For weight maintenance, is low-carb king?

[Effects of a low carbohydrate diet on energy expenditure during weight loss maintenance: randomized trial.]

Introduction

In long-term trials (longer than 12 months) researchers conducting many studies have consistently seen weight loss on all kinds of diets—from extremely low-carb to extremely low-fat. But maintaining weight loss is a struggle, with nearly all participants in these trials regaining some or all of their initially lost weight. A version of the carbohydrate-insulin model of obesity (CIMO) posits that this inability to keep weight off may be due to the pro-insulinogenic effects of refined and high glycemic carbohydrate in the diet.

This version of the CIMO hypothesis goes as follows: carbohydrate in the diet (particularly high glycemic and refined) elevates insulin secretion, which suppresses the release of stored body fat and drives fat that may be circulating in the bloodstream into storage. A decrease of circulating fat decreases the energy available for the body to use. This drop in energy availability can lead to a decline in energy expenditure and increase food intake. Thus, it is hypothesized that the development of obesity or weight regain is a consequence of carbohydrate-induced insulin production driving fat into storage, preventing it from being used for energy. This is in contrast to the energy balance model, which states that equally swapping carbohydrate for fat in the diet will not notably affect body fat levels nor energy expenditure.

Dr. David Ludwig, a supporter of the CIMO hypothesis, has just published a long-term, randomized trial designed to answer the question: Will varying the carbohydrate-to-fat ratio in the diet have an effect on energy expenditure during weight loss maintenance? If the CIMO hypothesis holds true, then a low-carb diet should increase energy expenditure relative to a low-fat diet.

Researchers conducting long-term diet studies have seen many participants fail to maintain their weight loss. The carbohydrate-insulin model of obesity hypothesizes that refined and high-glycemic carbs are a major contributor to this issue. The randomized trial under review examines the effects of various carbohydrate-to-fat ratios in the diet on energy expenditure during a period of weight maintenance.

Who and what was studied?

This $12 million trial was undertaken at Framingham State University and was partly funded by the Nutrition Science Initiative (NuSI). NuSI was co-founded by Gary Taubes, a prominent low-carb advocate and journalist, and a supporter of the CIMO. It is important to note that NuSI was allowed to comment on the study manuscript, but the study states that funders had "no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; approval of the manuscript; and decision to submit the manuscript for publication."

Of 1,685 participants screened, 234 were enrolled in this randomized trial. Those enrolled had a BMI of 25 or higher, a total bodyweight of less than 160 kilograms (353 pounds), and an average age of 37 years. Of those enrolled, 28.6% were male and 71.4% were female. The primary aim of this trial was to determine if diets differing in carbohydrate-to-fat ratios affected *total* energy expenditure, measured via doubly labeled water, during a weight loss maintenance phase. Doubly labeled water contains non-radioactive isotopes that can be measured when excreted via urine. The rate of excretion of these isotopes closely correlates with energy expenditure. This allowed for a more objective measure of energy expenditure in free-living participants over self-reported measures.

There were many secondary outcomes, including changes in *resting* energy expenditure (measured via indirect calorimetry, also known as respirometry), physical activity (measured via accelerometer), skeletal muscle work efficiency, and if pre-weight loss insulin secretion influenced changes in total energy expenditure. The study design can be seen in Figure 1.

The study had three parts: weight loss, weight stabilization, and weight maintenance. During the nine to 10-week weight loss phase, participants had to lose 10-14% of their starting body weight. After a two-week weight stabilization period, participants who hit the weight loss targets were randomized to a high (60%), moderate (40%), or low (20%) carbohydrate diet. During this 20-week weight maintenance phase, calorie intake was modified so that participants maintained their new weight within plus or minus two kilograms (plus or minus 4.4 pounds).

Wi-Fi scales were used daily for monitoring of bodyweight and meals were provided to all participants. Diet composition can be seen in Table 1. The relative amount of added sugars was held constant across all diets (15% of total carbohydrate) but the absolute amount varied across individuals. A sample menu can be seen here in Table 1.

Figure 1: Study design

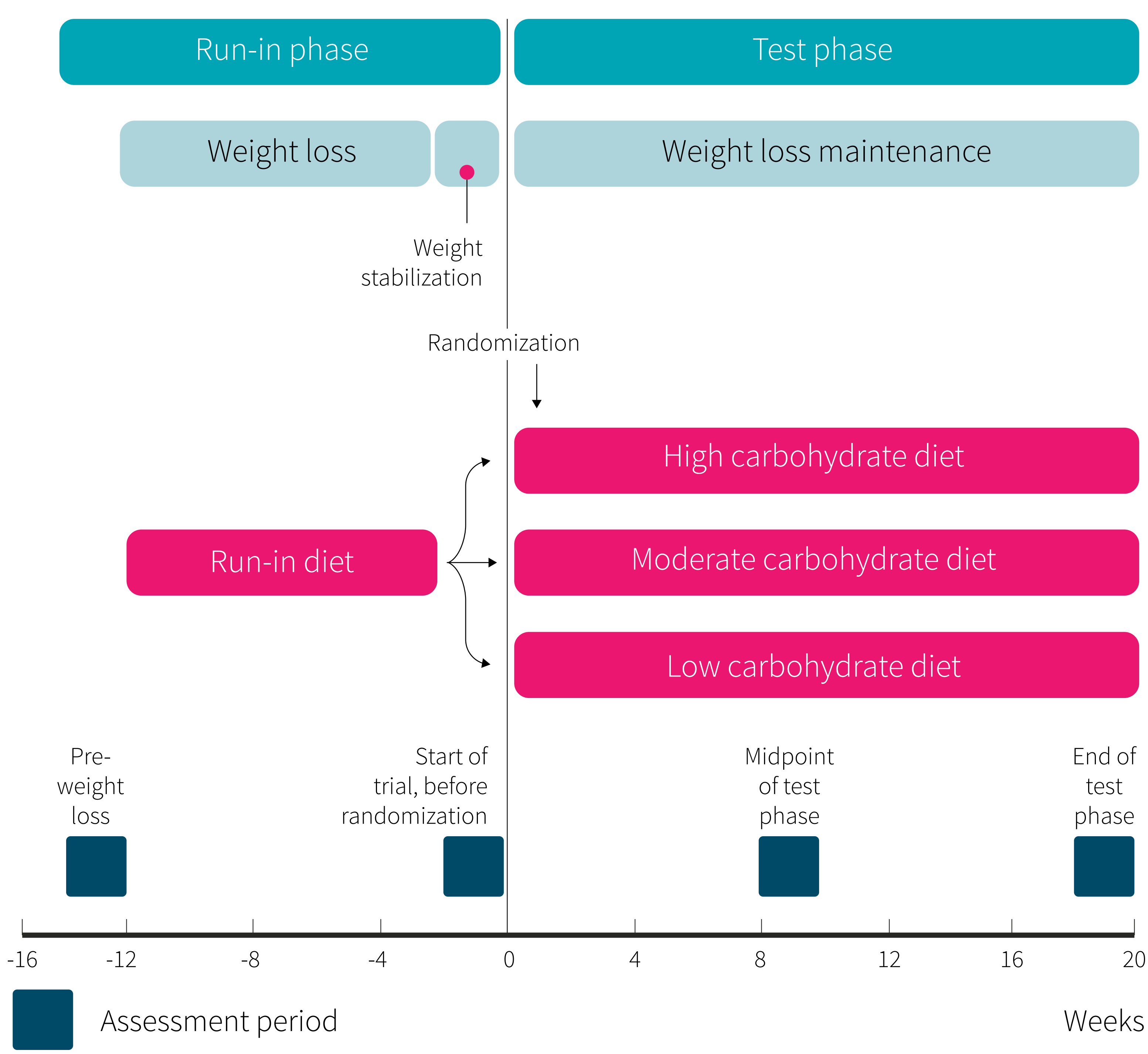


Table 1. Diet composition

	High	Moderate	Low
Energy (kcal)	2001	2001	2001
Carbohydrate (g / %)	305 *(59.2%)*	205 *(39.7%)*	105 *(20.3%)*
Fat (g / %)	48 *(20.9)*	92 *(40.1%)*	137 *(59.6%)*
Protein (g / %)	102 *(19.9%)*	104 *(20.2%)*	103 *(20.1%)*
Fiber (g)	33	28	22
Glycemic load	135	80	28
Saturated fat (% of total energy)	5.9	13.7	20.9
Monounsaturated fat (% of total energy)	8.2	15.9	25.1
Polyunsaturated fat (% of total energy)	5.3	8.6	11.3

Glycemic Load = (glycemic index/100) * net carbohydrate

This study's protocol was preregistered and the full methodology was previously published. Additionally, the study dataset and statistical code are available at the Open Science Framework.

This randomized trial enrolled 234 overweight participants. The primary endpoint was to see if adjusting the dietary carbohydrate-to-fat ratio affected total energy expenditure. After losing 12% (plus or minus 2%) of their starting bodyweight, participants were placed into a weight maintenance phase where calorie intake was adjusted to keep them within plus or minus two kilograms (plus or minus 4.4 pounds) of their new weight. Bodyweight was measured daily, food was provided, and energy expenditure was measured via doubly labeled water.

What were the findings?

Of the 234 participants recruited for the run-in phase, 164 achieved 12% (plus or minus 2%) weight loss and were randomized to high (n=54), moderate (n=53), or low (n=57) carb diets. Only 73.2% of initially randomized participants were able to maintain their weight loss within plus or minus two kilograms (plus or minus 4.4 pounds) by the study's end (n=120).

Two analyses were run: an intention-to-treat analysis, which includes data from all participants who were randomized regardless of whether they completed the study (n=162), and a per-protocol analysis, which only analyzes the data from people who completed the entire study (n=120). Diet type significantly affected total energy expenditure, with the low-carb group seeing an average increase in energy expenditure of about 60-200 kcal per day from baseline, as seen in Figure 2. When comparing the difference in energy expenditure between low- and high-carb, the low-carb group saw an average increase of about 190 kcal per day in the intention-to-treat analysis and about 280 kcal per day in the per-protocol analysis.

Additionally, there was a significant diet effect modification by pre-weight loss insulin secretion on total energy expenditure in the per-protocol, but not the intention-to-treat, analysis. In the per-protocol analysis, participants with the highest baseline insulin secretion levels saw the biggest increases in total energy expenditure on a low-carb diet. There were no significant effects of diet on resting energy expenditure, physical activity, or skeletal muscle work efficiency.

Participants in the low-carb diet group significantly increased their total energy expenditure compared to both the baseline measure (about 160-200 kcal per day) and to the high-carb group (about 190-280 kcal per day). No significant effects were observed for resting energy expenditure, physical activity, or skeletal muscle work efficiency. Participants with the highest baseline insulin secretion levels saw the biggest increases in total energy expenditure on a low-carb diet.

What does the study really tell us?

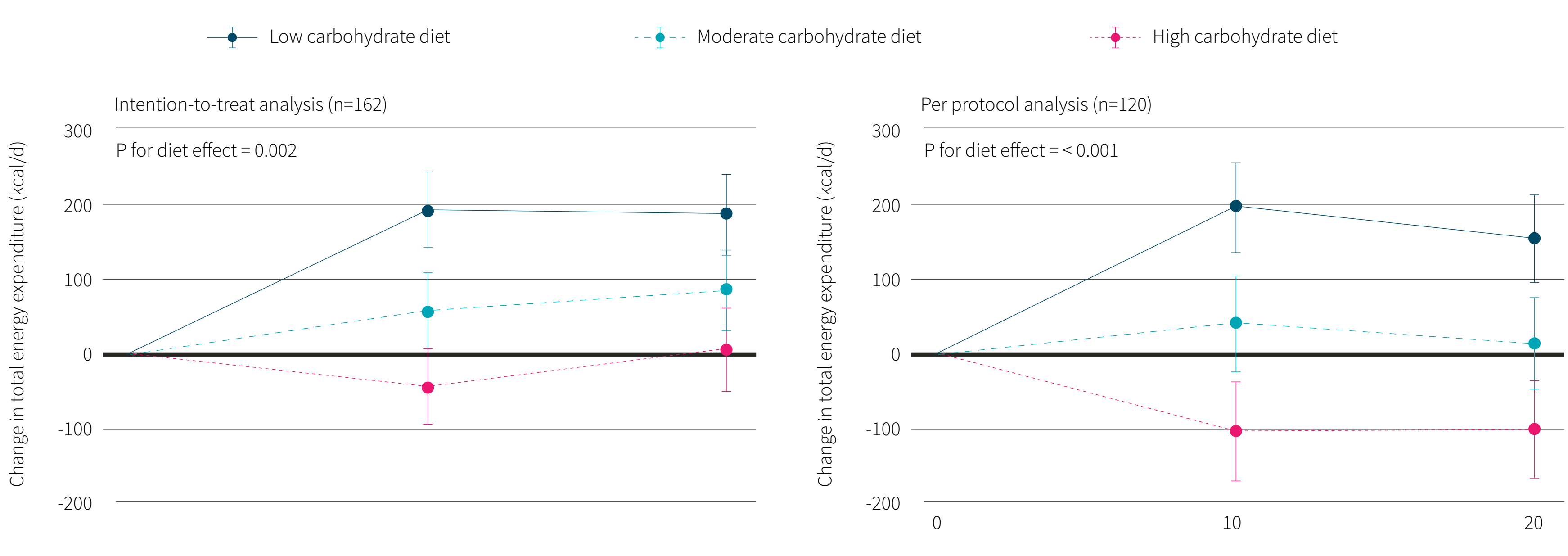
The results of this study provide a positive datapoint in favor of the CIMO. The reported increases in total energy expenditure for the low-carb diet group over the high-carb group are some of the largest ever seen in the literature. If these results are shown to be a true effect, this would implicate that a low-carb diet may be a superior strategy for people attempting to maintain their bodyweight after a period of weight loss.

This study had some key strengths in its design. The sample size was large, it was of relatively long duration (something difficult to do in diet studies), food was provided and biomarkers were used to track adherence, professional support was provided to keep adherence high, dietary protein was matched among all three diet arms, and it was a randomized trial. Participants were also monetarily compensated, which may have aided in adherence.

Among the study's limitations, there have been two notable points of criticism. The first argues that doubly labeled water has not been validated for use in a low-carb diet and may overestimate energy expenditure. This criticism gets at an important question: if the increase in energy expenditure observed in the low-carb group is a real effect, where did it come from? There are a few possible options:

- Resting energy expenditure could have increased.
- Physical activity levels could have increased.
- Skeletal muscle work efficiency could have

Figure 2: Results



decreased, meaning that more energy would have been expended to produce the same amount of work done compared to baseline.
- The thermic effect of food could have increased, meaning more energy would have been expended to digest food.

While there is no data on the last option, an implausibly large increase in the thermic effect of food would have to be seen for this option to meaningfully contribute to the changes reported for total daily energy expenditure. However, there is some data on the first three options. In the present study, there were no significant differences in resting energy expenditure between diet groups. However, there did seem to be a hint of a dose-response, and the low-carb group experienced an increase of about 30 kcal per day over the high-carb group. No dose-response was seen in physical activity time or time spent sedentary as both were statistically insignificant between groups. Measures of skeletal muscle work efficiency, while not significant, increased in the low-carb group (i.e., fewer calories used for the same amount of work). This is in the opposite of the expected direction if work efficiency were responsible, even partly so, for the increase in total energy expenditure.

As other measures of energy expenditure have not appeared to account for the increase seen with the doubly labeled water method, it is plausible that this method may overestimate energy expenditure on a low-carb diet. There are some human and animal study data that indicate this may be a real issue. This potential bias could also account for the dose-response effect seen in total energy expenditure between the high, moderate, and low-carb arms. However, a proper validation study would be needed to quantify how much, if any, bias this method may have introduced.

The second criticism argues that changes in total energy expenditure were compared to measures taken in the weight stabilization phase, which may have introduced some bias into the measure, and that comparing changes in total energy expenditure with the pre-weight loss measure as the baseline would have been more appropriate. A secondary analysis was conducted using the pre-weight loss measure as the comparison point. When analyzed in this manner, the results of total daily energy expenditure between diets no longer become significant.

Lastly, while food was provided to the participants, the results indicate there was a potentially large portion of food being consumed that was unaccounted for in the food intake measures. This too may have biased the results observed in total daily energy expenditure.

The study had some notable strengths in its design: preregistered design, provided food, large sample size, long duration, professional support provided to participants, and randomization. However, there are some open questions about the validity of using doubly labeled water to measure energy expenditure of people on a low-carb diet. Additionally, there is some debate about which time point should be used as the baseline measure: pre-weight loss or during weight stabilization.

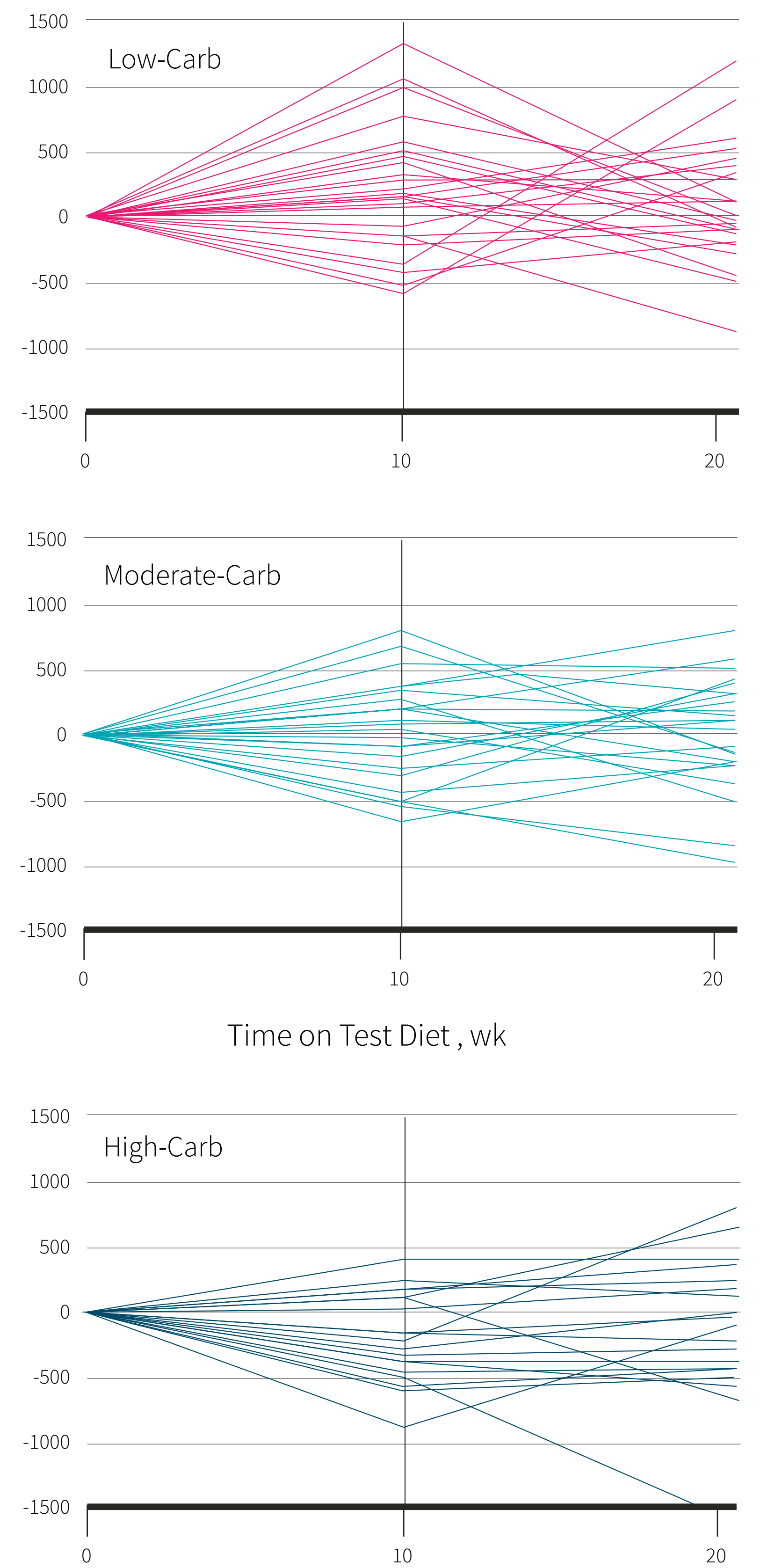
The big picture

An important but often overlooked aspect of weight change trials is that of individual variability. Take a look at the average change in total energy expenditure in Figure 2 and compare that to the individual changes in total energy expenditure in Figure 3. The individual responses are highly varied, with energy expenditure changes covering a an approximate 2,500 kcal spread.

This provides some indication that, if the increased energy expenditure on low-carb was a real effect, it may not apply to all who attempt it. Data from long-term, free-living studies is helpful to determine if this reported energy expenditure increase would have real-world effects. In these trials (12 months or longer), multiple RCTs have found that low-fat and low-carb diets yield small weight loss differences when compared head-to-head. These studies report minimal *between-group* differences, but these reports of group averages can be obfuscating. When examined, the individual weight changes *within* either dietary group can vary by a huge margin: some participants lose 30 kilograms (66 pounds) while others gain 10 kilograms (22 pounds).

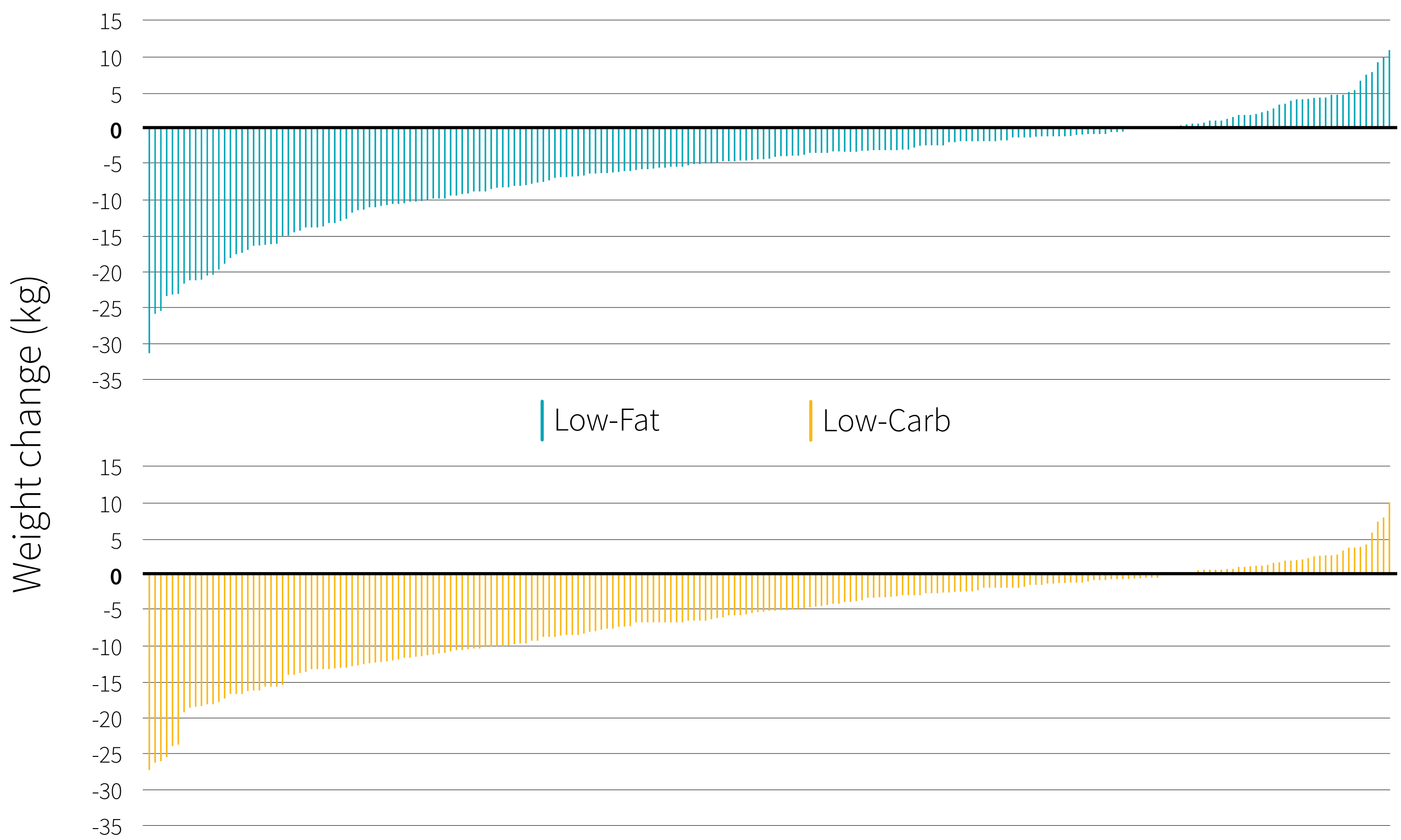
The DIETFITS trial, another NuSI funded study covered in ERD #41, Volume 2, can provide some additional insight. DIETFITS, which randomized 600 participants to a low-carb or low-fat diet for a year, had some notable strengths and outcome measures. It focused on diet-quality in both groups and did not advise either to restrict calories, it measured the effects of baseline insulin on weight loss, and it measured resting and estimated total energy expenditure. At the study's end, no significant differences in weight or fat loss between groups were seen and very similar individual weight loss profiles between groups were reported, as seen in Figure 4 (each bar represents the weight change of a single participant). Insulin secretion at baseline did not predict weight change in either group and neither resting or total energy expenditure was significantly different between groups.

Figure 3: Individual results



DIETFITS also saw similar completion rates between groups, with 76.8% of low-fat and 74.8% of low-carb participants completing the entire trial. A recent analysis of keto intervention studies saw no significant difference in dropouts when compared to the control diet groups. The present study also had similar between-group completion rates over the 20-week maintenance phase: 70.4% in the high-carb group, 73.6% in the moderate-carb group, and 75.4% in the low-carb group. These data all suggest that, if the low-carb energy expenditure increase is a real effect, it does not seem to translate into greater adherence or weight loss in the long-term, on average.

Figure 4: Total weight loss for each individual participant



Only one meta-analysis on the effects of carb-to-fat ratios in the diet on energy expenditure has been published to date. It reviewed 28 high-carb vs. low-carb or ketogenic low-carb trials where participants were in a metabolic ward or where all food was provided and protein and total calories were equal between groups. Overall, the results found that "both energy expenditure (26 kcal per day; P <.0001) and fat loss (16 grams per day; P <.0001) were greater with lower fat diets"—results that the authors go on to say are clinically meaningless differences. The total energy expenditure differences reported in the present study favors the low-carb group by a larger, and clinically relevant, margin than any of the previous 28 studies.

If the increased energy expenditure seen in the low-carb arm of the present study is a true effect, and not due to measurement bias, it could lead to better adherence and weight loss in the long run. However, in many long-term trials, adherence and weight loss between low- and high-carb diets are very similar on average, though this can vary on the individual level.

Frequently asked questions

What happened to body composition during this trial?

Body composition was assessed via DXA scans at three time-points during the study. While there is data on the baseline measures, no other time points were reported. It would be interesting to see how body composition changed over the course of the weight maintenance phase as this would be another data point to evaluate the changes in total energy expenditure reported. These data may be released in future publications.

How were blood lipids affected?

A full lipid profile was taken for each participant at four time-points. In this study, only changes for HDL-C and triglycerides were reported. In the per-protocol analysis (i.e., participants who completed the entire study), HDL-C was increased in the low-carb group by about 13 mg/dL (0.34 mmol/L) and by about 7.0 mg/dL (0.18 mmol/L) in the high-carb group. For triglycerides, a decrease of about 10 mg/dL (0.11 mmol/L) was seen for the low-carb group and increase of about 9.0 mg/dL (0.10 mmol/L) was seen in the high-carb group. Although measured, changes in total cholesterol and LDL-C were not reported.

What should I know?

This study reported a very large change in total energy expenditure with manipulation of the carb-to-fat ratio, favoring greater total energy expenditure increases in those on the low-carb diet. However, there are some open questions about the effects that doubly labeled water and the time point chosen as the baseline measure may have had on these results.

While this study adds an interesting datapoint in regard to post weight-loss weight maintenance, there is not enough overall data to provide a blanket recommendation to follow a low-carb diet or any other specific diet. Certainly, this strategy can be successful for many. However, long-term studies have not seen an overall advantage for this approach. ◆

Further reading

There has been *a lot* of debate around this study—more than could be covered in this review. If you want to do an even deeper dive, here are some additional articles. If you want to catch up first, check out previous ERD issues that covered both previous NuSI funded studies.

- ERD #22, Volume 2: Quoth the insulin hypothesis, "Nevermore"
- ERD #41, Volume 2: Low-fat or low-carb: can genes or insulin say which is right for you?

Dr. Kevin Hall has presented two papers critical of the study's methodology.

- No Significant Effect of Dietary Carbohydrate versus Fat on the Reduction in Total Energy Expenditure During Maintenance of Lost Weight: A Secondary Analysis
- Methodologic Issues in Doubly Labeled Water Measurements of Energy Expenditure During Very Low-Carbohydrate Diets

Dr. Hall and Dr. Ludwig have debated the above papers in the BMJ Rapid Response section.

- No Significant Effect of Dietary Carbohydrate versus Fat on the Reduction in Total Energy Expenditure During Maintenance of Lost Weight
- Author Response to Hall and Guo Regarding Data Reanalysis and Other Criticisms

Dr. Ludwig did a blog post about his study.

- The Case for a Low-Carb Diet Is Stronger Than Ever

Lastly, here are two papers presenting the case for and against the carbohydrate-insulin model of obesity.

- The Carbohydrate-Insulin Model of Obesity: Beyond "Calories In, Calories Out".
- The Carbohydrate-Insulin Model of Obesity Is Difficult to Reconcile With Current Evidence.

Given this recent study and some criticisms that have been levied against it, what's your take on the status carbohydrate-insulin model of obesity? Have your say, and see what your peers are saying, over at private ERD Facebook forum.