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Ludwig DS, Dickinson SL, Henschel B, Ebbeling CB, Allison DB. Do Lower-Carbohydrate Diets Increase Total Energy Expenditure? An Updated and Reanalyzed Meta-Analysis of 29 Controlled-Feeding Studies. J Nutr. 2021 Mar 11;151(3):482-490.

What We Know, Think We Know, or Are Starting to Know

The question of "is a calorie a calorie?" is as old as nutrition research, as the search to understand the factors regulating energy intake and energy expenditure are fundamental to understanding human nutrition [1]. Seemingly lost in this longstanding debate is that a calorie is simply a unit of energy [specifically heat]; it has no value beyond this.

Nevertheless, the simple unit of energy has been at the centre of one of the longest debates in nutrition: "calories in, calories out", i.e., that human body mass is ultimately influenced by the balance of energy consumed ["calories in"] vs. the level of energy expended ["calories out"].

This longstanding debate has also centred on low-carbohydrate diets, popularised by the claims of Dr Robert Atkins in the early 1970's that anyone restricting carbohydrates would be able to consume as much dietary fat as possible and not gain weight; in fact, lose weight [2].

This hypothesis that low-carbohydrate diets conferred a "metabolic advantage" gathered momentum in the 2000's with evidence that suggested low-carb diets resulted in greater weight loss compared to low-fat diets [3,4]. Despite more rigorous studies suggesting no significant differences in weight loss [5,6], the fight has waged on. In the red corner is David Ludwig, convinced low-carb diets defy our current models of energy expenditure, while Kevin Hall is in the blue corner taking these claims to task.

Can either of them deliver a knockout blow? It could be the present study...

The Study

The study was a systematic review and meta-analysis of trials examining the effects of lower carbohydrate diets on energy expenditure. To be included, the primary studies had to meet the following criteria:

- **Design**: Experimental studies that used either whole-room calorimetry* or doubly-labelled water* [***see Geek Box**, below, for further details on these methods] to measure energy expenditure. Studies were required to have provided all foods to participants.

- **Population**: Not specified.

- **Intervention**: Low-carbohydrate diets, i.e., "low" compared to a higher intake level irrespective of the absolute level of carbohydrate.

- **Control**: A high-carbohydrate diet, with protein and total energy intake matched between diets.
- **Outcome**: Total energy expenditure [TEE].

The effect size for the primary outcome of TEE was calculated as the difference in TEE between the lower- and higher-carbohydrate diets in each study. The effect size for each study was combined together in a meta-analysis. The analysis was conducted according to study duration comparing effects of studies <17-days or >17-days, respectively.

The analysis also compared the effects on TEE for each 10% decrease in carbohydrate intake contrasting the level of carbohydrate in the low- and high-carbohydrate diets. The outcomes were reported as TEE in kcal with 95% confidence intervals [CI].

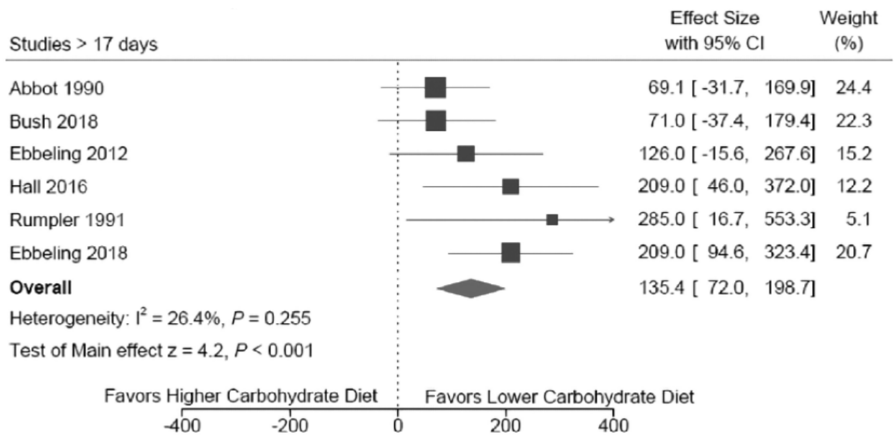
*Geek Box: Methods of Measuring Energy Expenditure in Humans

If you read metabolic ward studies, you may come across the term "respiratory chamber" and see that energy expenditure was measured by what is known as "calorimetry". This is often referred to as "whole-room calorimetry" and is where energy expenditure is assessed around the clock with a participant housed in an airtight room. Calorimetry measures the difference between oxygen [O_2] and carbon dioxide [CO_2] concentrations from the respiration of the participant in the room. As a fixed value for oxygen is supplied into the room, the rate and amount of carbon dioxide production provides data to calculate energy expenditure through the use of mathematical equations. As all macronutrients - proteins, fats, carbohydrates - contain carbon, the values of protein, carbohydrate, and fat oxidation can also be calculated from this data, indicating what substrate is being utilised after a participant has eaten a meal, and at what rate.

Another method of measuring energy expenditure is "doubly-labelled water" [DLW], which is considered the gold standard for assessing total energy expenditure in free-living humans. DLW uses stable isotope tracers, i.e., "labels" water [H_2O] with two very uncommon isotopes, deuterium [^2H] and oxygen-18 [^{18}O]. Thus, when that water is eventually excreted in urine, the two tracers - ^2H and ^{18}O – are easily identified. The difference between the rate of elimination of ^2H and ^{18}O from the body provides an indirect estimate of the production rate of CO_2. In turn, the daily rate of CO_2 production is used as the measure of total energy expenditure. DLW is consumed orally, making it very effective for 'in the field' research, and providing estimates of human energy expenditure in the real-world [compared to a lab]. Because it is consumed orally, and is safe, DLW can be used in all populations, including infants, and can provide a measurement of energy expenditure over long periods of time.

Results: 29 studies were included in the final analysis, including 617 total participants. The difference in carbohydrate intake between low-carb and high-carb groups in the included studies ranged from 8% to 77% energy, with an average difference of ~30%. The duration of the trials ranged from 1-day to 140-days, with an average of 4-days. In total, 23 trials were <17-days and 6 trials were >17-days.

Meta-Analysis by Study Duration: In the 23 trials of <17-days duration, low-carb diets had a lower TEE compared to high-carb diets of –50kcal/d [95% CI, –22 to –77kcal/d]. However, in trials >17-days duration low-carb diets showed an increased TEE by 135 kcal/d [95% CI, 72 to 198kcal/d].



***Forest plot** from the paper illustrating the effects of low-carb compared to high-carb diets on total energy expenditure in studies lasting >17-days duration.*

Analysis Per 10% Carbohydrate Decrease: In the shorter-term trials of <17-days duration, each 10% decrease in carbohydrate level resulted in a –14kcal/d [95% CI, –7 to –21kcal/d] decrease in TEE. Conversely, in the trials >17-days duration, each 10% decrease in carbohydrate level resulted in an increase in TEE by 50kcal/d [95% CI, 31 to 69kcal/d].

The Critical Breakdown

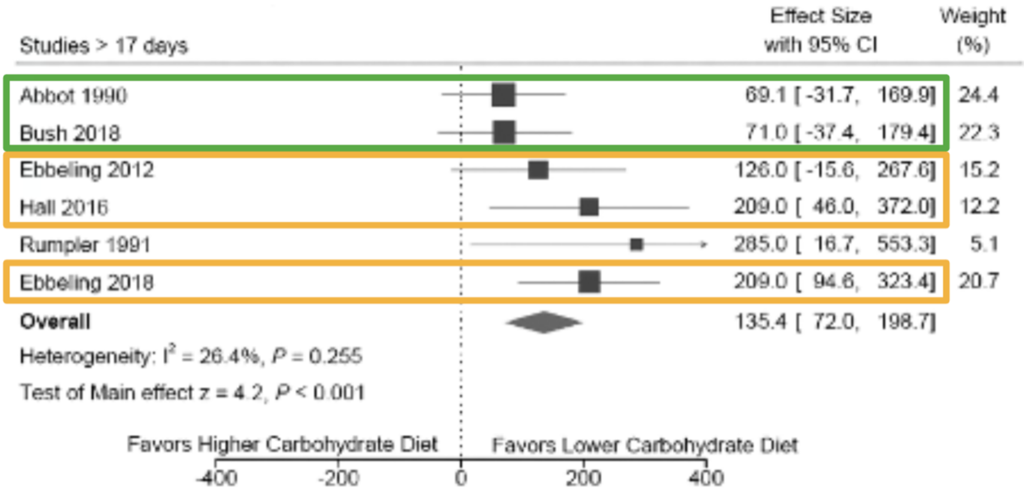
Pros: The inclusion criteria emphasised studies with provision of foods to participants, control of energy intakes and protein, and objective measures of energy expenditure. There was an appropriate exposure contrast in carbohydrate intakes between diets in included studies, with a 30–33% average difference between diets. This allowed for a more meaningful analysis of differences per 10% decrease in carbohydrate intake. The analysis according to study duration accounted for variation between studies and was more appropriate for combining the primary studies in a meta-analysis. For tightly controlled nutrition studies, the overall sample of 617 participants is larger than the previous meta-analysis of metabolic ward studies by Hall *et al*. [6].

Cons: While the primary included studies have some strengths, many trials had small sample sizes, lacked detail on randomisation [or did not randomise], and certain dietary details, in particular the composition of fats in the diets [which could influence energy expenditure]. Despite the paper identifying that the primary included studies varied in participant characteristics of weight, sex, age, and fitness levels, no data was presented on these characteristics in the paper, and each of these factors influence energy expenditure [to be fair, the authors draw attention to this lack of detail from the primary studies]. A major limitation of the analysis of studies >17-days is reliance on doubly-labelled water, which overestimates energy expenditure measurements of low-carb diets [7,8].

Key Characteristic

As with a previous study from Ludwig's group, which we covered as the very first ever Deepdive, the spectre of doubly-labelled water and low-carb diets rears its head again. The issue is that low-carbohydrate intake alters CO_2 production, leading to overestimations of energy expenditure [7,8].

To correct for this potential misestimation requires an additional measurement known as the "respiratory quotient" [RQ], which is the ratio of O_2 to CO_2 produced from metabolising macronutrients. Whole-room calorimetry measurements avoid this source of error, as RQ is calculated with the measurements of energy expenditure.



Now, take a look at the **forest plot** from the study above, which is now edited to represent which included studies used calculations of RQ from calorimetry [in **green**] and which used doubly-labelled water [in orange]. The difference is quite striking; while yes, the two studies by Abbott 1990 and Bush 2018 indicate greater energy expenditure on low-carb diets, the magnitude is far smaller than the estimates from the doubly-labelled water studies.

Interesting Finding

Given the criticisms in the previous section, let's now think about the two main effect sizes that this study holds forward: that on average low-carb diets lead to 135kcal/d greater TEE, and that for each 10% decrease in carbohydrate TEE increases by 50kcal/d.

What happens to this finding if some of the issues in the primary included studies are addressed? This was undertaken by Hall and Guyenet [9]; for the Hall *et al*. study included in the meta-analysis, whole-room calorimetry data was also available, and for the Ebbeling *et al*. 2018 study the adjustment for RQ lowered the energy expenditure value by 50%.

Using this data, a reanalysis indicated that low-carb diets over 14-days duration increased energy expenditure by 63kcal/d [95% CI, 24 to 102kca/dl] [9]. This estimate is right in line with the two studies in the original meta-analysis that did use whole-room calorimetry to assess TEE, and adds further evidence to the limitations of doubly-labelled water in assessing TEE of low-carb diets.

Relevance

"Hall vs. Ludwig" has become our generations "Keys vs. Yudkin" [see these Research Lectures on Keys' research on fats and Yudkin's research on sugar]. It arguably also shares a commonality, with Hall emphasising integrity and rigour in data analysis, while Ludwig seems determined only to prove what he already believes to be true anyway.

The determination of Ludwig *et al*. to demonstrate support for the "Carbohydrate-Insulin Model" [covered in another previous Research Lecture] has continually run up against a thorny issue: that science proceeds on the basis of evidence for or against a hypothesis. In this respect, that levels of insulin or glycaemic control act as a barrier to weight loss is unsupported either by tightly controlled metabolic ward studies or other interventions (5,10–14).

Which leaves us with the energy expenditure aspect of the claims. Do low-carb diets truly confer a "metabolic advantage"? The first question to ask is whether there is any true difference in energy expenditure on a low-carb diet, and it does appear that there is. One of Kevin Hall's metabolic ward studies illustrates this difference, where energy expenditure increased by ~57kcal/d on a ketogenic diet on average (12). This likely reflects increased oxygen consumption related to shifting into ketosis (12).

If the present study had conducted the meta-analysis using data that is corrected for measurement error of doubly-labelled water on low-carb diets, i.e., by using RQ in the calculations, it would have yielded results of a similar magnitude to the prior metabolic ward study from Hall *et al*. (9,12).

Then next question is, if there is a difference, does it lead to meaningful differences in human outcomes? And the answer to that, both in relation to measured fat oxidation and weight loss compared to a low-fat diet, is "no" (5,6,11,12). Given that any magnitude of increased energy expenditure is likely <100kcal/d, this is unsurprising.

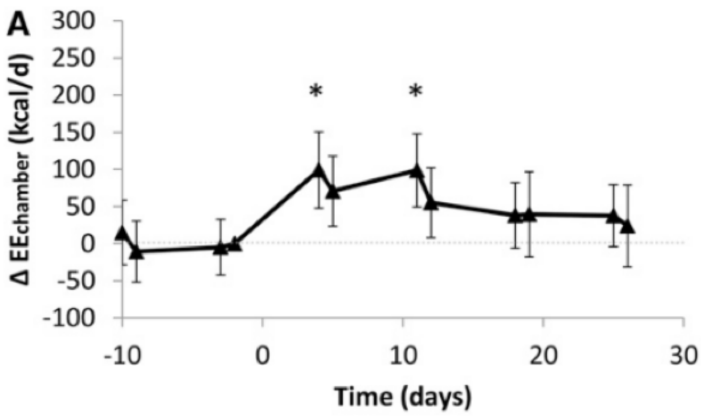


***Figure** from Hall et al. (12) illustrating the increase in energy expenditure following transition from a 4-week baseline diet to a ketogenic diet ["0" above]; energy expenditure measured using whole-room calorimetry increased by ~100kcal/d over the first week before declining steadily to the end of the 4-week phase on the diet. The average increase was 57kcal/d.*

Application to Practice

There are, of course, some reasons why low-carb diets may facilitate greater weight loss in the short-term, which relate to the substitution of carbs for higher dietary protein, satiety, and consumption of low energy density foods [see this previous Research Lecture]. And this may be a useful tool to deploy for an individual, should constructing a diet in this way suit them.

However, it is important to be clear on the *why* for low-carb diets, and at this point the evidence for the "Carbohydrate-Insulin Model" is confined to the mind of David Ludwig, and is conspicuously absent in published scientific research.

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