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Etiology and Pathophysiology

Extended calorie restriction suppresses overall and specific food cravings: a systematic review and a meta-analysis

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Summary

Background: Multiple studies have concluded that calorie restriction for at least 12 weeks is associated with reduced food cravings, while others have shown that calorie restriction may increase food cravings. We addressed this ambiguity in a systematic review and meta-analysis.

Methods: We searched for studies conducted on subjects with obesity, implemented calorie restriction for at least 12 weeks and measured food cravings pre-intervention and post-intervention. Our final eight studies mostly used the Food Craving Inventory. Other comparable methods were converted to a similar scale. We used the duration ≥12 weeks, but closest to 16 weeks for studies with multiple follow-ups and performed DerSimonian–Laird random-effects meta-analyses using the 'metafor' package in R software.

Results: Despite heterogeneity across studies, we observed reductions in pooled effects for overall food cravings (−0.246 [−0.490, −0.001]) as well as cravings for sweet (−0.410 [−0.626, −0.194]), high-fat (−0.190 [−0.343, −0.037]), starchy (−0.288 [−0.517, −0.058]) and fast food (−0.340 [−0.633, −0.048]) in the meta-analysis. Baseline body weight, type of intervention, duration, sample size and percentage of female subjects explained the heterogeneity.

Conclusions: Calorie restriction is associated with reduced food cravings supporting a de-conditioning model of craving reductions. Our findings should ease the minds of clinicians concerned about increased cravings in patients undergoing calorie restriction interventions.

Keywords: Calorie restriction, food craving inventory, food cravings, weight loss.

Abbreviations: ADA, American Diabetes Association; COEQ, Control of Eating Questionnaire; DM, subjects diagnosed with diabetes mellitus; F, Female; FCI, Food Craving Inventory; FCQ-T, Food Craving Questionnaire – trait version; HCb, high carbohydrate and protein breakfast; LC, low carbohydrate; LCb, low-carbohydrate breakfast; LCD, low-calorie diet; LF, low fat; LI, limited intake of specific type(s) of food; SE, standard error; VLCD, very-low-calorie diet.

Introduction

Food cravings could be defined as frequent, intense and irresistible desires to consume a particular type of food (1). Food cravings differ from hunger by their specificity (i.e. the desire to consume only a particular type of food) and intensity (i.e. high level of desire to consume the food) (2). Several validated measures have been developed and used to quantify food cravings (e.g. Food Craving Inventory [FCI] (1), Food Craving Questionnaire (3) and Control of

Eating Questionnaire (4)) as well as some study-specific questionnaires. Individuals with overweight and obesity have been shown to have higher levels of cravings for energy-dense food, particularly for high-fat food in individuals with type II diabetes mellitus (5). Moreover, in a cross-sectional study, body mass index was found to be weakly yet positively associated with cravings for high-fat food, sweet food, starchy food and fast food (6). Individuals who crave high-fat food have been shown to have higher body mass indices than individuals who crave for starchy food (7). Furthermore, food cravings have been shown to mediate the association between increased body mass index and eating behaviour that is characterized by some as addictive and also in people with eating disorders (8). As increased food cravings typically result in an increase in consumption of food (6), increased food cravings are particularly relevant to obesity.

There are two main theories regarding the aetiology of food cravings. One theory indicates that food cravings occur owing to an individual being deprived of energy, particular nutrients and/or specific types of food (9,10). However, this theory has little empirical support. Another evidence-based theory indicates that food cravings primarily occur owing to the development of associations between consumption of a specific type of food with a particular stimulus, environment or social context (e.g. special occasions). These theories suggest that food cravings are largely a conditioned response (11). In summary, while the majority of the literature appears to focus around these two theories (i.e. deficiency and conditioning), given the complexity of the phenomenon of food cravings, it is likely that the aetiology of food cravings may be multi-determined.

Extended calorie restriction has been shown to be an efficient modality for achieving weight loss (12). Nevertheless, based on the deficiency (i.e. nutrient/energy) theory of food cravings (9), it has been hypothesized that deficiencies in energy intake, particularly during weight loss, could enhance cravings (13). The rebound weight gain observed following the conclusion of extended calorie restriction interventions in several studies is commonly cited in support of the deficiency hypothesis (14). Conversely, there is evidence to suggest that restriction of caloric consumption and reduced intake of craved items of food for periods extending for at least 12 weeks may suppress food cravings (15–17). However, there are also some studies that have concluded that extended calorie restriction does not have a significant effect on food cravings (18) and may even increase food cravings (19).

To address this ambiguity, we aimed to qualitatively synthesize and quantitatively examine the findings of the available literature that examined, using a pre-intervention and post-intervention repeated-measures design, the effects of extended calorie restriction on overall and specific types of food cravings in a systematic review and meta-analysis. We hypothesized that intended restriction of energy intake by at least 500 kcal d^{-1} for periods extending at least 12 weeks would significantly reduce cravings for energy-dense food (e.g. sweet, high-fat and fast food) and overall food cravings compared with the pre-intervention state.

Methods

Search strategy

All the procedures conducted in the study were approved by the Texas Tech University Human Research Protection Program and were conducted in accord with the PRISMA guidelines. PubMed, Scopus, PsycINFO and Web of Science electronic databases were searched from 12 October 2015 to 14 October 2015 for scholarly work using specific key words and key word combinations (Table 1). The key words and MeSH terms were formatted according to the syntax of each search engine, with the aim of identifying all studies that examined the effects of extended calorie restriction on food cravings. Only the work published after December 1980 in English language was retrieved.

Outcomes of the initial search conducted on the electronic databases were narrowed down by removing duplicates. Titles and available abstracts of the remaining records were screened for the presence of pre-defined exclusion criteria: (i) non-availability of full-text publications in English language; (ii) textbooks, book chapters and review papers; (iii) non-human studies; (iv) not being an interventional study; (v) not implementing a calorie restriction intervention at least in one study arm; (vi) not quantitatively measuring food cravings before and after the intervention; (vii) duration being <2 weeks; (viii) including children who were <12 years of age; (ix) including individuals with a body mass index of <30 kg m^{-2}; and (x) including individuals diagnosed with eating disorders. Title and abstracts of both references and citations of the records that survived the described comprehensive screening process were screened to identify additional publications. Full-text manuscripts of the records that survived the initial screening process were examined for the exclusion criteria and for the quality of the methods. Particularly, studies that did not

Table 1 Keywords and keyword combinations used to screen the PubMed, Scopus, PsycINFO and Web of Science electronic databases

Food AND (crav* OR 'food Craving Inventory' OR FCI OR 'Food craving questionnaire' OR FCQ OR 'Food chocolate craving questionnaire' OR FCCQ OR 'Orientation to chocolate Questionnaire' OR OCQ OR ' Questionnaire on craving for sweet or Rich Foods' OR QCSRF) AND (calori* OR energy exp OR diet OR 'low calorie' OR 'low carbohydrate' OR 'low glycemic' OR 'low fat' OR 'weight loss' OR 'loss of weight' OR 'weight reduction' OR 'reduction of weight')

have at least one pure dietary calorie restriction intervention arm were excluded. Because a typical calorie restriction intervention lasts for at least 12 weeks, the studies that were shorter than 12 weeks in duration were excluded in the final stage of screening. One author (C. N. K.) reviewed all the publications to make the decisions regarding inclusion/exclusion based on the criteria. Ambiguous cases were discussed with the senior authors (J. A. D. and M. B.) before final decisions were made.

Risk of bias assessment in individual studies

Individual studies that met the eligibility criteria were evaluated for the risk of bias using the methods in the Cochrane Handbook (20). Each study was evaluated for each of the following criteria: random sequence generation, allocation concealment, blinding of outcome assessments, completeness of outcome data and selective reporting.

Data extraction and cleaning

First, data were extracted from the papers that survived screening for eligibility into pre-defined data fields. When a study was composed of multiple study arms, they were entered into the database as separate investigations, given that a dietary calorie restriction intervention of at least 12 weeks was implemented in each study arm. When food cravings were measured at multiple time points within a given study, the time point that was closest to 16 weeks, but was greater than 12 weeks, was used as the post-intervention time point. The database was compared with original sources to ensure accuracy.

When required information was missing, potential sources of such information (e.g. supplementary tables and figures, protocol papers and dissertations) were identified and examined in order to extract such data. Corresponding authors of three publications were contacted to obtain additional information related to the published studies and useful de-identified summary statistics of the analyses that were not reported in the original manuscripts.

Missing post-intervention versus pre-intervention change score standard deviations that could not be calculated or obtained from the authors were imputed from the marginal standard deviations using the method from the Cochrane Handbook, conservatively assuming that pre–post correlations of 0.25 for all pre–post Likert measures (20). As most of the publications that survived the screening protocol used the FCI to measure overall food cravings and cravings for certain categories of food (e.g. sweet food, high-fat food, starchy food, fast food and fruits and vegetables), studies that did not use FCI or an equivalent scale to measure food cravings were excluded from the meta-analysis. Overall and specific food cravings measured using alternative yet comparable scales to FCI and the respective standard deviations of the change scores were converted to a 1–5 scale.

Outcome measures

Pooled effect sizes for the post-intervention versus pre-intervention changes in overall food cravings and cravings for sweet food, high-fat food, starchy food, fast food and fruits and vegetables as measured by the FCI or an equivalent scale (converted to a 5-point scale as described earlier) were examined in the meta-analyses and subsequent meta-regression analyses as the primary outcome variables.

Meta-analyses and meta-regression analyses

Multiple DerSimonian–Laird random-effects meta-analyses (21) were performed on the completed database using the 'metafor' package in R statistical software (version 3.2.5) to examine whether pooled effect sizes for the post-intervention versus pre-intervention changes in overall food cravings and cravings for sweet food, high-fat food, starchy food, fast food and fruits and vegetables significantly differed from zero (i.e. no effect) (22). In an attempt to explain the heterogeneity of the outcomes, *post hoc* exploratory meta-regression analyses were performed controlling for the (i) baseline body weight (individuals with a higher baseline body weight tend to have a higher energy deficit when a constant reduced calorie level is prescribed; including baseline body weight was included to account for this heterogeneity in energy deficits); (ii) limited exposure to a certain category of food during the intervention (e.g. low-carbohydrate diets; low-fat diets) as compared with reduction of overall caloric intake via consumption of typical food (limiting exposure to a certain category of food is a potential source of heterogeneity in calorie restriction interventions); (iii) sample size of each study arm (studies with higher sample sizes are likely to have narrower standard errors and 95% confidence intervals; including sample size as an explanatory variable accounts for this variability in standard errors); (iv) percentage of female subjects (in calorie restriction interventions men and women differ based on their weight loss and loss of fat mass; they are also likely to show differential psychological and neurophysiological responses to calorie restriction); (v) percentage of individuals with type II diabetes mellitus (individuals with type II diabetes mellitus are known to show differential neurophysiological responses to food cues compared with otherwise healthy individuals; this may be a potential source of heterogeneity in food craving-related outcomes); (vi) duration of the intervention (durations of the included study arms ranged from 12 to 56 weeks; this was considered as a potential source of heterogeneity); (vii) change in body weight during the intervention (change in body weight was included as a

surrogate of the energy deficit and the level of adherence to the interventions); and (viii) mean age of the subjects (as variability of age could be a potential source of heterogeneity, age was included as a covariate). Multiple combinations of the aforementioned control variables were tested until at least 90% of the residual variance of the meta-analyses were explained by combinations of control variables.

Results

The outcomes of the initial database search and subsequent screening are summarized in a PRISMA flow chart (Fig. 1). All of the included studies recruited adults with obesity, implemented dietary calorie restriction interventions and examined food cravings at the baseline and following at least 12 weeks of the intervention. However, the interventions were substantially heterogeneous. For instance, subjects in some study arms were instructed and provided resources to restrict their energy intake by a certain number of calories (23–25) or by a percentage of their estimated energy intake (18), while participants of other studies were given a specific type of a diet to follow (e.g. low fat (17,24), low carbohydrate (17,19), high carbohydrate and protein (19) and vegetarian (24)) in addition to restricting their overall energy intake. The energy deficit also varied from low-calorie diets (15–19,23–25) to very-low-calorie diets (15,16). Female subjects outnumbered male subjects in all studies that reported the male : female ratio. Characteristics of the studies that survived the eligibility assessment protocol and were included in the meta-analysis are summarized in Table 2.

The outcomes of the risk of bias assessment of the studies that met eligibility and were included in the meta-analysis

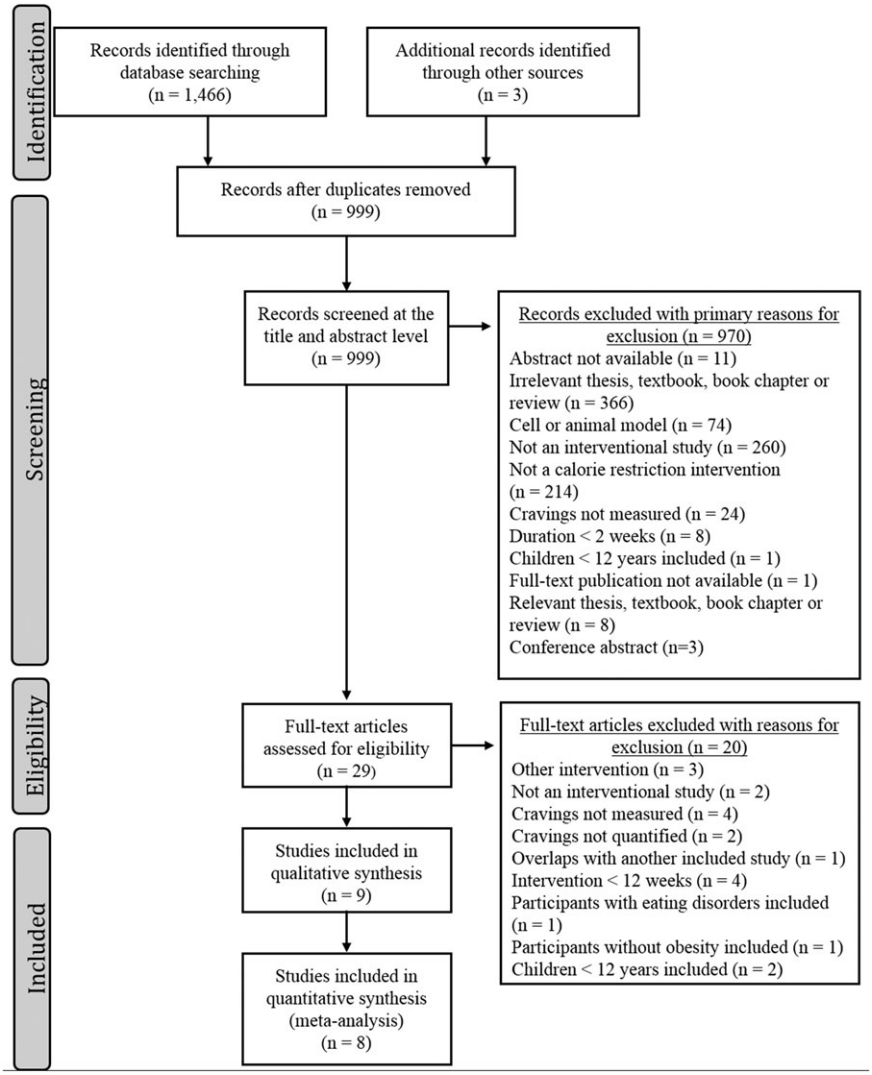

Figure 1 PRISMA flow chart of publication selection for the meta-analysis.

Table 2 Characteristics of the eight studies and their study arms that survived the screening protocol

	Group [*n*]	Participant characteristics (baseline)				Dietary intervention	Instructions regarding physical activity	Measure of food cravings	Duration (weeks) [completers]	Limited intake of specific type(s) of food
		Age (years)	F (%)	DM (%)	Weight (kg)					
Anton et al. (2012) (23)	Overall [811]	51.0 ± 9.0	63.5	0	93.0 ± 16.0	Subjects were randomly assigned to one of four diets: (i) LF (20% of energy) average protein (15% of energy); (ii) LF high protein (25% of energy); (iii) moderate fat (40% of energy) average protein; (iv) moderate fat high protein. Each diet caused a 750 kcal d^{-1} deficit from baseline energy requirement. Craving data of all subjects were pooled and analysed.	Not mentioned	FCI	26 [645]‡	Yes
Barnard et al. (2009) (24)	LF vegan [49]	56.7 ± ?	55.1	100	97.0 ± 22.9	Avoid high-fat food; vegetarian (10% energy from fat; 15% from protein; 75% from carbohydrate).	Same level as baseline	FCI	22 [47]* 74 [36]*	Yes
	ADA diet [50]	54.6 ± ?	66.0	100	99.3 ± 21.0	500–1,000 kcal d^{-1} deficit as per ADA 2003 guidelines (15–20% energy from protein; <7% from saturated fat; 60–70% from carbohydrate and monounsaturated fat).	Same level as baseline	FCI	22 [44]* 74 [41]*	Yes
Batra et al. (2013) (40)	Behaviour [94]	49.1 ± 10.1	73.0	?	94.5 ± 21.9	Used portion-size controlled menus to reduce energy intake (26% protein; 26% fat; 48% low glycaemic index carbohydrate) targeting a weight loss of 0.5–1 kg $week^{-1}$.	Not mentioned	FCI FCQ-T	26 [74]*	No
Greenway et al. (2010) (25)	Control [581]	43.7 ± 11.1	85.0	0	99.5 ± 14.3	Subjects were instructed at 12-weekly intervals to maintain a 500 kcal d^{-1} deficit based on WHO algorithm for calculating resting metabolic rate. Adherence was not assessed.	Generally instructed to increase (non-specific; adherence was not assessed)	COEQ	8 [511]† 56 [511]†	No

(*Continues*)

Table 2 (Continued)

	Group [*n*]	Participant characteristics (baseline)				Dietary intervention	Instructions regarding physical activity	Measure of food cravings	Duration (weeks) [completers]	Limited intake of specific type(s) of food
		Age (years)	F (%)	DM (%)	Weight (kg)					
Harvey et al. (1993) (15)	LCD [48]	52.0 ± 8.7	61.9	100	107.6 ± 19.1	1,000–1,200 kcal d^{-1} self-selected balanced diet (≤30% energy from fat; 55–60% from carbohydrate; 10–15% from protein as per ADA 1987 guidelines).	Not mentioned	Study specific	7 [42]* 13 [42]*	No
	VLCD [45]	53.6 ± 10.2	68.4	100	103.2 ± 16.6	400–500 kcal d^{-1} diet composed of lean meat, fish or fowl and an occasional liquid protein meal supplement.	Not mentioned	Study specific	7 [38]* 13 [38]*	Yes
Jakubowicz et al. (2012) (19)	HCb [96]	45.7 ± ?	59.4	0	91.2 ± 9.8	M: 1,600 kcal d^{-1}; F: 1,400 kcal d^{-1} by consumption of a 600 kcal high-carbohydrate-containing and high-protein-containing breakfast. Energy intake was monitored via self-completed check lists.	Same level as baseline	FCI	16 [87] ‡	No
	LCb [97]	46.5 ± ?	59.8	0	90.4 ± 9.2	M: 1,600 kcal d^{-1}; F: 1,400 kcal d^{-1} by consumption of a 300 kcal low-carbohydrate-containing breakfast. Energy intake was monitored via self-completed check lists.	Same level as baseline	FCI	16 [85]‡	Yes
Martin et al. (2006) (16)	LCD [39]	46.7 ± 12.6	76.9	?	96.5 ± 22.5	1,200 kcal d^{-1} composed of self-selected typical food (50% energy from carbohydrate; 20% from protein; 30% from fat).	Not mentioned	FCI	12 [19]*	No
	VLCD [59]	44.2 ± 11.1	74.5	?	123.1 ± 25.6	800 kcal d^{-1} via consumption of five standard meal replacement shakes per day composed of 80 g protein, 10 g fat and 97 g carbohydrate.	Not mentioned	FCI	6 [?] 12 [39]*	Yes
Martin et al. (2011) (17)	LC [153]	45.8 ± 9.3	68.4	?	103.7 ± 15.2	Limiting carbohydrate intake to <20 g d^{-1}	Not mentioned	FCI	13 [134]† 26 [134]†	Yes

(*Continues*)

Table 2 (Continued)

Group [*n*]	Participant characteristics (baseline)				Dietary intervention	Instructions regarding physical activity	Measure of food cravings	Duration (weeks) [completers]	Limited intake of specific type(s) of food
	Age (years)	F (%)	DM (%)	Weight (kg)					
					by consuming low-glycaemic-index vegetables.				
LF [154]	44.6 ± 10.2	67.2	?	103.4 ± 14.4	M: 1,500–1,800 kcal d^{-1}; F: 1,200–1,500 kcal d^{-1} (30% energy from fat; 15% from protein; 55% from carbohydrate).	Not mentioned	FCI	13 [136]† 26 [136]†	Yes

*Statistics used for the meta-analysis are from completers-only analyses.
†Statistics used for the meta-analysis are from intention-to-treat analyses where last observations of subjects who completed at least one post-intervention time point were carried forward (the number shown as completers is the number of subjects who completed at least one post-intervention time point).
‡Statistics used for the meta-analysis are from intention-to-treat analyses where the last observation was carried forward from the entire sample (the number shown as completers is the number of subjects who actually completed the respective time point).
?, data not available; ADA, American Diabetes Association; COEQ, Control of Eating Questionnaire; DM, subjects with type II diabetes mellitus; F, female; FCI, Food Craving Inventory; FCQ-T, Food Craving Questionnaire – trait version; HCb, high carbohydrate and protein breakfast; LC, low carbohydrate; LCb, low-carbohydrate breakfast; LCD, low-calorie diet; LF, low fat; *n*, sample size; VLCD, very-low-calorie diet.

are summarized in Table 3. Given that the current meta-analysis aimed to examine the post-intervention versus pre-intervention changes in food cravings within eligible study groups (rather than comparing with a control group), the influences of biases associated with random sequence generation, allocation concealment, blinding of participants and blinding of outcome assessments on the pooled outcomes were minimal. Completers-only analysis of food cravings was a potential risk of bias in four studies.

Six out of the nine studies that survived the screening protocol used the FCI to measure food cravings. In the FCI, subjects rated the frequency of development of food cravings to items of food categorized under six subscales on a 1–5 Likert scale: overall food cravings, and cravings for sweet food, high-fat food, starchy food, fast food, and fruits and vegetables. One study (15) used a study-specific questionnaire that examined the frequency of development of cravings for different categories of food on separate 1–5 Likert scales. Two subscales of the questionnaire used in the study represented cravings for high-fat food and starchy food. Given that the FCI also used 1–5 Likert scales to measure food cravings, the means and standard deviations of change in cravings in the aforementioned two categories during the calorie restriction interventions implemented in the study were used in the meta-analysis. Another study (25) used the Control of Eating Questionnaire, which measured the frequency of development of cravings for food with categories that were equivalent to cravings for sweet food, starchy food, fast food and fruits and vegetables on separate 0- to 100-mm visual analogue scales. Means and standard deviations of changes in food cravings for the aforementioned categories of food during the calorie

Table 3 Summary of risk of bias assessment of the studies included in the qualitative synthesis

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of outcome assessments (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)
Anton et al. (2012) (23)	?	+	+	+	+
Barnard et al. (2009) (24)	+	+	+	+	+
Batra et al. (2013) (40)	–	+	+	–	+
Greenway et al. (2010) (25)	+	+	+	+	+
Harvey et al. (1993) (15)	?	?	+	–	+
Jakubowicz et al. (2012) (19)	?	?	+	+	+
Martin et al. (2006) (16)	–	–	+	–	+
Martin et al. (2011) (17)	+	+	+	+	+

–, high risk of bias; ?, unclear risk of bias; +, low risk of bias.

restriction intervention in the study were therefore converted to a 1–5 scale that was comparable with the FCI using the following formula: 5-point scale = 1 + (0–100 mm scale/25). The remaining study (18) had to be excluded from the meta-analysis owing to the inability to convert the measurements of food cravings into scales comparable with the 1–5 Likert scale used in the FCI to measure frequency of development of cravings for sweet food, high-fat food, starchy food, fast food, fruits and vegetables and overall food cravings. The final cleaned database created from the eight studies included changes in overall food cravings (10 study arms) and changes in cravings for sweet food (11 study arms), high-fat food (23 study arms), starchy food (13 study arms), fast food (11 study arms) and fruits and vegetables (4 study arms).

Most studies and study arms that examined the effects of dietary calorie restriction on overall food cravings found a significant reduction compared with the baseline (Fig. 2a). Accordingly, the meta-analysis also revealed a significant reduction of overall food cravings compared with the baseline (–0.246 [–0.490, –0.001]). A similar reduction of cravings for sweet food (Fig. 2b; –0.410 [–0.626, –0.194]), high-fat food (Fig. 2c; –0.190 [–0.343, –0.037]), starchy food (Fig. 2d; –0.288 [–0.517, –0.058]) and fast food (Fig. 2e; –0.340 [–0.633, –0.048]) were seen in the meta-analysis. Cravings for fruits and vegetables did not significantly differ from zero in the meta-analysis conducted using the outcomes of four study arms (Fig. 2f; –0.038 [–0.350, 0.274]). Funnel plots created for overall food cravings and cravings for specific types of food (Fig. 3a–f) indicated that the study arms were heterogeneous. This was substantiated further by very high Higgins' I^2 statistics associated with all forms of food cravings (Fig. 2a–f) (26). However, on subsequent meta-regression analyses, combinations of pre-determined modifier variables completely (i.e. 100%) explained the residual variance in the meta-analyses conducted for overall food cravings and cravings for sweet food, starchy food, fast food and fruits and vegetables (Table 4). Modifier variables accounted for 96.5% of the residual variance in the meta-analysis conducted for cravings for high-fat food.

Visual examination of the funnel plots did not reveal evidence of publication bias (Fig. 3a–f). However, exploration of the models using the trim-and-fill method (27,28) revealed the possibility of missingness of one study with an effect size of 0.28 [–0.01, 0.57] for change in cravings for high-fat food (Fig. 3c); two studies with effect sizes of 0.23 [0.15, 0.30] and 0.27 [0.01, 0.52] for change in cravings for starchy food (Fig. 3d); and one study with an effect size of –0.46 [–0.59, –0.33] for cravings for fruits and vegetables (Fig. 3f). Meta-analyses conducted after including these estimated effect sizes of potentially missing studies revealed that pooled effects for changes in cravings for high-fat food and starchy food were still significantly lower than zero (–0.16 [–0.31, –0.01] and –0.22 [–0.42, –0.01]). Inclusion of the estimated effect size of a potentially missing study examining changes in cravings for fruits and vegetables did not result in a significant difference from zero (–0.12 [–0.40, 0.16]). Trim-and-fill test did not reveal evidence of publication bias in relation to change in overall food cravings or cravings for sweet food and fast food.

Discussion

Our meta-analysis indicated that calorie restriction for periods extending at least 12 weeks is associated with reductions in measures of overall food cravings and cravings for sweet food, high-fat food, starchy food and fast food, with the interventions invariably causing an energy deficit. Therefore, our findings do not support the notion that food cravings occur owing to a deficiency of energy or nutrients (9). Specifically, if the deficit theory were to hold true, one would expect to see increased craving resulting from extended caloric restriction.

Our results do however support the alternate explanation that craving develops as a result of a conditioned association between repeated consumption of a specific type of food with a particular stimulus, environment or an occasion (i.e. classical conditioning) (11). According to this theoretical perspective, subsequent exposure to the conditioned stimulus is thought to trigger food cravings. Thus, uncoupling the association between the consumption of the craved item of food and the stimulus would lead to suppression of overall food cravings. Dietary calorie restriction interventions largely limit the consumption of energy-dense food, while maintaining exposure to the stimuli, environments and occasions that were previously associated with consumption of specific types of food. Dissociation of consumption of food and associated stimuli could be a mechanism through which extended calorie restriction results in reductions of overall food cravings and cravings for energy-dense food. However, it should be noted that a food craving is likely a complex bio-psycho-social phenomenon that cannot be fully explained using a simple psychological model alone. Therefore, while our findings suggest that classical conditioning may be playing an important role in the development of food cravings, we note that the current focus of the literature is somewhat narrow and emphasize the need to examine other potential etiological and mechanistic influences (e.g. neurophysiological) to better understand this complex phenomenon.

While evidence regarding the effects of extended calorie restriction on neurophysiological mechanisms that regulate human ingestive behaviour is limited (29), there are some parallels that can be drawn. Neuroimaging studies conducted for varied purposes that were able to indirectly

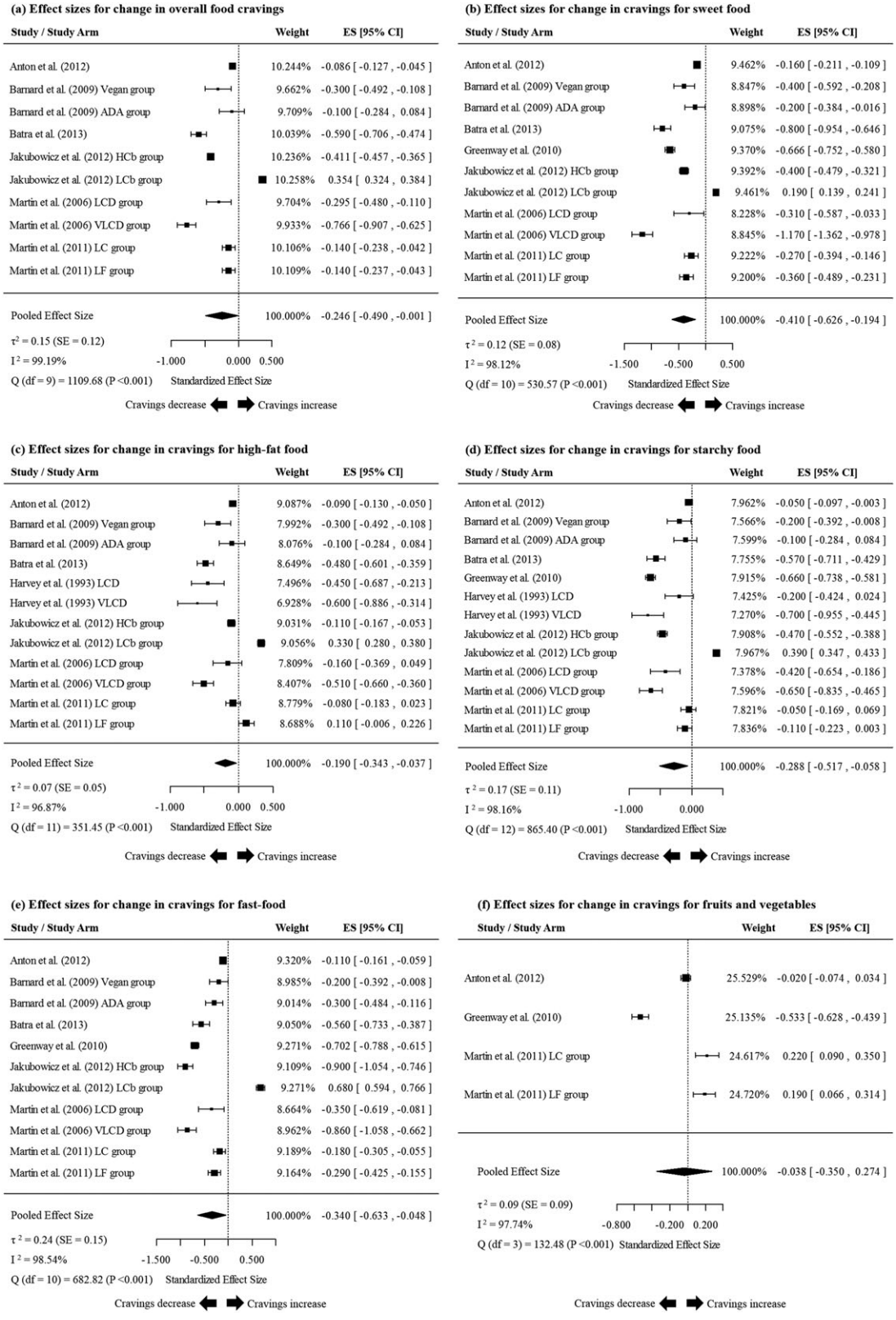

Figure 2 Results of the meta-analyses examining the pooled changes in (a) overall food cravings, (b) cravings for sweet food, (c) cravings for high-fat food, (d) cravings for starchy food, (e) cravings for fast food and (f) cravings for fruits and vegetables during extended calorie restriction interventions.

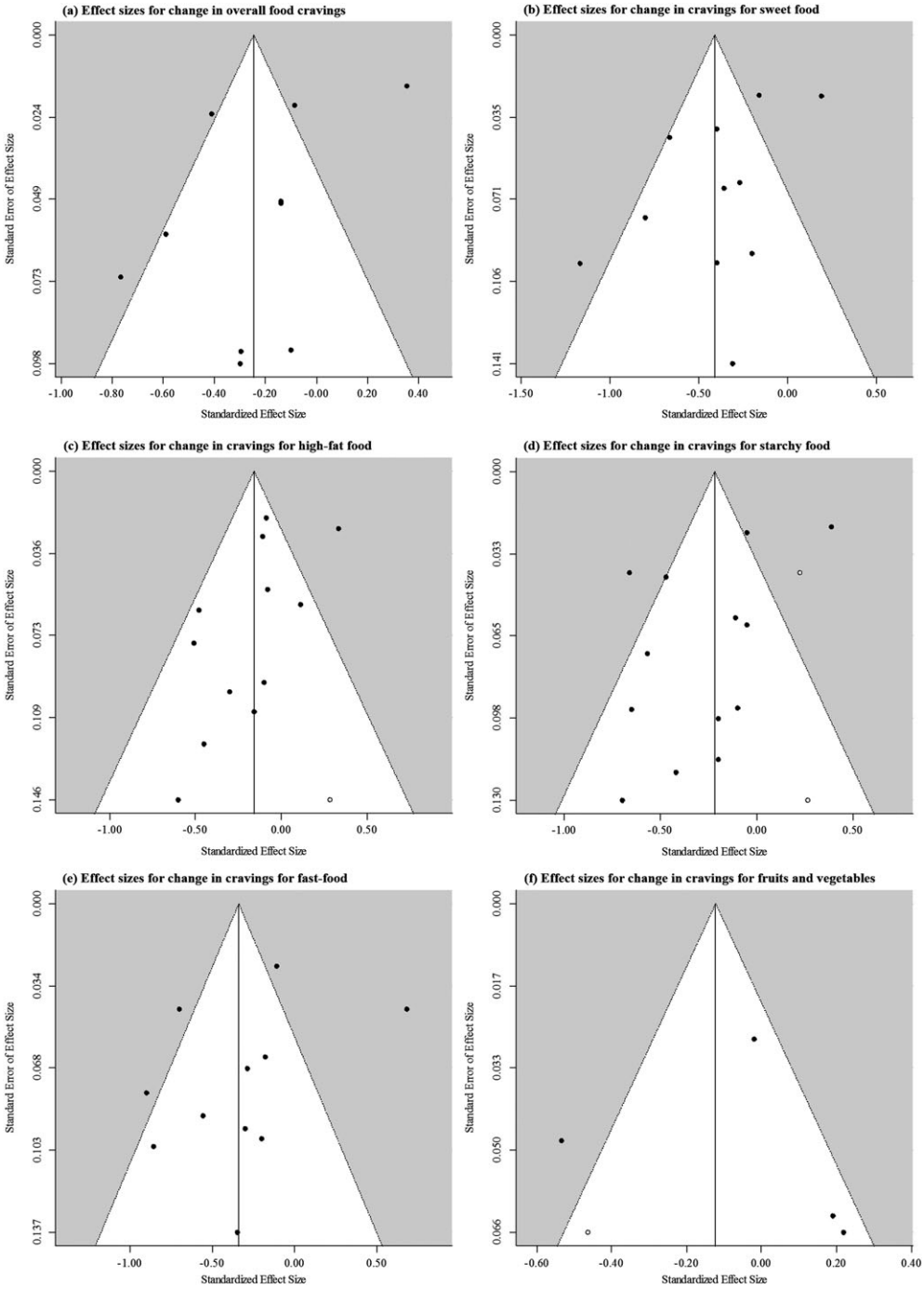

Figure 3 Funnel plots indicating the relationship between the effect sizes and standard errors of effect sizes of individual studies included in the meta-analyses examining the pooled changes in (a) overall food cravings, (b) cravings for sweet food, (c) cravings for high-fat food, (d) cravings for starchy food, (e) cravings for fast food and (f) cravings for fruits and vegetables during extended calorie restriction interventions. Shaded data points indicate effect sizes of observed studies. Unshaded data points indicate the effect sizes of potentially missing studies as determined by the trim-and-fill method.

examine this question indicate that extended calorie restriction may suppress food-cue reactivity of brain regions that regulate food reward (30–32) and are by extension often thought to be a neurophysiological surrogate for 'craving'. Similarly, regions that are often thought to 'suppress food cravings' show enhanced food-cue reactivity indicating increased executive inhibitory control over drives towards ingestion (30) (i.e. craving suppression). This enhancement of executive inhibitory control with a concurrent suppression of food reward provides a biological

Table 4 Results of the best-fitting models in the meta-regression analyses

Modifier	Estimate	SE	Z	P
Change in effect sizes of overall food cravings				
Intercept	2.621	0.180	14.668	1.035×10^{-48}
Baseline weight (kg)	−0.043	0.003	−15.605	6.757×10^{-55}
LI	0.707	0.026	27.381	4.675×10^{-165}
Sample size	−0.001	<0.001	−13.979	2.091×10^{-44}
Female (%)	0.016	0.004	3.654	2.585×10^{-04}
I^2 = 0.00%; R^2 = 100%; τ^2 = 0.00				
Change in effect sizes of for sweet food				
Intercept	3.151	0.227	12.873	9.286×10^{-44}
Baseline weight (kg)	−0.050	0.003	−15.229	2.277×10^{-52}
LI	0.564	0.043	13.141	1.910×10^{-39}
Sample size	−0.001	<0.001	−5.653	1.577×10^{-08}
Female (%)	0.019	0.004	4.939	7.866×10^{-07}
Duration (weeks)	−0.004	0.003	−1.723	8.494×10^{-02}
I^2 = 0.00%; R^2 = 100%; τ^2 = 0.00				
Change in effect sizes of high-fat food				
Intercept	3.016	0.356	8.474	2.377×10^{-17}
Baseline weight (kg)	−0.029	0.003	−9.381	6.556×10^{-21}
LI	0.3918	0.053	7.361	1.825×10^{-13}
Duration (weeks)	−0.030	0.005	−5.629	1.811×10^{-08}
Weight change (kg)	−0.003	0.006	−0.506	6.128×10^{-01}
I^2 = 39.02%; R^2 = 96.51%; τ^2 = 0.0021				
Change in effect sizes of starchy food				
Intercept	2.362	0.272	8.698	3.388×10^{-18}
Baseline weight (kg)	−0.036	0.003	−12.962	1.998×10^{-38}
LI	0.786	0.040	19.764	6.043×10^{-87}
Sample size	−0.001	<0.001	−6.783	1.178×10^{-11}
Female (%)	0.007	0.003	2.560	1.048×10^{-02}
Weight change (kg)	−0.009	0.004	−1.977	4.800×10^{-02}
I^2 = 0.00%; R^2 = 100%; τ^2 = 0.00				
Change in effect sizes of fast food				
Intercept	−9.286	1.296	−7.163	7.889×10^{-13}
Baseline weight (kg)	0.094	0.014	6.893	5.470×10^{-12}
LI	1.638	0.098	16.758	4.937×10^{-63}
Sample size	−0.001	<0.001	−14.652	1.313×10^{-48}
Subjects with DM (%)	-0.020	0.002	−11.116	1.043×10^{-28}
I^2 = 0.00%; R^2 = 100%; τ^2 = 0.00				
Change in effect sizes of fast food				
Intercept	0.426	0.048	8.851	8.701×10^{-19}
Duration (weeks)	−0.017	0.002	−11.505	1.240×10^{-30}
I^2 = 0.00%; R^2 = 100%; τ^2 = 0.00				

DM, diabetes mellitus; LI, limited intake of specific type(s) of food; SE, standard error.

rationale for the behavioural outcomes we have compiled in the present meta-analysis. While this is currently an evidence-based theoretical proposition, direct evidence from studies specifically designed to test this theory could further substantiate this conjecture.

In the meta-regression analyses, many explanatory variables were negatively associated with change in post-intervention versus pre-intervention food cravings, indicating that as each explanatory variable increased numerically, a greater reduction of cravings could be expected (Table 4). First, the meta-regression models predicted that as the baseline weight increased, a greater reduction in overall food cravings and cravings for sweet food, high-fat food and starchy food could be expected. Thus, the models suggest that extended calorie restriction may be more effective in suppressing food cravings in individuals with higher body weights. However, the association between initial body weight and change in cravings for fast food indicated that cravings for fast food seem to decrease to a lesser extent in individuals with a higher baseline body weight during a calorie restriction intervention. This unexpected finding needs further exploration. Second, the meta-regression models suggested that as the duration of intervention increased, the reduction in cravings for sweet food, high-fat food and fruits and vegetables was greater. As increased intervention durations could lead to the dissociation of consumption of craved food and associated stimuli to a greater extent, this finding further substantiates the theory that food cravings may be a conditioned response. Furthermore, this finding suggests that increasing the duration of a calorie restriction intervention may be an effective strategy for suppressing food cravings in individuals with obesity. Third, limited exposure to a particular type of food (e.g. low-fat diet and low-carbohydrate diet) was found to be decreasing the magnitude of reduction in overall and all specific forms of cravings, except for cravings for fruits and vegetables. Thus, limiting intake of a specific category of food during calorie restriction intervention may be counterproductive in reducing food cravings. When a calorie restriction intervention aims to decrease the overall calorie consumption via reduction of intake of a specific category

of food, it is likely to increase exposure to other categories of food. However, if the calorie restriction intervention does not target a specific category of food, it is more likely to reduce exposure to all categories of food. This greater reduction of exposure to food stimuli may explain the fact that interventions that did not aim to reduce consumption of a specific category of food were more successful in suppressing food cravings. This too is consistent with the classical conditioning theory of food cravings. Fourth, as the percentage of female subjects in a study increased, the magnitude of reduction in overall food cravings and cravings for sweet food and starchy food decreased. Thus, extended calorie restriction appears to be less effective in female subjects in reducing overall food cravings and cravings for sweet and starchy food. While this phenomenon needs further exploration in a well-controlled prospective clinical trial, our preliminary finding suggests the need to augment calorie restriction interventions prescribed to women with obesity with other forms of behavioural and psychological interventions (e.g. targeted cognitive behavioural interventions) to enhance craving management. While there was some heterogeneity in specific subgroups (e.g. women), overall, we did not observe a significant association between the change in body weight and the change in any form of food cravings. Thus, weight loss *per se* and possibly the associated reductions in adipose tissue appear not to be associated with the reductions of food cravings seen in extended calorie restriction interventions. Taken together, our meta-regression analyses indicated that having a higher baseline body weight, engaging in a longer calorie restriction intervention and not limiting exposure to specific categories of food and male gender but not weight loss *per se* are associated with achieving a greater reduction in food cravings during extended calorie restriction interventions.

Our findings address a common concern among clinicians who manage obesity; specifically, the worry that prescribing calorie restriction interventions could increase food cravings, thus reducing adherence to the prescribed regimes and increasing the risk of weight cycling (14,33,34). Our meta-analysis establishes empirically that prescribed calorie restriction interventions are associated with suppression of overall food cravings and cravings for specific categories of food such as sweet food, high-fat food and starchy food, suggesting that these concerns are likely unfounded. Furthermore, our findings indicate that increased food cravings do not appear to be a mechanism leading to the high failure rates observed in calorie restriction interventions targeting weight loss and weight loss maintenance.

While our meta-analysis answered the question whether extended calorie restriction suppresses food cravings in individuals with obesity, several questions regarding the effects of extended calorie restriction and food cravings remain unanswered. First, there is some evidence to suggest that extended calorie restriction is also associated with a reduction in hunger (35,36), while other interventional studies have shown that calorie restriction may have no effect on hunger (37). In this meta-analysis, we only examined the effects of calorie restriction on food cravings, which differs from hunger by definition. While it has been observed in clinical settings that individuals with food cravings tend to misunderstand food cravings as hunger and as such tend to give in to food cravings (2), future systematic reviews and meta-analyses should be aimed at examining the effects of extended calorie restriction on self-reported hunger. Third, we do not have a clear understanding of the effects of extended calorie restriction on the ability of an individual to resist food cravings as compared with giving in to food cravings. There is limited evidence to suggest that extended calorie restriction may be associated with a decreased frequency of giving in to food cravings (18). Few other studies have demonstrated that extended calorie restriction appear to increase dietary restraint in individual with obesity (24,38). Thus, future studies should examine the effects of extended calorie restriction on the proportion of instances where cravings are resisted by individuals who develop cravings. Furthermore, effects of extended calorie restriction on dietary restraint need to be elucidated.

The literature that was evaluated in the present systematic review and meta-analysis had some limitations. First, the included studies were heterogeneous in the types of dietary interventions, subject characteristics and durations. Despite this heterogeneity, the effect-size estimates of most studies and the pooled effect sizes clearly indicated reductions in food cravings along with calorie restriction interventions. Second, the scales used to measure food cravings were heterogeneous. However, we were able to convert several scales into a common 5-point scale to pool their outcomes in the meta-analysis. Third, food cravings was a secondary or a minor outcome in most of the studies. Fourth, data regarding actual energy intake during the intervention periods were not available in almost all studies. Thus, the results of the meta-analysis only indicated the outcomes of prescription of calorie restriction interventions. Fifth, sample characteristics of the studies that met the eligibility criteria (e.g. body weight and percentage of females) were restricted, limiting the ranges of the control variables included in the meta-regression models, thus limiting the generalizability of the outcomes of the meta-regression models. Moreover, several studies did not report the change scores of food cravings and the standard deviations of change scores. Partly owing to the limitations in the literature that was reviewed, the meta-analysis also had some limitations. The effect sizes were not necessarily independent, as some of the effect sizes were derived from studies and study arms conducted by the same groups of

investigators. We also did not have access to individual level data. Finally, even though food cravings are not limited to individuals with obesity (1,2,39), given that our systematic review and meta-analysis focused on the effects of calorie restriction on food cravings in a specific clinical population (i.e. individuals with obesity), our findings cannot be generalized to other populations (e.g. individuals without obesity).

The meta-analysis had several strengths. First, we used a systematic search strategy, which was sensitive in the initial stages and specific in the later scrutinizing stages. Second, when the data were not available, we obtained these missing data from the authors of original manuscripts and imputed missing data using a well-established and conservative approach. Finally, we performed a random-effects rather than a fixed effects meta-analysis; thus we avoided the invalid assumption that the heterogeneous group of studies we analysed had equal effect sizes and variances of effect sizes.

In conclusion, in this systematic review and meta-analysis, we found support for the previous, yet debated, finding of some studies that extended calorie restriction is associated with suppression of overall food cravings and cravings for energy-dense foods. This finding should ease the minds of clinicians who are concerned about increasing food cravings in patients who are prescribed dietary calorie restriction interventions.

Conflict of interest statement

No direct support was received related to the preparation of this manuscript. The Pennington Biomedical Research Center (PBRC)/Louisiana State University owns the FCI, which is one of the instruments used to assess food cravings in some of the studies reviewed in this meta-analysis. The co-author from PBRC (C. K. M.) is not an inventor; nor does he receive royalties from use of the FCI. The authors do not have any other conflicts of interest to declare.

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