Diet carbs versus fat: does it really matter for maintaining lost weight?

The most read article of 2018 published in The BMJ claimed that restricting dietary carbohydrates offers a metabolic advantage for maintaining lost weight, but the data may not support this conclusion.

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Key messages

- The latest battle in the perpetual diet wars claimed that low carbohydrate diets offer a metabolic advantage to burn more calories and thereby help patients maintain lost weight.
- However, analyzing the data according to the original pre-registered statistical plan resulted in no statistically significant effects of diet composition on energy expenditure.
- The large reported diet effects on energy expenditure calculated using the revised analysis plan depended on data from subjects with excessive amounts of unaccounted energy. Adjusting the data to be commensurate with energy conservation resulted in a diet effect that was less than half the value reported in the BMJ paper.
- Diet adherence is key to sustained weight loss, and no diet has yet demonstrated a clinically meaningful superiority for long-term maintenance of lost weight. More research is required to better understand the factors that sustain healthful diet changes over the long-term.

Proponents of low carbohydrate diets have long claimed that such diets cause greater calorie expenditure thereby providing patients with a "high calorie way to stay thin forever" [1]. Indeed, a substantial persistent increase in total energy expenditure (TEE) with a low carbohydrate diet could be an important advantage given that long-term maintenance of lost weight remains the most vexing clinical challenge in the treatment of obesity [2]. While most studies have found no clinically meaningful effect of the dietary carbohydrate to fat ratio on TEE [3], a recent randomized controlled trial by Ebbeling et al. reported substantial TEE differences between low and high carbohydrate diets during maintenance of lost weight [4]. But the data may not support this conclusion.

Reported data analysis was not conducted according to the original plan

Registering a clinical trial's primary outcome and statistical analysis plan *before data is collected* helps reduce bias and improves scientific reproducibility [5]. The original pre-registered protocol and analysis plan of Ebbeling et al. addressed whether the reduction in TEE during maintenance of lost weight depended on the dietary carbohydrate to fat ratio *when compared to the pre-weight loss baseline* – a design similar to a pilot study by the same authors [6]. Ebbeling et al. powered their study using these pilot data with the primary outcome being TEE during weight loss maintenance versus the pre-weight loss baseline. This pre-registered plan was in place for most of the study's history, including 7 of 8 protocol versions between 2014-2016.

However, the analysis plan was modified in 2017 after all cohorts had completed the trial and after primary data for the first two of three cohorts were returned to the unblinded principal investigators in Boston from the blinded doubly labeled water (DLW) laboratory in Houston. Nevertheless, according to the principal investigator, the Boston statistician who performed the data analyses was unblinded to the diet assignments only after all primary data were returned from the Houston lab and after the revised analysis plan was registered. The change in analysis plan was not acknowledged in the original manuscript submission and was not reported in a previous publication of the trial design [7].

The revised primary outcome compared TEE during weight loss maintenance to TEE measured in the immediate post-weight loss period rather than the originally planned pre-weight loss baseline. No reasons for the change were provided in the final protocol or statistical analysis plan. The final BMJ publication stated the original plan was an "error" and their Data Supplement listed three reasons for the change. First, post-weight loss TEE was closer to the time of diet randomization. Second, *pre-weight loss* TEE was "strongly confounded by weight loss". How this might happen is difficult to imagine. Finally, the original plan was claimed to be under-powered despite the study's design and power calculations being informed by pre-weight loss TEE data of the pilot study that did not measure TEE in the period immediately post-weight loss [6]. Interestingly, Ebbeling et al. justified the claim that the original plan was underpowered using a post hoc analysis showing that the original plan did not result in a significant diet effect.

The original plan was preferable for several reasons. First, it addressed the question of whether the *reduction* in TEE that accompanies maintenance of lost weight depends on the dietary carbohydrate to fat ratio. Second, the pre-weight loss baseline DLW measurements of the original plan were obtained in the routine situation when people were maintaining their habitual weight. In contrast, the revised plan relied on post-weight loss measurements that were obtained during the weight stabilization period when diet calories were increasing at a rate determined by each individual subject's recent rate of weight loss. The DLW method has never been validated in such a refeeding condition which introduces uncertainty into the calculations because the respiratory quotient was certainly not equal to the food quotient as assumed by Ebbeling et al. [8]. Furthermore, TEE measurements in the immediately post-weight loss period were potentially confounded by transient adaptive thermogenesis that typically becomes less severe after an extended weight stabilization period [9 10]. Therefore, post-weight loss DLW measurements should ideally have been conducted after subjects had stabilized at the lower body weight for several weeks.

Diet differences vanished when the primary data were analyzed according to the original plan

Despite the BMJ Editors' request to report the results of their original analysis plan, Ebbeling et al. argued against this because they were "concerned that the additional analysis would provide no meaningful biological insights – that is, no useful information about the nature of the relationship between dietary composition and energy expenditure." However, the results of the originally planned analyses provide very useful information.

We downloaded the individual subject data and SAS statistical analysis code on the Open Science Framework website (https://osf.io/rvbuy/) and reanalyzed the data according to the original plan. Because Ebbeling et al. claim that the per protocol group who maintained body weight to within ±2 kg of their post-weight loss value at randomization "provide a more accurate estimate of the true diet effects", we focus our attention on this group and provide the intention to treat analysis in the Appendix along with the modified SAS code.

When using the original analysis plan, we found no significant diet differences. Pairwise TEE comparisons with respect to the pre-weight loss baseline were not significant between diets (p>0.35) (Figure 1A). The low, moderate, and high carbohydrate groups decreased TEE by (mean ± SE) 262 ±72 kcal/d, 254±75 kcal/d, and 356±80 kcal/d, respectively, compared with the pre-weight loss baseline period (p=0.59 for the test of equivalence between the diets) (Figure 1B). The linear trend estimate was 24±27 kcal/d per 10% decrease in carbohydrate (p=0.38). The mean absolute weight losses at 10 and 20 weeks compared to the pre-weight loss baseline were well-matched and within 250 g between all diet groups (p>0.9), so any diet effects could not have been obscured by group differences in mean weight loss. Similar results were obtained when using weight-normalized TEE.

One possible reason the revised analysis plan of Ebbeling et al. led to a substantial apparent TEE increase with the low carbohydrate diet was the unlucky event that the decrease in TEE in the immediate post-weight loss period was 392±71 kcal/d in the low-carbohydrate group but only 271±73 kcal/d and 282±75 kcal/d in the moderate and high carbohydrate groups, respectively (Figure 1B). Despite being measured prior to diet randomization, this ~100 kcal/d greater TEE decrease in in the low carbohydrate group makes it possible that simple regression to the mean resulted in the subsequent reported increases in TEE in this group when using the post-weight loss anchor point. Indeed, there was no significant TEE difference between the moderate and high carbohydrate groups even using the post-weight loss TEE anchor as specified in the revised analysis plan (Figure 1A), but this comparison was not reported by Ebbeling et al.

Potentially important TEE differences between low and high carbohydrate diets in subjects with high insulin secretion

The substantial effect modification of TEE by baseline insulin secretion observed by Ebbeling et al. when using the post-weight loss TEE measurement as the anchor point was no longer significant when using the pre-weight loss TEE as the anchor point (p=0.36 for the test of equivalence between the diets). Nevertheless, for subjects in the highest insulin secretion tertile TEE was 383±196 kcal/d greater for the low versus high carbohydrate diets (p=0.053). Normalizing TEE for body weight also did not result in a significant overall TEE effect modification by baseline insulin secretion (p=0.29 for the test of equivalence between the diets), but the TEE difference between the low and high carbohydrate diets in the highest insulin secretion tertile was 386±173 kcal/d (p=0.03).

While not as large as the reported ~500 kcal/d effect size using the revised analysis plan, such TEE differences between low and high carbohydrate diets in subjects with the highest insulin secretion could be physiologically important. Was this effect corroborated by corresponding differences in measured components of energy expenditure? Unfortunately, it was not. Differences in resting energy expenditure (-32±49 kcal/d; p=0.52), total physical activity (45754±47821 counts/d; p=0.34), moderate to vigorous physical activity (-5±6 min/d; p=0.4), sedentary time (-9±30 min/d; p=0.77), skeletal muscle work efficiency at 10W (1±0.9 %; p=0.27), 25W (1.2±1.1 %; p=0.28) and 50W (0.5±0.8 %; p=0.48) were all not significantly different between the low and high carbohydrate diets when compared to the pre-weight loss baseline. Nevertheless, we cannot rule out possible differences in the thermic effect of food, sleeping energy expenditure, or another unmeasured factor contributing to TEE. Alternatively, the apparent TEE diet differences in the high insulin secretion group may have been due to chance or due to inaccurate DLW calculations [8]. None of the p-values have been adjusted for multiple comparisons.

Reported diet differences were inflated by subjects with implausible unaccounted energy

Although Ebbeling et al. provided the subjects with all their food to maintain a stable lower body weight, the measured energy intake was 422 ± 47 kcal/d ($p<0.0001$) less than TEE. Weight stability is not necessarily indicative of unchanging body energy stores, and the measured body fat changes have yet to be reported, but such large apparent energy deficits indicate that the subjects were likely consuming a substantial amount of unaccounted food and beverages despite the controlled-feeding design.

The law of energy conservation requires that accurate measurements of energy intake, TEE, and body weight change be quantitatively commensurate. Unfortunately, the data of Ebbeling et al. revealed extraordinary amounts of unaccounted energy. Assuming an energy content of 7700 kcal per kg of body weight change, there was 483 ± 39 kcal/d ($p<0.0001$) of unaccounted energy during the 20-week weight loss maintenance period (see the Appendix).

The large reported TEE diet effects according to the revised analysis plan depended on including subjects with excessive unaccounted energy. Figure 1C illustrates the significant attenuation of the diet effect when increasingly stringent thresholds were employed to remove subjects with excessive relative unaccounted energy ($r=0.78$; $p<0.0001$). The intercept of the best fit line was 30±3 kcal/d per 10% reduction in dietary carbohydrates and corresponds to the estimated diet effect on TEE when all energy is accounted. In other words, the TEE diet effect was less than half the value reported by Ebbeling et al. after adjusting the data to be commensurate with the law of energy conservation.

Diet adherence is the main determinant of long-term weight loss maintenance

Sustaining diet changes over the long-term is difficult, especially following weight loss when appetite is proportionately increased [11]. Most weight loss trials test the effects of counseling people to change their diets and generally result in substantial early reductions in energy intake, with TEE decreasing to a much lesser degree [2]. But long-term diet adherence appears to exponentially relax over time such that mean calorie intake after 1 year is within ~100 kcal/d of the pre-weight loss baseline with no clinically significant differences weight loss regardless of diet assignment [12,13].

Encouragingly, many individuals within each diet group achieve remarkable long-term weight losses [14]. Previously hypothesized biological determinants have not been predictive of long-term weight loss following low carbohydrate versus low fat diets [14]. Other biological predictors of diet responsiveness have been hypothesized [15-17], but it is equally plausible that social, psychological, and environmental factors may be the primary determinants of long-term success or failure of a diet prescription.

More research is required to better understand the factors that sustain healthful diet changes over the long-term. Some patients respond well to low carbohydrate diets, and there are many reasons such diets could be beneficial [18], but contrary to the claims of Ebbeling et al., they are unlikely to substantially offset the usual reduction in TEE during maintenance of lost weight.

Competing Interests

KDH has participated in a series of debates with Dr. David S. Ludwig, the senior author of the main study in question, regarding the merits and demerits of the carbohydrate-insulin model of obesity as well as the physiological response of the human body to isocaloric diets varying in the ratio of carbohydrates to fat.

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Figure Legend

Figure 1. A) Differences in total energy expenditure (TEE) in the per-protocol group consuming low and moderate carbohydrate diets compared to subjects consuming a high-carbohydrate diet. The gray bars indicate the lack of significant effect of diet on average TEE during weight loss maintenance as compared to the pre-weight loss baseline period according to the original analysis plan of Ebbeling et al. The green bars illustrate how the revised analysis plan resulted in a significant effect of the low carbohydrate diet on average TEE during weight loss maintenance as compared to the immediate post-weight loss period. B) Per-protocol changes in TEE for low, moderate, and high carbohydrate diet groups with respect to the pre-weight loss baseline period. Note the nominally greater TEE reduction in the low carbohydrate group compared to the other groups in the immediate post-weight loss period prior to diet randomization (blue bars), whereas similar TEE reductions were observed during 10 and 20 weeks of weight loss maintenance (orange bars). P-values correspond to within-group TEE differences between the immediate post-weight loss period and the average of 10 and 20 weeks. C) Per-protocol trend estimate for the TEE diet effect during weight loss maintenance (using the revised analysis plan) as a function of the threshold used to filter out subjects with excessive amounts of unaccounted energy. The rightmost data point includes all 120 per-protocol subjects with as much as 2300 kcal/d of unaccounted energy and corresponds to the diet effect size reported by Ebbeling et al. according to their revised analysis plan. The leftmost data point indicates a reduced effect size and includes 57 subjects with as much as 300 kcal/d of unaccounted energy. Error bars are ±SE.

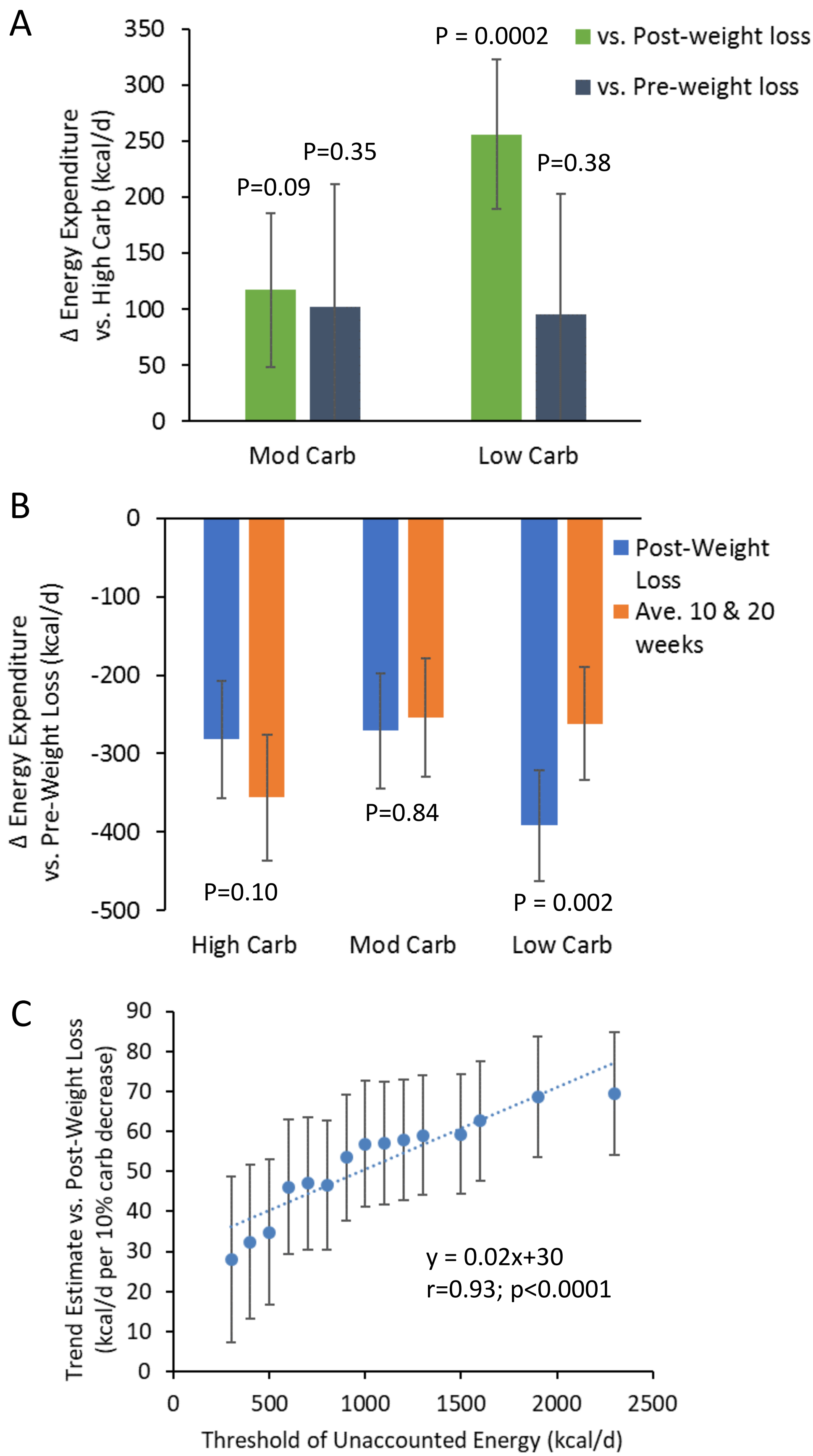
A
350
300
250
200
150
100
50
0
Δ Energy Expenditure vs. High Carb (kcal/d)
P=0.09
P=0.35
P = 0.0002
P=0.38
vs. Post-weight loss
vs. Pre-weight loss
Mod Carb
Low Carb
B
0
-100
-200
-300
-400
-500
Δ Energy Expenditure vs. Pre-Weight Loss (kcal/d)
Post-Weight Loss
Ave. 10 & 20 weeks
P=0.10
P=0.84
P = 0.002
High Carb
Mod Carb
Low Carb
C
90
80
70
60
50
40
30
20
10
0
Trend Estimate vs. Post-Weight Loss (kcal/d per 10% carb decrease)
y = 0.02x+30
r=0.93; p<0.0001
0
500
1000
1500
2000
2500
Threshold of Unaccounted Energy (kcal/d)

Figure 1

APPENDIX

Intention to treat analysis

In the intention to treat analysis according to the original plan, no significant differences in TEE were found between diet groups compared with the pre-weight loss baseline period; with the low, moderate, and high carbohydrate groups decreasing TEE by 240 ±64 kcal/d, 322±66 kcal/d, and 356±67 kcal/d, respectively (p=0.43 for the test of equivalence between the diets). Pairwise comparisons of TEE diet differences with respect to the pre-weight loss baseline were not significant between diets (p>0.35) (Figure S1A). The linear trend estimate was 29±23 kcal/d per 10% decrease in carbohydrate (p=0.21). Similar results were obtained using weight-normalized TEE data.

The measured energy intake was 460 ± 46 kcal/d (p<0.0001) less than TEE. When calculated according to the revised analysis plan of Ebbeling et al., the large TEE diet effect depended on including subjects with excessive unaccounted energy. Figure S1B illustrates the significant effect size attenuation when increasingly stringent thresholds were employed to remove subjects with excessive unaccounted energy (r=0.94; p<0.0001). The intercept of the best fit line was 30±2 kcal/d per 10% reduction in dietary carbohydrates and corresponds to the estimated diet effect size when all energy is accounted. In other words, the TEE diet effect was about half the value reported by Ebbeling et al. after adjusting the data to be commensurate with the law of energy conservation.

Unaccounted Energy

The law of energy conservation applied to human body weight (BW) dynamics requires that the following equality hold:

$$\rho \frac{dBW}{dt} = EI - TEE$$

where the left side of the equation is the rate of change in body energy stores with ρ being the energy density of the weight change. On the right side of the equation, EI is the metabolizable energy intake and TEE is the total energy expenditure. EI was controlled and periodically adjusted to ensure that BW was relatively stable (i.e., the left side of the equation was approximately zero).

Unaccounted energy, UE, was defined as:

$$UE = \left| EI - TEE - \rho \frac{dBW}{dt} \right|$$

which is ideally zero. We calculated UE from 0-10 weeks and from 10-20 weeks using the mean values of EI and TEE over each interval along with the estimated value of ρ = 7700 kcal/kg assumed by Ebbeling et al. for their EI adjustments [1]. Ideally, the body composition measurements would have provided a more accurate assessment of changes in body energy stores, but these data have not yet been made available by Ebbeling et al. [1].

Supplementary Figure Legend

Figure S1. A) Intention to treat analysis of differences in total energy expenditure (TEE) consuming low and moderate carbohydrate diets compared to subjects consuming a high-carbohydrate diet. The green bars illustrate the significant effect of the low carbohydrate diet on average TEE during weight loss maintenance as compared to the immediate post-weight loss period. The gray bars indicate the lack of significant effect of diet on average TEE during weight loss maintenance as compared to the pre-weight loss baseline period. B) Trend estimate for the TEE diet effect during weight loss maintenance (calculated using the revised plan comparing to the post-weight loss TEE) as a function of the threshold used to filter out subjects with excessive relative amounts of unaccounted energy. The rightmost data point includes all 162 subjects with as much as 2600 kcal/d of unaccounted energy and corresponds to the diet effect size reported by Ebbeling et al. according to their revised analysis plan. The leftmost data point indicates a reduced effect size and includes 81 subjects with as much as 300 kcal/d of unaccounted energy. Error bars are ±SE.

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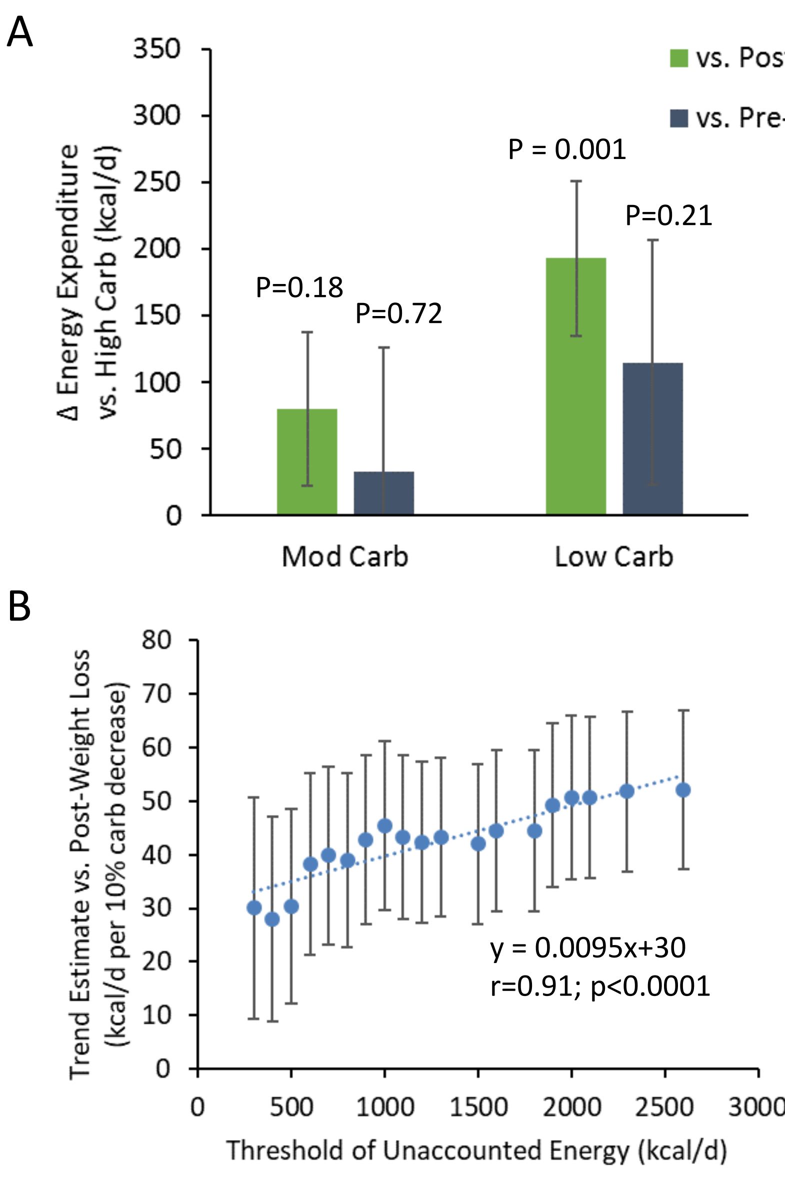
A
350
300
250
200
150
100
50
0
Δ Energy Expenditure
vs. High Carb (kcal/d)
vs. Post-weight loss
vs. Pre-weight loss
P=0.18
P=0.72
P = 0.001
P=0.21
Mod Carb
Low Carb
B
80
70
60
50
40
30
20
10
0
Trend Estimate vs. Post-Weight Loss
(kcal/d per 10% carb decrease)
y = 0.0095x+30
r=0.91; p<0.0001
0
500
1000
1500
2000
2500
3000
Threshold of Unaccounted Energy (kcal/d)

Figure S1