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Review

Do ketogenic diets really suppress appetite? A systematic review and meta-analysis

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Summary

Very-low-energy diets (VLEDs) and ketogenic low-carbohydrate diets (KLCDs) are two dietary strategies that have been associated with a suppression of appetite. However, the results of clinical trials investigating the effect of ketogenic diets on appetite are inconsistent. To evaluate quantitatively the effect of ketogenic diets on subjective appetite ratings, we conducted a systematic literature search and meta-analysis of studies that assessed appetite with visual analogue scales before (in energy balance) and during (while in ketosis) adherence to VLED or KLCD. Individuals were less hungry and exhibited greater fullness/satiety while adhering to VLED, and individuals adhering to KLCD were less hungry and had a reduced desire to eat. Although these absolute changes in appetite were small, they occurred within the context of energy restriction, which is known to increase appetite in obese people. Thus, the clinical benefit of a ketogenic diet is in preventing an increase in appetite, despite weight loss, although individuals may indeed feel slightly less hungry (or more full or satisfied). Ketosis appears to provide a plausible explanation for this suppression of appetite. Future studies should investigate the minimum level of ketosis required to achieve appetite suppression during ketogenic weight loss diets, as this could enable inclusion of a greater variety of healthy carbohydrate-containing foods into the diet.

Keywords: Appetite, ketogenic diet, ~~ketosis,~~ low carbohydrate, very-low-energy diet, ~~visual analogue scale.~~

Abbreviations: CCK, cholecystokinin; CHO, carbohydrate; KLCD, ketogenic low-carbohydrate diet; ~~PYY, peptide YY~~; VAS, visual analogue scale; VLED, very-low-energy diet.

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Introduction

Hunger is a major side effect of weight loss attempts, and, if the plethora of over-the-counter weight loss products and diet books claiming that you can 'diet without hunger' is anything to go by, it is also the most profitable. Compensatory increases in hunger (and appetite generally) in response to energy-restricted diets probably contribute to the high rate of attrition in weight loss attempts and the inability of individuals to maintain weight loss (1–4). These compensatory changes in appetite during weight loss are thought to be induced by alterations in expression of hypothalamic regulators of energy balance (5) as well as adaptive changes in gut function, which alter the concentration of appetite-regulating hormones, such as ghrelin (6–9), cholecystokinin (CCK) (8–10) and

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peptide YY (8,9,11). Thus, finding ways to 'block' the compensatory increase in appetite associated with energy-restricted diets represents the 'holy grail' of weight management.

Two dietary strategies that may suppress appetite are very-low-energy diets (VLEDs), which provide less than 3.4 MJ (800 kcal) per day (12), and ketogenic low-carbohydrate diets (KLCDs), which severely restrict dietary carbohydrate intake but allow *ad libitum* consumption of protein and fat. Paradoxically, despite severe energy restriction and rapid weight loss (12), VLEDs are frequently cited in the literature (13–18) and promoted in the lay press (19) as suppressing appetite. The efficacy of KLCDs is also often attributed to a suppression of appetite resulting in spontaneous decrease in energy intake (20–24). However, there is conjecture in the literature regarding whether, and how, VLEDs or KLCDs alter appetite. Studies have reported an increase (25,26), no change (10,17,24,27–30) and/or a decrease (13,14,20,28,31–33) in appetite during adherence to such diets. Thus, there is a need for stronger evidence base before we can conclude that VLEDs or KLCDs really do suppress appetite.

The supposed appetite suppression seen with both VLEDs and KLCDs is often hypothesized to be due to ketosis (15,34–39). Ketosis is a condition where the production of ketone bodies or 'ketones' (β-hydroxybutyrate, acetoacetate and acetone that are produced in the liver by ß-oxidation of free fatty acids) is increased, leading to elevations in their circulating concentrations. Ketosis is a coordinated metabolic response that provides an alternative fuel source derived from fat when glucose is in short supply. The level of circulating ketones is primarily determined by carbohydrate intake and the action of insulin. Modern VLEDs and KLCDs, respectively, provide approximately 40–60 and 20 g (initially) of dietary carbohydrate per day. Although both VLEDs and KLCDs typically result in ketosis, KLCDs can result in several fold higher circulating levels of ketones than VLEDs (20,29). Although ketosis is purported to be responsible for the appetite suppression associated with VLEDs and KLCDs, carbohydrate-restricted diets are counter-intuitive to evidence-based healthy eating guidelines as they involve elimination of whole groups of foods, and in particular those that are beneficial for health and/or weight management (i.e. whole grains, legumes, reduced-fat dairy, fruit) (40–42). Thus, if ketosis is indeed associated with suppression of appetite, it is pertinent to explore at what level of carbohydrate intake and circulating ketone levels this occurs, because such severe restriction of carbohydrate may not be necessary to prevent a compensatory increase in appetite. Indeed, there may be a 'threshold' for an appetite-suppressive effect at lower levels of ketosis (and accordingly a more liberal carbohydrate intake could potentially be allowed in the weight loss diet).

In light of current conjecture about the effect of ketogenic diets on appetite, the fact that VLEDs are frequently used and recommended for the treatment of obesity, as well as renewed interest in high protein, very-low-carbohydrate diets, clinicians and patients need clear, evidence-based information about what actually works for appetite suppression during weight loss interventions. Hence, we conducted a systematic review and meta-analysis to determine the effect of ketogenic diets on appetite. We specifically included dietary intervention studies that employed a within-subject, repeated measure of appetite before (when participants were in energy balance) and during (when participants were in ketosis) adherence to VLED or KLCD. A secondary aim was to use meta-regression to explore whether a dose–response or threshold effect existed between circulating ketone levels and appetite.

Methods

Selection criteria of studies for this review

Studies were included if they assessed subjective ratings of appetite in adults before ('baseline') and during adherence to VLED or KLCD in at least one study arm. We limited studies to those that assessed subjective appetite using visual analogue scale (VAS) questionnaires. VASs are a standardized and validated (43) system of appetite assessment that requires a response to a question such as 'How hungry do you feel now?' to be marked on a line (usually 100 mm in length) anchored at each end with opposing statements such as 'Not at all' and 'Extremely' (44). For inclusion in the meta-analyses, the baseline assessment had to be performed when participants were in energy balance (e.g. had not been on an energy-restricted diet prior to baseline assessment). We included randomized and non-randomized studies, provided that the study employed a within-subject, repeated measure for appetite assessment. The reason for this is that within-subject comparisons of appetite are considered to be more sensitive and accurate than between-subject comparisons (45).

We defined a 'ketogenic' diet as one that raised fasting blood concentrations of β-hydroxybutyrate to ≥0.3 mM (a level that is greater than that induced by an overnight fast ~0.1 mM and that has been associated with appetite suppression [29]), or in which participants tested positive for ketones in the urine using dipsticks. To reduce publication bias, we also included studies that did not measure or report blood or urinary ketone concentrations, but for which it was highly likely that participants were in ketosis. This was determined by comparing the rate of weight loss in the study with rates of weight loss arising from known ketogenic diets in similar populations, as well as considering the prescribed energy and carbohydrate composition of

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the intervention, or the circulating concentration of free fatty acids, which is known to be increased during ketosis. The specific rationale for each study included is detailed in Table S1 in the online supplementary file.

We excluded duplicate studies, studies where the intervention involved pharmacotherapy, if appetite was only assessed at baseline or if appetite was not assessed at baseline.

Search strategy

We searched electronic databases, namely, MEDLINE, PreMEDLINE, PubMed, Embase and PsycINFO, from inception until 13 December 2013 for original human research articles published in English. The reference lists of included studies were also searched. We employed a comprehensive search strategy combining two groups of key words (MeSH terms and/or free text) related to the type of intervention and outcome:

- Low carb* OR Diet, carbohydrate-restricted OR diet, reducing OR very low energy diet OR very low calorie diet OR protein sparing modified fast OR ketogenic diet OR ketogenic OR ketosis OR ketone bodies OR ketones
- Appetite OR hunger OR satiation OR satiety OR desire to eat OR visual analogue scale

Data collection and analysis

Selection of studies

Records were screened independently by two investigators (AAG and JA) at the abstract and title level. The full texts of potentially eligible studies were obtained and these two investigators applied the inclusion and exclusion criteria independently. Discrepancies were resolved by consensus with a third author (RVS).

Data extraction

We developed a data extraction sheet, which was pilot tested and refined accordingly. One author (AAG) extracted the data from all studies and a second author (JA) checked all data entry for accuracy.

Information was extracted from each included study on (i) study characteristics (primary author, year of publication, setting, duration [point of follow-up appetite assessment] and nutritional composition of intervention); (ii) baseline characteristics of the study population (sample size, sex, age, body mass index); (iii) weight loss outcomes; (iv) appetite assessment method and results (aspects [hunger, fullness etc.], time of day, frequency, reference period [i.e. 'present' – how hungry do you feel now; or 'retrospective' – how hungry did you feel today/this week?]), reporting format (i.e. single time point or average of several time points), results (all in mm out of 100); and, if applicable, (v) methodology for assessing ketones and results (type [blood or urine; β-hydroxybutyrate, acetoacetate or acetone], time points, results). Where information was missing, we contacted authors further information.

Data synthesis

In studies that randomized participants after the point in the intervention that was of interest for this meta-analysis, we pooled the intervention groups if they received the same ketogenic intervention up until the relevant time point (i.e. if participants were randomized to a weight maintenance intervention *after* 4–6 weeks on VLED, we were only interested in the data before and while adhering to the VLED) (46–52). One study included multiple ketogenic intervention arms (i.e. VLEDs differing in protein, fat or carbohydrate content), and we included all arms of that study as separate comparisons (53). We only identified two studies that compared a ketogenic diet with a non-ketogenic diet that also met our other inclusion criteria (20,54). However, the non-ketogenic comparison groups in these two studies were too dissimilar to be combined in a meta-analysis, and only one of these studies (20) used participants as their own control. Therefore, we only extracted information from ketogenic interventions and thus, all studies included in this meta-analysis provided data of 'pre-test' vs. 'post-test'.

It was our intention to include the five primary aspects of appetite as recommended by Blundell in 2010; fullness, satiety, hunger, desire to eat and prospective consumption (44). However, due to inconsistencies in terminology and the lack of reporting of questions used to assess these aspects of appetite, we had to make adjustments to the data from some studies. We combined analysis of studies that assessed 'fullness' (20,29,53) and those that assessed 'satiety' (47–52) into a single variable of 'fullness/satiety'. In one study that reported both fullness and satiety (55), we pooled the results into one variable. Although fullness and satiety may measure subtly different aspects of appetite, they are related to each other (43) and would be expected to change in the same direction.

To calculate nutritional composition of interventions a conversion of 17 kJ g^{-1} for protein and carbohydrate and 37 kJ g^{-1} for fat was applied to studies that reported nutritional composition as a percentage of energy. Kilocalories were converted to kJ by multiplying by 4.18. For the duration of intervention, we assumed 1 month to equal 4 weeks.

Data synthesis and analysis

Primary outcomes

The primary outcomes were the weighted mean difference in change in appetite (mm on a 100-mm scale) between baseline (when participants were in energy balance) and during adherence to VLED or KLCD (when participants

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were in ketosis). A random effects model was used to estimate separate effect sizes for fullness/satiety, hunger, desire to eat and prospective consumption. Changes in appetite variables were calculated by subtracting the mean rating measured during adherence to VLED or KLCD from the mean rating measured at baseline, so that the difference (positive or negative) would reflect the direction of change in appetite. For example, a negative difference for hunger and a positive difference for fullness/satiety both represent a decrease in appetite.

Secondary outcome

Meta-regression aims to relate the size of an effect to characteristics (potential 'effect modifiers') of the studies involved (56). Therefore, a secondary outcome was to use meta-regression to determine whether the change in appetite (as calculated above) was associated with the level of ketosis, i.e. whether higher circulating levels of β-hydroxybutyrate resulted in a greater difference in appetite. Meta-regression was to be performed only if heterogeneity was found to be present among studies, as this would indicate whether differences in the effect in each study existed.

Heterogeneity, risk of bias and quality assessment

Heterogeneity between studies was assessed using the I^2 statistic. Egger's test was used to investigate possible publication bias. Statistical significance was set at $P < 0.10$. The usual quality filters for randomized trials or observational epidemiologic studies were not applied to the studies selected for this work, as only 'pre-test' vs. 'post-test' data were assessed.

All statistical analyses were conducted using STATA software version 13.0 (StataCorp, College Station, TX, USA).

Results

Study selection

The systematic search resulted in 26 publications that met the inclusion criteria, 12 of which were included in the meta-analysis (Fig. 1). Fourteen publications were included in the review but were not included in the meta-analysis, nine did not have the required data (13,17,24–26,30,32) and five conducted baseline assessment of appetite when participants were not in energy balance (14,27,28,31,33). These publications excluded from the meta-analysis were reviewed qualitatively.

Characteristics of studies included in the meta-analysis

Interventions

The characteristics of studies included in the meta-analysis ($n = 12$) are shown in Table 1. All but one of these studies

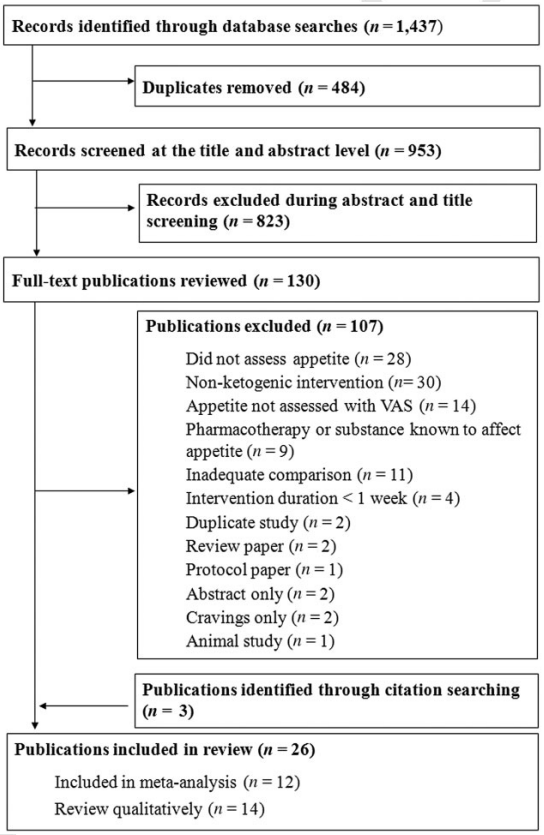

Figure 1 Flowchart of publication selection for the systematic review and meta-analysis. VAS, visual analogue scale.

was conducted entirely in an outpatient setting, with the duration of all the ketogenic interventions ranging from 4 to 12 weeks. The studies used different terminology to describe the interventions, and for consistency the term VLED is used to refer to all interventions providing less than 3.3 MJ (800 kcal) per day, and the term KLCD is used when referring to interventions that restricted carbohydrate intake to <10% of energy or ≤50 g day^{-1}, but that allowed *ad libitum* consumption of energy, protein and fat. Ten studies involved VLED interventions, and they prescribed similar daily intakes of energy (~2.1–2.4 MJ), protein (50–60 g), carbohydrate (45–52 g) and fat (<10 g) (29,30,46–52). There were slight differences in one study that provided varying daily protein (64–97 g), fat (2–23 g) and carbohydrate (28–42 g) intakes in the intervention groups (53). No studies reported the fibre content of the diet. All of the VLED studies allowed additional servings of fruit and vegetables (46,48–52), but more specific information was not reported; therefore, dietary prescriptions reported in Table 1 do not include these allowances. All studies

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Table 1 Characteristics of dietary interventions and participants at baseline, as well as weight loss outcome, in the 12 studies included in the meta-analysis of effects of ketogenic diets on subjective appetite

Study	Prescribed dietary intervention							Characteristics of participants at baseline				Outcome
	Setting	Ketogenic diet type	Duration (weeks)*	Energy (MJ day^{-1})	CHO (g day^{-1})	Protein (g day^{-1})	Fat (g day^{-1})	Sample size	Sex (% F)	Age (mean ± SD or range)	BMI (mean ± SD or range)	Weight loss (kg)*
Diepvens *et al.* (46)†	O	VLED	6	2.1	52	54	8	50	100	40.8 ± 9.5	28.7 ± 2.0	7.7
Hursel and Westerterp-Plantenga (47)†	O	VLED	4	2.1	52	54	8	80	55	44 ± 2	29.6 ± 2.0	7.1
Johnstone *et al.* (20)	I/O‡	KLCD	4	*Ad libitum*	4% of En	*Ad libitum*	*Ad libitum*	17	0	38 ± 10	35.1 ± 3.8	6.3
Kovacs *et al.* (48)†§	O	VLED	4	2.1	52	54	8	104	75	18, 60	29.7 ± 2.6	6.4
Lejeune *et al.* (50)†§	O	VLED	4	2.1	52	54	8	91	NR	18–60	29.4 ± 2.6	6.6
Lejeune *et al.* (49)†	O	VLED	4	2.1	52	54	8	113	NR	18–60	29.4 ± 2.6	6.2
Martin *et al.* (54)**	O	KLCD	12	*Ad libitum*	<20 g	*Ad libitum*	*Ad libitum*	134	67	45.8 ± 9.3	36.1 ± 3.3	9.5
Ratliff *et al.* (55)¶	O	KLCD	12	*Ad libitum*	<10% of En	*Ad libitum*	*Ad libitum*	28	0	40–70	25–37	6.3
Soenen *et al.* (53)†	O	VLED (αlac)	4	~2.4	42	95	2	34	82	18–80	31.7 ± 4.7	5.0
		VLED (SSP)	4	~2.4	43	97	2	25	68		29.9 ± 2.6	5.0
		VLED (SP)	4	~2.4	28	64	23	28	75		32.3 ± 6.1	5.9
Sumithran *et al.* (29)†	O	VLED	8	2.2	45	52	6.9	39	68	54.4 ± 10.9	34.7 ± 3.5	12.5
Westerterp-Platenga *et al.* (51)†§	O	VLED	4	2.1	52	54	8	148	NR	44.2 ± 10.3	29.5 ± 2.6	6.3
Westerterp-Platenga *et al.* (52)†	O	VLED	4	2.1	52	54	8	76	NR	18–60	29.6 ± 2.4	5.9

*At the time of assessment of appetite while on the ketogenic diet.
†Intervention included an allowance of fruit and/or vegetables, and this was not included in the nutritional information shown.
‡Allowed to leave hospital to go to work.
§Nutritional information assumed to be the same as described in Lejeune *et al.* (49).
¶Nutritional information obtained from another reference (77).
**Weight outcomes obtained from another reference (78).
BMI, body mass index; CHO, carbohydrate; En, energy; I, inpatient; KLCD, ketogenic low-carbohydrate diet; NR, not reported; O, outpatient; SD, standard deviation; SP, ••; SSP, ••; VLED, very-low-energy diet.

involving VLED reported average weight losses of greater than 1 kg week^{-1} and most commonly reported a mean weight loss of ~6 kg (range 5.0–12.5 kg) at the time of the appetite assessment. The remaining three studies used KLCD intervention (20,54,55). Although participants were not instructed to restrict their energy intake, it appeared that they did so in all three KLCD studies, as evidenced by mean weight losses of 6.3–9.5 kg. One study was a well-controlled in-patient study, where participants reduced their daily energy intake by 5.4 MJ (20), while the other two did not report energy intake.

Participants

Sample sizes in the different studies ranged from 17 to 148. Where reported, studies had a greater proportion of women than men. Participants in the 12 studies had similar ages (ranging from 30 to 55 years) and were overweight or obese (body mass index ≥25 kg m^{-2}). Information relating to the participants in each study is provided in Table 1.

Appetite methodology

Methods of appetite assessment used in the 12 studies included in this meta-analysis, and the aspects of appetite assessed, are shown in Table 2. The majority of studies ($n = 8$) assessed appetite in the morning in the fasted state. One study also assessed appetite after a standardized meal and reported area under the curve, but only the fasted appetite value was included in the meta-analyses for comparison with the other studies (29). Most VAS questions were asked in reference to the present state (e.g. 'How hungry do you feel now?') ($n = 11$) vs. retrospective enquiry (e.g. 'How hungry were you this week?') ($n = 1$). The results were typically reported in the format of a single time point ($n = 9$) or, depending on the time points at which appetite was assessed, as an average of several time points on the same day ($n = 3$) or over several days ($n = 1$). All studies reported results in mm on a 100-mm scale or cm on a 10-cm scale (which were converted to mm for the current meta-analysis).

Ketones

In studies included in the meta-analysis, ketosis was confirmed through objectively measured blood or urinary parameters. Table 3 shows the levels of β-hydroxybutyrate in the blood of participants at the time of appetite assessment while on the ketogenic diet, in the nine studies in which it was reported. All but one of these studies involved VLEDs, and the prescribed daily carbohydrate intake ranged from 45 to 52 g (not including fruit and vegetable allowances), resulting in similar (~0.5 mM) blood β-hydroxybutyrate levels. Levels of blood β-hydroxybutyrate were several fold higher in the KLCD

Table 2 Protocol for appetite assessment via visual analogue scales in the 12 studies included in the meta-analysis of effects of ketogenic diets on subjective appetite

Study	Aspects of appetite	Time of day	Reference	Reporting format	Assessment time points
Diepvens *et al.* (46)	Hunger	Morning/fasted and at 60, 120, 180 and 240 min after 1 MJ of yoghurt	Present	Average over 4 h (five measurements)	Baseline, week 6
Hursel and Westerterp-Plantenga (47)	Satiety, hunger	Morning/fasted	Present	Single measurement	Baseline, week 4
Johnstone *et al.* (20)	Fullness, hunger, desire to eat, prospective consumption	Hourly during waking hours (08:00–22:00 h)	Present	Average of 15 daily measurements	Daily for 4 weeks
Kovacs *et al.* (48)	Satiety, hunger	Morning/fasted	Present	Single measurement	Baseline, week 4
Lejeune *et al.* (50)	Satiety, hunger	Morning/fasted	Present	Single measurement	Baseline, week 4
Lejeune *et al.* (49)	Satiety, hunger	Morning/fasted	Present	Single measurement	Baseline, week 4
Martin *et al.* (54)	Hunger	NR	Retrospective (1 week)	Single measurement	Baseline, week 12
Ratliff *et al.* (55)	Fullness, satiety, hunger, desire to eat	NR	Present	Average of 5 days	Baseline, week 12
Soenen *et al.* (53)	Fullness, hunger, desire to eat, prospective consumption	Morning/fasted	Present	Single measurement	Baseline, week 4
Sumithran *et al.* (29)	Fullness, hunger, desire to eat, prospective consumption	Morning/fasted	Present	Single measurement	Baseline, week 8
Westerterp-Platenga *et al.* (51)	Satiety, hunger	Morning/fasted	Present	Single measurement	Baseline, week 4
Westerterp-Platenga *et al.* (52)	Satiety, hunger	Morning/fasted	Present	Single measurement	Baseline, week 4

NR, not reported.

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Table 3 Degree of ketosis attained in the nine studies included in the meta-analysis that also reported blood concentrations of β-hydroxybutyrate

Study	Ketogenic diet type	Prescribed CHO intake (g day^{-1})	Time point (weeks)	*n*	β-Hydroxybutyrate mM (mean ± SD)
Diepvens *et al.* (46)*	VLED	52	6	50	0.49 ± 0.38
Hursel and Westerterp-Plantenga (47)*	VLED	52	4	80	0.56 ± 0.24
Johnstone *et al.* (20)	KLCD	22	4	17	1.52 ± 1.64
Kovac *et al.* (48)*	VLED	52	4	104	0.50 ± 0.30
Lejeune *et al.* (50)*	VLED	52	4	91	0.53 ± 0.31
Lejeune *et al.* (49)*	VLED	52	4	113	0.51 ± 0.32
Sumithran *et al.* (29)*	VLED	45	8	39	0.48 ± 0.44
Westerterp-Platenga *et al.* (51)*	VLED	52	4	148	0.50 ± 0.32
Westerterp-Platenga *et al.* (52)*	VLED	52	4	76	0.50 ± 0.08

*Intervention included fruit and/or vegetable allowance, and ~~this~~ was not included in the carbohydrate information shown.
CHO, carbohydrate; KLCD, ketogenic low-carbohydrate diet; SD, standard deviation; VLED, very-low-energy diet.

intervention, in which participants consumed 22 g of carbohydrate per day (20). In the three studies included in the meta-analysis that did not report on blood β-hydroxybutyrate levels, two confirmed ketosis using urinary dipsticks (54,55). In one remaining study (53), ketones were not measured, but the reported increase in circulating free fatty acid concentrations were consistent with those reached during ketosis.

Main findings from the meta-analyses

Very-low-energy diet studies

A forest plot of the nine studies examining the effect of VLED on appetite is depicted in Fig. 2. All of these nine VLED studies assessed fullness/satiety. Individually, there were only four studies that found a significant increase in fullness/satiety. However, when data from all studies were considered in the meta-analysis, overall fullness/satiety increased by 6.5 mm (95% confidence interval [CI]: 4.3, 8.8). All of the VLED studies assessed hunger. Individually, none of these studies found a significant decrease in hunger during adherence to the VLED. When considering all studies in the meta-analysis overall, however, hunger decreased by 2.6 mm (95% CI: −4.9, −0.2). Only two studies assessed desire to eat and prospective consumption, which did not change significantly. No heterogeneity ($I^2 = 0.0\%$) was detected in any of the analyses. Egger's test for publication bias was significant for desire to eat ($P = 0.06$).

Ketogenic low-carbohydrate diet studies

A forest plot of the three studies examining the effect of KLCDs on appetite is depicted in Fig. 3. Only two of the studies assessed fullness/satiety, which did not increase significantly. All three studies assessed hunger, which decreased significantly by 5.5 mm (95% CI: −8.5, −2.5). Two studies assessed desire to eat, which decreased by 8.9 mm (95% CI: −16.0, −1.8). No heterogeneity ($I^2 = 0.0\%$) or publication bias was detected in any of the analyses.

Meta-regression

Meta-regression was not performed as the level of β-hydroxybutyrate was similar among all VLED studies (~0.5 mM) and only one KLCD diet measured β-hydroxybutyrate.

Qualitative evaluation of studies not included in the meta-analysis

Tables S2 and S3 in the online supplementary file provide detailed information on the intervention and participant characteristics, and appetite assessment methodology, respectively, of 14 studies that were excluded from the meta-analysis.

Nine studies (eight VLED, one KLCD) were excluded from the meta-analysis due to unavailability of data in the format used here. Of these, seven studies support the findings of the meta-analysis as they reported a significant decrease (13,32) or no significant change (10,17,24,57) in hunger, and one study reported no change in fasting hunger or satiety but significant decreases in hunger and increases in satiety when measured 2 h post-prandially (30). Two studies did not support the findings of the meta-analysis as they reported significant increases in hunger on VLED. However, in one study the appetite score was an average of scores taken over 2 weeks, which included the first few days on the VLED, in which appetite is known to be increased (25). In the other of these two VLED studies, despite reporting a significant increase in hunger, participants did not exhibit greater energy intake at a breakfast meal (26).

Five studies (all VLEDs) were excluded from the meta-analysis because the baseline assessment of appetite was not conducted under conditions of energy balance,

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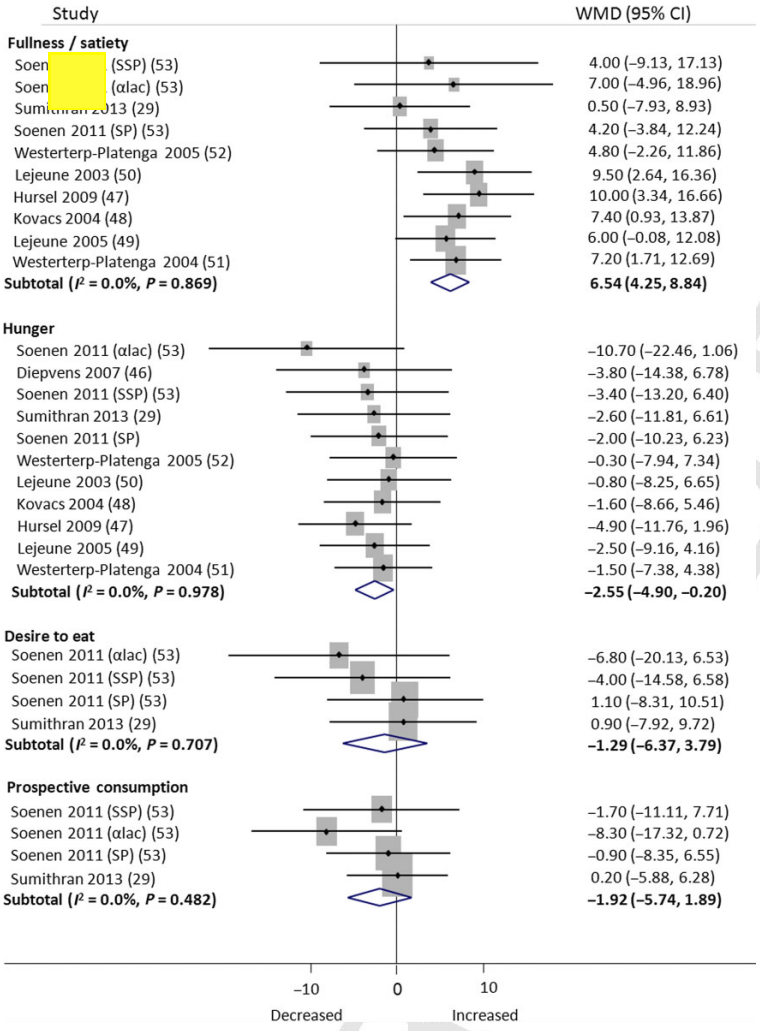

Figure 2 Forest plot of change in appetite assessed with visual analogue scales between baseline and in response to a very-low-energy diet. Eight studies (10 comparisons; n = 738) assessed fullness/satiety, nine studies (11 comparisons; n = 788) assessed hunger, two studies (four comparisons; n = 126) assessed desire to eat and two studies (four comparisons; n = 126) assessed prospective consumption. Plotted values are weighted mean differences (WMD) from a random effects model. Error bars depict 95% confidence intervals (CI). The I^2 statistic refers to heterogeneity.

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but was instead preceded by an energy-restricted diet (14,27,28,31,33). Compared with the baseline assessment of hunger measured during moderate-energy restriction, while adhering to VLED, participants in three studies showed significantly decreased hunger (14,31,33), participants in one study showed no change in hunger (27) and participants in another study on a liquid VLED showed no change in hunger and participants on the food-based VLED showed a significant decrease in hunger (28). That is, in all five of these excluded VLED studies, participants were either less hungry or were no hungrier while on the VLED compared with after the moderately energy-restricted diet. Although these studies are not directly comparable, with those included in the meta-analysis, they support the findings of the meta-analysis by showing that there was no increase in appetite while adhering to VLED.

Discussion

This study showed that individuals are significantly less hungry and exhibit significantly greater fullness/satiety while adhering to VLED compared with when they are in energy balance at baseline. This work also showed that individuals adhering to KLCD are significantly less hungry and have a significantly reduced desire to eat compared with baseline measures. Although the absolute changes in subjective appetite measures during VLED or KLCD may be considered small, and for some aspects of appetite were not significant, the more remarkable finding from this work, from a clinical perspective, is the clear lack of *increase* in hunger despite participants consuming a severely (in the case of VLEDs) or moderately (in the case of KLCDs) energy-restricted diet, and having lost

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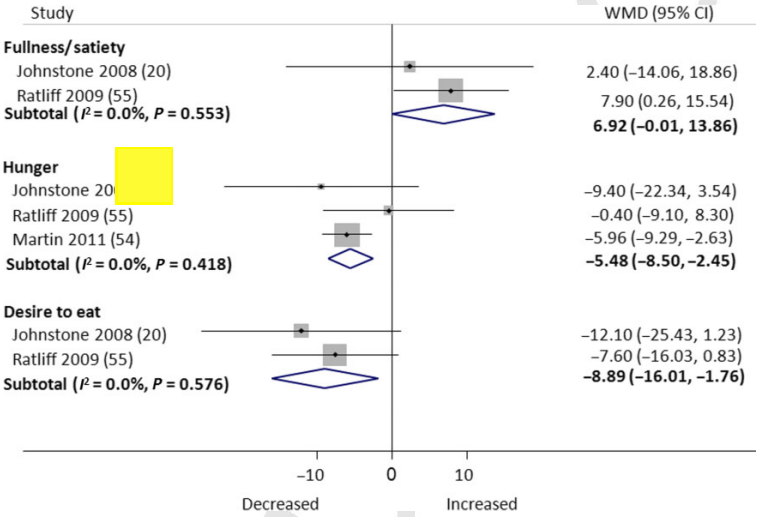

Figure 3 Forest plot of change in appetite assessed with visual analogue scales between baseline and in response to a ketogenic low-carbohydrate diet. Two studies (two comparisons; $n = 45$) assessed fullness/satiety, three studies (three comparisons; $n = 179$) assessed hunger and two studies (two comparisons; $n = 45$) assessed desire to eat. Plotted values are weighted mean differences (WMD) from a random effects model. Error bars depict 95% confidence intervals (CI). The I^2 statistic refers to heterogeneity.

significant amounts of weight. Thus, for clinicians seeking an effective method of weight loss that does not increase hunger, this meta-analysis provides clear evidence that VLEDs achieve this target. KLCDs also appear promising but, due to the limited number of these studies available for the present review, further investigation is needed.

A secondary aim of this work was to determine whether there is a dose–response or 'threshold' of circulating ketone levels for appetite suppression. However, it was not possible to realize this aim because there was a lack of difference in β-hydroxybutyrate levels among VLED studies and there was only one KLCD study that reported blood β-hydroxybutyrate levels. Nevertheless, it is important to note that the VLED studies that measured circulating ketone levels included in the meta-analysis showed blood β-hydroxybutyrate levels of ~0.5 mM, and none reported an increase in appetite. This finding suggests that if a threshold of circulating β-hydroxybutyrate for appetite control exists, it may be lower than 0.5 mM, and that higher levels (and accordingly more severe dietary carbohydrate restriction) may not be necessary to prevent an increase in appetite in response to energy restriction. Unfortunately, the carbohydrate intake required to achieve this level of ketosis cannot be inferred from the current dataset. Although all VLED studies provided approximately 50 g of carbohydrate per day (in formulated meal replacement products), these interventions also included additional allowances of fruits and vegetables, for which the nutritional information was not provided. Further support for the notion of a threshold of circulating ketone concentrations for the effect on appetite comes from studies that have investigated appetite in response to varying levels of ketosis. These studies found no difference in appetite between groups with higher or lower levels of ketosis (17,33,35,57,58), as indicated by circulating β-hydroxybutyrate concentrations of ~3.7 or 0.5–0.7 mM, respectively (17,57). The question whether appetite can be suppressed during weight loss at a low threshold of ketosis warrants investigation, as it would enable development of KLCDs that are more aligned with evidence-based healthy eating recommendations through inclusion of healthy (i.e. low glycaemic index) carbohydrate-containing foods such as whole grains, legumes, reduced-fat dairy and fruit.

From the current studies, it was not possible to determine whether the appetite suppression seen with ketogenic diets is indeed due to ketosis, or due to other factors such as an increased or decreased content of protein or fat in the diet or the restriction of carbohydrate. This is because the dietary intake of one particular macronutrient cannot be varied independently of the other macronutrients without affecting energy. For instance, the appetite suppression of KLCDs has been attributed to their high protein content (59). However, KLCDs involve only modest or no increases in absolute protein intake relative to normal diets (34,60). Moreover, increased protein intake cannot explain why appetite is suppressed during VLEDs, which, while relatively high in protein, provide absolute protein intakes of only ~50–60 g day^{-1} (which for obese persons is lower than the suggested normal intake of 0.8–1.2 g kg^{-1} body weight per day [39]). Additionally, increased protein intake cannot explain the observation of an 'absence of hunger' during starvation or fasting regimes (35,61) – an observation that historically led to the initial development VLEDs to mimic this benefit (15). Further, well-controlled studies have shown that when protein intake is matched, a ketogenic high-protein diet suppresses appetite more so than a non-ketogenic high-protein diet in obese (20) and in lean

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subjects (62), highlighting ketosis as a plausible factor common to both VLEDs and KLCDs that could suppress appetite. Besides protein, another factor that could conceivably explain the effect of ketogenic diets on appetite is dietary fat (63). However, the contrasting low levels of dietary fat intake during VLEDs with the relatively higher levels consumed during KLCDs suggest that dietary fat intake is not a common factor explaining the appetite-suppressive effect of both diets.

One line of evidence that ketosis plays a role in appetite suppression during both VLEDs and KLCDs is the observation that changes in perceived appetite and circulating concentrations of hormonal regulators of appetite coincide with increased or decreased concentrations of circulating ketones. For instance, appetite is increased during the first couple of days on VLED (or on a fasting regime), before marked increases in circulating ketone concentrations would be expected to occur (13,15,25,58). However, after the time when elevated circulating ketone levels are observed, perceived appetite (10,29,55) and circulating concentrations of hormonal regulators of appetite, namely, ghrelin (29,55) and CCK (10,14,29), have been shown to be no different from pre-VLED and/or pre-KLCD levels. Further, a study of people on VLED showed that circulating concentrations of the hunger-promoting hormone ghrelin were suppressed relative to baseline concentrations only in those participants who were in ketosis (defined as blood β-hydroxybutyrate levels ≥0.3 mM), with those who were not in ketosis showing an increase in circulating ghrelin levels relative to baseline (29). Consistent with the above observations is the finding that after a period of re-feeding that abolishes ketosis post-VLED, perceived appetite and circulating levels of ghrelin increased, whereas that of the appetite-suppressing hormone CCK decreased, compared with the levels found at baseline and in energy balance (10,29). The above studies provide support for the hypothesis that the now well-established changes in appetite, as well as the effect of changes in circulating levels of appetite-regulating hormones that have been shown to accompany diet-induced weight loss (1–4,8,9,42,64), appear to be 'blocked' during ketosis. There may be other factors (such as the protein, fat or carbohydrate content of the diet *per se*) contributing to the suppression of appetite during VLED or KLCD, but none of these dietary factors provides as consistent an explanation as ketosis for the appetite suppression in both diets.

Another line of evidence that ketosis is associated with appetite suppression (inferred from a reduction in energy intake and/or subjective appetite ratings) is that studies have shown elevations in circulating ketones and/or free fatty acids (two metabolites that are characteristically increased during fasting and therefore ketosis) affect appetite in humans (65,66) and animals (67–71). Recent studies have investigated the safety and tolerability of synthetic ketone esters (72,73). Although synthetic ketone esters were not developed for the purpose of appetite suppression, using them to artificially induce mild ketosis could be a novel strategy for weight management. For instance, if patients were able to reap the benefits of appetite suppression with ketosis while consuming a more balanced and sustainable dietary regime than a KCLD, they could potentially benefit from improved weight outcomes as well as avoiding potential side effects of long-term dietary imbalances (37,74,75). After all, VLEDs are only intended for short-term (several months) use, and the weight regain seen with KLCDs could be related to the unsustainably restrictive nature of the diet, as indicated by studies showing poor long-term adherence (76). However, whether treatment with exogenous ketones *per se* could suppress any increase in appetite or corresponding changes in appetite-regulating hormones remains to be seen, there are a multitude of metabolic and hormonal changes associated with ketosis that could be having an effect on appetite.

A limitation of this work is that we only evaluated studies by comparing 'pre-test' and 'post-test' data as we only identified two studies that used a within-subject comparison that compared a ketogenic diet with a non-ketogenic diet (20,54). Further, we only identified three KLCD studies that compared subjective appetite ratings with VAS despite a plethora of studies comparing weight loss outcomes between ketogenic and non-ketogenic diets. Another limitation of this work is that subjective appetite assessed with VAS is not necessarily synonymous with energy intake. However, the fact that people can actually adhere to VLEDs for several weeks to months at a time, as evidenced by the rapid and large weight losses achieved (12), suggests that they do indeed suppress any compensatory increase in appetite.

Conclusion

This systematic review and meta-analysis provides evidence that VLEDs significantly reduce appetite during weight loss. KLCD also show promise, but only a limited number of studies have addressed this question within the scope of our review. The findings of this study have important implications for the communication of information by clinicians to patients. Based on this meta-analysis, clinicians can advise patients that although they may indeed feel slightly less hungry (or more full or satisfied) while on VLED, the true benefit of VLED is in preventing an *increase* in appetite, and that this can help them to comply with a severe restriction of energy intake in order to achieve substantial weight losses, rather than the absence of hunger altogether. Although other contributory factors cannot be ruled out, ketosis appears to provide a plausible explanation for the suppression of appetite during adherence to a ketogenic diet. Future studies should investigate the minimum level of

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ketosis (and associated carbohydrate intake) to achieve this effect. From the present data, however, it would seem unnecessary to restrict carbohydrate intake to less than 50 g day^{-1} or to achieve blood β-hydroxybutyrate levels much greater than 0.5 mM, at least during VLED.

Conflict of interest statement

TPM and IDC have received research grants for clinical trials funded by Sanofi-Aventis, Allergan, Roche Products, MSD, BMS, NovoNordisk and GlaxoSmithKline. IDC was an Executive Steering Committee member for the SCOUT trial, is on the Organizing Committee of EXSCEL trial and has received payment for lectures from iNova Pharmaceuticals, Pfizer Australia, and Servier Laboratories (Australia). TPM acts as an advisory member to the Egg Nutrition Council and Nestle Nutrition. JF has received payment for the Optifast Scientific Board. AS and AAG have received payment from the Pharmacy Guild of Australia, and AS from Eli Lilly, for lectures.

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Supporting information

Additional Supporting Information may be found in the online version of this article, http://dx.doi.org/10.1111/obr.12230

Table S1 Justification for describing interventions from the 24 publications reviewed in this systematic review as 'ketogenic diets', whether the authors did not or did measure ketone concentrations in body fluids, and how ketone concentrations were assessed in those publications that did.

Table S2 Characteristics of dietary interventions and participants at baseline, as well as weight loss outcome, in the 14 studies excluded from the meta-analysis but included in the qualitative review of effects of ketogenic diets on subjective appetite.

Table S3 Protocol for appetite assessment via visual analogue scales in the 14 studies excluded from the meta-analysis of effects of ketogenic diets on subjective appetite.

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