Effects of Whey Protein Alone or as Part of a Multi-ingredient Formulation on Strength, Fat-Free Mass, or Lean Body Mass in Resistance-Trained Individuals: A Meta-analysis

Fernando Naclerio & Eneko Larumbe-Zabala

Sports Medicine

ISSN 0112-1642
Volume 46
Number 1

Sports Med (2016) 46:125-137
DOI 10.1007/s40279-015-0403-y

Springer

Sports Med (2016) 46:125–137
DOI 10.1007/s40279-015-0403-y

SYSTEMATIC REVIEW

Effects of Whey Protein Alone or as Part of a Multi-ingredient Formulation on Strength, Fat-Free Mass, or Lean Body Mass in Resistance-Trained Individuals: A Meta-analysis

Fernando Naclerio[1] · **Eneko Larumbe-Zabala**[2]

Published online: 24 September 2015

Abstract

Background Even though the positive effects of whey protein-containing supplements for optimizing the anabolic responses and adaptations process in resistance-trained individuals have been supported by several investigations, their use continues to be controversial. Additionally, the administration of different multi-ingredient formulations where whey proteins are combined with carbohydrates, other protein sources, creatine, and amino acids or derivatives, has been extensively proposed as an effective strategy to maximize strength and muscle mass gains in athletes.

Objective We aimed to systematically summarize and quantify whether whey protein-containing supplements, administered alone or as a part of a multi-ingredient, could improve the effects of resistance training on fat-free mass or lean body mass, and strength in resistance-trained individuals when compared with other iso-energetic supplements containing carbohydrates or other sources of proteins.

Methods A structured literature search was conducted on PubMed, Science Direct, Web of Science, Cochrane Libraries, US National Institutes of Health clinicaltrials.gov, SPORTDiscus, and Google Scholar databases. Main inclusion criteria comprised randomized controlled trial study design, adults (aged 18 years and over), resistance-trained individuals, interventions (a resistance training program for a period of 6 weeks or longer, combined with whey protein supplementation administered alone or as a part of a multi-ingredient), and a calorie equivalent contrast supplement from carbohydrates or other non-whey protein sources. Continuous data on fat-free mass and lean body mass, and maximal strength were pooled using a random-effects model.

Results Data from nine randomized controlled trials were included, involving 11 treatments and 192 participants. Overall, with respect to the ingestion of contrast supplements, whey protein supplementation, administered alone or as part of a multi-ingredient, in combination with resistance training, was associated with small extra gains in fat-free mass or lean body mass, resulting in an effect size of $g = 0.301$, 95 % confidence interval (CI) 0.032–0.571. Subgroup analyses showed less clear positive trends resulting in small to moderate effect size $g = 0.217$ (95 % CI −0.113 to 0.547) and $g = 0.468$ (95 % CI 0.003–0.934) in favor of whey and multi-ingredient, respectively. Additionally, a positive overall extra effect was also observed to maximize lower ($g = 0.316$, 95 % CI 0.045–0.588) and upper body maximal strength ($g = 0.458$, 95 % CI 0.161–0.755). Subgroup analyses showed smaller superiority to maximize strength gains with respect to the contrast groups for lower body (whey protein: $g = 0.343$, 95 % CI −0.016 to 0.702, multi-ingredient: $g = 0.281$, 95 % CI −0.135 to 0.697) while in the upper body, multi-ingredient ($g = 0.612$, 95 % CI 0.157–1.068) seemed to produce more clear effects than whey protein alone ($g = 0.343$, 95 % CI −0.048 to 0.735).

Electronic supplementary material The online version of this article (doi:10.1007/s40279-015-0403-y) contains supplementary material, which is available to authorized users.

✉ Fernando Naclerio
f.j.naclerio@gre.ac.uk

[1] Center for Sport Science and Human Performance, University of Greenwich, Medway Campus, Central Avenue, Chatham Maritime, Kent ME4 4TB, UK

[2] Clinical Research Institute, Texas Tech University Health Sciences Center, Lubbock, TX, USA

Limitations Studies involving interventions of more than 6 weeks on resistance-training individuals are scarce and account for a small number of participants. Furthermore, no studies with an intervention longer than 12 weeks have been found. The variation regarding the supplementation protocol, namely the different doses criteria or timing of ingestion also add some concerns to the studies comparison.

Conclusions Whey protein alone or as a part of a multi-ingredient appears to maximize lean body mass or fat-free mass gain, as well as upper and lower body strength improvement with respect to the ingestion of an iso-energetic equivalent carbohydrate or non-whey protein supplement in resistance-training individuals. This enhancement effect seems to be more evident when whey proteins are consumed within a multi-ingredient containing creatine.

Key Points

Resistance training combined with supplements containing whey protein in trained individuals is associated with extra increases in fat-free mass or lean body mass and upper and lower body maximal strength when compared with contrast groups consuming the same amount of energy from carbohydrate or other protein sources.

The effect of whey protein ingestion alone seems to be less clear than that reported with the ingestion of multi-ingredient supplements containing whey protein and creatine, but more evidence is still needed.

1 Introduction

Whey protein extracts have been proposed as an optimal supplement for strength and power athletes [1]. In comparison to other protein sources, whey protein has greater bioavailability and solubility along with a higher concentration of branched-chain amino acid (BCAA), specifically leucine [1–3]. Findings from two previous meta-analyses of randomized controlled trials (RCTs) support the positive effect of high-quality protein supplementation, including whey, to maximize the increase in muscle mass [4, 5] and strength [4] when combined with prolonged (≥4 weeks) resistance-training interventions. Nevertheless, it is important to highlight that the meta-analysis by Cermak et al. [4] included trained and untrained, younger and older participants. Furthermore, although the majority of the included studies used mainly whey protein, either alone or combined with other nutrients, a few of them used essential amino acids (EAA), milk, casein, egg, or meat. Miller et al. [5] analyzed the effect of whey protein combined with resistance exercise on body composition without distinction between individuals with different training backgrounds and body compositions (normal weight, overweight, or obese).

In summary, although several studies have analyzed the effect of whey protein supplementation on resistance-training performance and outcomes [6–9], only some of them have specifically focused on resistance-training individuals [3, 10–12]. Indeed, only a few studies were focused on recreationally or well strength-trained athletes, and have reported a positive effect of whey, administered alone or combined with other nutrients, to maximize strength [2, 13], lean body mass (LBM), or fat-free mass (FFM) gains [2, 14]. Methodological differences related to the study design and type of intervention, including supplementation strategies, would have been the cause of some controversies and inconsistencies regarding the most effective doses and methods of consumption for maximizing strength gains and muscle mass accretion in regular resistance-training athletes. In addition, the administration of different supplements containing only whey protein [3] or multi-ingredient formulas, where whey proteins are administered together with carbohydrates [15], other protein sources such as casein [16] and bovine colostrum [17], or enriched with amino acid [16], creatine, β-hydroxy-β-methylbutyrate, or L-carnitine [13, 18], have impeded a better understanding of the real effect of whey protein supplementation to support strength and muscle mass gains in resistance-trained individuals.

In summary, although several investigations examined the effects of whey protein on muscle mass accretion and strength improvement in resistance-trained individuals, to our knowledge, no study has integrated and quantitatively summarized these results. Therefore, the objective of the present meta-analysis is to examine the effect of whey protein administered alone or with other protein sources, amino acids, or derivatives, combined with resistance exercise, on the maximal strength, the LBM, or FFM, in middle to long randomized controlled trials conducted in resistance-trained adults.

2 Methods

Methods of the analysis and inclusion criteria were specified in advance, and documented in a protocol registered at the International Prospective Register of Systematic Reviews, PROSPERO (CRD 42014015437).

2.1 Search Strategy

A systematic review of literature was conducted in accordance with the recommended criteria provided in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [19, 20], and the guidelines described for systematic reviews in the nutrition field [21]. The respective procedures incorporated for the current meta-analysis were agreed between the authors in advance and included: identification, screening, eligibility, and inclusion/exclusion of studies. Search of literature was performed by using PubMed, Science Direct, Web of Science, Cochrane Libraries, US National Institutes of Health clinicaltrials.gov, SPORTDiscus, and Google Scholar, through August to September 2014 (with no lower date limit). We identified English-language publications in human populations eligible for review, including articles, abstracts from annual scientific conferences and congress presentations, or doctoral theses. Commentaries, reviews, or duplicate publications from the same study were not included in this analysis. In addition, manual searches of personal files were conducted along with screening of reference lists of previous protein supplementation reviews and identified articles [4, 5, 22] for inclusion. Combinations of the following keywords were used as search terms: "whey protein supplementation"; "multinutrient supplementation"; "multi-ingredient supplementation"; "resistance exercise"; "resistance training"; "strength exercise"; "strength training"; "one repetition maximum (1 RM)"; "maximum strength"; "weight lifting"; "body mass"; "muscle mass"; "fat free mass"; lean body mass"; "muscular hypertrophy". A summary of the search strategy is provided in Electronic Supplementary Material Appendix S1.

2.2 Inclusion and Exclusion Criteria

The inclusion criteria for this systematic review were the following: (1) the trial was randomized and controlled involving at least two groups, treatment and contrast (using placebo or other supplement); (2) the treatment combined prolonged (≥6 weeks) resistance-training intervention with whey protein containing supplementation; (3) the study measured primary outcome variables related to LBM, FFM, or upper and lower body maximal strength, and estimated from the 1 repetition maximum test (1-RM) measurements; (4) participants were healthy participants aged at least 18 years; (5) to be considered as trained individuals, participants had a minimum of 1 year of consistent strength training [23, 24]; (6) the study used whey protein isolate, concentrate, or hydrolysate, consumed in isolation, or combined with other nutrients (creatine, amino acids, L-carnitine) or protein sources (casein, soy, bovine colostrum) as a part of a multi-ingredient; (7) the effects of the treatment were compared to the effects of an iso-energetic contrast treatment (carbohydrate) or other supplements containing no whey protein; (8) data on total calories consumed from the whey protein-containing supplement or contrast nutrient were available; (9) dietary intake was monitored; (10) the publication presented sufficient data to calculate the mean differences; and (11) the abstract was published.

These criteria support the notion that the only difference between the experimental and contrast groups was the supplement intervention, and at least one of the aforementioned outcomes (LBM, FFM, upper or lower body 1-RM) was analyzed. We did not restrict our research to whether the whey protein was administered alone or as a part of a multi-ingredient mixed with other protein sources, amino acids, or derivatives (WP-MTN), but we recorded these variables as pre-specified factors for subgroup analyses.

There were no restrictions on the number of participants, nor for sex or level of performance (1-RM). Studies that included participants with a recent history (less than 1 month before the intervention) of supplementation including protein, amino acids, or derivatives such as creatine at baseline screening were excluded.

2.3 Identification of Relevant Studies

Potentially relevant articles were selected by (1) screening the titles; (2) screening the abstracts; and (3) if abstracts did not provide sufficient data, the entire article was retrieved and screened to determine whether it met the inclusion criteria; (4) when data were not accurately presented (only available from figures or graphs), authors were contacted and asked to provide the appropriate range of values.

2.4 Data Collection Process and Coding

The following qualitative and quantitative information was extracted from each included study: authors; publication year; baseline population characteristics; intervention and control procedures; study duration; blinding; sample size per group; nutrient profile of the administered supplements and contrast treatments; methods of ingestion and dose; study compliance; diet assessment; resistance training protocol including number of exercises, sets, repetitions, rest, intensity, and frequency; outcomes measured at pre- and post-intervention; group means and standard deviations for lean or fat free mass; and 1-RM values for upper body (1-RM UB) and lower body (1-RM LB) resistance exercises. To reduce bias caused by different types of strength assessment and exercise responses, only squat or leg press for the lower body and bench press exercises for the upper body using free weights or weight machines were considered as valid outcomes to express changes in maximal strength. In regard to the effects of whey protein or WP-MTN on FFM or LBM, the definition of FFM excludes lipids in the cell membranes, central nervous system, and bone marrow, while LBM is an anatomical term that would include some or all of these [25]. However, both variables share the muscle mass as the main component that would express changes as a consequence of exercise-related interventions in trained adults. Therefore, we have analyzed the outcomes affecting these variables together.

2.5 Assessment of Risk of Bias

Methodological information regarding the potential impact of bias was critically examined. Two reviewers ascertained individual study information independently as part of the quality control process. For each study, seven domains from the Cochrane collaboration tool for assessing the risk of bias [26] were scored with high, low, or unclear risk for bias: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and "other" issues (similarity in baseline characteristics and timing of outcome assessment). These seven domains assess the level of risk regarding selection bias, allocation bias, performance bias, detection bias, attrition bias, reporting bias, and other biases. The two authors performed the quality assessment independently, and their findings were compared and discussed until consensus was achieved. Each domain was scored as −1 for high risk, 0 for unclear risk, and 1 for low risk. Scores were then summed with a possible range of scores from −7 to 7. A table showing the assessment for each study is provided in Electronic Supplementary Material Appendix S2.

2.6 Statistical Analysis

A meta-analysis was performed using the Comprehensive Meta-Analysis Software, version 2.2.064 (Biostat, Englewood, NJ, USA). A random-effects model was selected based on the assumption of variability of true effects between studies. Four or more studies by outcome were required to generate weighted group mean differences, 95 % confidence intervals (CIs), and corresponding p values for heterogeneity. From the collected data, we used the pre- and post-values of mean, SD, and sample size, for both intervention and contrast groups. Pre- and post-SD values were calculated when studies reported standard error values instead of SD. The effect size was calculated using the Hedges' g. The primary meta-analysis compared the effect of any intervention using whey protein (alone or as a part of a multi-ingredient) with contrast in the analyzed outcomes (1-RM UB, 1-RM LB, and FFM or LBM).

Supplements including whey protein were considered the experimental treatment for the current meta-analysis. All other interventions such as carbohydrates, other protein sources, or multi-ingredient with no whey protein or creatine, were considered contrast groups. Studies using whey protein and WP-MTN including creatine were differentiated because the combination of whey protein with creatine [27, 28], in addition to other protein sources (casein; soy, colostrum), and/or enriched with amino acids [16] would affect body composition [28] and muscle strength [29] in resistance-trained individuals, and thus a differential effect from different whey protein combinations would be expected. Therefore, studies were classified into two distinct groups, as a moderator: (1) whey protein alone, or combined with small amounts (less than 20 % of the total) of other protein sources or amino acids including no creatine, and (2) whey protein administered as a part of a multi-ingredient (no more than 80 % of the total) combined with other protein sources, amino acid, or derivatives, including creatine (WP-MTN).

The secondary analyses included subgroup meta-analyses to determine the differences between the effect size of whey protein vs. contrast, and WP-MTN vs. contrast for each outcome variable. All primary and secondary effect sizes were interpreted using Cohen's [30] convention for small (0.2), medium (0.5), and large (0.8) effects.

The study of Kerksick et al. [16] analyzed a three parallel-group randomized design to test the effects of whey protein mixed with casein (treatment 1) or whey protein enriched with BCAA and L-glutamine (treatment 2) vs. a carbohydrate only placebo (treatment 3) on lean body mass and muscle strength. From this study, we considered the data obtained from treatments 1 and 2 to be included as independent treatments in the secondary analysis. Furthermore, the study of Cribb et al. [28] investigated a four parallel-group randomized design to compare the effects of whey protein only, whey protein mixed with creatine, carbohydrate mixed with creatine, and only carbohydrate, on different outcomes including LBM and maximal strength. From this investigation, we excluded the data of the carbohydrate plus creatine group (Table 1). Creatine has been extensively shown to be an effective supplement to maximize strength-training adaptation and increase body mass regardless of the adhesion of high-quality proteins or carbohydrates [13]. Thus, to specifically evaluate the effects of whey protein alone or as a part of a multi-ingredient, contrast supplements including creatine were excluded.

We examined the presence of studies with inflated standardized residual values (above 1.96 or below −1.96) to consider them as outliers. Publication bias was assessed

Table 1 Summary of the training studies included in the meta-analysis

Study	Participants[a]	Design	Supplement		Contrast	Length (weeks)	Training protocol	Supplementation protocol	Findings
Burke et al. 2001 [27]	Male ($n = 30$; age 18–31 years); RRT 3 years' experience	3 PG	WP ($n = 12$)	WP-MTN ($n = 11$)	CHO ($n = 7$)	6	PRT: 4 days/week split routine (4 sets × 10–12 to 6–8 reps per 1- to 2-min rest between sets)	1.2 g/kg/day administered in 4 equal serving across the day	↑ LBM[b,c,d,e] ↑ 1 RM BP[b,c,e] SQ[b,e]
Brown et al. 2004 [14]	Male ($n = 18$; age 19–25 years; 76–84 kg); RRT 1 year experience	3 PG[f]	WP ($n = 9$)	–	Soy protein ($n = 9$)	9	Maximal strength training involving 14 exercise (3 sets × 4–6 reps)	Three intakes of an 11-g protein bar (33 g in total) across the day	↑ LBM[b,e]
Cribb et al. 2006 [2]	Male ($n = 13$; age 19–35 years; 68–91 kg); RBB 2 years' experience	2 PG	WP ($n = 6$)	–	Casein ($n = 7$)	10	PRT: 3 days/week, 2 weeks (2 sets × 10–8 RM); 2 weeks (2 sets × 6 RM and 6 weeks 4 RM)	1.5 g/kg/day divided into 4 equal servings (breakfast, lunch, post-workout, and evening)	↑ LBM[b,g] ↑ 1 RM BP[b,g,e] ↑SQ[g,c,e]
Kerksick et al. 2006 [16]	Male ($n = 36$; age 31.0 years ± 8; 84.0 ± 12.9) kg; RRT 1 year experience	3 PG	WP + C ($n = 10$) WP + AA ($n = 15$)	–	CHO ($n = 11$)	10	PRT: 4 days/week (2 upper-body and 2 lower-body workouts) (10–6 RM per 2-min rest between sets)	1 daily intake of 48 g with water, juice, or milk <2 h post-workout or in the morning of non-training days	↑ FFM[b, c, d] ↑1 RM BP[b,e] ↑1 RM LP[b,e]
Cribb et al. 2007 [28]	Male ($n = 30$; age 24.5 ± 5 years; 78.5 ± 12 kg); RBB 2 years' experience	4 PG[h]	WP ($n = 5$)	WP-MTN ($n = 6$)	CHO ($n = 7$)	11	PRT: 3 days/week, 2 weeks 10–8 RM; 2 weeks 6 RM and 6 weeks 4 RM	1.5 g/kg/day divided into 3 equal servings (mid-morning, post-workout, and evening)	↑ LBM[b,e] ↑1 RM BP[b,g,c,e] SQ[b,g,c,e]
Ormsbee et al. 2012 [29]	Male ($n = 24$; age 24.0 ± 0.9 years; 83.7 ± 0.5 kg); RRT 3 years' experience	2 PG	–	WP-MTN ($n = 13$)	CHO ($n = 11$)	6	PRT: 3 days/week: 2 weeks 10 RM, 2 weeks 6 RM and 2 weeks 4 RM	Two 21-g intakes (pre- and post-workout)	↑ LBM[b,c,e] ↑ND 1 RM BP[b,e] ↑ND 1 RM LP[b,e]
Willems et al. 2012 [18]	Male ($n = 21$; age 21 ± 2 years; 74.5 ± 5.9 kg); 21 RRT 1 year experience	2 PG	–	WP-MTN ($n = 9$)	CHO ($n = 7$)	12	PRT: 4 days/week. Two 6-week training blocks. 70 % (12 reps) to 85 % (6 reps)	2 intakes of 60 g/day at breakfast and post-workout	↑ND 1 RM BP and LP
Cooper et al. 2013 [31]	Male ($n = 13$; age 23.5 ± 2.7 years; 80 ± 13 kg); RRT 2 years' experience	2 PG	–	WP-MTN ($n = 7$)	CHO ($n = 6$)	12	PRT: 4 days/week upper/lower split (4 sets per exercise of 6–12 reps at 65–80 %) 1 RM	2 intakes of 60 g/day at breakfast and post-workout	↑ND FFM ↑ ND 1 RM BP and SQ

Table 1 continued

Study	Participants[a]	Design	Supplement	Contrast	Length (weeks)	Training protocol	Supplementation protocol	Findings
Joy et al. 2013 [12]	Male ($n = 24$; age 21.3 ± 1.9 years; 76.08 ± 5.6 kg); RRT 1 year experience	2 PG	WP ($n = 12$) –	Rice protein ($n = 12$)	8	UPRT: 3 day/week. Hypertrophy days: 3 sets of 8–12 RM; strength days: 3 sets of 2–5 RM	1 post-work intake of 48 g	↑ FFM[b,e] ↑1 RM BP[b,e] LP[b,e]

BP bench press, *SQ* squat, *LP* leg press, *CHO* carbohydrates, *FFM* fat-free mass, *LBM* lean body mass, *WP-MTN* multi-ingredient, ND no significant differences from control group, *PG* parallel groups, *PRT* progressive resistance training, *reps* repetitions, *RM* repetitions maximum per set, *RBB* recreational body builders, *RRT* recreational resistance trained individuals, *UPRT* undulated periodized resistance training, *WP* whey protein, *AA* branched chain amino acid and glutamine, ↑ significant increase

[a] Only participants that have completed the study have been included

[b] Significantly different for WP or WP-MTN with respect to baseline

[c] Significantly different from WP-MTN to control

[d] Significantly different from WP-MTN to WP or from WP-C to WP + AA

[e] Significantly different from contrast groups (CHO, soy, casein, and rice group) at baseline

[f] Only two treatment groups were considered. The non-supplement only training group ($n = 9$) was excluded

[g] Significantly different from WP to control

[h] Only three treatment groups were considered. The CHO + creatine group ($n = 8$) was excluded

using funnel plots of effect size (horizontal axis) by standard error (vertical axis), the "Trim and fill" procedure for the random effects, and the Orwin Fail Safe *N* calculation.

3 Results

3.1 Study Selection

Figure 1 shows a diagram of the search strategy. The preliminary search identified 3370 relevant citations. After examining all 3370 titles, 149 publications were selected. Of those, 115 were excluded based on the abstract review. The remaining 34 publications were fully read and carefully examined by two reviewers. After this examination, 25 were excluded and therefore, a total of nine studies [2, 12, 14, 17, 18, 27–29, 31] were included in the meta-analysis.

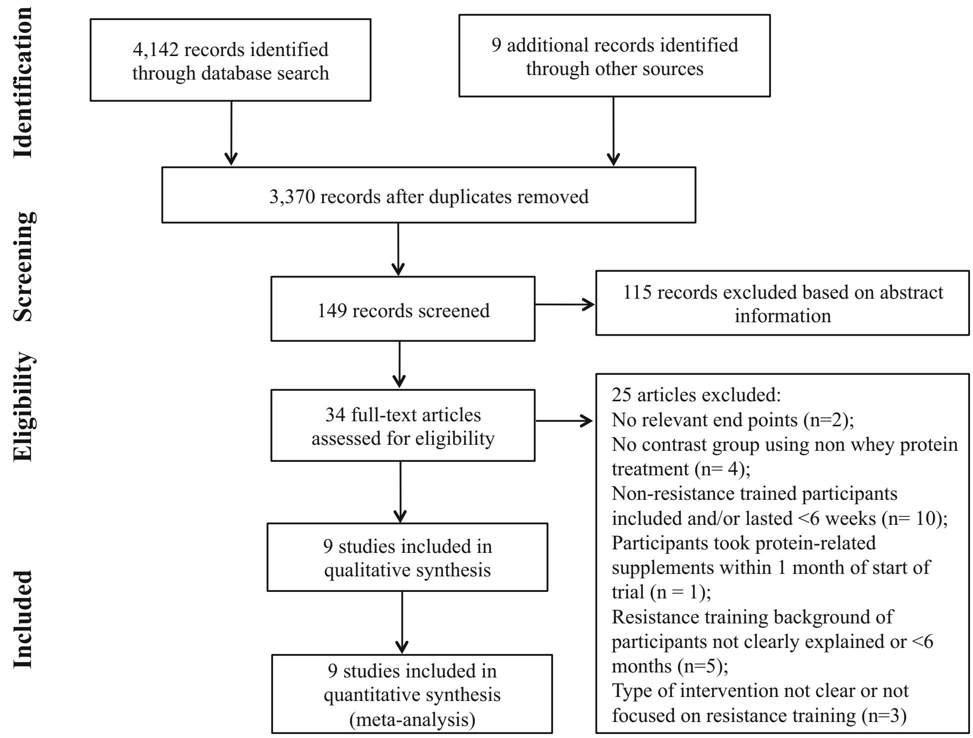
3.2 Characteristics of Included Studies

A total of nine studies, reporting results from 21 groups and involving a total of 192 male participants met all the inclusion criteria and were included in the review (Fig. 1). The publication dates ranged from 2001 to 2013. Descriptive study characteristics are shown in Table 1. All included studies had parallel designs. Total sample sizes within individual studies ranged from 13 to 36 participants (6–15 in treatment groups, and 7–12 in contrast groups), and ages from 18 to 50 years. Only one study [16] included participants aged older than 40 years. Resistance-training interventions ranged from a minimum of 6 to a maximum of 12 weeks. Differences in population included recreational resistance-training individuals in seven studies with 1 [12, 14, 16, 18], 2 [31], or 3 years [27, 29] of regular resistance-training experience. In addition, another two studies included recreational body builders [2, 28] with a minimum of 2 years of experience. Only Kerksick et al. [16] allowed participants to perform a complementary endurance training for no longer than 20 min at a time. No evidence of any relevant additional physical activity was identified for any of the other studies.

Participants included in whey protein and WP-MTN groups, or non-whey protein contrast group tended to ingest a greater amount of protein with respect to carbohydrates contrast groups (1.6–2.2 vs. 1.2–1.6 g/kg/day).

An isocaloric carbohydrate beverage was the contrast supplement in six studies [16, 18, 27–29, 31]. In the study by Brown et al. [14], protein bars were considered to compare whey with soy protein effects. In addition, a third non-supplemented (only resistance-training) group was tested. However, as the comparison of whey protein-containing supplement vs. a non-supplement conditions falls beyond the objective of this review, we excluded this

Fig. 1 Flow chart diagram of the study selection



group from the analysis. In the remaining two studies, the contrast supplements included casein [2] or a rice protein isolate [12]. A whey protein isolate was investigated as a treatment condition in one study [12] and hydrolyzed whey isolate (90 % protein, 3 % carbohydrate, and 1.5 % fat) was evaluated in two studies [2, 28]. Cribb et al. [28] also compared the effects of a WP-MTN administered through a loading phase (week 1) that contained 83 g of protein, <4.8 g of carbohydrate, <1 g of fat, 24 g of creatine monohydrate, followed by a maintenance phase supplement (weeks 2–11) that provide 96 g of protein, <5.5 g of carbohydrate, <1 g of fat, and 8.4 g of creatine monohydrate per day. Burke et al. [27] analyzed the effects of two treatment conditions, whey protein alone and a WP-MTN including 1.2 g of protein and 0.1 g of creatine monohydrate per kg/day mixed with others vitamins and nitrogenous-containing compounds such as inositol arginine and N-acetyl-cysteine. Kerksick et al. [16] were the only researchers who evaluated two treatment conditions; whey protein mixed with small amount of casein (8 g; 20 %) and BCAA (5 g; 12.5 %) and L-glutamine (3 g; 7.5 %).

Ormsbee et al. [29] analyzed two similar WP-MTNs containing whey protein, casein protein, BCAA, creatine, beta alanine, with or without caffeine. Cooper et al. [31] and Willems et al. [18] tested the effects of a WP-MTN composed of 50 % whey protein, 35 % carbohydrate, and 8.1 % fat, including 5.1 g of creatine monohydrate.

Protocol of supplementation, including dosages, number of intakes distribution, and timing, slightly varies between studies. Only three studies [2, 27, 28] considered dosages based on participants' body weight (1.5 g/kg/day), while the rest of the included trials considered absolute dosages ranging from 42 g (two servings of 21 g) [29] to 120 g (two servings of 60 g) [18, 31]. Regarding the distribution and timing, two studies considered a single daily post-workout intake [12, 16]; three studies divided the total dosages into two equal servings ingested at breakfast and post-workout [13, 18] or along the day [29]; the other four studies evaluated three [14, 28] or four [2, 27] servings per day, including one as a post-workout intake. Only one study [29] evaluated a pre- and post-workout administration protocol with two similar WP-MTN supplements, where the pre-workout formula was different, including anhydrous caffeine as well as other neuromuscular and fat burner-stimulating compounds.

Resistance-training protocols were not substantially different across studies. Seven studies [2, 17, 18, 27–29, 31] evaluated a three to five times per week of progressive resistance training protocol starting with moderate loads (65–75 % 1 RM) and 12–8 repetitions per sets, with progression towards heavier loads (80 to 90–95 % 1 RM) and 6–4 repetitions per set. Only one study [14] included a specific maximal-strength-only training program, involving sets of 4–6 repetitions for 9 weeks. Repetition maximum or set to failure strategy was considered to determine the training load in five studies [2, 12, 16, 28, 29] while the other four investigations used a partner to control and adjust training loads [14, 18, 27, 31]

Finally, Joy et al. [12] applied a 3 days per week, daily undulated periodized program, involving hypertrophy sessions (8–12 maximal repetitions per sets) and maximal strength workouts (2–5 maximal repetitions).

3.3 Lean Body Mass and Fat-Free Mass

The estimated overall effect of whey protein treatment vs. contrast was small ($n = 11$, $g = 0.301$, 95 % CI 0.032–0.571). No significant heterogeneity was found either within the 11 treatments [$Q\,(10) = 5.87, p = 0.826, I^2 = 0$] or between the two subgroups [$Q\,(1) = 0.74, p = 0.389$]. As shown in Fig. 2, both whey protein and WP-MTN supplementations were associated with a small increase in FFM or LBM when compared with contrast groups ingesting carbohydrates or other sources of protein. The subgroup analysis revealed smaller and non-statistically significant effect size for whey protein ($n = 7, g = 0.217$, 95 % CI −0.113 to 0.547), and medium and statistically significant effect for WP-MTN ($n = 4$, $g = 0.468$, 95 % CI 0.003–0.934). However, although whey protein studies [$Q\,(6) = 1.58$, $p = 0.954$, $I^2 = 0$] and -MTN studies ($Q\,(3) = 3.55$, $p = 0.314$, $I^2 = 15.5$) showed no statistical evidence of heterogeneity, the latter results should be taken with caution because of the small sample size ($n = 4$).

3.4 Lower Body Strength

The estimated overall effect of whey protein treatment vs. contrast was small ($n = 11$, $g = 0.316$, 95 % CI 0.045–0.588). No significant heterogeneity was found either within the 11 treatments [$Q\,(10) = 8.04$, $p = 0.625$, $I^2 = 0$] or between the two subgroups [$Q\,(1) = 0.05$, $p = 0.825$]. The secondary analysis revealed small and non-statistically significant effects for both subgroups: whey protein ($n = 7$, $g = 0.343$, 95 % CI −0.016 to 0.702), and WP-MTN ($n = 6$, $g = 0.281$, 95 % CI −0.135 to 0.697). No statistical evidence of heterogeneity was found within whey protein studies [$Q\,(5) = 3.08$, $p = 0.688$, $I^2 = 0$] or WP-MTN studies [$Q\,(4) = 4.92$, $p = 0.296$, $I^2 = 18.63$]. The effect size estimations for 1-RM LB studies are shown in Fig. 3.

3.5 Upper Body Strength

The estimated overall effect of whey protein treatment vs. contrast in 1-RM UB was medium ($n = 11$, $g = 0.458$, 95 % CI 0.161–0.755). The 11 treatments showed no significant heterogeneity [$Q\,(10) = 11.3$, $p = 0.334$, $I^2 = 11.53$]. The secondary analysis revealed no significant heterogeneity between whey protein and WP-MTN [$Q\,(1) = 0.91$, $p = 0.340$]. The averaged effect size for whey protein studies was small ($n = 7$, $g = 0.343$, 95 % CI −0.048 to 0.735), and medium for WP-MTN ($n = 6$, $g = 0.612$, 95 % CI 0.157–1.068). No statistical evidence of heterogeneity was found within whey protein studies [$Q\,(5) = 5.11$, $p = 0.402$, $I^2 = 2.18$] or WP-MTN studies [$Q\,(4) = 5.28$, $p = 0.260$, $I^2 = 24.26$]. The effect size estimations for 1-RM UB are shown in Fig. 4.

3.6 Outliers and Publication Bias

No studies were identified as outliers with large residual values from the average treatment effect, as z values ranged −1.75 to 1.77. Funnel plots showed an almost symmetrical plot, and the "trim and fill" procedure added three studies to

Reference name	Subgroup	Statistics for each study			Sample size	
		Hedges's g	Lower limit	Upper limit	Treatment	Contrast
Kerksick et al. (2006) [16]	WP	0.010	-0.74	0.76	15	11
Brown et al. (2004) (vs. soy) [14]	WP	0.034	-0.85	0.91	9	9
Joy et al. (2013) (vs. rice protein) [12]	WP	0.126	-0.65	0.90	12	12
Cribb et al. (2007) (WP) [28]	WP	0.207	-0.86	1.27	5	7
Kerksick et al. (2006) [16]	WP	0.220	-0.60	1.05	10	11
Burke et al. (2001) (WP) [27]	WP	0.560	-0.36	1.48	11	7
Cribb et al. (2006) (vs. casein) [28]	WP	0.605	-0.44	1.65	6	7
	WP	*0.217*	*-0.11*	*0.55*		
Ormsbee et al. (2012) [29]	WP-MTN	0.058	-0.72	0.83	13	11
Cribb et al. (2007) (MTN) [28]	WP-MTN	0.359	-0.66	1.38	6	7
Copper et al. (2012) [31]	WP-MTN	0.436	-0.59	1.46	7	6
Burke et al. (2001) (MTN) [27]	WP-MTN	1.243	0.27	2.22	12	7
	WP-MTN	*0.468*	*0.00*	*0.93*		
	Overall	**0.301**	**0.03**	**0.57**		

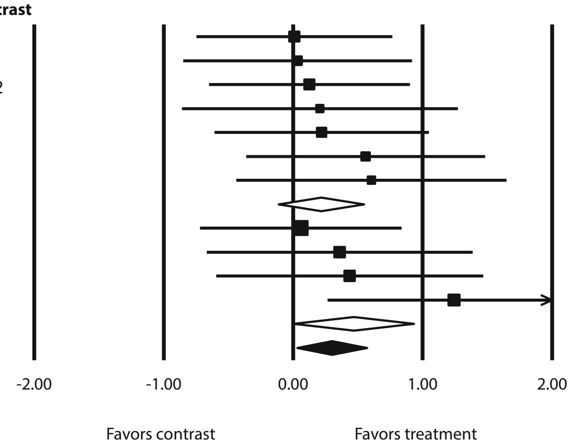


Fig. 2 Fat-free mass or lean body mass forest plot. Results of a random-effects meta-analysis shown as g effect size with 95 % confidence interval. The *white* and *black diamonds* represent the subgroups (WP and WP-MTN) and pooled (overall) standardized mean difference, respectively. *CI* confidence interval, *WP* whey protein, *MTN* multi-ingredient

Reference name	Subgroup	Statistics for each study			Sample size	
		Hedges's g	Lower limit	Upper limit	Treatment	Contrast
Kerksick et al. (2006) [16]	WP	0.133	-0.69	0.96	10	11
Burke et al. (2001) (WP) [27]	WP	0.139	-0.76	1.04	11	7
Kerksick et al. (2006) [16]	WP	0.148	-0.61	0.90	15	11
Joy et al. (2013) (vs. rice protein) [12]	WP	0.342	-0.44	1.12	12	12
Cribb et al. (2007) (WP) [28]	WP	0.611	-0.48	1.70	5	7
Cribb et al. (2006) (vs. casein) [2]	WP	1.172	0.06	2.28	6	7
	WP	*0.343*	*-0.02*	*0.70*		
Ormsbee et al. (2012) [29]	WP-MTN	-0.307	-1.09	0.47	13	11
Copper et al. (2012) [31]	WP-MTN	0.075	-0.94	1.09	7	6
Burke et al. (2001) (MTN) [27]	WP-MTN	0.328	-0.57	1.22	12	7
Cribb et al. (2007) (MTN) [28]	WP-MTN	0.727	-0.33	1.78	6	7
Willems et al. (2012) [18]	WP-MTN	0.975	-0.02	1.97	9	7
	WP-MTN	*0.281*	*-0.14*	*0.70*		
	Overall	**0.316**	**0.04**	**0.59**		

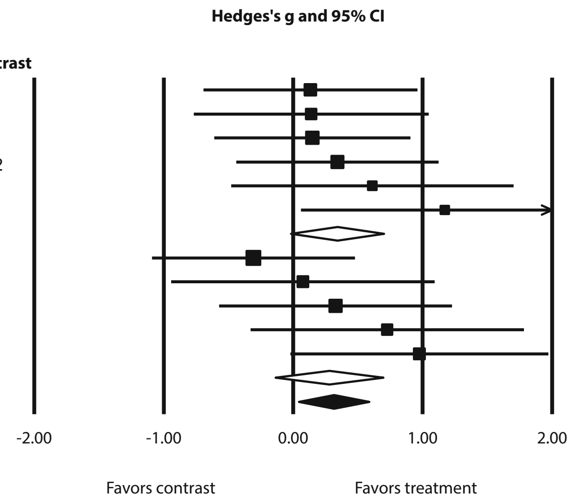


Fig. 3 1-RM lower body forest plot. Results of a random-effects meta-analysis shown as *g* effect size with 95 % confidence interval. The *white* and *black diamonds* represent the subgroups (WP and WP-MTN) and pooled (overall) standardized mean difference, respectively. *RM* repetition maximum, *CI* confidence interval, *WP* whey protein, *MTN* multi-ingredient

Reference name	Subgroup	Statistics for each study			Sample size	
		Hedges's g	Lower limit	Upper limit	Treatment	Contrast
Joy et al. (2013) (vs. rice protein) [12]	WP	0.030	-0.74	0.80	12	12
Kerksick et al. (2006) [16]	WP	0.072	-0.68	0.83	15	11
Kerksick et al. (2006) [16]	WP	0.134	-0.69	0.96	10	11
Burke et al. (2001) (WP) [27]	WP	0.305	-0.60	1.21	11	7
Cribb et al. (2007) (WP) [28]	WP	1.061	-0.08	2.20	5	7
Cribb et al. (2006) (vs. casein) [2]	WP	1.188	0.08	2.30	6	7
	WP	*0.343*	*-0.05*	*0.73*		
Ormsbee et al. (2012) [29]	WP-MTN	0.031	-0.74	0.81	13	11
Willems et al. (2012) [18]	WP-MTN	0.394	-0.55	1.34	9	7
Copper et al. (2012) [31]	WP-MTN	0.569	-0.47	1.61	7	6
Cribb et al. (2007) (MTN) [28]	WP-MTN	1.152	0.04	2.26	6	7
Burke et al. (2001) (MTN) [27]	WP-MTN	1.323	0.34	2.31	12	7
	WP-MTN	*0.612*	*0.16*	*1.07*		
	Overall	**0.458**	**0.16**	**0.75**		

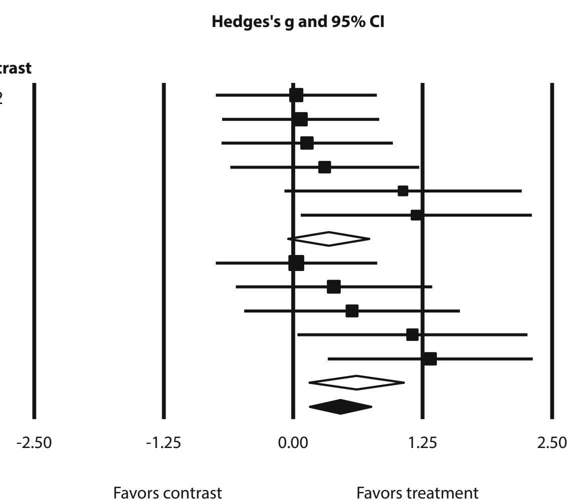


Fig. 4 1-RM upper body Forest plot. Results of a random-effects meta-analysis shown as *g* effect size with 95 % confidence interval. The *white and black diamonds* represent the subgroups (WP and WP-MTN) and pooled (overall) standardized mean difference, respectively. *RM* repetition maximum, *CI* confidence interval, *WP* whey protein, *MTN* multi-ingredient

the left of the mean effect that would slightly reduce the overall treatment effect to 0.22. The Orwin Fail Safe *N* value indicated that there would be need to locate 2.7 studies with null mean standard differences for every observed study for the treatment effect to be trivial (0.1). Based on these analyses, the risk of publication bias was considered small.

4 Discussion

The main finding of the present review was that combined supplements containing whey proteins with 6–12 weeks strength-training interventions would favor superior FFM or LBM, upper and lower body strength gains in treatment groups compared with the ingestion of carbohydrates or other protein sources in resistance-trained individuals. Additionally, statistical heterogeneity was not significant, indicating a low percentage of variability between the analyzed studies. Assessing potential sources of heterogeneity across treatments provides important insight into the impact of differences in study characteristics on results. The models herein appeared to be statistically homogeneous, with all *p* values for heterogeneity above 0.10 and I^2 well below 50 (commonly considered the standard demarcation for heterogeneity in meta-analyses) [32]. However, it was difficult to fully assess and identify the potential sources of between-study variation, given the few analyzed studies in each analytical model. We were able to identify some potential sources of heterogeneity across the studies included in this systematic review: participants' characteristics, supplement doses, supplement administration methods (e.g., timing), and training configuration. Indeed, results from the subgroup analysis showed to be less consistent and would need to be considered with caution. While whey protein and WP-MTN showed reliable beneficial effects to increase FFM/LBM and upper body strength, WP-MTN showed greater effectiveness, while the benefit of whey protein seemed to be less clear when compared with the effects elicited by the contrast treatments (Figs. 2, 4). Furthermore, with regard to lower body strength, we only found evidence for the overall effect producing significantly better effects than contrast supplements, while no significant evidence was observed for both whey protein and WP-MTN subgroups (Fig. 3) in a secondary analysis. It was difficult to explain the reasons for these results. Factors concerning study characteristics and designs, as well as the low number of treatments included in this meta-analysis, the high variability of the measured effect sizes (−0.02 or −0.14 to 0.70 in whey protein or WP-MTN, respectively), and also the lower sample size evaluated by the studies (≤15 participants per group) did not contribute to observe clear results.

In regard to FFM or LBM, the study of Burke et al. [27] reported significant and larger increases in LBM for the WP-MTN group compared with both contrast and whey protein treatments, as well as to the other studies included in this review (Fig. 2). Reasons for the larger positive effect of the WP-MTN treatment on LBM in this study, despite the short training intervention (6 weeks), may be because of participants' characteristics and/or differences in the supplementation and training protocols. Previous review of literature supported the notion that as the training level increases, the more relevant the role of protein supplementation to support the anabolic response to prolonged resistance-training interventions [4]. In comparison to Cooper et al. [13] and Ormsbee et al. [29], who used less resistance-trained experienced individuals, Burke et al. [27] evaluated recreational body builders, with a background of at least 3 years of resistance training.

Burke et al. [27] administered supplements based on participants' body mass (1.2 g of whey protein and 0.1 g of creatine per kg) divided in four equal servings throughout the day, which is a difference from the two servings per day protocol implemented by Cooper et al. [13] (breakfast and post-training) and Ormsbee et al. [29] (pre- and post-training). Moreover, the protocol by Burke et al. [27] required participants to consume a greater amount of protein and creatine when compared with other respective studies. For example, a total of 96 g of whey protein mixed with 8 g of creatine would have been administered for a typical 80-kg body mass participant by Burke et al. [27]. This amount is markedly higher when compared with the total 60 g of protein and 10.2 g of creatine, or the 42 g of the multi-ingredient protein supplements that would have been provided by Cooper et al. [31] or Ormsbee et al. [29], respectively.

Although the supplementation protocol and population evaluated by Burke et al. [27] were still fairly similar to that investigated by Cribb et al. [28], the training implemented in both aforementioned studies were slightly different. While Burke et al. [27] evaluated a 4 days per week training program, emphasizing hypertrophy (four sets of 10–12 to 6–8 repetitions per 1–2 min rest between sets) for the entire 6 weeks of intervention, participants in the study of Cribb et al. [28] underwent a 3 day per week resistance-training protocol, where only the first 4 weeks were focused on hypertrophy and the last 8 weeks were specifically oriented to strength increase (two sets of 6–4 RM per exercise at 80–85 to 90–95 % 1 RM) (Table 1). In fact, results from the two very similar studies published by Cribb et al. [2, 28] revealed a greater increase in maximal strength compared with the rest of the analyzed interventions (Figs. 3, 4).

In studies that maximized resistance-training outcomes in well-trained individuals, meaningful responses with respect to contrast treatment with large effect sizes (>0.8) have been mainly observed when whey protein or WP-MTN supplement doses were determined taking into account participants' body weight (1.2–1.5 g per kg) and consumed throughout the day in three to four servings including the post-workout consumption [2, 27, 28]. Only the study of Willems et al. [18] produced a large effect size in 1-RM LB ($g = 0.97$), after combining two intakes per day of a multi-ingredient containing carbohydrate, whey protein, creatine, glutamine, β-hydroxy-β-methylbutyrate, chromium, sodium, and potassium bicarbonate with 12 weeks of resistance-training intervention. However, the improvement achieved by the intervention group did not show to be different from the improvements observed in the contrast group. These findings suggest that combining resistance training with 1.2–1.5 g/kg/day of whey protein or WP-MTN administered in more than two servings per day (breakfast, lunch or pre workout, post-workout and/or night) would be appropriate to favor FFM/LBM and strength gains compared with the ingestion of carbohydrates or other protein sources in well-trained adult male individuals.

Whey protein is digested and absorbed rapidly, leading to a state of post-workout hyperaminoacidemia [5]. The high content of EAA and BCAA, particularly leucine, makes whey an optimal protein source to support and maximize muscle protein synthesis and attenuate the muscle protein breakdown at rest as well as following resistance exercises [33, 34]. These effects rely on the capacity to increase and prolong mammalian target of rapamycin signaling response to exercise and training [35] (for review see Vary and Lynch [36]).

The protein intake required to maximally stimulate muscle protein synthesis in young men was estimated in 0.24 g/kg per serving, achieving a minimum recommended daily intake of 0.72 g/kg to potentially maintain muscle mass at rest [34]. As whey protein contains about 50 % of EAA [7] and 11–12 % of leucine [37], about 120 mg/kg of EAA and ~28 mg/kg of leucine would be required to maintain an optimal anabolic environment. However, in resistance-trained individuals, a higher protein requirement between 1.4 and 2 g/kg/day [38] would be needed to support muscle mass maintenance and training adaptations. It is possible that the higher absolute daily protein intake in the treatment groups (1.6–2.2 vs 1.2–1.6 g/kg in the contrast groups) further influenced the observed trends [39].

Although whey protein would be more effective compared with other protein sources [40], when the amount of EAA and leucine are equivalent, the effects on muscle protein synthesis and training adaptations seem to be similar regardless of the source [12, 41]. Nevertheless, to obtain similar amounts of EAAs and leucine from plant-based proteins such as soy or rice, higher absolute protein intakes should be administered. Consequently, it results in a higher caloric intake, a greater digestion time including a slower release of amino acids to the periphery along with a greater oxidation and ureagenesis [34].

Because trained individuals have been shown to display a limited margin of improvement compared with novice or less trained counterparts [23], from the practical point of view regardless of the administration protocol, superiority observed owing to the ingestion of whey protein or WP-MTN supplements would have a meaningful impact for well-trained athletes. For example, the small to medium effect sizes of $g = 0.21$ and $g = 0.34$ determined for whey protein on FFM/LBM and 1-RM UB respectively, would still lead to an additional increment of around 1.3 or 3.5 kg respectively compared with isocaloric but less effective supplements. In addition, the medium effect size of $g = 0.28$ observed for WP-MTN on 1-RM LB would also be associated with an additional increase of about 5 kg compared with the contrast group. For a typical 80-kg, recreationally trained body builder with a 1-RM baseline performance of ~100 kg in bench press and ~120 kg in squat, as reported by Cribb et al. [28], these figures would represent an extra increment of about 2.3 % of body weight, 3.5 % of 1-RM bench press, and 4.1 % of 1 RM squat. These outcomes would be meaningful for a well-trained athlete after 6–12 weeks of training intervention.

4.1 Limitations and Future Studies

Although the currently available evidence from the analyzed RCTs supports a small to moderate beneficial effect of supplements containing whey protein (alone or administered as part of a multi-ingredient) on FFM or LBM, and upper and lower body strength gains in resistance-trained individuals, the small number of treatments included in this review represented an important limitation to the obtained results. More studies using larger sample sizes would be necessary to achieve more consistent results. The number of participants included in both interventions and contrast groups was small (ranged from 6 to 15). Furthermore, the duration of the interventions were limited to up to 12 weeks, which has shown to be an acceptable period of time to observe changes on muscle mass and strength [42]. Nevertheless, trained individuals would require longer and very well-controlled interventions to obtain more stable outcomes from resistance-training protocols [23]. Thus, studies involving more than 12 weeks and including more specific resistance training protocols, specifically focused on hypertrophy or strength, and properly integrated with the supplementation protocol (administered in terms of body weight; involving several daily servings distributed along the day, including the post-workout ingestion) would be necessary to obtain a more consistent response. Additionally, none of the included studies investigated female individuals. Although male and female individuals produce relatively similar responses to training and supplementation, future studies including resistance-trained female individuals should be designed.

Although speculative, based on the data presented in Figs. 2, 3, and 4, if more studies using larger samples over longer periods of intervention would have been available, a more consistent response in favor of both whey protein and WP-MTN would have been achieved for the three analyzed outcomes. Thus, longer term RCTs examining the effects of whey protein-containing supplements would be a significant contribution to the literature, provided they were designed to uncover the optimal dosage (in terms of grams per kilogram of body weight), serving methodology (numbers of intakes), the timing of consumption (breakfast, pre- and post-workout, or night), and integrated with a very well-designed and specific resistance-training program.

Nevertheless, authors understand that this type of study involving long interventions (>12 weeks to 1 or several years) with trained individuals is difficult to undertake, and represents a limiting factor that requires further analyses and additional efforts to maintain an appropriate control of the participants for the entire duration of the study.

5 Conclusions

Overall, the currently available evidence from RCTs would support the use of either whey protein or WP-MTN as an effective strategy to improve LBM or FFM, as well as upper and lower body strength in resistance-trained individuals. The extra beneficial effects of whey protein-containing supplement on FFM and maximal strength are most evident when consumed as a part of a multi-ingredient containing creatine, whilst whey protein alone seems to produce less clear results. However, more evidence of this is needed.

Acknowledgments The authors thank Alyssa Sherry from the Clinical Research Institute of Texas Tech University HSC and Dr. Bettina Karsten from the Centre for Sport Science and Human Performance, University of Greenwich for grammar review and editing of the manuscript.

Compliance with Ethical Standards

Funding GlaxoSmithKline-Maxinutrition and the University of Greenwich provided joint funding for the development of research projects on the effectiveness of nutritional supplements. This funding was used to help in the preparation of this review but did not affect its purpose or content.

Conflicts of interest Fernando Naclerio and Eneko Larumbe-Zabala declare that they have no conflicts of interest relevant to the content of this review.

References

1. Battermann W. Whey protein for athletes. Deutsche Milchwirtschaft. 1986;37(33):1010–2.
2. Cribb PJ, Williams AD, Carey MF, et al. The effect of whey isolate and resistance training on strength, body composition, and plasma glutamine. Int J Sport Nutr Exerc Metab. 2006;16:494–509.
3. Tang JE, Manolakos JJ, Kujbida GW, et al. Minimal whey protein with carbohydrate stimulates muscle protein synthesis following resistance exercise in trained young men. Appl Physiol Nutr Metab. 2007;32(6):1132–8.
4. Cermak NM, Res PT, de Groot LC, et al. Protein supplementation augments the adaptive response of skeletal muscle to resistance-type exercise training: a meta-analysis. Am J Clin Nutr. 2012;96(6):1454–64.
5. Miller PE, Alexander DD, Perez V. Effects of whey protein and resistance exercise on body composition: a meta-analysis of randomized controlled trials. J Am Coll Nutr. 2014;33(2):163–75.
6. Tipton K, Elliott TA, Cree MG, et al. Ingestion of casein and whey proteins result in muscle anabolism after resistance exercise. Med Sci Sports Exc. 2004;36(12):2073–81.
7. Reitelseder S, Agergaard J, Doessing S, et al. Whey and casein labeled with L-[1-13C]leucine and muscle protein synthesis: effect of resistance exercise and protein ingestion. Am J Physiol Endocrinol Metab. 2011;300(1):E231–42.
8. Hulmi JJ, Kovanen V, Selanne H, et al. Acute and long-term effects of resistance exercise with or without protein ingestion on muscle hypertrophy and gene expression. Amino Acids. 2009;37(2):297–308.
9. Tipton KD, Elliott TA, Cree MG, et al. Stimulation of net muscle protein synthesis by whey protein ingestion before and after exercise. Am J Physiol Endocrinol Metab. 2007;292:E71–6.
10. Cribb PJ, Hayes A. Effects of supplement timing and resistance exercise on skeletal muscle hypertrophy. Med Sci Sports Exc. 2006;38(11):918–1925.
11. Kraemer WJ, Solomon-Hill G, Volk BM, et al. The effects of soy and whey protein supplementation on acute hormonal reponses to resistance exercise in men. J Am Coll Nutr. 2013;32(1):66–74.
12. Joy JM, Lowery RP, Wilson JM, et al. The effects of 8 weeks of whey or rice protein supplementation on body composition and exercise performance. Nutr J. 2013;12(1):86.
13. Copper R, Naclerio F, Allgrove J, et al. Creatine supplementation with specific view to exercise/sports performance an update. J Int Soc Sports Nutr. 2012;9:33.
14. Brown EC, DiSilvestro RA, Babaknia A, et al. Soy versus whey protein bars: effects on exercise training impact on lean body mass and antioxidant status. Nutr J. 2004;3:22.
15. Kreider RB, Earnest CP, Lundberg J, et al. Effects of ingesting protein with various forms of carbohydrate following resistance-exercise on substrate availability and markers of anabolism, catabolism, and immunity. J Int Soc Sports Nutr. 2007;4:18.
16. Kerksick CM, Rasmussen CJ, Lancaster SL, et al. The effects of protein and amino acid supplementation on performance and training adaptations during ten weeks of resistance training. J Strength Cond Res. 2006;20(3):643–53.
17. Kerksick CM, Rasmussen C, Lancaster S, et al. Impact of differing protein sources and a creatine containing nutritional formula after 12 weeks of resistance training. Nutrition. 2007;23(9):647–56.
18. Willems ME, Sallis CW, Haskell JA. Effects of multi-ingredient supplementation on resistance training in young males. J Hum Kinet. 2012;33:91–101.
19. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med. 2009;6(7):e1000100.
20. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(7):e1000097.
21. Moher D, Tricco AC. Issues related to the conduct of systematic reviews: a focus on the nutrition field. Am J Clin Nutr. 2008;88(5):1191–9.
22. van Loon LJ. Is there a need for protein ingestion during exercise? Sports Med. 2014;44(Suppl 1):S105–11.
23. Peterson MD, Rhea MR, Alvar BA. Application of the dose-response for muscular strength: a review of meta-analytic efficacy and reliability for designing training prescription. Strength Cond J. 2005;19(4):950–8.
24. Rhea MR, Alvar BA, Burkett L, et al. A meta analysis to determine the dose response for strength development. Med Sci Sport Exerc. 2003;35(3):456–64.
25. Roche AF. Anthropometry and ultrasound, chap 9. In: Roche AF, Heymsfield SB, Lohman TG, editors. Human body composition. 1st ed. Champaign, IL: Human Kinetics; 1996. p. 167–89.
26. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928.
27. Burke DG, Chilibeck PD, Davidson KS, et al. The effect of whey protein supplementation with and without creatine monohydrate combined with resistance training on lean tissue mass and muscle strength. Int J Sport Nutr Exerc Metab. 2001;11(3):349–64.
28. Cribb PJ, Williams AD, Stathis CG, et al. Effects of whey isolate, creatine, and resistance training on muscle hypertrophy. Med Sci Sports Exerc. 2007;39(2):298–307.

29. Ormsbee MJ, Mandler WK, Thomas DD, et al. The effects of six weeks of supplementation with multi-ingredient performance supplements and resistance training on anabolic hormones, body composition, strength, and power in resistance-trained men. J Int Soc Sports Nutr. 2012;9(1):49.
30. Cohen J. Statistical power analysis for the behavioral sciences. 2nd ed. Mahwah: Lawrence Erlbaum; 1988.
31. Cooper R, Naclerio F, Larumbe-Zabala E, et al. Effects of a carbohydrate-protein-creatine supplement on strength performance and body composition in recreationally resistance trained young men. JOEP Online. 2013;16(1):72–85.
32. Littell JH, Corcoran J, Pillai V. Systematic reviews and meta-analysis New York. NY: Oxford University Press; 2008.
33. Burd NA, Tang JE, Moore DR, et al. Exercise training and protein metabolism: influences of contraction, protein intake, and sex-based differences. J Appl Physiol (1985). 2009;106(5):1692–701.
34. Devries MC, Phillips SM. Supplemental protein in support of muscle mass and health: advantage whey. J Food Sci. 2015;80(Suppl 1):A8–15.
35. Hulmi JJ, Tannerstedt J, Selanne H, et al. Resistance exercise with whey protein ingestion affects mTOR signaling pathway and myostatin in men. J Appl Physiol. 2009;106(5):1720–9.
36. Vary TC, Lynch CJ. Nutrient signaling components controlling protein synthesis in striated muscle. J Nutr. 2007;137(8):1835–43.
37. Hulmi JJ, Lockwood CM, Stout JR. Effect of protein/essential amino acids and resistance training on skeletal muscle hypertrophy: a case for whey protein. Nutr Metab (Lond). 2010;7:51.
38. Campbell B, Kreider RB, Ziegenfuss T, et al. International Society of Sports Nutrition position stand: protein and exercise. J Int Soc Sports Nutr. 2007;4(8):8.
39. Schoenfeld BJ, Aragon AA, Krieger JW. The effect of protein timing on muscle strength and hypertrophy: a meta-analysis. J Int Soc Sports Nutr. 2013;10(1):53.
40. Tang JE, Moore DR, Kujbida GW, et al. Ingestion of whey hydrolysate, casein, or soy protein isolate: effects on mixed muscle protein synthesis at rest and following resistance exercise in young men. J Appl Physiol (1985). 2009;107(3):987–92.
41. Norton L, Wilson GJ. Optimal protein intake to maximize muscle protein synthesis. AgroFood Ind Hitech. 2009;20:54–7.
42. Stark M, Lukaszuk J, Prawitz A, et al. Protein timing and its effects on muscular hypertrophy and strength in individuals engaged in weight-training. J Int Soc Sports Nutr. 2012;9(1):54.