

Whey Protein Supplementation in Resistance Training Individuals

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

Authors: Fernando Naclerio¹, Eneko Larumbe-Zabala²

Institution: 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)

Contact Author: Fernando Naclerio, Ph D.

Centre for Sport Science and Human Performance, University of Greenwich Medway Campus Central Avenue, Chatham Maritime, Kent ME4 4TB

Tel: +44(0)20831 8441; Fax: +44(0)20831 9805

E-mail: f.j.naclerio@gre.ac.uk

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 (MTN) formulations where whey proteins are combined with carbohydrates, other protein sources, creatine and amino acids or derivatives, have 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 to other iso-energetic supplements containing carbohydrates or other sources of proteins.

Design: A structured literature search was conducted on PubMed, Science Direct, Web of Science, Cochrane Libraries, U.S. National Institutes of Health clinicaltrials.gov, SPORTDiscus and Google Scholar databases. Main inclusion criteria comprised randomized controlled trial (RCT) study design, adults (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 9 RCTs 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 to 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) $g = 0.468$, (95% CI 0.003 to 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 to 0.588) and upper body maximal strength ($g = 0.458$, 95 % CI 0.161 to 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 to 1.068) seemed to produce more clear effects than whey protein alone ($g = 0.343$, 95 % CI -0.048 to 0.735).

Limitations

Studies involving interventions of more than 6 weeks on resistance training individuals are scarce and account for small number of participants. Furthermore, no studies with 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

1. 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.
2. 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 [2, 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 utilized mainly whey protein, either alone or combined with other nutrients, a few of them used essential amino acids (EAA), milk, casein, egg, or meat. On the other hand, the work of Miller et al. [5] analyzed the effect of whey protein combined with resistance exercise on body composition without distinction between individuals with different training background and body composition (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 [10, 11, 3, 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 [13, 2], 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], bovine colostrum [17], or enriched with amino acid [16], creatine, β -hydroxy β -methylbutyrate (HMB) 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, U.S. 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 [22, 4, 5] 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 (1RM)”; “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: i) the trial was

randomized and controlled involving at least two groups, treatment and contrast (using placebo or other supplement); ii) the treatment combined prolonged (≥ 6 weeks) resistance-training intervention with whey protein containing supplementation; iii) 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; iv) participants were healthy participants of at least 18 years old v) in order to be considered as trained individuals, participants had a minimum of 1 year of consistent strength training [23, 24]; vi) the study used whey protein isolate, concentrate or hydrolysate, consumed in isolation, or combined with other nutrients (creatine, amino acids, L-carnitine, etc.) or protein sources (casein, soy, bovine colostrum) as a part of a multi-ingredient; vii) the effects of the treatment were compared to the effects of an iso-energetic contrast treatment (carbohydrate) or other supplements containing no whey protein; viii) data on total calories consumed from the whey protein-containing supplement or contrast nutrient were available; ix) dietary intake was monitored x) the publication presented sufficient data to calculate the mean differences; xi) 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 (i) screening the titles; (ii) screening the abstracts; and (iii) if abstracts did not provide sufficient data, the entire article was retrieved and screened to determine whether it met the inclusion criteria; (iv) 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 SDs for lean or fat free mass; and 1-RM values for upper body (1-RM UB) and lower body (1-RM LB) resistance exercises. In order 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). 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, standard deviation (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) vs. 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 groups 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 groups 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 carbohydrate [13]. Thus, in order 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 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.

Table 1 about here

3 Results

3.1 Study selection

Fig. 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 9 studies [14, 27, 31, 2, 28, 12, 17, 29, 18] were included in the meta-analysis.

Fig. 1 about here

3.2 Characteristics of Included Studies

A total of 9 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 to 15 in treatment groups, and 7 to 12 in contrast groups), and ages from 18 to 50 years. Only one study [16] included participants 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 7 studies with one [14, 12, 16, 18], two [31], or three years [27, 29] of regular resistance training experience. In addition, another two studies included recreational body builders [2, 28] with a minimum of two years of experience. Only Kerksick et al. [16] allowed participants to perform a complementary endurance training for no longer than 20 minutes 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 greater amount of protein with respect to carbohydrates contrast groups (1.6 to 2.2 vs. 1.2 to 1.6 g/kg/d).

An isocaloric carbohydrates beverage was the contrast supplement in 6 studies [27, 31, 28, 16, 29, 18]. In the study by Brown et al. [14] protein bars were considered to compare whey versus soy protein effects. In addition, a third non-supplemented (only resistance training) group was tested. However as the comparison of whey protein-containing supplement versus a non-supplement conditions falls beyond the objective of this review, we excluded this 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 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, 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/d 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. 2012 [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 [27, 2, 28] considered dosages based on participants' body weight (1.5 g/kg/d), while the rest of the included trials considered absolute dosages ranging from 42 g (2 servings of 21 g) [29] to 120 g (2 servings of 60 g) [31, 18]. 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 [27, 2] servings per day, including one as 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 [27, 31, 2, 28, 17, 29, 18] evaluated a three to five times per week of progressive resistance training protocol starting with moderate loads (65 % to 75 % 1 RM) and 12 to 8 repetitions per sets, with progression toward heavier loads (80 % to 90-95 % 1RM) and 6 to 4 repetitions per set. Only one study [14] included a specific maximal-strength-only training program, involving sets of 4 to 6 repetitions for 9 weeks. Repetition maximum or set to failure strategy was considered to determine the training load in 5 studies [2, 28, 29, 12, 16] while other 4 investigations used a partner to control and adjust training loads [14, 27, 31, 18]

Finally, Joy et al. [12] applied a three days per week daily undulated periodized program, involving hypertrophy sessions (8 to 12 maximal repetitions per sets) and maximal strength workouts (2 to 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 to 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 to 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 due to the small sample size ($n = 4$).

Fig. 2 about here

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 to 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

Fig. 3 about here

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 to 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 to 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.

Fig. 4 about here

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 3 studies to 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 to 12 weeks strength training interventions would favor superior FFM or LBM, upper and lower body strength gains in treatment groups compared to 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 to the effects elicited by the contrast treatments (Fig. 2 and 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 to 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 due to 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 in order to support the anabolic response to prolonged resistance-training interventions [4]. In comparison to Cooper et al. [13] and Ormsbee et al. [29], who utilized 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 4 equal servings throughout the day, which is a difference from the 2 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 to 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 to 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 (4 sets of 10-12 to 6-8 repetitions per 1 to 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 (2 sets of 6 to 4 RM per exercise at 80-85% to 90-95% 1RM), (Table 1). In fact, results from the two very similar studies published by Cribb et al. [2, 28] revealed greater increase in maximal strength compared to the rest of the analyzed interventions (Fig. 3 and 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 to 1.5 g per kg) and consumed throughout the day in 3 to 4 servings including the post workout consumption [27, 2, 28].

Only the study of Willems et al. [18] produced large effect size in 1-RM LB ($g = 0.97$), after combining 2 intakes per day of a multi-ingredient containing carbohydrate, whey protein, creatine, glutamine, HMB, 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 to 1.5 g/kg/d of whey protein or WP-MTN administered in more than 2 servings per day (breakfast, lunch or pre workout, post workout and/or night) would be appropriate to favor FFM/LBM and strength gains compared to the ingestion of carbohydrates or other protein sources in well trained adult males.

Whey protein is digested and absorbed rapidly, leading to a state of post workout hyperaminoacidemia [5]. The high content of EAA, BCAA particularly leucine makes whey as 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 (mTOR) 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 to 12% of leucine [37] about 120mg/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 requirements between 1.4 to 2 g/kg/d [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 to 2.2 g/kg vs 1.2 to 1.6 g/kg in the contrast groups) further influenced the observed trends [39]. Although whey protein would be more effective compared to other protein sources [40], when the amount of EAA and leucine are equivalent, the effects on muscle protein synthesis and training adaptations seems to be similar regardless of the source [12, 41]. Nevertheless, in order 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].

Since trained individuals have been shown to display a limited margin of improvement compared to novice or less trained counterparts [23], from the practical point of view regardless of the administration protocol, superiority observed due 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 kg 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 1RM squat. These outcomes would be meaningful for a well-trained athlete after 6 to 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 in order 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 females. Although males and females produce relatively similar responses to training and supplementation, future studies including resistance trained females 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 g per kg 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 represent 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 lean body mass or fat free mass, as well as upper and lower body strength in resistance trained individuals. The extra beneficial effects of whey protein-containing supplement on fat free mass 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.

Compliance with Ethical Standards

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Conflicts of Interest

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

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

Study	Participants ^a	Design	Supplement		Contrast	Length	Training protocol	Supplementation protocol	Findings
			WP (n)	WP-MTN (n)					
Burke et al. 2001 [27]	Males (n=30; age. 18 to 31 y); RRT 3 years experience	3PG	WP (n=12)	WP-MTN (n=11)	CHO (n=7)	6 wk	PRT: 4 days/week split routine (4 sets x 10-12 to 6-8 reps per 1 to 2 min rest between sets)	1.2 g/kg/d administered in 4 equal serving across the day	↑ LBM ^{b c d e} ↑ 1RM BP ^{b c e} SQ ^{b e}
Brown et al. 2004 [14]	Males (n=18; age 19 to 25 y; 76 to 84 kg) RRT 1 year experience	3PG ^f	WP (n=9)	-	Soy protein (n=9)	9 wk	Maximal strength training involving 14 exercise (3 sets x 4-6 reps)	Three intakes of an 11g protein bars (33g in total) across the day	↑ LBM ^{b e}
Cribb et al. 2006 [2]	Males (n=13; age 19 to 35 y; 68 to 91 kg) RBB 2 years experience	2PG	WP (n=6)	-	Casein (n=7)	10 wk	PRT: 3 days/week, 2 weeks (2 sets x 10 to 8 RM); 2 weeks (2 sets x 6 RM and 6 weeks 4RM)	1.5 g/kg/d divided into 4 equal servings (breakfast, lunch, post-workout and evening)	↑ LBM ^{b g} ↑ 1RM BP ^{b g e} ↑ SQ ^{g c e}
Kerksick et al. 2006 [16]	Males (n=36; age 31.0 y old ±8; 84.0±12.9) kg; RRT 1 year experience	3PG	WP+C (n=10) WP+AA (n=15)	-	CHO (n=11)	10 wk	PRT: 4 days/week (2 upper-body and 2 lower-body workouts) (10 to 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} ↑ 1RM BP ^{b e} ↑ 1RM LP ^{b e}
Cribb et al. 2007 [28]	Males (n=30; age 24.5±5 y; 78.5±12 kg); RBB 2 years experience	4PG ^h	WP (n=5)	WP-MTN (n=6)	CHO (n=7)	11 wk	PRT: 3 days/week, 2 weeks 10 to 8 RM; 2 weeks 6 RM and 6 weeks 4RM	1.5 g/kg/d divided into 3 equal serving (midmorning, post-workout and evening)	↑ LBM ^{b e} ↑ 1RM BP ^{b g c e} SQ ^{b g c e}
Ormsbee et al. 2012 [29]	Males (n=24; age 24.0 ± 0.9 y; 83.7±0.5 kg.) RRT 3 years experience	2PG	-	WP-MTN (n=13)	CHO (n=11)	6 wk	PRT, 3 days/week: 2 weeks 10 RM, 2 weeks 6 RM and 2 weeks 4 RM	Two 21g intakes (pre and post workout)	↑ LBM ^{b c e} ↑ ND 1RM BP ^{b e} ↑ ND 1RM LP ^{b e}
Willems et al. 2012 [18]	Males (n=21; age 21±2 y; 74.5±5.9 kg) 21RRT 1 years experience	2PG	-	WP-MTN (n=9)	CHO (n=7)	12 wk	PRT, 4 days/week. Two 6-week training blocks. 70% (12 reps) to 85% (6 reps)	2 intakes of 60g/d at breakfast and post workout	↑ ND 1RM BP and LP
Cooper et al. 2013 [31]	Males (n=13; age 23.5±2.7 y 80 ± 13 kg); RRT 2 years experience	2PG	-	WP-MTN (n=7)	CHO (n=6)	12 wk	PRT, 4 days/week upper/lower split (4 sets per exercise of 6 to 12 reps at 65 to 80% 1RM)	2 intakes of 60g/d at breakfast and post workout	↑ ND FFM ↑ ND 1RM BP and SQ
Joy et al. 2013 [12]	Males (n 24; age 21.3 ± 1.9 y; 76.08 ± 5.6 kg); RRT 1 year experience	2PG	WP (n=12)	-	Rice protein (n=12)	8 wk	UPRT, 3 day/week. Hypertrophy days: 3 sets of 8-12 RM; strength days: 3 sets of 2 to 5RM	1 post work intake of 48g	↑ FFM ^{b e} ↑ 1RM BP ^{b e} LP ^{b e}

Notes: ^aonly participants that have completed the study have been included; ^bsignificantly different for WP or WP-MTN respect to baseline; ^csignificantly different from WP-MTN to control; ^dsignificantly different from WP-MTN to WP or from WP-C to WP+AA; ^esignificantly different from contrast groups (CHO, soy, casein and rice group) at baseline; ^fonly 2 treatment groups were considered. The non-supplement only training group (n=9) was excluded ^gsignificantly different from WP to control; ^honly three treatment groups were considered. The CHO+creatine group (n=8) was excluded. ↑= significant increase; 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.

Figure legends

Fig. 1 Flow chart diagram of the study selection

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 intervals; WP: whey protein; MTN; multi-ingredient

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 intervals; WP: whey protein; MTN; multi-ingredient

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 intervals; WP: whey protein; MTN; multi-ingredient

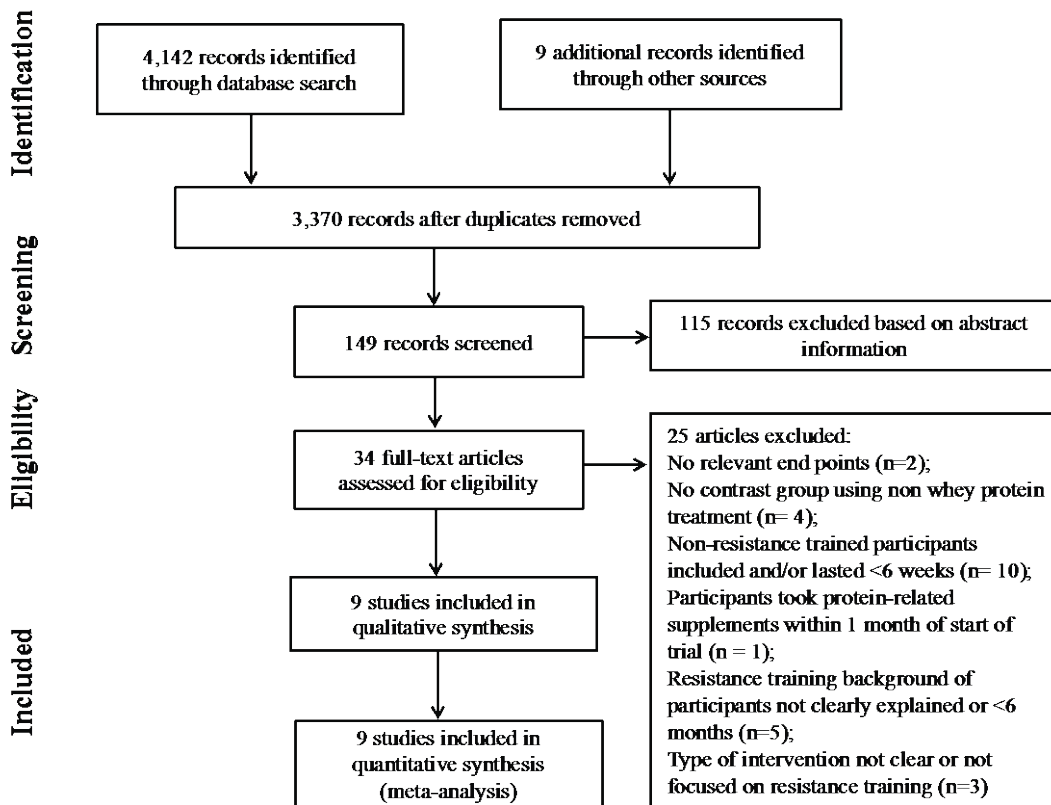


Fig. 1 Flow chart diagram of the study selection

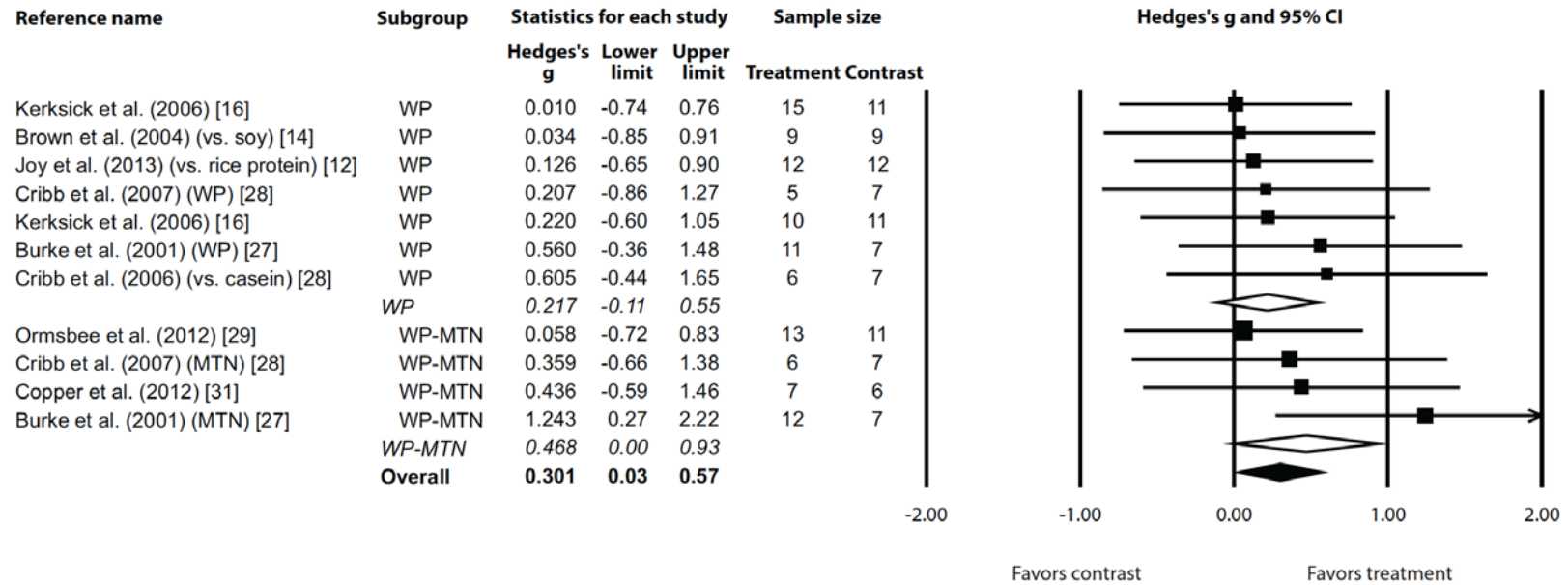


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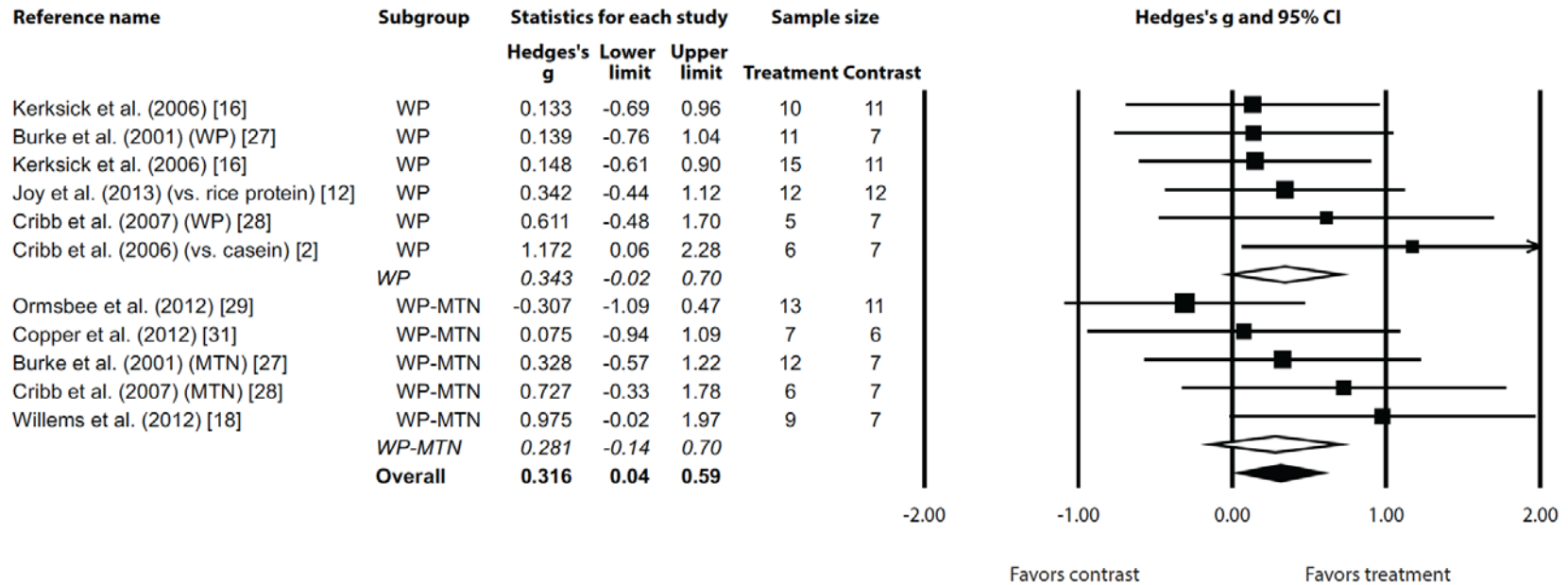


Fig. 3 1-RM lower body Forest plot. Results of a random-effects meta-analysis shown as g effect size with 95 % confidence interval. The white and black diamonds represent the subgroups (WP and WP-MTN) and pooled (overall) standardized mean difference respectively.

RM; repetition maximum; CI: confidence intervals; WP: whey protein; MTN; multi-ingredient

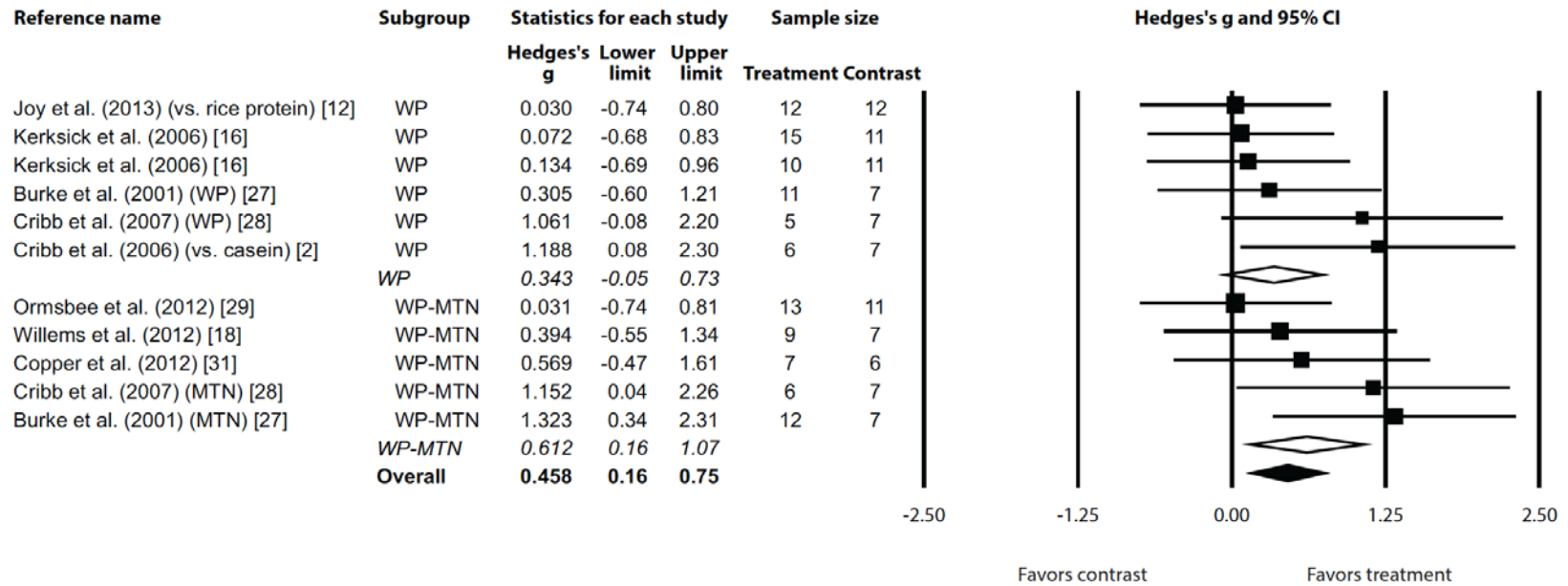


Fig. 4 1-RM upper body Forest plot. Results of a random-effects meta-analysis shown as g effect size with 95% confidence interval. The white and black diamonds represent the subgroups (WP and WP-MTN) and pooled (overall) standardized mean difference respectively.

RM; repetition maximum; CI: confidence intervals; WP: whey protein; MTN; multi-ingredient

