Etiology and Pathophysiology

Systematic review of the evidence for sustained efficacy of dietary interventions for reducing appetite or energy intake

J. C. G. Halford[1], U. Masic[1], C. F. M. Marsaux[2], A. J. Jones[1], A. Lluch[3], L. Marciani[4], M. Mars[5], S. Vinoy[6], M. Westerterp-Plantenga[7] and D. J. Mela[8]

[1]Institute of Psychology, Health and Society, University of Liverpool, Liverpool, UK, [2]European Branch of the International Life Sciences Institute (ILSI Europe), Brussels, Belgium, [3]Centre Daniel Carasso, Danone Nutricia Research, Palaiseau, France, [4]NIHR Nottingham Biomedical Research Centre at Nottingham University Hospitals NHS Trust and the University of Nottingham, Nottingham, UK, [5]Division of Human Nutrition, Wageningen University and Research, Wageningen, Netherlands, [6]R&D, Nutrition Department, Mondelēz International, Clamart, France, [7]NUTRIM School of Nutrition and Translational Research in Metabolism, Maastricht University, Maastricht, Netherlands, and [8]Unilever R&D Vlaardingen, Vlaardingen, Netherlands

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Address for correspondence: CFM Marsaux, International Life Sciences Institute, European Branch, ILSI Europe a.i.s.b.l., Brussels, Belgium.
Email: publications@ilsieurope.be

Summary

We assessed evidence for changes in efficacy of food-based interventions aimed at reducing appetite or energy intake (EI), and whether this could be used to provide guidance on trial design.
A systematic search identified randomized controlled trials testing sustained efficacy of diets, foods, supplements or food ingredients on appetite and/or EI. Trials had to include sufficient exposure duration (≥3 days) with appetite and/or EI measured after both acute and repeated exposures.
Twenty-six trials met the inclusion criteria and reported data allowing for assessment of the acute and chronic effects of interventions. Most (21/26) measured appetite outcomes and over half (14/26) had objective measures of EI. A significant acute effect of the intervention was retained in 10 of 12 trials for appetite outcomes, and six of nine studies for EI. Initial effects were most likely retained where these were more robust and studies adequately powered. Where the initial, acute effect was not statistically significant, a significant effect was later observed in only two of nine studies for appetite and none of five studies for EI.
Maintenance of intervention effects on appetite or EI needs to be confirmed but seems likely where acute effects are robust and replicable in adequately powered studies.

Keywords: Appetite, energy intake, satiety, study duration.

Abbreviations: EFSA, European Food Safety Authority; EI, energy intake; PRISMA, preferred reporting for systematic reviews and meta-analysis; RCT, randomized controlled trial; SACN, Scientific Advisory Committee on Nutrition (UK); VAS, visual analogue scales..

Introduction

Despite the broad literature of published studies on the effects of ingredients, foods and diets on both appetite and energy intake (EI), we still know surprisingly little about their enduring effects. This lack of knowledge is a fundamental conceptual, as well as regulatory, barrier to the substantiation of satiety-enhancing approaches to help control eating behaviour. The underlying scientific issues are whether, presumably through physiological processes and/or mechanisms of learning, the body adapts to foods that initially modulate appetite and whether these acute effects dissipate over time after repeated exposure.

In the current paper, we refer to 'adaptation' as a decrease in an observed behavioural (appetite or EI) response with repeated exposure to a specific dietary intervention, regardless of the possible mechanisms for this. Identification of dietary approaches less susceptible to adaptation could have practical implications for improving compliance with long-term weight control efforts. In addition, differences that may be observed among interventions could inform testable hypotheses to help in predicting and designing more sustained effects in future proposed dietary interventions.

The vast majority of controlled studies assessing the impact of specific foods or dietary interventions on appetite and EI have examined the acute effects of a single exposure to dietary manipulations, such as but not limited to preloads, on (i) rated appetite post ingestion (and/or over the remainder of the day), and (ii) EI and food choice at the next meal (and/or at eating occasions across the rest of the day; 24-h intake). Outcomes of these studies may indicate plausible beneficial effects; however, sustained efficacy can only be confirmed by testing after a period of repeated exposure. Weight change data from long-term weight loss or maintenance studies do not resolve this, because anthropometric outcomes reflected many factors together. Furthermore, weight loss interventions are often composed of a range of dietary and lifestyle changes and rarely include well-controlled assessments of appetite and EI.

Data obtained following a period of repeated exposure are necessary to judge if any evidence of adaptation manifests itself. Confirmation of reliable, sustained, effects are relevant to regulatory assessment (to substantiate a health claim) and to assure consumer confidence in commercial products and programmes that claim beneficial effects on appetite or EI. For this, it is essential to have an objective basis to determine whether or what duration of exposure would be needed to observe or exclude the possibility of adaptation. This has important implications for the designs and resources required for research trials. Guidance from the European Food Safety Authority (EFSA) notes that '[e]vidence for a sustained effect with continuous consumption of the food should also be provided in order to exclude adaptation' (1), although no specific duration is recommended for substantiating appetite or EI claims. In assessing the effects of different dietary carbohydrates on EI and satiety outcomes, the UK Scientific Advisory Committee on Nutrition (SACN) included trials with an intervention of three consecutive days or more (2). No basis for this criterion is given, and it is not clear if this duration is sufficient to exclude potential adaption. Moreover, given that for some dietary manipulations, the effects might develop rather than diminish over time, acute studies may produce false negative as well as false positive indications of longer-term efficacy.

In order to address these issues, a systematic review was conducted to identify literature testing whether chronic exposure to specific foods or dietary interventions (i.e. repeated administration of the relevant manipulation over a duration ≥3 days) alters reported acute effects on satiety or EI. Studies that incorporated both an acute and a chronic test of these effects were identified with a systematic literature search. Our analysis assessed the empirical evidence for adaptation to interventions (or, alternatively, the maintenance or gain of an effect over time), and whether this could also provide guidance on the design of studies to assess whether acute effects are likely to be sustained. In addition where possible, the type of food/dietary manipulation and the nature of the initial effects at acute testing were considered.

Method

Literature search

A systematic search of the literature was performed to identify randomized controlled trials (RCTs) testing both the acute and sustained efficacy of diets, foods, supplements or food ingredients on appetite and/or objectively measured EI. Trials had to include sufficient exposure duration (defined as repeated administration of the relevant manipulation over a duration ≥3 days) and have appetite and/or EI as outcomes after both acute and repeated exposures. The search was run using the OvidSP platform and Medline, FSTA and PsycINFO databases for papers in English published up to 17 January 2018. The full search strategy is described in Supporting Information Table S1. The PRISMA guidelines (3) were followed and the protocol published on the PROSPERO international prospective register of systematic reviews (CRD42015023686; www.crd.york.ac.uk/PROSPERO).

Inclusion and exclusion criteria

The search included RCTs published in refereed journals on healthy adults including those with overweight, obesity and pre-diabetes (no restrictions applied for gender or weight status) assessing exposures ≥3 days and including measurements of self-reported appetite feelings such as hunger, satiety, fullness, etc. (using Visual Analogue Scales [VAS] or analogous methods) and/or objectively measured (but not self-reported) *ad libitum* EI. Exclusion criteria included drug trials, non-RCTs, no first-dosing measurements (i.e. measure of acute effect) reported or insufficient description thereof, no inclusion of a closely energy-matched control and studies not in the aforementioned study population. Research published in non-refereed sources and other 'grey literature' (e.g. theses) were also excluded from consideration.

First and second phase screening

Each abstract (phase 1) and selected full text paper (phase 2) was screened for eligibility by pairs of researchers, independently, with further consensus reached by the remaining researchers upon disagreement within pairs. For phase 2, the decision on in- or exclusion of a paper required clarity on study design, population, manipulation, measures assessed and statistical analysis. Authors of papers where relevant information was missing or ambiguous were contacted. If the additional information received was appropriate, the paper was included. If not, or if authors failed to respond within 6 weeks, papers were excluded.

Data extraction and assessment of adaptation

All relevant details were extracted from papers passing phase 2. This included the statistical differences in means between conditions at initial intervention (test of acute effect), last post-intervention dosing (test of sustained effect) and interactions between conditions over the duration of the study (differences between conditions from first to last dosing), to assess whether effects were present and whether they changed after repeated exposure. The extracted data were confirmed by at least two co-authors. A criterion of $p < 0.05$ was used as the criterion for statistical significance for all analyses. The study findings pertaining to the acute and sustained effects on appetite and EI were used to draw conclusions. Wherever possible, conclusions were drawn from the primary rather than secondary or *post-hoc* (e.g. sub-group) analyses. Where relevant, effects reported at specific meals as well as total EI for the full day(s) were included. Where there were multiple repeated exposure measurements periods, the results of the final measurement point comparison or, if available, Time × Treatment analyses were used. In a few instances, outcomes were determined from the means and variance in figures and tables (4–6). All conclusions drawn from individual studies were initially agreed by at least two authors, and any highlighted uncertainties resolved by further discussion and consensus. A 'yes' (Y) or 'no' (N) was assigned to the observation (or absence, respectively) of a statistically significant beneficial effect on any appetite ratings (e.g. increased satiety or reduced hunger) or reduced EI relative to the control, in the relevant statistical analyses. This yielded four categories of outcome per study: (i) N/N = no beneficial treatment effect in initial nor after repeated exposure, (ii) Y/Y = initial beneficial treatment effect also present after repeated exposure (i.e. sustained effect), (iii) Y/N = initial beneficial treatment effect but absence thereof after repeated exposure, and (iv) N/Y = no beneficial treatment effect initially but observed after repeated exposure. Where studies reported multiple appetite rating scales, the observation of a statistically significant effect on any one scale was accepted as sufficient indication of an effect at that time point (for assessing whether adaptation occurred or not).

Estimates of statistical power

We generated *post-hoc* power calculations based on the method of Cohen (7). We applied a 'meaningful' effect size of $d = 0.67$, based on recommendations of ~10% difference in mean appetite ratings or a 500 kJ difference in EI (8) and parameters derived from Flint *et al.* (9) and Gregersen *et al.* (10), respectively, which suggest an assumed coefficient of variation of ~15%. Using this effect size, the *post-hoc* power calculations ($\alpha = 0.05$) were based on the within subjects comparison of the 'active treatment' or 'experimental' groups in each identified study. This provided an estimate of statistical power for each study and the basis to assess whether they were adequately powered (80%) to detect this size of effect. However, as the true size of effect is unknown, we also conducted sensitivity analyses based on small ($d = 0.20$), medium ($d = 0.50$) and large ($d = 0.80$) effects.

Risk of bias assessment

Risk of bias assessment focused on domains that have been applied in other recent systematic reviews on eating behaviour (11,12). Each included study was assessed for potential risk of bias by pairs of researchers independently, with any discrepancies resolved by consensus. Risk of bias was rated as 'low', 'high' or 'unclear' on each of four domains: power (low = power calculation reported and analyses based on sample size meeting the power criterion), intention-to-treat analysis (low = analyses based on 100% of subjects entering the study), drop-outs (low = less than 20% of subjects entering the study failing to complete) and incomplete outcome reporting (low = all measured outcomes and statistical analyses reported).

Results

From the total of 9680 unique title/abstract records identified, 178 papers were selected for full-text screening (Fig. 1). The majority of the studies were not specifically designed to assess physiological and behavioural adaptations to the interventions. This hindered the screening and review process as explicit reference to comparisons between initial and sustained exposures to the study manipulations were often lacking in the narrative text and data reporting. More than 25% of the papers assessed (51/178) had a potentially suitable design but were excluded as responses after either acute or sustained exposure were not assessed, making conclusions regarding adaptation impossible.

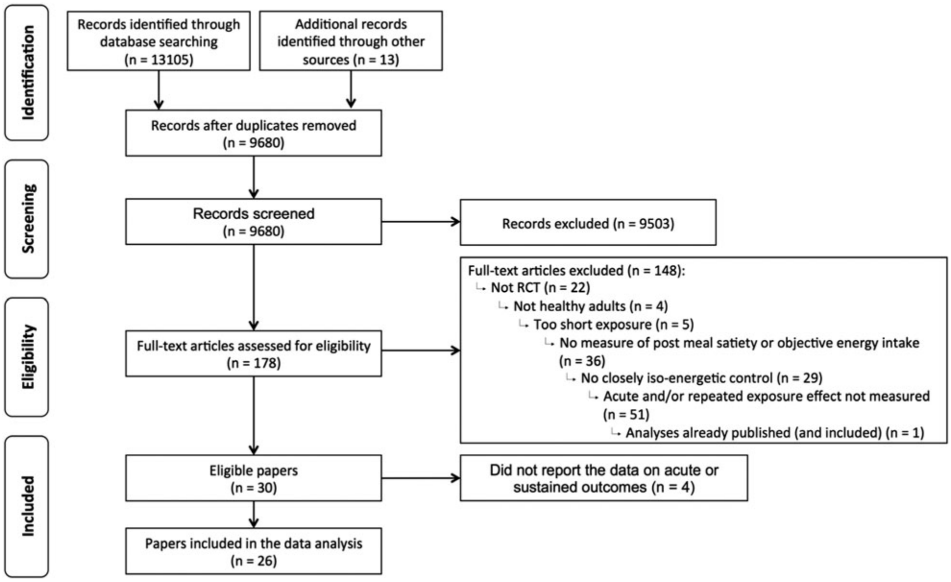

Figure 1 PRISMA flowchart of paper selection.

Initially, 32 papers were identified that met the stated inclusion criteria for either EI and/or appetite ratings. Two papers (13,14) were subsequently excluded, as we could not unequivocally determine if study participants had been exposed to the test interventions at the time of the initial measurement (i.e. whether there was an acute test of the treatment exposures). Therefore, 30 papers were eligible for inclusion in this review (Supporting Information Table S2). If a paper reported multiple studies or one study with multiple treatment arms/comparisons, only eligible comparisons (based on the inclusion/exclusion criteria) were considered and have been reported in the supplementary table (e.g. if comparisons of treatments differing in energy sources and energy content were included in the same study, only the former would be eligible). Furthermore, on detailed examination, four papers which met our design criteria (and are therefore included) measured but did not report data on either the acute or sustained outcomes. Thus, they are not part of the data analysis because no conclusions with regards to adaptation could be drawn. The remaining 26 papers included in the analysis are briefly described in Table 1.

Table 2 summarizes the results of these papers for the reported effects on appetite ratings and EI after acute and sustained exposure to interventions, coded as described in the Methods section.

Most (21/26) papers reported on effects of ingredient or dietary manipulations on appetite, and 14 of the 26 reported on effects of ingredient or dietary manipulations on EI, including nine papers reporting both outcomes. Numbers of studies with all different possible outcomes for acute and sustained effects on appetite and EI are given in Supporting Information Tables S3a and S3b, and described below.

Appetite ratings

Nine studies demonstrated significant initial differences between treatment and control in one or more appetite ratings (Table 2). Of these, six reported an initial beneficial effect was sustained after repeated exposure in most/all appetite rating scales (4,5,15–18). In contrast, three studies showed evidence of adaptation (loss of initially observed effect), although in each case the initial effect was only observed on one of multiple appetite scales (19–21). Of the 12 remaining studies which found no initial significant effects on appetite ratings, only two reported significant beneficial effects after repeated exposures (22,23).

Energy intake

Seven out of 14 studies demonstrated initial differences between treatment and control in EI, and a beneficial effect was sustained after repeated exposure in five of these (16,19,24–26). Of the seven studies where no initial effect was observed, none showed an effect after sustained exposure (Table 2).

Appetite ratings and energy intake compared

EI was measured in only two of the studies that observed adaptation (i.e. loss of a reported initial effect) in appetite ratings. In one case, a significant acute effect on EI was maintained (19). In the other case, neither an acute nor sustained effect on EI was apparent (20). Three other studies demonstrated adaptation (i.e. loss of a reported initial effect) in EI (17,27,28). Of these, only Wanders 2014 (17) also measured appetite and found the acute

Table 1 The 26 papers included in the analysis

Reference	Intervention	Exposure	Outcome measures
Alves 2014 (39)	High oleic or conventional unpeeled roasted peanuts (56 g) or control biscuits served with a milkshake (hypocaloric diet)	28 days (daily portion)	Appetite ratings
Astbury 2014 (19)	Whey protein and polydextrose snack bar or control snack bar	14 days (once a day)	Appetite ratings, EI
Bjerg 2015 (20)	Lactobacillus paracasei subsp. paracasei L. casei W8® or rice flour control provided in identical gelatine capsules	28 days (one capsule a day)	Appetite ratings, EI
Diepvens 2007 (22)	Olibra (250-g yoghurt containing 3-g milk fat and 5-g Olibra emulsion (2-g vegetable fat)) or control (250-g yoghurt containing 5-g milk fat) yoghurt provided during weight maintenance period after weight loss	18 weeks (twice a day)	Appetite ratings
Hogenkamp 2012 (28)	High-energy semi-solid or liquid novel food preload or low-energy semi-solid or liquid novel food preload	3 days (3 times a day) + breakfast on day 4	EI
Isaksson 2012 (15)	Whole grain rye porridge compared to isocaloric refined wheat bread control provided with jam and margarine	3 weeks (once a day)	Appetite ratings
Jones 2013 (40)	High dairy and calcium compared to low dairy and calcium control meal plans	12 weeks (3–4 times vs once a day)	Appetite ratings
Kovacs 2003 (31)	Capsule containing 15-mg enterostatin and 450-mg lactose compared to placebo control (500-mg lactose) with water; part of a high-fat diet	4 days (3 times a day)	Appetite ratings, EI
Logan 2006 (29)	Olibra (200-g yoghurt containing 12.5-g Olibra emulsion (5-g Olibra fat)) or control (200-g yoghurt containing 5-g milk fat)	3 weeks (once a day)	Appetite ratings, EI
Martens 2013 (24)	Two different protein sources (whey or soy) provided in three different relative protein contents	12 days (daily *ad libitum*)	Appetite ratings, EI
Martens 2014 (16)	Three diets differing in protein content (beef protein)	12 days (daily *ad libitum*)	Appetite ratings, EI
Martens 2015 (21)	Two diets differing in protein content - detailed dietary guidelines provided + shakes twice daily with extra protein (whey) vs carbohydrates (control)	12 weeks (dietary guidelines + shakes twice a day)	Appetite ratings
Neumann 2016 (6)	High carbohydrates compared to high protein control breakfast	8 days (once a day)	Appetite ratings
Pelkman 2007 (25)	Alginate-pectin mix beverage (1 or 2.8 g alginate) + calcium beverage compared to a no fibre + no calcium control beverage	7 days (twice a day)	Appetite ratings, EI
Pittaway 2007 (42)	Chickpea-rich diet (140-g chickpeas, chickpea bread and shortbread/day) compared to wheat-rich control diet (wholemeal wheat bread and higher wheat fibre breakfast cereals)	5 weeks (daily)	Appetite ratings
Rao 2015 (23)	Partially hydrolysed guar gum (2 g, 4 kcal) compared to dextrin control (2 g, 8 kcal) provided in yoghurt (125 g)	2 weeks (once a day)	Appetite ratings
Rebello 2012 (30)	Olibra (200-g yoghurt containing 2.1-g Olibra fat emulsion) or control (200-g yoghurt containing 1.95-g milk fat); part of a 1500-kcal diet	12 weeks (twice a day)	Appetite ratings, EI
Rigaud 1987 (4)	Fibre (vegetable, citrus and grain fibres) or control (lactose and starch mix) tablets with 300-mL water.	4 weeks (7 tablets 3 times a day)	Appetite ratings
Rondanelli 2012 (5)	Botanical extract supplement spray (containing a blend of botanical extracts) compared to control (excipients only) spray; part of a hypocaloric diet	30 days (3 sprays 5 times a day)	Appetite ratings
Rumpler 2006 (27)	High carbohydrates or protein or fat drinks	8 weeks (3 times a day)	EI
Saltzman 1997 (33)	Two *ad libitum* diets varying in fat to carbohydrates ratio: High-fat compared to Low-fat control	11 days (daily *ad libitum*)	EI
Sandberg 2016 (18)	Rye kernel bread (142 g, 15.6 g fibre) compared to white wheat flour-based bread control (121.4 g, 3.9 g fibre)	3 days (once a day)	Appetite ratings

(*Continues*)

Table 1 (Continued)

Reference	Intervention	Exposure	Outcome measures
Stubbs 1996a (26)	Three *ad libitum* diets with ratios of medium- to long-chain triglycerides (MCT) either 2:1, 1:1 or 1:2 (control), after 2-day maintenance diet	14 days (daily *ad libitum*)	EI
Stubbs 1996b (32)	Three *ad libitum* diets varying in fat to carbohydrates ratio: high-fat, medium-fat or control low-fat, after 2-day maintenance diet	14 days (daily *ad libitum*)	EI
Wadden 1985 (41)	Protein sparing modified fast diet (60-75 g/day protein and ≤ 450 kcal/day) compared to protein formula liquid control diet (liquid diet, 70 g/day protein, 420 kcal/day) after a 1-month low energy balanced diet	4 weeks (daily)	Appetite ratings
Wanders 2014 (17)	Pectin (10-g gel forming pectin) compared to control (2-g starch and 3-g gelatine mix) in isovolumetric (200 g) and isocaloric load	15 days (once a day)	Appetite ratings, EI

effects of treatment on appetite endured. Four of the five studies showing sustained effects on EI (16,19,24,25) also measured appetite, but a sustained effect was only found in one of these (16).

Statistical power

Assuming a meaningful change in appetite or EI of $d = 0.67$ (see Methods section), 14 of the 26 individual studies would have been adequately powered to detect this effect (>80%). The number of adequately powered studies decreases drastically if the true effect is smaller, as shown in the sensitivity analyses presented in Supporting Information Table S4. Unless the true effect is large ($d \sim 0.8$), then average statistical power of all studies would be <80%.

Risk of bias assessment

The risk of bias assessment of the included studies is reported in Supporting Information Table S5. Issues most frequently arising were lack of or unclear power calculations and failing to report results of analyses based on the intention-to-treat population.

Discussion

Given the high volume of research on appetite and EI, we found surprisingly few studies testing whether acute effects on these outcomes changed after chronic exposure to specific food or dietary interventions. Only 26 studies met the inclusion criteria and reported results with sufficient detail to assess the acute and chronic effects of ingredients, foods or whole diet manipulations.

For measures of appetite, results from initial, acute testing (i.e. a significant effect or not) were matched by results after sustained exposure in 16 of 21 cases (76%). The absence of acute efficacy was a strong indicator of likely absence of efficacy after sustained exposure (10 of 12 trials, 83%). While only six of nine studies (67%) with initially significant acute effects showed this after repeated exposure, those six studies were characterized by having demonstrated the acute effects on either the only scale used (4,5) or on a number of measures (15–18) (Table 2). In contrast, in the three studies where an initial effect on appetite was not sustained (19–21), the initial effect was observed on only one of several parameters, suggesting that the initial observed effect may not have been robust or replicable. Thus, confidence in the reliability of an initially observed acute effect on appetite seems to be an important (if obvious) basis for anticipating that the effect might be sustained over time.

For EI, acute results agreed with sustained results in 12 of 14 trials (86%). In all seven studies reporting no significant acute effects, there was also no significant effect after repeated exposure (29–33). Of the seven studies which demonstrated significant acute effects of manipulation on EI, five (71%) reported sustained effects (16,19,24–26). With the exception of (26), those studies were powered for EI, whereas both two studies reporting no sustained effects (17,27) failed to report power calculations.

Where initial differences in EI are found, the initial effect size may be relevant to the likelihood of an effect also being observed after sustained exposure. Rumpler *et al.* (27) had only 12 participants and noted considerable individual variation in EI during the study. The 10% (roughly 1.4 MJ/day) difference in EI seen at the start of that study was entirely absent at the end (week 8). In Wanders *et al.* (17) the pectin intervention showed a statistically significant but modest initial reduction in EI (−5.9% 0.54 MJ/day) on day one but no difference from control at day 15. In contrast, for example, Astbury *et al.* (19) reported an initial reduction of 16.2% (0.80 MJ) of test meal intake (Day 1) and a reduction of 19% (1.01 MJ) by Day 15. The other studies demonstrating retention of acute effects after sustained exposure did not report results in a way that allows for unambiguous interpretation of initial effect sizes. Although the number of studies is small, these results suggest that where a robust effect on EI is observed at initial exposure in adequately powered studies, the effect is likely to be sustained.

No distinction in patterns of responses could reliably be attributed to differences in the specific ingredient, food and diet interventions, nor putative physiological mechanisms

Table 2 Summary of acute and sustained effects reported in the 26 papers included in our analysis ('Y' or 'N': statistically significant beneficial effect Yes or No, respectively)[1]

Reference	Appetite ratings						Energy intake
	Hunger	Satiety	Fullness	Desire to eat	PFC	Other	
Isaksson 2012 (15)	Y/Y	Y/Y		Y/Y			
Rigaud 1987 (4)[2]	Y/Y						
Rondanelli 2012 (5)[3]		Y/Y					
Sandberg 2016 (18)	Y/Y	Y/Y		Y/Y			
Alves 2014 (39)	N/N	N/N	N/N		N/N		
Jones 2013 (40)						N/N[4]	
Neumann 2016 (6)[5]	N/N		N/N	N/N	N/N		
Pittaway 2007 (42)[6]		N/N					
Wadden 1985 (41)	N/N					N/N[7]	
Martens 2015 (21)	N/N	N/N	Y/N	N/N			
Rao 2015 (23)	N/Y (at 4 h only)	N/Y (at 4 h only)		N/N		N/N[8]	
Diepvens 2007 (22)	N/Y						
Stubbs 1996a (26)							Y/Y
Hogenkamp 2012 (28)							N/N
Saltzman 1997 (33)							N/N
Stubbs 1996b (32)							N/N
Rumpler 2006 (27)							Y/N[9]
Martens 2014 (16)	Y/Y	N/N	Y/Y	Y/Y			Y/Y
Martens 2013 (24)	N/N	N/N	N/N	N/N			Y/Y
Pelkman 2007 (25)	N/N		N/N		N/N	N/N[10]	Y/Y at dinner only
Kovacs 2003 (31)	N/N	N/N					N/N
Logan 2006 (29)	N/N		N/N	N/N	N/N	N/N[11]	N/N
Rebello 2012 (30)	N/N		N/N	N/N		N/N[12]	N/N
Astbury 2014 (19)	Y/N		N/N				Y/Y
Wanders 2014 (17)	Y/Y		Y/Y	Y/Y	Y/Y		Y/N
Bjerg 2015 (20)	N/N	N/N	Y/N		N/N	N/N or N/Y[13]	N/N

PFC, prospective food consumption.

[1]N/N: no beneficial treatment effect in initial nor after sustained exposure; Y/Y: initial beneficial treatment effect also present after sustained exposure; Y/N: initial beneficial treatment effect but absence thereof after sustained exposure; and N/Y: no beneficial treatment effect initially but observed after sustained exposure;
[2]Rigaud 1987: Interpreted from Figure 2 in paper;
[3]Rondanelli 2012: Interpreted from Figure 2 in paper
[4]Jones 2013: N/N for satisfaction;
[5]Neumann 2016: Interpreted from Figure 2 in paper;
[6]Pittaway 2007: No p-values reported;
[7]Wadden 1985: N/N for preoccupation with eating;
[8]Rao 2015: N/N for appetite and appetite score;
[9]Rumpler 2006: Carbohydrates vs fat only and self-selected EI;
[10]Pelkman 2007: N/N for overall score;
[11]Logan 2006: N/N for preoccupation with thoughts of food;
[12]Rebello 2012: N/N for food craving and desire to eat something sweet, salty or fatty;
[13]Bjerg 2015: N/N for desire to eat something fatty, sweet or savoury and N/Y for desire to eat something salty.

underlying these. This was in part due the paucity of studies, most using quite different interventions, which precludes such an analysis. Sustained effects on EI were observed for interventions of protein + whey diets, high protein diets, medium- vs long-chain triglycerides and alginate-pectin beverages. Sustained effects on appetite ratings were observed for interventions of whole grain rye porridge and bread, high beef protein diet, unspecified commercial fibre tablet (pre-main meals), *Griffonia simplicifolia* extract and a gel-forming dietary fibre. Sustained effects were also observed in a variety of paradigms, in subjects with a healthy weight and also in subjects with obesity/overweight (see Supporting Information Table S2).

There are a number of limitations to the evidence base and the implications that can be drawn from it. Because of the difficulty of defining search terms specific for studies with the eligible design features, it is possible that not all potentially relevant studies have been captured. We believe the systematic approach used here should have identified an unbiased, representative, set of the research literature that allows for generalized conclusions. However, we acknowledge that this evidence may be subject to publication bias, mainly as over-representation of academic research with 'positive' results. Additional searching of 'grey' literature (i.e. research reported outside of mainstream scientific journals) might in part have helped address this bias. On the other hand, there has also been a large amount of commercial ingredient activity in this topic area, which carries a potential bias toward selective publication of 'positive' results in non-refereed sources such as patents and technical reports. Furthermore, many grey literature sources lack sufficient detail for the relevant data extraction and quality assessment.

A further limitation is that most research testing the effects of prolonged interventions on EI or appetite includes only a pre-intervention baseline. The absence of an initial, acute intervention measure was a major reason why many otherwise-suitable studies could not be used for this analysis. Even within the papers that met our criteria, few had a design and data analysis and reporting that were absolutely clear and optimal for this purpose. Power calculations were missing or unclear in 70% of the eligible studies (Supporting Information Table S5), especially for appetite measures. This is similar to the level recently reported for a cross-section of eating behaviour research (34). Most studies had the 20–25 participants typically recommended to detect a 10% difference in appetite ratings or a 500-kJ difference in EI (8). Nevertheless, our *post-hoc* power analyses suggest that just over half of the included studies were sufficiently powered to detect an effect size of d = 0.67, which roughly reflects the difference recommended above for a typical acute appetite or EI test design (9,10). This is however a rather crude indicator, as it is impossible to estimate the 'true' effect size due to considerable study heterogeneity (alongside wider issues such as publication bias), especially if responses after chronic exposure become smaller or more variable. Adequate power is nevertheless one of a number of steps that can be recommended to improve the overall replicability and reporting of eating behaviour research (8,34).

A further difficulty in interpreting the maintenance of effects is the potential interplay between appetite ratings and EI. Only four of the nine studies that measured both appetite and EI reported agreement between acute and sustained results for both outcomes effects, including the only study reporting significant beneficial effects on both outcomes at acute and sustained time points (16). There are however some logical reasons why changes in appetite ratings and EI might not correspond, following either acute or sustained interventions. First, modest but significantly reduced appetite ratings do not necessarily result in significant changes in subsequent EI. Analyses of acute intervention data by Sadoul *et al.* (35) indicate that a reduction of ≥15 mm on a 100-mm appetite rating scale is needed to observe a consistent effect on EI. Moreover, Veldhorst *et al.* showed that with increases in satiety ratings of 30–50%, the reduction in subsequent EI is 15–25% (36). A reduction in appetite ratings without a change in EI may nevertheless be beneficial, e.g. for reducing dysphoria and improving compliance in the context of a controlled-energy weight control regimen (37). Second, treatments that induce changes in EI may influence appetite ratings under dynamic conditions. A sustained reduction in EI would usually imply a negative energy balance and eventual weight loss, which prompts counter-acting physiological and behavioural responses including increased hunger (38).

Further consideration of factors that might have influenced the results is limited by the nature of the evidence base. While we had no *a priori* hypotheses regarding the effects of energy balance conditions or weight status of the populations, almost all trials were carried out under eucaloric or *ad libitum* conditions and with subjects in the body mass index range of 20–30 kg/m^2. Only three of the 26 trials providing usable data were carried out as part of diets intentionally reduced in energy (5,39,40), and only three trials recruited subject populations with an initial mean BMI ≥30 (25,30,40). Therefore, *post-hoc* consideration of these factors would not be credible. It is also possible that results over sustained periods could reflect cognitive bias introduced by the interventions. However, only a very small number of trials used obviously different diets (41), or had products likely to be distinguished by subjects (15,18). In the latter case, blinded subjects would still not know which was 'test' or 'control', the manipulation of interest, or the hypothesised effects of the products. We therefore feel that in the overall evidence base bias due to cognitive influences would generally have been limited.

Taken as a whole, while the relevant data are limited and heterogeneous, it is reasonable to propose some general, tentative conclusions and recommendations on the basis of this evidence. An obvious recommendation is that studies should be designed *a priori* with sufficient power to decisively test for meaningful effects (34). Assuming studies are sufficiently powered, the data here suggest that interventions with no significant acute effects on EI or only limited effects (e.g. none or one of several scales) on appetite are unlikely to show any effects with sustained exposure. A possible exception to this may be for fermentable fibres e.g. as observed for Rao *et al.* (23), where changes in the microbiome with repeated exposure might enhance the production of metabolites affecting appetite or EI. Correspondingly, in most cases where a significant acute effect on EI or robust effect on appetite (e.g. significant for multiple scales) was observed, the effect was in most cases retained at subsequent testing over the timeframes of the studies here.

A potential implication of this analysis is that, at minimum, studies in the area of appetite and EI should include evidence that observed acute effects themselves are reliable. This point is also underscored by the recent review of eating behaviour research methodology by Robinson *et al.* (34). Given the nature of a typical design for studying appetite and EI effects of foods and ingredients, a single replication (especially within the same study) generally should not be a substantial added burden for researchers or subjects. This would enhance the credibility of results and provide a better basis for determining whether trials of sustained exposures are likely to be justified. However, the present evidence is too limited to say if acute testing alone might be sufficient, or if it is also necessary to demonstrate that effects are sustained after prolonged exposure. In future studies involving repeated exposures over time, inclusion (and replication) of initial acute tests of interventions at the start of studies, as well as repeating this at the end of the trials, would help to provide a more robust answer to this question.

Authors' Contributions

JCGH, AL, LM, MM, CFMM, UM, SV, MWP and DJM designed and conducted the research, and analysed data. AJJ designed and carried out the *post-hoc* analyses with UM. JCGH, MWP and DJM wrote the paper with additional input from CFMM, AJJ and UM. JCGH had primary responsibility for final content. All authors critically read and approved the final manuscript.

Conflict of interest statement

Each author has completed an ICMJE Conflict of Interest disclosure form. This work was conducted by an expert group of the European branch of the International Life Sciences Institute, ILSI Europe.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Table S1. Search strategy
Table S2. Description of all eligible studies
Table S3a. Numbers of studies with all different possible outcomes for acute and sustained effects on appetite
Table S3b. Numbers of studies with all different possible outcomes for acute and sustained effects on energy intake (EI)
Table S4. *Post-hoc* power analysis
Table S5. Risk of bias assessment and funding of studies included in the systematic review

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