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Efficacy of Low- and Very-Low-Energy Diets in people with Type 2 Diabetes Mellitus: A systematic review and meta-analysis of interventional studies

Running title: Efficacy of diets in people with Type 2 Diabetes

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Abstract

Aims

To systematically review and quantify the weight loss achieved by Low- and Very-Low-Energy Diets in people with type 2 diabetes mellitus.

Materials and Methods

Studies reporting the effects of diet-only interventions up to 1600kcal/day in people with type 2 diabetes mellitus were searched in MEDLINE, EMBASE, CINAHL until July 2018. Changes in the primary (body weight and body mass index) and secondary (HbA1c, blood lipids) outcomes according to energy restriction and duration of diet were modelled using restricted cubic splines.

Results

Forty-four studies (3817 participants) were included. The overall quality of the evidence was moderate and limited to short-term interventions up to four months. Baseline mean weight and body mass index were 92.1kg and 36.6kg/m^2. Very-Low-Energy Diets of 400kcal/day led to 5.4% weight loss at two weeks, increasing to 17.9% at three months. More modest reductions of 7.3% were observed on Low-Energy Diets of 1200kcal/day and 2.0% on 1600kcal/day after three months. No clear patterns emerged for secondary outcomes. Publication bias was significant for primary outcomes.

Conclusions

High-quality studies are required to support evidence-based Low- and Very-Low Energy prescription in people with type 2 diabetes. Available evidence would suggest variable reduction of body weight, ranging from 2% to 18%, after three months of Low- and Very-Low-Energy Diets.

Introduction

Overweight and obesity are defined by a body mass index (BMI) of 25-29.9 kg/m^2 and 30kg/m^2 or more, respectively, for the White population and by lower thresholds for other ethnicities.[1] An estimated 90% of adults with type 2 diabetes mellitus (T2DM) fall into these categories in the UK.[2] Obesity is associated with a higher risk of cardiovascular disease and all-cause mortality,[3-5] and effective weight management strategies are considered key to the prevention and treatment of all obesity-related diseases. In order to reduce body weight, international clinical guidelines recommend dietary modification, usually via supported daily energy restriction in combination with an increase in physical activity.[6,7] Current UK recommendations support an initial body weight loss of 5-10% in adults with T2DM who are overweight or obese, based on studies suggesting that this will confer wide-ranging benefits, including reduced cardiovascular risk and improved quality of life.[8-12] There is also growing evidence that more aggressive short-term energy restriction resulting in greater weight loss will have important effects on glucose control and potentially reverse some cases of T2DM.[13-15]

In this context, energy restriction through Low-Energy Diets (LED) between 800-1600kcal/day and Very-Low-Energy Diets (VLED) up to 800kcal/day have become important options to consider in the clinical management of patients with T2DM.[16,17] While dietary macronutrient composition is considered a component alongside energy restriction, there is ongoing discussion about the impact of different macronutrient compositions and dietary formats.[18] This results in a need for clinical practice to demonstrate the weight loss and clinical outcomes that energy restrictions in this population can achieve irrespective of diet type.

Previous meta-analyses in people with T2DM have either examined specific diet types such as VLEDs,[19,20] formula-diets,[21] high-protein diets[22] or low-carbohydrate diets,[23-26] or compared them with each other.[27-31] However, studies quantifying weight loss attained during dietary intervention according to daily energy restrictions are limited. Health-care professionals do not have ready access to weight loss data to help inform dietary prescriptions or to estimate the time required to achieve a weight loss target. To help clarify the evidence, we systematically reviewed and quantified the effects of diet interventions up to 1600kcal/day on body weight, HbA1c, blood pressure and blood lipids in people with T2DM.

Materials and Methods

The systematic review and meta-analysis are in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements.[32]

Literature search

We electronically searched MEDLINE, EMBASE and CINAHL from their inception to 6th July 2018 without restrictions on language. Search terms included “diabetes”, “very low calorie diet”, “low calorie diet”, “very low energy diet”, “low energy diet”, “VLCD”, “LCD” and “VLED”; details of the search strategy are reported in the **Supplementary Material**. To complement the database searches, we used both hand-searching and scanning of reference lists from primary studies and previous systematic reviews and meta-analyses.

Study selection and quality assessment

Two independent investigators (DK and FZ) screened titles and abstracts of the articles and determined inclusion of full-texts by consensus; discrepancy was resolved by arbitration. Where different studies potentially shared the same subjects, we emailed the authors for clarification and, where no response was obtained, we included only the study with the largest sample size. Studies were included if subjects with T2DM were prescribed any diet-only intervention reporting a daily energy intake lower than or equal to 1600 kilocalories (equivalent to 6694.4 kilojoules) with information on body weight or body mass index change during the intervention, either directly available or calculated from pre and post-intervention values. Interventional studies shorter than 6 days or (post-trial) observational follow-up were excluded. We defined the end of intervention as the termination of the diet prescription or, where multiple successive interventions (at different energy restrictions) were conducted in the same study, we selected only the first intervention. We excluded studies if the relevant outcome data were unavailable. Since our meta-analysis considered all diets as different doses of the same treatment, we evaluated study quality through a validated checklist by Downs and Black which we adapted for non-randomised intervention studies.[33] The criteria for grading study quality are described in the **Supplementary Material Table S1**. The scores obtained through this checklist reflect study quality only in so far as it affects the reliability or validity of our results.

Data extraction

Two authors (DK and FZ) extracted data from eligible studies, including: digital object identifier (DOI) or PubMed unique identifier number (PMID), first author, year of publication, the country in which the study was conducted, sample size and percentage of men, mean/median age and duration of diabetes, type of intervention by daily kilocalories target, the length of the intervention, and any criteria for stratification into study arms such as duration of diabetes or diet type. For the main outcomes, body weight and BMI, available measures at baseline, follow-up, and changes from baseline were extracted. For studies reporting outcomes at multiple time points, we used the last measured outcome. We extracted any data on the secondary outcomes HbA1c, systolic blood pressure, total serum cholesterol and serum triglycerides.

Conversions and imputations

For primary outcomes and diet interventions, we converted relevant measurements reported in units other than kilogram (kg), kg/m^2 or kilocalories (kcal). Where necessary, BMI was calculated from relative weights in Metropolitan Life Insurance Tables according to published formulae.[34] The secondary outcomes HbA1c, total serum cholesterol and serum triglycerides were likewise converted to percentage (%) and millimoles per litre (mmol/l), respectively.[35,36]

Weighted means were used to estimate average daily kilocalorie targets for diets where these differed among participants, as well as to calculate any baseline or outcome measures if reported separately for different subjects or groups in the same study arm. Mean and standard deviation were estimated from median and interquartile range according to formulae published in the Cochrane handbook and in the literature.[37-39] Changes from baseline in mean weight or BMI were calculated by subtracting the mean at end of the intervention from the mean at the baseline.

A study was evaluated as representative of the patient population and the usual settings for diet interventions if it recruited patients to whom diets would have been applied through outpatients or primary care (i.e. not inpatients for the duration of the study).

Statistical analyses

Characteristics of studies and participants are reported as mean and standard deviation or median and interquartile range (IQR) for continuous data according to their distribution and as number and percentage for categorical data.

We modelled reductions in body weight and BMI at different daily kilocalorie targets and durations. To account for any non-linearity, we modelled these outcomes using restricted cubic splines for the duration of follow-up and a linear term for mean daily kilocalories. The regression was weighted by the inverse of the variance of the study-specific outcome estimate. The choice of the number of knots for the spline was based on the Akaike Information Criterion and the Bayesian Information Criterion. For studies not reporting an error term for the changes in body weight or BMI from baseline, the correlation coefficient (rho) was derived from the mean of the correlation coefficients calculated from the data available in other studies, following current recommendations.[37] We modelled outcomes for 100-1600kcal and computed values for time intervals of 14 days, 30 days and thereafter at 30 day intervals (i.e. at 2 weeks, 1 month and thereafter monthly) for clinical usefulness and ease of understanding.

As data for secondary outcomes were incomplete, we used multiple correlation coefficients of 0.1, 0.3, 0.5, 0.7 and 0.9 to calculate standard errors of the change from baseline and adopted the knot placement used for the analyses of the primary outcomes.

To quantify the impact of subject and study characteristics on effect size, we conducted meta-regressions for sex, age of participants, duration of diabetes, year of study publication, study setting (inside or outside of hospital), drug treatment during and outside of the interventions as well as for study quality as assessed by checklist. We used a multivariable meta-regression with diet type (food-based, meal replacement or a combination) and daily kilocalorie prescription as the independent variables to assess any effects of diet type on the primary outcomes. To account for a possible effect of the macronutrient composition of the diets on changes in bodyweight and BMI, we used meta-regressions with isometric log-ratio transformation of the independent variable (carbohydrate, fat and protein content of each diet) in accordance with current methodology in nutritional epidemiology, also including daily kilocalorie prescription in the models.[40] We tested for publication bias with funnel plots and Egger's test.

Statistical modelling was done in R (Version 3.4.3); all other analyses, tables and graphs were produced using Stata (Version 15.0). Graphs were modified with Inkscape 0.92. Results are reported with 95% confidence intervals and $p<0.05$ was deemed statistically significant.

Results

Study selection and characteristics

After removing duplicates, we identified 856 studies of which 652 were excluded by title and abstract. The remaining 204 full texts were assessed and a total of 44 studies met the inclusion criteria. Of these, 31 were papers found through database searches, 7 from previous reviews and meta-analyses and 6 through hand searches (**Supplementary Material Figure S1**). The year of publication ranged from 1978 to 2017. The 44 studies included in the meta-analysis comprised a total of 51 distinct study arms, of which 48 reported changes in weight and 47 in BMI. No data on body weight was available in 2 studies with 3 study arms.[41,42] Data on BMI could not be obtained from a further 3 studies with 4 study arms.[43-45] Secondary outcomes were not reported consistently: sufficient data for inclusion in statistical analyses were reported in 18 studies for HbA1c, 8 for systolic blood pressure, 23 for total cholesterol and 24 for triglycerides (**Table S2**).

The mean number of participants was 78 (range 6-2597) for arms reporting body weight and 25 (range 6-192) when excluding UKPDS7 which had 2597 participants with information only for body weight (**Table 1** and **Figure S2**); for BMI, it was 25 (range 5-192). A total of 3817 participants were included (45.5% men); weighted mean age and duration of diabetes were 52.5 (range 34.6-62.1) and 1.5 (range 0-17.8) years, respectively. Weighted mean weight at baseline was 92.1 (SD 9.4) kg and BMI 36.6 (SD 4.0) kg/m^2. Weighted median duration of intervention was 91.3 days (range 6-112) and was related to daily kilocalorie targets (**Table 1** and **Figure S3**). The weighted mean daily target was 1186kcal (SD 337, range 23.2-1600). Low-Energy Diets with the least energy restrictions (>1200kcal/d) relied mainly on food (83%), while those with more severe energy restriction (800-1200kcal/d) used meal replacements (57%) or a mixed diet of food and meal replacements (43%).

Similarly, Very-Low-Energy Diets (≤800kcal/d) rarely consisted of food alone (6%) and more often of meal replacements (55%) or a mixed diet (16%), with some diets not being explained fully by the authors (23%) (**Figure S3**).

The quality of the included studies was generally moderate, with studies satisfying on average 6 out of 10 (range 2 to 8) criteria on the checklist (**Table S3**). In all studies, sufficient estimates were provided for either body weight, BMI, or both, including studies for which authors supplied this information on request.[13,46,47] This criterion was necessary for the study to be included in the meta-analysis. However, only in 37 studies the intervention was clearly described in terms of the composition of the diet, while 39 of the 44 studies included any data on both of our primary outcomes. Patient characteristics such as age, sex and duration of diabetes, were included in 39, 39 and 28 studies, respectively, and drug treatment before and during the study in 39 and 40 studies, respectively. Twenty-seven studies relied solely on interventions conducted in outpatients and were thus considered as having staff, places and facilities representative of the majority of patients. This included 52% (16/31) of studies using a Very-Low- and 85% (11/13) using a Low-Energy Diet. Sufficient information on losses to follow-up was provided by 26 studies. However, we found that in 15 of the 17 studies declaring any losses to follow-up participants were excluded from the analysis, with a median number of 4 participants dropping out (IQR 1-8, range 1-14).[44,48-60] The remaining two studies opted for an intention-to-treat analysis, reporting 21 (14% of all participants) and 4 (4%) drop outs, respectively.[13,46] Adherence was not quantitatively or systematically assessed in the large majority of studies.

Only five studies tried to recruit subjects randomly or consecutively. We could not confirm that subjects willing to participate in these studies were representative of those asked to participate. Randomisation of allocation for treatments included in the meta-analysis was only demonstrable in

7 studies.[13,44,46,51,56,59,61] Blinding of any kind was reported by one study and applied to researchers taking measurements.[61] Moreover, there were a number of other potential sources of bias including a variable duration of intervention [49,62] and exclusion of participants failing to achieve set weight loss targets. [57]

Body weight and body mass index

Changes in body weight were poorly related to baseline weight (**Figure S4;** adjusted R^2=0.0638; following removal of UKPDS7, adjusted R^2=0.0604).

Results of body weight reductions are reported for 400kcal/day, 800kcal/day, 1200kcal/day and 1600kcals daily which correspond to the lower and upper limits of VLEDs and LEDS according to accepted definitions. Results are reported in **Table 2** and are displayed separately for different time points (**Figure 1**) and kcal/day (**Figure 2**). Between 14 and 120 days, estimated body weight decreased from -5.4% to -25.2% on 400kcal/day diet and from -2.1% to -8.7% on a 1600kcal/day diet. Weight loss plateaued and was observed to reverse between 60 and 90 days for higher energy diets above 800kcal/day. For diets of 400 kcal/day, 800 kcal/day and 1200kcal/day, there was a weight loss of -5.4 (95% CI: -6.9 to -3.8), -4.3 (-5.0 to -3.6) and -3.2 (-4.9 to -1.5) %, respectively, at 14 days. By contrast, a diet of 1600kcal/day at 14days did not result in weight reduction, with the predicted values being -2.1 (-5.3 to 1.1) %. At 30 days, weight loss was -9.5 (-11.0 to -7.9) and -7.7 (-8.8 to -6.6) % on VLEDs and -6.0 (-7.6 to -4.4) and -4.2 (-6.8 to -1.7) % on LEDs. While the change from baseline increased at 60 days for 400kcal/day (-12.2%, -14.4 to -10.0), 800 kcal/day (-9.0%, -10.3 to -7.7) and for 1200 kcal/day (-5.8%, -7.8 to -3.9), it decreased for a 1600 kcal/day diet to -2.7% (-6.0 to 0.6). At 90 and 120 days, there was a predicted weight loss for all diets: 400 kcal/day, 800 kcal/day, 1200 kcal/day and 1600kcal/day. Weight loss was almost linear over time on VLEDs (**Figure**

2). On LEDs, weight loss plateaued over the second and the third month and accelerated again thereafter.

Effects on BMI followed a similar pattern. At 14 days, there was a decrease of -5.8 (-7.3 to -4.3) % on 400 kcal/day, -4.3 (-5.0 to -3.7) % on 800 kcal/day and -2.9 (-4.7 to -1.1) % on LEDs of 1200 kcal/day, but this was not observed on a 1600kcal/day diet (-1.4%, -4.6 to 1.9). At 30 days, all diets resulted in a reduction in BMI. Mirroring the changes in body weight, at 60 days BMI dropped for 400 kcal/day (-11.3%, -13.6 to -9.0), 800 kcal/day (-8.6%, -9.8 to -7.3) and 1200 kcal/day (-5.8%, -7.8 to -3.9) but not for 1600kcal/day diets (-3.1%, -6.5 to 0.3). Thereafter, BMI decreased significantly for 400kcal/day, 800kcal/day, 1200kcal/day and 1600kcal/day.

Secondary outcomes

Changes in HbA1c were related to baseline HbA1c (adjusted R^2 ranging from 0.490 to 0.542 for different correlation coefficients), as were changes in serum triglycerides (adjusted R^2=0.471-0.552) and, to a lesser extent, changes in systolic blood pressure (adjusted R^2=0.197-0.273) and total serum cholesterol (adjusted R^2=0.155-0.207) **(Table S4** and **Figure S5)**. For the secondary outcomes, we estimated effects at 60 and 90 days due to the paucity of available data: no clear trends emerged from these investigations (**Figure S6**). Lack of data did not permit any analyses for changes in systolic blood pressure.

Sensitivity analysis

We excluded UKPDS7 in a sensitivity analysis as this study comprised 69.0% (2597/3763) of all participants included in the meta-analysis on body weight and its study design was atypical in setting kilocalorie targets according to ideal body weight.[43] This affected the predicted changes in the primary outcome only minimally, most notably leading to a marginally larger predicted weight loss of -2.7% (-4.7 to -0.7) compared to -2.0% (-3.1 to -0.9) for 1600kcal diets at 90 days.

Meta-regressions

Meta-regression showed no significant differences in the outcomes either by the characteristics of the participants, i.e. sex, age of participants, year of publication; or setting in or outside of hospital, the usual treatment of the participants and the treatment during the study (**Figure S7**). Similar results were observed for duration of diabetes (p=0.676 for bodyweight, p=0.634 for BMI). There was insufficient data to assess differences in weight loss between people on insulin and other glucose lowering medications. Study quality did not affect either primary outcome (p=0.051 for body weight, p=0.063 for BMI). In multivariable meta-regression, diet types had no effect on changes in body weight (p=0.128) or BMI (p=0.130). There was a negative relationship between carbohydrate content and reductions in body weight and BMI (p=0.055 and p=0.106 respectively), which was also present but weaker for fat content (p=0.842 and 0.706). Protein content was positively related to reductions in body weight or BMI (p=0.52 and p=0.053) (**Table S5**).

Publication bias

The funnel plots for changes in body weight and BMI were highly suggestive of publication bias (Egger's p<0.001) (**Figure S8**). Excluding UKPDS7, which reported data only for body weight, the likelihood of publication bias still remained high (p<0.001).

Discussion

To our knowledge, this is the first study to systematically assess reduction in body weight and its effect on markers of metabolism following the application of energy restriction diets of 1600kcal or less in patients with T2DM.

Whilst the relationship between sustained energy deficit and weight loss in people with and without T2DM is well established, short term outcomes for prescriptions of Low- and Very-Low-Energy Diets are less well characterised, with previous meta-analyses concentrating upon diet type or constituents rather than energy restriction thresholds. Our results confirm that both types of diet are likely to achieve clinically impactful weight loss within four months. Very-Low-Energy Diets of 400kcal/day led to 5.4% weight loss at two weeks increasing to 17.9% at three months. More modest reductions of 7.3% were observed on Low-Energy Diets of 1200kcal/day and 2.0% on 1600kcal/day after the same period. The non-linear shape of the relationship between weight and time for LEDs is likely to reflect the gaps in the evidence, with only 4 studies reporting data on LEDs beyond 2 months.[43,46,56,59] Therefore, we hope our results can help delineate thresholds of energy restriction of less than 1600kcal/day using a generic dietary format that decision makers can apply to formulate targeted approaches to achieving 5%, 10% or 15% weight loss in people with T2DM.

Direct comparison of our results to recent systematic reviews and meta-analyses of Low- and Very-Low Energy Diets is difficult: most investigations, in participants with and without T2DM, have not quantified weight loss as a percentage of baseline or by daily kilocalorie intake and have instead reported results either by comparing diet-only interventions to each other or against multi-component interventions.[19,21-27,29-31,63-65] The only comparable investigation conducted in people with T2DM is a meta-analysis of 10 studies by Anderson et al. which showed a weight loss of 9.6% on

VLED at 6 weeks, which is similar to our estimates of -9.5% to -7.7% at 4 weeks and -12.2% to -9.0% for VLEDs of 400-800kcal/day at 8 weeks; conversely, no specific estimates were identified for weight loss on LEDs in people with type 2 diabetes.[20]

Findings from previous meta-analyses in people with T2DM suggest that changes in measures of diabetes control, HbA1c or fasting plasma glucose follow reductions in body weight.[20,31] We found that in people with T2DM there is insufficient evidence to confirm whether clinically relevant metabolic parameters, such as HbA1c, systolic blood pressure, total serum cholesterol and serum triglyceride, improve in tandem with body weight reductions over four months when applying generic energy restrictions. With only 4 studies (80 participants) reporting a mean age less than 40 years,[62,66-68] and no results specifying weight loss by ethnicity, more data are needed to allow for a targeted approach for different patient groups.

Diets with greater energy restriction tended to rely on meal replacements alone (total dietary replacement) or in combination with food, with only 2 studies using food-based diets of 1200kcal/d or less. This may reflect concerns about the nutritional completeness or ease of use of Low-Energy and Very-Low-Energy food-based Diets.[16]

The meta-regressions for the impact of macronutrient composition on changes in weight and BMI failed to reach statistical significance (at a threshold of 0.05). The direction of the relationship as indicated by the regression coefficient may suggest that lowering carbohydrate content and increasing protein content could impact these outcomes. These results are in line with previous meta-analyses, but more evidence is needed to determine if Low Calorie Diets or High Protein Diets are more effective than diets with other macronutrient compositions in lowering body weight and improving cardiometabolic risk factors in patients with T2DM.[22,23,25,26,69,70]

This study has a number of strengths. To our knowledge, this is the most comprehensive systematic investigation of VLED and LEDs in people with T2DM in terms of the number of studies included and the number of participants. We excluded multifaceted studies with intensive behavioural, pharmacological or surgical interventions to provide an accurate description of dietary-only deficit studies on weight loss. While NICE recommends multicomponent interventions in tackling obesity, it is also important to understand how much generic dietary restriction can contribute as part of such strategies or on their own.[16] In order to maximise the number of studies, we included data on both body weight and BMI as not all studies reported data on both outcomes. However, this may also indicate a need to standardise reporting using a core set of outcomes in weight management studies.

A possible weakness of this meta-analysis is that only 27 of 44 studies relied solely on outpatients. Due to possible low adherence, it is likely that weight loss achieved in practice is smaller than under the controlled conditions set by many intervention studies.[71] Therefore, there is still a potential to over-estimate the efficacy of the diets tested, which could be reflected in our analyses. This problem may also be compounded by the possibility of publication bias, which should be considered for the overall interpretation of the results.[72] The majority of studies were not randomised trials and regression to the mean cannot be excluded due to the lack of a control arm in most studies.[73] Limitations also include the focus on energy restriction level and duration as prescription (generic dietary format) rather than specific diets, although our meta-regressions did not show any effect due to diet format or macronutrient composition. While some studies assessed weight maintenance after the diet period, we restricted our analysis to the diet period only: therefore, our results are indicative only of weight loss achieved during dietary interventions. We did not include deficit diets at they would result in heterogeneous kcal/day dietary restriction among individuals.

Through modelling, we have described the effect of generic dietary deficit strategies on weight loss. These results can serve as a guide when deciding on the level of energy restriction needed to achieve a given weight loss target in clinical practice or when estimating the time required to reach a certain body weight before a clinical procedure. As an essential part of clinical guidelines for people with T2DM, we have also observed that the evidence for weight-reduction through dietary restriction is based on studies of moderate reporting quality and with substantial publication bias. In the face of continued uncertainty over the best approach for weight loss, we provide some evidence for a targeted approach based on the level of energy prescription. Large-scale studies evaluating the effects on weight loss, glucose control and cardiometabolic risk factors in community settings are warranted to fully understand the benefits of VLEDs and LEDs in people with T2DM.

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Data access and sharing

Databases and statistical codes are available on request from the corresponding author (DK).

Ethics

This article does not contain any study with human participants performed by any of the authors.

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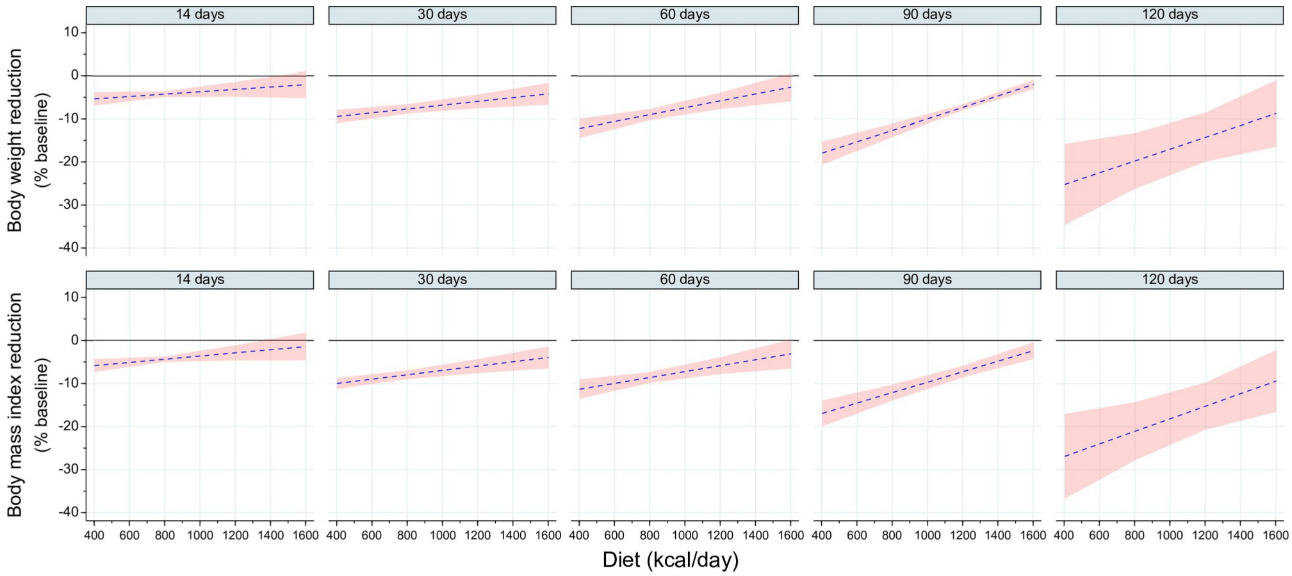
FIGURE LEGENDS

Figure 1: Estimated effects of diets on body weight and body mass index

Legend: Effects are shown for selected time points. Pink areas indicate 95% Confidence Interval.

Figure 2: Effects of individual diets over time

Legend: Effects are shown for selected daily kilocalorie targets. Pink areas indicate 95% Confidence Interval.



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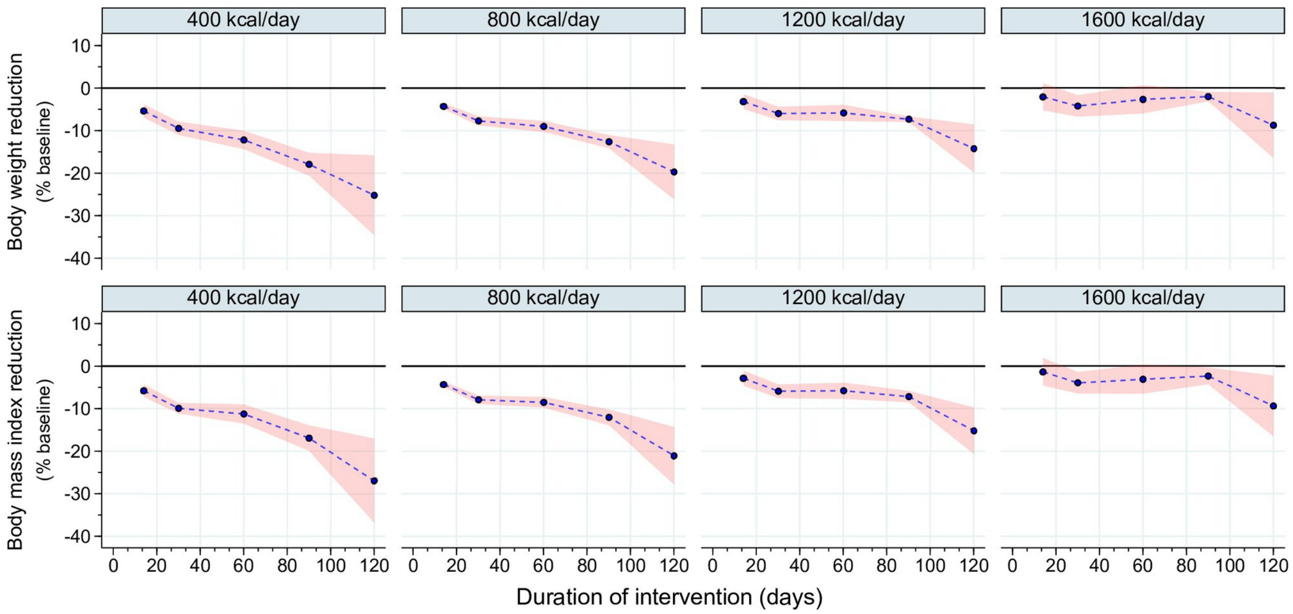

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Table 1: Characteristics of included studies

Study identifiers			Study design			Baseline characteristics						Change from baseline	
PMID/DOI	Author	Year	Stratification	Diet (kcal/day)	Duration (days)	n	Male (%)	Age (years)	Duration of diabetes (years)	Body weight (kg)	Body mass index (kg/m^2)	Body weight (%)	Body mass index (%)
723636	Greenfield	1978		50	10	8	25.0	44.5	10.6	91.2	31.0	-4.1	-4.1
7021580	Nagulesparan	1981	Duration of diabetes	500	52	8	37.5	45.4	10.5	93.0	34.9	-10.5	-10.5
				500	43	10	60.0	36.6	0.8	105.0	37.8	-6.9	-6.9
4044780	Henry	1985		330	40	30	10.0	53.0	9.0	99.1	37.1	-10.6	-10.6
3510922	Henry	1986		300	36	10	20.0	49.9	.	99.7	35.5	-11.1	-11.1
3355307	Amatruda	1988		420	40	6	0.0	52.0	13.3	106.0	41.5	-8.8	-8.8
3291612	Bauman	1988		896	23	62	100.0	58.0	10.2	105.7	34.6	-5.2	-5.1
2666069	Fukuda	1989		120	28	7	28.6	51.0	4.0	78.9	30.4	-9.0	-9.0
2613422	Inoue	1989		330	28	57	21.1	34.6	.	87.3	35.0	-12.5	-12.5
2693380	Weck	1989	Serum insulin	300	28	14	64.3	50.4	9.5	.	29.0	.	-11.4
				300	28	13	76.9	53.7	8.3	.	29.6	.	-11.8
2392060	UKPDS7	1990		1361	91	2597	.	52.0	0	87.1	.	-5.4	.
8077323	Kelley	1993		800	7	7	28.6	58.7	.	92.7	32.8	-2.4	-2.4
8082533	Anderson	1994	Diet type	820	84	20	55.0	.	.	104.3	.	-14.3	.
				800	84	20	50.0	.	.	105.1	.	-15.7	.
8288057	Gougeon	1994		400	42	7	14.3	36.3	4.5	93.7	35.8	-12.7	-12.7
8051339	Rotella	1994		420	15	29	89.7	55.6	8.3	86.1	35.3	-4.2	-5.7
10.1002/pdi.1960120611	Paisey	1995		520	91	14	50.0	53.9	.	100.2	34.3	-13.6	-15.3
9229194	Capstick	1997		425	84	13	53.8	50.3	8.7	113.6	40.0	-12.7	-12.7
10857959	Gougeon	2000		1315	28	13	46.2	51.0	4.9	110.0	41.0	-5.7	-5.7
11331427	Gougeon	2001		460	28	9	44.4	48.0	4.3	108.0	40.0	-9.2	-9.2
11874925	Parker	2002	Diet type	1600	56	26	34.6	60.3	.	97.7	34.8	-4.6	-4.6
				1600	56	28	35.7	62.1	.	91.4	33.3	-4.9	-4.9
11750274	Simonen	2002		23	91	10	80.0	51.5	.	92.3	31.7	-16.8	-16.8
12675647	Dhindsa	2003		750	56	40	55.0	52.0	6.1	119.0	40.6	-10.1	-9.9
14610532	Harder	2004		850	56	10	30.0	62.0	3.7	100.6	36.8	-11.2	-11.2
17134786	Jazet	2007		450	30	18	50.0	55.0	7.5	111.7	37.6	-10.5	-10.6
18078853	Lara-Castro	2008		700	6	7	28.6	43.0	.	103.0	37.0	-12.6	-5.4
20404829	Khoo	2010		875	56	19	100.0	58.1	.	112.7	35.1	-8.4	-8.5
21246185	Larsen	2011	Diet type	1530	91	46	39.1	58.8	8.6	95.5	34.3	-3.2	-3.1
				1530	91	53	56.6	59.6	8.7	94.6	33.4	-2.9	-2.8
21593800	Plum	2011		800	57	7	42.9	51.7	8.0	122.0	43.3	-9.0	-8.8
22146094	Baker	2012		800	84	24	50.0	54.4	7.8	108.9	38.1	-7.8	-7.9
22318758	Malandrucco	2012		400	7	14	50.0	60.3	4.8	114.3	44.8	-3.1	-3.1
22569236	Snel	2012		450	112	14	42.9	56.1	.	112.7	37.9	-21.0	-21.0
23610060	Jackness	2013		500	20	14	42.9	51.9	5.5	114.2	39.2	-7.3	-7.1
23847327	Lips	2013		600	21	12	0.0	.	.	112.0	40.2	-6.0	-6.2
25069603	Noren	2014		680	28	7	.	.	.	119.2	.	-7.5	.
24843744	Wycherley	2014		1557	112	33	51.5	56.9	.	101.0	35.5	-8.7	-8.5
25005809	Leonetti	2015		578	10	14	.	.	17.8	142.9	50.8	-6.4	-8.3
25683066	Steven	2015	Duration of diabetes	662	56	14	57.1	61.6	12.7	96.9	34.3	-14.3	-14.3
				662	56	15	46.7	52.1	2.3	99.0	34.2	-14.6	-14.9
27494531	Berk	2016		750	56	192	41.7	54.2	.	106.0	37.0	-7.4	-7.4
27833048	Carter	2016		1374	84	25	.	62.0	9.2	102.0	35.8	-7.8	-7.8
27135654	Cinkajzlova	2016		598	21	27	.	55.4	.	.	50.9	.	-5.9
27387696	Pournaras	2016		800	14	7	57.1	49.3	5.2	116.9	40.1	-4.1	-4.0
28230324	Baldry	2017		800	14	16	37.5	48.1	.	142.9	49.6	-3.6	-3.6
27894746	Berggren	2017		858	27	10	0.0	.	3.1	111.6	39.4	-7.3	-7.4
28989891	Bhatt	2017	Response to intervention	1000	84	6	66.7	41.0	3.9	84.5	30.5	-5.3	-6.1
				1000	84	6	66.7	38.5	2.1	82.5	31.3	-9.1	-12.1
29221645	Lean	2017		829	91	149	55.7	52.9	3.0	100.9	35.1	-14.4	-14.4

Table 2: Predicted changes in weight and BMI

kcal/day	Body weight reduction (% of baseline) (arms=48; participants=3763)					Body mass index reduction (% of baseline) (arms=47; participants=1173)				
	14 days	1 month	2 months	3 months	4 months	14 days	1 month	2 months	3 months	4 months
400	-5.4 (-6.9 to -3.8)	-9.5 (-11.0 to -7.9)	-12.2 (-14.4 to -10.0)	-17.9 (-20.6 to -15.2)	-25.2 (-34.6 to -15.8)	-5.8 (-7.3 to -4.3)	-10.0 (-11.2 to -8.7)	-11.3 (-13.6 to -9.0)	-16.9 (-19.9 to -14.0)	-26.9 (-36.8 to -17.1)
800	-4.3 (-5.0 to -3.6)	-7.7 (-8.8 to -6.6)	-9.0 (-10.3 to -7.7)	-12.6 (-14.2 to -11.0)	-19.7 (-26.2 to -13.2)	-4.3 (-5.0 to -3.7)	-7.9 (-9.0 to -6.9)	-8.6 (-9.8 to -7.3)	-12.1 (-13.9 to -10.2)	-21.1 (-27.8 to -14.3)
1200	-3.2 (-4.9 to -1.5)	-6.0 (-7.6 to -4.4)	-5.8 (-7.8 to -3.9)	-7.3 (-8.0 to -6.6)	-14.2 (-19.9 to -8.5)	-2.9 (-4.7 to -1.1)	-5.9 (-7.6 to -4.3)	-5.8 (-7.8 to -3.9)	-7.2 (-8.6 to -5.9)	-15.2 (-20.7 to -9.7)
1600	-2.1 (-5.3 to 1.1)	-4.2 (-6.8 to -1.7)	-2.7 (-6.0 to 0.6)	-2.0 (-3.1 to -0.9)	-8.7 (-16.5 to -1.0)	-1.4 (-4.6 to 1.9)	-3.9 (-6.5 to -1.4)	-3.1 (-6.5 to 0.3)	-2.3 (-4.3 to -0.4)	-9.4 (-16.6 to -2.2)