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Effect of short- and long-term protein consumption on appetite and appetite-regulating gastrointestinal hormones, a systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Aim: High-protein diets are considered as useful diets for weight loss programs. We collected randomized controlled trials that evaluated the effect of protein on appetite and gastrointestinal hormones involved in appetite regulation.

Methods: Trials were included if participants were healthy adults and isocaloric treatments were used in control and treatment arms. Random-effects model was used to calculate mean difference and 95% confidence intervals.

Results: In total, 49 publications for acute and 19 articles for long-term effect of protein were included. In acute interventions, protein decreased hunger (-7 mm visual analogue scale (VAS), $P<0.001$), desire to eat (-5 mm, $P = 0.045$), and prospective food consumption (-5 mm, $P = 0.001$) and increased fullness (10 mm, $P<0.001$) and satiety (4 mm, $P<0.001$). There was also a decrease in ghrelin (-20 pg/ml, $P<0.001$) and increase in cholecystokinin (30 pg/ml, $P<0.001$) and glucagon-like peptide-1 (GLP-1) (21 ng/ml, $P<0.001$), but no change in gastric inhibitory polypeptide and peptide YY was observed. Appetite markers were affected by protein doses < 35 g but ghrelin, cholecystokinin, and GLP-1 changed significantly after doses ≥ 35 g. Long-term ingestion of protein did not affect these outcomes, except for GLP-1 which showed a significant decrease.

Conclusion: Results of this meta-analysis showed that acute ingestion of protein suppresses appetite, decreases ghrelin, and augments cholecystokinin and GLP-1. Results of long-term trials are inconclusive and further trials are required before a clear and sound conclusion on these trials could be made.

1. Introduction

After decades of combat against obesity, obesity is still an important health concern around the world [1]. Since a number of obesity cases occur due to overeating, proper regulation of appetite may help in weight management programs as demonstrated by a recent meta-analysis [2]. Appetite is the desire or motivation to eat food. Appetite is determined by two contradictory feelings of satiety and hunger [3]. These feelings play important roles in controlling the amount of food and energy consumption and thus managing body weight [4]. Hence, appetite can be considered as a promising target for prevention and treatment of obesity.

The gut-brain axis is a bidirectional communication route between gastrointestinal tract and brain [5, 6]. One of the gut communications is exerted by gut endocrine system which induces neural circuits in hypothalamus and brainstem to regulate appetite and control feeding behavior. These hormones are secreted following sensing the presence (or absence) of macronutrients in the gastrointestinal tract. There are two major types of gastrointestinal hormones: orexigenic such as ghrelin and anorexigenic such as cholecystokinin (CCK) [5, 6].

For decades, high-protein diets have been used in weight loss programs [7, 8]. In fact, the role of protein in suppression of appetite has been put forward as a potential explanation for the high prevalence of obesity (especially among low-income populations) and also as a strategy for its treatment [9]. In addition, there is a protein leverage hypothesis which states that human body prioritizes protein over carbohydrate and fat [9]. According to this hypothesis, if a diet lacks sufficient protein, then the consumption of food increases in an attempt to obtain higher amount of protein from food, leading to overeating and increased risk of obesity [10]. In contrast, high-protein foods meet body protein needs and decline energy intake.

A number of clinical trials have investigated the effect of protein

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consumption on appetite sensations as well as appetite-regulating hormones. Here, we evaluated the effect of protein ingestion on appetite markers and a number of gastrointestinal hormones involved in appetite regulation. In addition, we performed an extensive subgroup analysis based on sex and BMI of participants as well of dose, protein source, and placebo type. We further questioned if the effect of protein on the assessed outcomes differs between short and longer term protein intake.

2. Methods

2.1. Search

PubMed, Scopus, and Embase were searched to find articles related to the effect of protein on appetite markers and gastrointestinal hormones involved in appetite regulation. The search was performed from the earliest available date until September 2019. No limitation on language was made. Search terms included appetite, satiety, satiation, fullness, hunger, ghrelin, cholecystokinin (CCK), glucagon-like peptide-1 (GLP-1), gastric inhibitory polypeptide (GIP), incretins, and peptide YY (PYY). These hormones are the mostly recognized gastrointestinal hormones involved in appetite regulation [11, 12]. Screening the library, reading the articles, and extraction of the data was performed by two independent investigators.

2.2. Eligibility criteria

Randomized controlled trials were included if the following criteria were met: 1) healthy subjects; 2) adult ages; and 3) isocaloric treatments in control and treatment arms. Both acute (i.e. short-term) and long-term (3 days to 9 months) trials were included. Acute trials were those in which the effect of protein was determined within few hours ($<$ 5.5 h) after protein consumption whereas in long-term trials the intervention period was between 3 days to 9 months. Trials were excluded in the case of any of the following situations: 1) participants involved in diseases or medical conditions such as diabetes, glucose intolerance, kidney failure, cancer, protein-energy malnutrition, sarcopenia, anorexia, bulimia, and carbohydrate craving; 2) ad libitum (or uncontrolled) consumption of protein supplements or protein meals; 3) high-protein ketogenic diets; 4) treatments combined with exercise; 5) protein treatments mixed with fiber; 6) examining proteins with unusual amino acid content, for instance, proteins enriched with specific amino acids such as leucine; 7) non-isocaloric control or control with the same amount of protein as treatment arm; 8) insufficient information for the time of measurements in long-term interventions; 9) reporting mean change in appetite markers throughout a day or over a number of days instead of reporting them at specific time points after a test meal; 10) expressing data as area under the curve instead of linear curve or instead of actual values at specific post-treatment time points; 11) insufficient information for the macronutrient composition of the diets or test meals or mean and standard deviation (SD) of the data; 12) repeated publications.

2.3. Outcomes

Investigated outcomes included hunger, fullness, satiety, desire to eat, and prospective food consumption as markers of appetite, and ghrelin, CCK, GLP-1, GIP, and PYY as gastrointestinal hormones involved in appetite regulation.

2.4. Data extraction

Mean and SD (or SE) of the data were collected in Excel sheets. Most articles reported the outcomes at different time points after ingestion of a test meal in the form of linear graphs. The 3 h post-treatment was recognized and used as the most common post-intervention time point measured but in studies with shorter post-treatment duration, the nearest time point to the 3 h was used. The values of linear graphs were quantified by Plot Digitizer software version 2.6.6 (Free Software Foundation Inc., USA).

2.5. Statistical analysis

Mean and SD of the difference between pre- and post-intervention data was used to calculate pooled effects. The random-effects inverse-variance model was used to obtain weighted mean difference and 95% confidence interval (CI). Between-study heterogeneity was evaluated using Cochrane χ^2 test and I^2. Publication bias was determined by Egger's test [13]. Subgroup analysis was performed based on participants' body mass index (BMI) (lean ($<$ 25 kg/m^2), overweight and obese ($\geq$ 25 kg/m^2), or both), protein dose ($<$ 35 g/day vs. $\geq$ 35 g/day), protein source (whey, casein (or dairy, milk, yogurt), meats/egg (veal, turkey, egg), vegetable (soy, wheat, gluten, pea), or mixed), and control type (carbohydrate, fat, or both). The cutoff point for protein dose was chosen according to the median of doses used in the trials. STATA software version 12.0 (StataCorp, USA) was used for data analysis. The trim-and-fill analysis was used to adjust any significant publication bias detected. $P < 0.05$ was considered statistically significant.

3. Results

Following the search of the databases, 8862 articles were found, of which 3805 were duplicates and excluded, the rest were screened, and at last 325 full texts were assessed according to the eligibility criteria described in the Methods (Supplemental Figure 1). Of these, 257 articles were excluded due to reasons described in Fig. 1 and 68 passed the eligibility stage and entered in the meta-analysis: 49 publications investigated acute effect of protein and 19 articles conducted long-term interventions. A total of 2740 and 1159 subjects participated in the acute and long-term interventions, respectively. Except 2 trials which had a parallel design, acute interventions had either a crossover or a within-subject design, meaning that all their participants experienced both treatment and control conditions. Long-term interventions were conducted in both parallel and crossover design. Characteristics of the short- and long-term trials are outlined in Supplemental Tables 1 and 2, respectively.

Among acute interventions, 13 trials had multiple arms based on various protein sources [14, 21, 28, 32, 36, 40, 41], protein doses [16, 18, 19], or divergent participants [22, 23, 38]. These studies were cited more than once. Likewise, among long-term interventions 6 trials were cited more than once due to using different proteins [45, 48, 50, 51] and different doses [44, 47].

In acute interventions, trials reported the outcomes at different times following protein load but 3 h was the mostly used time point. In longer trials, the length of the intervention varied between 3 days and 9 months. Parameters of interest were measured either in fasting state, pre- and post- protein ingestion, or at a specific time point during the day of measurement.

Whey protein was the mostly examined protein but there were also reports on protein from other sources such as casein, milk, yogurt, soy, beef, turkey, and egg. According to the inclusion criteria, it was necessary for the control group to be isocaloric with the treatment. Although some control meals contained protein but extra protein in the treatment group needed to be substituted with fat or carbohydrate in control in order to have isocaloric intakes in both groups. The actual dose of protein was calculated from subtraction of protein in the treatment and control groups (Supplemental Tables 1 and 2). The actual protein dose varied from 8.5 g to about 130 g per day.

Among 49 acute interventions, 28, 23, 18, 15, and 11 trials assessed hunger, fullness, desire to eat, prospective food consumption, and satiety, and 25, 15, 25, 12, and 11 trials examined ghrelin, CCK, GLP-1,

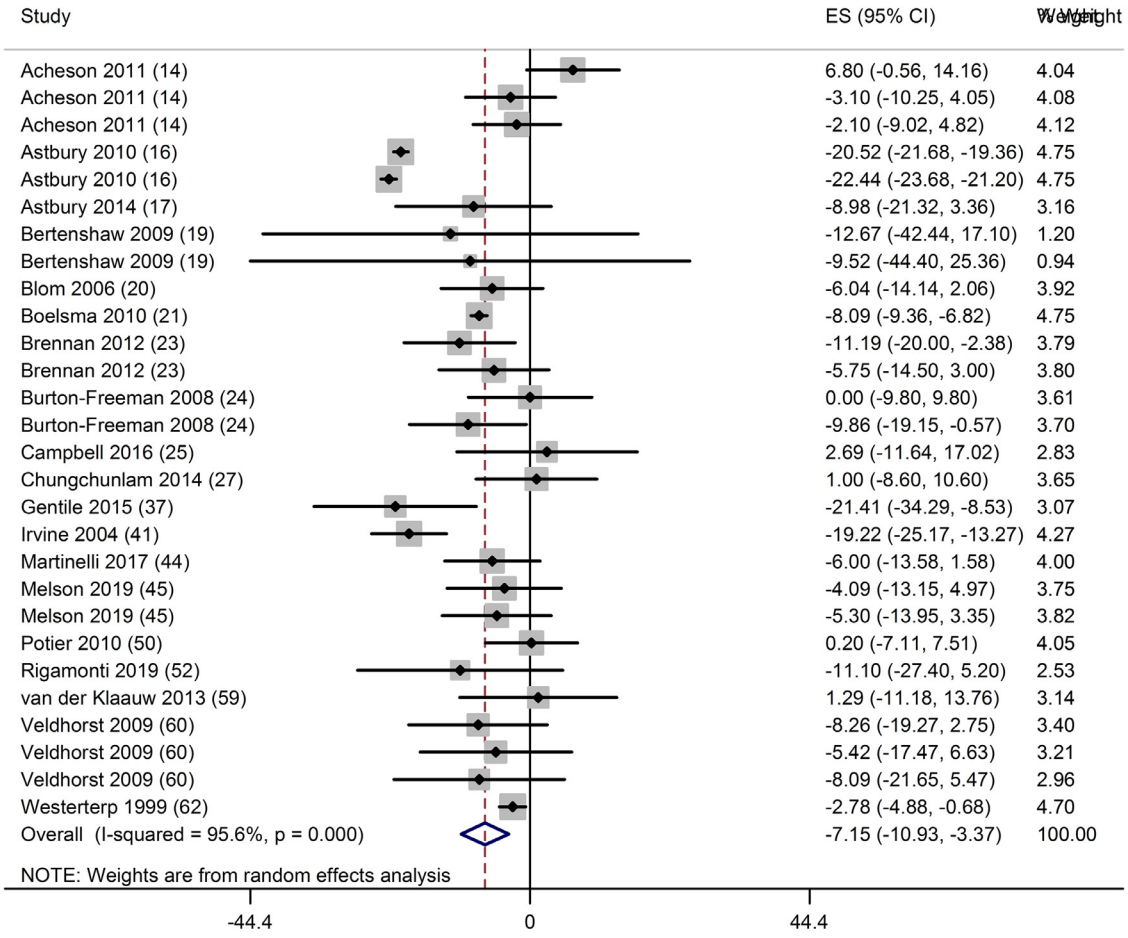

Fig. 1. Forest plot of clinical trials examining the effect of protein intake on the sensation of hunger in acute interventions. Data are presented as mean difference between treatment and control groups with 95% CIs.

GIP, and PYY respectively. Also, among 19 long interventions, 13, 13, 6, 4, and 8 studies assessed hunger, fullness, desire to eat, prospective food consumption, and satiety, and 6, 1, 6, 1, and 6 trials determined ghrelin, CCK, GLP-1, GIP, and PYY, respectively.

4. Acute interventions

Hunger, fullness, desire to eat, prospective food consumption, and satiety were the commonly assessed markers of appetite. The method of assessment was visual analogue scale (VAS) which is a tool that rates the perception of a sensation or feeling on a 100-mm horizontal line. This line is anchored at the ends by words that define bounds of the sensation.

Estimated pooled effects showed significant decrease in hunger (−7; 95% CI: −11, −3 mm; $P < 0.001$; $n = 28$) (Fig. 1), desire to eat (−5; 95% CI: −11, −0.1 mm; $P = 0.045$; $n = 18$) (Table 1), and prospective food consumption (−5; 95% CI: −8, −2 mm; $P = 0.001$; $n = 15$) (Table 1) and significant increase in fullness (10; 95% CI: 5, 14 mm; $P < 0.001$; $n = 23$) (Fig. 2) and satiety (4; 95% CI: 2, 6 mm; $P < 0.001$; $n = 11$) (Table 1) following consumption of protein. Also, there was a significant decrease in ghrelin (−20; 95% CI: −29, −12 pg/ml; $P < 0.001$; $n = 25$) (Fig. 3), significant increase in CCK (30; 95% CI: 17, 43 pg/ml; $P < 0.001$; $n = 15$) (Fig. 4) and GLP-1 (21; 95% CI: 13, 29 ng/ml; $P < 0.001$; $n = 25$) (Fig. 5), and no change in GIP (−2; 95% CI: −32, 28 ng/ml; $P = 0.891$; $n = 12$) (Table 1) and PYY (3; 95% CI: −24, 30 ng/ml; $P = 0.817$; $n = 11$). There was a high heterogeneity in the findings in all of the outcomes except for satiety ($I^2 = 0$), ranging from 69.7% to 98.4% ($P < 0.001$) (Table 1).

5. Long-term interventions

In long-term interventions, protein did not have a significant effect on hunger ($P = 0.077$; $n = 13$), fullness ($P = 0.165$; $n = 13$), desire to eat ($P = 0.676$; $n = 6$), prospective food consumption ($P = 0.210$; $n = 4$), satiety ($P = 0.213$; $n = 8$), ghrelin ($P = 0.535$; $n = 6$), and PYY ($P = 0.256$; $n = 6$), but GLP-1 decreased significantly (−7; 95% CI: −1.2, −0.02 ng/ml; $P = 0.008$; $n = 6$) (Table 1). CCK and GIP were assessed in only one trial. Except for ghrelin ($I^2 = 12.5\%$; $P = 0.335$), the results for other parameters had high heterogeneity ranging from 70.6% to 95.5% ($P < 0.05$).

6. Subgroup analysis for acute interventions

Subgroup analysis based on participants' BMI and sex, source and dose of protein, and placebo type is shown in Table 2 (for briefness only data of hunger, fullness, ghrelin, CCK, GLP-1, and GIP have been shown). In the dose subgroups, appetite markers were affected by protein doses < 35 g but ghrelin, CCK, and GLP-1 changed significantly by doses ≥ 35 g; although less substantial but still significant alteration was also observed in ghrelin in doses of < 35 g protein (Table 2). In the placebo subgroups, protein decreased hunger and ghrelin and increased fullness, CCK, GLP-1, and PYY compared to carbohydrate (data not shown for PYY). In some outcomes (fullness, CCK, GIP, and PYY), the number of trials with fat placebo was insufficient to allow making an accurate conclusion. Similarly, subgroup analysis based on protein source was not useful because of limited number of trials in protein sources other than whey. Whey was the most frequently examined protein for appetite investigations. In the whey subgroup, a significant

Table. 1
Pooled effect of protein on markers and hormones involved in appetite regulation in trials with short- and long-term interventions[1].

Outcomes	Studies (n)	Mean difference (95% CI)*	*P* value	Heterogeneity	*P* for heterogeneity
Acute effects					
Desire to eat (mm)	18	−5 (−11, −0.1)	0.045	97.7%	< 0.001
Prospective food consumption (mm)	15	−5 (−8, −2)	0.001	67.4%	< 0.001
Satiety (mm)	11	4 ([2], [6])	< 0.001	0%	0.54
GIP (ng/ml)	12	−2 (−32, 28)	0.891	95.2%	< 0.001
PYY (ng/ml)	11	3 (−24, 30)	0.817	95.6%	< 0.001
Long-term effects					
Hunger (mm)	13	5 (−0.5, 10)	0.077	85.8%	< 0.001
Fullness (mm)	13	3 (−1, 8)	0.165	87.9%	< 0.001
Desire to eat (mm)	6	−2 (−9, 6)	0.676	78.1%	< 0.001
Prospective food consumption (mm)	4	−11 (−28, 6)	0.210	95.5%	< 0.001
Satiety (mm)	8	3 (−2, 8)	0.213	79.5%	< 0.001
Ghrelin (pg/ml)	6	0.4 (−1, 2)	0.535	12.5%	0.335
CCK (pg/ml)	1	−0.03 (−0.2, 0.1)	0.540	–	–
GLP-1 (ng/ml)	6	−0.7 (−1.2, −0.02)	0.008	77.4%	<0.001
GIP (ng/ml)	1	13 (−23, 48)	0.494	–	–
PYY (ng/ml)	6	−3 (−8, 2)	0.256	70.6%	0.004

1 Mean difference and its standard deviation (SD) of control and intervention groups were used to calculate pooled effects (expressed as mean difference and 95% confidence interval). Statistical heterogeneity was assessed by I^2 test using random inverse-variance heterogeneity. CI: confidence interval.

reduction was observed in hunger and ghrelin and a significant increase was observed in fullness and GLP-1 following protein consumption, but no effect was observed on CCK, GIP, and PYY. Results of subgroup analysis based on sex showed that protein intake reduced hunger and increased fullness in both males and females but ghrelin was decreased and CCK was increased only in males. The number of trials with females was merely 2 for CCK and GLP-1 and no significant effect was observed for females in these outcomes. Likewise, subgroup analysis based on BMI was not successful because there were not enough trials in overweight/obese subgroup (Table 2).

7. Publication bias

Publication bias was detected for hunger (Egger's test $P = 0.02$), ghrelin (Egger's test $P = 0.01$), and CCK (Egger's test $P = 0.04$) in short-term trials but there was no bias in long-term interventions. Trim-

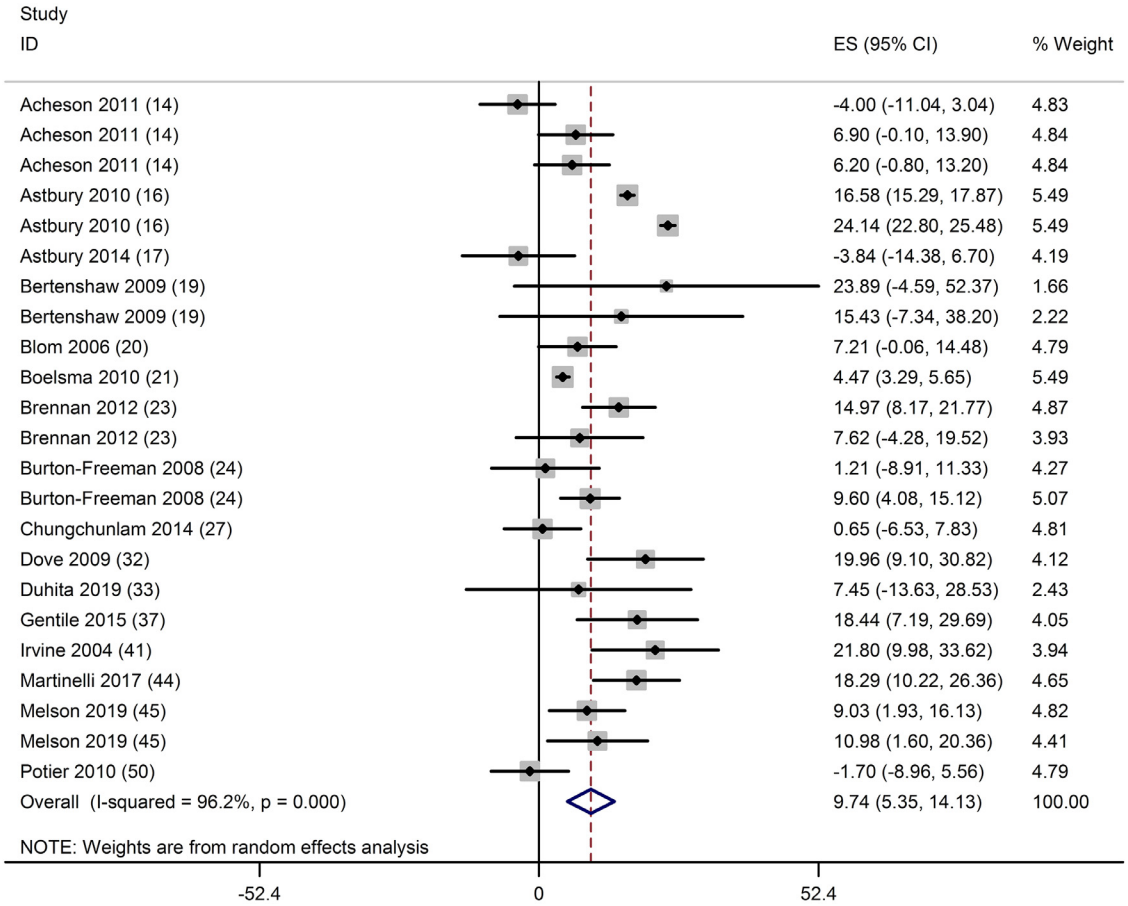

Fig. 2. Forest plot of clinical trials examining the effect of protein intake on the sensation of fullness in acute interventions. Data are presented as mean difference between treatment and control groups with 95% CIs.

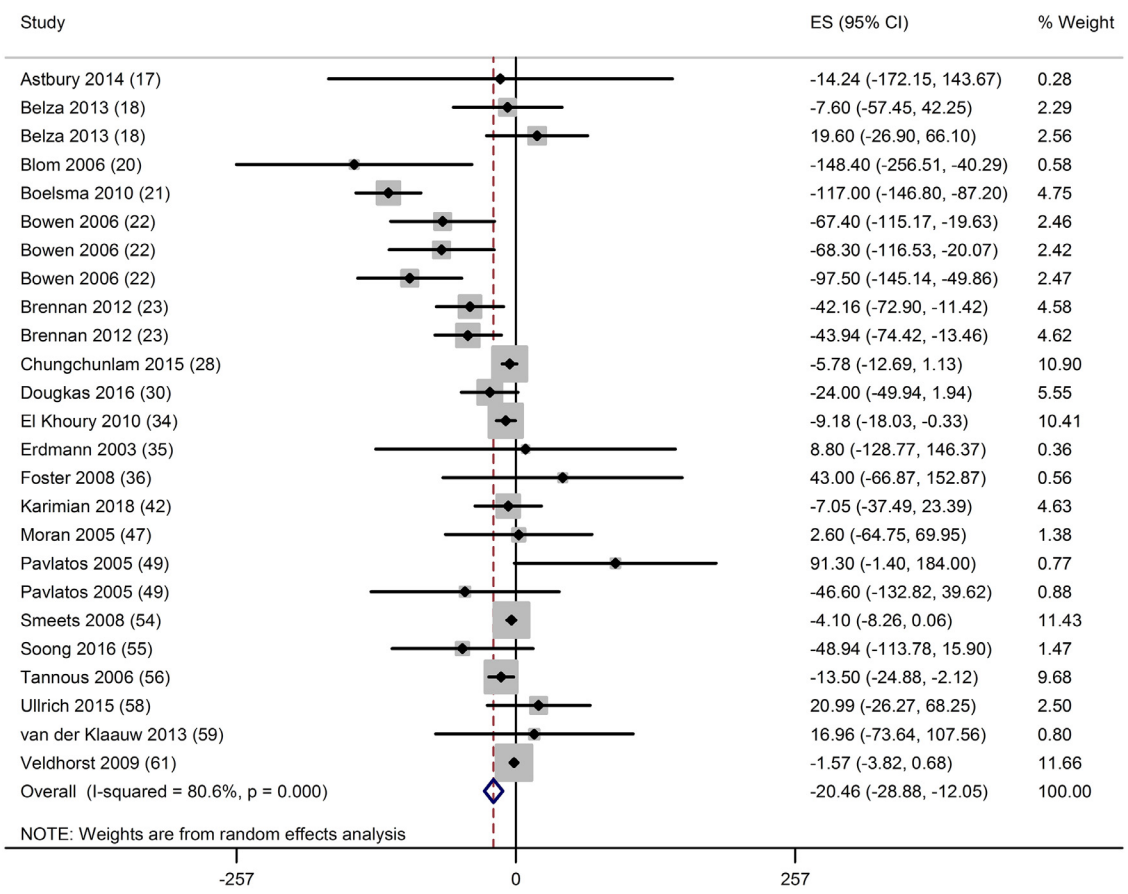

Fig. 3. Forest plot of clinical trials examining the effect of protein on ghrelin concentration in acute interventions. Data are presented as mean difference between treatment and control groups with 95% CIs.

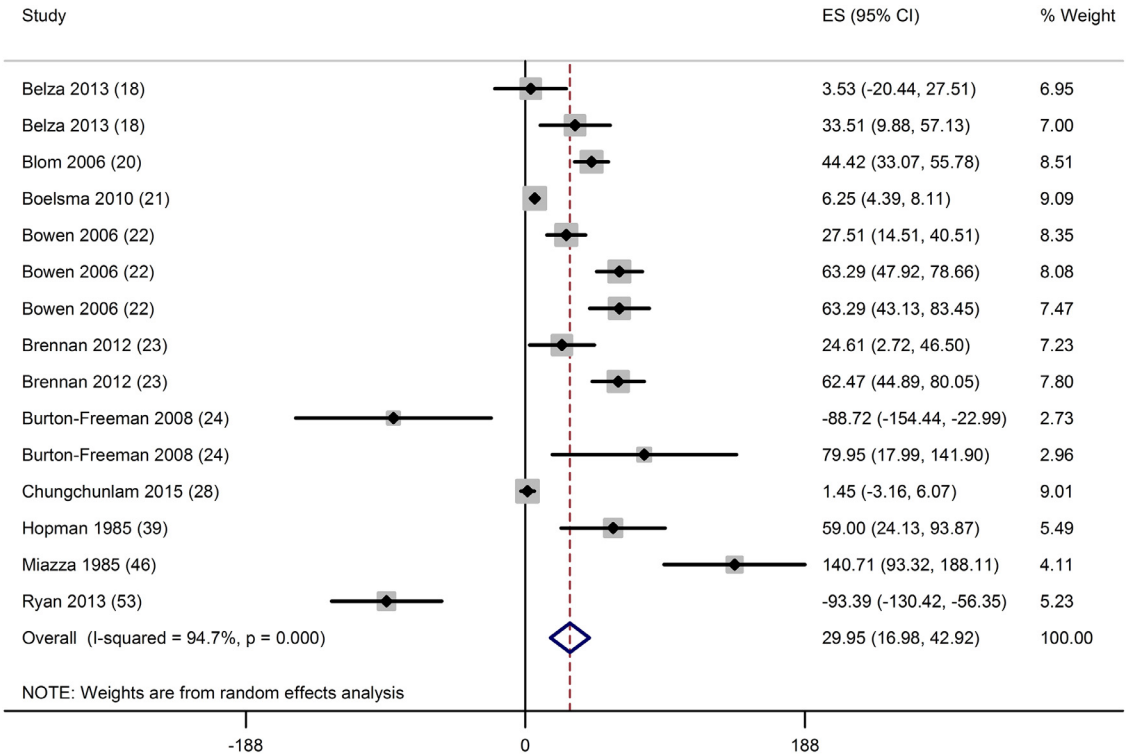

Fig. 4. Forest plot of clinical trials examining the effect of protein on CCK in acute interventions. Data are presented as mean difference between treatment and control groups with 95% CIs.

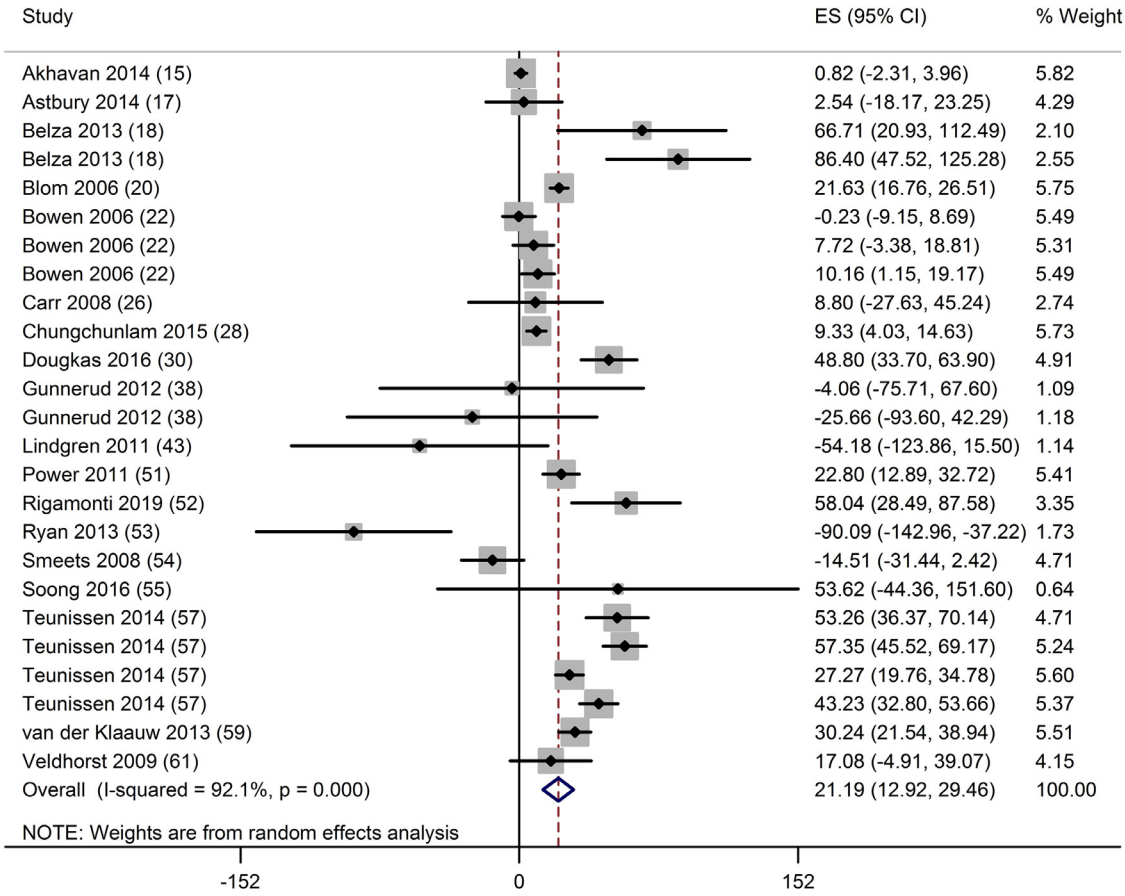

Fig. 5. Forest plot of clinical trials examining the effect of protein on GLP-1 in acute interventions. Data are presented as mean difference between treatment and control groups with 95% CIs.

and-fill analysis did not change the results, suggesting that the publication bias did not remarkably affect the results.

8. Discussion

Results of this meta-analysis showed that acute ingestion of protein suppressed appetite as evidenced by decreased sensation of hunger, desire to eat, and prospective food consumption, and increased fullness and satiety. Protein intake also decreased ghrelin and increased CCK and GLP-1 concentrations without affecting GIP and PYY. Long-term ingestion of protein did not significantly affect these outcomes, except for GLP-1 which showed a significant decrease.

9. Acute interventions

Overall, appetite is estimated by questioning five feelings of hunger, fullness, satiety, desire to eat, and prospective food consumption. Short-term interventions, where appetite was evaluated during hours after protein consumption, demonstrated suppression of appetite in all five types of feeling, providing a strong evidence for appetite-suppressing effect of protein shortly after consumption. A number of mechanisms have been suggested for this appetite suppression. Gut hormones including ghrelin, CCK, GLP-1, GIP, and PYY may play a role in this suppression [12]. Except ghrelin which is an orexigenic peptide that promotes hunger, the other mentioned gastrointestinal hormones are suggested to induce satiety. Cell culture studies have shown that products of protein digestion may induce signaling pathways involved in synthesis or secretion of the aforementioned gastrointestinal hormones [52]. For instance, CCK arouses vagus nerve to convey signals to the brain, activating noradrenergic satiety neurons in the solitary nucleus while decreasing mRNA expression of the vagal receptor of orexin-1 in nodose ganglion, inducing satiety while inhibiting the antagonist orexin signaling [53, 54]. Of incretin hormones, GLP-1 may render satiating effect by delaying gastric emptying and stimulating insulin synthesis and secretion [53] but GIP has not shown to delay gastric emptying [55]. The satiating effect of protein may also be mediated by mechanisms independent of the gut hormones. For instance, it has been suggested that high blood concentration of amino acids, particularly those that are not utilized for protein synthesis, may provoke satiety signals [54].

Results of this meta-analysis did not show the effect of protein on GIP and PYY. Previous studies using isocaloric meals have shown that meals containing carbohydrate and fat induced substantial rises in incretin hormones but protein had no effect [56]. In this regard, Elliott and colleagues studied circulating levels of GLP-1 and GIP following consumption of isocaloric meals containing carbohydrate, fat, or protein [56]. They found that both GLP-1 and GIP were secreted following consumption of carbohydrates and fat; although secretion occurred at slower rate after fat than after carbohydrates. Protein also stimulated GLP-1 section but GIP was not affected by protein meals [56].

10. Subgroup analysis of acute interventions

10.1. Dose subgroups

Trials on the dose-dependent effects of protein on appetite sensations and gastrointestinal hormones are quite conflicting. A number of trials have supported a positive dose-response relationship between dietary protein and appetite sensations and/or hormones [27, 18] while others have denied such relationship [19, 16]. Results of this meta-

Table. 2
Subgroup analysis based on participants' BMI and sex, protein source and dose, and placebo for the effect of protein on hunger, fullness, and concentrations of appetite-regulating hormones in short-term interventions.

Subgroup categorization	Studies (n)	Mean difference (95% CI)	P value	I^2	*P* for I^2		Studies (n)	Mean difference (95% CI)	P value	I^2	*P* for I^2
Hunger (mm)						Fullness (mm)					
BMI						BMI					
< 25 kg/m^2	22	−7 (−11, −3)	0.001	96.4%	< 0.001	< 25 kg/m^2	16	9 ([4], [15])	0.001	97.4%	< 0.001
≥ 25 kg/m^2	4	−7 (−14, 1)	0.08	57.9%	0.07	≥ 25 kg/m^2	4	10 ([4], [16])	0.002	41.4%	0.16
Both	2	−7 (−15, 1)	0.08	–	0.57	Both	2	14 ([2], [24])	0.02	55.6%	0.13
Sex						Sex					
Male	8	−8 (−9, −7)	< 0.001	0	0.82	Male	8	7 ([2], [11])	0.003	53.9%	0.03
Female	5	−7 (−14, −1)	0.03	64.8%	0.02	Female	3	9 (0.1, 17)	0.047	73.9%	0.02
Male/female	15	−7 (−12, −3)	0.001	93.4%	< 0.001	Male/female	11	12 ([7], [17])	< 0.001	94.3%	< 0.001
Protein source						Protein source					
Whey	18	−8 (−12, −3)	0.001	95.9%	< 0.001	Whey	15	9 ([3], [14])	0.002	97.5%	< 0.001
Casein/dairy	3	−10 (−21, 2)	0.10	84.3%	0.002	Casein/dairy	3	15 ([5], [24])	0.003	69.8%	0.04
Meat/egg	2	−8 (−15, −2)	0.008	0	0.39	Meat/egg	2	13 ([7], [19])	< 0.001	9.5%	0.29
Vegetable	3	−4 (−9, 1)	0.12	0	0.70	Vegetable	2	8 ([2], [14])	0.006	0	0.42
Mixed	2	−3 (−5, −1)	0.01	0	0.53	Mixed	–	–	–	–	–
Protein dose						Protein dose					
< 35 g	16	−9 (−15, −3)	0.002	96.9%	< 0.001	< 35 g	12	13 ([9], [17])	< 0.001	65.5%	0.001
≥ 35 g	12	−5 (−11, 2)	0.16	94.0%	< 0.001	≥ 35 g	10	6 (−2, 15)	0.11	98.3%	< 0.001
Placebo type						Placebo type					
CHO	23	−7 (−11, −3)	0.001	95.3%	< 0.001	CHO	21	9 ([5], [14])	< 0.001	96.5%	< 0.001
Fat	4	−12 (−19, −4)	0.003	55.0%	0.08	Fat	1	22 ([10], [30])	< 0.001	–	–
CHO/fat	1	−3 (−5, −1)	0.01	–	–	CHO/fat	–	–	–	–	–
Ghrelin (pg/ml)						CCK (pg/ml)					
BMI						BMI					
< 25 kg/m^2	13	−20 (−33, −7)	0.002	85.7%	< 0.001	< 25 kg/m^2	7	15 ([1], [26])	0.04	93.5%	< 0.001
≥ 25 kg/m^2	6	−4 (−8, −0.4)	0.03	0	0.55	≥ 25 kg/m^2	4	25 (−36, 86)	0.42	92.1%	< 0.001
Both	6	−57 (−81, −33)	< 0.001	27.9%	0.22	Both	4	54 ([30], [47])	< 0.001	83.3%	< 0.001
Sex						Sex					
Male	14	−42 (−62, −21)	< 0.001	84.1%	< 0.001	Male	11	21 ([2], [33])	0.04	95.2%	< 0.001
Female	3	6 (−51, 64)	0.84	60.5%	< 0.001	Female	2	34 (−42, 110)	0.38	83.7%	0.01
Male/female	8	−2 (−4, −0.3)	0.02	0	0.69	Male/female	2	98 ([18], 178)	0.02	86.5%	0.006
Protein source						Protein source					
Whey	8	−29 (−48, −10)	0.003	90.5%	< 0.001	Whey	7	7 (−7, 22)	0.30	93.9%	< 0.001
Casein/dairy	1	−24 (−50, 2)	0.07	–	–	Casein/dairy	2	98 ([18], 178)	0.02	86.5%	0.006
Meat/egg	4	−39 (−60, −18)	< 0.001	0	0.43	Meat/egg	2	44 ([7], [53])	0.02	85.7%	0.008
Vegetable	3	−76 (−11, −46)	< 0.001	0	0.46	Vegetable	2	63 ([39], [49])	< 0.001	0	1
Mixed	9	−7 (−12, −1)	0.02	15.6%	0.30	Mixed	2	19 (−11, 48)	0.22	67.2%	0.08
Protein dose						Protein dose					
< 35 g	9	−7 (−13, −2)	0.01	57.7%	0.01	< 35 g	5	21 (−16, 58)	0.27	87.7%	< 0.001
≥ 35 g	16	−29 (−50, −9)	0.006	83.5%	< 0.001	≥ 35 g	10	32 ([17], [37])	< 0.001	95.7%	< 0.001
Placebo type						Placebo type					
CHO	17	−32 (−45, −18)	< 0.001	84.3%	< 0.001	CHO	14	37 ([23], [61])	< 0.001	94.4%	< 0.001
Fat	7	−4 (−14, 6)	0.42	43.0%	0.10	Fat	1	−93 (−130, −56)	< 0.001	–	–
CHO/fat	1	9 (−129, 146)	0.90	–	–	CHO/fat	–	–	–	–	–
GLP-1 (ng/ml)						GIP (ng/ml)					
BMI						BMI					
< 25 kg/m^2	12	11 ([2], [20])	0.02	88.8%	< 0.001	< 25 kg/m^2	8	9 (−29, 47)	0.64	94.8%	< 0.001
≥ 25 kg/m^2	4	44 (−1, 90)	0.06	93.0%	< 0.001	≥ 25 kg/m^2	3	−15 (−60, 29)	0.50	90.2%	< 0.001
Both	9	28 ([13], [35])	< 0.001	92.8%	< 0.001	Both	1	−33 (−50, −17)	< 0.001	–	–
Sex						Sex					
Male	12	10 (−1, 20)	0.06	88.1%	< 0.001	Male	7	−4 (−44, 36)	0.84	97.0%	< 0.001
Female	2	31 (−16, 79)	0.20	90.1%	0.001	Female	1	−25 (−145, 94)	0.68	–	–
Male/female	11	30 ([19], [34])	< 0.001	86.2%	< 0.001	Male/female	4	4 (−40, 48)	0.86	84.7%	< 0.001
Protein source						Protein source					
Whey	11	10 (0.2, 19)	0.045	89.0%	< 0.001	Whey	5	4 (−57, 65)	0.90	97.6%	< 0.001
Casein/dairy	2	51 ([33], [43])	< 0.001	0	0.70	Casein/dairy	1	−36 (−55, −17)	< 0.001	–	–
Meat/egg	5	36 (−11, 83)	0.13	83.8%	0.01	Meat/egg	3	−8 (−52, 37)	0.74	32.9	0.80
Vegetable	2	15 ([2], [25])	0.02	71.7%	0.007	Vegetable	1	37 ([3], [46])	0.03	–	–
Mixed	5	37 ([13], [42])	0.003	90.7%	< 0.001	Mixed	2	−4 (−86, 78)	0.93	94.4%	< 0.001
Protein dose						Protein dose					
< 35 g	9	9 (−4, 22)	0.17	75.0%	< 0.001	< 35 g	5	12 (−14, 38)	0.37	86.6%	< 0.001
≥ 35 g	16	26 ([16], [31])	< 0.001	91.6%	< 0.001	≥ 35 g	7	−18 (−74, 38)	0.52	97.0%	< 0.001
Placebo type						Placebo type					
CHO	20	25 ([16], [29])	< 0.001	93.3%	< 0.001	CHO	10	6 (−27, 38)	0.73	95.4%	< 0.001
Fat	5	−14 (−58, 29)	0.52	76.7%	0.002	Fat	2	−34 (−51, −18)	< 0.001	0	0.44
CHO/fat	–	–	–	–	–	CHO/fat	–	–	–	–	–

I^2 indicates between-study heterogeneity. CHO, carbohydrate.

analysis showed that appetite may be induced more effectively by lower doses of protein while appetite hormones including ghrelin, CCK, and GLP-1 might be stimulated by higher doses. In agreement with our results, King et al. reported that ingestion of a small dose of whey protein immediately before meal increased satiety but could not induce GLP-1, GIP, and PYY responses [57]. Also, Veldhorst and colleagues reported that breakfasts with 25% energy from protein affected ghrelin and GLP-1 more effectively than breakfasts with 10% energy from protein [42].

10.2. Placebo subgroups

Protein decreased hunger and ghrelin and increased fullness, CCK, GLP-1, and PYY compared to carbohydrate. We could not compare the satiating effect of protein with fat because there were only a few trials with fat placebo. However, previous studies have found that protein has a more pronounced effect on suppressing appetite than fat [27]. In fact, fat has been found the least satiating macronutrient which suppresses hunger to a less extent than carbohydrate and particularly compared to protein [27, 58].

10.3. Other subgroups

The effect of various proteins on appetite markers have been compared in a number trials. However, the results have been conflicting. Some trials have found comparable subjective appetite ratings for proteins from different sources, for instance, from animal and plant sources [28, 59], or from casein, soy and whey sources [41, 36]. But there is also evidence for different satiating effect from various proteins. For instance, Acheson et al. observed a higher satiating effect from casein and soy compared to whey [14]. Also, in a trial by Teunissen et al. pea and milk proteins increased GLP-1 more than egg white protein [40]. However, due to the paucity of data in some protein types, subgroup analysis based on protein source did not give us much information for comparison of different proteins. Whey was the mostly examined protein which affected appetite markers as well as ghrelin and GLP-1. More trials need to be conducted on other protein sources, including casein, meat, egg, and plant proteins.

Most of the trials were conducted on males; so subgroup analysis produced unequal number of trials in sex subgroups. In spite of small number of trials in females, protein demonstrated significant effect on appetite markers in both males and females but the effect of protein on the gastrointestinal outcomes in women remained inconclusive. Moreover, unequal number of trials did not allow us to estimate the extent of the effects on males and females [60]. In this regard, Giezenaar et al. reported that consumption of whey protein suppressed hunger and increased CCK and GLP-1 concentrations in men more than that in women [60], suggesting that the satiating effect of protein may be stronger in men than in females.

Similar to protein source subgroups, subgroup analysis for BMI did not produce useful results because most of the trials had been performed on normal weight participants. Nevertheless, the few trials that have compared the effect of protein on appetite feelings found no difference in appetite suppression following protein intake between normal weight and obese individuals [61, 59].

10.4. Long-term interventions

GLP-1 was the only outcome with significant change over long-term interventions. The lack of protein effect on other outcomes including appetite markers may be explained by diversity in the study design and time of measurements in these trials compared to acute interventions. For instance, in acute trials the parameters were measured pre- and post- meal ingestion while in long-term interventions the time of measurements differed between trials, with some measuring the outcomes pre- and post- protein ingestion and others measuring them at a specific time point (for instance in fasting state or pre-lunch). Moreover, the form of administered protein in long-term trials varied from diet to snack or meals whereas in acute interventions protein was always administered in the form of snacks, beverages, or meals. When protein is administered in the form of diet, the satiating effect of protein may not be appropriately appeared. In this regard, Stubbs et al. reported that breakfasts with high protein content led to detectable change in hunger during hours between breakfast and lunch but the effect was not of sufficient magnitude to influence lunch-time intake [62]. In addition, in long-term trials higher doses of protein were given with an average of 33.6 g/day compared to 9.3 g/day in acute interventions. Comparably, higher doses have weaker effect on appetite feelings but stronger effect on gastrointestinal hormones [57, 42]. The number of long-term trials in each outcome was almost half of that of acute interventions and this reason may also contribute to the lack of protein effect in long-term trials. These differences may explain the difference in the results of short- and long-term trials.

10.5. Limitations

This was the first meta-analysis investigating the effect of protein on gastrointestinal hormones involved in appetite regulation. However, during meta-analysis we encountered several limitations. The number of reports on some of the gastrointestinal hormones especially in long-term investigations were limited. Likewise, there was insufficient number of trials in subgroups of protein source (e.g., meat, egg, and vegetable protein), fat placebo, and subjects with BMI $\geq$ 25 kg/m^2. Not all studies specified the form of hormones that they examined or had reported data on active form of hormones. The variability in the form of hormones that were measured as well as the variability in the method of measurement could also have influenced the results. The form of carbohydrates in studies that gave carbohydrates as placebo is also important. Moreover, the rate of absorption macronutrients can also affect secretion of gastrointestinal hormones like GLP-1 [56]. Long-term trials encountered more diversities, for instance, in the time of measurements and the form of protein administration (diet vs. supplement/meal).

10.6. Concluding remarks

According to the results of this meta-analysis acute ingestion of protein suppresses appetite, decreases ghrelin, and augments CCK and GLP-1. Due to numerous limitations, results of long-term trials are inconclusive and further well-designed and targeted trials are required before a clear and sound conclusion could be made.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.physbeh.2020.113123.

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