 years BFR: 67.2±5.2 CON: 69.1±7.1	D: 12 weeks F: 3 sessions per week TTS: 36	16	M: LL-BFR I: 20% of 1-RM E: LP, LE, LC, and CF C: 13.5 cm wide Pl: Each leg Pr: Individualized <300 mmHg R: While exercise	19	M: HL I: 60% of 1-RM E: Osteoarthritis exercise guideline	SPPB 400-m walk	MVC (isokinetic, knee, extension, 60-90-120°/s)	
Libardi et al./2015[33] (Brazil)	RCT	Inactive older individuals; >60 years BFR: 64±4 years HL: 65±3.7 years CON: 65±4 years	D: 12 weeks F: 2x resistance training + 2 x ET sessions per week TTS: 48	10	M: LL-BFR + ET I: 20-30 % of 1-RM E: 4 sets of 30/15/15/15 repetitions of LP C: 17.5 cm wide Pl: Each leg Pr: 67± 8 mmHg R: Entire training session	(A) 8 (B) 7	(A) M: HL + ET I: 70-80% 1-RM E: 4 sets of 10 repetitions of LP (B) M: No training I: NA E: Continue daily physical activity		LP 1-RM	
Yasuda et al./2014[34] (Japan)	RCT	Healthy men and women; 61-84 years BFR: 71.3±7.1 CON: 67.7±6.0	D: 12 weeks F: 2 sessions per week TTS: 24	9	M: LL-BFR I: 20-30% of 1-RM E: 4 sets of 30/20/15/10 of LE and LP C: 5 cm wide Pl: Each leg Pr: 200-270 mmHg R: Entire training sessions (Approx. 11 min)	10	M: No training I: NA E: Continue daily physical activity	30STS	LP 1-RM KE 1-RM	
Yasuda et al./2016[35] (Japan)	RCT	Physically active, healthy women; 61-86 years BFR: 70±6 HL: 72±7 CON: 68±6	D: 12 weeks F: 2 sessions per week TTS: 24	10	M: LL-BFR I: ~30% of 1-RM E: 4 sets of 30/20/15/10 of squat and LE C: 5 cm wide Pl: Each leg Pr: 160-200 mmHg R: 10-11 min	(A) 10 (B) 10	(A) M: HL-BFR I: 70-90% of 1-RM E: 4 sets of 30/20/15/10 of squat and LE (B) M: No training I: NA E: Continue daily physical activity		MVC (isometric, knee, flexion/extension, 40-80°) LP 1-RM KE 1-RM	
Yokokawa et al. /2008[36] (Japan)	RCT	Healthy men and women; ≥65 years BFR: 72.3±4.5 CON: 71.0±4.1	D: 8 weeks F: 2 sessions per week TTS: 16	24	M: LL-BFR I: 20-25% of 1-RM E: Half squat, forward lunge, calf rise, knee lift, crunch, LE, and KF C: 4.5 cm wide Pl: Each leg Pr: 70-150 mmHg R: Entire training sessions	27	M: Balance training I: NA E: Symmetrical and asymmetrical movements on balance mat	TUG 10-m walking time	MVC (isometric, left/right, knee, extension, 90°)	Single leg stance test (left/right leg)

Abbreviations: BFR, Blood-flow restriction; CF, Calf flexion; CON, Control group; ET, Endurance training; HL, High-load resistance training; HRR, Heart rate reserve; KE, Knee extension; KF, Knee flexion; LC, Leg curl; LE, Leg extension; LL, Low-load resistance training; LOP, Limb occlusion pressure; LP, Leg press; MVC, Maximum voluntary contraction; NA, Not applicable; SPPB, Short physical performance battery; TUG, Timed-up-and-go; 1-RM, One repetition maximum; 6MWT, Six-minute walk test; 30STS, 30s-sit-to-stand.

Table 2. Summary of included studies evaluating changes in physical performance.

Author/year reference	Outcomes	Intervention group and comparison group(s)	Mean difference (±SD)	Authors' conclusion: Significant within-group difference	Authors' conclusion: Significant between-group difference
Abe et al./2010[29]	30STS, repetitions	LL-BFR	NA	Yes[a]	Yes[b]
		No training	NA	NA	
	TUG, s	LL-BFR	NA	Yes[a]	Yes[a]
		No training	NA	NA	
†Clarkson et al./2017[30]	#30STS, repetitions	LL-BFR	4.0 (±0.9)	Yes[b]	Yes[a]
		LL	1.1 (±0.6)	Yes[a]	
	TUG, s	LL-BFR	-0.7 (±0.1)	Yes[b]	Yes[a]
		LL	-0.3 (±0.1)	Yes[b]	
	6MWT, m	LL-BFR	45.4 (±5.0)	Yes[b]	Yes[a]
		LL	10.7 (±5.3)	Yes[a]	
†Cook et al./2017[31]	SPPB, score out of 12	LL-BFR	0.7 (±1.2)	No	No
		HL	0.0 (±1.4)	No	
		LL-upper extremity	0.8 (±1.3)	No	
	400-m walk, $m \cdot s^{-1}$	LL-BFR	0.0 (±0.1)	No	No
		HL	0.0 (±0.1)	No	
		LL-upper extremity	0.0 (±0.1)	No	
†Harper et al./2019[32]	SPPB, score out of 12	LL-BFR	0.1 (NA)	No	No
		HL	0.8 (NA)	No	
	400-m walk, $m \cdot s^{-1}$	LL-BFR	0.0 (NA)	NA	No
		HL	0.0 (NA)	NA	
Yasuda et al./2014[34]	30STS, repetitions	LL-BFR	2.6 (±3.4)	Yes[a]	NA
		No training	0.4 (NA)	No	
Yokokawa et al./2008[36]	TUG, s	LL-BFR	-1.1 (±1.9)	Yes[b]	No
		Balance training	0.4 (NA)	NA	
	10-m walking time, s	LL-BFR	-0.5 (±0.7)	Yes[b]	No
		Balance training	-0.5 (NA)	NA	

Abbreviations: a, p<0.05; b, p<0.01; BFR, Blood-flow restriction; HL, High-load resistance training; LL, Low-load resistance training; NA, Not applicable; SPPB, Short physical performance battery; TUG, Timed-up-and-go; 6MWT, Six-minute walk test; 30STS, 30s sit-to-stand. †Data obtained after contact to corresponding author; #Primary outcome in the study.

SD for mean difference when mean and p-values were available: SD=((m)/TINV(P value;df))/√(1/n). Mean difference was defined as m, df is degrees of freedom and sample size was defined as n. When mean and 95% confidence intervals (CI) were accessible this formula was used to calculate SD: SD=((HCI-LCI/2/TINV(0.05;n-1)*√ (n)). HCI is the highest value of 95% of CI, LCI the lowest value of 95% CI, n the sample size of the groups, TINV (0.05;n-1)=t-value for a 95% CI from a sample size of n by using p-values for change over time[28]. In this systematic review, the significant level was defined as p<0.05.

Results

Study selection

In total, 1390 articles were identified from Embase (n=621), Medline (n=427), and Cochrane Library (n=342). Additionally, 65 studies were found by manual hand search of relevant systematic reviews and meta-analyses adding up to a total of 1455 articles (Figure 1). After removal of 503 duplicates, 952 articles were screened for title and abstract and 895 articles were excluded (mainly because of wrong intervention, population <60 years of age, or animal studies). In total, 57 full-text articles were assessed and matched against the eligibility criteria. Following that, 49 articles were excluded (mainly because of wrong study population, not articles, or wrong study design). Selection of the included studies is illustrated in the PRISMA flow diagram (Figure 1).

Study characteristics

A total of eight studies met the criteria for inclusion. The descriptive characteristics are summarised in Table

1. All study designs were RCT studies[29-36] and published from 2008[36] to 2019[32]. In total, 234 participants were included and the distribution was relatively equal between intervention (n=102) and controls (n=132) including three studies with two distinct comparator groups (n=29)[31,33,35]. The overall population ranged from 60 to 86 years and were represented by both genders, physically active or inactive healthy older individuals, and older patients with osteoarthritis. The training protocols ranged from six weeks[29,30] to twelve weeks[31-35] and training occurred from two to five sessions per week resulting in total training sessions from minimum 16[36] to maximum 48[33]. In total, 102 participants received LL-BFR consisting of walking[29,30] or resistance training[31-36]. All studies had a detailed description of the restriction protocol and in all studies the cuff was applied on the legs. The cuff width ranged from 4.5 cm[36] to 17.5 cm[33] and restriction pressure varied because of different ways to calculate the restriction pressure in the studies. The length of BFR per session depended on whether the cuff was deflated between the exercise and the number of exercises completed within each session. The length of restriction depended on the presence of deflation between the exercise and length of the training session. In three studies, the participants were exposed to 10-11 min of BFR during exercise sessions[30,34,3]5, one study reported approximately 5 min of BFR per exercise31, and four studies either performed restriction while participants were exercising and deflated the cuff during the pauses or occluded throughout the entire training session[29,32,33,36]. Four studies compared LL-BFR with no training[29,33-35], one study with LL training (without BFR)[30], one study with LL (upper extremity) exercises[31], one study with balance training[36], three studies with HL (60-80% 1-RM)[31-33], and one study with HL-BFR[35]. An overview of the outcome measures in the individual studies is presented in Table 1.

Outcomes

No studies reported data on falls. A total of six studies assessed physical performance (Table 2)[29-32,34,36], seven studies assessed lower extremity muscle strength or function (Table 3)29, 31-36, and one study assessed balance (Table 4)[36].

Physical performance

Six studies assessed physical performance measuring four outcomes: Short physical performance battery (SPPB), 30s sit-to-stand (30STS), Timed-up-and-go (TUG), and walking speed[29-32,34,36]. A total of 12 tests were reported. Overall, 67% (8/12) of the intervention groups showed a significant within-group improvement and 42% (5/12) displayed significant between-group effect when comparing LL-BFR with their respective control groups (two non-training and three LL control groups). No significant between-group effect was seen when comparing LL-BFR with HL (Table 2).

Short physical performance battery (SPPB)

Two studies assessed SPPB where 28 participants received LL-BFR (Table 2)[31,32]. None of the studies found any significant within-group improvement for LL-BFR or between-group effect.

30s sit-to-stand (30STS)

Three studies assessed 30STS where 30 participants received LL-BFR (Table 2)[29,30,34]. In two studies, a significant improvement was seen in 30STS repetitions for LL-BFR with a mean difference (±SD) from baseline to follow-up that ranged from 2.6 (±3.4) to 4.0 (±0.9)[30,34]. One study reported a significant improvement in the intervention group only but did not report mean (±SD)[29]. There was a significant between-group effect in 30STS repetitions completed between LL-BFR and one LL[30] as well as one non-training[29] control group. Finally, one study did not report between-group results[34].

Timed-up-and-go (TUG)

Three studies assessed TUG where 45 participants received LL-BFR (Table 2)[29,30,36]. In two studies, a significant improvement in TUG from baseline to follow-up was reported for LL-BFR with a mean difference (±SD) ranging from -0.7 (±0.1) to -1.1 (±1.9) s[30,36]. One study reported a significant improvement but did not report the mean (±SD)[29]. Significant between-group effects were seen between LL-BFR and one non-training and one LL control group[29,30] and no significant effect was seen between the LL-BFR and the one balance training group[36].

Walking speed

Four studies assessed walking speed using: 6 Minutes walking test (6MWT), 400-m walk, and 10-m walking time tests with 62 participants receiving LL-BFR (Table 2)[30-32,36]. In terms of within-group improvements, two studies showed significant improvements from baseline to follow-up with LL-BFR with mean differences (±SD) of 45.4 (±5.0)m (6MWT)[30] and -0.5 (±0.7)s (10-m walking time)[36]. The other study found no significant improvements[31] and one study did not report the conclusion of the study[32]. Significant between-group effect in walking speed was seen between LL-BFR compared with one LL control group[30] whereas no effects was seen between LL-BFR and the other control groups[31,32].

Muscle strength

Seven studies assessed lower extremity muscle strength or function and measured four outcomes: Maximum voluntary contraction (MVC) for isokinetic and isometric combined at different degrees, Leg press 1-RM (LP 1-RM), and Knee extension 1-RM (KE 1-RM)[29,31-36]. Overall, 56% (9/16) of the intervention groups showed a significant within-group improvement and 19% (3/16) displayed significant between-group effect when comparing LL-BFR to their respective non-training control groups. When comparing LL-BFR with

Table 3. Summary of included studies evaluating changes in lower extremity muscle strength or function.

Author/year reference	Outcomes	Intervention group and comparison group(s)	Mean difference (±SD)	Authors' conclusion	
				Significant within-group difference	Significant between-group difference
Abe et al. /2010[29]	MVC (isokinetic, knee, extension, 30-90-180°/s), Nm	LL-BFR	5.0 (±7.4) – 10.0 (±10.5)	Yes[a]	NA
		No training	-3.0 (NA) – 5.0 (NA)	No	
	MVC (isokinetic, knee, flexion, 30-90-180°/s), Nm	LL-BFR	5.0 (±7.4) – 6.0 (±8.7) MVC (flexion, 180°/s) 4.0 (±6.8)	Yes[a] No	NA
		No training	-2.0 (NA) – 4.0 (NA)	No	
	MVC (isometric, knee, extension, 75°), Nm	LL-BFR	13.0 (±19.4)	Yes[a]	NA
		No training	-3.0 (NA)	No	
†Cook et al. /2017[31]	MVC (isometric, knee, extension, 60°), Nm	LL-BFR	11.2 (±21.8)	No	No
		HL	19.3 (±3.9)	Yes[a]	
		LL-upper extremity	3.5 (±17.0)	No	
	LP 1-RM, kg	LL-BFR	18.7 (±15.3)	Yes[a]	No
		HL	31.7 (±28.6)	Yes[a]	
		LL-upper extremity	-0.2 (±16.1)	No	
	KE 1-RM, kg	LL-BFR	9.1 (±6.5)	Yes[a]	Yes[a]
		HL	21.2 (±13.0)	Yes[a]	
		LL-upper extremity	0.6 (±7.5)	No	
†Harper et al. /2019[32]	#MVC (isokinetic, knee, extension, 60-90-120°/s), Nm	LL-BFR	8.7 (NA)	NA	No
		HL	10.9 (NA)	NA	
†Libardi et al. /2015[33]	LP 1-RM, kg	LL-BFR	33.4 (±22.1)	Yes[b]	No
		HL+ ET	63.5 (±33.2)	Yes[b]	
		No training	-21.1 (NA)	No	
Yasuda et al. /2014[34]	LP 1-RM, kg	LL-BFR	45.0 (NA)	NA	Yes[b]
		No training	-1.0 (NA)	NA	
	KE 1-RM, kg	LL-BFR	14.0 (NA)	NA	Yes[b]
		No training	3.0 (NA)	NA	
Yasuda et al. /2016[35]	MVC (isometric, knee, extension, 40-80°), Nm	LL-BFR	NA	Yes[a]	NA
		HL-BFR	NA	No	
		No training	NA	No	
	MVC (isometric, knee, flexion, 40-80°), Nm	LL-BFR	NA	NA	NA
		HL-BFR	NA	NA	
		No training	NA	NA	
	LP 1-RM, kg	LL-BFR	NA	Yes[b]	NA
		HL-BFR	NA	Yes[b]	
		No training	NA	No	
	KE 1-RM, kg	LL-BFR	NA	No	NA
		HL-BFR	NA	No	
		No training	NA	No	
Yokokawa et al. /2008[36]	MVC (isometric, left, knee, extension, 90°), kg	LL-BFR	4.3 (±6.6)	Yes[b]	No
		Balance training	-0.8 (NA)	NA	
	MVC (isometric, right, knee, extension, 90°), kg	LL-BFR	1.6 (±20.1)	No	No
		Balance training	-1.2 (NA)	NA	

Abbreviations: a, p<0.05; b, p<0.01; BFR, Blood-flow restriction; ET, Endurance training; HL, High-load resistance training; KE, Knee extension; LL, Low-load resistance training; LP, Leg press; MVC, Maximum voluntary contraction; NA, Not applicable; 1-RM, One repetition maximum. †Data obtained after contact to corresponding author; #Primary outcome in the study.

HL only one outcome had significant between-group effect in favor of HL whereas no significant between-group effect was seen in the remaining 89% (8/9) outcomes (Table 3).

Maximum voluntary contraction (MVC) (isokinetic)

Two studies assessed MVC (isokinetic) where 27 participants received LL-BFR (Table 3)[29,32]. In one study, a significant within-group improvement from baseline to follow-up was reported with LL-BFR with mean differences (±SD) of 5.0 (±7.4) to 10.0 (±10.5)Nm (extension) and 5.0 (±7.4) to 6.0 (±8.7)Nm (flexion) except for fast-velocity (180°/s) knee flexor MVC where no change was observed[29]. The other study did not report their conclusion[32]. No significant between-group effect was seen between LL-BFR and one HL control group[32] while these data were not reported in the study comparing LL-BFR with the non-training control group[29].

Maximum voluntary contraction (MVC) (isometric)

Four studies assessed MVC (isometric) where 57 participants received LL-BFR (Table 3)[29,31,35,36]. In two studies, significant within-group improvements in strength from baseline to follow-up were reported in LL-BFR with mean differences (±SD) ranging from 4.3 (±6.6) to 13.0 (±19.4)Nm[29,36]. For one of these two studies, the results only represented the left leg[36]. One other study reported a significant within-group improvement for extension but did not report the mean (±SD)[35]. No significant between-group effect in strength were seen between LL-BFR and LL (upper extremities)[31] or one study with two balance training control groups[36]. In addition, conclusions of comparison between LL-BFR and two non-training groups[29,35] and one HL-BFR were not reported[35].

Leg press 1-repeated measurement (LP 1-RM)

Four studies assessed LP 1-RM where 41 participants received LL-BFR (Table 3)[31,33-35]. In two studies, significant within-group improvements from baseline to follow-up were seen with LL-BFR in strength with mean differences (±SD) ranging from 18.7 (±15.3) to 33.4 (±22.1) kg[31,33]. A significant between-group effect in strength between the LL-BFR and one non-training control group was reported[34] while no differences between LL-BFR and HL[31,33] or LL (upper extremity)[31] control groups were observed. Conclusions of comparison between LL-BFR and non-training as well as HL-BFR comparator groups were not reported[35].

Knee extension 1-repeated measurements (KE 1-RM)

Three studies assessed KE 1-RM where 31 participants received LL-BFR (Table 3)[31,34,35]. In one study, a significant within-group improvement from baseline to follow-up was seen with LL-BFR in strength with a mean difference (±SD) of 9.1 (±6.5) kg[31]. One study did not find any significant improvements[35] whereas another study did not report a conclusion[34]. A significant between-group effect was seen between LL-BFR and non-training controls[34]. One HL comparator group showed a significant improvement compared with LL-BFR and this LL-BFR group did not differ from a LL (upper extremity) comparator group[31]. Conclusions of comparisons between LL-BFR and one non-training and one HL-BFR comparator group were not reported[35].

Balance

One study assessed balance using the single leg stance test (left/right leg) with 24 participants receiving LL-BFR (Table 4)[36]. A significant within-group improvement in balance duration for the left leg was reported with LL-BFR showing a mean difference (±SD) of 2.6 (±5.5)s from baseline to follow-up. No significant improvement was seen for the right leg. There was no significant between-group effect in either leg.

Risk of bias within studies

The risk of bias in all the included studies regarding all domains were discussed among three reviewers (CG, KSC, and KT). If agreement could not be reached, conflicts were resolved by a fourth reviewer (JR). There were conflicts based on whether the insufficient reporting in the included studies should be categorised as high- or unclear risk of bias. Overall, most of the included studies generally had insufficient reporting and were categorised as having unclear risk of bias in most of the domains in the Cochrane 'Risk of Bias tool' (Figure 2). The majority of the studies were categorised as unclear risk of bias in the randomisation and allocation due to insufficient information about the sequence generation and no description of the method for the concealment. Only one study was rated low risk of performance bias[32] whereas the rest of the studies were rated high risk due to no blinding and the outcome likely to be influenced by the lack of blinding. Further, only one study described the blinding of outcome assessment and was categorised as low risk of detection bias[32]. The remaining studies were rated unclear due to insufficient information to permit judgement. Four studies were categorised as low risk of attrition bias as these studies had no drop-outs[29,30] or used intension-to-treat analysis[31,32]; whereas, the remaining four studies were rated unclear due to insufficient reporting to permit judgement. All the pre-specified primary and secondary outcomes were reported in the two studies with an available protocol and these studies were therefore categorised as low risk of reporting bias[30,32]. The remaining six studies were categorised as unclear risk of bias due to insufficient information[29,31,33-36].

Discussion

This systematic review identified eight studies assessing the effect of LL-BFR on falls risk in older adults above 60 years of age. This study found a tendency towards improvement in physical performance and muscle strength, whereas only sparse data were available on balance. No studies reported data on fall rates or proportion of fallers.

Table 4. Summary of included study evaluating changes in balance.

Author/year reference	Outcomes	Intervention group and comparison group(s)	Mean difference (±SD)	Authors' conclusion	
				Significant within-group difference	Significant between-group difference
Yokokawa et al./2008[36]	Single leg stance test (left), s	LL-BFR	2.6 (±5.5)	Yes[a]	No
		Balance training	6.3 (NA)	NA	
	Single leg stance test (right), s	LL-BFR	-12.2 (±33.8)	No	No
		Balance training	-7.4 (NA)	NA	

Abbreviations: a, p<0.05; b, p<0.01; BFR, Blood-flow restriction; LL, Low-load resistance training; NA, Not applicable.

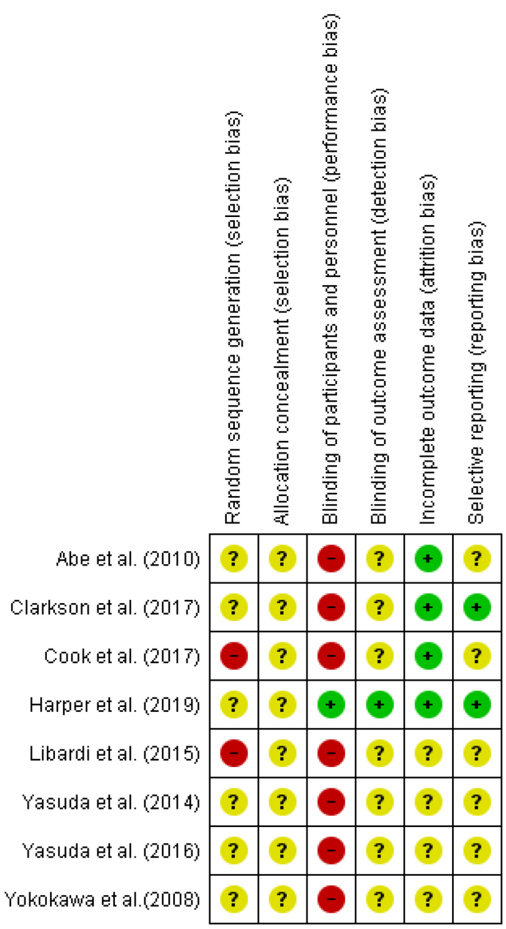

Figure 2. The risk of bias assessment for included studies evaluating changes in objective measures of physical performance, muscle strength, and balance following exercise intervention combined with blood-flow restriction.

Strengths and limitations of this review

This review had some limitations. Firstly, by not extracting data from gray literature or including non-English language literature there is a risk of selection bias. Secondly, none of the included studies assessed the effect on falls, which was our primary outcome, but our protocol predefined relevant risk factors for falling. In this way, this study was able to evaluate the overall effect of LL-BFR on falls risk by including studies assessing physical performance, muscle strength, and balance. Thirdly, due to insufficient number of studies, the low number of participants, and lack of homogeneity among the included studies it was judged inappropriate to conduct a meta-analysis[28]. Due to low power of the studies it is possible that potential benefits of LL-BFR are not shown. Finally, only two studies specified the primary outcome in either their protocol or published paper[30,32]. In the remaining studies, no information was given on primary or secondary outcomes making them at risk of reporting bias[29,31,33-36]. In this way, only two studies included our predefined outcome as their primary outcome[30,32]. The lack of clarity on primary and secondary outcomes may affect the robustness of our findings and potentially affect the external validity of our results due to uncertainty whether the tendency found in this systematic review is based on the conclusion of primary or secondary outcomes. Generally, most studies did not follow the CONSORT statements in reporting randomised trails[37] and scored unclear risk of bias resulting in poor quality of the studies (Figure 2). Therefore, more adequately powered and better quality studies are needed.

This review also had several strengths. Firstly, to improve transparency, the protocol followed the PRISMA-P guideline, was registered at PROSPERO, and the reporting followed the PRISMA statement. Secondly, a comprehensive literature search was conducted with assistance from a research librarian and additionally a hand search was performed from the reference lists of the included studies and from the previous related reviews and meta-analyses. Thirdly, two reviewers independently screened and assessed all articles and extracted data. Fourthly, this study only included data from RCTs to ensure highest quality of the included studies. Finally, when data reporting in the included studies was insufficient for our data analysis the respective corresponding authors were contacted. In this way, additional data were successfully obtained from 50% of the contacted authors making it possible to calculate mean difference (±SD) in most studies.

Comparisons with other studies and reviews

In this study physical performance was ranked as the clinically most important factor associated with falls risk and found that 67% (n=8) of the evaluated tests reported significant within-group improvements and 42% (n=5) between-group effect. Only two prior reviews of LL-BFR have looked at physical performance and none of them focused on older people[17,23]. In the systematic review by Clarkson et al.[17], they reported inconsistency regarding target populations, exercise prescription, and outcome measures but similar to our review indicated that BFR exercise has potential for improving physical performance. One other review also defined physical performance as an outcome[23], but due to limited data they also did not apply a meta-analysis and made no conclusion about the effect of LL-BFR.

The effect of LL-BFR on muscle strength has previously been investigated in several other reviews overall reporting a positive effect of LL-BFR on muscle strength[16,18,23-25]. None of these reviews have focused on individuals above 60 years of age. A study by Centner et al. assessed healthy people above 50 years and showed significantly greater effect of LL-BFR on muscle strength compared to LL but significantly less effect compared to HL training in their meta-analysis[18]. The latter was also reported in another review including both young and older people, but still concluded LL-BFR was a valid and effective approach to increase muscle strength for individuals with physical limitations not able to engage in HL[16].

Muscle strength was ranked as our second most important fall risk factor. This study found that 56% (n=9) of the evaluated tests reported significant within-group improvements in muscle strengths. The outcomes of our included studies were heterogeneous and the between-group effect depended strongly on the constitution of the control groups; i.e. a trend was observed that, if the treatment modality in the control-groups had an effect, between-group effect were less likely to be demonstrated. A total of 19% (n=3) of the evaluated tests reported between-group effects (two studies favoring LL-BFR compared to no training and one study favoring HL training compared to LL-BFR). Our findings are therefore consistent with other studies comparing LL-BFR to no training[17,38]. However, in our study only one of nine comparisons between LL-BFR and HL reported significant between-group effect indicating LL-BFR might not be inferior to HL in older people or that a difference was not seen due to low power.

No other reviews have assessed the effect of LL-BFR on balance. This study only found one study measuring balance as an outcome[36]. This study reported a significant improvement of LL-BFR but showed conflicting results between the two legs. This might be because the participants tended to put an uneven load on both legs[36]. Because this study could only find one study, a random effect can also not be ruled out.

No previous reviews have comprehensively investigated the effect of LL-BFR from a clinically relevant perspective such as fall risk. Furthermore, none of the studies have addressed whether their findings were of clinical significance. The reported minimally clinical important change estimates for SPPB in older adults is 0.3-0.8 points[39]. In our study, the calculated mean differences for SPPB were non-significant[31,32]. Minimal detectable change for TUG ranges from 2.9s in chronic stroke patients[40] to 3.5s in patients with Parkinson's disease[41]. The observed improvements in our study (0.7 (±0.1) to 1.1 (±1.9))s did not reach clinical significance either[30,36]. However, in our study the mean difference (±SD) of increase in 30STS repetitions from baseline to follow-up ranged from 2.6 (±3.4) to 4.0 (±0.9)[30,34] and was above the previously reported minimum clinical significant change of 2.6 repetitions in patients with osteoarthritis with high fall risk[42].

Evidence has shown that exercise reduces the risk of falls through improving physical performance, muscle strength, and balance[11,43]. This study aimed at addressing whether this would be likely for LL-BFR exercise as well, and did not find convincing evidence. One explanation of this is the characteristics of the included participants. Compared to reported scores of increased fall risk the included individuals performed TUG faster than 13s[43], SPPB score higher than 10 points[44], and were able to do more than 14 repetitions in 30STS[45]. This means the majority of the included participants in our study were characterised as physical independent and at low risk of falls when assessing their performance scores at baseline. In order to address the clinical effect of LL-BFR future studies need to assess frailer populations.

Conclusion

In conclusion, none of the included studies in this systematic review investigated the effect of LL-BFR on fall rates or proportion of fallers. Our study indicates that LL-BFR might improve physical performance and muscle strength in older adults above 60 years of age. Due to the low number of studies, few participants, and insufficient reported data this cannot be quantified. Further adequately powered and better quality studies looking at falls as an outcome on a frailer population are needed before introducing LL-BFR as an alternative exercise modality to decrease falls risk.

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Appendix

Appendix 1

Search string
Old OR older OR elderly OR aged OR exp aged OR frail elders OR frail elder AND low load BFR OR LL-BFR OR occlusion training OR KAATSU OR BFRE OR blood flow restriction OR BFR training OR ("vascular occlusion" and training) OR BFR

Appendix 2

Definitions of outcomes listed in order of predefined relevance
Main outcome
Fall rates or proportion of fallers
Additional outcome(s)
Physical performance • Short physical performance battery • Dynamic Gait index • 30s sit to stand • Five times sit to stand • Timed up and go • Walking speed • De Morton Mobility Index • Tinetti's score
Lower extremity muscle strength or function • Leg extensor power (Nottingham Power Rig, force plate) • Isokinetic Maximal Voluntary Contraction, knee (fast velocity) • Isokinetic Maximal Voluntary Contraction, hip (fast velocity) • Isokinetic Maximal Voluntary Contraction, ankle (fast velocity) • Isokinetic Maximal Voluntary Contraction, knee (slow velocity) • Isokinetic Maximal Voluntary Contraction, hip (slow velocity) • Isokinetic Maximal Voluntary Contraction, ankle (slow velocity) • Isometric Maximal Voluntary Contraction, leg press • Isometric Maximal Voluntary Contraction, knee • Isometric Maximal Voluntary Contraction, hip • Isometric Maximal Voluntary Contraction, ankle • 1-RM (repetition maximum), leg press • 5-RM, leg press • 10-RM, leg press • 1-RM, knee extensor • 5-RM, knee extensor • 10-RM, knee extensor
Balance • Berg-balance scale • Guralnik/ Tandem test • Tinetti's balance score • Sway; Postural balance • Postural stability test • Balance Evaluation System test • Unipedal stance test • Single leg stance test • One legged stance test