Journal of Science and Medicine in Sport 21 (2018) 75–83

Contents lists available at ScienceDirect

Journal of Science and Medicine in Sport

journal homepage: www.elsevier.com/locate/jsams

Review

Is inertial flywheel resistance training superior to gravity-dependent resistance training in improving muscle strength? A systematic review with meta-analyses

J. Vicens-Bordas[a,b,*], E. Esteve[a,b], A. Fort-Vanmeerhaeghe[c,b], T. Bandholm[d], K. Thorborg[d,e]

[a] Sportclínic, Physiotherapy and Sports Training Centre, Spain
[b] School of Health and Sport Sciences (EUSES), Universitat de Girona, Spain
[c] Blanquerna Faculty of Psychology, Education Sciences and Sport (FPCEE), Universitat Ramon Llull, Spain
[d] Physical Medicine & Rehabilitation Research – Copenhagen (PMR-C), Department of Physical and Occupational Therapy, Department of Orthopedic Surgery, Clinical Research Center, Amager-Hvidovre Hospital, Copenhagen University, Denmark
[e] Sports Orthopedic Research Center - Copenhagen (SORC-C), Department of Orthopedic Surgery, Amager-Hvidovre Hospital, University of Copenhagen, Denmark

ARTICLE INFO

Article history:
Received 4 June 2017
Received in revised form 31 August 2017
Accepted 6 October 2017
Available online 18 October 2017

Keywords:
Humans
Eccentric overload
Physiology
Muscular adaptations
Muscle strength
Hypertrophy

ABSTRACT

Objective: The primary aim of this systematic review was to determine if inertial flywheel resistance training is superior to gravity-dependent resistance training in improving muscle strength. The secondary aim was to determine whether inertial flywheel resistance training is superior to gravity-dependent resistance training in improving other muscular adaptations.
Design: A systematic review with meta-analyses of randomised and non-randomised controlled trials.
Methods: We searched MEDLINE, Scopus, SPORTDiscus, Web of Science and Cochrane Central Register of Controlled Trials with no publication date restrictions until November 2016. We performed meta-analyses on randomised and non-randomised controlled trials to determine the standardized mean difference between the effects of inertial flywheel and gravity-dependent resistance training on muscle strength. A total of 76 and 71 participants were included in the primary and secondary analyses, respectively.
Results: After systematic review, we included three randomised and four non-randomised controlled trials. In the primary analysis for the primary outcome muscle strength, the pooled results from randomised controlled trials showed no difference (SMD = −0.05; 95%CI −0.51 to 0.40; p = 0.82; I^2 = 0%). In the secondary analyses of the primary outcome, the pooled results from non-randomised controlled trials showed no difference (SMD = 0.02; 95%CI −0.45 to 0.49; p = 0.93; I^2 = 0%; and SMD = 0.03; 95%CI −0.43 to 0.50; p = 0.88; I^2 = 0%). Meta-analysis on secondary outcomes could not be performed.
Conclusion: Based on the available data, inertial flywheel resistance training was not superior to gravity-dependent resistance training in enhancing muscle strength. Data for other strength variables and other muscular adaptations was insufficient to draw firm conclusions from.

1. Introduction

Resistance training, also known as strength or weight training, is becoming more popular and widely used nowadays by a large number of people with a diversity of aims and goals.[1,2] Many modes and methods of resistance training exist and a multitude of variables can be adjusted in order to improve performance and physiological adaptations.[3,4] Most research on resistance training has used free weights and weight stack machines,[1,5] considered in this systematic review as gravity-dependent (GD) resistance training.

GD resistance exercises involve sequences of concentric, isometric and eccentric actions. During GD resistance exercises, a person's ability to perform a maximal concentric-isometric-eccentric cycle is limited by the force-velocity relationship.[6] When the concentric-isometric-eccentric cycle is performed during GD training bouts, muscles are capable of achieving greater absolute forces during

* Corresponding author.
E-mail address: jordi.vicensb@cadscrits.udg.edu (J. Vicens-Bordas).

https://doi.org/10.1016/j.jsams.2017.10.006
1440-2440/

eccentric than concentric actions,[7] therefore the eccentric phase is considerably under-loaded as it is limited by the load lifted during the concentric phase.[8] Eccentric actions using supramaximal loads, that is, loads greater than 1 repetition maximum (RM), is a potent stimulus for enhancements in neural and muscular adaptations[9] and could be considered crucial for optimising the effects of resistance training.[10–13] Accentuated eccentric training can be produced using GD devices, but a third-party assistance is required which may be a limitation in many circumstances. Unquestionably, neural and muscular adaptations and the rate of their development depend on the mode and method of training, initial training status, and the muscle group investigated.[1,14]

Berg and Tesch[15] introduced the first inertial flywheel resistance (FW) device for space travellers exposed to non-gravity environments.[16,17] Since then, FW resistance training has been used in detrained populations,[18] disabled populations,[19] healthy adults[20–23] and also amateur and semi-professional athletes.[24–28] When using FW resistance devices, the rotation of the devices' flywheel is initiated by a concentric muscle action – unwinding the flywheel's strap – followed by an eccentric muscle action – rewinding the flywheel's strap –, immediately producing subsequent concentric-eccentric cycles. The force applied in the eccentric action to bring the flywheel to a stop will rely on the kinetic energy generated during the concentric action and also the strategy to apply force to the last third of the eccentric action.[15] Hence, FW resistance devices allow for maximal concentric force throughout the range of motion and short periods of greater eccentric than concentric force, provided maximal effort and the appropriate technique are employed.[20,29] Moreover, the inertia used during the FW resistance exercise will alter the force, power and work relationship, affecting also the use of the stretch-shortening cycle during the coupled concentric-eccentric actions.[30] Finally, compared to isotonic loading (e.g. gravity-dependent), inertial loading ensures accommodated resistance, which permits maximal forces to be produced from the very first repetition and force decline throughout the set.[31] In comparison, the maximal muscle activation during gravity-dependent exercises seems to be present at contraction failure or "sticking point"[32] where a third-party assistance may be needed.

It has been shown that FW resistance training is effective in producing early gains and combating the deleterious effects in muscle mass and strength during simulated microgravity and bed rest conditions[17,33,34] and in chronic stroke patients.[19] Likewise, marked maximum voluntary isometric contractions improvements,[21] and early gains in muscle hypertrophy have been promoted in adults with only 5 weeks of training.[20,35,36] Some studies have found FW resistance training to be effective in injury prevention[27,37] and rehabilitation.[38,39] In addition, performance improvements[40] and a potentiation effect[28] have also been promoted following training with FW resistance training devices in trained individuals. Moreover, it has been shown that a combination of different FW exercises[25] or a combination of FW exercises with superimposed vibration enhances cutting performance in soccer players.[26] Considering that most daily activities and human motions (e.g. walking, running, climbing and lifting) include coupled concentric and eccentric muscle actions, involving the stretch-shortening cycle,[41,42] FW resistance training enables athletes to emphasize the eccentric phase of the action using a specific movement pattern with no need of a third party-assistance, compared to other training modes, which may optimally contribute to enhanced performance adaptations.[25,26,30] Although a recent systematic review[43] has been published comparing FW resistance training and GD resistance training for improving muscle strength, this current study is the first study to provide Level 1 evidence, solely based upon randomised controlled trials, on the topic. Hence, at this point it is not known whether FW resistance training is superior in improving performance and physiological adaptations when compared to GD resistance training.

The primary aim of this systematic review was to determine if inertial flywheel resistance training is superior to gravity-dependent resistance training in improving muscle strength. The secondary aim of this review was to estimate whether inertial flywheel resistance training is superior to gravity-dependent resistance training in improving other muscular adaptations, such as muscle structure, muscle activation and/or muscle histology.

2. Methods

The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA)[44] was used as a guideline for reporting of this study. Prior to the search, a review protocol based on PRISMA-P[45] was completed and registered at PROSPERO (ID = CRD42015020337). The review protocol was updated during the review process and is publically available at http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015020337.

MEDLINE, Scopus, SPORTDiscus, Web of Science and Cochrane Central Register of Controlled Trials (CENTRAL) were electronically searched with no publication date restrictions. The search included articles prior to 3 November 2016. Two blocks of keywords related to (1) inertial flywheel resistance device and (2) training intervention composed the search strategy. The complete search strategy can be seen in the supplementary material. The searches were customized to accommodate the layout and characteristics of each search engine and the application of additional free text words were based on the coverage of subject terms. A hand-search of the reference lists of relevant articles was also conducted for other potential relevant References.

Titles and abstracts identified in the search were downloaded into Mendeley Desktop (Glyph & Cog) cross references and duplicates were deleted. All publications potentially relevant for inclusion were independently assessed for inclusion by two reviewers (JVB and EE) and full texts were obtained if necessary. Any discrepancies were resolved during a consensus meeting, and a third reviewer was available if needed. Data from randomised (RCTs) and non-randomised (non-RCTs) controlled trials were included. We included studies with humans that participated into a resistance training intervention using an FW resistance device, as the sole intervention for the studied muscle group, and a comparator of GD resistance device. Studies had to report a measure of muscle strength as outcome. Whenever several publications reported data from the same trial, the "primary publication" was used. Only full text publications in English were considered.

For primary outcome, changes in muscle strength, such as maximal voluntary isometric and/or dynamic force (N), torque (Nm, Nm/kg, Nm/cm^2), power (W, W/kg, W/cm^2) and/or rate of force development (N/s) were considered. For secondary outcomes, changes in: muscle structure, such as muscle size measured as cross-sectional area (cm^2), muscle volume (cm^3 or mL), signal intensity (mean grey value), fascicle length (mm) and/or pennation angle (degrees); muscle activation, such as voluntary activation measured as electromyographic activity (μV, mV, %EMG$_{max}$); muscle histology, such as muscle proteins involved in hypertrophic signalling or substrate breakdown (mmol/kg dry wt, mmol kg^{-1} min^{-1}), water content proportion (%), and/or muscle fiber distribution (proportion fiber types (%), fiber CSA (μm); and possible adverse events as a result of the intervention, such as pain, discomfort or muscle soreness were considered.

Two reviewers (JVB and EE) independently extracted data using a specifically designed standardized form (see supplementary material). General study information, participants and intervention

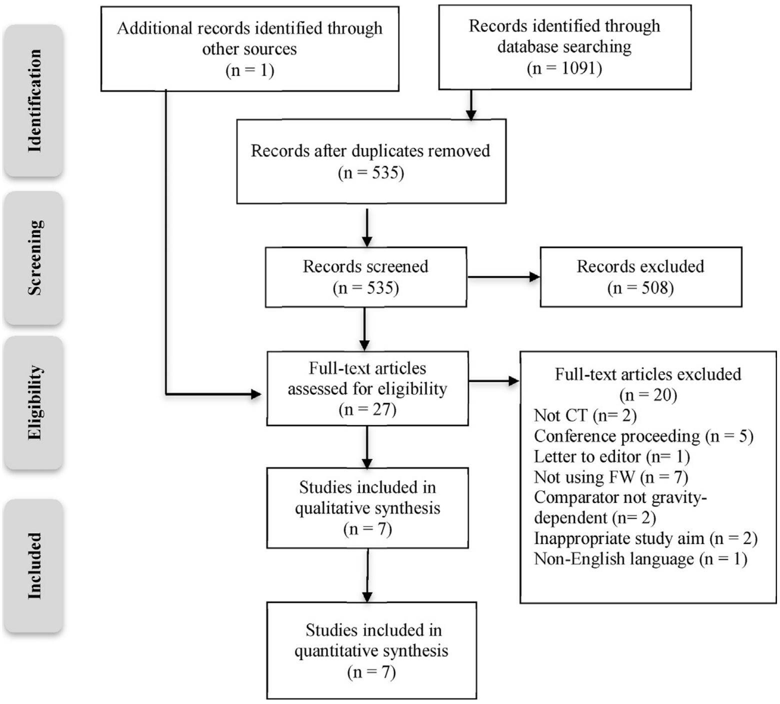


Fig. 1. Flow chart of included studies.

characteristics, and outcome measures were extracted. If data were not available from tables or the result section, the first author of the systematic review requested the missing data from the author(s). If the authors did not have access to their data, data on outcome measures were extracted from figures and graphs using AutoCAD 2015 (Autodesk, Inc., USA) by one author (JV). Another author (EE) verified the validity of the data extraction.

The studies included were assessed for the risk of bias by two independent raters (JVB and EE), with any disagreements resolved by consultation with a third party (KT). An assessment of the methodological quality was not implemented, as no evidence for such appraisals and judgments exists and therefore can be confusing when interpreting the results.[46] Using quality scales and summary scores is considered problematic, due to substantial variations between items and dimensions in scales covered, with little support relating to the internal validity of these evaluations.[47]

When assessing the RCTs mandatory bias items, the 'Cochrane Collaboration's tool for assessing risk of bias in randomised trials'[48] was used. Each bias domain was judged as high, low or unclear and provides a quote from the study report together with a justification for the judgment in the 'Risk of bias' table. When assessing the non-RCTs mandatory bias items, the 'Risk Of Bias in Non-Randomised Studies – of Interventions (ROBINS-I)'[49] was used. The ROBINS-I includes signalling questions alongside free-text boxes within each domain of bias to facilitate the judgements about the risk of bias. Each domain was judged as (1—low risk of bias; 2—moderate risk of bias; 3—serious risk of bias; 4—critical risk of bias; and, 5—no information). The risks of bias judgments were summarized across all studies included for each of the domains listed. Where information on risk of bias relates to unpublished data or correspondence with a trial list, it was noted in the 'Risk of bias' table.

With three or more RCTs included, we performed meta-analysis (primary analysis) using Review Manager Version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). For the primary outcome, changes in muscle strength, intervention effects were calculated using standardised mean differences (SMD) with 95% confidence intervals (CI), since all data were continuous. The mean change scores and standard deviations of the change scores from the intervention and control groups were used to calculate the SMD. If the standard deviations of the change scores were not reported, these were calculated using the formula,[46] where correlation coefficients were conservatively set at 0.5.[50] A positive SMD represents an effect in favour of FW resistance training interventions and a negative SMD an effect in favour of GD resistance training interventions. Effect sizes were categorised as small (0.2), medium (0.5) or large (0.8 or greater).[51] Statistical heterogeneity was explored using chi-squared statistic and visual inspection of the forest plot; and inconsistency was calculated using I^2 statistic. The chi-squared and I^2 statistics describe heterogeneity or homogeneity of the comparisons with $p < 0.05$ indicating heterogeneity.[52] A random-effects model was selected for the analysis.

With three or more non-RCTs included we performed meta-analyses (secondary analyses) on the primary outcome – changes in muscle strength –. Whenever three or more RCTs and non-RCTs reported data on secondary outcomes – changes in other muscular adaptations –, meta-analyses were performed.

The within-groups effect sizes and 95%CI on measures of strength and other muscular adaptations were calculated (post-hoc analyses) in order to analyse the magnitude of the differences within groups. Effect sizes were calculated for each study using the Hedges and Olkin's g and using the correction factor for small samples.[53] A positive effect size translates to positive adaptations to training.

3. Results

The initial search identified 1091 unique references (Fig. 1). One additional record was identified through examination of reference lists and citations of relevant articles. After identification of duplicates, 535 titles and abstracts were screened. Twenty-seven studies remained for further full text analysis. Subsequently, 20 studies

Table 1a
Characteristics of the included randomised controlled trials.

Study	Population N (m/f); age	Group: exercise (equipment)	Primary outcomes	Secondary outcomes	Results
Greenwood et al.[39]	History of knee injury FW 15 (9/6) GD 14 (7/7) 37 ± 13 years	FW: knee extension (Yoyo Technology Inc, Sweden) GD: knee extension (Health and Leisure, UK)	MVIC at 80° (N) CON and ECC peak force at 60° s^{-1} and CON at 180° s^{-1} (N) Peak power (W)	CSA (cm^2) Central neural activation (twitch superimposition)	MVIC: no differences between groups CON and ECC peak force (60° s^{-1}): No differences between groups CON and ECC peak force (180° s^{-1}): No differences between groups Peak power: no differences between groups CSA: no differences between groups Central neural activation: no differences between groups[$]
Onambélé et al.[54]	Healthy older subjects FW 12 (6/6) GD 12 (6/6) 69.9 ± SD 1.3 years	FW: knee extension (Yoyo Technology Inc, Sweden) GD: knee extension (Technogym, Italy)	MVIC at 90° (Nm) Peak isokinetic power (W) at 180° s^{-1}	EMG-RMS (mV)	MVIC: no differences between groups Peak power: Significant differences in favour to FW[*] EMG-RMS: no differences between groups
de Hoyo et al.[22]	Healthy and physically active subjects FW 11 male GD 12 male 22 ± SD 2 years	FW: front step on inertial device (Sport Teach & Tools, Spain) GD: half-squat on smith machine (FITLAND, Spain)	MVIC at 90° (N)		MVIC: no differences between groups

CON: concentric; CSA: cross-sectional area; ECC: eccentric; EMG-RMS: electromyographic activity root-mean square; FW: flywheel; GD: gravity-dependent; MVIC: maximum voluntary contraction; (m/f): (male/female).
[*] Significance at $p < 0.05$.
[$] Significant differences at baseline ($p < 0.05$).

Table 1b
Characteristics of the included non-randomised controlled trials.

Study	Population N (m/f); age	Exercise (equipment)	Primary outcomes	Secondary outcomes	Results
Caruso et al.[23]	Healthy untrained subjects FW 11 male; 58.6 ± SEM 2.2 GD 12 male; 56.2 ± SEM 2.8	FW: seated leg press (Yoyo Technology Inc, Sweden) GD: standard leg press	CON and ECC peak torque at 93° s^{-1} and 278° s^{-1} (Nm)	Leg muscle mass (kg)	CON and ECC peak torque (93° s^{-1}): no differences between groups CON and ECC peak torque (278° s^{-1}): no differences between groups Leg muscle mass: no differences between groups
Caruso et al.[24]	Healthy college-age subjects FW 9 (7/2) GD 10 (7/3) Control 9 (6/3)	FW: seated leg press (Yoyo Technology Inc, Sweden) GD: standard leg press	Average peak torque 3 first reps at 180° s^{-1} (Nm)	Estimated CSA (cm^2)	Average peak torque: no differences between groups CSA: no differences between groups
Norrbrand et al.[20]	Healthy subjects FW 7 male; 39.1 ± SD 9.1 GD 8 male; 39.4 ± SD 8.1	FW: unilateral Knee extension (Yoyo Technology Inc, Sweden) GD: knee extension (World Class, Sweden)	MVIC at 90° and 120° (N) Knee extension Power (W)	Muscle volume (ml)	MVIC 90°: differences in favour to FW[*] MVIC 120°: no differences between groups
Norrbrand et al.[21]	Healthy subjects FW 9 male; 38.8 ± SD 5 GD 8 male; 39.4 ± SD 8.1	FW: unilateral Knee extension (Yoyo Technology Inc, Sweden) GD: unilateral Knee extension (World Class, Sweden)	MVIC at 120° (N) RFD	EMG-RMS (mV)	MVIC: non-significant differences EMG-RMS: differences on eccentric EMG in favour to FW[*]

CON: concentric; CSA: cross-sectional area; ECC: eccentric; EMG-RMS: electromyographic activity root-mean square; FW: flywheel; GD: gravity-dependent; MVIC: maximum voluntary contraction; RFD: rate of force development; (m/f): (male/female).
[*] Significance at $p < 0.05$.

were excluded. The most common reason for exclusion (7 studies) was that an FW resistance device was not used. Five references were conference proceedings and were also excluded. In the end, 7 studies were included in the final review process.

The most relevant characteristics of the included studies are summarized in Table 1a for RCTs and Table 1b for non-RCTs. For an overview of the training parameters used in each study, see Supplementary Table 1a for RCTs and Supplementary Table 1b for non-RCTs.

Three individually RCTs[22,39,54] involving 76 participants are included in the review. Two RCTs[39,54] assessed both male and females while the other RCT[22] assessed only males. Participants in the RCTs were identified as either untrained[54] or physically active with limited experience in resistance training (less than 3 months).[22] The ages differed between studies, from young[22] to old[54] and a mixture of ages.[39] One study[39] included participants with a history of knee injury and did not report the training age or experience of the participants. Exercise selection for both the FW and GD groups was the same (knee extension).[39,54] Instead, the exercise differed between interventions in the other study (front step (FW) and half squat (GD)).[22] The duration of resistance training programs diverged from 6 to 12 weeks. The load used during GD interventions were 10 RM,[39] 80% of 1 RM[54] and also one study used the load that elicited the maximum power output.[22] During FW interventions, one study did not mention the inertia used during training,[39] while the others used the inertia that elicited the maximum power output.[22,54]

Four non-RCTs trials[20,21,23,24] comprising 83 participants are included in the review. Three of them[20,21,23] assessed only male while the other[24] assessed both males and females. One study did not report participant's age[24] while the others were performed in middle-aged and old subjects. Participants in the non-RCT studies were identified as either healthy untrained[23] or healthy.[20,21,24] Exercise selection for both the FW and GD groups was the same, leg press[23,24] or knee extension.[20,21] The duration of resistance training programs diverged from 5 to 10 weeks. The load used during GD interventions ranged from 7 RM to 10 RM. During FW interventions, two studies did not mention the inertia used during training,[23,24] while the other two used a 4.2 kg flywheel with a moment inertia of 0.11 kg m.[2,20,21]

The authors of the three RCTs[22,39,54] were contacted to provide extra information on the study's data. Only data from one author could be obtained,[39] one was extracted from the graphs[22] and for the other, standard deviations from change scores were calculated.[54]

Results of the risk of bias assessment are presented in Supplementary Table 2a for RCTs and Supplementary Table 2b for non-RCTs. For RCTs, the main source of bias was blinding of participants and outcome assessors. For the non-RCTs, moderate bias was found relating to confounding factors inherent to lack of randomisation, and also the blinding of outcome assessors and participants.

The three RCTs were included in the primary analysis.[22,39,54] In the primary analysis for the primary outcome, changes in muscle strength (MVIC), the pooled results showed no difference (SMD = −0.05; 95%CI −0.51 to 0.40; p = 0.82; Fig. 2a). No heterogeneity was present $I^2 = 0\%$ in this analysis.

The four non-RCTs[20,21,23,24] were included in the secondary analyses for the primary outcome (changes in muscle strength). Two analyses were performed which only differed in the inclusion of either the concentric or the eccentric peak torque from Caruso et al.[23] The pooled results showed no difference in any of the secondary analyses (SMD = 0.02; 95%CI −0.45 to 0.49; p = 0.93; $I^2 = 0\%$; Fig. 2b; and SMD = 0.03; 95%CI −0.43 to 0.50; p = 0.88; $I^2 = 0\%$; Fig. 2c). Finally, analyses on secondary outcomes could not be performed for any RCT or non-RCT due to heterogeneity of outcomes between studies.

Within-groups effect sizes were calculated (post-hoc analyses) for each study in order to present the magnitude of the effects of each training intervention on primary and secondary outcomes for RCTs and non-RCTs. On primary outcome for RCTs (Supplementary Table 3a), small to large effects were present on MVIC and concentric and eccentric peak force for both FW and GD interventions. In addition, small effects were present on peak power for both FW and GD interventions. On secondary outcomes, medium effects were present for both FW and GD interventions. For the FW group, a large effect on central neural activation but a small negative effect on EMG-RMS was present, whereas small effects were present for GD in both central neural activation and EMG-RMS. For non-RCTs (Supplementary Table 3b), on primary outcome, small and medium effect sizes were present on MVIC, whereas no effect or small effects were present for concentric and eccentric peak torque. On muscle volume and CSA, no effects were present for GD and small effects for FW.

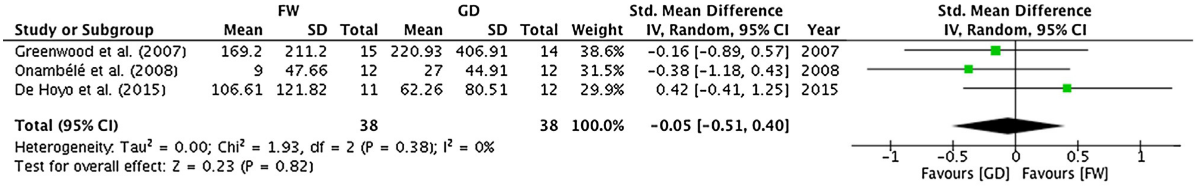
4. Discussion

In this systematic review and meta-analyses where the primary aim was to determine whether FW resistance training was superior to GD resistance training in improving muscle strength, superiority of FW compared to GD resistance training could not be documented.

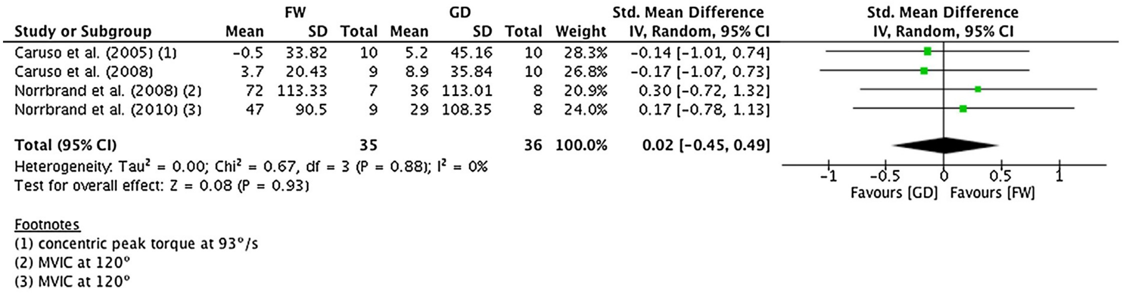
A recent systematic review including a meta-analysis by Maroto-Izquierdo et al.[43] was published in 2017. The study investigated muscle size and functional adaptations to FW resistance training compared to GD resistance exercise in athletes and healthy subjects. While this study claimed to compare FW resistance training against GD resistance training on RCTs, most of the studies included in the review did not use GD resistance training group as a comparator.[55] To the best of our knowledge, the present study is therefore the first systematic review and meta-analysis to exclusively provide Level 1 evidence of the efficacy of FW resistance training compared to GD resistance training on muscle strength and other muscular adaptations.

Our study reveals that for maximal voluntary isometric contraction (MVIC), no differences are present in RCTs between FW and GD resistance training (SMD = −0.05; 95%CI −0.51 to 0.40). Unfortunately, concentric and eccentric muscle strength measures could not be included in the meta-analyses of RCTs, as only one study[39] covered this outcome. However, two non-RCTs[23,24] were included in the secondary analyses using measures of concentric and eccentric muscle strength. The pooled results for non-RCTs showed no differences on muscle strength in any of the secondary analyses (SMD = 0.02; 95%CI −0.45 to 0.49 and SMD = 0.03; 95%CI −0.43 to 0.50). Although CIs for these estimates overlapped both groups, suggesting uncertainty in the point estimate, we interpret these findings as being unclear and that more data are required to improve confidence in the interpretation of these outcomes.

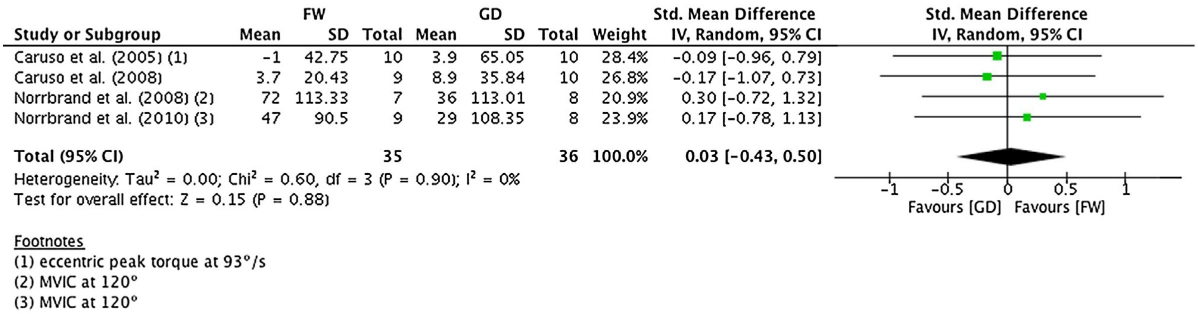
Based on post-hoc analyses, small to large within-group effect sizes were found in RCTs for both FW and GD resistance training interventions on muscle strength measures. Those results indicate similar improvements in strength can be achieved using both resistance training modes. In non-RCTs greater within-group effect sizes were found for FW resistance training on MVIC strength measures but greater within-group effect sizes were found for GD on concentric and eccentric measures of strength. The diversity on the improvements could either be due to a lack of randomization, the heterogeneity between participants or even differences in exercise selection and loading used in each study. Nonetheless, those results only represent within-group effect sizes and comparisons between FW and GD cannot be drawn from these post-hoc analyses. Other studies in the literature not using an active control group, showed improvements on MVIC of 39%[36] and 10–12%[56] following 5 weeks of FW resistance training. Askling et al.[37] found improvements in both concentric and eccentric isokinetic strength at $60^\circ\ s^{-1}$, after a FW resistance training intervention on the hamstring muscle group. Fernandez-Gonzalo et al.[18] found a 25% and 20% improvement on 1 RM for men and women respectively, after 6 weeks of training on a FW supine squat device without a control group. A previous systematic review with meta-analyses[10] found no differences in MVIC improvements between participants exercising either eccentrically or concentrically suggesting both training stimulus produce similar MVIC adaptations. Roig and colleagues[10] showed that eccentric training is more effective at increasing eccentric strength and muscle mass than concentric training. The large effect size found in Greenwood et al.[39]



a: Strength changes (MVIC) of RCTs forest plot



b: Strength changes of non-RCTs forest plot (concentric peak torque at $93^{o}s^{-1}$)



c: Strength changes of non-RCTs forest plot (eccentric peak torque at $93^{o}s^{-1}$)

Fig. 2. (a) Strength changes (MVIC) of RCTs forest plot. (b) Strength changes of non-RCTs forest plot (concentric peak torque at $93^{\circ}\,s^{-1}$). (c) Strength changes of non-RCTs forest plot (eccentric peak torque at $93^{\circ}\,s^{-1}$).

on eccentric peak torque at $60^{\circ}\,s^{-1}$ after FW resistance training might indicate a great stimulus for eccentric adaptations. However, this point remains unclear at this moment since meta-analyses of eccentric measures could not be performed due to lack of studies covering this outcome and eccentric adaptations therefore need further attention in future investigations.

Meta-analysis of other muscular adaptations could not be implemented due to the heterogeneity of type of outcomes from the included studies. Based on post-hoc analyses, both GD and FW resistance training showed medium within-group effect sizes in the increment of the vastus lateralis CSA.[39] For non-RCTs, no within-group effects were found for GD resistance training but small effects were found for FW resistance training in CSA and muscle volume. Similar increases were found in healthy men and women after FW resistance training, such as a 5% in leg muscle mass,[18] a 6% in muscle volume[35] and a 7% in CSA.[36] Other muscular adaptations such fascicle length and pennation angles have been found to be a 10% and 8% increase respectively after 5 weeks of FW resistance training.[36] As it has been demonstrated,[57–60] concentric loading leads to greater muscle pennation angles by adding sarcomeres in parallel, and eccentric loading leads to longer fascicles lengths and decreased pennation angles by adding sarcomeres in series, with disparities between muscle groups. Pennation angles and fascicle lengths adaptations after FW resistance training remain unclear at present. In addition, on behalf of muscle volume and muscle mass, FW resistance training shows some potential but no comparison against GD resistance training can be made at this point. Importantly, considerations regarding (1) the equipment, such as magnetic resonance imaging, computed tomography or ultrasound, used to measure other muscular adaptations, (2) the methodology and (3) reliability of the measures from practitioners are needed in order to obtain valid results and be able to compare muscle adaptations after training interventions.[61]

Based on post-hoc analyses, one of the RCTs[54] analysed the adaptations on muscle activation using EMG-RMS, while another RCT[39] analysed adaptations on the central neural activation using the twitch superimposition technique. While Greenwood et al.[39] found greater central neural activation, Onambélé et al.[54] found reduced muscle activation after FW resistance training. The only non-RCT analysing muscle activation[21] found that FW resistance training increased the vastus lateralis activation (EMG-RMS) while GD resistance training did not. The same study also showed that muscle activity was angle-specific depending on exercise mode. During FW resistance training, the greater muscle activity was present at the eccentric phase (almost isometric at 90°), instead during GD resistance training, the greater muscle activity was present at the concentric phase near full extension at 150°. This greater eccentric muscle activation is indicative of greater mechanical tension during the eccentric phase when using FW compared to GD resistance training, resulting in more robust stimulus promoting enhanced protein synthesis and eventually leading to greater muscle hypertrophy.[21] However, other factors such as nutrition, recovery and the training methods used also need to be considered when assessing muscle hypertrophy.[4,62,63] Other studies confirm the greater muscle activation during FW resistance training[29,36,64] while others do not.[35] Although muscle activity will not explain muscle hypertrophy[65,66] it will explain the intensity of a muscle's contraction. Hence, a combination of muscle activity and muscle hypertrophy outcomes will be needed to monitor both training adaptations.

Although meta-analyses of performance adaptations such as jumping or sprinting were not the aim of this study, two RCTs[22,39] and one non-RCT[24] reported outcomes on performance adaptations. Greenwood et al.[39] showed no difference between groups on vertical jumping performance. de Hoyo et al.[22] showed greater effects after GD than FW resistance training in the countermovement jump and similar effects in change of direction sprints. Finally, Caruso et al.[24] showed similar adaptations on jumping performances, but the FW group tended to be better on depth jumps involving the longer stretch-shortening cycle, while the GD group tended to be better on a four-jump test, where faster stretch-shortening cycle is needed. It has to be mentioned that this study combined the leg press exercise with a calf press exercise, which may have contributed to the greater performance in a four-jump test. Therefore, further studies giving information regarding the loading protocol (inertia) and the strategy used to stop the FW may be needed in order to better understand adaptations to jumping performance. Other studies in the literature have shown the efficacy of FW resistance training on performance adaptations.[25,27,37] Although more evidence is needed, the potential application of FW resistance training to performance adaptations is promising because of the high level of specificity that can be applied during some tasks. Accordingly, in some sports where decelerations and changes of directions are crucial, FW devices allow to include both bilateral and unilateral exercises with an eccentric emphasis. Furthermore, FW devices such as conic pulleys allow for performance of exercises on a multi-planar accentuation – specifically in the sagittal and transverse planes –, in order to produce performance enhancements.[25]

While FW resistance training produces higher eccentric forces compared to GD resistance training,[21] when an appropriate strategy is used, adverse effects such as injuries or delayed onset of muscle soreness after FW resistance training have not been documented. However, as with any training mode, adverse effects such as delayed onset of muscle soreness can be present but prevented by appropriately progressing the loading scheme.[67] Even though a loading scheme for FW resistance training remains to be established, the subjects can modulate their effort during FW resistance training.[16] As FW resistance training is an accommodated resistance, it also permits to modulate the intensity during the exercise.[16] Therefore FW resistance training is considered to be a safe training mode provided that is supervised by qualified professionals and consistent with the needs, goals and abilities of the subjects.

The main limitations of this study is that a very few RCTs on this subject are published and that a wide range of the participants age exists in the included studies. FW resistance training is a unique training mode that is increasing its popularity among the research community. However, more studies, preferably RCTs, are needed in order to diminish the risk of bias as this will allow researchers to draw more robust conclusions. In addition, more homogeneous research on studies' outcomes, exercise interventions (exercise selection and loading) and subjects' training experience is needed to understand the efficacy of FW resistance training compared to GD resistance training. Certainly, experienced athletes in FW resistance training maximize the benefits of this training by having greater coordination and using an appropriate technique.[29] None of the interventions of the included studies lasted longer than 12 weeks. The short-term nature of those interventions may impede to draw conclusions regarding the long-term effectiveness of FW resistance training. For RCTs, the main source of bias was lack of blinding of participants and outcome assessors. For the non-RCTs, moderate biases were found relating to confounding factors inherent to lack of randomisation, and also the lack of blinding of participants and outcome assessors. Although the inclusion of non-RCTs in the review broadens the spectrum of evidence, the results from the RCTs should be considered the greatest source of evidence.[46] Another limitation of this review with meta-analyses may be the inclusion of power and rate of force development as measures of strength. However, this limitation did not affect any conclusions in relation to the primary outcome (strength), as no data on power was included in the analysis regarding the primary outcome. In the future it may be important not to include measures of strength and power in combination in future updates, and look at these physical qualities separately.

5. Conclusions

This systematic review and meta-analyses showed that inertial flywheel resistance training is not superior to gravity-dependent resistance training on enhancing muscle strength. The conclusion is based upon the current available literature where only three RCTs qualified for meta-analysis. Data for other strength variables and other muscular adaptations were insufficient to draw firm conclusions. We encourage practitioners to try to perform RCTs in order to control for confounding variables and produce a convincing body of evidence. Future research should aim to investigate eccentric strength adaptations and performance and structural adaptations in order to understand the role of inertial flywheel resistance training.

Practical implications

- Inertial flywheel resistance training is not superior to gravity-dependent resistance training for muscle strength improvements.
- Outcomes on eccentric muscle strength, muscle structural and performance adaptations comparing inertial flywheel to gravity-dependent resistance training could not be documented.

Acknowledgement

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jsams.2017.10.006.

References

1. Ratamess NA, Brent A, Evetoch T et al. Progression models in resistance training for healthy adults. *Med Sci Sports Exerc* 2009; 41(3):687–708. http://dx.doi.org/10.1249/MSS.0b013e3181915670.
2. Lloyd RS, Faigenbaum AD, Stone MH et al. Position statement on youth resistance training: the 2014 international consensus. *Br J Sports Med* 2014; 48(7):498–505. http://dx.doi.org/10.1136/bjsports-2013-092952.
3. Lesinski M, Prieske O, Granacher U. Effects and dose–response relationships of resistance training on physical performance in youth athletes: a systematic review and meta-analysis. *Br J Sports Med* 2016; 50(13):781–795. http://dx.doi.org/10.1136/bjsports-2015-095497.
4. Wernbom M, Augustsson J, Thome R. The influence of frequency, intensity, volume and mode of strength training on whole muscle cross-sectional area in humans. *Sport Med* 2007; 37(3):225–264. http://dx.doi.org/10.2165/00007256-200737030-00004.
5. Kraemer WJ, Ratamess NA. Fundamentals of resistance training: progression and exercise prescription. *Med Sci Sports Exerc* 2004; 36(4):674–688. http://dx.doi.org/10.1249/01.MSS.0000121945.36635.61.
6. Hill A. The heat of shortening and the dynamic constants of muscle. *Proc R Soc B Biol Sci* 1938; 126(843):136–195. http://dx.doi.org/10.1098/rspb.1938.0050.
7. Hortobágyi T, Hill JP, Houmard JA et al. Adaptive responses to muscle lengthening and shortening in humans. *J Appl Physiol* 1996; 80(3):765–772.
8. Dudley GA, Tesch PA, Miller BJ et al. Importance of eccentric actions in performance adaptations to resistance training. *Aviat Space Environ Med* 1991; 62(6):543–550.
9. Douglas J, Pearson S, Ross A et al. Chronic adaptations to eccentric training: a systematic review. *Sport Med* 2016:1–25. http://dx.doi.org/10.1007/s40279-016-0628-4.
10. Roig M, O'Brien K, Kirk G et al. The effects of eccentric versus concentric resistance training on muscle strength and mass in healthy adults: a systematic review with meta-analysis. *Br J Sports Med* 2009; 43(8):556–568. http://dx.doi.org/10.1136/bjsm.2008.051417.
11. Aagaard P. The use of eccentric strength training to enhance maximal muscle strength, explosive force (RDF) and muscular power – consequences for athletic performance. *Open Sports Sci J* 2010; 3(1):52–55. http://dx.doi.org/10.2174/1875399X01003010052.
12. Folland JP, Williams AG. The adaptations to strength training. *Sport Med* 2007; 37(2):145–168. http://dx.doi.org/10.2165/00007256-200737020-00004.
13. Walker S, Blazevich AJ, Haff GG et al. Greater strength gains after training with accentuated eccentric than traditional isoinertial loads in already strength-trained men. *Front Physiol* 2016; 7:149. http://dx.doi.org/10.3389/fphys.2016.00149.
14. Campos GER, Luecke TJ, Wendeln HK et al. Muscular adaptations in response to three different resistance-training regimens: specificity of repetition maximum training zones. *Eur J Appl Physiol* 2002; 88(1–2):50–60. http://dx.doi.org/10.1007/s00421-002-0681-6.
15. Berg HE, Tesch PA. A gravity-independent ergometer to be used for resistance training in space. *Aviat Space Environ Med* 1994; 65(8):752–756.
16. Tesch PA, Fernandez-gonzalo R, Lundberg TR. Clinical applications of iso-inertial. *Resist Exerc* 2017; 8. http://dx.doi.org/10.3389/fphys.2017.00241.
17. Berg HE, Tesch PA. Force and power characteristics of a resistive exercise device for use in space. *Acta Astronaut* 1998; 42(1–8):219–230. http://dx.doi.org/10.1016/S0094-5765(98)00119-2.
18. Fernandez-Gonzalo R, Lundberg TR, Alvarez-Alvarez L et al. Muscle damage responses and adaptations to eccentric-overload resistance exercise in men and women. *Eur J Appl Physiol* 2014; 114(5):1075–1084. http://dx.doi.org/10.1007/s00421-014-2836-7.
19. Fernandez-Gonzalo R, Fernandez-Gonzalo S, Turon M et al. Muscle, functional and cognitive adaptations after flywheel resistance training in stroke patients: a pilot randomized controlled trial. *J Neuroeng Rehabil* 2016; 13(1):37. http://dx.doi.org/10.1186/s12984-016-0144-7.
20. Norrbrand L, Fluckey JD, Pozzo M et al. Resistance training using eccentric overload induces early adaptations in skeletal muscle size. *Eur J Appl Physiol* 2008; 102(3):271–281. http://dx.doi.org/10.1007/s00421-007-0583-8.
21. Norrbrand L, Pozzo M, Tesch PA. Flywheel resistance training calls for greater eccentric muscle activation than weight training. *Eur J Appl Physiol* 2010; 110(5):997–1005. http://dx.doi.org/10.1007/s00421-010-1575-7.
22. de Hoyo M, Sañudo B, Carrasco L et al. Effects of traditional versus horizontal inertial flywheel power training on common sport-related tasks. *J Hum Kinet* 2015; 47(1):155–167. http://dx.doi.org/10.1515/hukin-2015-0071.
23. Caruso JF, Hamill JL, Hernandez DA et al. A comparison of isoload and isoinertial leg press training on bone and muscle outcomes. *J Strength Cond Res* 2005; 19(3):592–598.
24. Caruso JF, Coday MA, Ramsey CA et al. Leg and calf press training modes and their impact on jump performance adaptations. *J Strength Cond Res* 2008; 22(3):766–772. http://dx.doi.org/10.1519/JSC.0b013e31816a849a.
25. Gonzalo-Skok O, Tous-Fajardo J, Valero-Campo C et al. Eccentric overload training in team-sports functional performance: constant bilateral vertical vs. variable unilateral multidirectional movements. *Int J Sports Physiol Perform* 2016; 12(7):951–958 https://doi.org/10.1123/ijspp.2016-0251.
26. Tous-Fajardo J, Gonzalo-Skok O, Arjol-Serrano JL et al. Enhancing change-of-direction speed in soccer players by functional inertial eccentric overload and vibration training. *Int J Sports Physiol Perform* 2016; 11(1):66–73. http://dx.doi.org/10.1123/ijspp.2015-0010.
27. de Hoyo M, Pozzo M, Sañudo B et al. Effects of a 10-week in-season eccentric-overload training program on muscle-injury prevention and performance in junior elite soccer players. *Int J Sports Physiol Perform* 2015; 10(1):46–52. http://dx.doi.org/10.1123/ijspp.2013-0547.
28. de Hoyo M, de la Torre A, Pradas F et al. Effects of eccentric overload bout on change of direction and performance in soccer players. *Int J Sports Med* 2014; 36(4):308–314. http://dx.doi.org/10.1055/s-0034-1395521.
29. Tous-Fajardo J, Maldonado RA, Quintana JM et al. The flywheel leg-curl machine: offering eccentric overload for hamstring development. *Int J Sports Physiol Perform* 2006; 1(3):293–298.
30. Martinez-Aranda LM, Fernandez-Gonzalo R. Effects of inertial setting on power, force, work and eccentric overload during flywheel resistance exercise in women and men. *J Strength Cond Res* 2016:1. http://dx.doi.org/10.1519/JSC.0000000000001635.
31. Norrbrand L. *Acute and early chronic responses to resistance exercise using flywheel or weights*, Mid Sweden University, 2010.
32. Kompf J, Arandjelović O. Understanding and overcoming the sticking point in resistance exercise. *Sport Med* 2016; 46(6):751–762. http://dx.doi.org/10.1007/s40279-015-0460-2.
33. Alkner BA, Berg HE, Kozlovskaya I et al. Effects of strength training, using a gravity-independent exercise system, performed during 110 days of simulated space station confinement. *Eur J Appl Physiol* 2003; 90(1-2):44–49. http://dx.doi.org/10.1007/s00421-003-0850-2.
34. Alkner BA, Tesch PA. Efficacy of a gravity-independent resistance exercise device as a countermeasure to muscle atrophy during 29-day bed rest. *Acta Physiol Scand* 2004; 181(3):345–357. http://dx.doi.org/10.1111/j.1365-201X.2004.01293.x.
35. Tesch PA, Ekberg A, Lindquist DM et al. Muscle hypertrophy following 5-week resistance training using a non-gravity-dependent exercise system. *Acta Physiol Scand* 2004; 180(1):89–98. http://dx.doi.org/10.1046/j.0001-6772.2003.01225.x.
36. Seynnes OR, de Boer M, Narici MV. Early skeletal muscle hypertrophy and architectural changes in response to high-intensity resistance training. *J Appl Physiol* 2006; 102(1):368–373. http://dx.doi.org/10.1152/japplphysiol.00789.2006.
37. Askling C, Karlsson J, Thorstensson A. Hamstring injury occurrence in elite soccer players after preseason strength training with eccentric overload. *Scand J Med Sci Sport* 2003; 13(4):244–250. http://dx.doi.org/10.1034/j.1600-0838.2003.00312.x.
38. Romero-Rodriguez D, Gual G, Tesch PA. Efficacy of an inertial resistance training paradigm in the treatment of patellar tendinopathy in athletes: a case-series study. *Phys Ther Sport* 2011; 12(1):43–48. http://dx.doi.org/10.1016/j.ptsp.2010.10.003.
39. Greenwood J, Morrissey MC, Rutherford OM et al. Comparison of conventional resistance training and the fly-wheel ergometer for training the quadriceps muscle group in patients with unilateral knee injury. *Eur J Appl Physiol* 2007; 101(6):697–703. http://dx.doi.org/10.1007/s00421-007-0548-y.
40. Gual G, Fort-Vanmeerhaeghe A, Romero-Rodríguez D et al. Effects of in-season inertial resistance training with eccentric overload in a sports population at risk for patellar tendinopathy. *J Strength Cond Res* 2016; 30(7):1834–1842. http://dx.doi.org/10.1519/JSC.0000000000001286.
41. Nicol C, Avela J, Komi PV. The stretch-shortening cycle: a model to study naturally occurring neuromuscular fatigue. *Sports Med* 2006; 36(11):977–999.
42. Cormie P, McGuigan MR, Newton RU. Changes in the eccentric phase contribute to improved stretch-shorten cycle performance after training. *Med Sci Sports Exerc* 2010; 42(9):1731–1744. http://dx.doi.org/10.1249/MSS.0b013e3181d392e8.
43. Maroto-Izquierdo S, García-López D, Fernandez-Gonzalo R et al. Skeletal muscle functional and structural adaptations after eccentric overload flywheel resistance training: a systematic review and meta-analysis. *J Sci Med Sport* 2017; 20(10):943–951 https://doi.org/10.1016/j.jsams.2017.03.004.
44. Liberati A, Altman DG, Tetzlaff J et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Ann Intern Med* 2009; 151(4). http://dx.doi.org/10.1371/journal.pmed.1000100.
45. Shamseer L, Moher D, Clarke M et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2015; 349(3):g7647. http://dx.doi.org/10.1136/bmj.g7647.
46. Higgins JPT, Green S, editors. *Cochrane handbook for systematic reviews of interventions version 5.1.0.*; 2011. www.handbook.cochrane.org.
47. Jüni P, Altman DG, Egger M. Systematic reviews in health care: assessing the quality of controlled clinical trials. *BMJ* 2001; 323(7303):42–46.
48. Higgins JPT, Altman DG, Gotzsche PC et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011; 343:d592. http://dx.doi.org/10.1136/bmj.d5928.
49. Sterne JA, Hernán MA, Reeves BC et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016:i4919. http://dx.doi.org/10.1136/bmj.i4919.

50. Follmann D, Elliott P, Suh I et al. Variance imputation for overviews of clinical trials with continuous response. *J Clin Epidemiol* 1992; 45(7):769–773. http://dx.doi.org/10.1016/0895-4356(92)90054-Q.
51. Cohen J. *Statistical Power Analysis for the Behavioral Sciences*, 2nd ed. USA, Lawrence Erlbaum Associates, 1988.
52. Higgins JPT, Thompson SG, Deeks JJ et al. Measuring inconsistency in meta-analyses. *BMJ Br Med J* 2003; 327(7414):557–560. http://dx.doi.org/10.1136/bmj.327.7414.557.
53. Hedges LV, Olkin I. Statistical methods for meta-analysis. *J Educ Stat* 1988; 13(1):75. http://dx.doi.org/10.2307/1164953.
54. Onambélé GL, Maganaris CN, Mian OS et al. Neuromuscular and balance responses to flywheel inertial versus weight training in older persons. *J Biomech* 2008; 41(15):3133–3138. http://dx.doi.org/10.1016/j.jbiomech.2008.09.004.
55. Vicens-Bordas J, Esteve E, Fort-Vanmeerhaeghe A et al. Letter to the Editor: skeletal muscle functional and structural adaptations after eccentric overload flywheel resistance training: a systematic review and meta-analysis. *J Sci Med Sport* 2017. http://dx.doi.org/10.1016/j.jsams.2017.09.001 [ahead of print].
56. Tesch PA, Trieschmann JT, Ekberg A. Hypertrophy of chronically unloaded muscle subjected to resistance exercise. *J Appl Physiol* 2004; 96(4):1451–1458. http://dx.doi.org/10.1152/japplphysiol.01051.2003.
57. Reeves ND, Maganaris CN, Longo S et al. Differential adaptations to eccentric versus conventional resistance training in older humans. *Exp Physiol* 2009; 94(7):825–833. http://dx.doi.org/10.1113/expphysiol.2009.046599.
58. Franchi MV, Atherton PJ, Reeves ND et al. Architectural, functional and molecular responses to concentric and eccentric loading in human skeletal muscle. *Acta Physiol (Oxf)* 2014; 210(3):642–654. http://dx.doi.org/10.1111/apha.12225.
59. Timmins RG, Ruddy JD, Presland J et al. Architectural changes of the biceps femoris long head after concentric or eccentric training. *Med Sci Sports Exerc* 2016; 48(3):499–508 https://doi.org/10.1249/MSS.0000000000000795.
60. Blazevich AJ, Cannavan D, Coleman DR et al. Influence of concentric and eccentric resistance training on architectural adaptation in human quadriceps muscles. *J Appl Physiol* 2007; 103(5):1565–1575. http://dx.doi.org/10.1152/japplphysiol.00578.2007.
61. Kwah LK, Pinto RZ, Diong J et al. Reliability and validity of ultrasound measurements of muscle fascicle length and pennation in humans: a systematic review. *J Appl Physiol* 2013; 114(2013):761–769. http://dx.doi.org/10.1152/japplphysiol.01430.2011.
62. Schoenfeld BJ. The mechanisms of muscle hypertrophy and their application to resistance training. *J Strength Cond Res* 2010; 24(10):2857–2872. http://dx.doi.org/10.1519/JSC.0b013e3181e840f3.
63. Schoenfeld BJ. Potential mechanisms for a role of metabolic stress in hypertrophic adaptations to resistance training. *Sport Med* 2013; 43(3):179–194. http://dx.doi.org/10.1007/s40279-013-0017-1.
64. Norrbrand L, Tous-Fajardo J, Vargas R et al. Quadriceps muscle use in the flywheel and barbell squat. *Aviat Space Environ Med* 2011; 82(1):13–19. http://dx.doi.org/10.3357/ASEM.2867.2011.
65. Earp JE, Stucchi DT, DeMartini JK et al. Regional surface electromyography of the vastus lateralis during strength and power exercises. *J Strength Cond Res* 2016; 30(6):1585–1591. http://dx.doi.org/10.1519/JSC.0000000000001405.
66. Narici MV, Hoppeler H, Kayser B et al. Human quadriceps cross-sectional area, torque and neural activation during 6 months strength training. *Acta Physiol Scand* 1996; 157(2):175–186. http://dx.doi.org/10.1046/j.1365-201X.1996.483230000.x.
67. Cheung K, Hume PA, Maxwell L. Delayed onset muscle soreness. *Sport Med* 2003; 33(2):145–164. http://dx.doi.org/10.2165/00007256-200333020-00005.