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Abstract

This review aims to investigate whether interventions that enhance satiety and/or reduce hunger lead to beneficial effects on body weight management in the context of overweight and obesity. A comprehensive review protocol was prepared before conducting a systematic search in PubMed identifying 517 papers with 12 meeting the inclusion criteria. A thorough risk of bias assessment was performed based on the Cochrane collaboration's tool for assessing risk of bias. Based on a meta-analysis, the average of 75 subjects exposed to satiety enhancing and/or hunger reducing foods during >8 weeks coincidently reduced their body weight by 3.60 (1.05; 6.15) kg (mean (95% confidence interval)) more compared to controls. Two studies analyzed whether individual reductions in appetite were associated with body weight. Decreased ad libitum energy intake after exposure to the satiety enhancing and/or hunger reducing interventions explained 58% ($P<0.001$) and 23% ($P<0.001$) of the variations in the subsequent weight losses over 12 and 8 weeks, respectively. Robust acute effects on appetite were found equally likely to be linked to improved body weight management as sustained effects. Satiety enhancing and/or hunger reducing interventions are supported to improve body weight management, but studies specifically designed to demonstrate a causal link remain needed.

1 Introduction

Obesity is an increasing global public health challenge and today's main approach in prevention and treatment of obesity is promotion of a healthy diet and physical exercise[1]. Many interventions are known to result in weight loss; however, enhanced appetite, i.e. increased feelings of hunger and lack of satiety, have been found to reduce adherence to the required reductions in energy intake and consequently to limit weight loss and to make weight loss maintenance a real challenge[2–4].

Appetite, and hence the ability to control energy intake, is to a high degree influenced by interaction between tonic and episodic signals aiming to regulate energy homeostasis[5–7]. These signals ultimately influence centers in the brain involved in eating behavior, especially hypothalamus, hindbrain and brainstem[8–11]. Centers in the hypothalamus also play a role in the psychological stimuli of hedonic appetite; i.e. the desire and cravings for food especially associated with highly palatable foods, which is mediated by cognitive reward[10,12]. Although anatomically separated, these homeostatic and hedonic systems are functionally highly integrated and both are affected by a plethora of signals from peripheral organs influencing our motivation to eat[13]. Feelings of hunger and satiety play major roles in controlling how much energy is consumed, and accordingly, levels of perceived hunger and satiety may predict the individual's ability to manage their body weight[14]. It has been shown that the orexigenic hormone (ghrelin) increases, whereas anorexigenic hormones (e.g. glucagon-like peptide-1 (GLP-1), peptide YY (PYY) and leptin) decrease following weight loss[15–17]. Thereby, it seems reasonable to assume that these counteracting mechanisms, may at least partly, limit weight loss and be important for the failed weight loss maintenance typically seen even after very successful weight loss[18]. Furthermore, energy expenditure, both at rest as well as the costs of weight-bearing physical activities, is reduced after weight loss. Energy expenditure is reduced even after reaching energy balance, which adds to the challenge of achieving further weight loss and especially to maintain the weight loss by means of continuous attempts to restrict energy intake[19,20].

Thus, it seems reasonable to consider appetite as a promising target in the progression towards more effective means to be used for prevention and treatment of obesity. New and innovative food concepts, designed to have satiety enhancing and/or hunger reducing capacities, including within-meals satiation and post-meal satiety, may be useful tools in the struggle for successful sustained body weight management, health improvement and decreased risk of chronic disease[5,21,22].

Although administration of pharmaceuticals that reduce appetite (e.g. GLP-1 analogs[23]) result in weight loss[24], pharmaceutical's effects on appetite have seldom been assessed in the same study as assessment of the effects on body weight management, making the link between appetite and body weight management less obvious. Nevertheless, it is not questioned that the effect on appetite is the main mechanism by which these drugs lead to weight loss. However, there is presently no consensus that consumption of foods with enhanced capacity to reduce appetite will have a beneficial effect on body weight management in the context of overweight and obesity. Hence, an authoritative body like the European food safety authority (EFSA) does not consider a reduction in appetite to be a "beneficial physiological effect" per se in the context of body weight management when evaluating health claims application. In their "Guidance on the scientific requirements for health claims related to appetite ratings" it is stated that "evidence for a sustained effect on appetite ratings and on body weight with continues consumption of the food should be provided"[25].

Currently, there is intense interest in foods characterized by their improved satiety enhancing and/or hunger reducing capacities based on the assumption that if included in the diet, these will assist the consumer in achieving energy restriction and thereby help to lose/maintain body weight. However, these hypotheses call for studies conducted without bias to reveal whether true inter-relationships between these variables are reliable and valid. The outcome of these examinations have both theoretical and practical value; they will disclose processes that operate in the expression of human appetite, and they will indicate whether specific foods exist that have the capacity to influence appetite and, in turn, modulate body weight. Clarification is required in an area, which is largely affected by opinions and hyperbole and where data can be reported ambiguously.

The usefulness of reducing appetite in order to regulate body weight is highly debated[26–28]. The connection between single self-reported appetite evaluations, the following energy intake and if this subsequently has the ability to affect body weight regulation, has been questioned[29,30]. Nevertheless, it seems plausible to assume that robust effects on feelings of appetite are likely to influence energy intake, and if an intervention is able to reduce feelings of appetite sufficiently to reduce energy intake, ultimately body weight management must be improved.

Therefore, this review aims to summarize and discuss the existing evidence from clinical trials investigating whether interventions that enhance satiety and/or reduce hunger lead to beneficial effects on body weight management in the context of overweight and obesity.

2 Method

Using the PRISMA guidelines, a comprehensive review protocol identifying objectives (including PICO (patient/population; intervention; comparison; outcome) and methods was prepared in collaboration between the authors in advance of the systematic literature search[31]. The search strategy and requirements for the studies to be eligible for inclusion is described below.

2.1 Search strategy

After screening of MeSH term index list as well as testing numerous different combinations of search terms in order to conduct a search providing the most hits, the following search terms were selected as the final search syntax: '("appetite" OR "satiety" OR "satiation" OR "satiety response" OR "hunger" OR "hunger response" OR "hungry") AND ("body weight changes" OR "body weight maintenance" OR "weight loss" OR "weight gain")'. Search on title/abstract were combined with search on medical subject headings (MeSH terms) restricted to clinical trials in humans reported in English. The systematic automated literature search was done in PubMed and identified studies potentially eligible for inclusion and available on PubMed up to February 22, 2019 (Figure 1).

2.2 Inclusion and exclusion criteria

In order to provide an overview of the current body of evidence on the assumed link between reduced appetite and beneficial effects on body weight management; the following conditions were required for studies to be included in this review. The study populations eligible comprised adults and adolescents with overweight or obesity but otherwise healthy. Long-term interventions (≥8 weeks intervention was defined as long-term) assessing difference in acute and/or sustained appetite along with potential changes in body weight over the study period were required. Significant differences in appetite between the intervention and control were required in order to be able to examine whether differences in the effect on appetite could be linked to body weight management. Differences in the effect on appetite could be assessed within or between subjects as long as an effect of the intervention compared to a relevant control was demonstrated. Potential difference in the effect on appetite was assessed either by acute effects measured at baseline after a single exposure or by sustained effects after repeated exposures. To demonstrate sustained effects on appetite, appetite measurements needed to be performed after a long-term intervention with repeated exposures of the intervention products, where a sustained difference in appetite between intervention and control should be demonstrated. Body weight management assessed as body

weight maintenance, weight loss and/or weight gain/regain in kg monitored in laboratory settings was required.

2.3 Assessments of appetite

In appetite research, three methodologies are commonly used: Ad libitum energy intake assessed after exposure to a test food/product or meal; self-reported appetite evaluations, typically using visual analogue scales (VAS); biological markers of appetite assessed through blood samples obtained in response to a meal[32]. At least one of the two first mentioned methodologies had to be applied in the studies in order to be eligible for this review. Additionally, appetite was required to be monitored in laboratory settings in order for the results to be comparable and to minimize bias from unstandardized measurements[33,34]. The most common type of VAS for assessments of self-reported appetite evaluations comprises a 100 mm horizontal line with words anchored at each end expressing the most positive and most negative feeling of a given appetite sensation. Appetite sensations can be expressed by different wordings, but most often "hunger", "desire to eat" and "prospective consumption" are used as markers favoring motivation to eat, whereas "satiety" and "fullness" are used as markers of a reduced motivation to eat[32]. Other validated scales used to assess self-reported appetite evaluations were also accepted and found suitable for comparisons, as long as they were used in laboratory settings. It can be expected that feelings of appetite translate into behavior and thereby is reflected in energy intake. Nevertheless, some reports argue that appetite ratings may not necessarily be related to energy intake[29,30]. In this review, we chose to examine appetite based on both methodologies as self-reported appetite evaluations were found to be relevant though not necessarily translated into energy intake in a laboratory setting. In real life, we expect that an individual's perception of appetite has a great impact on what is actually consumed. In order for the effect on the perception of appetite to have an impact on body weight, a lower energy intake is necessary. Thereby, both of these methodologies for assessing appetite were found relevant for this review; however, results on appetite from energy intake were separated from self-reported appetite evaluations and not directly compared.

2.4 Type of interventions

Interventions including use of foods/meals, food supplement and pharmaceuticals were included and all interventions are referred to as "*foods"* in this review. In order to identify studies investigating interventions solely affecting appetite and not energy metabolism etc., studies including pharmaceuticals were evaluated carefully in order to identify whether a potential effect of

the drug on energy metabolism could be ruled out based on its mode of actions. For the same reason, interventions including different levels of physical activity were evaluated as non-eligible.

2.5 Study selection

After each search, two independent authors identified papers eligible for full-text screening on the basis of titles and abstracts. Full-text screening was then performed by three independent authors. All three authors discussed data extraction, interpretation of results and risk of bias, which was ultimately recorded by one author. If need for further clarifications, consensus on interpretation of results was discussed between all authors.

2.6 Meta-analysis

A random effects meta-analysis was performed on the differences in body weight change (kg) between subjects exposed to satiety enhancing and/or hunger reducing foods compared to controls in the respective studies. If mean difference in body weight change (95% confidence interval (CI)) (kg) was not directly reported in the studies, the effect sizes were calculated based on reported changes within each group. If no standard deviation, standard error of mean or 95% CI for the changes in body weight between groups or within each group was reported, the corresponding authors were asked to provide these data. If data was not available, the 95% CI was imputed based on the average SEM from the other studies[35]. The assessments of appetite were categorized according to whether appetite was assessed as energy intake from an ad libitum meal and self-reported appetite evaluations, energy intake from an ad libitum meal alone or self-reported appetite evaluations alone. The meta-analysis was carried out using Stata/SE 15.1 (StataCorp).

2.7 Risk of bias assessments

The studies were rated based on whether they support that satiety enhancing and/or hunger reducing interventions are linked with beneficial effects on body weight management (+) or not (-). Additionally, based on the Cochrane collaboration's tool for assessing risk of bias[35] and on known major sources of bias within appetite research, the following criteria were assessed: random sequence generation (selection bias); allocation concealment (selection bias); blinding of participants and personnel (performance bias); blinding of outcome assessment (detection bias); incomplete outcome data (attrition bias); selective reporting (evaluated for self-reported appetite evaluations) (reporting bias); power calculation; drop outs; other bias. Risk of bias was rated as

"Low" or "High" according to predefined specifications (see Supplementary material Table 1) or "Unclear" if no information on a potential bias was reported.

3 Results

From the total of 517 unique papers identified, screening based on titles and abstracts resulted in a selection of 38 papers for full-text screening. A total of 12 papers met the predefined inclusion criteria and were accordingly found eligible for inclusion in this review. The reference lists of these 12 eligible papers were subsequently screened and additional 12 potentially relevant papers were selected for full-text screening. However, these were subsequently excluded for further considerations (Figure 1). Of the final 12 papers included, 4 tested acute and 9 sustained effects on appetite (Table 1 and Table 2, respectively).

178 **Table 1 Acute effects of appetite assessed after a single exposure on body weight management.**

Reference Intervention	Population (n (M/F), age(years), BMI(kg/m^2))	Design (type, length, compliance)	Body weight (kg) (Mean±SEM change in I and C + Mean (95%CI) difference I vs. C after intervention)	Appetite assessed after a single exposure (Mean difference I vs. C prior to intervention)		R*
				Energy intake	Self-reported appetite evaluations	
Chambers et al. 2015 Supplement: I: Inulin-propionate ester C: Inulin-control	49 (19/30), 54.5±1.5, 25-40	DB P RCT, 24 weeks, 95% (no difference, P=0.864)	I: ↔ (-1.0±3.0, P=0.062) C: ↔ (+0.4±2.9, P=0.559) Difference: ↔ (-1.4 (-3.07; 0.27), P=0.099)	↓ (-162 kcal, P<0.01)		-
Dennis et al. 2010 Food: I: Hypocaloric diet + 500 ml bottled water C: Hypocaloric diet alone	48 (18/30), 62.4±1.1, 32.8±1.1	NB P RCT, 12 weeks, I: 90% (consumption of water controlled)	I: ↓ (-7.4±0.6, P<0.001) C: ↓ (-5.2±0.6, P<0.001) Difference: ↓ (-2.3 (-3.61; -0.99), P<0.001)	↓ (-43 kcal, P=0.009)		+
Jakubowicz et al. 2012 Food; Isocaloric low carbohydrate diets but with different breakfasts: I: High carbohydrate and protein (high calorie breakfast) C: Low carbohydrate (low calorie breakfast)	144 (58/86), 47.1±6.8, 32.3±1.9	NB P RCT, 16 weeks calorie restriction + 16 week follow up, NR (food checklists used but data not reported)	I: ↓ (?) (-7.0±0.7, P=NR) C: ↑ (?) (+11.7±0.7, P=NR) Difference: ↓ (-18.7 (-21.23; -16.17), P<0.0001)		Satiety: ↑ ($AUC_{240\ min}$: +66%, P<0.0001) Hunger: ↓ ($AUC_{240\ min}$: -46%, P<0.0001)	+
Wang et al. 2015 Food; Isoenergic breakfasts: I: Egg C: Steamed bread	156 (80/76), 14.6±2.2, 32.1+1.7	NB P RCT, 12 weeks, No difference (data not reported)	I: ↓ (?) (-2.3, (calculated from %), P=NR) C: ↓ (?) (-0.1, (calculated from %), P=NR)	↓ (-116 kcal, P<0.001)	Satiety: ↑ (120 min: +8.4 mm, P<0.001; 180 min: +10.3 mm, P<0.001) Fullness: ↑ (120 min:	+

Reference Intervention	Population (n (M/F), age(years), BMI(kg/m^2))	Design (type, length, compliance)	Body weight (kg) (Mean±SEM change in I and C + Mean (95%CI) difference I vs. C after intervention)	Appetite assessed after a single exposure (Mean difference I vs. C prior to intervention)		R*
				Energy intake	Self-reported appetite evaluations	
			Difference: ↓ (-2.2, P<0.001)		+14.7 mm, P<0.001; 180 mi: +10.1 mm, P<0.001) Hunger: ↓ (120 min: -10.4 mm, P<0.001; 180 min: -10.6 mm, P<0.001) Prospective consumption: ↓ (120 min: -9.8 mm, P<0.001; 180 min: -9.7 mm, P<0.001)	

M=Male; F=Female; SEM=Standard error of mean; I=Intervention; C=Control; CI=Confidence interval; DB=Double-blinded; SB=Single-blinded; NB=Non-blinded; P=Parallel; RCT=Randomized controlled trial; NR=not reported; AUC=Area under the curve; ↑=Increase/higher; ↓=Decrease/lower; ↔=unchanged/no difference; (?)=Significance of difference is unknown.

*R=Rating of the study. The rating represents whether the study supports that satiety enhancing and/or hunger reducing interventions are linked with beneficial effects on body weight management (+) or not (-).

The grey areas indicate that the parameters were not assessed.

3.1 Are acute effects on appetite after a single exposure to satiety enhancing and/or hunger reducing foods linked to beneficial effects on body weight management?

3.1.1 Support from studies assessing the acute effects on appetite based on energy intake from an ad libitum meal after a single exposure of satiety enhancing and/or hunger reducing foods

The studies from the groups of Dennis and Wang found the lower energy intake from the ad libitum meals to be linked to superior weight losses in the intervention groups compared to the control groups (Table 1)[36,37]. Wang et al. found individual changes in ad libitum energy intake to be strongly associated with weight loss, explaining 58% of the variation ($P<0.001$)[37].

Body weight maintenance also tended to be different between the groups in the study by Chambers et al.. The intervention group tended to lose weight, whereas the body weight in the control group pointed towards weight gain. This tendency was, according to the authors, further supported by the fact that none of the participants in the intervention group had substantial weight gain (≥5% from baseline body weight) compared with 4 of 24 (17%) in the control group ($P=0.033$)[38]. Thus, there is some support for the reduced appetite found after a single exposure in the intervention group compared to the control group to be linked to beneficial changes in body weight during the following intervention period in this study (Table 1).

3.1.2 Support from studies assessing the acute effects on appetite based on self-reported evaluations after a single exposure of satiety enhancing and/or hunger reducing foods

The studies by Jakubowicz et al. and Wang et al. found lower reported motivation to eat in the intervention groups after consumption of the intervention foods compared to the control groups to be linked to superior weight loss regardless of the scales used[37,39]. The latter study thereby consistently found a reduced appetite in the intervention group both when assessed as ad libitum energy intake as well as based on self-reported appetite evaluations, resulting in compelling overall evidence from this study[37]. In the study by Jakubowicz et al., the reported reduced appetite in the intervention group compared to the control group was found after a single exposure of the intervention food prior to a 16 week intervention period with calorie restriction (1600 kcal for men and 1400 kcal for women). After that, the participants were instructed to continue to consume the intervention foods for an additional 16 weeks, but during this time, they were instructed to eat as motivated by appetite. Comparable weight loss was found in both groups after the 16 weeks of calorie restriction (intervention group: -13.5±2.3 kg; control group: -15.1±1.9 kg, $P=0.11$), but additional weight loss was found after the following 16 weeks in the intervention group, whereas

the control group regained weight, resulting in a substantial difference between the intervention and the control group[39] (Table 1/Table 2).

218 **Table 2 Sustained effects of appetite assessed after repeated exposures on body weight management.**

Reference Intervention	Population (n (M/F), age(years), BMI(kg/m^2))	Design (type, length, compliance)	Body weight (kg) (Mean±SEM change in I and C + Mean (95% CI) difference I vs. C after intervention)	Appetite assessed after repeated exposures (Mean difference I vs. C after intervention)		R*
				Energy intake	Self-reported appetite evaluations	
Blundell et al. 2017 Pharmaceutical: I: Semaglutide (1.34 mg/ml) dose-escalated to 1.0 mg C: Placebo Both administered once weekly	28 (18/9), 42, 33.8	DB CO RCT, 12 weeks + 5-7 weeks wash-out, Pharmacokinetics profile assessed after 4, 8 and 12 weeks supported compliance	I: ↓ (?) (-5.0, P=NR) Control: ↑ (?) (+1.0, P=NR) Difference: ↓ (?) (-6.0, P=NR)	(only assessed after intervention) Difference: ↓ (Ad libitum lunch: -1255 kJ, P<0.0001; Ad libitum total day time energy intake: -3036 kJ, P<0.0001)	Satiety: ↑ (?) (Fasting VAS rating: ~ +5 (read on Figure 2C in original paper), P=NR) Fullness: ↑ (?) (Fasting VAS rating: ~ +15 (read on Figure 2C in original paper), P=NR) Hunger: ↓ (?) (Fasting VAS rating: ~ -20 (read on Figure 2C in original paper), P=NR) Prospective consumption: ↓ (?) (Fasting VAS rating: ~ -15 (read on Figure 2C in original paper), P=NR)	+
Diepvens et al. 2007 Supplement: I: Olibra (a novel fat emulsion; 5 gram provided in 250 gram yoghurt per day) C: Placebo (5 gram milk provided in 250 gram yoghurt per day)	50 (0/50), 40.8±9.5, 28.7±2.0	DB P RCT, 6 weeks very low-calorie formula diet (500 kcal/day) + 18 weeks intervention, NR (evaluated every week by personal interview with a dietician but data not reported)	I: ↔ (+1.13±0.7, P>0.05) Control: ↑ (+2.95±0.6, P<0.001) Difference: ↓ (-1.82 (-3.67; 0.00), P=0.05)		Hunger: ↓ ($AUC_{240\ min}$: -16.2 mm, P<0.05)	+

Reference Intervention	Population (n (M/F), age(years), BMI(kg/m^2))	Design (type, length, compliance)	Body weight (kg) (Mean±SEM change in I and C + Mean (95% CI) difference I vs. C after intervention)	Appetite assessed after repeated exposures (Mean difference I vs. C after intervention)		R*
				Energy intake	Self-reported appetite evaluations	
Jakubowicz et al. 2012 Food; Isocaloric low carbohydrate diets but with different breakfasts: I: High carbohydrate and protein (high calorie breakfast) C: Low carbohydrate (low calorie breakfast)	144 (58/86), 47.1±6.8, 32.3±1.9	NB P RCT, 16 weeks calorie restriction + 16 weeks intervention, NR (food check lists used but data not reported)	I: ↓ (?) (-7.0±0.7, P=NR) C: ↑ (?) (+11.7±0.7, P=NR) Difference: ↓ (-18.7 (-21.23; -16.17), P<0.0001)		Satiety: ↑ ($AUC_{240\ min}$:+65% , P<0.0001) Hunger: ↓ ($AUC_{240\ min}$: -51%, P<0.0001)	+
Kamphuis et al. 2003 Supplement: I: Conjugated linoleic acid (CLA) (Tonalint™ CLA 75% TG - 9.11-Octadecadienoic acid, 10.12-Octadecadienoic acid) C: Oleic acid Capsules to be taken before breakfast, lunch and dinner every day. Two different doses were provided of I and C, respectively (1.8 and 3.6 gram/day). Results presented with low and high dose combined	54 (26/28), 38.0±8.0, 27.8±1.5	DB P RCT, 3 weeks very low-calorie formula diet (500 kcal/day) + 13 weeks intervention, NR	I: ↔ (+2.4±1.1, P>0.05) C: ↔ (+1.8±1.2, P>0.05) Difference: ↔ (+0.6 (-4.05; 5.25), P>0.05)	I: ↔ (0.0) C: ↔ (0.0) Difference: ↔ (+23.8 kcal, P>0.05)	Satiety: ↑ (~ +10 mm (read in Figure 3 in original paper), P<0.05) Fullness: ↑ (~ +10 mm (read in Figure 2 in original paper), P<0.05) Hunger: ↓ (~ -20 mm (read on Figure 4 in original paper), P<0.05)	-
Kudiganti et al. 2016 Supplement: I: Meratrim (flower heads of	60 (24/26), 38.1±1.7, 28.3±0.3	DB P RCT, 16 weeks, 95% (no difference, data not reported)	I: ↓ (?) (-5.1±0.4, P=NR) C: ↓ (?) (-1.1±0.5, P=NR)		Composite appetite score: ↓ (-183.8, P<0.001)	+

Reference Intervention	Population (n (M/F), age(years), BMI(kg/m^2))	Design (type, length, compliance)	Body weight (kg) (Mean±SEM change in I and C + Mean (95% CI) difference I vs. C after intervention)	Appetite assessed after repeated exposures (Mean difference I vs. C after intervention)		R*
				Energy intake	Self-reported appetite evaluations	
Sphaeranthus indicus (S. indicus) and the fruit rinds of Garcinia mangostana (G. mangostana), 3:1) C: Only excipients			Difference: ↓ (-4.0 (-3.18; -4.82), P<0.0001)			
Martin et al. 2011 Pharmaceutical: I: Lorcaserin (10 mg twice daily) C: Placebo	57 (18/39), 48.7±12.7, 35.6±4.8	DB P RCT, 8 weeks, NR	I: ↓ (-3.8±0.4, P<0.05) C:↓ (-2.2±0.5, P<0.05) Difference: ↓ (-1.6 (-2.88; -0.32), P<0.01)	I: ↓ (-470 kcal, P<0.05) C: ↓ (-205 kcal, P<0.05) Difference: ↓ (-264 kcal, P<0.05)	Fullness: (NR) Hunger: (NR) Desire to eat: (NR) Prospective consumption: ↓ (-13 mm, P=0.004)	+
Rigaud et al. 1990 Supplement; Hypocaloric diet including fiber capsules (mixture of beet, barley, citrus (approximately 90% insoluble fiber)): I: 7 gram fiber C: 1 gram fiber	52 (11/41), 36.9±2.3, 29.3±0.8	DB P RCT, 24 weeks, NR (counting of capsules every month but data not reported)	I: ↓ (-5.5±0.7, P=0.0001) C: ↓ (-3.0±0.5, P<0.0001) Difference: ↓ (-2.5 (-4.25; -0.75), P=0.005)		Hunger: ↓ (?) (~ -23 mm, P=NR)	+
Rondanelli et al. 2009 Supplement: I: N-oleyl-phosphatidylethanolamine/ epigallocatechin-3-gallate (PhosphoLEAN™) complex C: Placebo	138 (32/106), 39.5±11, 25-35	DB P RCT, 8 weeks, I: 94%; C: 73%, P<0.001	I: ↓ (?) (-3.28 (-4.1; -2.5), P=NR) C: ↓ (?) (-2.67 (-3.5; -1.8), P=NR) Difference: ↔ (-0.61 (-1.76; 0.54), P=0.296)		Fullness: ↑ (+0.79 mm, P=0.041)	-

Reference Intervention	Population (n (M/F), age(years), BMI(kg/m^2))	Design (type, length, compliance)	Body weight (kg) (Mean±SEM change in I and C + Mean (95% CI) difference I vs. C after intervention)	Appetite assessed after repeated exposures (Mean difference I vs. C after intervention)		R*
				Energy intake	Self-reported appetite evaluations	
One capsule before lunch and one before dinner every day						
Sofer et al. 2011 Food; Standard low calorie diet (20% protein, 30–35% fat, 45–50% carbohydrates providing 1.300–1.500 kcal/day): I: Carbohydrates provided mostly at dinner C: Carbohydrates provided throughout the day	66 (32/34), 42.8±7.1, 33.2±3.7	NB P RCT, 24 weeks, NR (comprehensive inquiry and estimate adherence to dietary regimen and caloric intake was evaluated by a dietician and incompliance resulted in exclusion)	I: ↓ (-11.6±0.8, P<0.0001) C: ↓ (-9.06±0.8, P<0.0001) Difference: ↓ (-2.54 (-2.94; -2.14), P=0.024)		Satiety: ↑ (HSSc: +20%, P=0.03)	+

M=Male; F=Female; SEM=Standard error of mean; I=Intervention; C=Control; CI=Confidence interval; DB=Double-blinded; SB=Single-blinded; NB=Non-blinded; CO=Cross-over; P=Parallel; RCT=Randomized controlled trial; NR=not reported; VAS=Visual analogue scale; AUC=Area under the curve; HSSc=Hunger-satiety score; ↑=Increase/higher; ↓=Decrease/lower; ↔=unchanged/no difference; (?)=Significance of difference is unknown.

*R=Rating of the study. The rating represents whether the study supports that satiety enhancing and/or hunger reducing interventions are linked with beneficial effects on body weight management (+) or not (-).

The grey areas indicate that the parameters were not assessed.

3.2 Are sustained effects on appetite after repeated exposures to satiety enhancing and/or hunger reducing foods linked to beneficial effects on body weight management?

3.2.1 Support from studies assessing the sustained effects on appetite based on energy intake from an ad libitum meal after repeated exposures of satiety enhancing and/or hunger reducing foods

In the studies from the groups of Blundell and Martin, reduced energy intake from an ad libitum meal in the intervention groups was found to result in pronounced weight loss compared to the control groups (Table 2)[40,41]. This was further supported by the latter group showing a positive association between individual reduction in energy intake and reduction in body weight. The individual reductions in ad libitum energy intake in this study explained 23% of the variation in weight reduction ($P<0.001$)[41].

3.2.2 Support from studies assessing the sustained effects on appetite based on self-reported evaluations after repeated exposures of satiety enhancing and/or hunger reducing foods

The studies from the groups of Blundell, Diepvens, Jakubowicz, Kudiganti, Martin, Rigaud, and Sofer all found reduced appetite in the intervention groups compared to the control groups after repeated exposures to be linked to superior weight losses (Table 2)[39–45]. Blundell et al. and Jakubowicz et al. found reduced appetite in the intervention groups compared to the control groups regardless of the scales used[39,40]. Kudiganti et al. reported the self-reported appetite evaluations in the form of a composite appetite score while Sofer et al. by reported satiety assessed as a mean of a hunger-satiety score (HSSc)[43,45]. Martin et al. demonstrated reductions in evaluations of "prospective consumption" in the intervention group compared to the control group, whereas evaluations of "hunger", "desire to eat" and "fullness" did not differ significantly between the groups, but these data were not shown in more detail[41]. Self-reported evaluations favoring motivation to eat were reported only as "hunger" in the studies from the groups of Diepvens and Rigaud. A very clear effect on appetite was demonstrated in the studies by the groups of Martin, Rigaud and Sofer, where appetite decreased within the intervention groups after the intervention compared to baseline despite weight losses in these studies[41,44,45]. In contrast to the findings in these seven studies, the studies from the groups of Kamphuis and Rondanelli found no difference in weight development despite reduced appetite in the intervention groups compared to the control groups[46,47]. The first study consistently found a reduced motivation to eat in the intervention group

compared to the control group regardless of the scales used. This was also in line with findings in the second study; however, only approximately 1 mm higher "fullness" score in the intervention group compared to the control group was shown[47].

3.3 Overall effects of satiety enhancing and/or hunger reducing foods on body weight management

Based on the mean difference in body weight change (kg) after exposure to satiety enhancing and/or hunger reducing foods compared to controls in the respective studies, the meta-analysis was conducted to provide an overview of the overall results (Figure 2). Overall, subjects exposed to satiety enhancing and/or hunger reducing foods coincidently reduced their body weight by 3.60 (1.05; 6.15) kg (mean (95% CI)) more compared to controls. The studies were closely weighed in the random effects analysis; however, there was high uncertainty around the estimate (I^2=98%). A sensitivity analysis excluding the two most deviating studies by Blundell et al. and Jakubowicz et al. resulted in a reduction but it remained high (I^2=75%), with a lower body weight change relative to the control of -1.96 (-2.72; -1.20) kg. Comparable results were found in the fixed effects analysis including all the studies with a body weight change relative to control of -3.54 (-3.89; -3.20); I^2=98%).

3.4 Evaluations of risk of bias

The risk of bias assessment of the studies included is summarized in Figure 2 and reported in more detail in Supplementary material Table 1. The majority of the studies were conducted as double-blinded and those that were not, were due to inability to blind because of obvious differences between intervention and control foods. The majority of the studies reported complete outcome data; showed no sign of reporting bias; and experienced low drop-out rates. All studies were categorized as randomized, but the majority lacked detailed description of the randomization sequence along with lack of description of allocation concealment procedure. Additionally, none of the studies reported whether blinded data was assessed before breaking the allocation concealment. Several of the studies did not report whether a power calculation was performed in advance of the study. One study failed to reach 80% power, but this was not evaluated as a risk of bias as difference between intervention and control was detected anyway. One study assessed weight management using a cross-over design, which was evaluated to introduce a risk of bias.

4 Discussion

Overall, the current literature supports a potential link between enhanced satiety/reduced hunger and beneficial effects on body weight management. Only two studies reported whether individual data on appetite (assessed as ad libitum energy intake in both studies) were associated with beneficial effects on body weight management and they reported relatively strong associations[37,41]. Along with the results from our meta-analysis, these results support a beneficial effect on body weight management of interventions that enhance satiety and/or reduce hunger. In the context of overweight and obesity, although rather moderate, the overall effect size on body weight change may be clinically relevant, especially considering weight loss maintenance. This was found regardless of whether the analysis was based on acute or sustained effects on appetite and whether appetite was assessed as energy intake or self-reported appetite evaluations. Theoretically, an alternative interpretation of the results could be that reduced body weight leads to reduced energy needs, which ultimately causes the reduced appetite. However, as several studies have shown that the motivation to eat increases after diet-induced weight loss[15–17], this interpretation does not seem biologically relevant.

4.1 Level of evidence from each of the studies

The study from the group of Blundell assessed weight management using a cross-over design, introducing a risk of bias. The order of drug treatment (intervention/placebo) was taken into account in the analyses of the effects on weight. When placebo was given during the second period, the body weight slightly increased. This was likely due to a rebound effect after weight loss during administration of the active treatment. Nevertheless, a very clear sustained enhanced satiety/reduced hunger was shown in the intervention group (Table 2)[40]. In the studies by the groups of Jakubowicz and Sofer, the interventions consisted of different breakfasts in the intervention and the control group as a part of an isocaloric diet and isocaloric diets with different meal patterns, respectively. Appetite was assessed after exposure to the different breakfasts and before each meal for a 24 hour period, respectively. Thereby the differences in weight losses can be explained by the reduced appetite rather than differences in the entire diets. Dennis et al. tested acute effect on appetite using a cross-over design at baseline with a following parallel intervention period. Assessing the acute effect on appetite in a cross-over design in all the subjects increased the validity of this study. Body weight was then assessed in each group after the following intervention period with repeated exposure to the allocated foods[36]. The inconsistent results on self-reported appetite evaluations

reported in the study by Martin et al. introduce a risk of bias and consequently these results do not provide as strong evidence supporting that satiety enhancing and/or hunger reducing interventions are linked with beneficial effects on body weight. It is, furthermore, not reported whether the analyses of the self-reported appetite evaluations were adjusted for multiple testing in this study. However, a potential adjustment is unlikely to affect the effect seen on the evaluation of "prospective consumption" as the p-value is relatively low (P=0.004). In the studies from the groups of Diepvens and Riguad, it is unknown whether it was predefined to assess hunger only, or whether additional self-reported appetite evaluations were assessed but not reported based on the effects they found.

With the findings of increased motivation to eat after diet-induced weight loss[15–17], it can be argued that a rather strong sustained effect on appetite is shown when appetite remains decreased despite a larger weight loss compared to the control groups[41,44,45]. Hence, unchanged appetite after diet-induced weight loss should not necessarily be interpreted as a lack of sustained effect on appetite. This was found by Kudiganti et al. who reported maintained level of appetite in the intervention group despite greater weight loss compared to the control group while the control group showed an increased appetite after the weight loss, as could be expected after diet-induced weight loss (Table 2)[43]. In the study by Rondanelli et al., the effect on appetite may have been too weak to affect body weight, possibly explaining why similar weight losses were found in both groups. However, Kamphuis et al. demonstrated differences in appetite of magnitudes comparable to those reported in the studies from the groups of Blundell, Diepvens, Jakubowicz, Kudiganti, Martin, Rigaud, and Sofer, but Kamphuis did not find this effect to be linked to improved body weight management[39–46]. It should be noted that appetite was also assessed based on energy intake in this study and no difference was found between the intervention and the control group in this parameter (Table 2)[46]. This may indicate that the reduced feelings of appetite shown after repeated exposures to this intervention may not have been sufficient to translate into differences in eating behavior and therefore no differences in body weight should be expected. However, in the studies by Blundell et al. and Martin et al., the reduced motivation to eat translated into reduced energy intake resulting in greater weight loss in the intervention groups compared to the control groups[40,41].

4.2 Acute vs. sustained effects on appetite

The four studies assessing acute effects on appetite we identified, all supported the link between enhanced satiety/reduced hunger and improved body weight management. This suggests that it may

be sufficient to show an effect on appetite after a single exposure to a food. However, this is likely dependent on the specific mechanisms involved in altering the appetite after consumption. Some foods may have satiety enhancing and/or hunger reducing capacities when provided once, but the effect may be attenuated if the body is able to adapt to the manipulation. In order to affect body weight management, we assume that the effect of the food has to be sustained; thus, leading to decreased accumulated energy intake. Sustained reduction in appetite after repeated exposures of satiety enhancing and/or hunger reducing foods resulted in superior body weight management in seven out of nine studies identified. A sustained effect is obviously required in order for the food to have an effect on energy balance and hence be able to affect body weight management. Nevertheless, the sustained satiety enhancing effect may not necessarily be detectable after a long-term intervention with repeated exposures using a traditional study design for a controlled study. As previously discussed, the normal response to weight loss includes an increase in the motivation to eat[15,17]. A progressively attenuated net effect on appetite should therefore be expected following an intervention that in itself results in decreased motivation to eat, which then leads to weight loss. To demonstrate the true sustained effect on appetite after weight loss, the proper study design should therefore include a weight-matched control group for comparison; demonstrating whether an effect on appetite is maintained after repeated exposures that lead to weight loss. The second best alternative could be to minimize the duration of repeated exposures so the reduction in body weight is still very small; thus, at least reducing this problem. There is no consensus regarding which duration of repeated exposures of a specific food is needed to demonstrate that an effect on appetite can be considered sufficiently sustained to have a beneficial effect on body weight management. Evaluations of whether demonstrated acute effects on appetite translate into sustained effects were recently reviewed by Halford et al.[48]. Their results suggest that in most cases where a robust acute effect on appetite was observed, the effect was likely to be sustained, particularly when assessing energy intake [48]. These authors arrived at this conclusion despite the fact that potential counteracting effects of weight loss were not taken into account in this review. Therefore, the results of our review (which has focused on effects of foods on body weight) should be considered alongside the Halford et al. review. Taken together we feel that these two review papers provide an up to date comprehensive objective assessment of the science in this area.

4.3 Assessments of appetite from ad libitum energy intake vs. self-reported appetite evaluations

From the meta-analysis and the studies that use both methods, we noted that results are quite consistent regardless if appetite is assessments as energy intake from an ad libitum meal or self-reported appetite evaluations (Figure 2)[37,40,41]. However, the evidence supporting a link between enhanced satiety/reduced hunger and improved body weight management seems to be more robust when appetite is assessed as energy intake compared to self-reported appetite evaluations (Figure 2). Self-reported appetite evaluations are probably affected by personal psychological matters to a greater extent than energy intake, thereby introducing more individual and day to day variation[34]. Additionally, self-reported appetite evaluations may be more prone to self-reporting bias than energy intake[32]. However, despite the fact that energy intake reflects behavior, the measure may also be affected by self-reporting and especially social desirability bias, as the subject may be aware that the investigator monitors how much food is consumed[49]. The laboratory settings are needed in order to standardize the appetite measurements, but the standardization may result in stylized behavior that may not be truly typical of the subject's usual behavior[50].

Gastrointestinal hormones believed to be involved in appetite control are not evaluated in this review. However, it is well documented that gastric bypass surgery promotes weight loss and improve the following body weight maintenance[51] and that it is largely mediated by profound post-prandial changes in gastrointestinal hormone secretion associated with enhanced satiety/reduced hunger[52,53]. Biological markers of appetite were assessed in five of the included studies[37–39,42,43], but differences between the intervention and the control groups were only reported in three of these[37–39]. After a single exposure to the foods, the orexigenic hormone ghrelin was found to be lower[37,39] and the anorexigenic hormones GLP-1 and PYY were found to be higher in the intervention groups compared to the control groups[37,38] in line with previous findings on associations between a number of gastrointestinal hormones and appetite[54,55]. From these studies, the differences in appetite detected by self-reported assessments are consistent with those reflected in objective measures, thus increasing the validity of the findings. As changes in eating behavior resulting in decreased energy intake are needed for the satiety enhancing and/or hunger reducing foods to improve body weight management, the subjective measures are necessary for investigating the aim of this review. The objective measures may provide a plausible mechanism validating the subjective assessments, but they do not necessarily reflect behavior.

4.4 Limitations of the review

Publication bias (the tendency to publish positive rather than negative findings)[56] cannot be ruled out and may have influenced the positive conclusions regarding a link between consumption of foods with satiety enhanced and/or hunger reducing properties and body weight management in the context of overweight and obesity.

Finally, apart from two studies, the analyses in this review are based on assessments done on group levels. Rather more studies assessing relationship between individual data on appetite and effects on body weight management are required.

5 Conclusion

The evidence from the available literature supports the supposition that intake of foods that leads to post-ingestive enhancement of satiety/reduced hunger compared to "regular foods" may be linked to improved body weight management in the context of overweight and obesity. Based on the available literature, it may therefore be appropriate to hypothesize that appetite continues to be a promising target for novel food concepts, supplements and medical devices. Nevertheless, the number of studies is currently limited and with methodological issues that limit demonstrations of a causal link. This outcome highlights the need for studies specifically designed to demonstrate a causal link between enhanced satiety/reduced hunger of foods designed to be used for body weight management. This strategy may expand the "toolbox" needed to help people manage body weight in order to maintain health and wellbeing throughout life.

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Table 1 Acute effects of appetite assessed after a single exposure on body weight management.

M=Male; F=Female; SEM=Standard error of mean; I=Intervention; C=Control; CI=Confidence interval; DB=Double-blinded; SB=Single-blinded; NB=Non-blinded; P=Parallel; RCT=Randomized controlled trial; NR=not reported; AUC=Area under the curve; ↑=Increase/higher; ↓=Decrease/lower; ↔=unchanged/no difference; (?)=Significance difference is unknown.
*R=Rating of the study. The rating represents whether the study supports that satiety enhancing and/or hunger reducing interventions are linked with beneficial effects on body weight management (+) or not (-).
The grey areas indicate that the parameters were not assessed.

Table 2 Sustained effects of appetite assessed after repeated exposures on body weight management.

M=Male; F=Female; SEM=Standard error of mean; I=Intervention; C=Control; CI=Confidence interval; DB=Double-blinded; SB=Single-blinded; NB=Non-blinded; CO=Cross-over; P=Parallel; RCT=Randomized controlled trial; NR=not reported; VAS=Visual analogue scale; AUC=Area under the curve; HSSc=Hunger-satiety score; ↑=Increase/higher; ↓=Decrease/lower; ↔=unchanged/no difference; (?)=Significance of difference is unknown.
*R=Rating of the study. The rating represents whether the study supports that satiety enhancing and/or hunger reducing interventions are linked with beneficial effects on body weight management (+) or not (-).
The grey areas indicate that the parameters were not assessed.

Figure 1 PRISMA flow chart explaining the systematic literature search in PubMed identifying studies potentially eligible for inclusion and available on PubMed up to February 22, 2019.

After screening of MeSH term index list as well as testing numerous different combinations of search terms in order to conduct a search providing the most hits, the following search terms were selected as the final search syntax: '("*appetite"* OR *"satiety"* OR *"satiation"* OR "*satiety response"* OR *"hunger"* OR *"hunger response"* OR *"hungry"*) AND ("*body weight changes"* OR *"body weight maintenance"* OR *"weight loss"* OR *"weight gain"*)'
The reference lists of these 12 eligible papers were subsequently screened and additional 12 potentially relevant papers were selected for full-text screening. However, these were subsequently excluded for further considerations.

Figure 2 Meta-analysis of mean difference in body weight change with 95% CI (kg) between exposure to satiety enhancing and/or hunger reducing foods and matching control foods in each of the studies.

CI=Confidence interval
Assessments of appetite are classified according to whether appetite was assessed as energy intake from an ad libitum meal and self-reported appetite evaluations, energy intake from an ad libitum meal alone or self-reported appetite evaluations alone. The grey marks around the mean from each study indicates the weight of the evidence from each study assessed in a random effects analysis; the blue diamonds summarizes the total mean differences according to the assessments of appetite and finally for the overall result with width of the diamonds indicating the 95% CI.
Only the studies from the groups of Chambers and Rondanelli directly reported the mean difference in body weight change (95% CI) (kg). For the remaining studies, the effect sizes were calculated based on reported changes within each group. No standard deviation, standard error of mean (SEM) or 95% CI for the changes in body weight within each group was reported in the studies from the groups of Blundell and Wang. The corresponding authors were asked to provide these data, but data could not be made available for this review. The 95% CI was therefore imputed based on the average SEM from the other studies[36].
Risk of bias was assessed based on the following categories: A: Random sequence generation (selection bias); B: Allocation concealment (selection bias); C: Blinding of participants and personnel (performance bias); D: Blinding of outcome assessment (detection bias); E: Incomplete outcome data (attrition bias); F: Selective reporting (evaluated for self-reported appetite evaluations) (reporting bias); G: Power calculation; H: Drop outs; I: Other bias. Risk of bias was rated as "Low" or "High" according to predefined specifications (see Supplementary material Table 1) or "Unclear" if no information on a potential bias was reported.