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Effects of Resistance Training with Blood Flow Restriction on Muscle Strength and Biomarkers in Older People: A Systematic Review of Randomized Clinical Trials

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SUMMARY

Background. Blood flow restriction (BFR) is a technique that utilizes inflatable cuffs to partially restrict arterial inflow and modulate venous flow in the active musculature through gradual mechanical compression.
Objective. This systematic review aimed to analyze the effects of resistance training (RT) with BFR on muscle strength and biomarkers in older individuals.
Methods. This systematic review followed the PRISMA criteria. We searched MEDLINE (via PubMed), Scopus, Embase, Web of Science, and ScienceDirect databases for randomized controlled trials (RCTs) that investigated muscle strength and biomarkers in older individuals submitted to physical exercise, specifically RT with BFR.
Results. The initial database search yielded 423 publications based on our research methodology. After applying the selection criteria, 9 RCTs were included. The mean age of participants in the experimental group (EG) and control group (CG) was 69 years. The total sample size consisted of 339 participants (259 in the EG and 80 in the CG). The publication years of the included studies ranged from 2013 to 2022. The mean intervention duration across the studies was 11 weeks, with 3 sessions per week.
Conclusions. Based on the RCTs included in this systematic review, RT with BFR has shown effectiveness in improving muscle strength, increasing muscle cross-sectional area, and enhancing biomarkers associated with protein synthesis.
Study registration. PROSPERO (CRD42023411569).

KEY WORDS

Aged; biomarkers; blood flow restriction; exercise; muscle strength.

INTRODUCTION

In recent decades, the elderly population has experienced a rise in early-onset chronic diseases and an increased prevalence of multimorbidity. Aging is associated with an elevated risk of developing cardiovascular diseases, neurological degeneration, and non-communicable diseases. This natural process of senescence involves progressive physiological deterioration, resulting in a decline in functional capacity and a deterioration of quality of life and functional autonomy (1, 2).

Among the degenerative processes in aging, sarcopenia is highlighted, a geriatric syndrome with the main characteristics of musculoskeletal tissue reduction, decreased strength, and changes in physical capacity. Other pathophysiological processes are involved in sarcopenia, such as mitochondrial disorder, and the inflammatory and hormonal changes from its normal state leading to an adverse health state (3-5).

Physical exercise, especially resistance training (RT), reduces the risk of developing cardiovascular and metabolic diseases, helps maintain cognitive function, and improves physical abilities, which suffer decline due to the natural aging process, as balance and coordination reduction. Older people who perform RT reduce the effects of sarcopenia by improving levels of functional autonomy and activities of daily living (6, 7).

Blood flow restriction (BFR) is a method that uses inflatable cuffs to partially generate arterial inflow and cause venous flow in the active musculature with gradual mechanical compression. The BFR can cater to older individuals and those with physical limitations by enabling the use of lighter loads, without compromising the outcomes of muscle strength and hypertrophy (8-10).

The effects of BFR show an improvement in muscle strength and functional performance and an increase in muscle cross-section area. Patients over 50 years of age have more effectiveness in muscle hypertrophy, reducing atrophy, and improving strength. Thus, BFR can be an excellent method for gaining muscle strength in older people and an option for those who have restrictions on high-load exercise practices (11-13).

In addition to the possible morphofunctional adaptations resulting in increased muscle strength and hypertrophy, RT may also improve certain aging-related biomarkers. These biomarkers include type III procollagen propeptide (P3NP), insulin-like growth factor 1 (IGF-1), serum levels of klotho and fibroblast growth factor (FGF23), musculoskeletal predictors, tumor necrosis factor alpha (TNF-α), interleukin (IL), and endothelial predictors (14, 15).

Therefore, this study aimed to analyze the effects of physical exercise, specifically RT with BFR, on muscle strength and biomarkers in older people.

METHODS

This systematic review of randomized clinical trials (RCTs) was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria (16) and was approved by the International Prospective Register of Systematic Reviews (PROSPERO) under number CRD42023411569.

Search strategies

For study management, EndNote online 20.0.1 software was used in the literature search. Then, the inclusion criteria were applied according to the theme researched and the descriptors used. The databases used were MEDLINE (via PubMed), Scopus, Embase, Web of Science, and ScienceDirect from May 28 to 30, 2023. The electronic search was conducted by two independent and experienced researchers without language or time filters. Any conflict was resolved by a third reviewer. The search terms used were grouped into a single Boolean phrase: “Aged” OR “Older” OR “Elderly” AND “Blood Flow Restriction Therapy” OR “Blood Flow Restriction Exercise”. Keywords related to the topic were selected based on a literature review and verified by the Medical Subject Headings (MeSH) and Health Sciences Descriptors (DeCS) metadata systems.

Selection criteria

Inclusion criteria were performed according to the PICOS (17) strategy as follows:

- Population: older people (aged ≥ 60 years) of both sexes.
- Intervention: BFR.
- Comparison: other interventions and/or control group (CG).
- Outcome: muscle strength, muscle hypertrophy, and biomarkers.
- Study design: RCTs that analyzed the effects of RT with BFR in older people.

We excluded systematic reviews and meta-analyses, non-human animal studies, studies with participants aged < 55 years, and studies that did not use physical exercise with BFR as a primary intervention.

Risk of bias assessment

The Cochrane Collaboration tool, available at https://training.cochrane.org/handbook/, was used to assess the risk of bias. Two experienced authors independently assessed the risk of bias. Any discrepancies were resolved by a third author. The bias of the following sources was evaluated: 1) random sequence generation; 2) allocation concealment; 3) blinding of participants and staff; 4) concealment of outcome assessments; 5) incomplete outcome data; 6) selective notification; 7) other bias. Each domain has a risk of bias set to “low”, “uncertain”, or “high risk of bias”. The final score assigned is the highest rating among the domains evaluated in each RCT (18).

Methodological quality assessment

To assess the methodological quality, the Tool for the assEssment of Study qualiTy and reporting in EXercise (TESTEX) was used. TESTEX is applied for studies involving physical exercises. TESTEX is a 15-point scale used in experimental studies, including internal validity assessment criteria and presentation of the statistical analysis used. It is attributed 1 point to each criterion defined in the scale and zero point in the absence of these indicators. The scale comprises the following criteria: 1) specification of inclusion criteria; 2) random allocation; 3) allocation secrecy; 4) similarity of groups in the initial or baseline phase; 5) rater blinding (for at least one key outcome); 6) measurement of at least one primary outcome in 85% of the allocated subjects (up to three points); 7) intention-to-treat analysis; 8) comparison between groups of at least one primary outcome (up to two points); 9) report measures of variability for all reported outcome measures; 10) monitoring of activities in CG; 11) relative exercise intensity remained constant; 12) characteristics of exercise volume and energy expenditure (19).

Data extraction

The following study characteristics were extracted: authors, year of publication, country of origin, characteristics of the study population (age, sex, and sample size), and intervention data, including general and specific exercises, intervention duration (weeks), volume of training (training frequency, in times per week), form of evaluation, and results.

RESULTS

A total of 423 publications were found from the database search following the proposed research methodology (MEDLINE via PubMed = 186; Scopus = 71; Embase = 67; Web of Science = 39; ScienceDirect = 60). After using the selection criteria, a total of 9 RCTs were included in the present systematic review (**figure 1**).

Figure 2 shows the results of the risk of bias analysis using the Cochrane Collaboration tool. Of the 9 studies included in this systematic review, 89% (n = 8) showed bias in participant blinding and 67% (n = 6) in rater blinding.

Table I presents the methodological quality assessment using TESTEX. Among the domains used by the tool, information on energy expenditure, monitoring of the CG, and blinding of evaluators reduced the methodological quality of most studies, but did not compromise the total score. All studies had a score > 10.

Table II shows the studies and sample characteristics. The mean age of the participants was 69 years in the experimental group (EG) and CG. The total number of participants was 339 (259 in the EG and 80 in the CG). The years of the publications ranged between 2013 and 2022. **Table III** presents the data on the intervention, exercises, training volume, evaluation, and results of the included studies. The average intervention time of the studies was 11 weeks, with 3 sessions per week. The time per session was not reported in the studies.

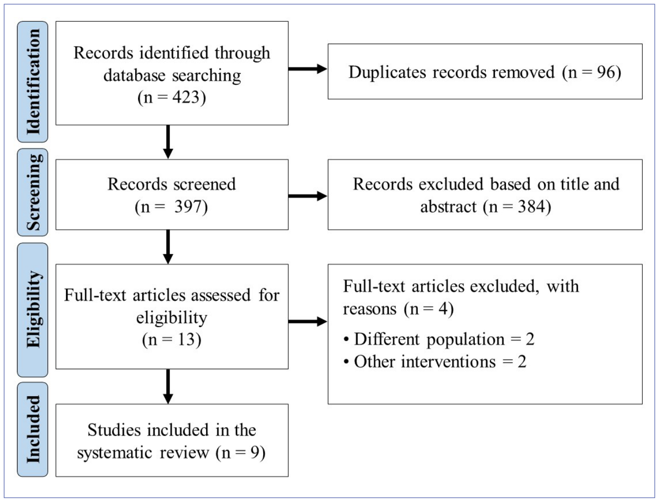

Figure 1. Flowchart.

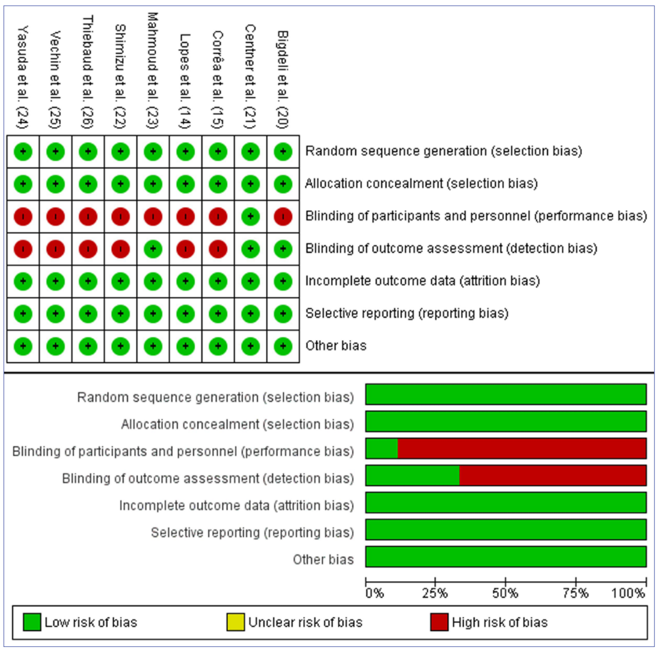

Figure 2. Bias risk analysis.

Table I. Methodological quality assessment.

Study	Study quality					Sub-total (0 to 5)	Study Reporting										Sub-total (0 to 10)	Total (0 to 15)
	1	2	3	4	5		6a	6b	6c	7	8	8b	9	10	11	12		
Bigdeli *et al.* (20)	1	1	1	1	1	5	1	1	1	1	1	1	1	0	1	0	8	13
Corrêa *et al.* (15)	1	1	1	1	0	4	1	0	1	1	1	1	1	0	1	0	7	11
Centner *et al.* (21)	1	1	1	1	1	5	1	1	1	1	1	1	1	1	1	0	9	14
Shimizu *et al.* (22)	1	1	1	1	0	4	1	1	1	1	1	1	1	1	1	0	9	13
Mahmoud *et al.* (23)	1	1	1	1	1	5	1	0	1	1	1	1	1	0	1	0	7	12
Yasuda *et al.* (24)	1	1	1	1	0	4	1	1	1	1	1	1	1	1	1	0	9	13
Vechin *et al.* (25)	1	1	1	1	0	4	1	1	1	1	1	1	1	0	1	0	9	13
Thiebaud *et al.* (26)	1	1	1	1	0	4	1	0	1	1	1	1	1	1	1	0	8	12
Lopes *et al.* (14)	1	1	1	1	0	4	1	1	1	1	1	1	1	1	1	0	9	13

Study quality: 1 = specific eligibility criteria; 2 = type of randomization specified; 3 = hidden allocation; 4 = similar groups at baseline ; 5 = raters were blinded (at least one main outcome); 6 = outcomes assessed in 85% of participants (6a = 1 point if more than 85% completed; 6b = 1 point if adverse events were reported; 6c = if exercise attendance was reported); 7 = intention-to-treat statistical analysis; 8 = statistical comparison between groups was reported (8a = 1 point if between-group comparisons are reported for the primary outcome variable of interest; 8b = 1 point if statistical comparisons between groups are reported for at least one secondary measure); 9 = point measures and measures of variability for all outcome measures that were reported; 10 = activity monitoring in the control group; 11 = relative exercise intensity remained constant; 12 = exercise volume and energy expenditure were reported.

Table II. Study data.

Authors	Country	Age (years: mean ± SD)	Characteristics	Groups (n)
Bigdeli *et al.* (20)	Iran	EG1: 67.6 ± 5.1 EG2: 66.3 ± 4.6 CG: 69.3 ± 7.4	Healthy men	EG1: 10 EG2: 10 CG: 10
Corrêa *et al.* (15)	Brazil	EG1: 58 ± 6 EG2: 58 ± 7 CG: 58 ± 5	Men and women with kidney disease	EG1: 35 EG2: 35 CG: 35
Centner *et al.* (21)	Australia	EG1: 61.7 ± 5.5 EG2: 56.6 ± 6.1 CG: 62.5 ± 10.5	Healthy men	EG1: 11 EG2: 11 CG: 8
Shimizu *et al.* (22)	Berlin	EG1: 70 ± 4 EG2: 72 ± 4	Healthy men and women	EG1: 20 EG2: 20
Mahmoud *et al.* (23)	Egypt	EG1: 59.05 ± 1.83 EG2: 60.17 ± 2.09	Men and women with kidney disease	EG1:18 EG2: 17
Yasuda *et al.* (24)	Japan	EG1: 70 ± 6 EG2:72 ± 7 CG: 68 ± 6	Healthy women	EG1: 10 EG2: 10 CG: 10
Vechin *et al.* (25)	Brazil	EG1: 66 ± 5 EG2:62 ± 3 CG: 65 ± 2	Healthy men and women	EG1: 8 EG2: 8 CG: 7
Thiebaud *et al.* (26)	USA	EG1: 59 ± 2 EG2: 62 ± 2	Post-menopause women	EG1: 6 EG2: 8
Lopes *et al.* (14)	Brazil	EG1: 71 ± 6 EG2: 73 ± 7 CG: 72 ± 8	Healthy men and women	EG1: 12 EG2: 10 CG: 10

SD: standard deviation; EG: experimental group; CG: control group; USA: United States of America.

Table III. Data extracted from included studies.

Studies	Intervention	Exercise protocol	VT	Assessment	Results ($p < 0.05$)
Bigdeli *et al.* (20)	EG1: RT + BFR: 2-4 × 10 at 50% of 1 RM at weeks 1 and 2 with 10% increase every 2 weeks EG2: RT: 2-4 × 10 at 25% of 1RM weeks 1 and 2, 30% of 1RM weeks 3 and 4, 35% of 1RM weeks 5 and 6 CG: did not perform exercises	Dumbbell fly on a Swiss ball; wall squat with a Swiss ball; triceps extension while lying on a Swiss ball; forward lunge on a Bosu ball; shoulder press while standing on a Bosu ball; medicine ball squat throw; standing biceps curl with dumbbells on a Bosu ball; leg curl with a power band while lying on a Bosu ball; seated row with power bands on Bosu; crunches with a medicine ball; medicine ball hyperextension from the ground	3 ×/week 6 weeks	Biomarkers; muscle strength	EG1: ↔ P3NP; ↑ Knee extension; ↑ Chest press EG2: ↓ P3NP; ↑ Knee extension; ↑ Chest press
Corrêa *et al.* (15)	EG1: RT (1-3 × 10-12): 2 months at 50% 1RM, 2 months at 60% 1RM, and 2 months at 70% 1RM EG2: RT + BFR: 50% total occlusion; 2 months at 30% 1RM, 2 months at 40% 1RM, and 2 months at 50% 1RM CG: did not perform exercises	Bench press, seated row, shoulder press, triceps pulley, barbell curls, leg press 45°, leg extension, and leg curl	3 ×/week 24 weeks	Biomarkers	EG1: ↔ FGF23; ↔ creatinine; ↑ Cystatin C; ↔ urinary protein excretion; ↓ TNF-α; ↔ MCP-1; ↓ IL-6; ↑IL-10; ↑IL-15; ↓ IL-17a; ↓ IL18 EG2: ↔ FGF23; ↔ creatinine; ↑ Cystatin C; ↔ urinary protein excretion; ↓ TNF-α; ↔ MCP-1; ↔ IL-6; ↑IL-10; ↑IL-15; ↓ IL-17a; ↓ IL18
Centner *et al.* (21)	EG1: RT + BFR with collagen: 1-3 × 30/ 3 × 15-20% of 1RM with 30 s of recovery. A vascular occlusion pressure of 50% was assumed EG2: RT + BFR with placebo: 1-3 × 30/ 3 × 15-20% of 1RM with 30 s of recovery. A vascular occlusion pressure of 50% was assumed CG: only supplementation, did not perform exercises	Leg press 45°	NI 8 weeks	Biomarkers; muscle strength	EG1: ↑ % CSA quadriceps; ↔ % 1 RM; ↔IGF-1; ↔ ROS EG2: ↑ CSA; ↔ % 1RM; ↔ IGF-1; ↔ ROS
Shimizu *et al.* (22)	EG1: RT: 3 × 20 with 30 s recovery at 20% of 1RM EG2: RT + BFR: 3 × 20 with 30 s recovery at 20% of 1RM	Leg extension, leg press, rowing, and chest press,	3 ×/week 4 weeks	Biomarkers; muscle strength	EG1: ↔ leg extension; ↔ Leg press; ↔ Rowing; ↔ Chest press; ↔ $TcPO_2$; ↔ RHI; ↔ vWF; ↔ TM EG2: ↑ leg extension; ↑ Leg press; ↑ Rowing; ↔ Chest Press; ↔ $TcPO_2$; ↑ RHI; ↔ vWF; ↔ TM

Studies	Intervention	Exercise protocol	VT	Assessment	Results ($p < 0.05$)
Mahmoud *et al.* (23)	EG1: RT + BFR (n = 9): 4 × 15-30 at 50% occlusion (118 mm/Hg)/ RT (n = 9): 10% of 1RM EG2: RT + BFR (n = 9): 4 × 15-30: 70% occlusion (119 mm/Hg)/ RT (n = 8): 30% of 1RM	Leg extension	3 ×/week 8 weeks	Muscle strength	EG1: ↓VAS; ↑ Leg extension; ↑CSA quadriceps EG2: ↓VAS; ↑ Leg extension; ↑CSA quadriceps
Yasuda *et al.* (24)	EG1: RT + BFR: 4 × 30; 15; 15; 15 with 30s of recovery between sets and 90s between exercises; occlusion pressure of 161 ± 12 mmHg EG2: Medium to high intensity elastic training: 3 × 13; 13; 12 with 30 s of recovery between sets and 90 s between exercises CG: did not perform exercises	Squat; leg extension	2 ×/week 12-24 weeks	Muscle strength	EG1: ↑leg extension; ↔ squat; ↑ CSA quadriceps EG2: ↔ leg extension; ↔ squat; ↔ CSA quadriceps
Vechin *et al.* (25)	EG1: RT: 4 × 10 at 70-80% of 1RM with 30 s recovery EG2: BFR (71 ± 9 mmHg): 1 × 30 + 3 × 15 at 20-30% of 1RM with 30 s recovery CG: did not perform exercises	Leg press	2 ×/week 12 weeks	Muscle strength	EG1: ↑ Leg press; ↑ CSA quadriceps EG2: ↔ Leg press; ↑ CSA quadriceps
Thiebaud *et al.* (26)	EG1: RT: 3 × 10 at 70-90% of 1RM with 30 s recovery EG2: RT + BFR: 1 × 30 + 2 × 15 at 10-30% of 1RM	Supine leg press, supine chest press, right and left hip extension, and right and left hip flexion	3 ×/week 8 weeks	Muscle strength	EG1: ↑ chest press; ↑ Seated row; ↑ Shoulder press; ↔ Lower members; ↔ muscle thickness EG2: ↑ chest press; ↑ Seated row; ↑ Shoulder press; ↔ Lower members; ↔ muscle thickness
Lopes *et al.* (14)	EG1: RT: 3 × 10 at 70% of 1RM EG2: RT + BRF: 3 × 10 to 30% of 1RM and 50% occlusion pressure CG: RT: 3 × 10 at 30% of 1RM	Elbow flexion, leg press, pulley elbow extension, knee extension	3 ×/week 12 weeks	Biomarkers; muscle strength	EG1: ↔ IGF-1; ↔ hs-CRP; ↔ TNF-α; ↔ IL-6; ↑ Hand grip strength; ↔ Peak torque extension; ↔ Total work extension EG2: ↑ IGF-1; ↔ hs-CRP; ↔ TNF-α; ↔ IL-6; ↑ Hand grip strength; ↔ Peak torque extension; ↔ Total work extension

EG: experimental group; CG: control group; VT: volume of training; LIRE-BFR: low intensity resistance exercise with blood flow restriction; RT: resistance training; P3NP: type III procollagen propeptide; IGF-1: insulin-like growth factor 1; ROS: reactive oxygen species; $TcPO_2$: transcutaneous oxygen pressure; RHI: reactive hyperemia index; vWF: von Willebrand factor; TM: trombomodulina; FGF23: serum levels of klotho and fibroblast growth factor 23; TNF-α: Tumor necrosis factor alpha; IL: interleukin; MCP-1: Monocyte chemoattractant protein-1; RM: repetition maximum; CRP: C-reactive protein; hs-CRP: high-sensitivity methods; VAS: Visual Analogue Scale; CSA: cross-sectional area; s: seconds; ×/week: times per week.

DISCUSSION

This study aimed to analyze the effects of RT with BFR on muscle strength and biomarkers in older people. The most evident results were increases ($p < 0.05$) in muscle strength, hypertrophy, and positive changes in biomarkers of aging in the groups that received RT with BFR as an intervention.

All studies (14, 15, 20-26) showed that RT with BFR generated increases in muscle strength and/or improvements in biomarkers. It is noteworthy that the prevalence of sarcopenia ranges from 3% to 24% depending on the diagnostic criteria used, leading to loss of muscle strength, and negatively altering physiological biomarkers (27).

Muscle strength was analyzed in the studies of Bigdeli *et al.* (20), Centner *et al.* (21), Mahmoud *et al.* (23), Shimizu *et al.* (22), Yasuda *et al.* (24), and Lopes *et al.* (14). All studies used RT with BFR in one of the groups, showing increases ($p < 0.05$) in muscle strength and/or cross-section are when compared to other types of RT (conventional and elastic band). However, there was an increase in muscle strength using RT in the studies of Bigdeli *et al.* (20), Vechin *et al.* (25), Thiebaud *et al.* (26), and Lopes *et al.* (14). Knee extension, leg press, and squat exercises were used to assess the strength of the lower limbs. Exercises for the chest, back, biceps, triceps, and shoulder muscle groups were used for the upper limbs. Corroborating this, a pilot RCT, conducted by Harper *et al.* (28), used RT with BFR with low load in 35 older people, 3 times a week, for 12 weeks and showed increases in muscle strength.

Biomarkers were investigated by Bigdeli *et al.* (20), Centner *et al.* (21), Shimizu *et al.* (22), and Correa *et al.* (15). The studies of Bigdeli *et al.* (20) and Correa *et al.* (15) showed improvements ($p < 0.05$) in biomarkers P3NP, FGF23, cystatin, TNF, IL-10, IL-15, IL-17, and IL-18 in the groups that performed RT with BFR. However, studies by Centner *et al.* (21), Shimizu *et al.* (22), and Lopes *et al.* (14) found no differences in biomarkers. Corroborating this, Kargaran *et al.* (29) analyzed 24 older women who performed 20 min of walking with BFR, 3 times per week, for 8 weeks, and found improvements in biomarkers P3NP and brain-derived neurotrophic factor (BDNF).

One limitation of this study is the limited number of RCTs investigating RT with BFR in older individuals. Conducting a systematic review with a larger number of RCTs would facilitate a meta-analysis, thereby providing greater certainty for professionals in their decision-making regarding the use of this technique.

CONCLUSIONS

Based on the RCTs included in this systematic review, RT with BFR has shown effectiveness in increasing muscle strength, enhancing muscle cross-sectional area, and improving biomarkers associated with protein synthesis. However, it is important to interpret the extracted data cautiously to mitigate potential biases, including studies with small sample sizes. Future studies should further investigate the integration of RT with the BFR method to explore additional physical variables (*e.g.*, muscle power and fall reduction), physiological variables (*e.g.*, bone remodeling), and mental variables (*e.g.*, depression) among older individuals. Such studies have the potential to provide valuable insights into the effects of this type of training within this specific population.

FUNDINGS

None.

DATA AVAILABILITY

All data used in this review is appropriately cited.

CONTRIBUTIONS

DGL: conceptualization, data extraction, writing – original draft. ASA, YAB: data extraction, writing – original draft. OBN, DGL, AVSF, GGC: data analysis, writing – review & editing. MGC, JBPC, RGSV: writing – original draft, writing – review & editing.

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

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