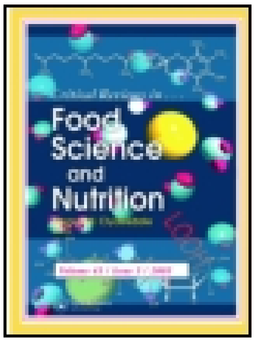

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REVIEW

A systematic review and meta-analysis: Effects of protein hydrolysate supplementation on fat-free mass and strength in resistance-trained individuals

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ABSTRACT
The quality of the existing evidence on the effects of protein hydrolysate supplementation on fat-free mass (FFM) and upper and lower body strength under resistance exercise intervention has not been evaluated. We conducted a structured literature search in PubMed, Web of Science, Cochrane Library, and Scopus database. A random effect model was used with continuous data of FFM and upper and lower body strength for healthy participants over 18 years old who received resistance training for ≥4 weeks and took protein hydrolysate or equivalent control supplements. Sensitivity and subgroup analyses were also conducted. Data from 330 participants in eight studies showed that supplemental protein hydrolysate had a positive effect on the FFM (n = 13, SMD = 0.36, 95% confidence interval (CI): 0.16–0.56, *P* = 0.000) and lower (n = 7, SMD = 0.43, 95% CI: 0.16–0.69, *P* = 0.001) and upper (n = 5, SMD = 0.17, 95% CI: −0.06–0.41, *P* = 0.145) body strength of resistance-trained individuals compared with placebo, showing an increase in physical fitness and muscle strength. However, the current evidence is insufficient to establish ingestion recommendations.

KEYWORDS
muscle strength; peptide; physical fitness; sports nutrition

Introduction

Resistance exercise training can effectively stimulate muscle protein synthesis (MPS) (Chesley et al. 1992; Phillips et al. 1997; Damas et al. 2015), resulting in skeletal muscle mass and strength changes (Goldberg et al. 1975; Warburton, Nicol, and Bredin 2006; Schoenfeld, Ogborn, and Krieger 2016). By reducing fat quality and increasing lean body mass, resistance exercises bring physical improvement (Demling and DeSanti 2000; Zdzieblik et al. 2017). This can be further enhanced by the additional intake of protein hydrolysate (Beelen et al. 2008; Cribb et al. 2006; Schmitz, Hofheins, and Lemieux 2010; Farup et al. 2014). Protein hydrolysis produces peptides that are different from their parent proteins in physical and chemical properties, with better digestion and absorption rates (Morifuji et al. 2009; Manninen 2009; Koopman et al. 2009). It has been reported that peptides can transport amino acids to a greater extent to cooperate with body changes caused by resistance exercise (van Loon 2007); peptides have also become popular among resistance-trained athletes.

Presently, many studies have evaluated the effectiveness of resistance exercise combined with protein hydrolysate supplements. In conjunction with the training program, the intake of soybean peptides (Wang et al. 2004; You 2017), wheat peptides (Pan et al. 2015), collagen peptides (Zdzieblik et al. 2015), casein hydrolysis (Demling and DeSanti 2000), beef protein hydrolysis (Naclerio et al. 2017), and whey protein hydrolysis (Tang et al. 2009) has had different effects on muscle strength, fat reduction, and weight gain. Conversely, there is study has not found that protein hydrolysates derived from whey and soy protein increase the mass or strength of skeletal muscle throughout the body (Brooks Mobley et al. 2017). Meanwhile, training plans and supplementary programs to maximize the effectiveness of joint intervention have also been widely discussed. For example, it is recommended to take 15 g of specific collagen peptides every day after exercise given its dose-dependent effect on the increase in lean body weight (Zdzieblik et al. 2017). For beef or whey protein hydrolysate, the supplementation dose was often higher than that of 15 g/d in several experiments (Naclerio et al. 2017; Lollo, Amaya-Farfan, and De Carvalho-Silva 2011; Lollo et al. 2014). Previous studies have suggested that taking protein hydrolysis before and during exercise can increase the muscle usage of amino acids in a more timely manner (Manninen 2009). Current studies are now inclined toward postexercise supplementation (Naclerio et al. 2017; Oertzen-Hagemann et al. 2019; Kirmse et al. 2019; Jendricke et al. 2019) and trying to involve protein hydrolysis intake at night (Beelen et al. 2008). Although several studies on related issues have been thus far conducted, the results are controversial and providing proper sports nutrition strategies is difficult.

In the face many conclusions, participant population, nutritional habits, dose regimens, energy or high nutrient intake, and the exercise or training program itself should be

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carefully considered with the results (Jäger et al. 2017). Therefore, conducting a systematic review and meta-analysis to reach a comprehensive and unbiased conclusion as much as possible is necessary. Unfortunately, there are no evidence-based answers on the effectiveness and program of protein hydrolysates on fat-free mass (FFM) and upper and lower body strength enhancement in resistance-trained individuals.

Therefore, this article selects healthy individual, 18 years and older, to explore the possible effects of protein hydrolysate supplements on the improvement of physical fitness and strength brought about by resistance training. We analyzed the joint intervention of resistance training and protein hydrolysate through changes in FFM and upper and lower body strength. We hope to provide a reference for the scientific and practical intake of peptides in sports nutrition to fill relevant gaps.

Methods

Study design

The study follows The Preferred Reporting Items for Reviews and Meta-Analyses (PRISMA) statements (Moher et al. 2015; Shamseer et al. 2015) and Cochrane Handbook V5.2 (Higgins and Green 2017). The selected trial conforms to the PICOS principle - P (Population): "Healthy people 18 years old and above", I (Intervention): "protein hydrolysate supplementation and resistance training", C (Comparators): "same conditions with placebo", O (Outcome):"on fat-free mass, upper and lower body strength", S (study design): "randomized controlled trial". The main sources are based on electronic databases: PubMed, Web of Science, Cochrane Library and Scopus, secondary sources are included in the articles cited by the study from the above-mentioned databases. Unrestricted research publication year (until February 2020, with no lower date limit) and language, in order to minimize the bias of these two aspects.

Search strategy

Search terms include medical subject words (MeSH) and free text words related to key concepts. The specific search is as follows: ("peptide supplement*" OR "peptides supplement*" OR "polypeptides supplement*" OR "protein hydrolysates") AND ("sport*" OR "athletic*" OR "exercise*" OR "physical activity*" OR "physical exercise*" OR "acute exercise*" OR "isometric exercise*" OR "aerobic exercise*" OR "exercise training*").

Inclusion and exclusion

The authors (SM and ZWJ) independently searched the literature and selected them according to the following steps: (1) preliminary screening: reading the title and abstract, selecting the literature that might be included (2) re-screened: reading the full text (emphasis on the evaluation of the material method), and the qualified are included against the criteria. Remove duplicate studies during the screening process, i.e. literature that may be the same study. (3) if there is any uncertainty, add information, re-screen (4) if there is controversy, invite a third party (WGC) to participate in the discussion. EndNote X9 is used for data logging and document management during the review process.

Including studies that met the following criteria: (1) healthy participants at least 18 years old; (2) not requiring uniform participants' gender, race, exercise level, whether or not to train ahead of time, etc.; (3) nutritional supplements used for intervention are derived from protein hydrolysates, consumed alone or in combination with other nutrients (amino acids, carbohydrates); (4) provides clear information on the intake of supplements: daily intake, intake time, etc.; (5) combined with protein hydrolysate intervention, resistance training of more than 4 wk is conducted at least 3 times per week; (6) measures at least one major variable related to LBM or FFM, upper and lower body maximum strength (estimated by 1 repeated maximum test (1-RM) measurement); (7) provides sufficient data for follow-up statistical analysis.

Studies with the following conditions were excluded: (1) the participants had a recent history of supplementation (less than 1 month prior to intervention), including derivatives such as proteins, peptides, creatine, etc. (2) the participants were suffering from illness or injury, (3) no real control conditions, (4) non-randomized controlled trials, such as case reports, case series or prospective trials without control groups, and (5) studies were conducted for clinical or therapeutic purposes.

Data extraction

Design data extraction table, extract (1) general information: trial name, author, year; (2) baseline data: age, gender, degree of training, etc.; (3) quality data: random, blind, parallel grouping; (4) intervention data: supplement type, dose, intervention duration, ingestion mode, resistance training type, exercise duration, etc.; (5) outcome data: intervention effect, statistical significance, etc. (6) data: continuous data extraction mean, standard deviation, number of research objects.

For missing data, when contacting the author is unable to obtain them, deduction is made from the calculation. In addition, if there are multiple experimental or control groups in the experiment, each eligible group is meta-analyzed as a separate data set. The extract is performed independently by the two authors (SM and ZWJ) and is agreed upon through negotiation to resolve differences or a third party (WGC) decision.

Risk of bias in individual studies

The authors (SM and ZWJ) independently used The Cochrane Collaboration's tool for assessing risk of the bias in the randomized trials to assess multi-domain risks

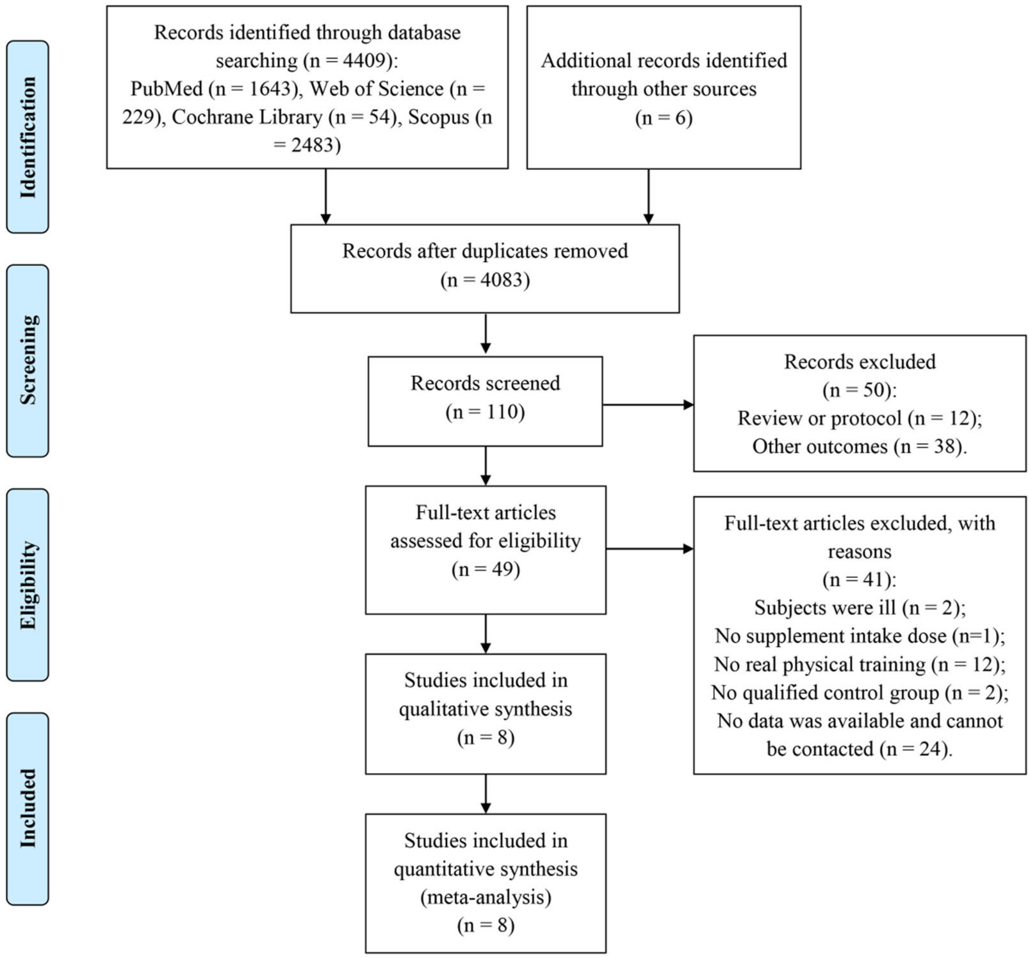

Figure 1. PRISMA flow chart of the study selection.

(Higgins et al. 2011): selection bias, performance bias, detection bias, attrition bias, reporting and other bias (with differences in baseline and dietary assessment as the source of this bias). For all studies, the review authors assessed a low, unclear, or highly bias risk based on judgment. We reached consensus through negotiation or third-party (WGC) arbitration. Draw the Risk of bias table with Review Manager (RevMan) version 5.3.

Data syntheses

Changes from baseline are selected for data analyses, for the study of raw data without SD (standard deviation) of change, impute a Δ SD using correlation coefficient, the formula can be found below (Higgins and Green 2017). For studies of baseline or final values SD deletions, derivation is calculated based on SE.

$$\mathrm{Corr_E} = \frac{\mathrm{SD^2_{E,\,baseline}} + \mathrm{SD^2_{E,\,final}} - \mathrm{SD^2_{E,\,change}}}{2\times\mathrm{SD_{E,\,baseline}}\times\mathrm{SD_{E,\,final}}} \tag{1}$$

$$\mathrm{SD_{E,\,change}} = \sqrt{\mathrm{SD^2_{E,\,baseline}} + \mathrm{SD^2_{E,\,final}} - (2\times\mathrm{Corr}\times\mathrm{SD_{E,\,baseline}}\times\mathrm{SD_{E,\,final}})} \tag{2}$$

In Using the inverse-variance method with random effects model, the intervention effect and the accuracy of summarized estimation can be obtained in the form of SMD (the standardized mean difference) measured in Hedges'g, and 95% confidence interval. Heterogeneity was evaluated according to I^2, with a significant difference in $P > 0.1$. For various characteristics or factors among the studies, subgroup analysis was used to determine the interaction between the subcombination effect size and the grouping factors (Zhang 2016). And the reliability of the results was discussed through sensitivity analysis by eliminating the included studies in turn. Finally, funnel plot and Egger's linear regression were used to test possible publication bias.

According to Cohen's convention to interpret the magnitude of SMD: <0.2, trivial; 0.2–0.5, small; 0.5–0.8, moderate; and >0.8, large (Cohen 1988). I^2 value was used to quantify heterogeneity: 0% to 40%: might not be important; 30% to 60%: may represent moderate heterogeneity; 50% to 90%: may represent substantial heterogeneity; 75% to 100%: considerable heterogeneity, showing the effect of heterogeneity on meta-analysis (Higgins and Green 2017).

All the above analyses were done using Stata SE 12.0.

Results

Study selection

The PRISMA flow diagram illustrates the filtering process (Figure 1). Based on the title and abstract, 110 articles were selected for follow-up screening. Sixty articles were excluded because of its type or inconsistency with the PICOS principles. Among the 49 articles available in full text, 8 were qualitatively and quantitatively analyzed, excluding articles on illness and articles with no specific supplement intake information, no real exercise conditions, no qualified control, and no available data (which cannot be linked or calculated).

Study characteristics

Participant characteristics

A total of 13 treatment groups from eight studies were reported, and 330 healthy participants were divided into the test (n = 139, 8–40 in each group) and control (n = 191, 6–37 in each group) groups. Six studies were conducted only among men, accounting for 73% of the total. The average age of the participants was 24.2 ± 3.2 years of age and that of one group was 39.9 ± 7.8 years of age. The number of trained individuals accounted for 69% of the total, and the participants in five studies had more than 1–3 years of resistance training experience. Additionally, three studies selected professional athletes (middle-distance runner and soccer player) (Table 1).

Supplementation characteristics

The protein hydrolysate supplements were soybean peptide, glutathione, collagen peptide, or those derived from whey and beef protein hydrolysate. The control supplements were mainly CHO, protein (whey protein and casein), and silicon dioxide. On training days, the majority of supplements were dissolved in liquids and taken after exercise. Daily intake was based on the body mass of an individual, 1–2.2 g/kg/d or at an absolute dose, with an average intake of 16.2–2.2 g/d. In particular, Hwang took capsule supplements 1 h before exercise, while Lollo et al. (2014) took double supplements before and after exercise. On nontraining days, additionally, time points are varied. The overall duration of supplementation in each trial was between 8 and 12 weeks (66 ± 23 days). One study was not supplemented on nontraining days and lasted for 20 d (Table 1).

Resistance training characteristics

Professional athletes take combined high-intensity professional, resistance, and endurance training 5–7 d/week and 1–2 times a day. Amateurs take linear progressive resistance training, including squats, bench press, dead lift, bent-over row, extension, –to 80% 1-RM. They train for 3–4 d/week for 8–12 weeks, 1–4 sets per exercise and 10–15 repetitions per set (3 ± 1 set/exercise and 11 ± 1 rep/set) (Table 1).

Risk of bias within studies

There is no research on the existence of high risk in sequence generation. Seven studies did not adequately describe the hidden methods of allocation or thus led to potential selection bias, which was stated in one study (Naclerio et al. 2017) and was avoided. Except for one study (Wang et al. 2004) without a blind method, all studies adopted a double-blind design, and the implementation of blind removal performance bias made the actual results more reliable, which also meant that there was a greater risk of measuring bias in theory if the blind method was not applied to those who evaluated the outcome. Nevertheless, the relative importance of the field needs to be noted. For highly objective outcome indicators, it may be considered that it is not important to test the evaluator. Two studies (Wang et al. 2004; Oertzen-Hagemann et al. 2019) did not describe the situation of attrition; in five studies, uncompleted training plans and injury were excluded as the main causes, and loss was not related to the real outcome. It is unclear whether all the results of the eight trials were reported, but the outcome indicators of the meta-analysis were included. Additionally, baseline characteristics and dietary monitoring were not measured in two studies (Wang et al. 2004; Hwang et al. 2018) and only recorded, but not analyzed, in two studies (Lollo, Amaya-Farfan, and De Carvalho-Silva 2011; Lollo et al. 2014); therefore, ruling out the effects of nonexperimental risks is difficult (Figure 2).

Heterogeneity and intervention effect

For the three outcome measures presented, there were no significant heterogeneity in each treatment group (FFM: n = 13, I^2 = 0%, $P = 0.684$; 1-RM lower power: n = 7, I^2 = 0%, $P = 0.550$; 1-RM upper power: n = 5, I^2 = 8.9%, $P = 0.355$). Compared with the control group, protein hydrolysate supplementation had small and significant increase in FFM (n = 13, SMD = 0.36, 95% confidence interval (CI): 0.16–0.56, $P = 0.000$) and upper body strength (n = 5, SMD = 0.43, 95% CI: 0.16–0.69, $P = 0.001$) during resistance training. There was also a slight improvement in the strength of the lower body (n = 7, SMD = 0.17, 95% CI: −0.06–0.41, $P = 0.145$) (Figure 3).

Sensitivity analyzes

The effect was combined after sequentially excluding the treatment group; the hollow scatter was located on both sides of the vertical line of SMD. The Δ SMD of FFM varied from −0.04 to +0.05, and the offset of 95% CI was less than 0.07. Thus, the excluded study did not significantly impact the intensity of protein hydrolysate supplement intervention and the accuracy of summary evaluation. Similarly, the effect of protein hydrolysates on lower body strength did not significantly decline or improve. In terms of 1-RM lower power, the degree of change was slightly larger; for example, when Jendricke (2019) was removed from the 1-RM upper power assessment, the positive effect of protein hydrolysate supplementation decreased by 0.12. This may be attributed to the primary outcome measures of upper power, and the synergism of protein hydrolysates in upper body strength should be treated with caution.

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

Study (author, year, ref)	Design	Participants	Supplementation details: Type of supplementation	Supplementation details: Intake	Supplementation details: Frequency × Duration	Training details: Exercises in each training session	Training details: Frequency × Duration	Findings
Wang et al. (2004)	RCT, 3PG	Male (n = 21, age 22.24 ± 2 years); middle-distance runner	EG: Soybean peptides (n = 8) CG1: CHO (n = 6) CG2: Contrast drinks (n = 7)	2 intakes of 8 g after the first and second exercise in the form of a drink	5 d/wk × 4 wk (twice a day)	Heavy training: RT + endurance training	5 d/wk × 4 wk (twice a day)	↑ FFM[b,]
Lollo, Amaya-Farfan, and De Carvalho-Silva (2011)	RCT, DB, 3PG	Male (n = 24, age 19 ± 1.4 years); soccer training 3 years' experience	EG: Hydrolyzed whey protein (n = 8) CG1: Whey protein (n = 8) CG2: Casein (n = 8)	1 g/kg/d contained in a bottle after the daily training session during the experimental period	7 d/wk × 8 wk	Soccer training: RT + endurance training	6-8 d/wk × 8 wk (normally twice a day)	↑ FFM[b]
Lollo et al. (2014)	RCT, DB, 3PG	Male (n = 24, age 18 ± 0.8 years); soccer training 3 years' experience	EG: Hydrolyzed whey protein (n = 8) CG1: Maltodextrin (n = 8) CG2: Whey protein (n = 8)	1.5 g/kg/d contained in a bottle administered after daily training or consumed in rest of non-exercise days	7 d/wk × 8 wk (twice a day)	Soccer training: RT + endurance training	6 d/wk × 8 wk	↑ FFM ↑ 1-RM SJ
Naclerio et al. (2017)	RCT, DB, 3PG	Male (n = 15) + Female (n = 12) (age 25.9 ± 5.9 years); regular recreationally training 2 years' and RT 1 month' experience	EG: Hydrolyzed beef protein (n = 9) CG1: CHO (n = 9) CG2: Whey protein (n = 9)	20 g/d administered diluted in 250 mL of cold orange juice after each training or in the morning of non-training days	7 d/wk × 8 wk	upper-body and lower-body program: 3 sets × 12 reps (abdominal crunch × 20 reps) at 1-RM per 2-3 min rest between sets	3 d/wk × 8 wk (alternated with habitual recreational recreationally training)	↑ FFM
Hwang et al. (2018)	RCT, DB, 3PG	Male (n = 75, age 20.47 ± 2.42 years); RT 1 years' experience	EG: GSH + L-citrulline (n = 25) CG1: Cellulose (n = 25) CG2: L-citrulline malate (n = 25)	2.2 g/kg/d delivered in seven capsules administered 1 h prior to exercise or in the morning with breakfast on non-exercise days	7 d/wk × 8 wk	upper-body and lower-body program: 3 sets × 10 reps at 70%- 80% 1-RM per 2 min rest between sets	4 d/wk × 8 wk	↑ FFM ↑ 1-RM LP[b] BP
Oertzen-Hagemann et al. (2019)	RCT, DB, 2PG	Male (n = 25, age 24.2 ± 2.6 years); resistance-untrained[e]	EG: Collagen peptide (n = 12) CG: Silicon dioxide (n = 13)	15 g/d consumed dissolved in 250 mL water after each training or at a similar time point of non-training days	7 d/wk × 12 wk	upper-body and lower-body program: 1 set × 10 reps at 50% 1-RM followed by 3 sets × 10 reps at 70% 1-RM per 2 min rest between sets	3 d/wk × 12 wk	↑ FFM[b] ↑ 1-RM SQ[b] BP[b]
Kirmse et al. (2019)	RCT, DB, 2PG	Male (n = 57, age 24 ± 3 years); moderately resistance-trained	EG: Collagen peptide (n = 29) CG: Silicon dioxide (n = 28)	15 g/d administered dissolved in 250 mL water after each training or ingested 24 h after the previous ingestion on non-exercise days	7 d/wk × 12 wk	upper-body and lower-body program: 1 set × 10 reps at 50% 1-RM followed by 3 sets × 10 reps at 70% 1-RM per 2 min rest between sets	3 d/wk × 12 wk	↑ LBM[b] ↑ 1-RM SQ[b] BP[b]
Jendricke et al. (2019)	RCT, DB, 2PG	Female (n = 77, age 39.9 ± 7.8 years); no RT experience or untrained for several years	EG: Specific collagen peptides (n = 40) CG: Silicon dioxide (n = 37)	15 g/d consumed dissolved in 250 mL water after each training or at the same time on non-training days	7 d/wk × 12 wk	upper-body and lower-body program: 2 weeks 3 set × 15 reps, 2 weeks 3 set × 12 reps, 4 weeks 3 set × 10 and 4 weeks 3 set × 8 reps	3 d/wk × 12 wk	↑ FFM[b,c] ↑ 1-RM LS[b,c] HG[b,c]

BP, bench press; CG, control group; CHO, carbohydrates; DB, double blind; FFM, fat-free mass; HG, handgrip strength; LBM, lean body mass; LP, leg press; LS, Leg strength; PD, Pull-down; PG, parallel groups; RCT, randomized controlled trial; reps repetitions, RM, repetitions maximum; RT, resistance training; SJ, squat jump; SQ, squat; ↑ significant increase; ↓ significant decrease; d, day; wk, week.

Note:
[a]Only participants that have completed the study have been included;
[b]Significant within-group difference for peptides or protein hydrolysate with respect to baseline;
[c]Significant between-group difference from peptides or protein hydrolysate to control;
[d]Significantly different from contrast groups at baseline;
[e]Data was estimated.

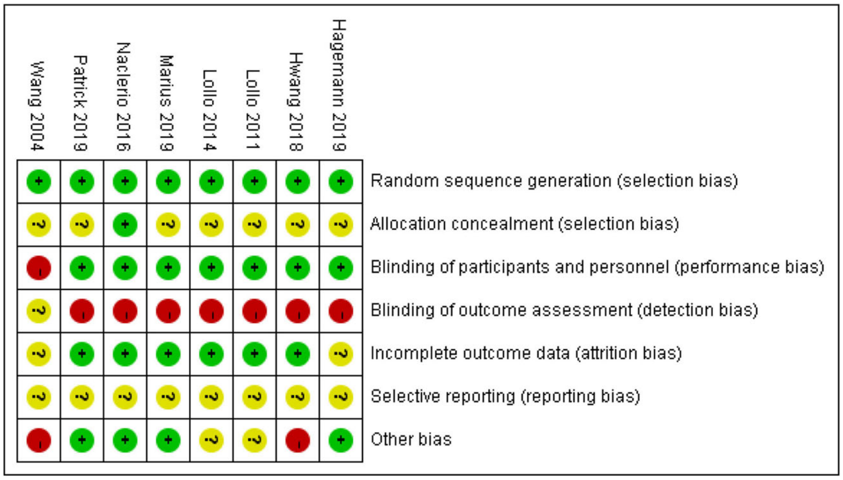

Figure 2. Risk of bias assessments for studies in meta-analysis.

Publication bias

In the funnel plot, the samples were all located in the funnel, and subjective judgment was asymmetrically distributed around the middle and bottom, in which the FFM and 1-RM lower power samples were more concentrated on the axis; this indicates that its sample size and accuracy are larger than that of 1-RM upper power. According to Egger's test, the indices of $P > | \mathrm{t} |$ were 0.597, 0.827, and 0.985 for FFM and upper and lower strength, respectively; this meant that there were no obvious publication biases in the three indicators and that the result was stable. It should be noted that the sensitivity of regression analysis is poor when less than 20 original studies were included in the meta-analysis (Higgins and Green 2017).

Subgroup analyzes

A subgroup analyses was conducted according to various characteristics or factors. The results showed that the protein hydrolysate intervention on FFM had different degrees of gain due to the training experiences, type of control supplement, intake dose, time, duration, and resistance exercise duration of the population, and there may be quantitative interaction. Alternatively, there were many qualitative interactions in the analysis of 1-RM lower power-related characteristics and factors, such as a supplement subgroup (SMD = 0.22 for peptide; SMD = −0.22 for protein hydrolysate), which may be confounding with collinearity; therefore, the overall effect of the subgroup is considered to be the most relevant result. Similarly, although the five analytical factors in the 1-RM upper and lower groups also showed the differential intervention effect of protein hydrolysates, the influence of confounding factors caused by the small sample size should not be ignored.

In addition to the moderate heterogeneity shown in untrained participants, the I^2 of FFM and 1-RM lower power was 0%–27% ($P > 0.1$), showing a small, nonsignificant heterogeneity. However, when protein hydrolysates were taken before and after exercise, its intervention effect on FFM showed significant heterogeneity ($P = 0.057$), and attention should be paid to the reliability of the results (Table 2).

Discussion

At present, the effects of protein hydrolysate supplementation on individuals on resistance training were not evaluated and analyzed. Therefore, this study explored this problem from the aspects of FFM and strength. The results showed that the intake of protein hydrolysate had a minor enhancement on the improvement of FFM and upper and lower body strength under the intervention of resistance training and improved physical fitness. Additionally, controversial characteristics, such as participant population, dose regimen, intervention cycle, energy intake, and training plan, were considered as much as possible, and the role of subgroup interaction in the positive intervention effect of protein hydrolysate was discussed in combination with subgroup analysis.

The existing meta-analysis on the combination of nutrition and exercise tends to focus on men (Bergia, Hudson, and Campbell 2018). For example, protein supplement studies believed that there was no significant difference in MPS and catabolism between men and women after resistance training (Burd et al. 2009), and protein hydrolysate supplement studies also show the same results (FFM: SMD (male) = 0.36, 95% CI: 0.12–0.61; SMD (female) = 0.37, 95% CI: −0.08–0.82); however, it should be noted that the participants in the female subgroup were all from the same experiment, and the average age (39.9 ± 7.8 years) was higher than that in the male subgroup (25.2 ± 3.3 years). Considering that muscle mass decreases by 3%–5% every decade after 30 years of age (Patel et al. 2013) and with the development of muscle anabolism resistance and inflexibility (Wall et al. 2015), the effect of age was discussed. It was found that age 30 was not a significant tipping point for peptides to improve muscle quality under resistance exercise intervention, and age subgroup had a similar efficiency (FFM: SMD (≤30) = 0.36, 95% CI: 0.13–0.59; SMD (>30) = 0.37, 95% CI: −0.08–0.82). Other analyses showed that protein supplementation in resistance exercise intervention programs for

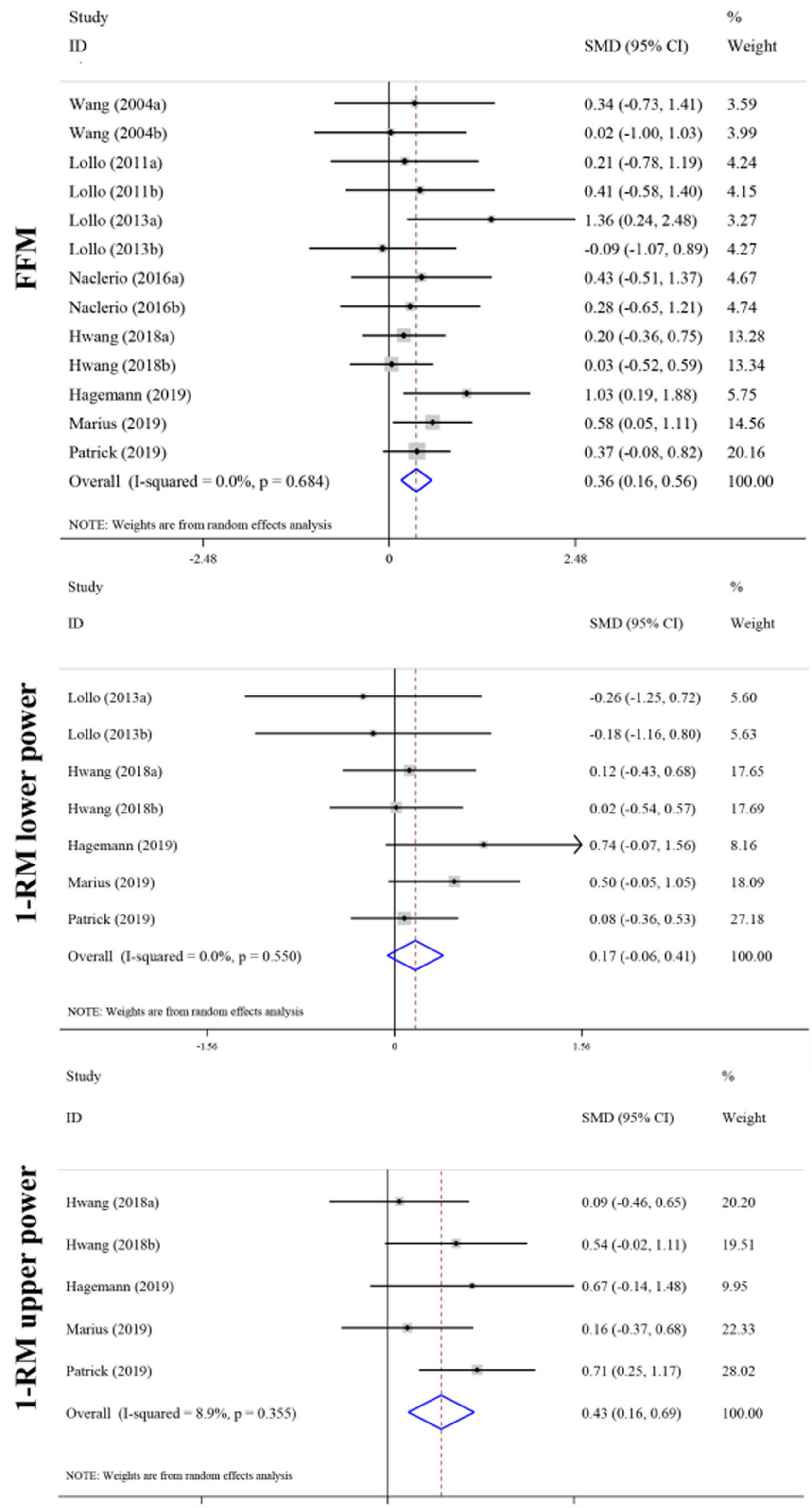

Figure 3. Forest plot. Results of a random-effects meta-analysis shown Hedges'g effect size with 95% confidence interval. The blue diamonds represent the overall SMD, CI confidence interval.

people over 50 years old increased muscle mass and strength by 38% and 33%, respectively, in just three months (Cermak et al. 2012). Physical improvement was also achieved in older people (≥65 years) (Denison et al. 2015). Combined with the synergistic effects of taking proteins, protein hydrolysate shows potential for intervention in older participants. Therefore, more rigorous and complete conclusions are expected to be drawn in trials with a more extensive female base and a broader age gradient, which can be used as a reference for research design, diet, and exercise recommendations.

Additionally, the participants were divided into groups according to whether they had training experience or not,

Table 2. Summary of subgroup analysis results.

	FFM				1-RM lower power				1-RM upper power			
Subgroup	Total n_1/n_2	SMD	(95% CI)	I^2 (%)	Total n_1/n_2	SMD	(95% CI)	I^2 (%)	Total n_1/n_2	SMD	(95% CI)	I^2 (%)
Overall	8/330	0.36**	(0.16, 0.56)	0	5/258	0.17	(−0.06, 0.41)	0	4/234	0.43**	(0.16, 0.69)	8.9
Participant												
1. Gender												
Male	6/226	0.36**	(−0.12, 0.61)	1.8	4/181	0.21	(−0.07, 0.48)	0	3/157	0.31*	(0.02, 0.61)	0
Female	1/77	0.37	(0.08, 0.82)	NA	1/77	0.08	(−0.36, 0.53)	NA	1/77	0.71**	(0.25, 1.17)	NA
Mixed	1/27	0.35	(−0.31, 1.01)	0								
2. Age (years)												
≤30	7/253	0.36**	(0.13, 0.59)	0	4/181	0.21	(−0.07, 0.48)	0	3/157	0.31*	(0.02, 0.61)	0
>30	1/77	0.37	(−0.08, 0.82)	NA	1/77	0.08	(−0.36, 0.53)	NA	1/77	0.71**	(0.25, 1.17)	NA
3. Type												
Professional	5/261	0.34	(−0.08, 0.76)	0	1/24	−0.22	(−0.92, 0.48)	0				
Amateur	3/69	0.37**	(0.14, 0.60)	0	4/234	0.22	(−0.02, 0.47)	0				
4. Experience												
Trained	6/228	0.31*	(0.07, 0.54)	0	3/156	0.14	(−0.15, 0.43)	0	2/132	0.26	(−0.06, 0.57)	0
Untrained	2/102	0.60	(−0.02, 1.22)	45.6	2/102	0.32	(−0.30, 0.94)	48.1	2/102	0.70**	(0.30, 1.10)	0
Supplementation												
1. Type												
Peptide	5/255	0.35**	(0.12, 0.58)	0	1/24	0.22	(−0.02, 0.47)	0				
Protein hydrolysate	3/75	0.39	(−0.01, 0.80)	0	4/234	−0.22	(−0.92, 0.48)	0				
2. Type of control												
CHO	4/48	0.44	(−0.01, 0.88)	10.7	2/33	0.03	(−0.45, 051)	0				
Protein	3/33	0.20	(−0.28, 0.69)	0	1/8	−0.18	(−1.16, 0.80)	NA				
Silicon dioxide	3/78	0.54**	(0.22, 0.86)	0	3/78	0.35	(−0.02, 0.71)	20.4				
Overall	8/159	0.43**	(0.21, 0.65)	0	5/119							
3. Dose												
Absolute dose (≤20 g/d)	6/282	0.35**	(0.13, 0.57)	0	4/234	0.22	(−0.02, 0.47)	0				
Based on body mass (>20 g/d)	2/48	0.43	(−0.15, 1.01)	23.4	1/24	−0.22	(−0.92, 0.48)	0				
4. Protein content of total energy intake												
≤15%	3/75	0.39	(−0.01, 0.80)	0	1/24	−0.22	(−0.92, 0.48)	0				
>15%	3/209	0.31*	(0.05, 0.57)	0	3/209	0.22	(−0.02, 0.47)	0				
Overall	6/284	0.33**	(0.12, 0.55)	0	4/233							
5. Time of ingestion												
After the training	6/231	0.44**	(0.19, 0.69)	0	3/159	0.35	(−0.02, 0.71)	20.4	3/159	0.50**	(0.12, 0.87)	23.9
Before the training	1/75	0.11	(−0.28, 0.51)	0	1/75	0.07	(−0.32, 0.46)	0	1/75	0.31	(−0.13, 0.76)	20.0
Both	1/24	0.61	(−0.81, 2.03)	72.5*	1/24	−0.22	(−0.92, 0.48)	0				
6. Duration												
<30d	1/21	0.17	(−0.57, 0.91)	0								
30d< x ≤ 64d	3/126	0.20	(−0.10, 0.51)	0	1/75	0.07	(−0.32, 0.46)	0	1/75	0.31	(−0.13, 0.76)	20.0
>64d	4/183	0.57**	(0.20, 0.94)	27.3	4/183	0.23	(−0.08, 0.55)	10.4	3/159	0.50**	(0.12, 0.87)	23.9
Resistance training												
1. Type												
RT	3/69	0.37**	(0.14, 0.60)	0								
ET + RT	5/261	0.34	(−0.08, 076)	0								
2. Duration												
<30d	2/48	0.27	(−0.22, 0.76)	0								
30d< x ≤ 40d	4/234	0.38**	(0.10, 0.65)	15.9	4/234	0.22	(−0.02, 0.47)	0				
>40d	2/48	0.43	(−0.15, 1.01)	23.4	1/24	−0.22	(−0.92, 0.48)	0				

CI, confidence interval; ET, endurance training; FFM, fat-free mass; I^2, heterogeneity; NA, not applicable; n_1, number of trials; n_2, number of participants; RM, repetitions maximum; RT, resistance training; SMD, standard mean difference. *Significant ($P < 0.05$). **Highly significant ($P < 0.01$).

and it was found that people without resistance training experience had a greater improvement in muscle mass and strength. This may be because resistance training induces MPS to exceed muscle protein breakdown (MPB) for a long time (Brook et al. 2015), weakening the resilience of MPS response to it (Phillips et al. 1999). The study also showed that the muscle strength of the "untrained" increased by 40%, that of the "middle trainer" increased by 20%, and that of the "elite" increased by only 2% (Kraemer et al. 2009) during 4–2 weeks of resistance training. However, the protein supplement trial concluded the opposite: compared with the placebo group, the trained participants showed a 0.4-fold increase in FFM (Cermak et al. 2012). Thus, protein supplements are more helpful in individuals on resistance training compared with novice trainees to increase FFM (Morton et al. 2018). Alternatively, there is a dynamic balance between MPS and MPB in untrained participants, and it is significantly influenced by supplements and exercise (Børsheim et al. 2002). Therefore, the effect of the intervention is more likely to change because of the differences in population, dose, exercise intensity, etc. Additionally, in this study, inexperienced participants consumed collagen peptides, the special interventions of its on muscles, such as stimulation of extracellular matrix molecules were unknown (Schunck and Oesser 2013).

In addition to collagen peptides, the protein hydrolysates involved in the analysis come from soy, whey, and beef protein, but when the content of essential amino acids (EAAs) and leucine are equal, regardless of the source, the effects on MPS and training adaptation seem similar (Joy et al. 2013; Naclerio and Larumbe-Zabala 2016). Therefore, we should consider the quality and quantity of hydrolysates. The studies concluded that hydrolysis did not change the content of EAAs and Leu compared with maternal protein (Lollo et al. 2014; Naclerio et al. 2017); however, the results of the subgroup analysis showed that a more significant improvement was achieved when taking peptide than when taking protein. This indicating that the increase in peptides changes of absorption kinetics, which determine the more excellent nutritional value of protein hydrolysate (Manninen 2009; Saadi et al. 2015). Based on this view, there may also be differences in the effects of intervention among hydrolyzed products having different peptide ratios and peptide characteristics, such as length, molecular weight, and amino acid composition, after diverse hydrolysis. However, according to the proportion of the peptides grouped, compared with the intake of amino acids and proteins, it was found that the high proportion of peptides did not lead to a more significant improvement in FFM during resistance exercise (FFM: SMD (peptide) = 0.35, 95% CI: 0.12–0.58; SMD (protein hydrolysate) = 0.39, 95% CI: −0.01–0.80). Because most studies did not provide accurate information on hydrolysis methods and products (i.e., the accuracy of grouping and the level of analysis are controversial), the results should be treated with caution. From another viewpoint, in healthy men, Brooks Mobley et al. (2017) combined 12 weeks of resistance training and supplementation of proteins or hydrolysates containing the same amount of Leu (from whey and soy protein) but did not find that the above supplements provided a gain in increasing the mass or strength of the body skeletal muscle. In order to equate the amount of EAAs and leucine, more soybean or rice and other plant proteins were ingested than whey protein (Devries and Phillips 2015). This suggests that the source of food determines the quality of peptides and that the intake of supplements can also have a nonnegligible effect on the results.

The International Society of Sports Nutrition believes that the optimal protein intake is generally 0.25 g/kg or an absolute dose of 20–40 g, although age and current resistance exercise stimulation are the determinants to maximize MPS. Ideally, protein should be evenly distributed and taken every 3–4 hours (Jäger et al. 2017). The analysis results showed that supplementation of more than 20 g hydrolysates per day could effectively improve defatted body weight, suggesting that the intake of fewer peptides had a positive result on the body composition of individuals on resistance training and thus these individuals should avoid the intake of higher levels of protein, which leads to higher calorie intake and digestion time (Devries and Phillips 2015). However, determining the amount of peptide supplementation is difficult because supplements are taken in the form of protein hydrolysates in some studies, and more trials are needed to explore daily peptide intake to meet the demand and avoid excess calories. There are differences in the effects of the intake of amino acids, protein hydrolysates, or proteins before or after exercise (van Loon, Kies, and Saris 2007).

Similarly, the results showed that the impact of protein hydrolysate intake after exercise on muscle enhancement under resistance exercise intervention was better than that before and after exercise, and it would have a more positive effect if it was taken before and after exercise, but the dose difference was not considered here. Preexercise intake provides amino acids for consumption during and after exercise, while the significance of postexercise intake lies in that the MPS rate reaches its peak within 3 h after exercise (Burd et al. 2011), and the usage of amino acids increases. Furthermore, further stimulating the increase in muscle protein in the recovery process, that is, injury repair, is needed (van Loon, Kies, and Saris 2007). However, there is a significant heterogeneity in the double intake subgroup, which needs to be cautiously treated. It is worth mentioning that FFM and strength have the exact positive correlation with supplement intake days and resistance exercise days (the former is longer than the latter). What is needed here is the potential importance of nontraining day supplements, which needs to be further explored.

In the resistance training scheme, it can be seen, with hydrolysis supplementation, the improvement effect increases with the increase in exercise duration. However, participants who exercised for 40 d or more tended to train 6 d or more per week and were more trained to adapt to a significant intensity. Therefore, the exercise program of 8–12 weeks, 3–4 d/week is more suitable for reference, which is also more in line with the American College of Sports Medicine's novice and intermediate training recommendations (Kraemer et al. 2009). In addition to duration and frequency, we can also analyze the characteristics of muscle contraction speed, load strength, resistance motion type, etc.; however, this will not be discussed here because of the limited set of factors included in the study.

It should be noted that, for decreasing weight and physical strength, protein hydrolysate supplementation showed the opposite intervention effect in several of the same subgroup characteristics, such as the increase in the lower body strength of men or the upper body strength of women induced by the resistance movement with supplementary peptides and gender-independent gains in FFM. For example, relative to protein, peptides are more conducive to improving weight loss in resistance exercise, but lower body strength shows a negative effect. Some trials have demonstrated that the addition of bioactive peptides to strength training programs does not appear to provide an advantage in the development of upper and lower body strength (Zavala et al. 2016) and collagen peptides intake does not significantly affect changes in muscle strength (Kirmse et al. 2019; Oertzen-Hagemann et al. 2019). In this study, we consider the effect of the combination of resistance exercise and peptide supplementation on the factors that have a decisive effect on strength, such as cross-sectional muscle area, muscle fiber type, primary muscle length, and whether it causes the opposite synergy between muscle weight and strength. Unfortunately, the lack of data makes it impossible to conduct an in-depth analysis. We should also pay attention to the effects of small sample size, a possible deviation caused by multifactor subgroup confounding factors, heterogeneity between treatment groups, etc.

Conclusion

Conclusively, the systematic review and meta-analysis demonstrated that protein hydrolysate supplementation improved the FFM and lower and upper body strength of resistance-trained individuals, showing an increase in physical fitness and muscle strength. There were also different intervention effects cause by factors such as the training degree of the participants, the dose of supplements, and exercise time.

Disclosure statement

No potential conflict of interest was reported by the authors.

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