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RESEARCH

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Resistance exercise training improves disuse-induced skeletal muscle atrophy in humans: a meta-analysis of randomized controlled trials

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Abstract

Background This meta-analysis aimed to determine whether resistance exercise training (RET) can attenuate the loss of muscle volume and function in anti-gravitational muscles, especially quadriceps and calf muscles, during immobilization/disuse conditions.

Methods A comprehensive literature search was conducted to identify randomized controlled trials comparing RET vs. no exercise during immobilization/disuse. Searches were conducted in databases including Web of Science, PubMed, EBOSCO, and Cochrane Library, without imposing a time limit until 20 March, 2023. Studies reporting outcomes related to muscle volume, MVC, peak power, concentric peak force, eccentric peak force, isometric MVC torque of knee extension, isometric MVC torque of knee flexion were included. Data were pooled using random-effects models.

Results Eleven randomized controlled trials were finally included. RET elicited substantial benefits for preserving quadriceps muscle volume ($n=5$, MD = 252.56, 95% CI = 151.92, 353.21, $p<0.001$). RET demonstrated a statistically significant preventive effect on the reduction of MVC in both quadriceps ($n=4$, MD = 338.59, 95% CI = 247.49, 429.69, $p<0.001$) and calf muscles ($n=3$, MD = 478.59, 95% CI = 160.42, 796.77, $p<0.01$). Peak power of quadriceps muscles ($n=4$, MD = 166.08, 95% CI = 28.44, 303.73, $p<0.05$) and calf muscles ($n=2$, MD = 176.58, 95% CI = 102.36, 250.79, $p<0.001$) were elevated after RET intervention. RET significantly ameliorated the weakening of both concentric and eccentric peak force in quadriceps (concentric: $n=2$, MD = 470.95, 95% CI = 355.45, 586.44, $p<0.001$; eccentric: $n=1$, MD = 351.51, 95% CI = 254.43, 448.58, $p<0.001$) and calf muscles (concentric: $n=2$, MD = 867.52, 95% CI = 548.18, 1186.86, $p<0.001$; eccentric: $n=1$, MD = 899.86, 95% CI = 558.17, 1241.55, $p<0.001$). Additionally, the diminishing of isometric MVC torques of knee extension ($n=6$, MD = 41.85, 95% CI = 20.93, 62.77, $p<0.001$) and knee flexion ($n=4$, MD = 13.20, 95% CI = 8.12, 18.77, $p<0.001$) were enhanced significantly after RET intervention.

Conclusions RET effectively minimized deterioration of muscle volume and muscle function during immobilization/disuse, particularly in anti-gravitational muscles. RET should be recommended to maintain muscle and neuromuscular health for spaceflight, bed rest, immobilization/disuse conditions. Further research is needed to explore the effects of RET in more diverse populations and under various disuse conditions. More high-quality research will be required to demonstrate the aforementioned benefits conclusively.

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Keywords Resistance exercise training, Simulated weightlessness, Muscle atrophy, Bed rest

Introduction

Disuse atrophy (DA) and weakness are common consequences during unloading such as spaceflight, bed rest, immobilization/disuse [1]. Previous researchers has reported that the highest rates of alteration in muscle strength and size have been documented to occur during the initial stages of disuse or mechanical unloading, the decline in muscle strength with unloading is greater than the decline in muscle volume, and likely contributed to the rapid neuromuscular loss of function in the early period [2, 3]. Therefore the countermeasures to successfully regain muscles function should be worked from early on during DA. DA conditions exert a greater impact on anti-gravitational muscles, studies [4] indicate that spaceflight-induced DA results in rapid muscle loss of approximately 15% in quadriceps and gastrocnemius muscles within 2 weeks, while head-down bed rest models demonstrate similar losses of up to 17% after 84 days, and 15 days of immobilization causes a significant decline in both volume (-2.8%) and thickness (-12.9%) of the medial gastrocnemius muscle. These findings indicate that the quadriceps and calf muscles are more susceptible to the effects of DA.

Resistance exercise training (RET) has been demonstrated as an effective countermeasure to prevent unloading-induced muscle atrophy and weakness [1, 5]. Indeed, concentric, eccentric and isometric muscle contractions performed against external resistance can help maintain muscle volume and function during DA [6, 7]. Understanding the efficacy of RET in counteracting disuse-related muscle weakening is critical for developing optimized exercise recommendations and countermeasures for space travelers, bedridden patients, casted individuals or other individuals undergoing disuse/immobilization to stay physically conditioned. However, the effect of resistance training indicated by limited clinical applications in preventing muscle weakening during simulated weightlessness is still inconclusive [8].

Therefore, a meta-analysis of randomized controlled trials was conducted to evaluate the overall effectiveness of resistance exercise in counteracting muscle atrophy and weakness during conditions such as spaceflight, prolonged bed rest and limb immobilization/disuse. By synthesizing data from multiple experimental trials, a meta-analysis can provide more comprehensive and higher-level evidence than individual studies alone. This meta-analysis aimed to determine if RET can attenuate the loss of muscle volume and function in anti-gravitational muscles, especially the quadriceps and calf muscles which are most affected by DA.

Method

Study protocol

The protocol of this meta-analysis was registered in the International Prospective Register of Systematic Reviews (PROSPERO), ID: CRD42023414999.

Search strategy

This review was conducted in accordance with the 2020 update of the PRISMA statement [9]. A comprehensive search of the literature was performed using electronic databases such as Web of Science, PubMed, EBOSCO, and Cochrane Library. The search included publications from the inception of each databases to 20 March 2023 and utilized the following search terms:

(sport OR exercise* OR physical activity* OR physical exercise* OR exercise training* OR resistance training OR strength training OR weight-lifting strengthening program* OR weight lifting strengthening program* OR weight-lifting exercise program* OR weight lifting exercise program* OR weight-bearing strengthening program* OR weight bearing strengthening program* OR weight bearing exercise program*) AND (muscle atrophy OR muscle wasting OR muscle loss OR disuse atrophy OR disuse muscle wasting OR disuse muscle loss OR muscle function) AND (astronaut* OR cosmonaut* OR space travel OR space exploration* OR spaceflight* OR spaceflight OR space mission OR space traveler* OR microgravity OR micro gravity OR artificial gravity OR weightless OR weightlessness OR simulated weightlessness OR weightlessness-induced OR microgravity OR bed rest OR bed-rest OR bedrest OR bedridden OR immobilization OR limb immobilization OR non-mobile OR non mobile OR unloading OR dry immersion OR head down tilt bed rest OR head-down bed rest).

The literature screening criteria was shown in Table 1.

Data extraction and quality assessment

Xian G and Yanbing Z independently conducted literature screening, extraction, checking, and negotiating the differences through Xinxin L. After the reading text was preliminarily screened, the reading summary and the full text were determined whether it was included. If necessary, we contacted the author to obtain the original data. RoB 2 tool (revised tool for Risk of Bias in randomized trials) [10] was used to assess the quality of included research.

Statistical analysis

All outcome measures were presented as means and standard deviations (SDs). The mean differences (MDs)

Table 1 Inclusion and exclusion criteria

		Description
Inclusion criteria	Population	18 + years old, with no mental or physiological diseases
	Intervention	subjects underwent bed rest or spaceflight or limb immobilization, meanwhile had RET as intervention
	Comparison	subjects only had bed rest or spaceflight or limb immobilization as intervention
	Outcome	(1) muscle volume a: muscle volume of quadriceps (It is strictly stipulated that the data must be obtained through magnetic resonance imaging (MRI)) (2) muscle function b: MVC of quadriceps muscles, c: MVC of calf muscles, d: peak power of quadriceps muscles, e: peak power of calf muscles, f: concentric peak force of quadriceps muscles, g: concentric peak force of calf muscles, h: eccentric peak force of quadriceps muscles, i: eccentric peak force of calf muscles, j: isometric MVC torque of knee extension, k: isometric MVC torque of knee flexion
	Study design	randomized controlled trials
Exclusion criteria		(1) self-control, crossover study or research with no control group, (2) conference abstracts or study without full text, (3) literature with incomplete data, (4) non-English literature, (5) no muscle size, strength or function related outcomes

RET resistance exercise training, *MVC* maximal voluntary contraction

between intervention and control groups were calculated, along with their corresponding 95% confidence intervals (CIs), using a random-effects model based on the inverse variance method to account for heterogeneity across studies. Statistical significance was evaluated using a threshold of $P < 0.05$. To assess heterogeneity between studies, the I^2 statistic was calculated, with values over 50% indicating moderate to high heterogeneity. All data analyses were conducted using Review Manager (RevMan) software, version 5.3, following the guidelines of the Cochrane Collaboration.

Results

Study selection and information

The comprehensive search yielded a total of 1763 articles. Given that there are inherently few randomized controlled clinical trials intervening with resistance exercise training for limb immobilization/disuse, in order to ensure the comprehensive inclusion of all relevant studies, this meta-analysis did not restrict the duration of limb immobilization/disuse nor did it impose limitations on the type, intensity, or other criteria for selecting literature related to resistance exercise training. After removing 364 duplicates and 1388 articles that did not meet the screening criteria, 11 randomized controlled trials remained and were included in this meta-analysis. The flow chart of studies identification was illustrated in Fig. 1. The included research information was shown in Table 2.

Risk of bias

The Cochrane Collaboration Risk of Bias tool [22] was used to objectively evaluate the quality of evidence from the included studies. Each study was rated as having either a “low risk”, “high risk”, or “unclear risk” of bias for each of the bias domains. The bias ratings for all included studies are summarized in Fig. 2.

Due to the nature of the resistance exercise intervention, all studies were rated as "high risk" of bias for the allocation concealment and blinding of participants and personnel domains. Allocation concealment and blinding are challenging to achieve in exercise training studies. Participants and researchers are typically aware of group allocation, and it is difficult to blind participants to an exercise intervention. Although this may potentially bias the study results, exercise interventions can still provide valuable and clinically relevant information as long as the randomized allocation to groups is achieved during the study design. The other bias domains were evaluated independently for each study based on reported methodology.

Results of meta-analysis

All the statistical results were shown in Table 3. The results showed that RET produced significant effects on all indicators related to muscle volume and muscle function (all $p < 0.05$).

Muscle volume

Five studies reported muscle volume of quadriceps outcomes (Fig. 3). As illustrated, RET significantly maintained the muscle volume of quadriceps during immobilization/disuse ($p < 0.001$).

Muscle function

(1) Maximal voluntary contraction (MVC)

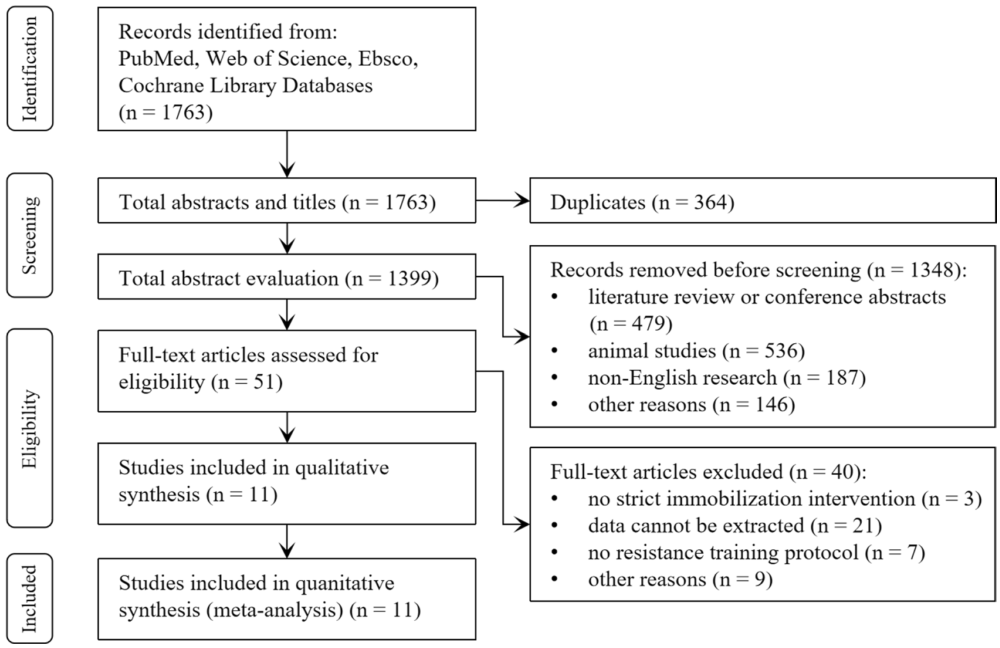

Fig. 1 PRISMA flow diagram

Three studies reported MVC of quadriceps muscles and 2 studies researched MVC of calf muscles in outcome. The results indicated that RET had a significant preventive effect on attenuation of MVC of quadriceps muscles ($p < 0.001$) (Fig. 4a) and calf muscles ($p < 0.01$) (Fig. 4b).

(2) Peak power

Peak power of quadriceps muscles was observed in 3 studies, and 1 study but 2 different time points researched peak power of calf muscles. The results showed that RET significantly improved peak power of quadriceps muscles ($p < 0.05$) (Fig. 5a) and calf muscles ($p < 0.001$) (Fig. 5b).

(3) Concentric peak force and eccentric peak force

Two studies examined the effect of concentric peak force and 1 study but 2 time points investigated the effect of eccentric peak force. After the respective meta-analysis, it could be observed that RET significantly ameliorated the weakening of concentric peak force of quadriceps muscles ($p < 0.001$) (Fig. 6a) and calf muscles ($p < 0.001$) (Fig. 6b). In the meantime, the declines of eccentric peak force of quadriceps muscles ($p < 0.001$) (Fig. 6c) and calf muscles ($p < 0.001$) (Fig. 6d) were significantly mitigated by RET intervention.

(4) Isometric MVC torque of knee extension and knee flexion

Six studies involved the isometric MVC torque of knee extension and 4 studies compared the isometric MVC torque of knee flexion. As shown in Fig. 7, the diminishing of isometric MVC torques of knee extension ($p < 0.001$) (Fig. 7a) and knee flexion ($p < 0.001$) (Fig. 7b) were enhanced significantly after RET intervention.

Discussion

This meta-analysis provided compelling evidence that RET effectively mitigated the decline in muscle volume and impaired function of the quadriceps and calf muscles, which undergo disuse atrophy under conditions such as prolonged bed rest and immobilization/disuse of limbs.

In situations such as spaceflight, extended bed rest, limb immobilisation and unloading, muscle atrophy and decline in muscle strength appear very rapidly. According to previous research [2], the initial phases of disuse exhibit the most pronounced rates of muscle strength deterioration and atrophy, with these changes subsequently plateauing. Furthermore, it is noteworthy that within the first two weeks of disuse, the reduction in muscle strength proceeds at a considerably faster pace compared to the development of muscle atrophy. Different disuse models result in varying

Table 2 Included research information

First Author	Subject (Exe/Ctrl)	Gender (M/F)	Age (M ± SD)	Immobilization/ disuse type	Period	Type of RET	Intensity	Frequency	Outcomes
Akima [11]	6/5	11/0	Exe: 22.4 ± 3.5 Ctrl: 21.0 ± 3.5	unilateral lower-limb suspension	20 days	Intense interval training	40–80% VO_{2peak}	2–3 times/ week	a
Alkner [12]	8/9	17/0	Exe: 32 ± 4 Ctrl: 33 ± 5	6° head-down tilt bed rest	90 days	Flywheel training	maximal concentric and eccentric actions	2–3 times/ week	b, c, d, e, f, g, h, i, j
Holt [13]	8/8	0/16	Exe: 33 ± 1 Ctrl: 34 ± 1	6° head-down tilt bed rest	60 days	Interval training	40–80% VO_{2peak}	2–3 times/ week	j, k
Kramer [14]	12/11	23/0	Exe: 30 ± 7 Ctrl: 28 ± 6	6° head-down tilt bed rest	60 days	countermovement jumps and repetitive hops	mixed intensity	5–6 times/ week	d, f, j, k
Kubota [15]	9/6	15/0	Exe: 22.3 ± 0.5 Ctrl: 23.2 ± 1.5	unilateral lower-limb suspension	14 days	isometric training	mixed intensity	7 times/week	j, k
Mulder [16]	7/9	16/0	Exe: 31.1 ± 5.1 Ctrl: 33.1 ± 7.8	6° head-down tilt bed rest	60 days	dynamic bilateral squat exercises, dynamic unilateral and bilateral calf raise exercises	mixed intensity	3 times/week	j
Ogawa [17]	7/8	15/0	Exe: 31.3 ± 7.6 Ctrl: 34.0 ± 7.1	6° head-down tilt bed rest	48 days	bilateral squat, single-leg heel raises and double-leg heel raises	mixed intensity	3 times/week	a
Trappe [18]	6/6	12/0	Exe: 32 ± 2 Ctrl: 32 ± 2	6° head-down tilt bed rest	84 days	maximal concentric and eccentric supine squats	mixed intensity	2–3 times/ week	a, b, d, f, h
Gallagher [19]	8/9	17/0	Exe: 33 ± 1 Ctrl: 32 ± 1	6° head-down tilt bed rest	84 days	knee extensor and plantar flexor resistance exercise	mixed intensity	2–3 times/ week	a, b, c
Tesch [20]	10/11	14/7	Exe: 42 ± 8 Ctrl: 40 ± 9	unilateral lower-limb suspension	35 days	unilateral knee extensor resistance exercise	mixed intensity	2–3 times/ week	a
Bamman [21]	8/8	18/0	Exe: 30.4 ± 2.4 Ctrl: 29.9 ± 2.4	6° head-down tilt bed rest	14 days	leg press exercise	80–85% 1 RM	3–4 times/ week	j, k

Exe exercise group, *Ctrl* control group

a: muscle volume of quadriceps

b: maximal voluntary contraction of quadriceps muscles

c: maximal voluntary contraction of calf muscles

d: peak power of quadriceps muscles

e: peak power of calf muscles

f: concentric peak force of quadriceps muscles

g: concentric peak force of calf muscles

h: eccentric peak force of quadriceps muscles

i: eccentric peak force of calf muscles

j: isometric maximal voluntary contraction torque of knee extension

k: isometric maximal voluntary contraction torque of knee flexion

degrees of muscle mass and strength loss. Additionally, disuse alters muscle tissue composition, decreases adaptations in the nervous system and reduces neuromotor control [23]. Muscle disuse atrophy diminishes quality of life, mobility, and independence, and is associated with increased chronic diseases and mortality [24]. Thus, understanding and preventing it is crucial for human health.

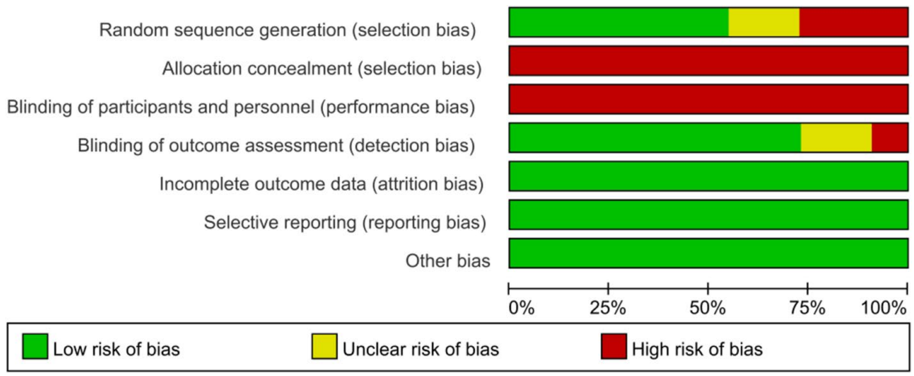

Fig. 2 Risk of bias of included studies

Table 3 Effect of RET during simulated weightlessness on muscle volume and function

Outcome	Number of study	Sample (Exe/Ctrl)	Effect size (95% CI)	*P*-value	I^2(%)
muscle volume of quadriceps	5	37/39	252.56 (151.92, 353.21)	$p<0.001$	54
MVC of quadriceps muscles	3	30/33	338.59 (247.49, 429.69)	$p<0.001$	0
MVC of calf muscles	2	24/27	478.59 (160.42, 796.77)	$p=0.003$	0
peak power of quadriceps muscles	3	34/35	166.08 (28.44, 303.73)	$p=0.02$	93
peak power of calf muscles	1	16/18	176.58 (102.36, 250.79)	$p<0.001$	0
concentric peak force of quadriceps muscles	2	22/24	470.95 (355.45, 586.44)	$p<0.001$	0
concentric peak force of calf muscles	1	16/18	867.52 (548.18, 1186.86)	$p<0.001$	0
eccentric peak force of quadriceps muscles	2	22/24	351.51 (254.43, 448.58)	$p<0.001$	0
eccentric peak force of calf muscles	1	16/18	899.86 (558.17, 1241.55)	$p<0.001$	0
isometric MVC torque of knee extension	6	67/75	41.85 (20.93, 62.77)	$p<0.001$	79
isometric MVC torque of knee flexion	4	37/39	13.20 (8.12, 18.77)	$p<0.001$	0

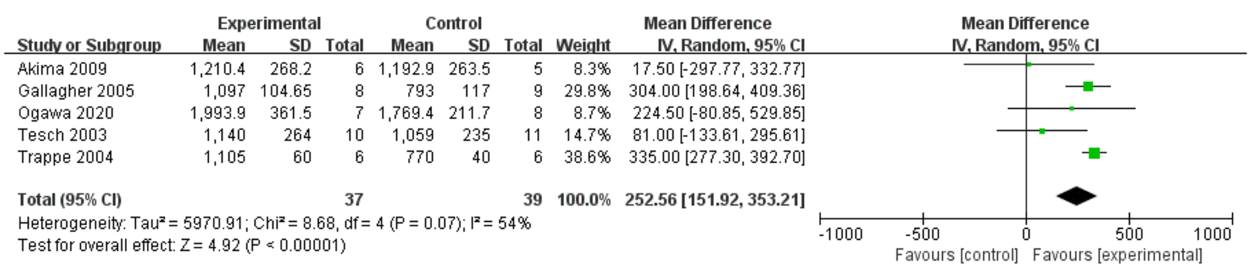

Fig. 3 Effect of RET during immobilization/disuse on muscle volume (cm^2) of quadriceps

RET counteracts DA via a mechanical loading stimulus that increases net protein balance (e.g. muscle protein synthesis – muscle protein breakdown) chiefly through a vast increase in muscle protein synthesis [25]. These alterations in net protein balance associated with RET function to mitigate the typical decrements in muscle size and structure seen with DA [26, 27]. This balance is critical for maintaining the muscle mass and integrity necessary for optimal performance and function. The volume of quadriceps muscles declined by approximately 18% without RET during weightlessness in the selected studies [17–19], while this decrease was halved by RET intervention. Furthermore, RET attributed a range of neurological and morphological adaptations include satellite cells activated, changes in fibre type, muscle architecture, myofilament density and the structure of connective tissue and tendons [28].

RET plays a crucial role in sustaining muscle force and rapid force [29]. MVC, an indicator reflecting muscular strength, demonstrates a significantly slower decline in

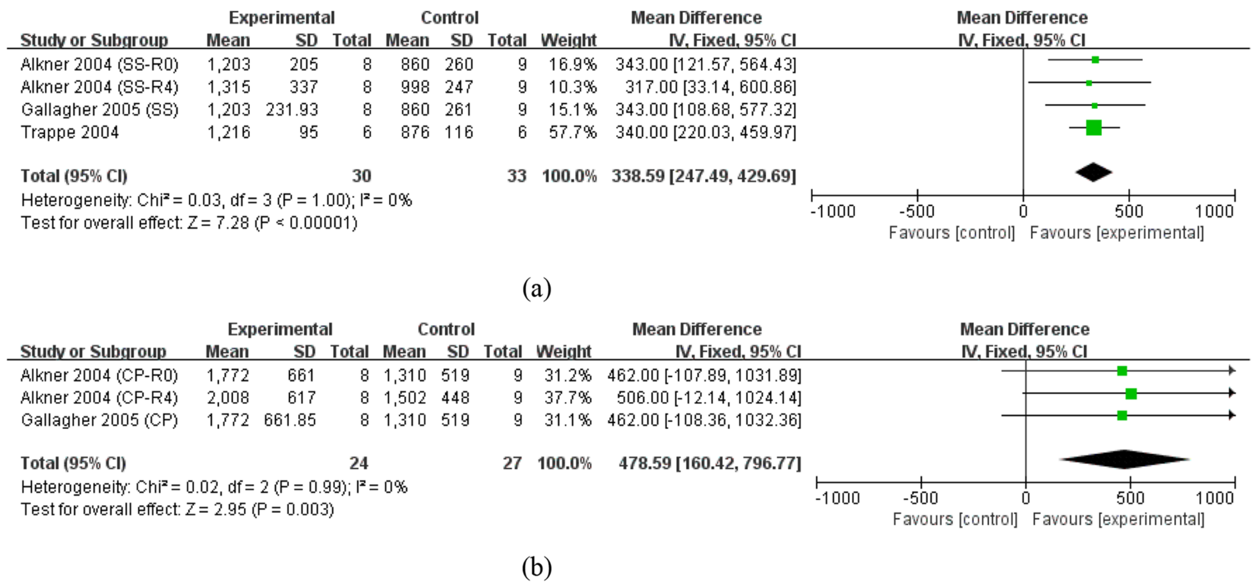

Fig. 4 Effect of RET during immobilization/disuse on MVC: (**a**) MVC (N) of quadriceps muscles, (**b**) MVC (N) of calf muscles

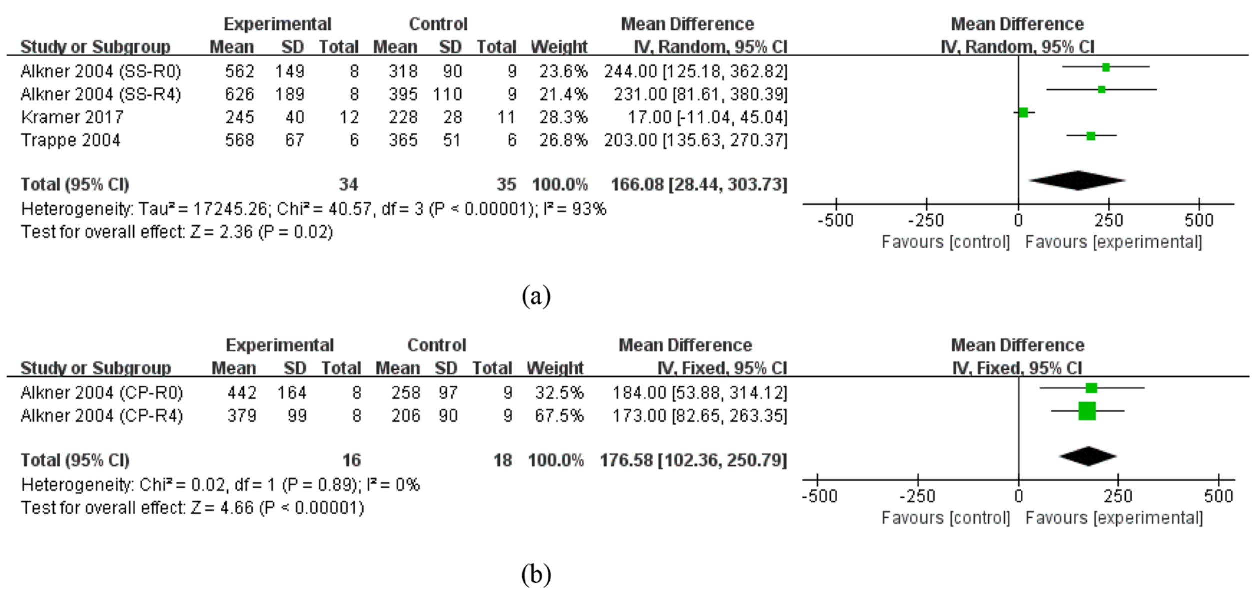

Fig. 5 Effect of RET during immobilization/disuse on peak power: (**a**) peak power (N) of quadriceps muscles, (**b**) peak power (N) of calf muscles

response to disuse when subjected to RET [30]. These findings demonstrated that RET improved both muscle quantity and quality, thereby preserving strength [31]. The more pronounced effects observed in the quadriceps muscles may attributed to their greater involvement during resistance exercise [32, 33]. Improving muscle strength is essential for optimizing health, physical performance and quality of life, especially with long-duration spaceflight or prolonged immobilization [34]. Under such circumstance, RET can minimize secondary complications from muscle loss and dysfunction, including impairments in mobility, decreased proprioception, and compromised balance [35].

Evidence suggests that RET could increase motor unit recruitment through neurological adaptations, particularly during early phases of unloading [36, 37]. These neural adaptations serve as crucial factors in sustaining muscle fiber excitation and overall performance [38].

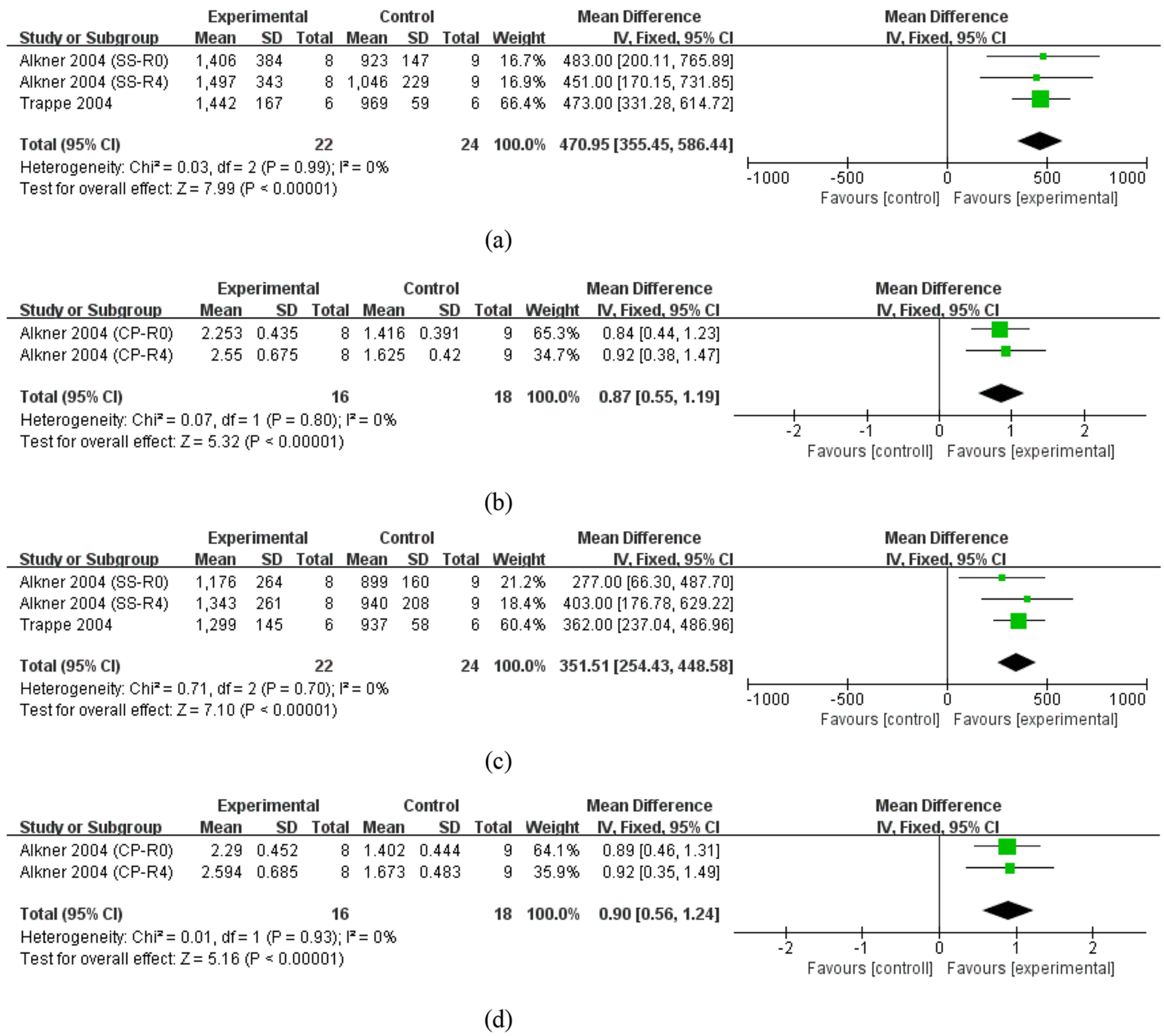

Fig. 6 Effect of RET during immobilization/disuse on concentric peak force and eccentric peak force: (**a**) concentric peak force (N) of quadriceps muscles, (**b**) concentric peak force (kN) of calf muscles, (**c**) eccentric peak force (N) of quadriceps muscles, (**d**) eccentric peak force (kN) of calf muscles

Meanwhile, RET's capacity to provide resistance across the full range of motion helps preserve joint flexibility and mobility [39], which are essential for improving muscle function. Maintaining the range of motion with RET also helps optimize posture, stability and locomotion [40]. Specifically, RET improves concentric, eccentric and isometric peak forces in the quadriceps and calf muscles, with the most pronounced effects observed in the quadriceps muscles [41]. These protective benefits across various muscle actions highlight RET's multifaceted role in mitigating disuse-induced muscle dysfunction. Some studies also reported that RET increased peak force, likely due to neurological changes enhancing motor unit recruitment and firing rates [12, 18]. These findings highlight the potential of RET to not just preserve but enhance muscle function through neuromuscular adaptations [42]. Beyond its mechanical and neurological benefits, the metabolic benefits of RET further reinforce its role in muscle maintenance. By promoting efficient energy expenditure, enhancing oxygen and nutrient delivery, and facilitating waste removal, RET helps to meet the physiological demands of performance. Combining RET with adjunct interventions such as passive limb movement [43], compression therapy (e.g., compression garments) [44], or anabolic supplementation [45] may amplify these metabolic and circulatory

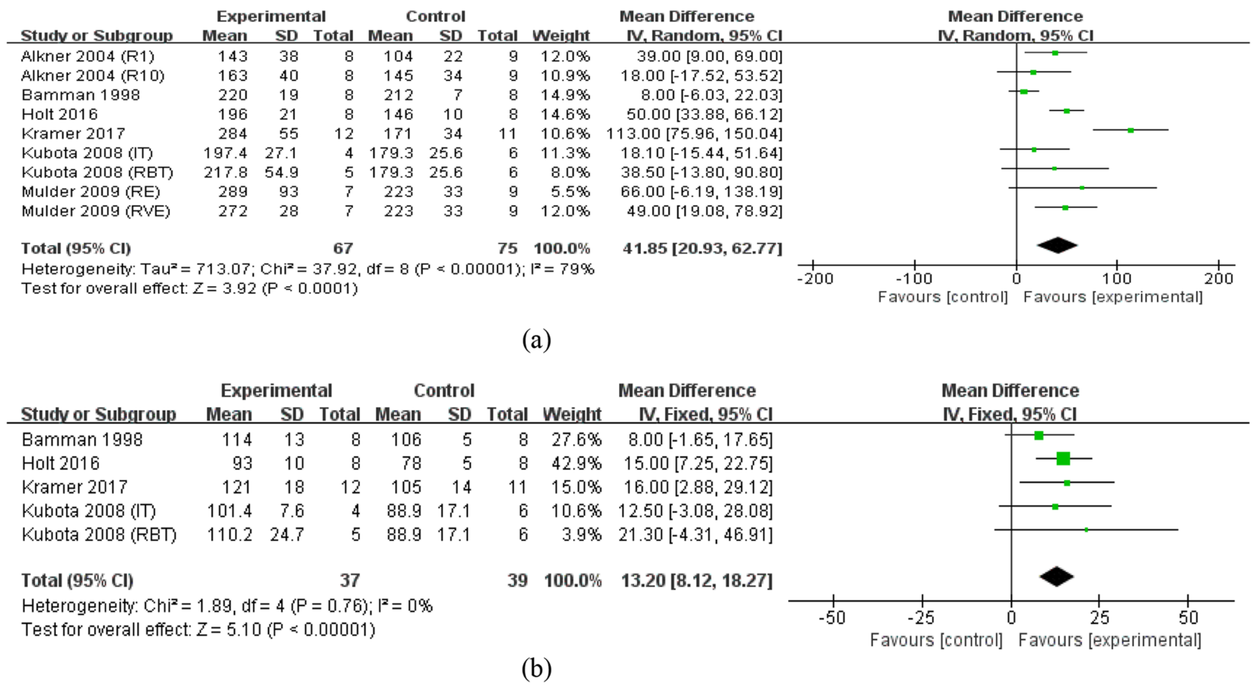

Fig. 7 Effect of RET during immobilization/disuse on isometric MVC torque of knee extension and knee flexion: (**a**) isometric MVC torque (Nm) of knee extension, (**b**) isometric MVC torque (Nm) of knee flexion

benefits. Future research should explore the synergistic effects of these combined strategies to maximize therapeutic outcomes. However, it is noteworthy that the aforementioned research findings are solely applicable to a specific population (healthy individuals), and it remains unknown whether other populations would yield different results.

RET induced mechanical contraction is a strong exogenous stimulus able to counteract the atrophic effects induced by muscle disuse. However, various variables associated with resistance exercise, such as frequency, intensity, and contraction speed, can potentially lead to different outcomes in terms of changes in muscle mass, strength, and function. It is known that training volume is inversely related to intensity and that it may modulate the muscular systems [46]. Engaging in RET with nearly any load, conducted over numerous repetitions and multiple sessions per week, may be more efficacious for promoting muscle hypertrophy. Conversely, utilizing higher loads with a reduced number of repetitions is more effective in augmenting muscular strength in health people [47]. But combination of various training frequencies, volumes, and intensities in disuse-induced skeletal muscle atrophy may or may not be determinant in promoting muscle adaptations as observed in normal conditions [48]. However, a study suggested that RET may not effectively mitigate the detrimental effects of muscle unloading on neuromuscular function [49]. In our present study, although improvements in muscle volume and indicators related to muscle function were observed following RET during limb immobilization/disuse, the study was unable to generalize an effective training model for resistance exercise, encompassing a summation of the exercise type, intensity, frequency, and duration. As a result, the optimal training parameters—such as intensity, frequency, and duration—that could provide protective benefits against muscle unloading require further detection.

This is the first meta-analysis that targeted RET on disuse atrophy induced under immobilization/disuse. A major strength of this review is the inclusion of only RCTs, which is considered the gold standard for assessing interventions. Furthermore, this review included multiple models of immobilization/disuse including bed rest and limb immobilization, which enhanced the generalizability of the findings.

Limitations

Despite the strengths of including multiple RCTs and employing rigorous methodology, several limitations should be considered in future research. Firstly, variability in RET programs and DA models introduced heterogeneity, hindering the identification of an optimized, evidence-based protocol. To address this, future studies should prioritize the standardization and systematic design of RET interventions, focusing on specific muscle groups and immobilization/disuse models while exploring optimal training parameters such as intensity, frequency, and duration. Additionally, combining RET with complementary interventions could enhance its metabolic and circulatory benefits. Such interventions include nutritional supplementation, neuromuscular electrical stimulation (NMES), compression therapy, and passive limb movement. Investigating these multimodal approaches may provide more comprehensive strategies for counteracting disuse atrophy. Moreover, the subjects included in this study were all healthy adults, which implying that the results of this study cannot be generalized to other populations. Future research should examine the effects of RET during immobilization/disuse on other populations, such as adolescents, individuals with diseases, and the elderly. Long-term follow-up studies are also necessary to evaluate sustained benefits and mitigate plateau effects. Finally, personalized adjustments to RET programs should be explored to ensure interventions meet the diverse needs of various populations.

Conclusions

In summary, this meta-analysis provides compelling evidence that RET, targeting anti-gravitational muscles, can progressively and effectively mitigate the deterioration of muscle volume and impairment of muscle function resulting from prolonged immobilization or disuse. RET should be an integral component of exercise countermeasures, particularly for maintaining health and performance during spaceflight, bed rest, immobilization/disuse conditions. Optimizing RET to counteract weakening caused by various factors and in diverse populations should be explored in future studies.

Authors' contributions

Conceptualization, X.G.; methodology, X.G.,Y.Z., X.L.; formal analysis, Y.Z., X.L.; data curation, X.G., Y.Z., X.L., J.M.; writing-original draft preparation, X.G.; writing-review and editing, X.G. All authors have read and agreed to the published version of the manuscript.

Clinical trial number

Not applicable.

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Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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