European Journal of Sport Science

ISSN: 1746-1391 (Print) 1536-7290 (Online) Journal homepage: http://www.tandfonline.com/loi/tejs20

The efficacy of resistance training in hypoxia to enhance strength and muscle growth: A systematic review and meta-analysis

Domingo J. Ramos-Campo, Brendan R. Scott, Pedro E. Alcaraz & Jacobo A. Rubio-Arias

To cite this article: Domingo J. Ramos-Campo, Brendan R. Scott, Pedro E. Alcaraz & Jacobo A. Rubio-Arias (2017): The efficacy of resistance training in hypoxia to enhance strength and muscle growth: A systematic review and meta-analysis, European Journal of Sport Science, DOI: 10.1080/17461391.2017.1388850

To link to this article: http://dx.doi.org/10.1080/17461391.2017.1388850

European Journal of Sport Science, 2017
https://doi.org/10.1080/17461391.2017.1388850

REVIEW ARTICLE

The efficacy of resistance training in hypoxia to enhance strength and muscle growth: A systematic review and meta-analysis

DOMINGO J. RAMOS-CAMPO[1,2], BRENDAN R. SCOTT[3], PEDRO E. ALCARAZ[1,2], & JACOBO A. RUBIO-ARIAS[1,2]

[1]*Department of Physical Activity and Sport Science, Sport Science Faculty, Catholic University of Murcia, Murcia, Spain;* [2]*UCAM Research Center for High Performance Sport, Murcia, Spain &* [3]*School of Psychology and Exercise Science, Murdoch University, Perth, Australia*

Abstract

Recent studies have reported that resistance training in hypoxia (RTH) may augment muscle size and strength development. However, consensus on the effects of RTH via systematic review and meta-analysis is not yet available. This work aimed to systematically review studies which have investigated using RTH versus normoxic resistance training (NRT) to improve muscular size and strength, and to perform a meta-analysis to determine the effect of RTH on these adaptive parameters. Searches were conducted in PubMed, Web of Science and the Cochrane Library from database inception until 17 June 2017 for original articles assessing the effects of RTH on muscle size and strength versus NRT. The effects on outcomes were expressed as standardized mean differences (SMD). Nine studies (158 participants) reported on the effects of RTH versus NRT for muscle cross-sectional area (CSA) ($n = 4$) or strength ($n = 6$). RTH significantly increased CSA (SMD = 0.70, 95% confidence intervals (CI) 0.05, 1.35; $p = .04$) and strength (SMD = 1.88; 95% CI = 1.20, 2.56; $p < .00001$). However, RTH did not produce significant change in CSA (SMD = 0.24, 95% CI −0.19, 0.68, $p = .27$) or strength (SMD = 0.20; 95% CI = −0.27, 0.78; $p = .23$) when compared to NRT. Although RTH improved muscle size and strength, this protocol did not provide significant benefit over resistance training in normoxia. Nevertheless, this paper identified marked differences in methodologies for implementing RTH, and future research using standardized protocols is therefore warranted.

Keywords: *Environmental physiology, musculoskeletal, performance, strength, training*

Highlights

- Intermittent hypoxic resistance training (IHRT) is a novel training method that is proposed to improve muscular development and strength gains.
- This systematic review with meta-analysis reports that while IHRT is effective for increasing muscle size and strength, these improvements are not consistently shown to be greater than resistance training in normoxia.
- Available studies into IHRT have applied vastly different training programs, levels of hypoxia, and types of participants; these divergent methodologies have likely impacted on the results of studies in this area.
- Additional studies could include trained athletes, and investigate the efficacy of high-load circuit-based training in order to increase metabolic stress during IHRT.

Introduction

Skeletal muscle is an adaptable tissue that can be altered in responses to a given stimulus. Most notably, resistance training has a potent effect on the size and strength of muscle (Kraemer, Fleck, & Evans, 1996). Traditionally, acute resistance exercise variables have been manipulated to provide a desired training stimulus, including the muscle action, loading and volume, exercise selection and performance order, inter-set rest periods, repetition velocity and training frequency (Bird, Tarpenning, & Marino, 2005). Although certain controversy exists,

Correspondence: Domingo Jesús Ramos Campo, Department of Physical Activity and Sport Science, Sport Science Faculty, UCAM Universidad Católica San Antonio de Murcia Campus de los Jerónimos, N° 135 Guadalupe, Murcia 30107, España. E-mail: domingojesusramos@gmail.com; djramos@ucam.edu

resistance exercises protocols than maximize muscle fibre recruitment, time-under-tension and metabolic stress appear to contribute to intramuscular anabolic signalling (Gonzalez, Hoffman, Stout, Fukuda, & Willoughby, 2016). In recent years, altering the intramuscular environment via hypoxia has received research interest as another method to enhance the physiological experience of resistance training (Scott, Slattery, Sculley, & Dascombe, 2014). This was originally investigated by restricting blood flow to the exercising muscles to elicit localised hypoxia, which has been repeatedly shown to increase muscle size and strength even when lifting very light loads (Scott, Loenneke, Slattery, & Dascombe, 2015a). However, considering that this strategy can only be applied to limb muscles, researchers have also begun to examine whether performing resistance exercise in systemic hypoxia (via breathing hypoxic air) can provide similar benefits for whole-body training sessions (Ho, Kuo, Liu, Dong, & Tung, 2014; Manimmanakorn, Hamlin, Ross, Taylor, & Manimmanakorn, 2013; Nishimura et al., 2010).

Considering that one of the fundamental responses to exercise in hypoxia is an increased reliance on anaerobic metabolism, the benefits of resistance training in hypoxia (RTH) are thought to be mediated largely by increases in metabolic stress (Scott, Goods, & Slattery, 2016). Increased metabolic stress has been reported in several RTH investigations (Kon et al., 2010; Kon, Ikeda, Homma, & Suzuki, 2012; Ramos-Campo et al., 2017a, 2017b; Scott, Slattery, Sculley, Lockhart, & Dascombe, 2017), and is likely related to increased motor unit recruitment (Scott et al., 2017), which indicates that a larger portion of the muscle is stimulated to adapt during exercise. In addition, large endocrine responses have been observed following RTH (Kon et al., 2010, 2012; Yan, Lai, Yi, Wang, & Hu, 2016), although the importance of systemic increases in hormone concentrations for muscle hypertrophy has been questioned (Schoenfeld, 2013a; West, Burd, Staples, & Phillips, 2010).

Considering that athletes in most sports undertake resistance training to enhance physical performance and/or attenuate injury risk while competing, there has been growing interest in RTH from sporting organisations in recent years (Inness et al., 2016). Hypoxic training strategies such as RTH may also have therapeutic benefits for clinical populations who cannot tolerate vigorous exercise, such as those suffering from musculoskeletal impairments (Millet, Debevec, Brocherie, Malatesta, & Girard, 2016). However, despite these potential benefits for RTH, there is conjecture regarding whether RTH can actually facilitate greater muscle size and strength than the equivalent normoxic resistance training (NRT) (Ho et al., 2014). Therefore, the aim of this work was to systematically review the studies which have investigated using RTH to improve muscular size and strength, and to perform a meta-analysis to determine the effect of RTH on these adaptive parameters.

Methods

Study design

The methodological process was based on the recommendations indicated by the PRISMA declaration (Moher, Liberati, Tetzlaff, Altman, & Prisma Group, 2009). The eligibility criteria were established by the authors. For the meta-analysis, only experimental/quasi-experimental research that studied resistance training under a simulated hypoxic environment was considered. The study was approved by the University's Institutional Science Ethics Committee

Data sources and search profile

A comprehensive literature search was performed using PubMed-Medline, Web of Science and the Cochrane Library from database inception through 17 June 2017. The database searches were performed independently by two authors (JARA and DJRC) and the results obtained were the same. The following combination terms was used: "strength training" or "resistance training" or "weight training". The Boolean operator "AND" was used to combine these descriptors with: "hypoxia" or "altitude" or "hypoxic training". The flow diagram of the search process is shown in Figure 1.

Selection criteria

The specific inclusion criteria were: (1) studies examining the effect of resistance training under hypoxia for at least 4 weeks on strength performance (via repetition maximum tests) and/or cross-sectional area (CSA) and/or and lean mass; (2) the presence of a control group (NRT); (3) studies published in English and (4) studies provide information of outcomes both at baseline and follow-up. Research studies were excluded if they: (1) used a sample population with pathologies or not between 18 and 65 years of age; (2) were not an original investigation published in full; (3) did not specify the tests to be evaluated; (4) applied hypoxia via natural altitude training camps (i.e. not during resistance training alone) or other local hypoxia techniques such as blood flow restriction (5) did not provide or specify

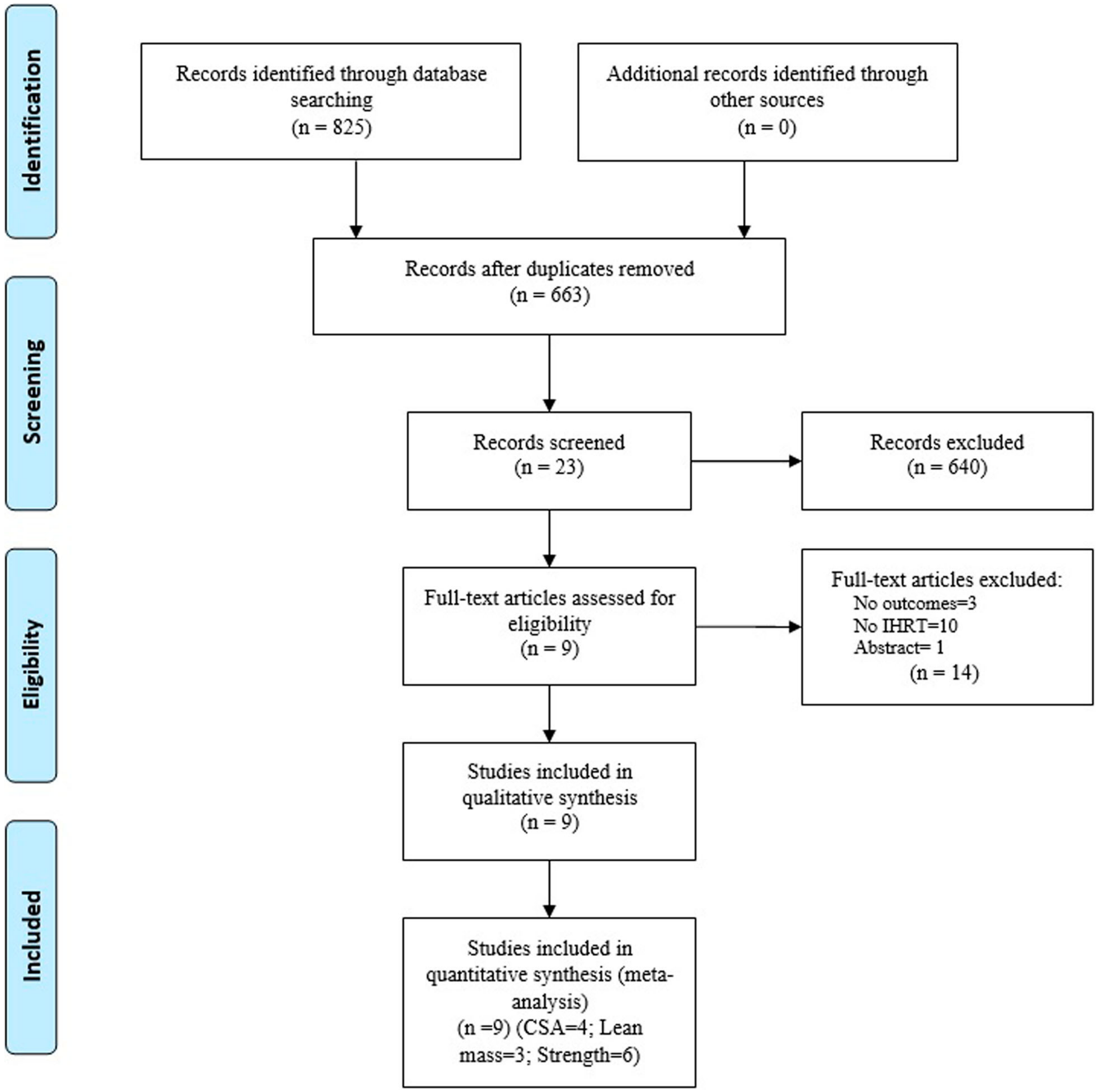

Figure 1. Search process flow diagram.

numerical data and (6) examined acute effects of interventions.

Study selection and data extraction

Retrieved articles were reviewed independently by two authors (JARA and DJRC) to choose potentially relevant articles; all disagreements on inclusion/exclusion were discussed and resolved by consensus. References of potentially relevant articles were also searched to find additional studies, and authors of selected studies were contacted for non-reported information. Two authors (JARA and DJRC) independently extracted data from the included studies. The following information was extracted: authors of the paper, number of participants included in each group, inspired fraction of oxygen (FiO_2), and the training status (untrained: subjects was not involved in regular resistance training program for at least 6 months before the study) (Ho et al., 2014); trained: participants achieved at least 12 months continuous resistance training history immediately prior to the study (Inness et al., 2016), age, weight and relative fat mass of participants. Regarding the characteristics of the resistance training programs, the information extracted included: the type of exercise, relative load lifted, training frequency (sessions/week), sets and repetitions performed, duration of training (weeks), total number of sessions, and the outcomes measured (e.g. strength performance, CSA and/or lean mass). When the article presented the results by figures, two authors (JARA and DJRC) determined the values of the outcome using a digitizer software. When there was a greater disagreement of 3%, a third experienced investigator (PEA) also digitized the data, and the mean of the two closest assessments was used for further analysis.

Evaluation of the methodology of the studies selected

The methodological quality of the selected studies was assessed with the Cochrane risk-of-bias tool (Higgins et al., 2011) that is comprised of the following parameters: (1) random sequence generation (selection bias); (2) allocation concealment (selection bias); (3) blinding of participants and personnel (performance bias); (4) blinding of outcome assessment (detection bias); (5) incomplete outcome data (attrition bias); (6) selective reporting (reporting bias) and (7) other bias. For each study, each item was described as having either a low risk of bias, an unclear risk of bias or a high risk of bias. Risk of bias was assessed independently by two authors (JARA and DJRC) using the Cochrane risk-of-bias tool (Higgins et al., 2011).

Data synthesis and statistical analysis

The meta-analysis and the statistical analysis were conducted using the Review Manager software (RevMan 5.2; Cochrane Collaboration, Oxford, UK). A random effects meta-analysis was conducted to determine summary effect of resistance training under hypoxia on strength performance, CSA and total lean mass. The effects of training on these outcomes between hypoxic and control groups were expressed as standard mean differences (SMD) and their 95% confidence intervals (CI). Differences within groups were calculated as SMD between the follow-up and baseline times, and threshold values for SMD were >0.2 (small), >0.6 (moderate), >1.2 (large) and >2.0 (very large) (Hopkins, Marshall, Batterham, & Hanin, 2009). The heterogeneity between the studies was evaluated through the I^2 statistic, and between-study variance using the tau-square (Tau^2) (Higgins, Thompson, Deeks, & Altman, 2003). The I^2 values of 30–60% represented a moderate level of heterogeneity. A p value < .1 suggests the presence of substantial statistical heterogeneity. The publication bias was evaluated through an asymmetry test as estimated from a funnel plot. A p value of less than 0.05 was considered to be statistically significant.

Results

Study selection

After the evaluation of 663 abstracts from primary sources, 640 were excluded; 23 were assessed as full texts. From these, 14 studies were excluded (Figure 1). Thus, nine studies ($n = 83$ for CSA;$n = 60$ for lean mass and $n = 143$ for strength performance) were included (Chycki et al., 2016; Friedmann et al., 2003; Ho et al., 2014; Inness et al., 2016; Kon et al., 2014; Kurobe et al., 2015; Manimmanakorn et al., 2013; Nishimura et al., 2010; Yan et al., 2016). One study (Yan et al., 2016) reported two different levels of hypoxia compared to the same control group in normoxia. All studies were published between 2003 and 2016 and had sample sizes in the range of 12–20 participants. Four analysed the effects of RTH on CSA (Friedmann et al., 2003; Kon et al., 2014; Manimmanakorn et al., 2013; Nishimura et al., 2010), three investigated the effects on lean mass (Chycki et al., 2016; Kon et al., 2014; Yan et al., 2016) and six studies analysed the effects of RTH on strength performance (Ho et al., 2014; Inness et al., 2016; Kon et al., 2014; Kurobe et al., 2015; Nishimura et al., 2010; Yan et al., 2016).

Participants were mostly trained subjects with mean age (SD) ranging from 21.2 (1.9) to 28.4 (1.6) (Table I). Fat mass ranged from 11.1 (6.5)% (Ho et al., 2014) to 17.3 (1.8)% (Kon et al., 2014), although some studies did not report fat mass (Table I). Exercise program duration ranged from 4 to 8 weeks with a frequency of 2–3 sessions per week. Two studies used low-load RTH and NYH (6 sets of more than 25 repetitions at 20–30% of 1-RM) (Friedmann et al., 2003; Manimmanakorn et al., 2013), and one study implemented high-load resistance training (two to four sets of three to six repetitions with ≥75% of 1-RM) (Inness et al., 2016). The remainder of the studies investigated moderate-load resistance training, similar to that typically prescribed to facilitate muscle hypertrophy (3–5 sets of 10 repetitions at 70% of 1-RM) (Chycki et al., 2016; Ho et al., 2014; Kon et al., 2014; Kurobe et al., 2015; Nishimura et al., 2010; Yan et al., 2016). Seven studies used lower limb exercise (Chycki et al., 2016; Friedmann et al., 2003; Ho et al., 2014; Inness et al., 2016; Kon et al., 2014; Manimmanakorn et al., 2013; Yan et al., 2016), while others used multijoint upper body exercises such as bench press (Chycki et al., 2016; Kon et al., 2014), or single-joint arm flexion and extension exercise (Kurobe et al., 2015; Nishimura et al., 2010) (Table I).

Table I. Main characteristics of included studies in the meta-analysis.

Study	FiO_2	Participants	Training status	Age (years)	Weight (kg)	Fat mass (%)	Exercise	Weeks	Sessions	Session/ week	Repetitions	Sets	Intensity (% 1-RM)
Chycki et al. (2016)	12,9	6 (M)	Rec. resistance trained	21,0 (2,4)	80,6 (12,3)	23,3 (4,6)	Bench press + squat	6	12	2	10	3	70
	21	6 (M)		23,3 (4,6)	81,1 (7,5)	18,3 (3,0)							
Friedmann et al. (2003)	12	10 (M)	Untrained	25,1 (2,9)	77,0 (9,0)		Knee ext	4	12	3	25	6	30
	21	9 (M)		24,3 (2,5)	72,9 (9,0)								
Ho et al. (2014)	15	9 (M)	Rec.trained	21,4 (2,2)	66,5 (8,2)	11,1 (6,5)	Squat	6	18	3	10	3	70
	20	9 (M)		21,2 (1,9)	67,9 (9,5)	11,5 (4,9)							
Inness et al. (2016)	14,3	10 (M)	Strength trained		83,1 (7,5)		Squat + deadlift + lunge	7	21	3	2–4	2–4	75
	20	10 (M)			80,2 (12,0)								
Kon et al. (2014)	14,4	9 (M)	Rec. resistance trained	28,4 (1,6)	68,2 (2,2)	16,1 (1,3)	Bench press + leg press	8	16	2	10	5	70
	21	7 (M)		28,2 (1,4)	65,8 (3,7)	17,3 (1,8)							
Kurobe et al. (2015)	12,7	6 (M)	Untrained	23,0 (1,0)	60,2 (1,6)		Elbow ext	8	24	3	10	3	70
	21	7 (M)											
Manimmanakorn et al. (2013)	80% SpO_2	10 (F)	Well-trained netball players				Knee fl and ext	5	15	3	ext (each set): 28/ 24/22±2 fl:36/31/26±3	6 (3 ext + 3 fl)	20
	21	10 (F)											
Nishimura et al. (2010)	16	7 (M)	Untrained	22,7 (2,7)	66,8 (6,0)	12,3 (3,0)	Elbow fl and ext	6	12	2	10	4	70
	21	7 (M)		21,6 (1,6)	65,0 (8,1)	12,8 (4,5)							
Yan et al. (2016)	12,6	8 (M)	Rec. trained	22,2 (2,6)	70,5 (10,0)	12,0 (3,4)	Barbell back squat	5	10	2	10	5	70
	16	9 (M)				10,1 (3,1)							
	21	8 (M)				12,7 (5,6)							

Note: M: male; F: female; fl: flexion; ext: extension; FiO_2: inspired fraction of oxygen; Rec: recreationally; kg: kilogram; 1-RM: one-repetition maximum; mean (standard deviation).

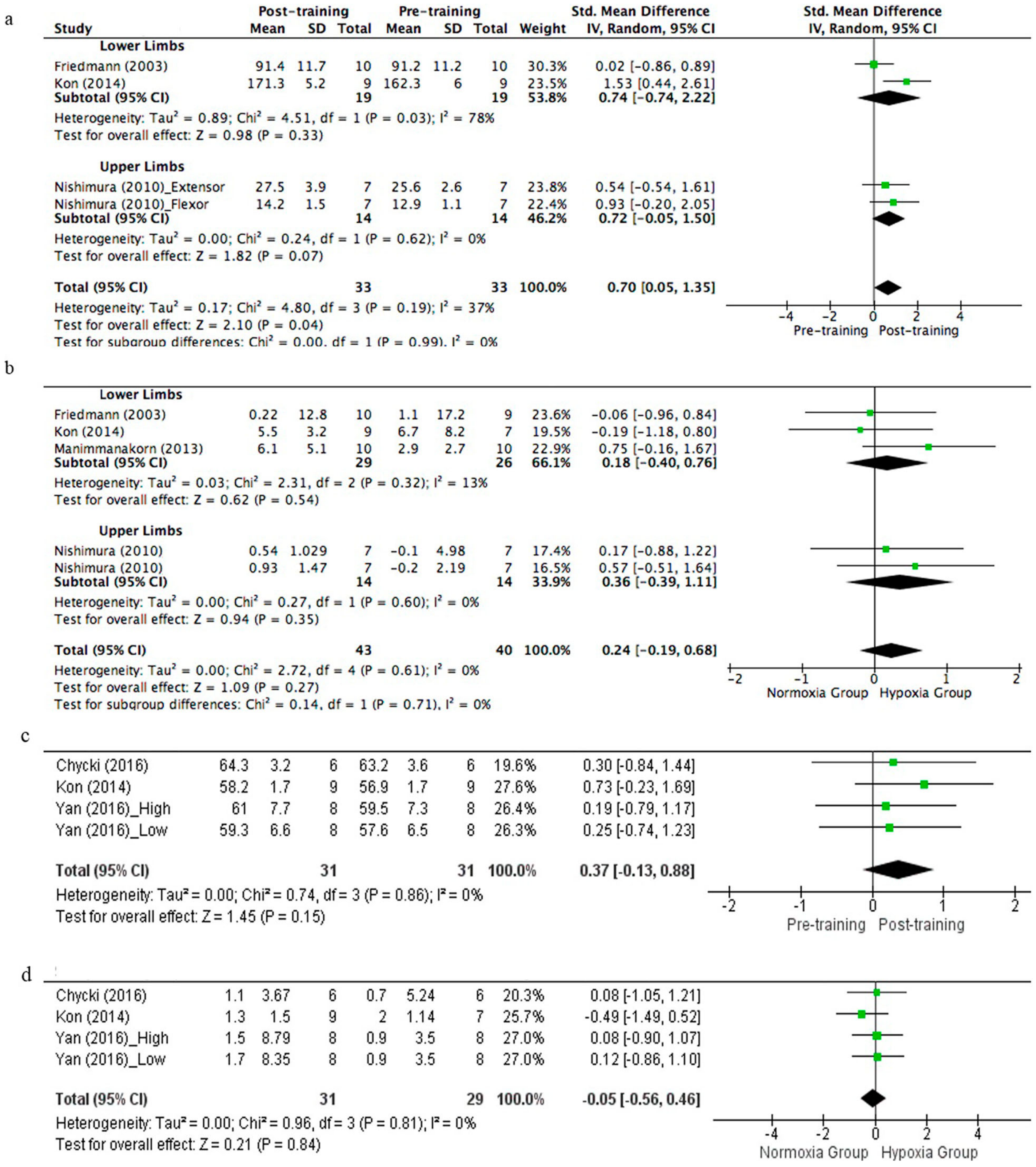

Figure 2. (a) Total effects of resistance training program on CSA pre-training vs. post-training; (b) total effects of resistance training program on CSA control group vs. hypoxic group; (c) total effects of resistance training program on Lean Mass (Dual-energy X-ray Absorptiometry) pre-training vs. post-training; and (d) total effects of resistance training program on Lean Mass control group vs. hypoxic group.

Meta-analyses

Changes in muscle size. In four groups from three studies which analysed the effects of resistance training under hypoxia on CSA (Friedmann et al., 2003; Kon et al., 2014; Manimmanakorn et al., 2013; Nishimura et al., 2010), significant increases were observed after the training programme (Figure 2 (a)) (SMD = 0.70, 95% CI 0.05, 1.35; $p = .04$). However, no significant differences were found between RTH and NRT programmes (Figure 2 (b)) (SMD = 0.24, 95% CI −0.19, 0.68, $p = .27$). The three studies (Chycki et al., 2016; Kon et al., 2014; Yan et al., 2016) (including four groups) which investigated the effects of RTH on total lean mass did not observe significant improvement (SMD = 0.37, 95% CI −0.13, 0.88; $p = 0.15$) after the training (Figure 2(c)), or differences when compared with a NRT control group (SMD = −0.05, 95% CI −0.56, 0.46, $p = .84$) (Figure 2(d)). Heterogeneity of effects was low among studies for CSA, and lean mass ($I^2 = 0\%$).

Changes in muscle strength. In the five groups included from four studies which implemented RTH for the lower limbs (Ho et al., 2014; Inness et al., 2016; Kon et al., 2014; Yan et al., 2016), favourable effects were observed on strength performance after resistance training under hypoxia (SMD = 1.66; 95% CI = 0.81, 2.50; $p = .0001$) (Figure 3(a)). Similarly, in four groups from three studies which implemented RTH for the upper limbs (Kon et al., 2014; Kurobe et al., 2015; Nishimura et al., 2010), a significant improvement was also observed after the training programme (SMD = 2.32; 95% CI = 1.03, 3.61; $p = .0004$) (Figure 3(a)). Regarding the effects on both upper and lower limbs, a significant effect on strength performance was observed after the training (SMD = 1.88; 95% CI = 1.20, 2.56; $p < .00001$). However, resistance training under hypoxia ($n = 74$) did not produce significant change in strength performance value (SMD = 0.20; 95% CI = −0.27, 0.78; $p = .23$) when compared to NRT ($n = 69$) (Figure 3(b)). Heterogeneity of effects was low among studies for strength performance ($I^2 = 0\%$).

Risk-of-bias assessment

Risk-of-bias assessment is shown in supplemental file. Overall, the risk of bias was high in all studies due to lack of random sequence of participants, the allocation concealment and the blinding of participants and researchers to assigned training conditions.

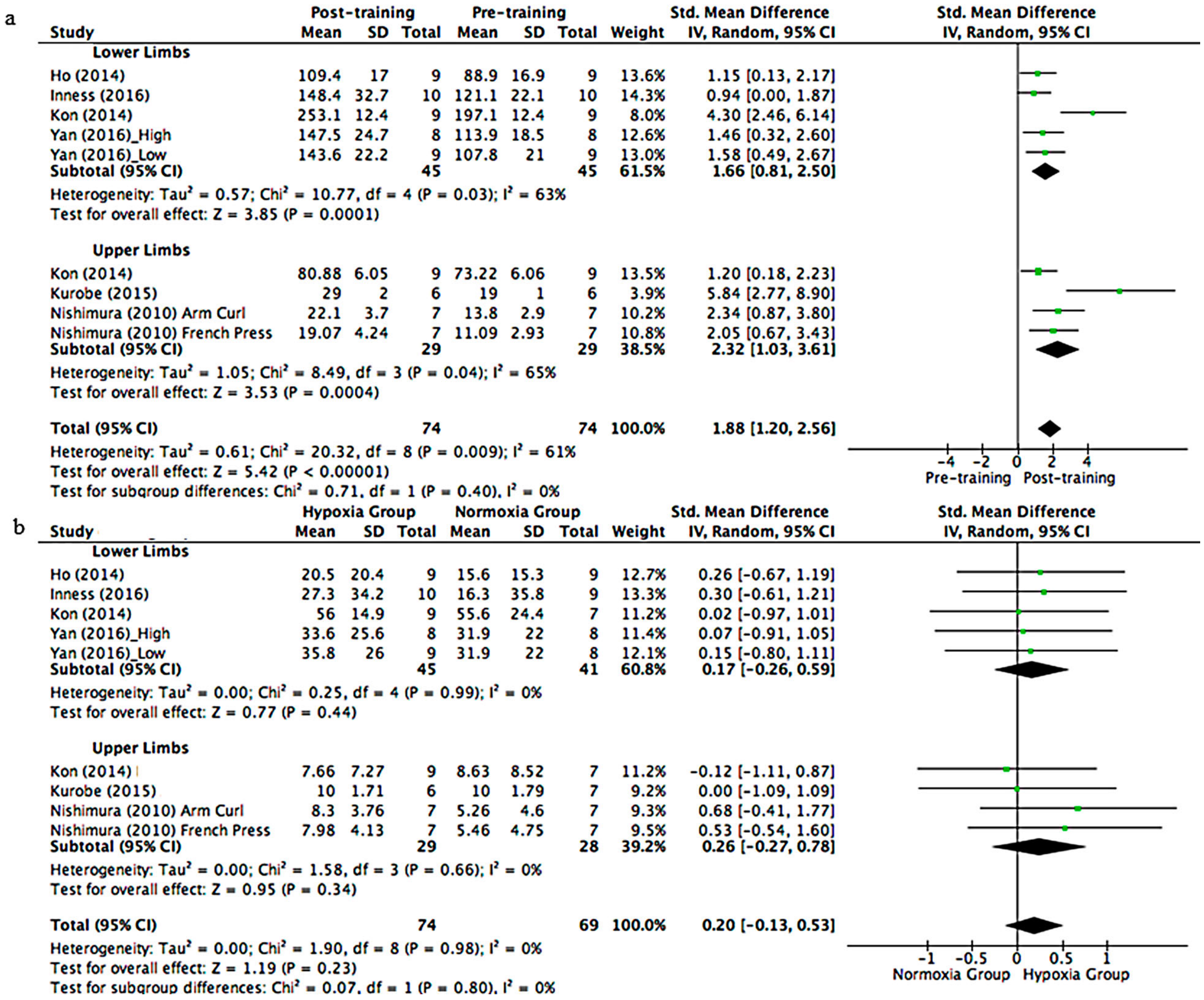

Figure 3. Total effects of resistance training program on 1-RM of upper and lower limb: (a) pre-training vs. post-training and (b) control group vs. hypoxic group.

Discussion

This paper aimed to systematically review studies which have examined RTH as a means of enhancing muscular hypertrophy and strength responses. The major findings indicate for the first time via meta-analysis that RTH does significantly improve muscular size and strength performance; however, these adaptations are not significantly greater than those observed after the same training in normoxia. Although these findings do not appear to support the use of RTH over NRT, this paper also highlights notable differences in the methodologies used between studies which may impact on the potential efficacy of RTH, and have led to inconsistent results between investigations.

Changes in muscle size

Although the interplay of mechanisms which facilitate muscular development are still being elucidated, resistance exercises protocols which maximize muscle fibre recruitment, time-under-tension and metabolic stress appear to benefit intramuscular anabolic signalling (Gonzalez et al., 2016), and therefore, muscle growth. Similarly, the mechanisms by which RTH may improve strength performance and increase muscular size likely include increased metabolic stress (Feriche, García-Ramos, Morales-Artacho, & Padial, 2017; Scott et al., 2016), and a resultant hypoxia-mediated increases in motor unit recruitment (Scott et al., 2017). Cellular swelling, resulting from metabolite accumulation in the cells, may also increase protein synthesis and decrease protein degradation, which would result in net protein accretion and muscle hypertrophy (Loenneke, Wilson, & Wilson, 2010). Nevertheless, despite these potential hypoxia-related mechanisms, our meta-analysis showed no statistically significant differences in hypertrophy adaptations following RTH versus NRT.

In the current study, a significant and large effect was observed for increases in muscle CSA after periods of RTH. However, when comparing muscular development between RTH and the equivalent NRT, there was a small and nonsignificant effect (SMD = 0.24, 95% CI −0.19, 0.68). In addition, there was no significant effect for changes in lean body mass between pre- and post-training time points for RTH, and no difference in lean body mass between hypoxic and normoxic training were found (SMD = −0.05, 95% CI −0.56, 0.46). Nevertheless, two separate studies have reported significantly larger increases in CSA following RTH when compared to the NRT group (Manimmanakorn et al., 2013; Nishimura et al., 2010), while another study observed significantly increased lean mass due to RTH when compared to NRT (Chycki et al., 2016). In addition, Kurobe et al. (2015) reported that increases in muscle thickness of the elbow extensors were significantly larger following RTH compared with NRT (note: this paper was excluded from our muscle size analyses as hypertrophy was not measured via CSA or lean mass). Considering these findings, it appears that RTH may provide a small added benefit for muscular development over the same training performed in normoxia (as evidenced by a small SMD in favour of RTH for CSA); however, the collective findings from this meta-analysis did not observe this effect to be significant. It is important to recognize that the disparate findings between studies published in this area are very likely due to alterations in the structure of the exercise performed and how manipulating the training structure may be affected by hypoxia.

To illustrate, research into RTH has employed varying inter-set rest intervals which range from 30 (Manimmanakorn et al., 2013) to 180 seconds (Inness et al., 2016). Although hypoxia increases reliance on anaerobic metabolism during resistance exercise and can therefore increase markers of metabolic stress (Kon et al., 2010, 2012; Ramos-Campo et al., 2017a, 2017b), longer inter-set recovery periods may increase the clearance of metabolic products from the muscles prior to the next set (Scott, Slattery, & Dascombe, 2015b). In addition, hypoxia has been demonstrated to slow, but not stop, phosphocreatine resynthesis rates following muscular contractions (Haseler, Hogan, & Richardson, 1999). It therefore stands to reason that if exercise is structured with longer than necessary inter-set recovery periods, the degree of metabolic stress in the muscles will not accumulate as it would if shorter rest periods are used, because more time is available for removal of metabolic by products and for resynthesis of phosphocreatine stores. Considering these factors along with the importance of metabolic stress for muscle hypertrophy (Gonzalez et al., 2016), it is likely that for RTH to have benefits for hypertrophy over NRT, relatively brief inter-set rest periods are necessary to take advantage of the hypoxic stimulus (Scott et al., 2015b).

It is clear that RTH place more reliance on anaerobic energy production, via an increment of blood lactate, alterations in acid–base balance (Ramos-Campo et al., 2017a), and excess post-exercise oxygen consumption (Ramos-Campo et al., 2017b). Ramos-Campo et al. (2017a) observed significant increases in blood lactate and decreases in pH during RTH under high levels of hypoxia (13% FiO_2) versus the same protocol under normoxia. However, similar to the research from Kon et al.

(2010), Ramos-Campo et al. (2017a) did not find significant differences in blood lactate or pH values between NRT and the RTH protocol performed in moderate hypoxia (16% FiO_2). These results indicate that the level of hypoxia may impact on metabolic stress via a dose–response relationship that has not yet been established for RTH. Interestingly, a recent review from Gonzalez et al. (2016) suggested that exercise-induced metabolic stress may also play a role in acute activation of mTORC1 signalling. As mentioned before, metabolic stress results from exercise that primarily relies on anaerobic glycolysis as its major energy provider. Lactate directly affects muscle cells in vitro by increasing satellite cell activity as well as mTOR and p70S6k phosphorylation (Oishi et al., 2015), and these biochemical signalling responses are therefore likely to be primary mediators if any benefits are to be gained from RTH.

Changes in muscle strength

Considering alterations in muscle strength, a large effect was observed for improved RM test performance between pre- and post-training values after RTH. However, our results indicate that hypoxic training was not significantly more effective than the same training under normoxia, and only a small effect was observed between RTH compared with NRT for muscle strength (SMD = 0.20; 95% CI = −0.27, 0.78). As previously discussed, these findings may be related to inconsistencies in the exercise structure used between studies. This is because the potential for improved strength following RTH is thought to be largely mediated through hypertrophic adaptations (Scott et al., 2014), and to our knowledge, hypoxia-mediated neural adaptations have not yet been discovered. Interestingly though, one study has employed high-load training with long inter-set rest periods (180 seconds) for strength-trained subjects, and observed significantly enhanced strength the RTH group despite no significant changes in lean mass (Inness et al., 2016). However, the authors stated that the mechanisms underpinning improved strength, but not hypertrophy, in their study are difficult to reconcile as it is not known how hypoxia could augment neural adaptations to resistance training.

As it cannot be justified solely from the findings of Inness et al. (2016) that RTH produces greater neural adaptations than NRT, these adaptations to RTH may be approached from another perspective. For instance, the Inness et al. (2016) study is the only one carried out with highly resistance-trained men. It is known that training status can affect adaptations to power training in high-level athletes, possibly due to a plateau in strength and different neuromuscular strategies being employed (Baker, 2001) Therefore, based on the findings from Inness et al. (2016), it is possible that RTH may provide benefit for enhancing strength in already resistance-trained participants when a plateau in strength is reached. Nevertheless, the exact mechanisms by which this could occur have not been elucidated, and further evidence to this point is needed.

As highlighted previously, a potential limitation of this meta-analysis is the different training programs applied in the included studies. Although the heterogeneity of the outcomes studied was low, these varying approaches to RTH may have modified the muscular development and strength adaptations observed. To illustrate, the duration of RTH programs ranged between 4 and 8 weeks, and included training frequencies of two to three sessions per week (total sessions = 10–24). Furthermore, the training sessions differed in the manipulation of acute exercise variables; these included exercise protocols comprised of between 2 and 6 sets of 3–36 repetitions at 20->75% of 1-RM, and using different types of exercise (i.e. lower limb versus upper limb, multi-joint versus single-joint). In addition, the inter-set rest periods used ranged from 30 to 180 seconds, which would likely alter the metabolic stress and potential adaptive responses associated with RTH, as discussed previously (Scott et al., 2015b).

In addition, factors aside from acute exercise variables differed considerably between the studies included in this paper. The actual FiO_2 implemented in hypoxic conditions ranged from 13% to 16%, and it is possible that the level of hypoxia may impact on the magnitude of adaptations to RTH following a dose–response relationship (though this is yet to be investigated). In addition, the training status of participants used in these studies included untrained, recreationally trained and well-trained individuals. With increased metabolic stress being a likely driver for hypoxia-related hypertrophy, it is possible that well-trained individuals and athletes with already enhanced abilities to complete anaerobic exercise (e.g. improved buffering capacity) may not receive an equivalent physiological stimulus during RTH compared to an untrained individual. Finally, apart from the study by Manimmanakorn et al. (2013), a paucity of research has investigated the effects of RTH on women. Previous research using blood flow restriction to facilitate increased metabolite accumulation during knee extension exercise has shown that females have a greater muscular endurance capacity compared with males, possibly due to differences in muscle fibre type composition, glycogen usage or adenosine triphosphate breakdown (Labarbera, Murphy, Laroche, & Cook, 2013). It is therefore possible that adaptations to RTH may be different between males and females.

Although divergent methodologies have been employed and disparate findings published between the investigations included in this paper, some clear trends have emerged. Importantly, RTH was found to cause significant increases in muscle CSA and strength. While the results from this meta-analysis suggest that RTH does not augment these responses over those observed following NRT, the addition of hypoxia may still have additional benefits. For example, Kon et al. (2014) reported that plasma vascular endothelial growth factor and capillary-to-fiber ratio were significantly higher following 8 weeks of RTH compared with NRT, and these responses were accompanied by an increase in muscular endurance. These results follow the data obtained by Vogt et al. (2001) showing that high intensity training under hypoxia increases vascular endothelial growth factor and evokes an adaptation in HIF-1 pathway. Therefore, exercise in hypoxia appears to result in a large range of functional adaptations in skeletal muscle (Lundby, Calbet, & Robach, 2009).

It is important for those seeking to implement RTH that they also consider the impacts of hypoxia on exercise performance. Data indicate that breathing hypoxic air during traditionally structured high-load resistance exercise (5 × 5 repetitions with 80% 1-RM and 180 seconds inter-set rest) does not cause declines in performance during training (Scott, Slattery, Sculley, Hodson, & Dascombe, 2015c), while performing high-load RTH using a circuit-based format (3 × 3 exercises at 6-RM with 35 seconds rest between exercises and 180 seconds rest between circuits) does result in decreased bench press (Ramos-Campo et al., 2017a) and half-squat (Ramos-Campo et al., 2017b) performance. These divergent findings are likely related to the structure of exercise and resultant metabolic stress, as Scott et al. (2015c) did not observe hypoxia to augment blood pH or lactate values, while Ramos-Campo et al. (2017a, 2017b) observed hypoxia to augment blood markers of metabolic stress (pH and lactate), and heightened post-exercise energy cost and oxygen consumption.

Practical implications

Although research investigating RTH is in its infancy, this study has provided an opportunity to make recommendations for both practitioners and researchers in this field. While no significant benefits were observed for RTH compared with NRT, small effects were evident in favour of larger increases in muscle CSA and strength following RTN. This suggests that some individuals may benefit more from RTH compared with normoxia, which would be important in well-trained athletic cohorts where small changes in physical attributes are difficult to achieve, and may therefore be meaningful (Inness et al., 2016). Further research is required to investigate these responses in more detail, but it appears that the efficacy of RTH strategies have been impacted by large variations in the structure of exercise performed and the level of hypoxia implemented. Exercise should be designed to elicit increases in metabolic stress under hypoxia, which may be achieved by using relatively brief inter-set rest periods and sufficient repetition volume (Scott et al., 2015b). Considering the findings from studies which have demonstrated benefits for RTH, inter-set rest periods should be very brief for low-load exercise (~30% 1-RM; ~30 seconds) and brief for moderate-load exercise (~70% 1-RM; ~60 seconds). RTH should be undertaken in moderate-level hypoxia ($FiO_2 = 13–16\%$), though it is not known whether a dose–response relationship exists for the level of hypoxia on muscular development. Finally, it is possible that RTH may impair performance during training (Ramos-Campo et al., 2017a, 2017b), though this has not been consistently demonstrated (Scott et al., 2015c). Taken together, these preliminary findings indicate that RTH may be more suitable for individuals who are training for muscular hypertrophy, whereby the aim is to elicit a substantial metabolic stimulus, rather than those seeking to optimize maximal strength and power, where an emphasis is placed on complete recovery between sets and concentric performance during repetitions.

Conclusions

The current meta-analysis concludes that while RTH does result in significant increases in muscular size and strength, these responses may not be larger than NRT. Nevertheless, the findings from this meta-analysis are likely impacted by the divergent methodologies employed in RTH studies, particularly around the structure of exercise, level of hypoxia used and the types of participants recruited. The findings of this meta-analysis indicate the importance of additional detailed studies to analyse the effects of this novel training stimulus on muscular size and strength performance.

Acknowledgements

We thank all authors of the original works cited in the present study, who readily assisted us by either sharing their manuscripts or providing additional data required for this meta-analysis.

Disclosure statement

No potential conflict of interest was reported by the authors.

Supplemental data

Supplemental data for this article can be accessed http://dx.doi.org/10.1080/17461391.2017.1388850.

ORCID

Domingo J. Ramos-Campo http://orcid.org/0000-0002-8890-4244

References

Baker, D. (2001). A series of studies on the training of high-intensity muscle power in rugby league football players. *Journal of Strength and Conditioning Research*, *15*(2), 198–209.

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 Medicine*, *35*, 841–851.

Chycki, J., Czuba, M., Gołaś, A., Zając, A., Fidos-Czuba, O., Młynarz, A., & Smółka, W. (2016). Neuroendocrine responses and body composition changes following resistance training under *Normobaric hypoxia*. *Journal of Human Kinetics*, *53*(1), 31–98.

Feriche, B., García-Ramos, A., Morales-Artacho, A. J., & Padial, P. (2017). Resistance training using different hypoxic training strategies: A basis for hypertrophy and muscle power development. *Sports Medicine-Open*, *3*(1), 881.

Friedmann, B., Kinscherf, R., Borisch, S., Richter, G., Bärtsch, P., & Billeter, R. (2003). Effects of low-resistance/high-repetition strength training in hypoxia on muscle structure and gene expression. *Pflügers Archiv – European Journal of Physiology*, *446*(6), 742–751.

Gonzalez, A. M., Hoffman, J. R., Stout, J. R., Fukuda, D. H., & Willoughby, D. S. (2016). Intramuscular anabolic signaling and endocrine response following resistance exercise: Implications for muscle hypertrophy. *Sports Medicine*, *46*(5), 671–685.

Haseler, L. J., Hogan, M. C., & Richardson, R. S. (1999). Skeletal muscle phosphocreatine recovery in exercise-trained humans is dependent on O 2 availability. *Journal of Applied Physiology*, *86* (6), 2013–2018.

Higgins, J. P., Altman, D. G., Gøtzsche, P. C., Jüni, P., Moher, D., Oxman, A. D., & Sterne, J. A. (2011). The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ: British Medical Journal*, *343*, d5928.

Higgins, J. P., Thompson, S. G., Deeks, J. J., & Altman, D. G. (2003). Measuring inconsistency in meta-analyses. *BMJ: British Medical Journal*, *327*(7414), 557.

Ho, J. Y., Kuo, T. Y., Liu, K. L., Dong, X. Y., & Tung, K. (2014). Combining normobaric hypoxia with short-term resistance training has no additive beneficial effect on muscular performance and body composition. *The Journal of Strength & Conditioning Research*, *28*(4), 935–941.

Hopkins, W., Marshall, S., Batterham, A., & Hanin, J. (2009). Progressive statistics for studies in sports medicine and exercise science. *Medicine and Science in Sports and Exercise*, *41*(1), 3.

Inness, M. W., Billaut, F., Walker, E. J., Petersen, A. C., Sweeting, A. J., & Aughey, R. J. (2016). Heavy resistance training in hypoxia enhances 1RM squat performance. *Frontiers in Physiology*, *7*, 502.

Kon, M., Ikeda, T., Homma, T., Akimoto, T., Suzuki, Y., & Kawahara, T. (2010). Effects of acute hypoxia on metabolic and hormonal responses to resistance exercise. *Medicine and Science in Sports and Exercise*, *42*(7), 1279–1285.

Kon, M., Ikeda, T., Homma, T., & Suzuki, Y. (2012). Effects of low-intensity resistance exercise under acute systemic hypoxia on hormonal responses. *The Journal of Strength and Conditioning Research*, *26*(3), 611–617.

Kon, M., Ohiwa, N., Honda, A., Matsubayashi, T., Ikeda, T., Akimoto, T., & Russell, A. P. (2014). Effects of systemic hypoxia on human muscular adaptations to resistance exercise training. *Physiological Reports*, *2*(6), e12033.

Kraemer, W. J., Fleck, S. J., & Evans, W. J. (1996). Strength and power training: Physiological mechanisms of adaptation. *Exercise and Sport Sciences Reviews*, *24*(1), 363–398.

Kurobe, K., Huang, Z., Nishiwaki, M., Yamamoto, M., Kanehisa, H., & Ogita, F. (2015). Effects of resistance training under hypoxic conditions on muscle hypertrophy and strength. *Clinical Physiology and Functional Imaging*, *35*(3), 197–202.

Labarbera, K. E., Murphy, B. G., Laroche, D. P., & Cook, S. B. (2013). Sex differences in blood flow restricted isotonic knee extensions to fatigue. *The Journal of Sports Medicine and Physical Fitness*, *53*(4), 444–452.

Loenneke, J. P., Wilson, G. J., & Wilson, J. M. (2010). A mechanistic approach to blood flow occlusion. *International Journal of Sports Medicine*, *31*(1), 1–4.

Lundby, C., Calbet, J. A., & Robach, P. (2009). The response of human skeletal muscle tissue to hypoxia. *Cellular and Molecular Life Sciences*, *66*(22), 3615–3623.

Manimmanakorn, A., Hamlin, M. J., Ross, J. J., Taylor, R., & Manimmanakorn, N. (2013). Effects of low-load resistance training combined with blood flow restriction or hypoxia on muscle function and performance in netball athletes. *Journal of Science and Medicine in Sport*, *16*(4), 337–342.

Millet, G. P., Debevec, T., Brocherie, F., Malatesta, D., & Girard, O. (2016). Therapeutic use of exercising in hypoxia: Promises and limitations. *Frontiers in Physiology*, *7*, 224. doi:10.3389/fphys.2016.00224

Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G., & Prisma Group. (2009). Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Medicine*, *6*(7), e1000097.

Nishimura, A., Sugita, M., Kato, K., Fukuda, A., Sudo, A., & Uchida, A. (2010). Hypoxia increases muscle hypertrophy induced by resistance training. *International Journal of Sports Physiology and Performance*, *5*(4), 497–508.

Oishi, Y., Tsukamoto, H., Yokokawa, T., Hirotsu, K., Shimazu, M., Uchida, K., & Hashimoto, T. (2015). Mixed lactate and caffeine compound increases satellite cell activity and anabolic signals for muscle hypertrophy. *Journal of Applied Physiology*, *118*(6), 742–749.

Ramos-Campo, D. J., Rubio-Arias, J. A., Dufour, S., Chung, L., Ávila-Gandía, V., & Alcaraz, P. E. (2017a). Biochemical responses and physical performance during high-intensity resistance circuit training in hypoxia and normoxia. *European Journal of Applied Physiology*, *117*(4), 809–818.

Ramos-Campo, D. J., Rubio-Arias, J. Á., Freitas, T. T., Camacho, A., Jiménez-Diaz, J. F., & Alcaraz, P. E. (2017b). Acute physiological and performance responses to high-intensity resistance circuit training in hypoxic and normoxic conditions. *The Journal of Strength & Conditioning Research*, *31* (4), 1040–1047.

Schoenfeld, B. J. (2013a). Postexercise hypertrophic adaptations: A reexamination of the hormone hypothesis and its applicability to resistance training program design. *The Journal of Strength & Conditioning Research*, *27*(6), 1720–1730.

Schoenfeld, B. J. (2013b). Potential mechanisms for a role of metabolic stress in hypertrophic adaptations to resistance training. *Sports Medicine*, *43*(3), 179–194.

Scott, B. R., Goods, P. S., & Slattery, K. M. (2016). High-intensity exercise in hypoxia: Is increased reliance on anaerobic metabolism important? *Frontiers in Physiology*, *7*, 637. doi:10.3389/fphys.2016.00637

Scott, B. R., Loenneke, J. P., Slattery, K. M., & Dascombe, B. J. (2015a). Exercise with blood flow restriction: An updated evidence-based approach for enhanced muscular development. *Sports Medicine*, *45*(3), 313–325.

Scott, B. R., Slattery, K. M., & Dascombe, B. J. (2015b). Intermittent hypoxic resistance training: Is metabolic stress the key moderator? *Medical Hypotheses*, *84*(2), 145–149.

Scott, B. R., Slattery, K. M., Sculley, D. V., & Dascombe, B. J. (2014). Hypoxia and resistance exercise: A comparison of localized and systemic methods. *Sports Medicine*, *44*(8), 1037–1054.

Scott, B. R., Slattery, K. M., Sculley, D. V., Hodson, J. A., & Dascombe, B. J. (2015c). Physical performance during high-intensity resistance exercise in normoxic and hypoxic conditions. *The Journal of Strength & Conditioning Research*, *29*(3), 807–815.

Scott, B. R., Slattery, K. M., Sculley, D. V., Lockhart, C., & Dascombe, B. J. (2017). Acute physiological responses to moderate-load resistance exercise in hypoxia. *The Journal of Strength & Conditioning Research*, *31*(7), 1973–1981.

Vogt, M., Puntschart, A., Geiser, J., Zuleger, C., Billeter, R., & Hoppeler, H. (2001). Molecular adaptations in human skeletal muscle to endurance training under simulated hypoxic conditions. *Journal of Applied Physiology*, *91*(1), 173–182.

West, D. W., Burd, N. A., Staples, A. W., & Phillips, S. M. (2010). Human exercise-mediated skeletal muscle hypertrophy is an intrinsic process. *The International Journal of Biochemistry & Cell Biology*, *42*(9), 1371–1375.

Yan, B., Lai, X., Yi, L., Wang, Y., & Hu, Y. (2016). Effects of five-week resistance training in hypoxia on hormones and muscle strength. *The Journal of Strength & Conditioning Research*, *30*(1), 184–193.