DOSE-RESPONSE OF WEEKLY RESISTANCE TRAINING VOLUME AND FREQUENCY OF MUSCULAR ADAPTATIONS IN TRAINED MALES

By

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ABSTRACT

Purpose: Debate exists over how to best manipulate resistance exercise training (RET) volume, the number of weekly sets per muscle group, to optimize muscular adaptations. A linear dose-response relationship between RET volume and hypertrophy has been proposed for ≤10-12 weekly sets. The present study aimed to understand the impact of low-to-very high weekly RET volume on muscular adaptations in trained young males over 6-weeks of RET. **Methods:** Forty-nine RET-experienced males (n=49) were randomly allocated to a LOW (n=17), moderate (MOD; n=15) or HIGH (n=17) volume group, performing 9, 18 or 27 weekly sets of bicep RET, respectively, for 6-weeks. RET was performed once (LOW) or twice (MOD and HIGH) weekly. Post-exercise protein intake was controlled and dietary intake and external training volume were recorded. Prior-to and following RET, assessments of bicep muscle thickness (MT), isometric and 1RM strength were performed. **Results:** MT significantly increased in all groups (4.4±7.7%, 8.4±9.9% and 5.6±5.0% for LOW, MOD, HIGH, respectively, P<0.05 for all) as did 1RM strength (7.6±5.6%, 11.2±5.5% and 11.7±4.3% for LOW, MOD, HIGH, respectively, P<0.05 for all). Isometric strength only significantly increased in the HIGH (8.5±15.1%, P=0.025). There were no significant differences between groups in any MT or indices of strength. **Conclusion:** Our findings demonstrate no differences in muscular adaptations to short-term RET between low-to-high weekly volumes, in trained individuals. However, given the greater number of 'non-responders' to low-volume weekly RET, it seems that moderate volume RET, performed over two weekly sessions, provides sufficient stimulus to maximize muscular adaptations.

INTRODUCTION

The importance of skeletal muscle

Skeletal muscle plays a crucial, and at times underappreciated role, in an individual's daily life. A large muscle mass, relative to total body mass, has been shown to have numerous health and lifestyle benefits. These include obesity prevention, increased insulin sensitivity and increased bone health throughout a life span (Wolfe, 2006). Skeletal muscle acts as the body's store of amino acids (AA) which can be used in times of need, such as starvation, as gluconeogenic precursors or to enhance the rate of recovery from injury or illness (Wolfe, 2006). A greater muscle mass in youth can enhance locomotion and strength to benefit sporting or physical performance whilst also providing the basis for healthy aging and a reduced mortality risk (Wolfe, 2006). It is therefore advantageous to increase skeletal muscle mass, through hypertrophy, to maximize the subsequent benefits.

Mechanisms of skeletal muscle mass enhancement through resistance training

Resistance exercise training (RET) is a well-known stimulus for increasing both hypertrophy and strength. RET creates mechanical tension and metabolic stress to activate pathways that start the muscle building process (Schoenfeld, 2010). Phillips et al. (1997) highlighted an elevation in the rate of muscle protein synthesis (MPS) and overall net protein balance (NPB) for 48 hours following a single bout of resistance exercise; thus showing a hypertrophic response. However, the consumption of post exercise protein is needed to promote long term skeletal muscle hypertrophy as long-term RET alone sees an increase in muscle protein breakdown (MPB), alongside MPS, causing a negative NPB (Biolo et al., 1995, Phillips, 2004). The consumption of post exercise protein supports RET by suppressing the increase in MPB (Phillips, 2004), to promote a positive NPB and ensure a hypertrophic response (Willoughby et al., 2007, Cermak et al., 2012). Molecular signaling proteins and their responses to both RET and protein supplementation further highlight their combined importance for hypertrophy. RET has been shown to increase the phosphorylation of the mechanistic target of rapamycin complex 1 (mTORC1) pathway (Terzis et al., 2008). Both (Drummond et al., 2009) and (Bodine et al., 2001) have shown in the absence of mTORC1 activity, RET induced increases in MPS and hypertrophy are absent respectively. Additionally, RET has been shown to increase the phosphorylation of p70S6 kinase (p70S6K (Terzis et al., 2010)) and protein kinase B (PKB (Mitchell et al., 2012)), both of which are key proteins in the mTORC1 pathway. Post RET protein supplementation can further RET induced phosphorylation, and therefore activity of mTORC1 (Drummond et al., 2008), further highlighting its importance. Even without the additive effect of protein supplementation it is clear to see that RET forms the main foundation of a potent stimulus to enhance the molecular signaling proteins and subsequent MPS that are essential for increasing muscle mass.

Manipulation of resistance training variables to optimize hypertrophy

The manipulation of RET variables can result in altered molecular signaling, MPS and ultimately hypertrophy (Bird et al., 2005) . The desire to optimize hypertrophy has lead to significant investigation of multiple RET variables including intensity (Holm et al., 2008, Wernbom et al., 2007), frequency (Schoenfeld et al., 2015, Schoenfeld et al., 2016a, Brigatto et al., 2018), inter-set rest period (Schoenfeld et al., 2016b, McKendry et al., 2016, Grgic et al., 2017), contraction type (Ato et al., 2016) and contraction time (Burd et al., 2012, Hackett et al., 2018). One key variable that has also undergone investigation is RET volume, defined as the product of sets, repetitions and load to be expressed as total tonnage (kg). RET volume is considered to be the one of the most important variables, and may in fact supersede other variables in importance, when driving skeletal muscle hypertrophy (Figueiredo et al., 2018). Manipulation of other variables such as intensity and frequency is potentially ineffective when volume is equated between groups (Candow and Burke, 2007, Mitchell et al., 2012, Schoenfeld et al., 2014, Grgic et al., 2018). It is even argued that the manipulation of these variables is ultimately designed to alter the total RET volume per session (Figueiredo et al., 2018, Grgic et al., 2018). However, at present it is difficult to categorically claim RET volume is the most effective RET variable for driving skeletal muscle hypertrophy. More importantly, despite the known importance of RET volume, questions still exist with regards to the best practice for it's practical implementation; specifically the optimal number of weekly sets per muscle group.

A large proportion of the current literature supports the existence of a linear dose-response relationship between the number of weekly sets per muscle group and skeletal muscle hypertrophy (Ronnestad et al., 2007, Sooneste et al., 2013, Radaelli et al., 2013, Radaelli et al., 2015, Correa et al., 2015). Other studies argue against this relationship and claim that even at relatively low RET volumes (i.e. <10 weekly sets) additional sets pose no significant additional benefit (Ostrowski et al., 1997, McBride et al., 2003, Galvao and Taaffe, 2005, Cannon and Marino, 2010, Bottaro et al., 2011, Mitchell et al., 2012, Radaelli et al., 2014, Ribeiro et al., 2015). Meta-analysis inspection however does show support for a linear response (Krieger, 2010, Schoenfeld et al., 2017). Schoenfeld et al. (2017) meta-analysis provides the latest, most complete review of the existing literature. By examining effect size (ES) and confidence intervals (CI), which are argued crucial for identifying relationships in sport science research (Bernards et al., 2017), they reported 13 of the 15 studies included (some of which did not report significant findings) to be right of centre, supporting the linear dose-response relationship between the number of weekly sets per muscle group and skeletal muscle hypertrophy. They concluded an additional set per muscle group equates to a 0.37% increase in muscle size (ES = 0.023) and that a higher number of weekly sets per muscle group equates to a 3.9% increase in muscle size (ES = 0.241) compared to a lower number weekly sets. However it must be noted that this meta-analysis was hindered by methodological limitations of the existing literature and more importantly a paucity of research into very high training volumes (i.e. >10-12 weekly sets)(Schoenfeld et al., 2017). This ultimately prevents the authors from uncovering the full extent of the linear relationship and whether a theoretical threshold for RET volume induced skeletal muscle hypertrophy exists.

A question therefore remains regarding the continuation of the linear dose-response relationship between the number of weekly sets per muscle group and skeletal muscle hypertrophy, with very high RET volumes (i.e. >10-12 weekly sets per muscle group). Whilst no definitive answer can yet be drawn a number of studies provide some evidence for and against a continuation. Radaelli et al. (2015) tested 6, 18, and 30 weekly sets per muscle group for six months in recreationally trained males and found significantly greater increases in upper arm muscle thickness with the greatest RET volume, which suggests a continuation of the linear dose-response relationship. However another study by Amirthalingam et al. (2017) ,which included 18 or 28 weekly sets of bicep based RET over six weeks with resistance-trained males, found no difference in changes in bicep muscle thickness between the groups and actually found greater increases in arm lean body mass in the lower volume group. This therefore supports the existence of a threshold and a possible plateau, beyond which no additional benefits are gained. Molecular signaling evidence in rats might also support the existence of a threshold or plateau. Tibana et al. (2017) reported that following eight weeks of 12 or 24 RET sets per week in rats, there was no difference between groups for muscle cross sectional area and that the higher RET volume caused the down regulation of proteins involved in muscle protein synthesis. The emergence of evidence leaning towards a threshold has caused some to theorize an inverted U relationship between the number of weekly sets per muscle group and skeletal muscle hypertrophy (Figueiredo et al., 2018). However, at present there is a paucity of evidence to confirm or deny this relationship, meaning that no clear conclusion can yet be drawn regarding the exact relationship between the number of weekly sets per muscle group and skeletal muscle hypertrophy at very high RET volumes.

Limitations within the current literature

Besides the lack of research exploring very high RET volumes hindering the current understanding, much of the research at lower RET volumes lacks methodological control (Schoenfeld et al., 2017), which might influence the rate of hypertrophy alongside RET volume (see table 1). One such area for concern is the training status of participants. As pointed out by Schoenfeld et al. (2017) there is a paucity of research with resistance-trained participants. The use of participants naïve to RET might cause both RET-induced MPS (Damas et al., 2015) and neural adaptations to RET (Carroll et al., 2001) to vary greatly between participants, thus distorting the rate of increase in muscle mass and strength. A small sample size is another concern, causing a number of studies to be underpowered, thus increasing the chances of a type II error and suppressing any significant findings (Schoenfeld et al., 2017). Regardless of the training status and sample size the frequent practice of taking sets to complete volitional failure is both concerning, as it might induce overtraining and subsequent catabolic effects at the highest volumes (Schoenfeld, 2010), and arguably unnecessary. It has been reported the muscle is maximally activated 3-5 repetitions short of a 15RM (Sundstrup et al., 2012) and that hypertrophy plateaus two repetitions short of complete volitional failure (Sampson and Groeller, 2016), making the risk of training to failure needless. In fact some have proposed a repetitions in reserve (RIR) model (Zourdos et al., 2016) which uses the Borg category ratio scale (CR-10; (Buckley and Borg, 2011)), to allow for manipulation of RET intensity and training close to volitional failure on a set by set basis by predicting the total number

Table 1: A summary of potential methodological limitations within the existing literature that might influence the rate of hypertrophy, reducing experimental control and/or limit the current understanding of the relationship between RT volume and skeletal muscle hypertrophy. × indicates the study failed to include this in their methodology and ✓ indicates it was present.

Study	Resistance training status	Sample size	Failure or non-failure training	Dietary control/monitoring	Post exercise protein supplementation	External training control/monitoring	Number of weekly sets per muscle group
Starkey et al (1996)	Untrained	48	Failure	×	×	×	LOW: 3, HIGH: 9
Ostrowski et al (1997)	Trained	27	Failure	×	×	×	LOW: 3-7, MOD: 6-14, HIGH: 12-28
Rhea et al (2002)	Trained	18	Failure	×	×	✓	LOW: 3, HIGH: 5
McBride et al (2003)	Untrained	28	Failure	×	×	✓	LOW: 2, HIGH: 12
Galvao and Taaffe (2005)	Untrained	28	Failure	✓	×	×	LOW: 5, HIGH: 9
Ronnestad et al (2007)	Untrained	21	Failure	✓	✓	✓	LOW: 3-6, HIGH: 9-18
Cannon and Marino (2010)	Untrained	31	Non-failure	✓	✓	×	LOW: 3, HIGH: 9
Bottaro et al (2011)	Untrained	30	Failure	✓	×	✓	LOW: 2, HIGH: 6
Mitchell et al (2012)	Untrained	18	Failure	×	✓	×	LOW: 3, HIGH: 9
Sooneste et al (2013)	Untrained	8	Failure	×	×	✓	LOW: 2, HIGH: 6
Radaelli, Botton et al (2014)	Untrained	20	Failure	✓	×	✓	LOW: 4, HIGH: 12
Radaelli and Fleck (2014)	Untrained	48	Failure	✓	×	✓	LOW: 6, MOD: 18, HIGH: 30
Radaelli, Wilhelm et al (2014)	Untrained	27	Failure	✓	×	✓	LOW: 4, HIGH: 12
Correa et al (2015)	Untrained	36	Failure	✓	×	✓	LOW: 3, HIGH: 9
Ribeiro et al (2015)	Untrained	30	Failure	✓	×	×	LOW: 4, HIGH: 10

of repetitions to failure, whilst ensuring it failure is not reached by leaving a pre-determined number of repetitions in reserve. Previously a strong correlation ($r \geq 0.93$; $p<.05$) between estimated-repetitions-to-failure and actual-repetitions-to-failure has been established (Hackett et al., 2012). Awareness of participant's dietary intake is also lacking in a number of studies. As dietary intake, especially dietary protein, can influence RET induced muscle remodeling (Cermak et al., 2012, Stokes et al., 2018), it should be monitored to account for a potentially significant additional stimulus that might distort the relationship between RET volume and skeletal muscle hypertrophy. Post exercise protein supplementation is also neglected by some of the literature. As previously mentioned post exercise protein intake provides an additional stimulus to promote a positive NPB (Phillips, 2004) and augment molecular signaling (Drummond et al., 2008). Additionally it can maximally stimulate MPS in all participants, provided a sufficient dose is ingested (Morton et al., 2015, Macnaughton et al., 2016). Whilst a single bout of resistance exercise elevates the MPS response to protein nutrition for up to 48 hours post-exercise, it is still preferential to consume protein sooner rather than later to maximize the MPS response (Churchward-Venne et al., 2012, Kumar et al., 2009). Studies that neglect post-exercise protein supplementation may fail to standardize post exercise protein intake and subsequently may fail to maximize individual muscle growth, especially in participants with a greater lean body mass. Much like dietary awareness, an awareness or control of external training is limited in much of the literature. It is necessary to at least be aware of participants external training habits, especially of the muscle group of interest, as it is likely to alter the extent of RET induced muscle remodeling. Overall it is arguable that no one study fully controlled for all confounding variables and that multiple variables might be influencing much of the existing research (see table 1). This might explain why a number of studies presented right leaning findings (i.e. favouring a linear response), as reported by Schoenfeld et al. (2017), but failed to reach statistical significance. Therefore in order to ensure accurate and reliable findings, regarding the relationship between weekly RET volume and skeletal muscle hypertrophy, a greater deal of experimental control needs to be enforced.

Why is a better understanding needed?

The current lack of understanding of the relationship between weekly RET volume and skeletal muscle hypertrophy, at very high RET volumes, makes it difficult to provide practitioners with clear recommendations for their RET programmes. It remains unclear whether an optimal number of weekly sets per muscle group exist to optimize skeletal muscle hypertrophy and whether training beyond a certain volume attenuates skeletal muscle remodeling. As previously mentioned there is a paucity of research with resistance trained individuals, which arguably hinders the current research based conclusions (Schoenfeld et al., 2017). Clarification of the relationship between skeletal muscle hypertrophy and very high weekly RET volumes, with resistance-trained individuals, is therefore required. This will identify the full extent of the previously established linear relationship between RET volume and hypertrophy (Schoenfeld et al., 2017) as well as potentially identify a theorized threshold, or inverted U relationship (Figueiredo et al., 2018). This knowledge would help provided accurate recommendations for future RET programmes, which could subsequently help improve sporting performance (Harries et al., 2012), combat sarcopenia (Evans and Campbell, 1993) or improve the health of the general population (Wolfe, 2006).

Aims and hypothesis

At present the relationship between very high weekly RET volumes (i.e. >10-12 weekly sets per muscle group) and skeletal muscle hypertrophy remains undefined. It is unclear whether greater hypertrophy is achieved with very high RET volumes, seeing the linear dose response relationship (Schoenfeld et al., 2017) continue beyond 10 weekly sets, or whether a threshold exists at which point a plateau or inverted U relationship occurs. Therefore the purpose of the present study was to compare changes in bicep muscle thickness after six weeks (i.e. the early phases of hypertrophy (Brook et al., 2015)) of 9, 18 or 27 weekly bicep based RET sets in resistance-trained males; whilst also ensuring a high internal validity, to identify the relationship between very high weekly RET volumes and skeletal muscle hypertrophy. It was hypothesized that muscular adaptations to RET would be greater in response to 18 vs. 9 weekly sets (performed over two and one weekly session(s), respectively), but would not increase further with 27 weekly sets performed over two weekly sessions.

METHODS

Participants

Fifty-one (n=51) male participants, aged 18-35 yrs (Table 2), volunteered to participate in the study. Participants had ≥1 yr of RET experience (≥3 times weekly). Participants were deemed healthy via a general health questionnaire and were excluded if diabetic, a regular smoker or lactose intolerant. Participants were omitted if they reported drinking alcohol 24 h prior to a session and/or trained their biceps externally. Ethical approval was granted by the University of Birmingham (#ERN-16_1084) in accordance with the 7th version of the declaration of Helsinki. All participants gave informed written consent to participate.

Table 2: Participant Characteristics

	LOW (n=17)	MOD (n=15)	HIGH (n=17)
Age (years)	20.1±1.2	19.5±1.4	20.5±1.2
Height (cm)	179.6±4.0	177.0±7.6	181.1±6.7
Weight (kg)	81.3±8.3	76.3±10.2	82.0±10.7
Body fat (%)	22.7±4.2	21.5±6.5	21.7±5.6

Values are expressed as mean ± SD.

Study design

Participants were randomly allocated to a low (LOW; n=17), moderate (MOD; n=15) or high (HIGH; n=17) weekly RET volume group. Participants trained their elbow flexors, focusing on the biceps brachii, under a moderate-to-high intensity with varying weekly volume for six weeks. One week prior to training, participants underwent pre-training assessments of anthropometric characteristics, muscle architecture, isometric and isotonic strength. LOW trained once per week and both MOD and HIGH trained twice weekly. Post-exercise protein supplementation was controlled and participants were asked to record external RET and diet throughout. One week after training completion, participants repeated pre-training assessments.

Pre and post-training assessments

Anthropometric characteristics: Height and weight were recorded using a stadiometer and digital weighing scales. A bioelectrical impedance scanner (Bodystat, Quadscan 4000, Douglas, Isle of Man, UK) was used to measure body fat percentage, with electrodes attached to the back of the hand and either side of the ipsilateral ankle.

Muscle thickness: Biceps brachii MT was measured in both arms via ultrasound (Diasus Application Specific Ultrasound, Dynamic Imaging Ltd, Livingston, UK). Participants were seated in an upright position facing the operator, with their arm relaxed in a supine extended position. The ultrasound probe (7.5mHz transducer (L5-10mHz probe)) was covered in a transmission gel (Henleys Medical Supplies, Hertfordshire, UK) and placed parallel to the muscle fibres at 50% the distance between the supraglenoid tubercle and radial tuberosity. Five images were taken of each arm. The site of biceps MT assessment was marked weekly and photographed to keep track of the precise scan location. Ultrasound images were analyzed using ImageJ (version 1.51i), with MT measuring as the distance between the superficial and deep aponeuroses (Figure 1). The highest quality image (i.e. the image with the clearest, most parallel aponeuroses) was used to measure MT. The same un-blinded operator performed all scans to reduce intra-operator variability and ensure, as best as possible, accurate and reproducible results (ultrasound coefficient of variance based on all obtained images ~0.7%). The same operator also conducted all the analysis of the ultrasound images.

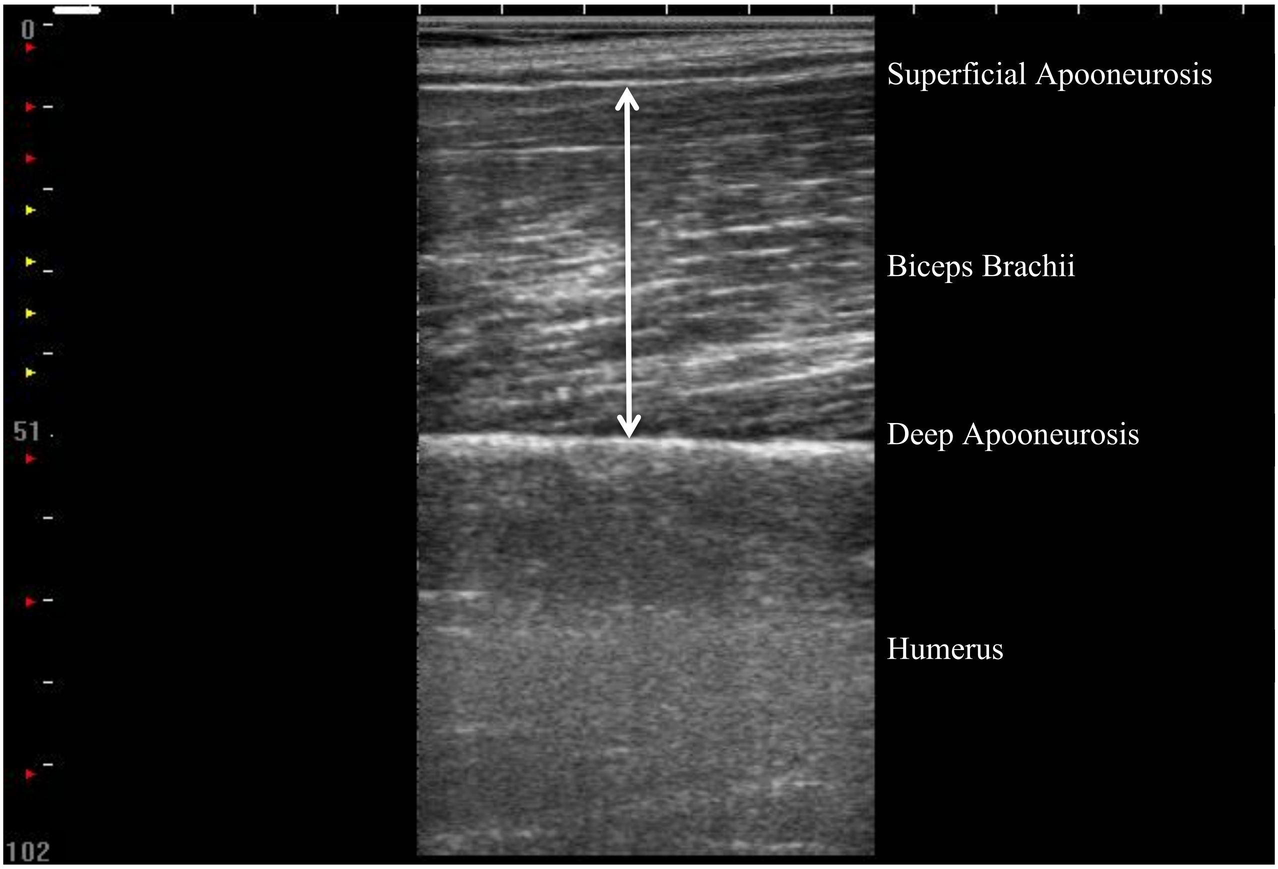

Figure 1: Example of an ultrasound scan used to assess muscle thickness.

Maximal isometric strength: Bicep isometric strength was assessed using a KinCom dynamometer (Chattanooga Group Inc, Hixson, Tennessee, USA). The dynamometer was calibrated to measure the peak torque of the elbow flexors during a maximal voluntary isometric contraction. Participants were secured in a seated position with straps across their shoulders, torso and waist. The dominant arm was secured in a flexed position at 55° with the elbow flexion attachment, with arm lever length being recorded. Participants were instructed to *"push up as hard as possible"* against the lever pad for 3 s to produce a peak torque. Participants were given 120 s rest between a total of 6 attempts, comprising an initial three sub-maximal warm-ups, and three maximal "all-out" efforts. On screen instructions and verbal commands informed the participant when to begin and cease contracting. Of the three maximal attempts, the highest score was recorded.

Maximal isotonic strength: The maximum load that could be lifted in a single repetition (1RM) was recorded for a seated supine bicep curl, supine grip bent over row and supine pulldown exercise. Participants completed a seated supine bicep curl warm up of three sets of 10 repetitions with an unloaded 9kg bar. Participants then self-selected a load they felt would elicit volitional fatigue after 4-5 repetitions. This was adjusted in each subsequent set to ensure fatigue after 3-4 repetitions, 2-3 repetitions and, finally, 1 repetition. Sets were separated by 2 min of passive rest, and multiple 1RM attempts separated by 3 min. Verbal encouragement was provided by the researchers throughout. Failure to lift the load or lifting with incorrect technique disqualified the attempt.

Resistance training programme

Participants completed six weeks of bicep-based RT, no familiarization to each exercise was performed due to the resistance trained nature of our participants. LOW trained once per week and both MOD and HIGH trained twice per week. Multiple training sessions were separated by at least 48 h. LOW and MOD training sessions consisted of 9 sets (three sets of each exercise performed in the pre-training assessments). The first weekly HIGH training session consisted of 5 sets of seated supine bicep curls and supine grip bent over rows and 4 sets of supine grip pulldowns. The second

HIGH session consisted of 4 sets of the first two exercises and 5 sets of supine grip pulldowns. Participants performed 10-12 repetitions per set, using the RIR model (Zourdos et al., 2016). Exercise training intensity was monitored after each set using the Borg category ratio scale (CR-10; (Buckley and Borg, 2011), with 10 being maximal effort. Participants aimed to end their sets with ~2 RIR, (i.e. target score of ~8 on the CR-10). The load lifted in the first set was ~75% of 1RM, which was altered accordingly in subsequent sets and training sessions, should the RIR score fall outside the desired 8. Participants were instructed on correct lifting technique and were supervised throughout to maintain form and tempo (3-1; eccentric-to-concentric contractions). Rest periods of 3 min were given between sets. Training sessions were performed at a time convenient for the participants, who were encouraged to train at the same time of day throughout. Verbal encouragement was given and participants could choose to play music. Participants consumed 40g of whey protein in 250ml of water after every RET session to ensure maximal stimulation of post-exercise MPS in all participants (Macnaughton et al., 2016). One week following the final training session participants underwent post-training assessments. All tests were performed in an identical manner, on the same day and same time of day as each participant's pre-training assessments.

Dietary and training control

Participants were instructed to maintain their normal dietary and supplement intake. Participants were forbidden from consuming any caffeine on the day of testing and RET sessions. External training was permitted; however participants were requested to avoid exercises that incorporated the elbow flexors (a verbal list was given) and encouraged to check with a member of the research team on their external upper-body routine. Participants recorded diet and external training in self-report diaries. Diet was recorded over 3 days of every training week (2 weekdays and 1 weekend). external training diaries were submitted every two weeks. Diet diaries were assessed using

DietPlan6 (Forestfield Software Ltd, Horsham, UK). Training diaries were analysed to determine upper- and lower-body weekly RET (expressed as total tonnage).

Statistical analysis

Data was analyzed using SPSS (version 22, IBM Statistics, Chicago, Illinois, USA). A one-way ANOVA was used to compare baseline physical characteristics between groups, and repeated measures ANOVA was used to assess the significance of each measure; pre-to-post, as well as between groups. Bonferroni post hoc tests were used to examine differences where significant effects were found. Significance was set at $p<0.05$. Individual raw data (i.e. pre and post values) was used for statistical analysis and percent change from pre-to- post RT was calculated for muscle thickness and strength. Normality of distribution was assessed using the Kolmogorov-Smirnov analysis. Tabulated data are expressed as means ±SD and figures as means ±SEM.

RESULTS

Participants

Forty-nine participants (n=49) completed the study with two withdrawing due to non-compliance with external training and/or alcohol restrictions. Training adherence for the completed participants was 99.2% (482 out of 486 sessions attended), and all were included in the final analysis (LOW; n=17, MOD; n=15 and HIGH; n=17). There were no significant differences in any physical characteristics (Table 2).

Training volume

Total study-specific RET volume (Figure 2) differed significantly between each group, whereby HIGH>MOD>LOW at every time point (weeks 1-6; P<0.05 for all). Training volume did not significantly change over the 6-week intervention for LOW, but did increase weekly from week 3 onwards for MOD and HIGH only (P<0.05).

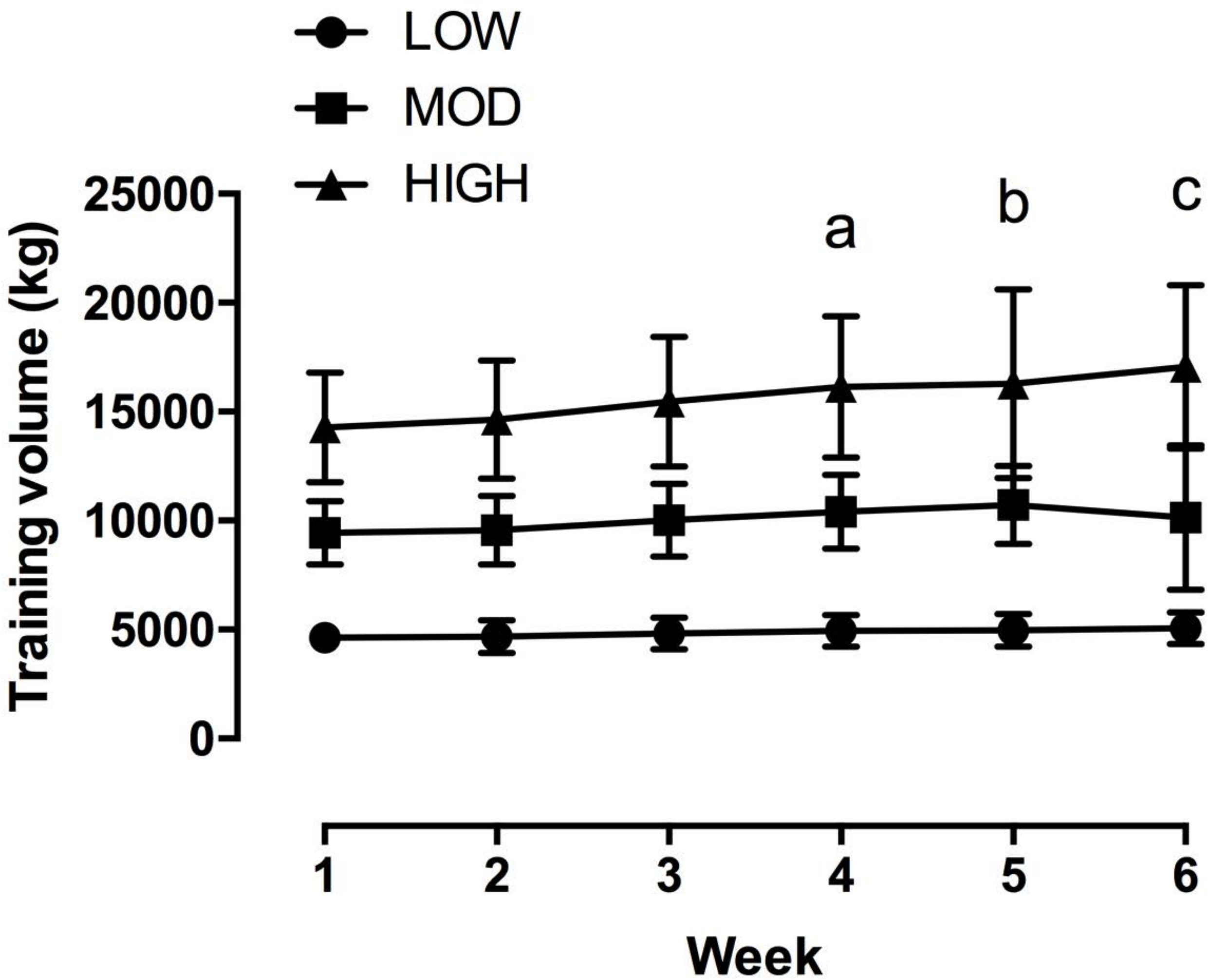

Figure 2: Weekly study RET volume. *a, b, c* indicates significantly different from RET volume at week 3, 4 and 5, respectively, for MOD and HIGH. Significance was set at P<0.05. Data are expressed as means ±SD.

Muscle thickness and arm circumference

Bicep MT data are presented as absolute group means and individual % change in Figure 3A and B, respectively. There were no significant between-group differences in MT prior to training. From pre-to-post-training, MT increased in LOW by 1.11±3.1cm (P=0.019), in MOD by 1.19±3.28cm (P<0.001) and in HIGH by 1.98±4.07cm (P=0.002), with no difference between groups in the relative change. Individual data revealed that 4 participants in LOW, 1 in MOD and 1 in HIGH had a negative MT response to RET.

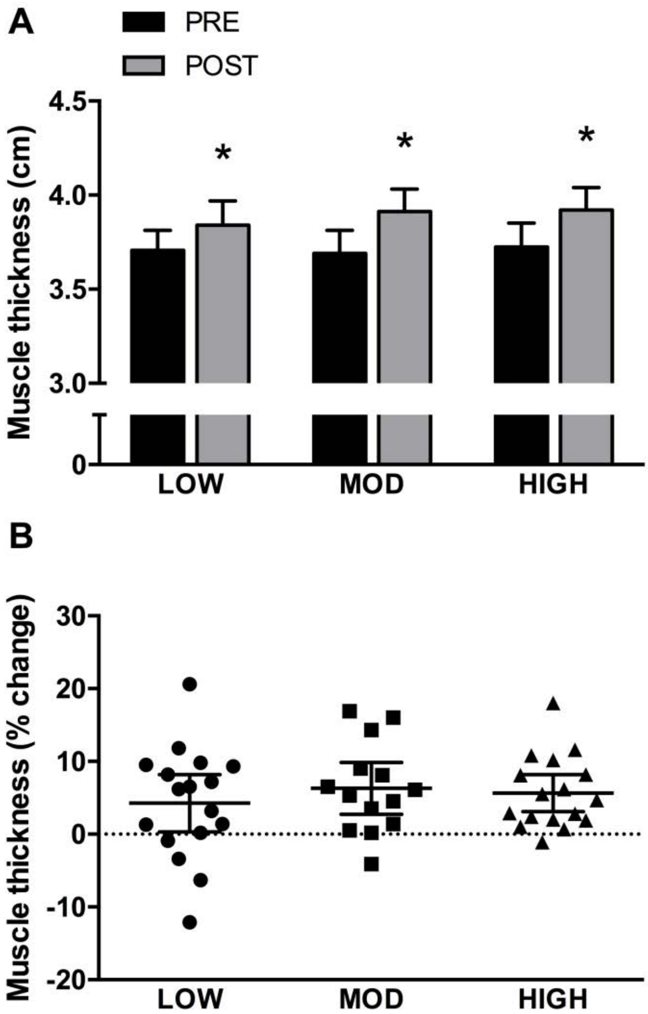

Figure 3: Biceps muscle thickness (MT). Data presented as means ±SD and (A) and individual % change from pre-to-post RET (B). Central line in 2B represents the group mean and bars represent 95% confidence intervals. Significance was set at P<0.05

Isometric and Isotonic strength

Isometric strength is presented as absolute group means and individual % change in Figure 4A and B, respectively. There was no significant between-group difference in isometric strength prior to training. From pre-to-post-training, isometric strength increased only for HIGH (19.8±40.7 Nm; P = 0.025), but not LOW and MOD (11.1±31 and 11.9±32.8 Nm, respectively), with no between-group difference in the relative change. Individual data revealed that 7 participants in LOW, 5 in MOD and 5 in HIGH had a negative isometric strength response.

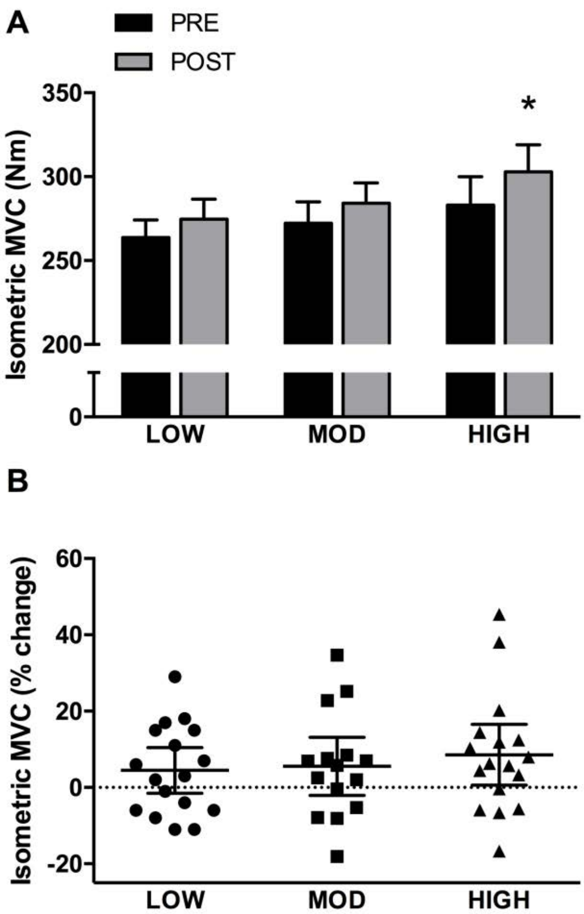

Figure 4: Isometric maximal voluntary contraction (MVC). Data are presented as means ±SD and (A) and individual % change from pre-to-post RET (B). Central line in 3B represents the group mean and bars represent 95% confidence intervals. Significance was set at P<0.05.

Isotonic strength is presented as absolute group means and individual % change in Figure 5A and B, respectively. Data are expressed as the combined increase in 1RM for all 3 training exercises. There was no significant between-group difference in 1RM strength prior to training. From pre-to-post-training, total 1RM strength increased in LOW by 16.1±9.7 kg, in MOD by 24.3±9.3 kg and in HIGH by 27.9±10.2 kg ($P < 0.001$ for all groups), with no between-group difference in the relative change. Individual data revealed that no participants in LOW, MOD or HIGH had a negative isotonic strength response.

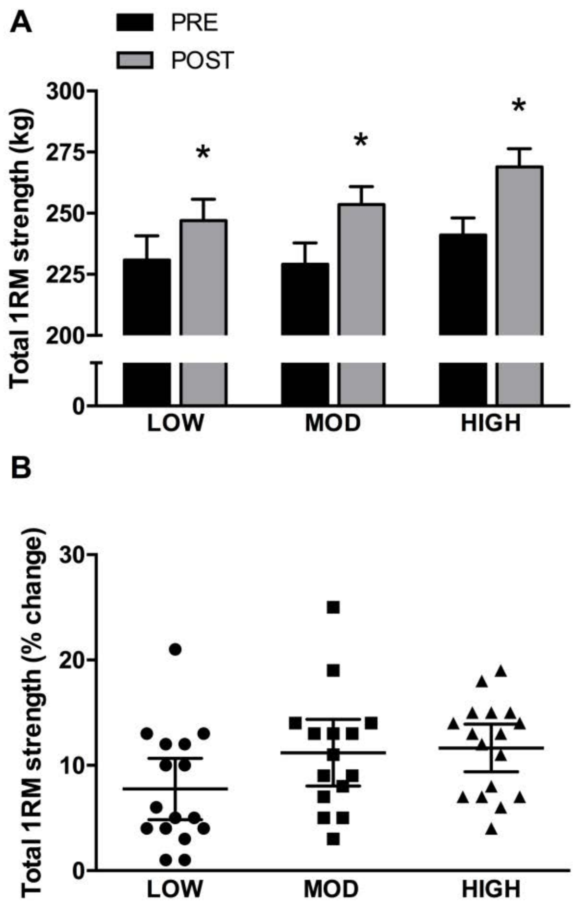

Figure 4: Total 1RM strength presented as means ±SD and (A) and individual % change from pre-to-post RET (B). Total 1RM strength change is the product of biceps curl, supine grip pulldown and bent-over row exercises. Central line in 4B represents the group mean and bars represent 95% confidence intervals. Significance was set at $P<0.05$.

Table 3: Dietary constituents and external RT volume throughout the 6 weeks of RT.

	LOW (n=17)			MOD (n=15)			HIGH (n=17)		
	WK 1-2	WK 3-4	WK 5-6	WK 1-2	WK 3-4	WK 5-6	WK 1-2	WK 3-4	WK 5-6
Energy (kcal)	2208±592	1788±399	2278±504	2458±751	2289±826	2320±709	2497±767	2110±840	2576±626
Protein (g)	1.60±0.38	1.50±0.27*	1.67±0.33	1.84±0.34	1.83±0.24	1.74±0.07	1.72±0.42	1.61±0.35	1.65±0.29
Fat (g)	1.22±0.40	0.98 ±0.24	1.11±0.29	1.72±0.22	1.60±0.33	1.65±0.12	1.33±0.20	1.11±0.36	1.29±0.21
Carbohydrate (g)	3.66±1.04	3.74±0.84	3.98±0.63	3.64±0.60	3.8±0.72	3.56±0.75	3.68±0.77	3.55±0.91	3.70±0.66
Total external volume (kg)	35268 ±29549	30083 ±38166	24895 ±31857	31244 ±31147	24550 ±33492	43513 ±36608	37121 ±24368	29942 ±26362	20089 ±29726
Upper-body external volume (kg)	18426 ±15014	16024 ±19755	10905 ±11052	18128 ±16455	15118 ±16355	22622 ±18915	22721 ±11474	14471 ±11573	13979 ±16040
Lower-body external volume (kg)	16945 ±16553	13233 ±21832	17013 ±20760	10426 ±17354	11582 ±16590	20508 ±22658	14400 ±14234	17007 ±16899	11043 ±15752

Energy and macronutrient intake are presented as daily intake, with macronutrients expressed relative to body mass. External RET volume is expressed as total over weeks 1-2, 3-4 and 5-6. * Significant between group difference at the same time point ($P<0.05$). Data are expressed as mean ±SD.

Dietary intake and external training

Dietary constituents as well as external RET volume are presented in Table 3. There were no significant within or between-group differences for total energy, fat or carbohydrate intake across the 6-week RET programme. There were no significant between groups differences for protein intake, however protein intake in LOW was significantly lower in weeks 3-4 compared to weeks 1-2 (P=0.046) and weeks 5-6 (P=0.007). There were no significant within or between-group differences in total, upper-body or lower-body external RET volume.

DISCUSSION

The existence of a graded dose response relationship between skeletal muscle hypertrophy and RET volume is largely accepted at lower volumes (i.e. <10-12 weekly sets) (Schoenfeld et al., 2017). However, the present study is one of the first to demonstrate the existence of a plateau in muscle adaptations to moderate and high weekly RET volume, over a short-term training program in trained individuals. Specifically, our findings indicate that over six-weeks of RET, 9 weekly sets of biceps training (LOW), performed in a single weekly session, elicited muscle thickness (MT) and strength increases that did not statistically differ from 18 and 27 weekly sets, performed over two weekly sessions (MOD and HIGH, respectively). This finding is in contrast to our initial hypothesis, in which we theorized muscular adaptations to RET would be greater in response to 18 and 27 weekly sets compared with 9 sets.

Whilst no significant differences existed between groups for MT or any measure of strength, individual absolute data appeared to reveal a greater number of non-responders (i.e. negative or no increase in changes in MT, strength or both), in LOW compared to MOD or HIGH. It is plausible this is a result of the number of weekly sets per group, but it cannot be ruled out that it is a result of participant or measurement variance, meaning these participants might have not undergone a true non-response, despite initial impressions (Atkinson et al., 2018). However, it remains widely accepted that some individuals respond to a lesser extent following RET and therefore may need a greater RET stimuli/volume to maximize intramuscular signaling and MPS responses (Davidsen et al., 2011). Therefore, based on this knowledge and the lesser absolute responses of some in the LOW group in the present study, 9 weekly sets performed in one weekly session might be insufficient volume for some trained individuals, and that 18 weekly sets performed over two weekly sessions should form the basis of any recommendations.

As previously mentioned, a graded dose-response relationship between skeletal muscle hypertrophy and RET volume is largely accepted at relatively low volumes (Schoenfeld et al., 2017). Limited research is available to support whether this theory holds true with moderate-to-high weekly training volumes. Previously, Radaelli et al. (2015) reported greater increases in elbow flexor MT with 30 weekly sets per muscle group vs. 6 or 18 sets, in previously untrained individuals. Mechanistically, both acute (Terzis et al., 2010, Burd et al., 2010) and chronic (Mitchell et al., 2012) studies have reported associations between mTORC1-mediated signaling/MPS and RET volume, at volumes ≤9 sets. Similar to our observation of no relationship between RET volume and muscular adaptations over short-term training, Amirthalingam et al. (2017) reported no difference in bicep MT between 18 or 28 weekly sets, and recommended 4-6 sets per exercise in a single RET session. Further to this, there is evidence to suggest a similar plateau in the relationship between RET volume and both MPS and mTORC1-mediated signaling at very high volumes. Tibana et al. (2017) reported a down-regulation in the expression of a number of key proteins implicated in MPS following 24 vs. 12 weekly sets, albeit in rodents. Whether a similar response occurs in humans is unclear as, to the best of our knowledge, no studies have examined the molecular signaling or MPS response to very high RET volumes. Further support for our finding of the absence of any relationship between weekly RET volume and muscular adaptations comes from reports that professional bodybuilders typically train 3-6 sets per exercise (Hackett et al., 2013), equating to 9-18 weekly sets per muscle. Whilst evidence has been found to support the extension of the graded-dose relationship between RET volume and skeletal muscle hypertrophy with very high volumes in untrained individuals over a prolonged period (Radaelli et al., 2015), our findings indicate no such relationship in trained individuals over a short-term RET programme.

Consideration of the experimental design/methodology must be made when interpreting the findings of the present study. In contrast to Radaelli et al. (2015), we studied individuals who were fully accustomed to RET, which would minimize issues of variability in MPS responses (Damas et al., 2015, Wilkinson et al., 2008) and neural contributions (Carroll et al., 2001) to muscular adaptation. Furthermore, studying trained individuals would reduce the incidence and severity of any edema, through the repeated-bout effect (Nosaka et al., 2001), which may otherwise have influenced our MT measurements. However, the duration of the MPS response to RET is attenuated in RET-accustomed individuals (Damas et al., 2015, Wilkinson et al., 2008, Tang et al., 2008), which may explain the greater adaptive response in untrained individuals reported by Radaelli et al. (2015) compared with our findings. In addition to training status, the discrepancy between our findings and those of Radaelli et al. (2015) could also have been influenced by the duration of the RET intervention. Although 6-weeks of RET has consistently been found to induce muscle hypertrophy (DeFreitas et al., 2011, Baroni et al., 2013, Seynnes et al., 2007) and represents the most active phase of muscle remodeling (Brook et al., 2015), this time-frame may not have been sufficient to promote divergent changes in biceps MT between groups. Indeed, others have failed to detect any difference in MT between different RET volumes over 6-weeks (Amirthalingam et al., 2017, Radaelli et al., 2014). It could therefore be suggested that any difference in muscular adaptations to RET with different volume strategies may manifest in the latter stages of training

(Schoenfeld et al., 2017). Previously 12 vs 4 weekly sets have been found to induce no MT differences between group over 6-weeks (Radaelli et al., 2014), whereas the same volumes over a 20-week RET-programme have (Radaelli et al., 2013). Thus, we cannot discount that an extended version of our RET protocol might have revealed differences in muscular adaptations between groups. It is also important to acknowledge that the training frequency used herein could be viewed as a confounding factor, as LOW completed their training over one weekly set, whereas MOD and HIGH completed their training volume over two weekly sets. Schoenfeld et al. (2016a) concluded that a RET frequency of ≥2 times per week is required to maximize muscle hypertrophy when volume is equated, which was not the case in the present study. Additionally, the argument can be made that splitting the total LOW volume over two weekly sessions (i.e. 4-to-5 sets in each session) might be insufficient to maximize post-exercise muscle remodeling. Another draw back of the present study is the lack of a control group. Without this group it is difficult to identify whether participants were true non-responders or whether this perceived response was down to participant or measurement variability. Additionally it is also difficult to rule out a learning effect as an explanation for our strength findings. As all groups changed similarly in 1RM it is possible that gradual familiarization of training might have driven the pre-to-post response, despite the previously resistance trained nature of our participants. Our lack of a familiarization period prior to the study also makes it difficult to rule out this possibility. Despite potential limitations, it is also important to highlight the strength and reliability of our MT measure assessed by ultrasound (Franchi et al., 2018) and that the potentially confounding factors of external RET, dietary intake and post-RET protein intake were closely monitored and/or controlled, which has not always been the case in previous studies of RET volume and muscular adaptations (Schoenfeld et al., 2017).

PRACTICAL APPLICATIONS

Optimizing RET volume to optimize muscular adaptations to training an important line of investigation. Although others have proposed a possible linear dose-response relationship between weekly RET volume and muscle hypertrophy, previous studies have largely investigated the adaptive response to relatively low weekly RET volumes, or have focused their investigations on untrained individuals. The present findings demonstrate that training a muscle group for >9 weekly sets once a week, lifting a moderate load and eliciting a high degree of effort, offers no superior benefit for increasing muscle thickness and strength during the short-term for the majority of individuals. However, the absence of muscle adaptation to 9 weekly sets in some individuals, suggests that performing a moderate weekly volume of 18 sets, split over two weekly sessions, would ensure optimal muscular adaptations are achieved.

CONCLUSIONS

In conclusion, the present study demonstrates no difference in muscular adaptations between 9, 18 and 27 weekly RET sets over the course of a short-term programme in trained individuals. These findings indicate that relatively low weekly RET volume is sufficient to optimize muscular adaptations in the majority of trained individuals over a short-term RET programme. Future studies should seek to understand whether similar discordance between RET volume and adaptive remodeling in different muscle groups is evident over a longer duration programme (i.e. ≥11 weeks) and whether the frequency over which weekly training volume is completed exerts a strong influence on these responses.

REFERENCES

AMIRTHALINGAM, T., MAVROS, Y., WILSON, G. C., CLARKE, J. L., MITCHELL, L. & HACKETT, D. A. 2017. Effects of a Modified German Volume Training Program on Muscular Hypertrophy and Strength. *J Strength Cond Res,* 31, 3109-3119.

ATKINSON, G., WILLIAMSON, P. & BATTERHAM, A. M. 2018. Exercise training response heterogeneity: statistical insights. *Diabetologia,* 61, 496-497.

ATO, S., MAKANAE, Y., KIDO, K. & FUJITA, S. 2016. Contraction mode itself does not determine the level of mTORC1 activity in rat skeletal muscle. *Physiol Rep,* 4.

BARONI, B. M., GEREMIA, J. M., RODRIGUES, R., DE AZEVEDO FRANKE, R., KARAMANIDIS, K. & VAZ, M. A. 2013. Muscle architecture adaptations to knee extensor eccentric training: rectus femoris vs. vastus lateralis. *Muscle Nerve,* 48, 498-506.

BERNARDS, J. R., SATO, K., HAFF, G. G. & BAZYLER, C. D. 2017. Current Research and Statistical Practices in Sport Science and a Need for Change. *Sports (Basel),* 5.

BIOLO, G., MAGGI, S. P., WILLIAMS, B. D., TIPTON, K. D. & WOLFE, R. R. 1995. Increased rates of muscle protein turnover and amino acid transport after resistance exercise in humans. *Am J Physiol,* 268, E514-20.

BIRD, S. P., TARPENNING, K. M. & MARINO, F. E. 2005. Designing resistance training programmes to enhance muscular fitness: a review of the acute programme variables. *Sports Med,* 35, 841-51.

BODINE, S. C., STITT, T. N., GONZALEZ, M., KLINE, W. O., STOVER, G. L., BAUERLEIN, R., ZLOTCHENKO, E., SCRIMGEOUR, A., LAWRENCE, J. C., GLASS, D. J. & YANCOPOULOS, G. D. 2001. Akt/mTOR pathway is a crucial regulator of skeletal muscle hypertrophy and can prevent muscle atrophy in vivo. *Nature Cell Biology,* 3, 1014-1019.

BOTTARO, M., VELOSO, J., WAGNER, D. & GENTIL, P. 2011. Resistance training for strength and muscle thickness: Effect of number of sets and muscle group trained. *Science & Sports,* 26, 259-264.

BRIGATTO, F. A., BRAZ, T. V., ZANINI, T., GERMANO, M. D., AOKI, M. S., SCHOENFELD, B. J., MARCHETTI, P. H. & LOPES, C. R. 2018. Effect of Resistance Training Frequency on Neuromuscular Performance and Muscle Morphology after Eight Weeks in Trained Men. *J Strength Cond Res*.

BROOK, M. S., WILKINSON, D. J., MITCHELL, W. K., LUND, J. N., SZEWCZYK, N. J., GREENHAFF, P. L., SMITH, K. & ATHERTON, P. J. 2015. Skeletal muscle hypertrophy adaptations predominate in the early stages of resistance exercise training, matching deuterium oxide-derived measures of muscle protein synthesis and mechanistic target of rapamycin complex 1 signaling. *FASEB J,* 29, 4485-96.

BUCKLEY, J. P. & BORG, G. A. 2011. Borg's scales in strength training; from theory to practice in young and older adults. *Appl Physiol Nutr Metab,* 36, 682-92.

BURD, N. A., ANDREWS, R. J., WEST, D. W. D., LITTLE, J. P., COCHRAN, A. J. R., HECTOR, A. J., CASHABACK, J. G. A., GIBALA, M. J., POTVIN, J. R., BAKER, S. K. & PHILLIPS, S. M. 2012. Muscle time under tension during resistance exercise stimulates differential muscle protein sub-fractional synthetic responses in men. *Journal of Physiology-London,* 590, 351-362.

BURD, N. A., HOLWERDA, A. M., SELBY, K. C., WEST, D. W., STAPLES, A. W., CAIN, N. E., CASHABACK, J. G., POTVIN, J. R., BAKER, S. K. & PHILLIPS, S. M. 2010. Resistance exercise volume affects myofibrillar protein synthesis and anabolic signalling molecule phosphorylation in young men. *J Physiol,* 588, 3119-30.

CANDOW, D. G. & BURKE, D. G. 2007. Effect of short-term equal-volume resistance training with different workout frequency on muscle mass and strength in untrained men and women. *J Strength Cond Res,* 21, 204-7.

CANNON, J. & MARINO, F. E. 2010. Early-phase neuromuscular adaptations to high- and low-volume resistance training in untrained young and older women. *J Sports Sci,* 28, 1505-14.

CARROLL, T. J., RIEK, S. & CARSON, R. G. 2001. Neural adaptations to resistance training - Implications for movement control. *Sports Medicine,* 31, 829-840.

CERMAK, N. M., RES, P. T., DE GROOT, L. C., SARIS, W. H. & VAN LOON, L. J. 2012. Protein supplementation augments the adaptive response of skeletal muscle to resistance-type exercise training: a meta-analysis. *Am J Clin Nutr,* 96, 1454-64.

CHURCHWARD-VENNE, T. A., BURD, N. A. & PHILLIPS, S. M. 2012. Nutritional regulation of muscle protein synthesis with resistance exercise: strategies to enhance anabolism. *Nutrition & Metabolism,* 9.

CORREA, C. S., TEIXEIRA, B. C., COBOS, R. C., MACEDO, R. C., KRUGER, R. L., CARTERI, R. B., RADAELLI, R., GROSS, J. S., PINTO, R. S. & REISCHAK-OLIVEIRA, A. 2015. High-volume resistance training reduces postprandial lipaemia in postmenopausal women. *J Sports Sci,* 33, 1890-901.

DAMAS, F., PHILLIPS, S., VECHIN, F. C. & UGRINOWITSCH, C. 2015. A Review of Resistance Training-Induced Changes in Skeletal Muscle Protein Synthesis and Their Contribution to Hypertrophy. *Sports Medicine,* 45, 801-807.

DAVIDSEN, P. K., GALLAGHER, I. J., HARTMAN, J. W., TARNOPOLSKY, M. A., DELA, F., HELGE, J. W., TIMMONS, J. A. & PHILLIPS, S. M. 2011. High responders to resistance exercise training demonstrate differential regulation of skeletal muscle microRNA expression. *J Appl Physiol (1985),* 110, 309-17.

DEFREITAS, J. M., BECK, T. W., STOCK, M. S., DILLON, M. A. & KASISHKE, P. R., 2ND 2011. An examination of the time course of training-induced skeletal muscle hypertrophy. *Eur J Appl Physiol,* 111**,** 2785-90.

DRUMMOND, M. J., DREYER, H. C., FUJITA, S., VOLPI, E. & RASMUSSEN, B. B. 2008. Leucine-enriched essential amino acid and carbohydrate ingestion in women increases skeletal muscle mTOR and Akt/AS160 signaling. *Faseb Journal,* 22.

DRUMMOND, M. J., FRY, C. S., GLYNN, E. L., DREYER, H. C., DHANANI, S., TIMMERMAN, K. L., VOLPI, E. & RASMUSSEN, B. B. 2009. Rapamycin administration in humans blocks the contraction-induced increase in skeletal muscle protein synthesis. *J Physiol,* 587**,** 1535-46.

EVANS, W. J. & CAMPBELL, W. W. 1993. Sarcopenia and age-related changes in body composition and functional capacity. *J Nutr,* 123**,** 465-8.

FIGUEIREDO, V. C., DE SALLES, B. F. & TRAJANO, G. S. 2018. Volume for Muscle Hypertrophy and Health Outcomes: The Most Effective Variable in Resistance Training. *Sports Medicine,* 48**,** 499-505.

FRANCHI, M. V., LONGO, S., MALLINSON, J., QUINLAN, J. I., TAYLOR, T., GREENHAFF, P. L. & NARICI, M. V. 2018. Muscle thickness correlates to muscle cross-sectional area in the assessment of strength training-induced hypertrophy. *Scand J Med Sci Sports,* 28**,** 846-853.

GALVAO, D. A. & TAAFFE, D. R. 2005. Resistance exercise dosage in older adults: single- versus multiset effects on physical performance and body composition. *J Am Geriatr Soc,* 53**,** 2090-7.

GRGIC, J., LAZINICA, B., MIKULIC, P., KRIEGER, J. W. & SCHOENFELD, B. J. 2017. The effects of short versus long inter-set rest intervals in resistance training on measures of muscle hypertrophy: A systematic review. *Eur J Sport Sci,* 17**,** 983-993.

GRGIC, J., SCHOENFELD, B. J., DAVIES, T. B., LAZINICA, B., KRIEGER, J. W. & PEDISIC, Z. 2018. Effect of Resistance Training Frequency on Gains in Muscular Strength: A Systematic Review and Meta-Analysis. *Sports Med,* 48**,** 1207-1220.

HACKETT, D. A., DAVIES, T. B., ORR, R., KUANG, K. & HALAKI, M. 2018. Effect of movement velocity during resistance training on muscle-specific hypertrophy: A systematic review. *Eur J Sport Sci,* 18**,** 473-482.

HACKETT, D. A., JOHNSON, N. A. & CHOW, C. M. 2013. Training practices and ergogenic aids used by male bodybuilders. *J Strength Cond Res,* 27**,** 1609-17.

HACKETT, D. A., JOHNSON, N. A., HALAKI, M. & CHOW, C. M. 2012. A novel scale to assess resistance-exercise effort. *J Sports Sci,* 30**,** 1405-13.

HARRIES, S. K., LUBANS, D. R. & CALLISTER, R. 2012. Resistance training to improve power and sports performance in adolescent athletes: A systematic review and meta-analysis. *Journal of Science and Medicine in Sport,* 15**,** 532-540.

HOLM, L., REITELSEDER, S., PEDERSEN, T. G., DOESSING, S., PETERSEN, S. G., FLYVBJERG, A., ANDERSEN, J. L., AAGAARD, P. & KJAER, M. 2008. Changes in muscle size and MHC composition in response to resistance exercise with heavy and light loading intensity. *J Appl Physiol (1985),* 105**,** 1454-61.

KRIEGER, J. W. 2010. Single Vs. Multiple Sets of Resistance Exercise for Muscle Hypertrophy: A Meta-Analysis. *Journal of Strength and Conditioning Research,* 24**,** 1150-1159.

KUMAR, V., SELBY, A., RANKIN, D., PATEL, R., ATHERTON, P., HILDEBRANDT, W., WILLIAMS, J., SMITH, K., SEYNNES, O., HISCOCK, N. & RENNIE, M. J. 2009. Age-related differences in the dose-response relationship of muscle protein synthesis to resistance exercise in young and old men. *Journal of Physiology-London,* 587, 211-217.

MACNAUGHTON, L. S., WARDLE, S. L., WITARD, O. C., MCGLORY, C., HAMILTON, D. L., JEROMSON, S., LAWRENCE, C. E., WALLIS, G. A. & TIPTON, K. D. 2016. The response of muscle protein synthesis following whole-body resistance exercise is greater following 40 g than 20 g of ingested whey protein. *Physiol Rep,* 4.

MCBRIDE, J. M., BLAAK, J. B. & TRIPLETT-MCBRIDE, T. 2003. Effect of resistance exercise volume and complexity on EMG, strength, and regional body composition. *Eur J Appl Physiol,* 90, 626-32.

MCKENDRY, J., PEREZ-LOPEZ, A., MCLEOD, M., LUO, D., DENT, J. R., SMEUNINX, B., YU, J., TAYLOR, A. E., PHILP, A. & BREEN, L. 2016. Short inter-set rest blunts resistance exercise-induced increases in myofibrillar protein synthesis and intracellular signalling in young males. *Exp Physiol,* 101, 866-82.

MITCHELL, C. J., CHURCHWARD-VENNE, T. A., WEST, D. W., BURD, N. A., BREEN, L., BAKER, S. K. & PHILLIPS, S. M. 2012. Resistance exercise load does not determine training-mediated hypertrophic gains in young men. *J Appl Physiol (1985),* 113, 71-7.

MORTON, R. W., MCGLORY, C. & PHILLIPS, S. M. 2015. Nutritional interventions to augment resistance training-induced skeletal muscle hypertrophy. *Front Physiol,* 6, 245.

NOSAKA, K., SAKAMOTO, K., NEWTON, M. & SACCO, P. 2001. How long does the protective effect on eccentric exercise-induced muscle damage last? *Med Sci Sports Exerc,* 33, 1490-5.

OSTROWSKI, K. J., WILSON, G. J., WEATHERBY, R., MURPHY, P. W. & LYTTLE, A. D. 1997. The effect of weight training volume on hormonal output and muscular size and function. *Journal of Strength and Conditioning Research,* 11, 148-154.

PHILLIPS, S. M. 2004. Protein requirements and supplementation in strength sports. *Nutrition,* 20, 689-695.

PHILLIPS, S. M., TIPTON, K. D., AARSLAND, A., WOLF, S. E. & WOLFE, R. R. 1997. Mixed muscle protein synthesis and breakdown after resistance exercise in humans. *Am J Physiol,* 273, E99-107.

RADAELLI, R., BOTTON, C. E., WILHELM, E. N., BOTTARO, M., BROWN, L. E., LACERDA, F., GAYA, A., MORAES, K., PERUZZOLO, A. & PINTO, R. S. 2014. Time course of low- and high-volume strength training on neuromuscular adaptations and muscle quality in older women. *Age (Dordr),* 36, 881-92.

RADAELLI, R., BOTTON, C. E., WILHELM, E. N., BOTTARO, M., LACERDA, F., GAYA, A., MORAES, K., PERUZZOLO, A., BROWN, L. E. & PINTO, R. S. 2013. Low- and high-volume strength training induces similar neuromuscular improvements in muscle quality in elderly women. *Exp Gerontol,* 48, 710-6.

RADAELLI, R., FLECK, S. J., LEITE, T., LEITE, R. D., PINTO, R. S., FERNANDES, L. & SIMAO, R. 2015. Dose-response of 1, 3, and 5 sets of resistance exercise on strength, local muscular endurance, and hypertrophy. *J Strength Cond Res,* 29, 1349-58.

RIBEIRO, A. S., SCHOENFELD, B. J., PINA, F. L. C., SOUZA, M. F., NASCIMENTO, M. A., DOS SANTOS, L., ANTUNES, M. & CYRINO, E. S. 2015. Resistance training in older women: Comparison of single vs. multiple sets on muscle strength and body composition. *Isokinetics and Exercise Science,* 23, 53-60.

RONNESTAD, B. R., EGELAND, W., KVAMME, N. H., REFSNES, P. E., KADI, F. & RAASTAD, T. 2007. Dissimilar effects of one- and three-set strength training on strength and muscle mass gains in upper and lower body in untrained subjects. *J Strength Cond Res,* 21, 157-63.

SAMPSON, J. A. & GROELLER, H. 2016. Is repetition failure critical for the development of muscle hypertrophy and strength? *Scand J Med Sci Sports,* 26**,** 375-83.

SCHOENFELD, B. J. 2010. The mechanisms of muscle hypertrophy and their application to resistance training. *J Strength Cond Res,* 24**,** 2857-72.

SCHOENFELD, B. J., OGBORN, D. & KRIEGER, J. W. 2016a. Effects of Resistance Training Frequency on Measures of Muscle Hypertrophy: A Systematic Review and Meta-Analysis. *Sports Med,* 46**,** 1689-1697.

SCHOENFELD, B. J., OGBORN, D. & KRIEGER, J. W. 2017. Dose-response relationship between weekly resistance training volume and increases in muscle mass: A systematic review and meta-analysis. *J Sports Sci,* 35**,** 1073-1082.

SCHOENFELD, B. J., POPE, Z. K., BENIK, F. M., HESTER, G. M., SELLERS, J., NOONER, J. L., SCHNAITER, J. A., BOND-WILLIAMS, K. E., CARTER, A. S., ROSS, C. L., JUST, B. L., HENSELMANS, M. & KRIEGER, J. W. 2016b. Longer Interset Rest Periods Enhance Muscle Strength and Hypertrophy in Resistance-Trained Men. *J Strength Cond Res,* 30**,** 1805-12.

SCHOENFELD, B. J., RATAMESS, N. A., PETERSON, M. D., CONTRERAS, B., SONMEZ, G. T. & ALVAR, B. A. 2014. Effects of different volume-equated resistance training loading strategies on muscular adaptations in well-trained men. *J Strength Cond Res,* 28**,** 2909-18.

SCHOENFELD, B. J., RATAMESS, N. A., PETERSON, M. D., CONTRERAS, B. & TIRYAKI-SONMEZ, G. 2015. Influence of Resistance Training Frequency on Muscular Adaptations in Well-Trained Men. *J Strength Cond Res,* 29**,** 1821-9.

SEYNNES, O. R., DE BOER, M. & NARICI, M. V. 2007. Early skeletal muscle hypertrophy and architectural changes in response to high-intensity resistance training. *J Appl Physiol (1985),* 102**,** 368-73.

SOONESTE, H., TANIMOTO, M., KAKIGI, R., SAGA, N. & KATAMOTO, S. 2013. Effects of training volume on strength and hypertrophy in young men. *J Strength Cond Res,* 27**,** 8-13.

STOKES, T., HECTOR, A. J., MORTON, R. W., MCGLORY, C. & PHILLIPS, S. M. 2018. Recent Perspectives Regarding the Role of Dietary Protein for the Promotion of Muscle Hypertrophy with Resistance Exercise Training. *Nutrients,* 10.

SUNDSTRUP, E., JAKOBSEN, M. D., ANDERSEN, C. H., ZEBIS, M. K., MORTENSEN, O. S. & ANDERSEN, L. L. 2012. Muscle activation strategies during strength training with heavy loading vs. repetitions to failure. *J Strength Cond Res,* 26**,** 1897-903.

TANG, J. E., PERCO, J. G., MOORE, D. R., WILKINSON, S. B. & PHILLIPS, S. M. 2008. Resistance training alters the response of fed state mixed muscle protein synthesis in young men. *Am J Physiol Regul Integr Comp Physiol,* 294**,** R172-8.

TERZIS, G., GEORGIADIS, G., STRATAKOS, G., VOGIATZIS, I., KAVOURAS, S., MANTA, P., MASCHER, H. & BLOMSTRAND, E. 2008. Resistance exercise-induced increase in muscle mass correlates with p70S6 kinase phosphorylation in human subjects. *Eur J Appl Physiol,* 102**,** 145-52.

TERZIS, G., SPENGOS, K., MASCHER, H., GEORGIADIS, G., MANTA, P. & BLOMSTRAND, E. 2010. The degree of p70 S6k and S6 phosphorylation in human skeletal muscle in response to resistance exercise depends on the training volume. *Eur J Appl Physiol,* 110**,** 835-43.

TIBANA, R. A., FRANCO, O. L., CUNHA, G. V., SOUSA, N. M. F., SOUSA NETO, I. V., CARVALHO, M. M., ALMEIDA, J. A., DURIGAN, J. L. Q., MARQUETI, R. C., NAVALTA, J. W., LOBO, M. O., VOLTARELLI, F. A. & PRESTES, J. 2017. The Effects of Resistance Training Volume on Skeletal Muscle Proteome. *Int J Exerc Sci,* 10**,** 1051-1066.

WERNBOM, M., AUGUSTSSON, J. & THOMEE, R. 2007. The influence of frequency, intensity, volume and mode of strength training on whole muscle cross-sectional area in humans. *Sports Med,* 37**,** 225-64.

WILKINSON, S. B., PHILLIPS, S. M., ATHERTON, P. J., PATEL, R., YARASHESKI, K. E., TARNOPOLSKY, M. A. & RENNIE, M. J. 2008. Differential effects of resistance and endurance exercise in the fed state on signalling molecule phosphorylation and protein synthesis in human muscle. *J Physiol,* 586**,** 3701-17.

WILLOUGHBY, D. S., STOUT, J. R. & WILBORN, C. D. 2007. Effects of resistance training and protein plus amino acid supplementation on muscle anabolism, mass, and strength. *Amino Acids,* 32**,** 467-77.

WOLFE, R. R. 2006. The underappreciated role of muscle in health and disease. *Am J Clin Nutr,* 84**,** 475-82.

ZOURDOS, M. C., KLEMP, A., DOLAN, C., QUILES, J. M., SCHAU, K. A., JO, E., HELMS, E., ESGRO, B., DUNCAN, S., GARCIA MERINO, S. & BLANCO, R. 2016. Novel Resistance Training-Specific Rating of Perceived Exertion Scale Measuring Repetitions in Reserve. *J Strength Cond Res,* 30**,** 267-75.