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Resistance Training Load Effects on Muscle Hypertrophy and Strength Gain: Systematic Review and Network Meta-analysis

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ABSTRACT

LOPEZ, P., R. RADAELLI, D. R. TAAFFE, R. U. NEWTON, D. A. GALVÃO, G. S. TRAJANO, J. L. TEODORO, W. J. KRAEMER, K. HÄKKINEN, and R. S. PINTO. Resistance Training Load Effects on Muscle Hypertrophy and Strength Gain: Systematic Review and Network Meta-analysis. *Med. Sci. Sports Exerc.*, Vol. 53, No. 6, pp. 1206–1216, 2021. **Purpose:** This study aimed to analyze the effect of resistance training (RT) performed until volitional failure with low, moderate, and high loads on muscle hypertrophy and muscle strength in healthy adults and to assess the possible participant-, design-, and training-related covariates that may affect the adaptations. **Methods:** Using Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, MEDLINE, CINAHL, EMBASE, SPORTDiscus, and Web of Science databases were searched. Including only studies that performed sets to volitional failure, the effects of low- (>15 repetitions maximum (RM)), moderate- (9–15 RM), and high-load (≤8 RM) RTs were examined in healthy adults. Network meta-analysis was undertaken to calculate the standardized mean difference (SMD) between RT loads in overall and subgroup analyses involving studies deemed of high quality. Associations between participant-, design-, and training-related covariates with SMD were assessed by univariate and multivariate network meta-regression analyses. **Results:** Twenty-eight studies involving 747 healthy adults were included. Although no differences in muscle hypertrophy between RT loads were found in overall ($P = 0.113–0.469$) or subgroup analysis ($P = 0.871–0.995$), greater effects were observed in untrained participants ($P = 0.033$) and participants with some training background who undertook more RT sessions ($P = 0.031–0.045$). Muscle strength improvement was superior for both high-load and moderate-load compared with low-load RT in overall and subgroup analysis (SMD, 0.60–0.63 and 0.34–0.35, respectively; $P < 0.001–0.003$), with a nonsignificant but superior effect for high compared with moderate load (SMD, 0.26–0.28, $P = 0.068$). **Conclusions:** Although muscle hypertrophy improvements seem to be load independent, increases in muscle strength are superior in high-load RT programs. Untrained participants exhibit greater muscle hypertrophy, whereas undertaking more RT sessions provides superior gains in those with previous training experience. **Key Words:** STRENGTH TRAINING, VOLITIONAL FAILURE, MUSCLE HYPERTROPHY, MUSCLE STRENGTH

Resistance training is a popular and effective modality to improve muscle function, functional performance, and health parameters in a wide range of healthy and clinical populations. Among the many expected outcomes, increases in muscle size and strength are considered important and desirable by individuals and clinicians either for performance or health and functional improvement. In the 1940s, DeLorme and Watkins (1) proposed undertaking resistance exercise sets until neuromuscular volitional failure to maximize such benefits. Although a vast body of research work in this area has been published (2–7), issues regarding how to optimize resistance training outcomes remain (8,9). Furthermore, controversies regarding how volitional failure is operationalized call into question the implementation of this technique in populations other than strength athletes, as

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participants' motivation and tolerance, discomfort, and neuromuscular fatigue affect the performance and results related to this training program.

Load selection has been considered an important resistance training variable to successfully increase muscle size and strength across different populations (10). Considering Henneman's size principle (i.e., motor units are recruited from smallest to largest) (11), studies have advocated in favor of either high loads (12–15) or both low and high loads (16) to achieve maximal or near-maximal recruitment of motor units during fatiguing contractions to induce muscle hypertrophy. Although this is a topic of intense debate in the literature, when low-load sets are performed until volitional failure, neuromuscular fatigue necessitates increasing percentage recruitment of the motor unit pool, and through this mechanism (12), such training may produce a meaningful drive for muscle hypertrophy. For example, Mitchell et al. (6) and Lim et al. (5) have reported that 10 wk of resistance training until volitional failure in untrained men at low and high loads (30% and 80% of 1 repetition maximum (1-RM)) resulted in similar increases in quadriceps femoris muscle volume (6.8% and 7.2%, respectively) and muscle fiber cross-sectional area of the vastus lateralis (ranging from 15% to 20% in both groups). These findings indicate that muscle hypertrophy may be more responsive in untrained individuals because of the large window for adaptation, masking differential effects of training modalities and dosages (17), and not show an obvious load-dependent relationship when resistance training sets are performed until volitional failure (6,18). In contrast, Schoenfeld and colleagues (7) reported that 8 wk of resistance training at high loads (2–4 RM) induced greater strength gains in recreationally trained men compared with moderate loads (8–12 RM), whereas increases in elbow extensor and quadriceps femoris muscle thickness were higher for the moderate-load group. Consequently, it is unclear as to loading effects on muscle hypertrophy when resistance training is undertaken until volitional failure. Furthermore, despite previous meta-analyses examining low (≤60% of 1-RM) and higher resistance training load (>60% of 1-RM) effects on muscle strength and hypertrophy (9,19), the lack of meta-analyses comprising a large number of studies comparing well-defined ranges of load such as low- (<60% of 1-RM), moderate- (between 60% and 79% of 1-RM), and high-load resistance training (≥80% of 1-RM) through robust meta-analytic approaches such as network meta-analysis precludes the determination of an appropriate load for outcomes of interest in healthy adults with different pretraining genetic and morphological characteristics.

Other issues comparing resistance training loads are related to the heterogeneity of study designs such as the participants involved (men vs women or combined), training status (untrained vs recreationally trained vs strength athletes), experimental design (between- and within-subject), assessed outcomes (lower-, upper-, and whole-body), and training prescription (number of sessions; operational definition of volitional failure and its implementation and verification). These different characteristics among studies may preclude the accurate evaluation of an optimal resistance training load, considering specific methodological or resistance training prescription characteristics when full and similar recruitment of the motor unit pool is achieved. As a result, the purposes of the review and analysis are to 1) analyze the effect of resistance training performed until failure with low, moderate, and high loads on muscle hypertrophy and muscle strength in healthy adults and 2) assess the possible participant-, design-, and training-related covariates that may affect the hypertrophy and strength gains.

METHODS

Study selection procedure. The study was undertaken in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (20,21), and the method used was based on the minimum criteria established by the Cochrane Back Review Group (22). The review included published data from experimental studies that evaluated the effects of low (<60% of 1-RM, or >15 RM), moderate (between 60% and 79% of 1-RM, or 9–15 RM), and high (≥80% of 1-RM, or ≤8 RM) loads in resistance training performed until volitional failure in healthy adults (23). The primary outcomes of this review were muscle hypertrophy (i.e., defined as a measure of muscle mass or size) and muscle strength (i.e., defined by 1-RM tests). Studies were excluded when 1) they did not present sufficient information regarding the comparisons between different loads or pretraining and posttraining values in the resistance training programs; 2) interventions were shorter than 6 wk; 3) specific outcomes for this review or sufficient information were not reported (e.g., baseline and postintervention assessment, and within- and between-group mean difference); 4) resistance training involving blood flow restriction protocols; and 5) written in a language other than English. In the search strategy, titles and abstracts were first independently evaluated. When abstracts did not provide sufficient information, they were selected for full-text evaluation. Eligibility was assessed independently by two authors (P. L. and J. L. T.), with differences resolved by consensus.

The search was conducted up to December 2019 using the following electronic databases: MEDLINE, CINAHL, EMBASE, SPORTDiscus, and Web of Science. The terms used were as follows: "resistance training until failure" and "muscle hypertrophy" or "muscle strength" in association with a list of sensitive terms to search for experimental studies. In addition, a manual search was performed in the reference lists provided in the selected articles as well as in a previous systematic review (9) to detect studies potentially eligible for inclusion. The search strategy used is shown in the Supplemental Digital Content Table S1 (see in Supplemental Digital Content 1, literature search strategy, http://links.lww.com/MSS/C233).

Data extraction. The data extraction was performed via a standardized form. Information regarding participants, resistance training protocols, outcomes, and assessment techniques was collected. Study characteristics, intervention duration, number of sessions, sex, experimental design, training status, assessed outcomes, and resistance training prescription method were extracted, along with the main outcomes, whereas outcomes were extracted in their absolute units (e.g., kilograms for 1-RM assessments; millimeters or centimeters for muscle thickness). When graphs were used instead of numerical data, the graphs were measured using a specific tool for data extraction (WebPlotDigitizer, San Francisco, CA).

Assessment of risk of bias. The risk of bias of individual studies was evaluated according to the second version of the Cochrane risk-of-bias tool for randomized trials (RoB 2) (24), focusing on different aspects of trial design, conduct, and reporting. Each assessment using the RoB 2 tool is focused on the outcome level. The six-item instrument used to evaluate each included randomized controlled trial in each outcome of interest is as follows: 1) randomization process, 2) deviation from intended interventions, 3) missing outcome data, 4) measurement of the outcome, 5) selection of the reported result, and 6) overall analysis. Overall risk of bias was expressed as "low risk of bias" if all domains where classified as low risk, "some concerns" if some concern was raised in at least one domain but not classified as at high risk in any other, or "high risk of bias" if at least one domain was classified as high risk, or have multiple domains with some concerns (24).

Data analysis. In the network meta-analysis, the pooled-effect estimates were obtained from the standardized mean difference (SMD) of baseline to the final assessment of the intervention for each group. When studies did not provide standard deviation (SD) of change in the outcomes, these values were estimated using a correlation coefficient (r) of 0.5 and the equation:

$$\mathrm{SD}_{\mathrm{change}} = \sqrt{\mathrm{SD}^2_{\mathrm{baseline}} + \mathrm{SD}^2_{\mathrm{final}} - (2r \times \mathrm{SD}_{\mathrm{baseline}} \times \mathrm{SD}_{\mathrm{final}})}$$

as per the Cochrane Handbook guideline (25). Furthermore, to avoid overestimating the weight of a study by entering it multiple times in the analysis (25), experimental groups from the studies were combined when considered within the same resistance training load group (e.g., three sets of 30–40 RM and three sets of 100–150 RM defined as low-load resistance training [2]), as well as outcomes when considered within the same outcome category (e.g., lower-body muscle hypertrophy or upper-body muscle strength). Analyses were conducted for overall studies, and a subgroup analysis was provided for best-quality studies based on the risk of bias assessment. The network meta-analysis was performed following the current Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline items (26,27): 1) a network geometry was created to explore the comparisons between resistance training loads; 2) transitivity was tested by fitting a network inconsistency assumption along with Q test and side-splitting analyses between indirect and direct comparisons; and 3) effect size (ES) was generated considering the heterogeneity and the inconsistency level in the models. Statistical significance was assumed when the SMD reached an α value ≤0.05. According to Cohen (28), ES values of 0.0 to ≤0.5 indicate small; 0.51 to 0.79, medium; and ≥0.8, large effects. Furthermore, an estimation of the probability to be the best resistance training program for the outcome was provided based on the consistency values and expressed as a percentage. Outliers were explored by sensitivity analyses omitting one study at a time, generating pooled estimates, and comparing with the original estimates. To check for the presence of publication bias, a network funnel plot and the Egger's test were used, with a significant publication bias considered if the P value was <0.1 (29). The network meta-analysis was conducted using R (R Core Team, 2019) with the package *netmeta* (30). Forest plots presented for the outcome measures are after sensitivity analysis adjustments.

To test the association between SMD and specific covariates such as year of publication, experimental design (i.e., between-subject vs within-subject), sex (i.e., women vs men), training status (i.e., untrained vs recreationally trained), number of sessions, assessed outcomes (i.e., lower- vs upper-body outcomes), and the prescription method (i.e., %1-RM vs RM), univariate and multivariate network meta-regressions were used (31). Dichotomy variables were coded as 0 and 1, whereas continuous variables were used in the model to explain the variations in muscle hypertrophy and strength among all comparisons. The network meta-regression was conducted using Stata 14.0 with the package *mvmeta* (31).

RESULTS

Studies included. All studies selected reported the aim to compare the effect of different resistance training loads (i.e., low, moderate, or high) on muscle hypertrophy and strength in healthy men and women. We retrieved 5924 studies, 2629 of which were retained for screening after duplicate removals. Of these, 2515 were excluded, and 114 full-text articles were assessed for eligibility (Fig. 1). The eligibility assessment resulted in a total of 28 (2–7,32–53) studies included in the present review, network meta-analyses, and meta-regression, of which 24 studies (3–7,32–40,42–53) examined muscle hypertrophy and 23 studies (2–7,32,33,35,38–48,50–52) examined muscle strength. During the eligibility assessment, one of the authors from the studies of Au et al. (54) and Morton et al. (43) was contacted for further information, and it was confirmed that the study of Au et al. (54) was a follow-up analysis from Morton et al. (43). As a result, only the study of Morton et al. (43) was included in the systematic review.

Participants and intervention characteristics. A total of 747 healthy men and women with an average age of 23.4 ± 3.0 yr participated in the included studies. Seventeen studies compared low- versus high-load resistance training (2,5,6,33,34,36,38,39,42–46,49–51,53), four compared low- versus moderate-load (35,40,47,52), five compared moderate- versus high-load (7,32,37,41,48), and two studies compared low- versus moderate- versus high-load (3,4). Most of the studies involved men (19 of 28, or 67.9% [2–7,34,38–42, 44–48,53]) and untrained participants (21 of 28, or 75.0% [2–6,32–39,42,44–46,49–52]; Table S2, Supplemental Digital Content 2, characteristics of included studies, http://links.lww.com/MSS/C234). None of the studies included highly strength-trained individuals as defined by 1-RM test values reported in

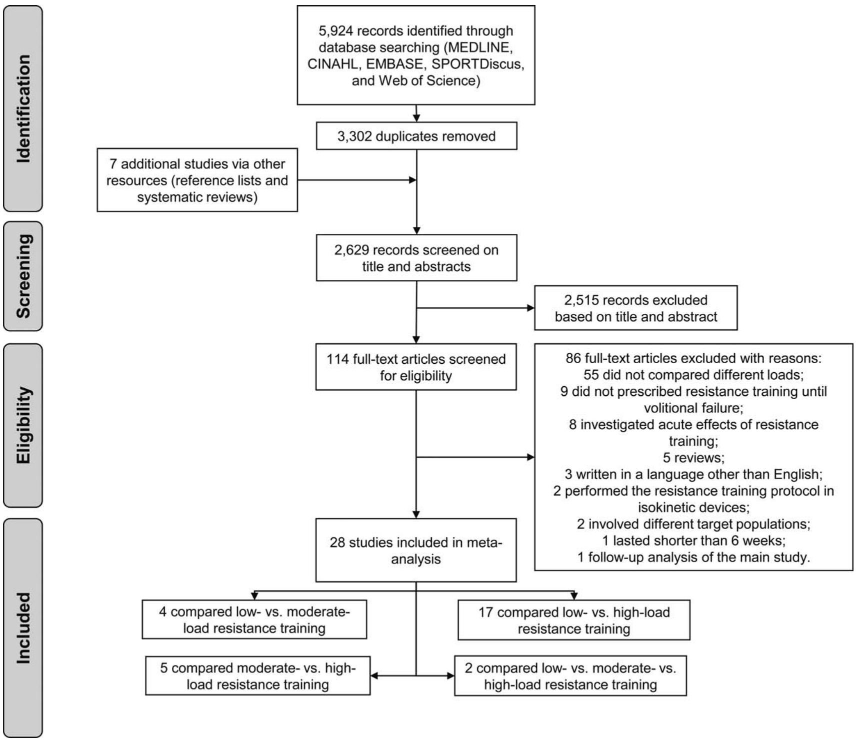

FIGURE 1—Flowchart of study selection process.

studies involving elite athletes (average relative strength of 2.0 body weights for back squat and 1.5 body weights for bench press (55,56).

The mean exercise intervention duration was 8.9 ± 2.1 wk, with an average of 24.6 ± 7.5 sessions (range, 16–48). Most of the studies undertook a between-subject experimental design (22 of 28, or 78.6% [2,3,5,7,32–38,40–43,46–49,51–53]) and prescribed the resistance training program by repetitions maximum (18 of 28, or 64.3% [2,3,7,32,35–37,40–43,46–49,51–53]; Table S2, Supplemental Digital Content 2, characteristics of included studies, http://links.lww.com/MSS/C234). Regarding the assessments, muscle hypertrophy was assessed for the lower limbs in 15 studies (3–7,32,35–39,43,44,49,50), followed by 8 studies assessing the upper limbs (4,7,32, 34,45,47,48,50) and 5 studies assessing the whole body (e.g., dual-energy x-ray absorptiometry) (33,40,42,46,53), whereas lower-body muscle strength was assessed in 20 studies (3–7,32,33,35,38–44,46, 48,50–52), followed by 12 studies assessing upper-body muscle strength (2,4,7,33,40,41,43,45,47,48,50,51), all using the 1-RM test. Eighteen studies reported the total volume performed during the intervention (4,5,7,32–35,37–45,48,50). The number of studies among the resistance training loads for muscle hypertrophy and muscle strength is shown in the network geometry (Fig. 2, panels A and B, respectively).

Risk of bias assessment. For muscle hypertrophy, 87.5% of the studies have *some concern* (21 of 24 studies

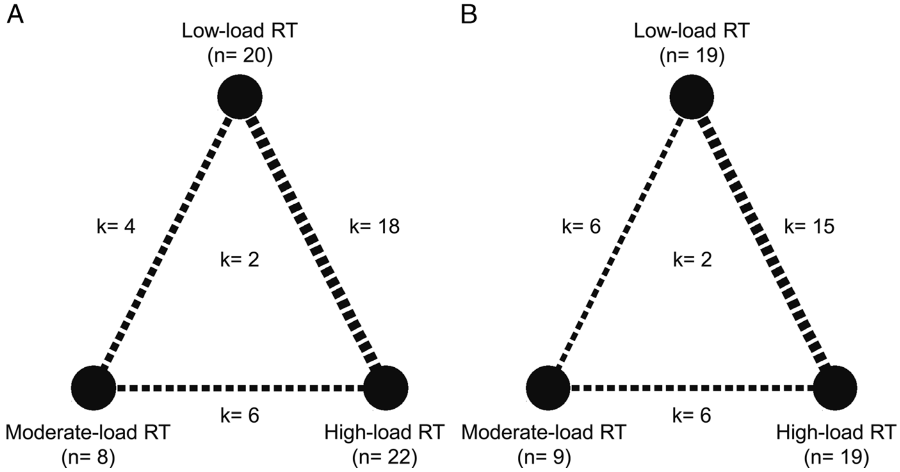

FIGURE 2—Network geometry of studies examining muscle hypertrophy (n = 24; A) and muscle strength (n = 23; B). *k*, number of comparisons; RT, resistance training.

TABLE 1. Risk of bias of included studies.

Outcome	Randomization Process	Deviation from Intended Interventions	Missing Outcome Data	Measurement of the Outcome	Selection of the Reported Result	Overall Bias
Muscle hypertrophy (*n* = 24)						
Low risk	0	24 (100%)	24 (100%)	13 (54.2%)	24 (100%)	0
Some concerns	23 (95.8%)	0	0	8 (33.3%)	0	21 (87.5%)
High risk	1 (4.2%)	0	0	3 (12.5%)	0	3 (12.5%)
Muscle strength (*n* = 23)						
Low risk	0	23 (100%)	23 (100%)	0	23 (100%)	0
Some concerns	20 (87.0%)	0	0	23 (100%)	0	20 (87.0%)
High risk	3 (13.0%)	0	0	0	0	3 (13.0%)

[3–7,33–39,43–50,53]), whereas the remaining have a *high risk* (3 of 24 studies, or 12.5% [32,40,42]) in the overall risk of bias assessment (Table 1). The concerns in muscle hypertrophy assessment were mainly due to the *randomization process* as studies did not report concealment allocation (some concerns: 23 of 24 studies, or 95.8% [3–7,32–40,43–50,53]) or did not follow any randomization (high risk: 1 of 24 studies, or 4.2% [42], 4.2%). Furthermore, studies were considered to have some concerns in the measurement of the outcome (8 of 24 studies, or 33.3% [4,7,38,39,44,47,48,50]) when evaluating muscle hypertrophy through unblinded evaluations and evaluations requiring technician or assessor direct analysis and interpretation (e.g., muscle ultrasound imaging), whereas they had a high risk (3 of 24 studies, or 12.5% [32,40,42]) when they did not use a reliable technique of assessment (e.g., skinfold or circumference). In the subgroup analysis for muscle hypertrophy, best-quality studies were those considered with low risk on the measurement of the outcome (3,5,6,33–37,43,45,46,49,53).

In the muscle strength overall risk of bias assessment, 87.0% of the studies have some concern (20 of 23 studies [3–7,32,33,35,38–41,43–48,50,52]), whereas the remaining have a high risk (3 of 23 studies, or 13.0% [2,42,51]; Table 1). The concerns were mainly due to the randomization process as studies did not report concealment allocation (some concerns: 20 of 23 studies, or 87.0% [3–7,32,33,35,38–41,43–48,50,52]) or if the participants were not randomly assigned in the experimental groups (high risk: 3 of 23 studies, or 13.0% [2,42,51]), and on the measurement of the outcome (some concerns: 23 of 23 studies, or 100% [2–7,32,33,35,38–48,50–52]) as studies assessed muscle strength with no blinding of testers. In the subgroup analysis for muscle strength, best-quality studies were considered those not presenting high risk in overall risk of bias assessment (3–7,32,33,35,38–41,43–48,50,52). The individual risk of bias assessment is shown in Supplemental Digital Content Figures S1A and B (Supplemental Digital Content 3, individual risk of bias assessment, http://links.lww.com/MSS/C235).

Resistance training load effects on muscle hypertrophy. Thirty-five comparisons were undertaken on muscle hypertrophy involving 24 studies (3–7,32–40,42–53). The results from the consistency network meta-analysis provided no differences in muscle hypertrophy between high- and low-load, moderate- and low-load, or high- and moderate-load resistance training ($P = 0.113$–0.469; Table 2 and Fig. 3). The heterogeneity was $I^2 = 0\%$. Furthermore, no differences between the loads were observed in the subgroup analysis involving the best-quality studies (number of comparisons = 16, $I^2 = 0\%$, $P = 0.871$–0.995; Table 2). Although the results of the consistency model indicate that moderate-load (84.5%) and high-load resistance training (75.8%) are the best load for muscle hypertrophy in overall and high-quality subgroup analyses, respectively, the ES values were unlikely to be considered meaningful (small ES: range, −0.09 to 0.15). The inconsistency between direct and indirect comparisons was not significant in the network analysis for all studies ($Q = 6.2$, $P = 0.103$) or in the subgroup analysis ($Q = 0.3$, $P = 0.957$), as well as in the node-splitting analysis across comparisons between load groups (all studies: $P = 0.424$–0.914; best-quality studies: $P = 0.615$–0.760). No publication bias was identified after the inspection of funnel plots asymmetry by Egger's test ($P = 0.497$–0.909).

In the univariate network meta-regression, the covariates (i.e., year of publication, experimental design, sex, training status, number of sessions, assessed limb, and prescription method) did not explain the variation in muscle hypertrophy

TABLE 2. Network meta-analysis consistency models for muscle hypertrophy and muscle strength in studies comparing low-, moderate-, and high-load resistance training in healthy adults.

Outcome	Comparisons		*k*	Sample	Pooled SMD	95% CI	*P*	Best Intervention Probability
Muscle hypertrophy	High vs low	All	19	347	0.12	−0.06 to 0.29	0.241	Overall analysis: 84.5% for moderate-load resistance training
		Best-quality	12	274	0.10	−0.14 to 0.33	0.871	Best quality: 75.8% for high-load resistance training
	Moderate vs low	All	7	128	0.20	−0.04 to 0.44	0.113	
		Best-quality	2	88	−0.06	−0.54 to 0.42	0.929	
	High vs moderate	All	9	107	−0.09	−0.33 to 0.16	0.469	
		Best-quality	2	51	0.15	−0.34 to 0.65	0.995	
Muscle strength	High vs low	All[a]	19	403	0.60	0.38 to 0.82	**<0.001**	Overall analysis: 98.2% for high-load resistance training
		Best-quality	16	325	0.63	0.38 to 0.88	**<0.001**	Best quality: 98.2% for high-load resistance training
	Moderate vs low	All[a]	9	152	0.34	0.05 to 0.62	**0.003**	
		Best-quality	9	152	0.35	0.05 to 0.65	**0.002**	
	High vs moderate	All[a]	10	125	0.26	−0.02 to 0.54	0.068	
		Best-quality	10	125	0.28	−0.02 to 0.58	0.066	

Bold values are significant.

[a] Adjustment after sensitivity analysis omitting one study at a time.

k, Number of comparisons.

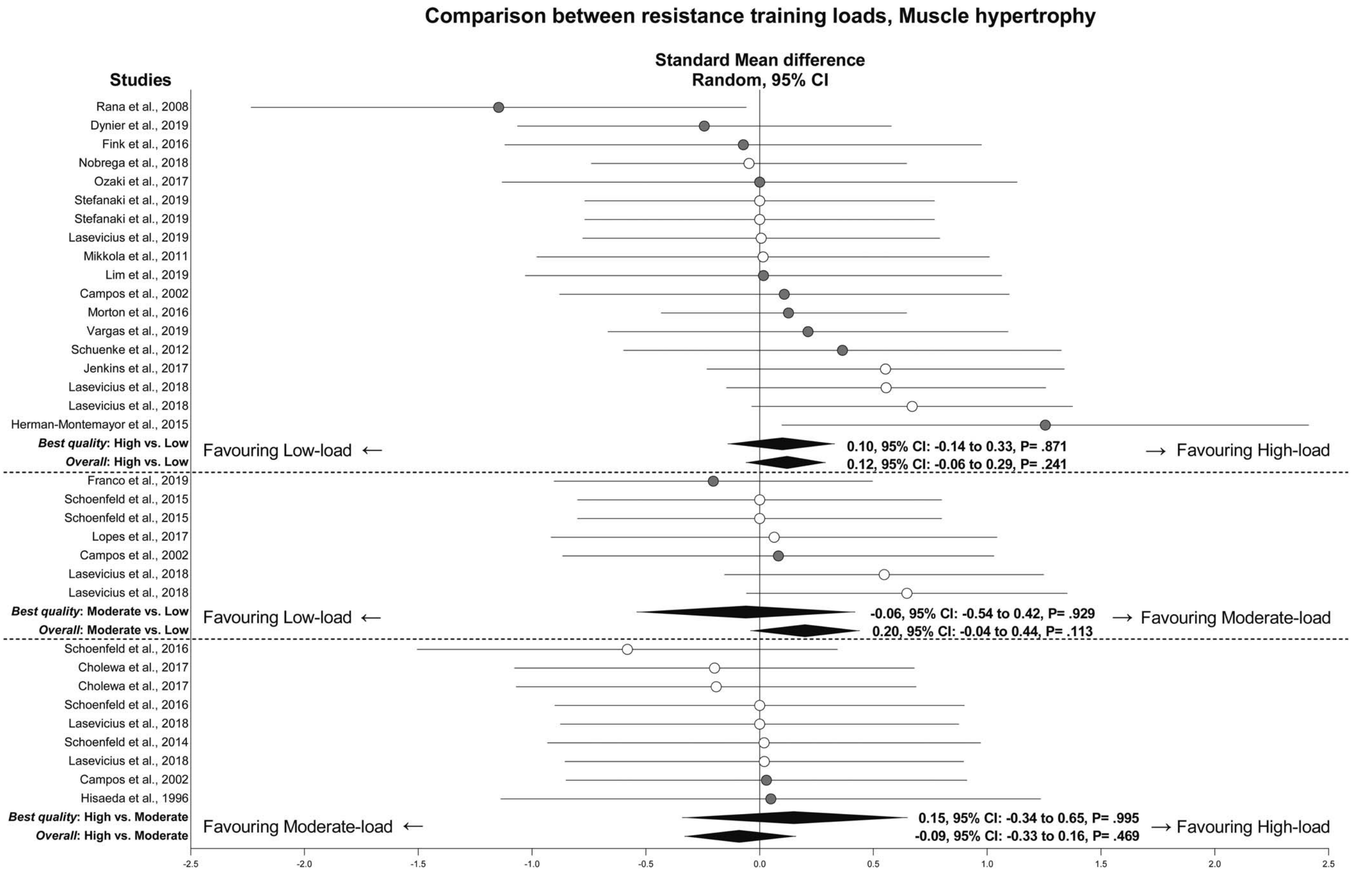

FIGURE 3—SMD effects between low-, moderate-, and high-load resistance training performed until volitional failure on muscle hypertrophy. Overall and subgroup analyses conducted with a network random-effects model. *Gray and white circles* represent study-specific estimates based on risk of bias assessment (low risk, and some concern or high risk of bias, respectively); *diamonds* represent pooled estimates of random-effects meta-analysis.

gains (P = 0.278–0.986; Supplemental Digital Content Table S3, Supplemental Digital Content 4, univariate meta-regression results, http://links.lww.com/MSS/C236). Regarding the multivariate model, there was a significant interaction for training status (P = 0.033), with untrained participants presenting higher effects on muscle hypertrophy in low- versus high-load resistance training comparison (Table 3). The number of sessions seems to influence the results in both moderate- versus low-load (P = 0.031) and high- versus moderate-load (P = 0.045) resistance training, with a higher number of sessions resulting in greater effects on muscle hypertrophy (Table 3). The remaining variables (i.e., year of publication, experimental design, sex, assessed limb, and prescription method) were not significant in explaining variations in muscle hypertrophy (P = 0.145–0.999).

Resistance training load effects on muscle strength. Thirty-nine comparisons were undertaken on muscle strength assessed by a 1-RM test involving 23 studies (2–7,32,33,35, 38–48,50–52). Visual inspection of funnel plots indicated a presence of publication bias (P = 0.014), and the study of Anderson and Kearney (2) was considered an outlier in the analysis. After the adjustment, the consistency network meta-analysis results show that high-load (SMD, 0.60; 95% confidence interval [CI], 0.38–0.82) and moderate-load (SMD, 0.34, 95% CI, 0.05–0.62) resulted in higher muscle strength effects when compared with low-load resistance training (P < 0.001 and 0.003, respectively). A nonsignificant effect (P = 0.068) was found favoring high-load when compared with moderate-load resistance training (Table 2 and Fig. 4). The heterogeneity was I^2 = 39.9%, with no presence of publication bias (P = 0.277). The results of the consistency models indicate that high-load resistance training has a probability of 98.2% to induce greater effects on muscle strength, also sustained in subgroup analyses (k = 36; Table 2) with heterogeneity I^2 = 43.7% and no effect of publication bias (P = 0.350). The inconsistency between direct and indirect comparisons was not significant in the network analysis for all studies (Q = 5.3, P = 0.150) and for subgroup analysis (Q = 4.4, P = 0.219), as well as in the node-splitting analyses (all studies: P = 0.588–0.892; best-quality studies: P = 0.674–0.871).

In the univariate network meta-regression, older studies accounted for the variation in muscle strength in the overall analysis (P = 0.021), whereas the remaining variables did not explain variation in muscle strength (i.e., experimental design, sex, training status, number of sessions, assessed limb, and prescription method; P = 0.097–0.984; Table S3, Supplemental Digital Content 4, univariate meta-regression results, http://links.lww.com/MSS/C236). Regarding the multivariate model, older studies (P = 0.023) and those with men (P = 0.037) presented higher effects on muscle strength in the low- versus high-load resistance training comparison (Table 3). The remaining variables

TABLE 3. Network meta-regression models for muscle hypertrophy and muscle strength.

Comparison	Covariates	Range	Coef ± SE	95% CI	*P*
Muscle hypertrophy					
High vs low	Year of publication	2002–2019	0.05 ± 0.05	−0.04 to 0.14	0.244
	Experimental design	Between- vs within-group	0.00 ± 0.33	−0.64 to 0.64	0.999
	Sex	Women vs men	0.22 ± 0.40	−0.64 to 1.01	0.583
	Training status	Untrained vs recreationally trained	−1.38 ± 0.65	−2.67 to −0.11	**0.033**
	Number of sessions	12–48	0.01 ± 0.01	−0.02 to 0.05	0.518
	Assessed limb	Lower- vs upper-body	0.03 ± 0.25	−0.46 to 0.52	0.902
	Prescription method	%1-RM vs RM	1.02 ± 0.70	−0.35 to 2.40	0.145
Moderate vs low	Year of publication	2002–2019	0.02 ± 0.05	−0.07 to 0.11	0.627
	Experimental design	Between- vs within-group	−0.66 ± 0.86	−2.34 to 1.03	0.447
	Sex	Women vs men	0.70 ± 0.76	−0.80 to 2.19	0.360
	Training status	Untrained vs recreationally trained	−1.15 ± 0.82	−2.76 to 0.46	0.161
	Number of sessions	16–24	0.09 ± 0.04	0.01 to 0.16	**0.031**
	Assessed limb	Lower- vs upper-body	−0.11 ± 0.31	−0.70 to 0.49	0.725
	Prescription method[a]	%1-RM vs RM	—	—	—
High vs moderate	Year of publication	1996–2018	−0.03 ± 0.03	−0.09 to 0.03	0.342
	Experimental design	Between- vs within-group	0.36 ± 0.70	−1.00 to 1.74	0.604
	Sex	Women vs men	0.48 ± 0.66	−0.82 to 1.78	0.471
	Training status	Untrained vs recreationally trained	0.23 ± 0.65	−1.05 to 1.51	0.721
	Number of sessions	16–33	0.08 ± 0.04	0.01 to 0.15	**0.045**
	Assessed limb	Lower- vs upper-body	−0.14 ± 0.31	−0.74 to 0.46	0.651
	Prescription method[a]	%1-RM vs RM	—	—	—
Muscle strength					
High vs low	Year of publication	1982–2019	−0.11 ± 0.05	−0.20 to −0.15	**0.023**
	Experimental design	Between- vs within-group	−0.47 ± 0.58	−1.60 to 0.66	0.411
	Sex	Women vs men	1.03 ± 0.50	0.06 to 2.00	**0.037**
	Training status	Untrained vs recreationally trained	0.73 ± 1.15	−1.53 to 3.00	0.526
	Number of sessions	12–48	−0.01 ± 0.03	−0.06 to 0.04	0.715
	Assessed limb	Lower- vs upper-body	0.28 ± 0.45	−0.60 to 1.16	0.535
	Prescription method	%1-RM vs RM	−1.79 ± 1.15	−4.05 to 0.47	0.121
Moderate vs low	Year of publication	2002–2019	−0.06 ± 0.23	−0.52 to 0.39	0.787
	Experimental design[a]	Between- vs within-group	—	—	—
	Sex	Women vs men	−0.95 ± 4.26	−9.30 to 7.40	0.823
	Training status	Untrained vs recreationally trained	1.65 ± 3.68	−5.56 to 8.86	0.654
	Number of sessions	16–27	−0.08 ± 0.07	−0.23 to 0.06	0.263
	Assessed limb	Lower- vs upper-body	−0.20 ± 0.49	−1.16 to 0.76	0.677
	Prescription method	%1-RM vs RM	−2.34 ± 4.26	−10.7 to 6.01	0.583
High vs moderate	Year of publication	2002–2017	0.04 ± 0.23	−0.40 to 0.48	0.848
	Experimental design[a]	Between- vs within-group	—	—	—
	Sex	Women vs men	−1.99 ± 4.06	−9.94 to 5.98	0.625
	Training status	Untrained vs recreationally trained	0.91 ± 3.37	−5.70 to 7.53	0.786
	Number of sessions	16–38	−0.07 ± 0.07	−0.20 to 0.06	0.283
	Assessed limb	Lower- vs upper-body	−0.48 ± 0.53	−1.52 to 0.55	0.360
	Prescription method	%1-RM vs RM	−1.02 ± 4.04	−8.95 to 6.90	0.800

Bold values are significant.

[a] Collinearity detected given the insufficient number of observations.

%1-RM, percentage of 1-RM.

did not explain variations in muscle strength in the comparisons (i.e., experimental design, training status, number of sessions, assessed limb, and prescription method; $P = 0.121–0.823$, Table 3).

DISCUSSION

There are three important findings from our systematic review and network meta-analysis of the dose–response relationship between resistance training load and gains in muscle hypertrophy and strength. First, in untrained and recreationally trained individuals (i.e., not strength athletes), muscle hypertrophy gains are likely to be similar regardless of resistance training load when performed to volitional failure over relatively short periods of intervention. In line with the physiological adaptation principle of *diminishing returns*, untrained participants exhibit greater muscle hypertrophy compared with those with even modest prior experience in resistance training. Furthermore, undertaking more resistance training sessions provides superior muscle size gains in those with previous training experience. Second, effects on muscle strength are load dependent, with higher loads resulting in greater gains over the relatively short interventions reviewed. Finally, the results for muscle hypertrophy and strength were maintained even when only the higher-quality studies were considered, that is, studies with less risk of bias. Therefore, although improvements in muscle hypertrophy seem to be load independent for untrained and recreationally trained individuals, muscle strength increases are superior with high-load resistance training programs of short duration.

The inclusion of experimental studies using repetitions until volitional failure is based on ensuring that a similar stressful stimulus was undertaken by all participants in the resistance training programs (57). Although performing resistance training until volitional failure is one way to eliminate a large amount of individual variability related to between-subject endurance capacity (i.e., individuals who are able to complete different numbers of repetitions at a given relative load) and ensures methodological feasibility when comparing different resistance training loads (57), other approaches have been

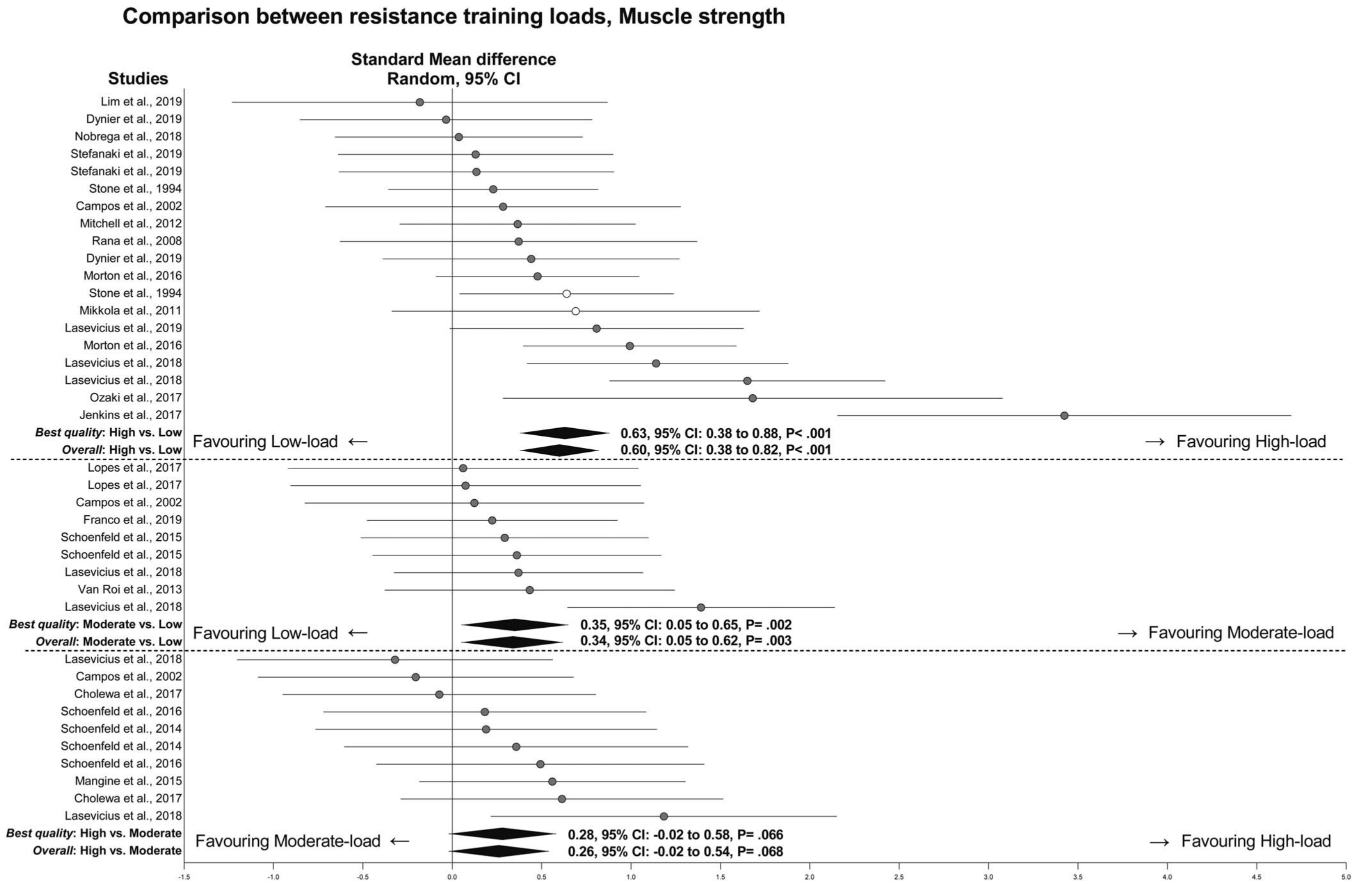

FIGURE 4—SMD effects between low-, moderate-, and high-load resistance training performed until volitional failure on muscle strength. Overall and subgroup analyses conducted with a network random-effects model. *Gray and white circles* represent study-specific estimates based on risk of bias assessment (low risk, and some concern or high risk of bias, respectively); *diamonds* represent pooled estimates of random-effects meta-analysis.

successfully used such as RM zones and percentage of 1-RM, where failure is not mandated but monitored to stay within a training range. Therefore, although exercising until volitional failure is not mandatory for neuromuscular adaptations (58,59), it was the strategy required to compare the efficacy of different resistance training load protocols (57).

Our findings are that performing as many repetitions as possible per set with different loads over relatively short interventions leads to similar muscle hypertrophy in individuals with none or moderate resistance training experience. It seems that any training load can produce a similar magnitude of muscle hypertrophy for different participants (men and women) and muscles assessed (lower- and upper-body). Thus, over relatively short training interventions in untrained or novice subjects, sets to failure are one strategy for gaining muscle hypertrophy, regardless of the load undertaken in resistance training. With other strategies, albeit beyond the scope of this review, if performed with a load that activates a high percentage of motor units, hypertrophy is likely to occur. However, it is important to note that the practical application may still favor the use of a lower number of repetitions using moderate to high loads as the performance of low loads until volitional failure results in higher discomfort due to the higher number of repetitions, longer time under muscular tension, and time required (60).

As revealed by the meta-regression, muscle hypertrophy derived from low-, moderate-, and high-load resistance training regimes, despite the modest and nonsignificant difference between them, seems to be affected by training status and number of sessions completed, that is, volume. Untrained participants exhibit a greater magnitude of muscle hypertrophy compared with those recreationally trained. As reported in previous literature, trained muscles may already present with an increased cross-sectional area (61) and lower anabolic signaling as observed in reduced AMPK and Akt phosphorylation after a resistance training session (62), resulting in an attenuated hypertrophic response in participants with previous resistance training experience. However, our findings also indicate greater muscle hypertrophy in recreationally trained participants who undertake a higher number of sessions compared with those undertaking less. It seems that participants with longer experience in resistance training (range, 2–7 yr) (7,40,41,43,47,48,53), although still not highly trained, require a higher volume of training to produce the same or greater hypertrophic adaptation exhibiting the principle of *diminishing returns*. Thus, although there were no differences between training loads for muscle hypertrophy, the meta-regression results suggest that novice participants are likely to experience superior gains than those with previous experience in resistance training undertaking the same volume, whereas a greater number of sessions may provide additional muscle hypertrophy for those with experience in resistance training. Given the lack of studies with more than 14-wk duration, any interpretation of these results for longer periods should be viewed with caution.

In contrast to muscle hypertrophy, muscle strength, as defined by 1-RM testing, was found to be dependent on high loads. This finding is expected following 1) the principle of *specificity* (13) as participants allocated in higher-load resistance training groups trained more closely to the requirement for the 1-RM test and presented greater transfer to this outcome, and 2) a combination of both neural and skeletal muscle adaptations derived from higher-load resistance training programs resulting in greater effects on muscle strength (38,63–65). Moreover, the magnitude of change in low- versus high-load resistance training was consistent with that previously reported by Schoenfeld et al. (9) and across all load comparisons favoring the highest loads. Regarding the difference between moderate- and high-load resistance, this comparison approached statistical significance ($P = 0.072$), and the ES of ~0.3 suggests a possible superior gain with high-load training protocols.

Interestingly, within the limitations of the relative paucity of training studies in which women were subjects, in the low- versus high-load comparison, men derived greater muscle strength benefits than women, whereas women improved their strength more than men in comparisons involving moderate-load training. These results may be related to sex differences in prior experience with resistance training and perceived exertion with resistance training sessions as previously suggested (66–68), and possible discrepancies between the prescribed and complied resistance training dosage (35). Moreover, the different time-course adaptations between men and women may also account for differential maximal strength gains over prolonged resistance training periods (63,64). However, we are unable to confirm this because of the short duration of the studies analyzed (ranging from 6 to 12 wk), lack of training variables reported in the studies undertaken by women (32,33,35–37,49–52), and the inability for a more robust narrative concerning studies of longer duration that did not make intensity comparisons in their designs (e.g., see Ref. [69]). Regarding the year of publication as a covariate, this variable was used because of the different results on muscle strength between current (5,9) and past literatures (2,51). These differences are likely to be related to study design, conduct, and control because well-designed studies tend to get smaller effects and reducing bias over the years (70). The larger effect found in the study by Anderson and Kearney (2) also seems to be explained by the low-load resistance training prescription involving more repetitions than any other study (Table S2, Supplemental Digital Content 2, characteristics of included studies, http://links.lww.com/MSS/C234), driving the heterogeneity and significance of this covariate in the muscle strength model. Furthermore, omitting the studies with a high risk of bias (2,42,51) also reduced the significance of this covariate in the model.

The strengths of the present review, network meta-analysis, and meta-regression are as follows: 1) a large number of studies ($n = 28$) with up to 747 healthy adults; 2) a model involving simultaneous comparison among low-, moderate-, and high-load resistance training; and 3) methodological feasibility for comparing different resistance training loads (i.e., statistical transitivity in the network meta-analysis model). In addition, considering previous findings on this topic (9,19), the present review also extends the results on muscle hypertrophy and strength, taking into account different moderators of resistance exercise response such as participants, training status, experimental design, assessed outcomes, and training prescription when different resistance training loads are undertaken until volitional failure. However, the present study has some limitations worthy of comment. First, studies included in the present review were mostly of low quality because of concerns regarding the randomization process and measurement of the outcome. Nonetheless, we used a subgroup analysis involving the "best-quality" studies to minimize such bias, and the results were maintained with minimal differences in the consistency analysis. Second, the present investigation excluded nonspecific muscle strength/performance measures such as maximal voluntary contraction and muscle endurance due to the variability in methods used to assess these outcomes and relevance to our specified outcomes, which would have increased the heterogeneity among studies. Therefore, our results regarding muscle strength should not be extended to nonspecific muscle strength tests such as isometric or isokinetic muscle strength tests. Third, although recreationally trained participants were included in our analyses, the strength levels reported in the studies were relatively modest, and certainly, the present results cannot be extrapolated for highly strength-trained individuals (e.g., bodybuilders, collegiate athletes in structured and supervised strength and conditioning programs, and power or strength athletes). Fourth, several studies (4,5,33,37,38,43–45,50,52) have performed multiple 1-RM testing throughout the study duration (range, 3–5 times). This may also be considered an issue masking an even greater difference between low- versus moderate- and high-load resistance training programs because of the number of exposures to maximal strength tests and the potential increases in muscle strength not related to the intervention *per se* (71). Fifth, the assessment of muscle size presents numerous challenges when evaluating training effects with regard to load, movement, range, and type of contraction, all influencing regional hypertrophy and further complicated by location of measurement, technology, and methodology (72). Finally, the present investigation included mostly studies undertaken in young adults (23.4 ± 2.9 yr) and should be interpreted with caution when extrapolated to different populations, as exercising until volitional failure is not considered a feasible resistance training prescription for all (73).

In summary, the present study explored the resistance training dosage for muscle hypertrophy and strength in healthy young adults. Our findings suggest that to promote muscle hypertrophy, varying loads of resistance training can be undertaken, and one strategy is to perform the exercise to the point of volitional failure. However, other approaches for maximizing recruitment of the motor unit pool maybe as effective, without the issues described previously regarding performing high numbers of repetitions with light loads. Thus, a practical application of our results is that a high-load resistance training program (≥80% of 1-RM, or ≤8 RM) can target both outcomes in shorter periods of training, whereas a moderate range of repetitions (9–15 RM) should be part of the resistance training program for those who do not tolerate exercising at higher (i.e., higher intensity or higher resistance) loads, eliciting gains in muscle hypertrophy and muscle strength superior to a low-load program. Furthermore, our results can also be applied to those participants with experience in resistance training, indicating a superior muscle hypertrophy effect undertaking more resistance training sessions.

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