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1 **Abstract**

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

17 **1 Introduction**

18 Obesity is an increasing global public health challenge and today's main approach in prevention and
19 treatment of obesity is promotion of a healthy diet and physical exercise¹. Many interventions are
20 known to result in weight loss; however, enhanced appetite, i.e. increased feelings of hunger and
21 lack of satiety, have been found to reduce adherence to the required reductions in energy intake and
22 consequently to limit weight loss and to make weight loss maintenance a real challenge²⁻⁴.

23 Appetite, and hence the ability to control energy intake, is to a high degree influenced by interaction
24 between tonic and episodic signals aiming to regulate energy homeostasis⁵⁻⁷. These signals
25 ultimately influence centers in the brain involved in eating behavior, especially hypothalamus,
26 hindbrain and brainstem⁸⁻¹¹. Centers in the hypothalamus also play a role in the psychological
27 stimuli of hedonic appetite; i.e. the desire and cravings for food especially associated with highly
28 palatable foods, which is mediated by cognitive reward^{10,12}. Although anatomically separated, these
29 homeostatic and hedonic systems are functionally highly integrated and both are affected by a
30 plethora of signals from peripheral organs influencing our motivation to eat¹³. Feelings of hunger
31 and satiety play major roles in controlling how much energy is consumed, and accordingly, levels
32 of perceived hunger and satiety may predict the individual's ability to manage their body weight¹⁴.
33 It has been shown that the orexigenic hormone (ghrelin) increases, whereas anorexigenic hormones
34 (e.g. glucagon-like peptide-1 (GLP-1), peptide YY (PYY) and leptin) decrease following weight
35 loss¹⁵⁻¹⁷. Thereby, it seems reasonable to assume that these counteracting mechanisms, may at least
36 partly, limit weight loss and be important for the failed weight loss maintenance typically seen even
37 after very successful weight loss¹⁸. Furthermore, energy expenditure, both at rest as well as the costs
38 of weight-bearing physical activities, is reduced after weight loss. Energy expenditure is reduced
39 even after reaching energy balance, which adds to the challenge of achieving further weight loss
40 and especially to maintain the weight loss by means of continuous attempts to restrict energy
41 intake^{19,20}.

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

47 Although administration of pharmaceuticals that reduce appetite (e.g. GLP-1 analogs²³) result in
48 weight loss²⁴, pharmaceutical's effects on appetite have seldom been assessed in the same study as
49 assessment of the effects on body weight management, making the link between appetite and body
50 weight management less obvious. Nevertheless, it is not questioned that the effect on appetite is the
51 main mechanism by which these drugs lead to weight loss. However, there is presently no
52 consensus that consumption of foods with enhanced capacity to reduce appetite will have a
53 beneficial effect on body weight management in the context of overweight and obesity. Hence, an
54 authoritative body like the European food safety authority (EFSA) does not consider a reduction in
55 appetite to be a "beneficial physiological effect" *per se* in the context of body weight management
56 when evaluating health claims application. In their "Guidance on the scientific requirements for
57 health claims related to appetite ratings" it is stated that "evidence for a sustained effect on appetite
58 ratings and on body weight with continues consumption of the food should be provided"²⁵.

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

68 The usefulness of reducing appetite in order to regulate body weight is highly debated²⁶⁻²⁸. The
69 connection between single self-reported appetite evaluations, the following energy intake and if this
70 subsequently has the ability to affect body weight regulation, has been questioned^{29,30}. Nevertheless,
71 it seems plausible to assume that robust effects on feelings of appetite are likely to influence energy
72 intake, and if an intervention is able to reduce feelings of appetite sufficiently to reduce energy
73 intake, ultimately body weight management must be improved.

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

77 **2 Method**

78 Using the PRISMA guidelines, a comprehensive review protocol identifying objectives (including
79 PICO (patient/population; intervention; comparison; outcome) and methods was prepared in
80 collaboration between the authors in advance of the systematic literature search³¹. The search
81 strategy and requirements for the studies to be eligible for inclusion is described below.

82 **2.1 Search strategy**

83 After screening of MeSH term index list as well as testing numerous different combinations of
84 search terms in order to conduct a search providing the most hits, the following search terms were
85 selected as the final search syntax: (“*appetite*” OR “*satiety*” OR “*satiation*” OR “*satiety*
86 *response*” OR “*hunger*” OR “*hunger response*” OR “*hungry*”) AND (“*body weight changes*” OR
87 “*body weight maintenance*” OR “*weight loss*” OR “*weight gain*”). Search on title/abstract were
88 combined with search on medical subject headings (MeSH terms) restricted to clinical trials in
89 humans reported in English. The systematic automated literature search was done in PubMed and
90 identified studies potentially eligible for inclusion and available on PubMed up to February 22,
91 2019 (Figure 1).

92 **2.2 Inclusion and exclusion criteria**

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

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

110 2.3 Assessments of appetite

111 In appetite research, three methodologies are commonly used: *Ad libitum* energy intake assessed
112 after exposure to a test food/product or meal; self-reported appetite evaluations, typically using
113 visual analogue scales (VAS); biological markers of appetite assessed through blood samples
114 obtained in response to a meal³². At least one of the two first mentioned methodologies had to be
115 applied in the studies in order to be eligible for this review. Additionally, appetite was required to
116 be monitored in laboratory settings in order for the results to be comparable and to minimize bias
117 from unstandardized measurements^{33,34}. The most common type of VAS for assessments of self-
118 reported appetite evaluations comprises a 100 mm horizontal line with words anchored at each end
119 expressing the most positive and most negative feeling of a given appetite sensation. Appetite
120 sensations can be expressed by different wordings, but most often “hunger”, “desire to eat” and
121 “prospective consumption” are used as markers favoring motivation to eat, whereas “satiety” and
122 “fullness” are used as markers of a reduced motivation to eat³². Other validated scales used to assess
123 self-reported appetite evaluations were also accepted and found suitable for comparisons, as long as
124 they were used in laboratory settings. It can be expected that feelings of appetite translate into
125 behavior and thereby is reflected in energy intake. Nevertheless, some reports argue that appetite
126 ratings may not necessarily be related to energy intake^{29,30}. In this review, we chose to examine
127 appetite based on both methodologies as self-reported appetite evaluations were found to be
128 relevant though not necessarily translated into energy intake in a laboratory setting. In real life, we
129 expect that an individual’s perception of appetite has a great impact on what is actually consumed.
130 In order for the effect on the perception of appetite to have an impact on body weight, a lower
131 energy intake is necessary. Thereby, both of these methodologies for assessing appetite were found
132 relevant for this review; however, results on appetite from energy intake were separated from self-
133 reported appetite evaluations and not directly compared.

134 2.4 Type of interventions

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

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

141 2.5 Study selection

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

147 2.6 Meta-analysis

148 A random effects meta-analysis was performed on the differences in body weight change (kg)
149 between subjects exposed to satiety enhancing and/or hunger reducing foods compared to controls
150 in the respective studies. If mean difference in body weight change (95% confidence interval (CI))
151 (kg) was not directly reported in the studies, the effect sizes were calculated based on reported
152 changes within each group. If no standard deviation, standard error of mean or 95% CI for the
153 changes in body weight between groups or within each group was reported, the corresponding
154 authors were asked to provide these data. If data was not available, the 95% CI was imputed based
155 on the average SEM from the other studies³⁵. The assessments of appetite were categorized
156 according to whether appetite was assessed as energy intake from an *ad libitum* meal and self-
157 reported appetite evaluations, energy intake from an *ad libitum* meal alone or self-reported appetite
158 evaluations alone. The meta-analysis was carried out using Stata/SE 15.1 (StataCorp).

159 2.7 Risk of bias assessments

160 The studies were rated based on whether they support that satiety enhancing and/or hunger reducing
161 interventions are linked with beneficial effects on body weight management (+) or not (-).
162 Additionally, based on the Cochrane collaboration's tool for assessing risk of bias³⁵ and on known
163 major sources of bias within appetite research, the following criteria were assessed: random
164 sequence generation (selection bias); allocation concealment (selection bias); blinding of
165 participants and personnel (performance bias); blinding of outcome assessment (detection bias);
166 incomplete outcome data (attrition bias); selective reporting (evaluated for self-reported appetite
167 evaluations) (reporting bias); power calculation; drop outs; other bias. Risk of bias was rated as

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

170 **3 Results**

171 From the total of 517 unique papers identified, screening based on titles and abstracts resulted in a
172 selection of 38 papers for full-text screening. A total of 12 papers met the predefined inclusion
173 criteria and were accordingly found eligible for inclusion in this review. The reference lists of these
174 12 eligible papers were subsequently screened and additional 12 potentially relevant papers were
175 selected for full-text screening. However, these were subsequently excluded for further
176 considerations (Figure 1). Of the final 12 papers included, 4 tested acute and 9 sustained effects on
177 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 <i>et al.</i> 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 <i>et al.</i> 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 <i>et al.</i> 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 <i>et al.</i> 2015 Food; Isoenergetic 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) | |

179 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;
180 P=Parallel; RCT=Randomized controlled trial; NR=not reported; AUC=Area under the curve; ↑=Increase/higher; ↓=Decrease/lower; ↔=unchanged/no difference;
181 (?)=Significance of difference is unknown.
182 *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
183 on body weight management (+) or not (-).
184 The grey areas indicate that the parameters were not assessed.

185 3.1 Are acute effects on appetite after a single exposure to satiety enhancing and/or
186 hunger reducing foods linked to beneficial effects on body weight management?

187 3.1.1 Support from studies assessing the acute effects on appetite based on energy intake from an
188 *ad libitum* meal after a single exposure of satiety enhancing and/or hunger reducing foods
189 The studies from the groups of Dennis and Wang found the lower energy intake from the *ad libitum*
190 meals to be linked to superior weight losses in the intervention groups compared to the control
191 groups (Table 1)^{36,37}. Wang *et al.* found individual changes in *ad libitum* energy intake to be
192 strongly associated with weight loss, explaining 58% of the variation (P<0.001)³⁷.

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

201 3.1.2 Support from studies assessing the acute effects on appetite based on self-reported
202 evaluations after a single exposure of satiety enhancing and/or hunger reducing foods
203 The studies by Jakubowicz *et al.* and Wang *et al.* found lower reported motivation to eat in the
204 intervention groups after consumption of the intervention foods compared to the control groups to
205 be linked to superior weight loss regardless of the scales used^{37,39}. The latter study thereby
206 consistently found a reduced appetite in the intervention group both when assessed as *ad libitum*
207 energy intake as well as based on self-reported appetite evaluations, resulting in compelling overall
208 evidence from this study³⁷. In the study by Jakubowicz *et al.*, the reported reduced appetite in the
209 intervention group compared to the control group was found after a single exposure of the
210 intervention food prior to a 16 week intervention period with calorie restriction (1600 kcal for men
211 and 1400 kcal for women). After that, the participants were instructed to continue to consume the
212 intervention foods for an additional 16 weeks, but during this time, they were instructed to eat as
213 motivated by appetite. Comparable weight loss was found in both groups after the 16 weeks of
214 calorie restriction (intervention group: -13.5 ± 2.3 kg; control group: -15.1 ± 1.9 kg, P=0.11), but
215 additional weight loss was found after the following 16 weeks in the intervention group, whereas

216 the control group regained weight, resulting in a substantial difference between the intervention and
217 the control group³⁹ (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 <i>et al.</i> 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, Pharmacokinetic s 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: ↓ (<i>Ad libitum</i> lunch: -1255 kJ, P<0.0001; <i>Ad libitum</i> 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 <i>et al.</i> 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 <i>et al.</i> 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 <i>et al.</i> 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 <i>et al.</i> 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 <i>et al.</i> 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 <i>et al.</i> 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 <i>et al.</i> 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 <i>et al.</i> 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) | + |

219 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;
220 CO=Cross-over; P=Parallel; RCT=Randomized controlled trial; NR=not reported; VAS=Visual analogue scale; AUC=Area under the curve; HSSc=Hunger-satiety
221 score; ↑=Increase/higher; ↓=Decrease/lower; ↔=unchanged/no difference; (?)=Significance of difference is unknown.
222 *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
223 on body weight management (+) or not (-).
224 The grey areas indicate that the parameters were not assessed.

225 3.2 Are sustained effects on appetite after repeated exposures to satiety enhancing
226 and/or hunger reducing foods linked to beneficial effects on body weight
227 management?

228 3.2.1 Support from studies assessing the sustained effects on appetite based on energy intake from
229 an *ad libitum* meal after repeated exposures of satiety enhancing and/or hunger reducing
230 foods

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

237 3.2.2 Support from studies assessing the sustained effects on appetite based on self-reported
238 evaluations after repeated exposures of satiety enhancing and/or hunger reducing foods

239 The studies from the groups of Blundell, Diepvens, Jakubowicz, Kudiganti, Martin, Rigaud, and
240 Sofer all found reduced appetite in the intervention groups compared to the control groups after
241 repeated exposures to be linked to superior weight losses (Table 2)³⁹⁻⁴⁵. Blundell *et al.* and
242 Jakubowicz *et al.* found reduced appetite in the intervention groups compared to the control groups
243 regardless of the scales used^{39,40}. Kudiganti *et al.* reported the self-reported appetite evaluations in
244 the form of a composite appetite score while Sofer *et al.* by reported satiety assessed as a mean of a
245 hunger-satiety score (HSSc)^{43,45}. Martin *et al.* demonstrated reductions in evaluations of
246 “prospective consumption” in the intervention group compared to the control group, whereas
247 evaluations of “hunger”, “desire to eat” and “fullness” did not differ significantly between the
248 groups, but these data were not shown in more detail⁴¹. Self-reported evaluations favoring
249 motivation to eat were reported only as “hunger” in the studies from the groups of Diepvens and
250 Rigaud. A very clear effect on appetite was demonstrated in the studies by the groups of Martin,
251 Rigaud and Sofer, where appetite decreased within the intervention groups after the intervention
252 compared to baseline despite weight losses in these studies^{41,44,45}. In contrast to the findings in these
253 seven studies, the studies from the groups of Kamphuis and Rondanelli found no difference in
254 weight development despite reduced appetite in the intervention groups compared to the control
255 groups^{46,47}. The first study consistently found a reduced motivation to eat in the intervention group

256 compared to the control group regardless of the scales used. This was also in line with findings in
257 the second study; however, only approximately 1 mm higher “fullness” score in the intervention
258 group compared to the control group was shown⁴⁷.

259 3.3 Overall effects of satiety enhancing and/or hunger reducing foods on body 260 weight management

261 Based on the mean difference in body weight change (kg) after exposure to satiety enhancing and/or
262 hunger reducing foods compared to controls in the respective studies, the meta-analysis was
263 conducted to provide an overview of the overall results (Figure 2). Overall, subjects exposed to
264 satiety enhancing and/or hunger reducing foods coincidentally reduced their body weight by 3.60
265 (1.05; 6.15) kg (mean (95% CI)) more compared to controls. The studies were closely weighed in
266 the random effects analysis; however, there was high uncertainty around the estimate ($I^2=98\%$). A
267 sensitivity analysis excluding the two most deviating studies by Blundell *et al.* and Jakubowicz *et*
268 *al.* resulted in a reduction but it remained high ($I^2=75\%$), with a lower body weight change relative
269 to the control of -1.96 (-2.72; -1.20) kg. Comparable results were found in the fixed effects analysis
270 including all the studies with a body weight change relative to control of -3.54 (-3.89; -3.20);
271 $I^2=98\%$).

272 3.4 Evaluations of risk of bias

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

285 4 Discussion

286 Overall, the current literature supports a potential link between enhanced satiety/reduced hunger
287 and beneficial effects on body weight management. Only two studies reported whether individual
288 data on appetite (assessed as *ad libitum* energy intake in both studies) were associated with
289 beneficial effects on body weight management and they reported relatively strong associations^{37,41}.
290 Along with the results from our meta-analysis, these results support a beneficial effect on body
291 weight management of interventions that enhance satiety and/or reduce hunger. In the context of
292 overweight and obesity, although rather moderate, the overall effect size on body weight change
293 may be clinically relevant, especially considering weight loss maintenance. This was found
294 regardless of whether the analysis was based on acute or sustained effects on appetite and whether
295 appetite was assessed as energy intake or self-reported appetite evaluations. Theoretically, an
296 alternative interpretation of the results could be that reduced body weight leads to reduced energy
297 needs, which ultimately causes the reduced appetite. However, as several studies have shown that
298 the motivation to eat increases after diet-induced weight loss¹⁵⁻¹⁷, this interpretation does not seem
299 biologically relevant.

300 4.1 Level of evidence from each of the studies

301 The study from the group of Blundell assessed weight management using a cross-over design,
302 introducing a risk of bias. The order of drug treatment (intervention/placebo) was taken into account
303 in the analyses of the effects on weight. When placebo was given during the second period, the
304 body weight slightly increased. This was likely due to a rebound effect after weight loss during
305 administration of the active treatment. Nevertheless, a very clear sustained enhanced satiety/reduced
306 hunger was shown in the intervention group (Table 2)⁴⁰. In the studies by the groups of Jakubowicz
307 and Sofer, the interventions consisted of different breakfasts in the intervention and the control
308 group as a part of an isocaloric diet and isocaloric diets with different meal patterns, respectively.
309 Appetite was assessed after exposure to the different breakfasts and before each meal for a 24 hour
310 period, respectively. Thereby the differences in weight losses can be explained by the reduced
311 appetite rather than differences in the entire diets. Dennis *et al.* tested acute effect on appetite using
312 a cross-over design at baseline with a following parallel intervention period. Assessing the acute
313 effect on appetite in a cross-over design in all the subjects increased the validity of this study. Body
314 weight was then assessed in each group after the following intervention period with repeated
315 exposure to the allocated foods³⁶. The inconsistent results on self-reported appetite evaluations

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

325 With the findings of increased motivation to eat after diet-induced weight loss¹⁵⁻¹⁷, it can be argued
326 that a rather strong sustained effect on appetite is shown when appetite remains decreased despite a
327 larger weight loss compared to the control groups^{41,44,45}. Hence, unchanged appetite after diet-
328 induced weight loss should not necessarily be interpreted as a lack of sustained effect on appetite.
329 This was found by Kudiganti *et al.* who reported maintained level of appetite in the intervention
330 group despite greater weight loss compared to the control group while the control group showed an
331 increased appetite after the weight loss, as could be expected after diet-induced weight loss (Table
332 2)⁴³. In the study by Rondanelli *et al.*, the effect on appetite may have been too weak to affect body
333 weight, possibly explaining why similar weight losses were found in both groups. However,
334 Kamphuis *et al.* demonstrated differences in appetite of magnitudes comparable to those reported in
335 the studies from the groups of Blundell, Diepvens, Jakubowicz, Kudiganti, Martin, Rigaud, and
336 Sofer, but Kamphuis did not find this effect to be linked to improved body weight management³⁹⁻⁴⁶.
337 It should be noted that appetite was also assessed based on energy intake in this study and no
338 difference was found between the intervention and the control group in this parameter (Table 2)⁴⁶.
339 This may indicate that the reduced feelings of appetite shown after repeated exposures to this
340 intervention may not have been sufficient to translate into differences in eating behavior and
341 therefore no differences in body weight should be expected. However, in the studies by Blundell *et*
342 *al.* and Martin *et al.*, the reduced motivation to eat translated into reduced energy intake resulting in
343 greater weight loss in the intervention groups compared to the control groups^{40,41}.

344 4.2 Acute vs. sustained effects on appetite

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

347 be sufficient to show an effect on appetite after a single exposure to a food. However, this is likely
348 dependent on the specific mechanisms involved in altering the appetite after consumption. Some
349 foods may have satiety enhancing and/or hunger reducing capacities when provided once, but the
350 effect may be attenuated if the body is able to adapt to the manipulation. In order to affect body
351 weight management, we assume that the effect of the food has to be sustained; thus, leading to
352 decreased accumulated energy intake. Sustained reduction in appetite after repeated exposures of
353 satiety enhancing and/or hunger reducing foods resulted in superior body weight management in
354 seven out of nine studies identified. A sustained effect is obviously required in order for the food to
355 have an effect on energy balance and hence be able to affect body weight management.
356 Nevertheless, the sustained satiety enhancing effect may not necessarily be detectable after a long-
357 term intervention with repeated exposures using a traditional study design for a controlled study. As
358 previously discussed, the normal response to weight loss includes an increase in the motivation to
359 eat^{15,17}. A progressively attenuated net effect on appetite should therefore be expected following an
360 intervention that in itself results in decreased motivation to eat, which then leads to weight loss. To
361 demonstrate the true sustained effect on appetite after weight loss, the proper study design should
362 therefore include a weight-matched control group for comparison; demonstrating whether an effect
363 on appetite is maintained after repeated exposures that lead to weight loss. The second best
364 alternative could be to minimize the duration of repeated exposures so the reduction in body weight
365 is still very small; thus, at least reducing this problem. There is no consensus regarding which
366 duration of repeated exposures of a specific food is needed to demonstrate that an effect on appetite
367 can be considered sufficiently sustained to have a beneficial effect on body weight management.
368 Evaluations of whether demonstrated acute effects on appetite translate into sustained effects were
369 recently reviewed by Halford *et al.*⁴⁸. Their results suggest that in most cases where a robust acute
370 effect on appetite was observed, the effect was likely to be sustained, particularly when assessing
371 energy intake⁴⁸. These authors arrived at this conclusion despite the fact that potential
372 counteracting effects of weight loss were not taken into account in this review. Therefore, the
373 results of our review (which has focused on effects of foods on body weight) should be considered
374 alongside the Halford *et al.* review. Taken together we feel that these two review papers provide an
375 up to date comprehensive objective assessment of the science in this area.

376 4.3 Assessments of appetite from *ad libitum* energy intake vs. self-reported appetite 377 evaluations

378 From the meta-analysis and the studies that use both methods, we noted that results are quite
379 consistent regardless if appetite is assessments as energy intake from an *ad libitum* meal or self-
380 reported appetite evaluations (Figure 2)^{37,40,41}. However, the evidence supporting a link between
381 enhanced satiety/reduced hunger and improved body weight management seems to be more robust
382 when appetite is assessed as energy intake compared to self-reported appetite evaluations (Figure
383 2). Self-reported appetite evaluations are probably affected by personal psychological matters to a
384 greater extent than energy intake, thereby introducing more individual and day to day variation³⁴.
385 Additionally, self-reported appetite evaluations may be more prone to self-reporting bias than
386 energy intake³². However, despite the fact that energy intake reflects behavior, the measure may
387 also be affected by self-reporting and especially social desirability bias, as the subject may be aware
388 that the investigator monitors how much food is consumed⁴⁹. The laboratory settings are needed in
389 order to standardize the appetite measurements, but the standardization may result in stylized
390 behavior that may not be truly typical of the subject's usual behavior⁵⁰.

391 Gastrointestinal hormones believed to be involved in appetite control are not evaluated in this
392 review. However, it is well documented that gastric bypass surgery promotes weight loss and
393 improve the following body weight maintenance⁵¹ and that it is largely mediated by profound post-
394 prandial changes in gastrointestinal hormone secretion associated with enhanced satiety/reduced
395 hunger^{52,53}. Biological markers of appetite were assessed in five of the included studies^{37-39,42,43}, but
396 differences between the intervention and the control groups were only reported in three of these<sup>37-
397 39</sup>. After a single exposure to the foods, the orexigenic hormone ghrelin was found to be lower^{37,39}
398 and the anorexigenic hormones GLP-1 and PYY were found to be higher in the intervention groups
399 compared to the control groups^{37,38} in line with previous findings on associations between a number
400 of gastrointestinal hormones and appetite^{54,55}. From these studies, the differences in appetite
401 detected by self-reported assessments are consistent with those reflected in objective measures, thus
402 increasing the validity of the findings. As changes in eating behavior resulting in decreased energy
403 intake are needed for the satiety enhancing and/or hunger reducing foods to improve body weight
404 management, the subjective measures are necessary for investigating the aim of this review. The
405 objective measures may provide a plausible mechanism validating the subjective assessments, but
406 they do not necessarily reflect behavior.

407 4.4 Limitations of the review

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

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

415 **5 Conclusion**

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

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

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

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

569 The grey areas indicate that the parameters were not assessed.

570

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

572 M=Male; F=Female; SEM=Standard error of mean; I=Intervention; C=Control; CI=Confidence interval; DB=Double-
573 blinded; SB=Single-blinded; NB=Non-blinded; CO=Cross-over; P=Parallel; RCT=Randomized controlled trial;
574 NR=not reported; VAS=Visual analogue scale; AUC=Area under the curve; HSSc=Hunger-satiety score;

575 ↑=Increase/higher; ↓=Decrease/lower; ↔=unchanged/no difference; (?)=Significance of difference is unknown.

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

578 The grey areas indicate that the parameters were not assessed.

579

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

582 After screening of MeSH term index list as well as testing numerous different combinations of search terms in order to
583 conduct a search providing the most hits, the following search terms were selected as the final search syntax:

584 (“*appetite*” OR “*satiety*” OR “*satiation*” OR “*satiety response*” OR “*hunger*” OR “*hunger response*” OR “*hungry*”)
585 AND (“*body weight changes*” OR “*body weight maintenance*” OR “*weight loss*” OR “*weight gain*”)

586 The reference lists of these 12 eligible papers were subsequently screened and additional 12 potentially relevant papers
587 were selected for full-text screening. However, these were subsequently excluded for further considerations.

588

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

591 CI=Confidence interval

592 Assessments of appetite are classified according to whether appetite was assessed as energy intake from an *ad libitum*
593 meal and self-reported appetite evaluations, energy intake from an *ad libitum* meal alone or self-reported appetite
594 evaluations alone. The grey marks around the mean from each study indicates the weight of the evidence from each
595 study assessed in a random effects analysis; the blue diamonds summarizes the total mean differences according to the
596 assessments of appetite and finally for the overall result with width of the diamonds indicating the 95% CI.

597 Only the studies from the groups of Chambers and Rondanelli directly reported the mean difference in body weight
598 change (95% CI) (kg). For the remaining studies, the effect sizes were calculated based on reported changes within each
599 group. No standard deviation, standard error of mean (SEM) or 95% CI for the changes in body weight within each
600 group was reported in the studies from the groups of Blundell and Wang. The corresponding authors were asked to
601 provide these data, but data could not be made available for this review. The 95% CI was therefore imputed based on
602 the average SEM from the other studies³⁶.

603 Risk of bias was assessed based on the following categories: A: Random sequence generation (selection bias); B:
604 Allocation concealment (selection bias); C: Blinding of participants and personnel (performance bias); D: Blinding of
605 outcome assessment (detection bias); E: Incomplete outcome data (attrition bias); F: Selective reporting (evaluated for
606 self-reported appetite evaluations) (reporting bias); G: Power calculation; H: Drop outs; I: Other bias. Risk of bias was
607 rated as “Low” or “High” according to predefined specifications (see Supplementary material Table 1) or “Unclear” if
608 no information on a potential bias was reported.