Quoth the insulin hypothesis, “Nevermore”

Energy expenditure and body composition changes after an isocaloric ketogenic diet in overweight and obese men

Introduction

Adversarial collaboration is when researchers who hold conflicting opinions gather to conduct experiments that will help to resolve or reduce their differences. The present study was a product of this process. The Nutrition Science Initiative (NuSI), co-founded by Gary Taubes (champion of the carbohydrate-insulin hypothesis of obesity), assembled a team of experts to run a clinical trial designed to answer the question: Will very-low-carbohydrate ketogenic diets lead to greater energy expenditure, and thus fat loss, when compared to a high carbohydrate diet?

Ketogenic diets usually take the form of severely restricted carbohydrate intakes, usually down to around 5% of total calories. Taubes has hypothesized that whenever someone goes on a diet, they "will remove the most fattening carbohydrates from the diet and some portion of total carbohydrates as well. And if we lose fat, this will almost assuredly be the reason why" (Why We Get Fat, p. 144-47). Prior research conducted by Dr. Kevin Hall, lead researcher of the study under review, has not supported this hypothesis. When investigating mechanisms of fat loss, Dr. Hall's pilot study showed that a reduction in carbohydrate was not necessary for fat loss nor was any metabolic advantage (i.e. increased metabolism) for fat loss seen when insulin secretion was reduced by 22% while on a low-carb diet. That trial (covered in our blog post and in ERD #11, Volume 2) had some limitations, though, such as its short 6-day duration. The present study aims to expand on this research, by conducting a two-month trial that compares a high-carbohydrate to a ketogenic diet.

As there are different versions of the carbohydrate-insulin hypothesis of obesity, it's important to clarify which one is being tested. The hypothesis being examined here proposes the following: carbohydrate in the diet elevates insulin secretion, which suppresses the release of stored body fat and drives circulating fat to be stored. A decrease of circulating fatty acids leaves less total energy available for use by organs like the heart, liver, and muscles, which can lead to a decline in energy expenditure and promote hormonal signaling, resulting in increased food intake. Thus, it is posited that the development of obesity is a consequence of carbohydrate-induced insulin production driving fat into storage, preventing it from being oxidized for energy.

It would then stand to reason that reducing the amount of carbohydrate consumed, while keeping variables such as total calories and protein intakes constant, should result in a drop of insulin secretion, causing a cascade reaction that would allow for increased energy expenditure and increased fat loss. The competing calories in, calories out (CICO) hypothesis maintains that exchanging carbohydrate for fat will not notably affect body fat levels nor energy expenditure. This study was designed to test which of these hypotheses might be true.

A team of researchers, recruited by the Nutrition Science Initiative (NuSI), conducted a study to test the carbohydrate-insulin hypothesis of obesity. This hypothesis states that the development of obesity is brought about through elevated insulin, caused by too much carbohydrate in the diet, driving fat into storage and preventing it from being oxidized for energy.

Who and what was studied?

Seventeen men between the ages of 18-50 (average age: 33) who were overweight or obese were admitted to a metabolic ward for this cross-over study. In a metabolic ward, participants are confined to a building where all food intake is strictly measured and controlled, so as to be certain of how many calories are consumed. This offers a major advantage over free-living studies that can be fraught with inaccurate self-reported food intake.

To give you an idea of how stringently food is monitored, here are some of the policies participants had to comply with: All meals were consumed under observation of the research staff. While visitors were permitted, they could only meet with participants in a common area under supervision to ensure no exchanges of food were made. Additionally, one of the study sites did not have the metabolic chambers (where energy expenditure, as broken down in Figure 1, is measured) and the metabolic ward (where participants live) in the same location. In this case, all participants were transported to and from these sites under supervision to make sure they didn't sneak any food.

While participants were overweight or obese (BMI between 25-35), they were otherwise healthy and had been weight-stable in the six months prior to the trial. People on a reduced (less than 30%) or high-carbohydrate (greater than 65%) diet were excluded from the trial.

Two diets were employed during this eight-week study and were designed in partnership with Jeff and Brittanie Volk, two advocates for low-carb diets. The macronutrient profiles of each are shown in Figure 2. For the first four weeks, all participants consumed a

Figure 1: Components of energy expenditure

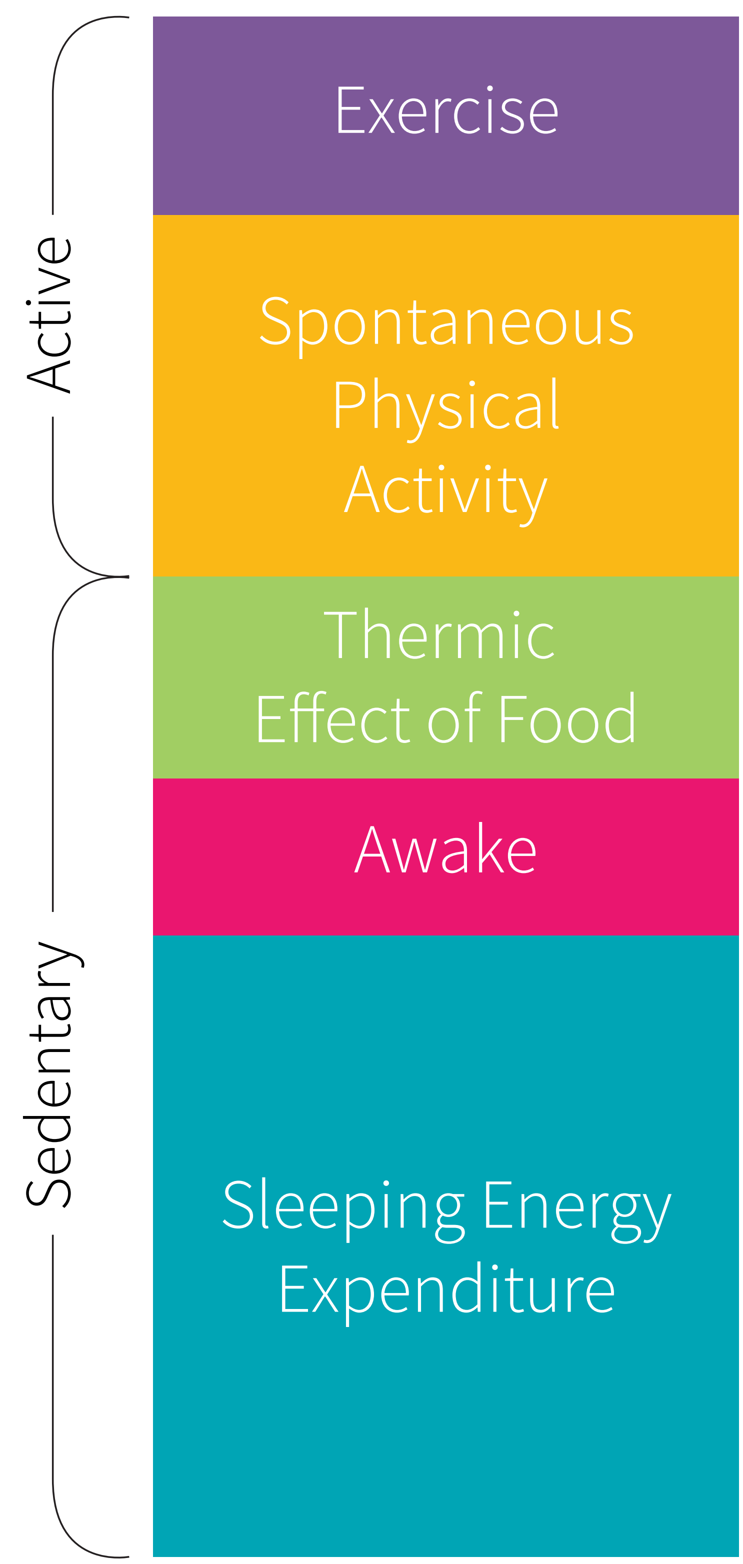
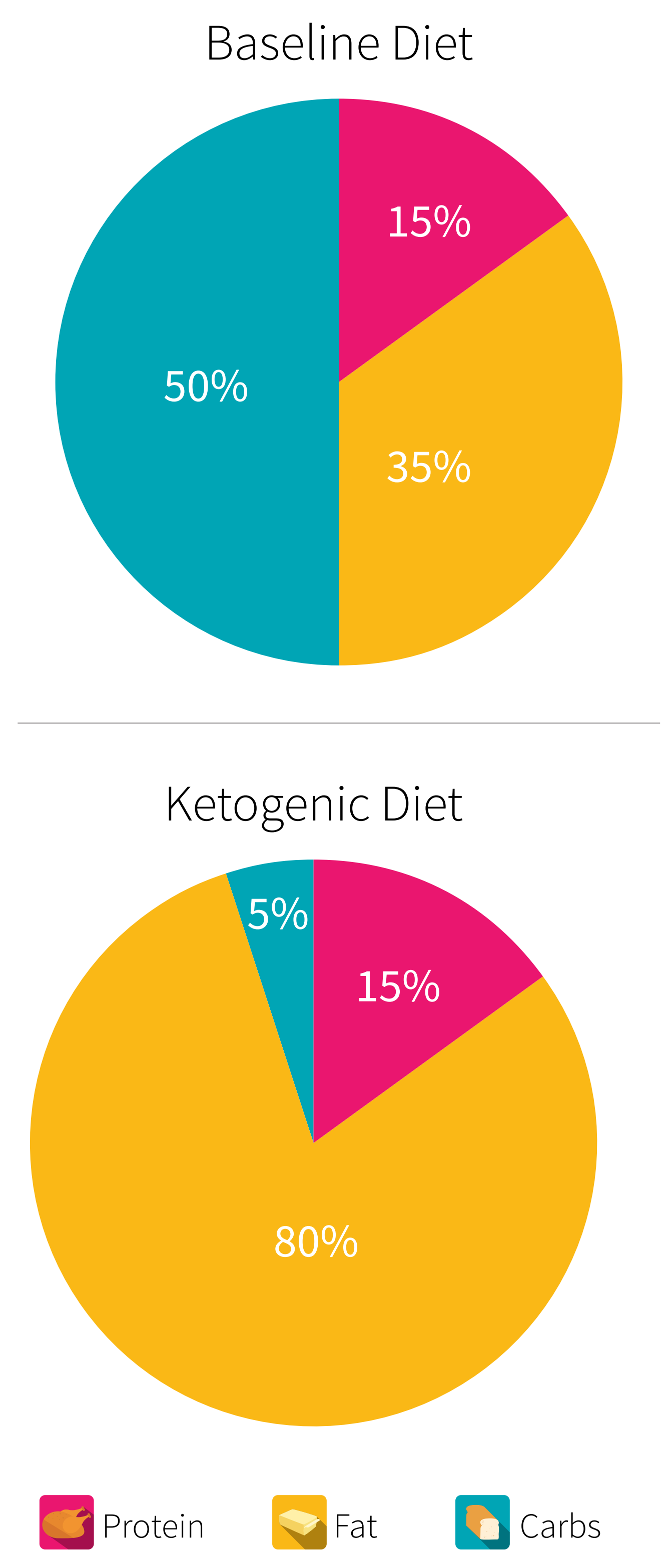


Figure 2: Macronutrient contents of the diets



2,398 kcal high-carbohydrate baseline phase (BP) that was 15% (91 grams) protein, 50% (300 grams) carbohydrate, and 35% (91 grams) fat. Of the carbohydrate content, 49% (147 grams) was sugar, but much of this was from naturally occurring sugars, as large amounts of added or liquid sugars were not used in the baseline phase. For reference, the average American adult consumes about 71 grams of **added** sugar per day. Aside from the higher sugar intake, this macronutrient composition is believed to represent a typical American diet.

In the second four-week period, participants ate a 2,394 kcal ketogenic diet (KD) that was protein matched to the BP diet at 15% (91 grams), 5% (31 grams) carbohydrate, and 80% (212 grams) fat. During the KD period, there was nearly a 10-fold decrease in carbohydrate intake and sugar consumption dropped by 93%, from 147 grams to 10 grams. Sample menus can be seen in Table 1.

It's important to note that energy intakes were altered weekly for the first two weeks of the BP. This was done to try and ensure everyone remained weight-stable. Fifteen days into the baseline phase, no more adjustments were made and daily caloric intake remained the same for the rest of the study. The compositions mentioned above represent the seven-day average BP and KD diets during the isocaloric periods.

There were two primary endpoints of this study: changes in energy expenditure and 24-hour respiratory quotient. This last measure is designed to see which substrate the body is primarily drawing energy from: fat or carbohydrate. Energy expenditure was measured every week by placing the participants in the metabolic chambers for two days. Results were corroborated by having participants drink doubly labeled water twice during the trial, once during each diet. Secondary endpoints looked at changes in body composition as

Table 1: Sample menus used in the trial

Baseline Phase	Ketogenic Diet
Breakfast	
Egg and potato hash with berries	Ham & Swiss omelet over spinach
Morning Snack	
Peanuts, oil-roasted, salted	Cheddar cheese
Chewy granola bar, chocolate chunk, low fat	Almonds, oil-roasted, salted
Lemonade, from concentrate	Bouillon cube, beef + Olive oil
Lunch	
Turkey burger with hot potato salad	Kielbasa with chilled mustard sauce & sautéed cabbage
Afternoon Snack	
Pretzel sticks	Celery with buffalo chicken dip
Wheat crackers & American cheese spread	
Dinner	
Cheese steak sandwich and pineapple	Spicy hamburger, sautéed squash, & mushrooms

measured by dual-energy X-ray absorptiometry (DXA), which were taken four times during the study. Various blood and urine measurements were also taken as exploratory measures.

Finally, as if being confined to a ward for two months wasn't hard enough, everyone had to exercise daily by cycling for 90 minutes. If you were wondering: Yes, these participants were financially compensated for their time.

Seventeen male participants (BMI 25-35) were confined to a metabolic ward for two months. Everyone consumed a high-carbohydrate baseline phase diet for four weeks prior to being switched to a ketogenic diet for the second four weeks. The primary endpoints were differences in energy expenditure and respiratory quotient. A major secondary endpoint was change in body composition. Exploratory blood and urine tests were also conducted.

What were the findings?

All 17 participants completed the study. While the researchers had aimed to keep participant weight stable over the trial, a loss of fat mass loss was recorded during the last six weeks of the study. The study is focused on the last six weeks, not the entire eight, because calories were still being adjusted in the first two-week period of the trial in an attempt to find the caloric intake that would keep participant weight stable. The last six weeks are when calories were set for good, thus providing the most reliable time period for analysis.

Much has been made of the fat loss numbers in this study, which have been broken down into four parts: Total Fat Loss, BP-2 (weeks 3-4), KD-1 (week 5-6), KD-2 (weeks 7-8).

Total Fat Loss - Participants lost 2.2 pounds (one kilogram) over the last six weeks of the study. Participants lost as much fat in the last two weeks of the BP (rate of 0.55 pounds/week) as they did over the four weeks KD (rate of 0.27 pounds/week).

BP-2 (weeks 3-4) - Although researchers noted a significant 1.1 pound (0.5 kilograms) loss of fat during this two-week period, no adjustments to food intake could be made at this point to try and prevent further loss as the caloric intake of every participant had been locked

How does a DXA scan work?

DXA scans (dual x-ray absorptiometry) is one of the most accurate ways to measure changes in lean mass, body fat, and bone density. Two methods with greater accuracy are computerized tomography (CT) scan or undergoing an autopsy, where the different components are cut out and weighed (we do not recommend this later method, as you have to be dead as a prerequisite).

When you get a DXA scan, you lay down on a bed while a robotic arm moves up and down the length of your body, emitting very low-level X-rays and measuring how many get absorbed. The whole process if fairly quick, usually taking 3-10 minutes, and it typically delivers measurements that are within 3% accuracy. Traditionally, DXA scans were employed to measure bone density to help detect or track development of osteoporosis. Modern machines can use equations to help calculate body fat and lean mass.

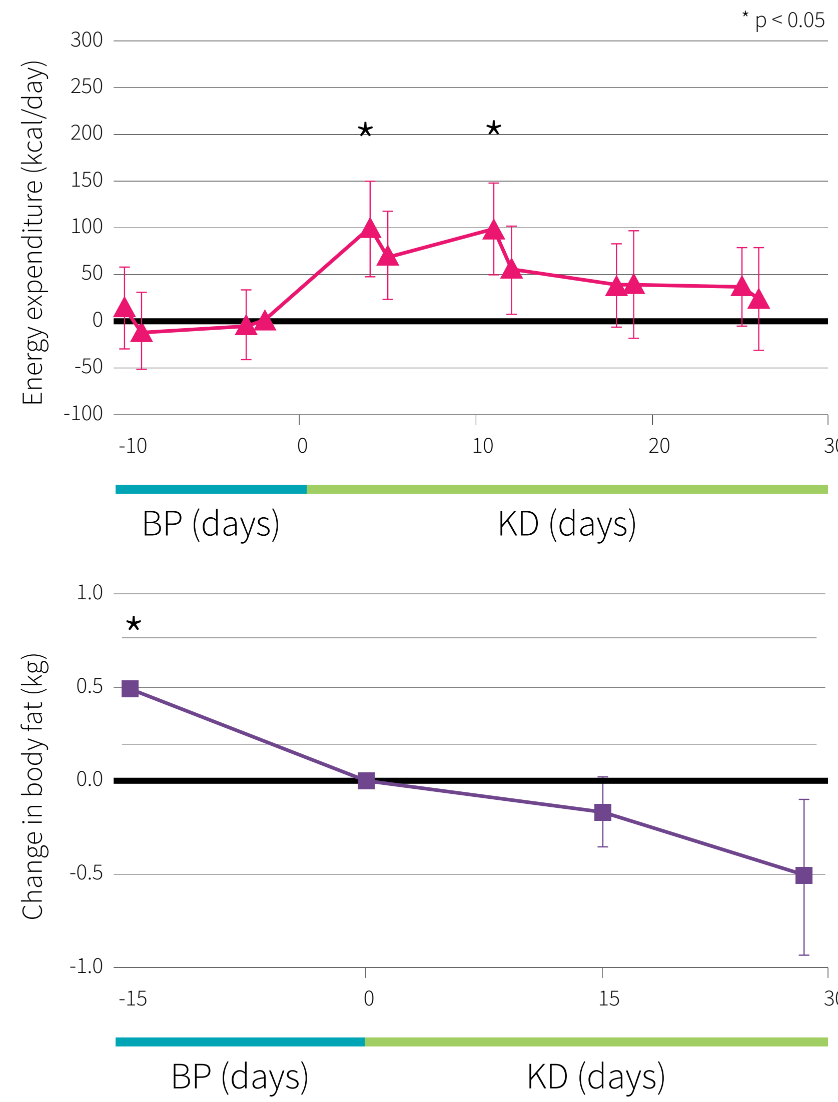
in. Adjusting them at this point would have confounded the results of the study.

KD-1 (week 5-6) - For the first two weeks of the KD phase, energy expenditure increased significantly. Participants were burning about 100 kcals more per day for 10 days. But (as shown in Figure 3) while energy expenditure increased, participants curiously experienced a slowdown in the rate of fat mass lost, losing only 0.44 pounds (0.2 kilograms) during KD-1. This indicates that, even though they were using more energy, stored fat mass was not utilized as much during this increase. However, protein loss significantly increased over this same period. It is possible that the increased utilization of protein (likely for gluconeogenesis, during which protein can be used to create glucose) accounted for some of the energy expenditure. This effect would diminish after the body becomes better adapted to running on ketones. Utilizing protein is an energy-intensive process compared to fat or carbohydrate. This increased protein use on low-carbohydrate diets has also been seen in Dr. Hall's previous metabolic ward study. The utilization of stored glucose (glycogen) may have also displaced fat as an energy source during KD-1 as well.

KD-2 (weeks 7-8) - The spike in energy expenditure seen in KD-1 was not sustained in KD-2, where expenditure levels almost returned to baseline levels. The rate of fat loss picked up a bit here, as participants lost 0.66 pounds (0.3 kilograms) of fat, but this rate still remained lower compared to BP-2. It's possible that the participants' metabolisms had become well-adjusted to the ketogenic diet and were not relying so heavily on protein and glycogen oxidation anymore, allowing it to burn dietary fat more efficiently.

Comparing energy deficits over the last two weeks of both diet phases (BP-2 vs. KD-2, when participant's bodies had "settled in" to their diets), no significant differences were observed in either the DXA scans or the

Figure 3: Results of fat loss and energy expenditure



doubly labeled water. These data, when added together with the lower rate of fat loss seen during the KD indicates that a ketogenic diet does not confer an advantage to fat loss over a high-carb diet when matched for calories and protein.

After transitioning to the KD, insulin secretion decreased by 47% and participants shifted to predominantly burning dietary fat as fuel by day five. Despite the sharp drop in carbohydrate consumption and insulin secretion, no significant increases in fat loss were observed in the KD phase compared to the BP phase. This finding indicates that a large decrease in insulin secretion does not provide a fat loss advantage over diets that produce higher total daily insulin secretion when matched for calories and protein.

All participants completed the study. While energy expenditure increased (for ~10 days) and daily insulin secretions fell by 47% on the KD diet, no significant increases in fat mass loss were observed compared to the BP. The rate of fat loss slowed in the KD phase while energy expenditure increased. This fat loss rate picked up in the last two weeks of the KD but never surpassed that of the BP. These findings indicate no metabolic advantage to a ketogenic diet over a high-carbohydrate diet when calories and protein intake are matched.

What does the study really tell us?

This study provides more evidence supporting the calories in, calories out model of obesity. The carbohydrate-insulin hypothesis predicts that diets high in carbohydrate will drive up insulin and therefore increase fat mass accumulation while decreasing fat loss. However, the BP was high in carbohydrate, in particular, refined carbohydrate (147 grams of sugar per day!) and the rate of fat loss was slightly faster than the KD phase.

Proponents of the insulin model have indicated that a ketogenic diet should provide a metabolic advantage to the tune of 300-600 more kcals burned per day due to increased energy expenditure. And yet, while the KD reduced carbohydrate intake by 89.7% and insulin secretion decreased by nearly 50%, no sustained energy expenditure increases were seen beyond the first 10 days and fat mass loss did not accelerate. In fact, loss of fat actually decreased during the period in which participant energy expenditure increased. If the keto diet period had continued long enough, energy expenditure and fat loss rate would probably have converged with the baseline diet.

This study was initially designed to keep people weight stable throughout the trial. That clearly did not happen, as average fat mass loss was 2.2 pounds (one kilogram) over the course of six weeks. While not a substantial rate of fat loss (0.33 pounds per week), it still may be a marginal confounder for this study. On the other hand, if the KD condition were to provide a large metabolic advantage, as predicted by the carbohydrate-insulin hypothesis, there should have been a substantial increase in fat loss while participants were on the ketogenic diet, despite earlier fat loss. That effect was not borne out.

No study is without limitations. The authors did not measure energy lost in fecal content and did not have a control group that didn't receive the KD over the second half of the study. Nor did they have a group that received the diets in reverse order. The trial also used a protein intake level that may be lower than what some real-life ketogenic dieters employ. And the results cannot necessarily be extrapolated wholesale to women or men who have a BMI lower than 25, higher than 35, or who have various health conditions.

The hypothesis that low-carbohydrate diets provide a metabolic advantage of up to 300-600 additional calories burned per day was not seen in this well-controlled metabolic ward study.

The big picture

"Our data do not support the carbohydrate–insulin model predictions of physiologically relevant increases in (energy expenditure) or greater body fat loss in response to an isocaloric (ketogenic diet)."

This study shows that a ketogenic diet may not be a weight loss magic bullet, and it also gives us data indicating that a CICO model may start to reach its limits at macronutrient extremes, at least over periods of weeks. Energy expenditure and fat loss were different on two diets supplying the same calorie intake. These were due to different macronutrient compositions.

The findings of this study are a bit anticlimactic. Imagine if the results had come back that a ketogenic diet could blast your metabolism into the stratosphere. It would have been incredible. The public health approach to treating obesity would (in an ideal world) have experienced a cosmic shift. Alas, no such paradigm-altering results were observed. These findings build on prior research showing that insulin is not the primary regulator of body fat.

But do not despair, there is a bright side to this all. People who dread the thought of a keto diet or don't particularly care for the low-carb approach can be sure that it is not the only route to sustainable fat loss.

It's possible to go on a well-planned, whole-foods based, ketogenic diet. Some people find that a very-low-carb or reduced carbohydrate approach work best for them. Many people report feeling less hungry on a low-carb or ketogenic diet in a real world setting. Often, these increased feelings of satiety brought about through higher protein intakes that often occur on low-carb diets. If this is you, then keep at it, because in the end adherence is king. If you force yourself into a pattern of eating you can't reliably sustain, your chances of failure are high.

Keto diets have not been shown to significantly increase your metabolism. Want to go low-carb? Do it. Want to go high-carb? Do it. Want to become a Breatharian, eat no food ever again, and only subsist on the air you breathe? Please don't do that. Both high-carb, low-carb, and somewhere-in-the-middle-carb approaches can work for weight loss, so choose the one that fits your lifestyle best.

Frequently asked questions: XXL Edition

Studies like this one tend to generate a lot of press, so many misconceptions and questions abound. To cut through some of the hype, we're bringing you another round of the F.A.Q: XXL Edition, to shed some light onto these queries.

Won't the diet order mess up the rate of fat loss for the second four-week period of the study?

The diet order would likely have little effect on the results of the study. It could in theory, but only slightly and not nearly enough to explain the slowdown in fat

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loss observed in the first two weeks of the KD phase. The researchers even adjusted the calculations for energy expenditure to take into account the weight loss and this did not shift the results in any meaningful way.

Lead author Dr. Hall explains: "The study was designed such that the baseline run-in diet was intended to match the typical composition of the subjects' habitual diet. We screened out people whose habitual diet was too different in composition. Therefore, randomizing the diet order would introduce a significant order effect that could confound the interpretation of the data given that the ketogenic diet would represent an extreme change from their habitual diet upon entry to the study."

There were missing data for some of the metabolic chamber measurements. Won't this affect the final analysis?
The researchers collected a total of 272 days' worth of metabolic chamber data. Six data points had to be excluded due to chamber malfunctions: two from the BP phase and four from the KD phase. This accounts for 2.2% of all chamber data collected, so it is possible but unlikely that these exclude data points would significantly alter the analysis.

What effect does the small sample size have on the study results?
Good research practices dictate that you perform a power calculation before you begin an intervention trial. This calculation will give you the number of people you will need to recruit into your study to ensure that you can detect significant differences between groups. The researchers of this study did perform this calculation and found that 16 subjects were needed to reliably detect a change of ~150 kcal/day in energy expenditure measured in the chamber between BP and KD. In their actual study, they recruited 17 subjects, all of whom completed the trial.

What should I know?

The big takeaway is that a ketogenic diet does not appear to confer a fat loss advantage over high-carbohydrate diets when calories and protein are strictly matched (at least in this population and in the context of the limitations of this study). How should you apply this knowledge to your everyday life? Easy, pick the eating style that you can stick with over the long term. This study is not bashing ketogenic or low-carb diets, but merely pointing out that they probably don't confer fat-burning super-powers. ◆

While this study won't end the Carb Wars, it provides some useful fuel for discussion. Not ketogenic fuel though. Discuss it at the ERD Facebook forum.