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Do Lower-Carbohydrate Diets Increase Total Energy Expenditure? An Updated and Reanalyzed Meta-Analysis of 29 Controlled-Feeding Studies

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ABSTRACT

Background: The effect of macronutrient composition on total energy expenditure (TEE) remains controversial, with divergent findings among studies. One source of heterogeneity may be study duration, as physiological adaptation to lower carbohydrate intake may require 2 to 3 wk.

Objective: We tested the hypothesis that the effects of carbohydrate [expressed as % of energy intake (EI)] on TEE vary with time.

Methods: The sample included trials from a previous meta-analysis and new trials identified in a PubMed search through 9 March 2020 comparing lower- and higher-carbohydrate diets, controlled for EI or body weight. Three reviewers independently extracted data and reconciled discrepancies. Effects on TEE were pooled using inverse-variance-weighted meta-analysis, with between-study heterogeneity assessed using the I^2 statistic. Meta-regression was used to quantify the influence of study duration, dichotomized at 2.5 wk.

Results: The 29 trials ranged in duration from 1 to 140 d (median: 4 d) and included 617 participants. Difference in carbohydrate between intervention arms ranged from 8% to 77% EI (median: 30%). Compared with reported findings in the prior analysis ($I^2 = 32.2\%$), we found greater heterogeneity ($I^2 = 90.9\%$ in the reanalysis, 81.6% in the updated analysis). Study duration modified the diet effect on TEE ($P < 0.001$). Among 23 shorter trials, TEE was reduced on lower-carbohydrate diets (−50.0 kcal/d; 95% CI: −77.4, −22.6 kcal/d) with substantial heterogeneity ($I^2 = 69.8$). Among 6 longer trials, TEE was increased on low-carbohydrate diets (135.4 kcal/d; 95% CI: 72.0, 198.7 kcal/d) with low heterogeneity ($I^2 = 26.4$). Expressed per 10% decrease in carbohydrate as %EI, the TEE effects in shorter and longer trials were −14.5 kcal/d and 50.4 kcal/d, respectively. Findings were materially unchanged in sensitivity analyses.

Conclusions: Lower-carbohydrate diets transiently reduce TEE, with a larger increase after ∼2.5 wk. These findings highlight the importance of longer trials to understand chronic macronutrient effects and suggest a mechanism whereby lower-carbohydrate diets may facilitate weight loss. *J Nutr* 2021;151:482–490.

Keywords: obesity, dietary carbohydrate, low-carbohydrate diet, dietary fat, carbohydrate-insulin model, energy expenditure, feeding study, metabolism

Introduction

According to some thinking, on a calorie-per-calorie basis, all sources of metabolizable energy are alike in their effects on body energy stores and weight for practical purposes (1). In this view, any major effects on body weight resulting from macronutrient-focused diets, ranging from very-low-carbohydrate to very-low-fat, result from changes in energy intake, as influenced by hunger, satiety, or other factors, not total energy expenditure (TEE). In support of this view, a recent meta-analysis of 28 feeding trials (2) found that TEE was slightly reduced on lower- versus higher-carbohydrate diets (−25.5 kcal/d, 95% CI: −32.2, −18.8 kcal/d; $I^2 = 32.2\%$), a difference that was considered clinically insignificant. However, the median duration of included studies was 4 d, and the potential effect of intervention duration was not reported. Experimental and mechanistic studies suggest that the process of physiological adaptation to lower carbohydrate intake may require at least 2 to 3 wk (3–13), raising the possibility that transient and longer-term metabolic effects may have been conflated.

On a conventional diet, the brain relies upon glucose for energy requirements. With restriction of carbohydrate to <50

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to 100 g/d (<10% to 20% of dietary energy), ketones and ketoacids such as B-hydroxybutyrate (BOHB)—derivates of fatty acids that cross the blood–brain barrier—replace glucose as the major energy source for the brain, reducing demand for gluconeogenic substrates from protein, thus preserving lean mass. But even with total elimination of dietary carbohydrate (e.g., fasting), the concentration of BOHB rises slowly, reaching steady state only after 2 to 3 wk (14). Further adaptations that may occur over weeks to months relate to the efficiency of BOHB transport into the brain (15), changes in muscle and liver metabolism (16–18), mitochondrial number and function (19, 20) oxidative stress and inflammation (19–21), and hormonal responses (22, 23). In time-course studies, negative nitrogen balance (indicative of lean mass loss) (24–26), fatigue (27), increased hunger (28), and decreased exercise tolerance (18) are characteristically observed with initiation of a ketogenic diet, but these adverse responses typically resolve after a few weeks. Even with moderate changes in macronutrient proportion (i.e., not sufficient to elicit ketosis), metabolic pathways facilitating a shift from carbohydrate to fat oxidation may adapt over several weeks (29). Thus, a reduction in dietary carbohydrate may transiently suppress TEE through multiple mechanisms, including, but not limited to, reduced voluntary physical activity level, perhaps due to fatigue. If this hypothesis is true, it might help explain heterogeneity among clinical trials and inform the design of weight-loss treatments.

To test the hypothesis, we reanalyzed and updated the prior meta-analysis, with a specific focus on heterogeneity and effect modification by trial duration.

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Supplemental Tables 1 and 2, with Supplemental References, are available from the "Supplementary Data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/jn.
The full dataset and statistical code used in this study are available at Open Science Framework (53).
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Abbreviations used: BOHB, B-hydroxybutyrate; D-L, DerSimonian-Laird; DLW, doubly-labeled water; EI, energy intake; REML, Restricted Maximum Likelihood; TEE, total energy expenditure; tiab, title/abstract; WRC, whole-room calorimetry.

Methods

We followed PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines for article selection, data extraction, data analysis, and reporting.

Search strategy and study selection

We included all 28 trials in the original meta-analysis, except as described below, and conducted a PubMed search on 9 March 2020 to identify new trials since 2016 that satisfied the search criteria as originally specified (2): (energy expenditure [tiab] or metabolic rate [tiab] or energy balance [tiab] or nutrient balance* [tiab] or fat balance* [tiab] or carbohydrate balance* [tiab] or fat oxidation [tiab] or fat mass [tiab] or body fat [tiab] or body composition [tiab]) AND (dietary carbohydrate [mh] or low-carb* [tiab] or high-carb* [tiab] or dietary fat [mh] or high-fat [tiab] or low-fat [tiab] or dietary protein [mh] or highprotein [tiab] or low-protein [tiab] or macronutrient* [tiab] or diet composition [tiab] or dietary composition [tiab]) AND (indirect calorimetry [mh] or indirect calorimetry [tiab] or calorimeter [tiab] or calorimetry [tiab] or metabolic chamber* [tiab] or respiration chamber* [tiab] or respiratory chamber* [tiab] or doubly labeled water [tiab] or doubly labelled water [tiab]) AND (men [tiab] or women [tiab] or human* [tiab] or subject* [tiab] or volunteer* [tiab] or adults [tiab] or children [tiab] or adolescent* [tiab]).

Trials were eligible if they met all of the following criteria: *1*) compared the effects of lower- versus higher-carbohydrate diets regardless of absolute levels of dietary carbohydrate proportion, *2*) controlled energy intake or body weight, *3*) controlled dietary protein, *4*) provided foods to participants to enhance treatment differentiation, and *5*) utilized whole-room calorimetry (WRC) or doubly labeled water (DLW) to measure TEE. Trials were excluded if they had additional interventions (e.g., different levels of prescribed physical activity) the effects of which could not be separated from the dietary intervention.

Our updated analysis excluded 2 studies in the original meta-analysis: Verboeket-van de Venne et al. (30), which was based on the same trial as Verboeket-van de Venne and Westerterp (31) (Klaas Westerterp, Maastricht University, personal communication 2020) and Shepard et al. (32), which had the same participants as Eckel et al. (33) (James Hill, University of Alabama, Birmingham, personal communication 2020). Three new trials published after the original meta-analysis were included, Ebbeling et al. (34), Bush et al. (35) and Begaye et al. (36) for a total of 29 after the above-mentioned exclusions.

Data extraction

Data were extracted independently by 3 co-investigators, with any identified differences resolved through conversation. For trials with ≥3 test diets, the 2 diets with the most extreme differences in carbohydrate content were included. When repeated measurements were reported, the last time point that had data on both diets was used, unless the primary outcome in the trial specified an average of time points and all were either <2.5 or >2.5 wk [as was the case with Ebbeling et al. (34)]. We excluded any time points on which ad libitum (uncontrolled) food intake occurred. When both DLW and WRC were available, we utilized DLW because of the plausibly greater accuracy of the former for adaptive thermogenesis (37). See **Supplemental Tables 1** and **2** for additional details, including data extraction and minor methodological differences from the previous meta-analysis.

Effect size calculation for each study

The effect size for each trial was calculated as the mean difference in TEE comparing the lower-carbohydrate versus the higher-carbohydrate diet. Changes from baseline were compared when data were available. Standard errors of the effect size were calculated when data were available from individual participant data or from SDs of each diet along with the estimated correlation between diets in crossover studies (38). When data were unavailable, correlation between diets was imputed using the mean of the correlations for other studies with the same design ($r = 0.80$ comparing change scores; $r = 0.83$ comparing end

points). Similarly, SEs of changes from baseline were calculated from the SDs of TEE at baseline and end point; correlation was imputed when needed based on the mean correlation between time points ($r = 0.88$). In the original meta-analysis, a correlation of 0.95 was used to calculate SEs (2), which we utilized in a sensitivity analysis. When data were extracted for subgroups, we calculated a combined effect size for the study, weighted by the inverse variances (39, 40).

Meta-analysis

We performed meta-analysis in Stata version 16 (StataCorp LLC) (41) to calculate the pooled effect sizes. To replicate the original work, we used fixed effects and random effects with DerSimonian-Laird (D-L). For the updated analysis, we used random effects with Restricted Maximum Likelihood (REML) (40, 42–44). Heterogeneity was assessed using the standard Cochran's Q statistic, calculated as the weighted sum of squared differences between individual study effects and the pooled effect across studies, as follows:

$$Q = \sum_{i=1}^{n} w_i (x_i - \bar{x}_w)^2 \quad (1)$$

where n is the number of studies, x_i is the effect size for study i, w_i is the weight for study i, and $\bar{x}_w$ is the pooled weighted effect across studies. The I^2 statistic (45) describes the percentage of variation across studies due to heterogeneity rather than sampling error, where $I^2 = 100\% \times (Q - \text{df})/Q$.

We first reanalyzed the effect sizes and CIs presented for the 28 studies included in the original publication meta-analysis (2). We then updated the analysis by re-extracting the data, calculating the effect sizes and CIs, and excluding and adding studies as described above, for the final 29 studies.

Because study duration accounted for a large degree of heterogeneity, we performed the meta-analysis separately for shorter and longer trials. Several authors have proposed 2 to 3 wk as the minimum time required for metabolic adaptation to reduced carbohydrate intake (4, 6–8, 13). We therefore dichotomized the cohort at 2.5 wk (shorter trials, ≤17 d; longer trials, >17 d), which provided an adequate sample to meta-analyze both groups. We also conducted sensitivity analyses dichotomized at 2 and 3 wk (as described below). Because the time course of physiological adaptation has not been precisely determined (and this process may be influenced by carbohydrate difference and baseline participant characteristics), other cutoffs could have been chosen to dichotomize duration. For conservativeness, we also report the P value for the interaction involving study duration using a Bonferroni adjustment for all 11 possible cutoffs among the included trials (i.e., ≤1, 2, 3, 4, 7, 9, 10, 14, 15, 18, and 28 d).

We performed primary analyses on the difference in TEE as presented in the trials. To take into account variability in treatment intensity (i.e., the magnitude of difference in dietary carbohydrate between trials), we also calculated TEE per 10% decrease in carbohydrate as a proportion of energy intake (EI) on the low- versus high-carbohydrate diet, assuming linearity. For example, in Dirlewanger et al. (46), the mean difference in TEE was −65 kcal/d, and the difference in carbohydrate as %EI was 30%, giving (−65/30) × 10 = −21.7 kcal/d per 10% decrease in carbohydrate as %EI. The 95% CIs were also adjusted accordingly. Because the carbohydrate-adjusted mean difference is differently scaled, it cannot be directly compared with the original TEE outcome.

Meta-regression

Using meta-regression with REML random effects, we included potential effect modifiers to determine how they *1*) affected the overall estimated means and *2*) accounted for variability in effects across studies. To evaluate the heterogeneity, we explored variability due to study duration, differences in carbohydrate amounts between diets, and TEE method (DLW or WRC). We recoded study duration into a binary variable: 0 for study duration <2.5 wk (≤17 d) and 1 for study duration >2.5 wk (>17 d). The difference in carbohydrate as %EI between diets was calculated and re-coded as a mean-centered variable by subtracting the mean difference of 33.2% across studies to aid interpretation of TEE effects at the mean level of the difference in carbohydrate.

We used the *meta regress* command in Stata 16 (41) to perform random-effects meta-regression allowing for residual heterogeneity (i.e., variance among studies that cannot be explained by the covariates) (47). The proportion of residual variation due to heterogeneity between studies, given by I^2_{res}, was calculated as follows:

$$I^2_{res} = max\left[0,\ \left\{Q_{res} - (n-k)\right\}/Q_{res}\right] \quad (2)$$

where Q_{res} is the weighted sum of squares of the residuals from a fixed-effects meta-regression, n is the number of studies, and k is the number of covariates included in the model. The R^2 estimates the proportion of between-study variance (τ^2) explained by the covariates included in the model.

Sensitivity analyses

We conducted 6 sensitivity analyses to examine potential biases that might have arisen in the trials or from the analytic approach for the meta-analysis. First, we used a higher correlation (0.95) when calculating the SE for differences between diets in the crossover studies, as well as for changes from baseline, consistent with the original meta-analysis (2). Second, we examined how outcomes changed with a shorter adaptation period, dichotomizing studies at ≤14 d versus >14 d, thus moving 1 trial [Eckel et al. (33)] from the shorter to the longer group. Third, we examined how outcomes changed with a longer adaptation period, dichotomizing studies at ≤21 d versus >21 d, thus moving 1 trial [Abbott et al. (48)] from the longer to the shorter group. Fourth, for Rumpler et al. (49), we used final data only, rather than change, because the baseline (Day 0) data were obtained after prior exposure to the test diets. Fifth, we used data for Hall et al. (50) with revised Respiratory Quotient, as proposed by Hall et al. (51). Sixth, we addressed a methodological issue specific to Hall et al. (50). In this non-randomized crossover design, all participants received the higher-carbohydrate diet first. However, due to a miscalculation, they were underfed and progressively lost weight throughout the trial. Consequently, mean weight was about 2.3 kg less during the last 2 weeks on the lower-carbohydrate diet vs last 2 weeks on the higher-carbohydrate diet. To estimate the potential impact, we used the "expert mode" of the NIH Body Weight Planner (52) to calculate how energy requirement would change for a hypothetical individual with the characteristics of the average participant (male, age 33 years, initial weight 87.4 kg) following 2.3 kg weight loss over 28 days (assuming height of 180 cm and physical activity level of 1.6). The anticipated suppression of energy expenditure indicated by this calculation, 50 kcal/d, was added to the lower-carbohydrate diet in that trial.

Verification of analyses and transparency

All calculations of effect sizes and SEs (in Microsoft Excel; Microsoft Corporation) and meta-analyses (in Stata 16) were verified by a second statistician. The full dataset and statistical code used in this study are available at Open Science Framework (53).

Results

Trial characteristics

A total of 29 eligible trials with 617 participants were identified (**Figure 1**) over a 38-y period, from 1982 to 2020. Study duration varied widely, from 1 to 140 d (median, 4 d; mean, 13.0 d), including 23 shorter trials and 6 longer trials. The difference in dietary carbohydrate between intervention arms ranged from 8% to 77% of total energy intake (median, 30%; mean, 33.2%). Four trials measured TEE by DLW (1 shorter, 3 longer trials) and 25 by WRC (22 shorter, 3 longer trials). In addition to these design characteristics considered in statistical

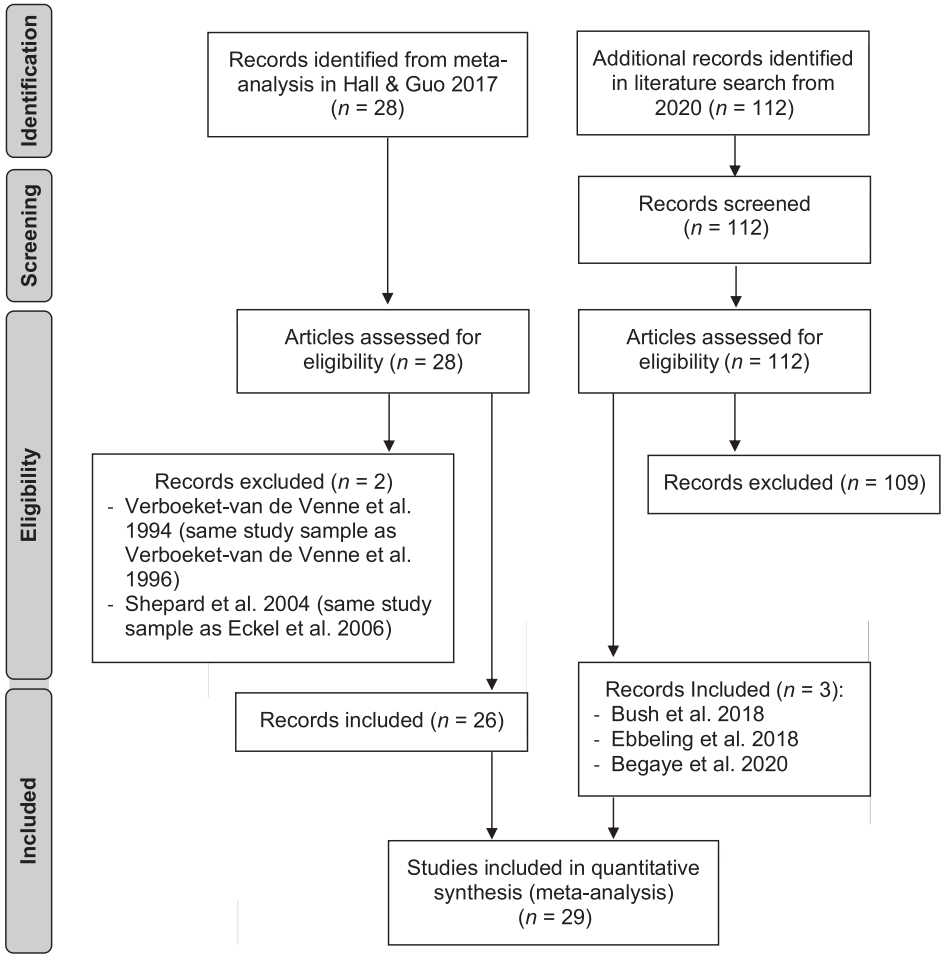

FIGURE 1 PRISMA flow chart of trials comparing the effects of lower- and higher-carbohydrate diets on total energy expenditure. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

models, trials also varied in other aspects (e.g., randomization, crossover vs parallel, use of a run-in period, dietary energy level) and baseline participant characteristics (e.g., weight status, sex, age, fitness level, and health status).

Reproduction of original meta-analysis

In the original meta-analysis (2) with 28 trials, the reported mean difference in a D-L random-effects model was −25.5 kcal/d (95% CI: −32.2, −18.8 kcal/d), favoring the higher-carbohydrate diet. Reanalyzing the original data, we obtained a D-L random-effects mean estimate of −38.6 kcal/d (95% CI: −63.5, −13.7 kcal/d), an REML random-effects mean estimate of −45.0 kcal/d (95% CI: −82.6, −7.3 kcal/d), and a fixed-effects mean estimate of −25.5 kcal/d (95% CI: −32.2, −18.8 kcal/d). We observed a discrepancy in estimates of heterogeneity. Whereas the original meta-analysis reported an I^2 of 32.2%, we calculated Cochran's $Q = 297.1$ (df = 27) and $I^2 = 90.9\%$ from the fixed-effects and D-L random-effects models and $I^2 = 96.3\%$ from the REML model.

Heterogeneity related to study duration and macronutrient difference

Table 1 displays between-study heterogeneity and variability in meta-regression models accounting for the 3 covariates of interest, with the 29 trials in the updated analysis. The overall heterogeneity between studies without effect modifiers was $I^2 = 81.6$. Study duration accounted for the most variability in TEE differences across studies ($R^2 = 57.2\%$) and reduced the residual heterogeneity furthest among the univariate meta-regressions, to $I^2_{res} = 65.9\%$. Effect modification by study duration remained significant ($P < 0.001$) with Bonferroni correction for all 11 possible ways of dichotomizing duration. Additional inclusion of the difference in carbohydrate between experimental diets ($P = 0.002$) increased the between-study variability explained in the model to 76.5%, reducing I^2_{res} to 51.0%. TEE method (DLW or WRC) did not account for significant additional heterogeneity in models that also included study duration.

Updated meta-analysis considering study duration and macronutrient differences

As study duration accounted for the most heterogeneity across studies, we performed meta-analysis separately for the shorter- and longer-duration trials. As shown in Table 2 and Figure 2, results from the REML random-effects models indicated that the lower-carbohydrate diet had modestly lower TEE among the shorter-duration studies of −50.0 kcal/d (95% CI: −77.4, −22.6 kcal/d; $P < 0.001$, $I^2 = 69.8$) and substantially higher TEE among the longer studies of 135.4 kcal/d, (95% CI: 72.0, 198.7 kcal/d; $P < 0.001$, $I^2 = 26.4$). Taking into account dietary differences, the results per 10% decrease in

TABLE 1 Effect of study design aspects (effect modifiers) on heterogeneity in TEE outcome among 29 trials comparing lower- and higher-carbohydrate diets[1]

Modifiers	*P*	Q_{res} [2]	I^2_{res} [3], %	τ^2 remaining[4]	R^2 [5], %
Overall (no modifier)	—	124.2	81.6	6036	—
Univariate					
Study duration	<0.001	84.7	65.9	2586	57.2
Difference in carbohydrate	0.001	82.1	71.8	3534	41.5
TEE method[6]	0.004	103.6	73.4	3660	39.4
Multivariate					
Study duration	<0.001	54.3	51.0	1420	76.5
Difference in carbohydrate	0.002				
Study duration	<0.001	84.1	67.1	2659	56.0
TEE method	0.919				
Difference in carbohydrate	<0.001	56.3	46.4	1173	80.6
TEE method	<0.001				
Study duration	0.011	49.7	46.2	1141	81.1
Difference in carbohydrate	0.001				
TEE method	0.130				

[1] TEE, total energy expenditure.
[2] Q_{res} is Cochran's Q statistic for heterogeneity remaining after effect modifiers included.
[3] I^2_{res} is the percentage of variation across studies due to heterogeneity remaining after modifiers included.
[4] τ^2 is the between-study variability remaining after modifiers included.
[5] R^2 is the percentage of variability (τ^2) explained by the modifiers in each model.
[6] Whole-room calorimetry vs doubly labeled water.

carbohydrate as %EI, respectively, are −14.5 kcal/d (95% CI: −21.0, −7.9 kcal/d; $P < 0.001$) and 50.4 kcal/d (95% CI: 31.4, 69.4 kcal/d; $P < 0.001$). Results of the 6 sensitivity analyses indicated that the primary findings were unchanged in terms of direction and statistical significance. Consistent with the hypothesized duration of the adaptive process, the mean effect among longer studies was weakened by dichotomizing at 2 wk and strengthened by dichotomizing at 3 wk.

Discussion

In this updated and reanalyzed meta-analysis, we found that heterogeneity among trials comparing the effect of lower- versus higher-carbohydrate diets on TEE is greater than previously reported (2), consistent with hypothesized effect modification by trial duration and/or additional factors. With control for duration and macronutrient difference, heterogeneity decreased

TABLE 2 Meta-analysis on TEE difference among 29 trials comparing lower- and higher-carbohydrate diets[1]

Variable	Estimated mean difference	95% CI	*P*
Primary analysis			
TEE difference			
Shorter duration	−50.0	−77.4, −22.6	<0.001
Longer duration	135.4	72.0, 198.7	<0.001
TEE difference per 10% difference in carbohydrate			
Shorter duration	−14.5	−21.0, −7.9	<0.001
Longer duration	50.4	31.4, 69.4	<0.001
Sensitivity analyses			
Using correlation of 0.95 for crossover studies			
Shorter duration	−51.0	−77.2, −24.8	<0.001
Longer duration	133.0	67.2, 198.8	<0.001
Using short vs long duration cutoff at 14 d			
Shorter duration	−48.6	−76.3, −20.8	0.001
Longer duration	111.1	27.6, 194.5	0.009
Using short vs long duration cutoff at 21 d			
Shorter duration	−45.9	−73.5, −18.3	0.001
Longer duration	156.5	84.5, 228.5	<0.001
Using final data (instead of change) in Rumpler et al. (49)			
Shorter duration	−50.0	−77.4, −22.6	<0.001
Longer duration	128.5	66.4, 190.6	<0.001
Adjusting for ΔRQ in Hall et al. (50, 51)			
Shorter duration	−50.0	−77.4, −22.6	<0.001
Longer duration	125.1	65.6, 184.6	<0.001
Accounting for progressive weight loss in Hall et al. (50)			
Shorter duration	−50.0	−77.4, −22.6	<0.001
Longer duration	144.6	74.7, 214.5	<0.001

[1] Difference is lower-carbohydrate diet minus higher-carbohydrate diet; see Methods for details of models. RQ, Respiratory Quotient; TEE, total energy expenditure. Shorter duration, ≤17 d; longer duration, >17 d

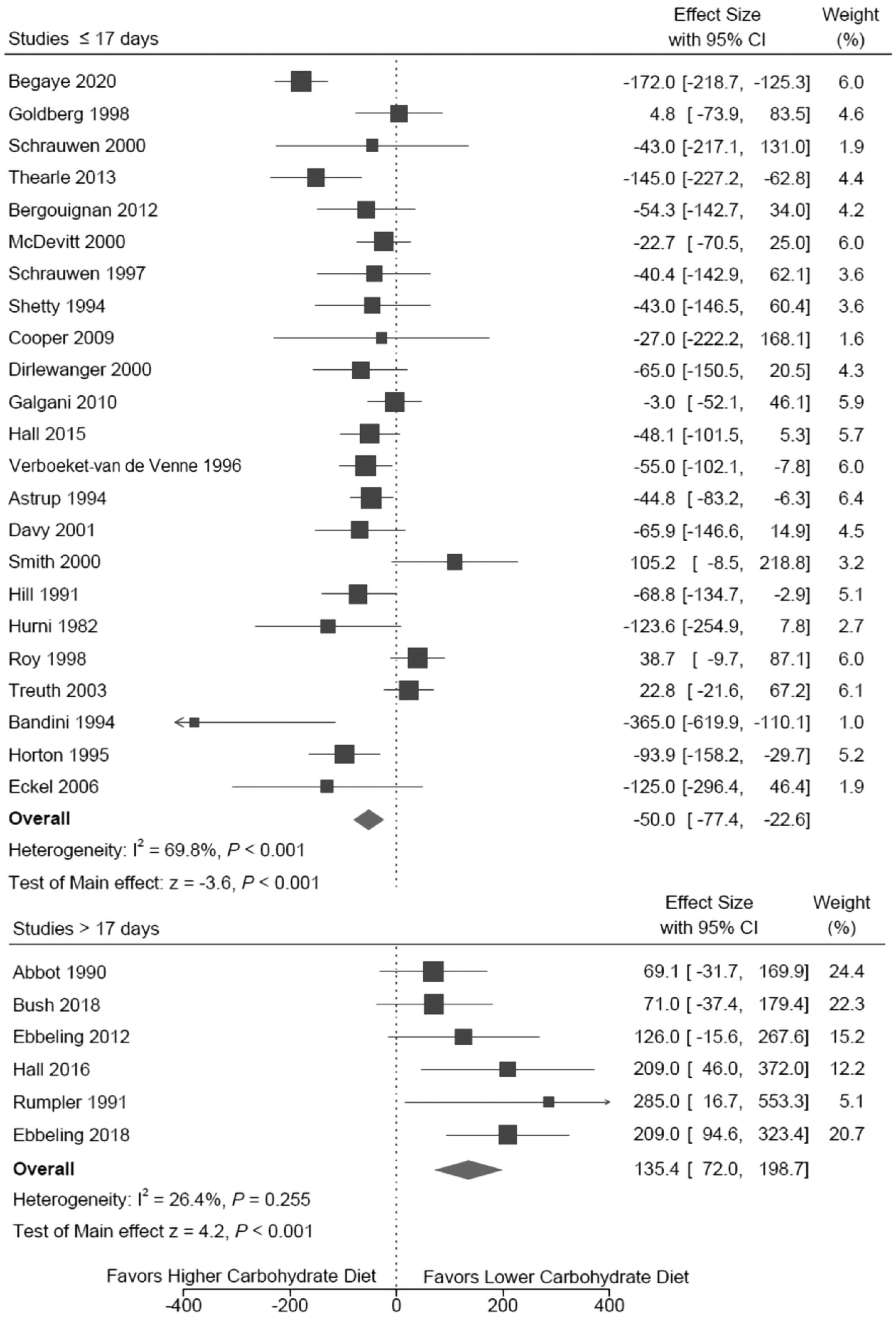

FIGURE 2 Forest plot of total energy expenditure effect among 29 trials comparing lower- and higher-carbohydrate diets. Trials are listed according to intervention duration in ascending order (i.e., shortest duration at top). Full citations for the individual trials can be found in Supplementary Data.

substantially in our study. Among trials <2.5 wk, the lower-carbohydrate diets slightly reduced TEE, with reduced remaining heterogeneity. By contrast, among trials of >2.5 wk, the lower-carbohydrate diet substantially increased TEE—by ~50 kcal/d for every 10% decrease in carbohydrate as %EI—with minimal residual heterogeneity. These results suggest that the shorter versus longer studies have examined different physiological states. The former consist of trials in which participants experienced varying degrees of metabolic adaptation to carbohydrate reduction; the latter consist of trials of sufficient duration to allow for adequate adaptation and to produce a consistent finding.

This finding supports a prediction of the carbohydrate-insulin model (4, 54–58) and suggests a mechanism whereby dietary carbohydrate reduction could aid in the prevention and treatment of obesity. According to this model, the high insulin-to-glucagon ratio with a diet high in glycemic load (mathematical product of glycemic index and carbohydrate amount) shifts the partitioning of metabolic fuels from oxidation in lean tissue to storage in adipose tissue. If the effects observed here persist over the long term, then reducing dietary carbohydrate intake by half from 60% of energy intake (a typical level for low-fat diets) would increase energy expenditure by ~150 kcal/d, counterbalancing (if not compensated for by other factors) much of the secular increase in energy intake thought by some to underlie the obesity epidemic (59).

Consistent with our findings, short- versus long-term effects often differ in studies of dietary interventions (60). For instance,

the rapid initial weight loss with very-low-calorie diets is not indicative of the effectiveness of these highly restrictive approaches for chronic obesity treatment. Thus, apart from mechanistic examination of the adaptive process per se, short-term studies comparing diets with differing macronutrient composition are likely to yield misleading estimates of long-term effects.

A main strength of this reanalysis is the ability to test a physiological hypothesis with adequate power, revealing an effect of macronutrients not apparent in the original analysis (2). We used a conservative statistical adjustment to examine how study duration affects outcome, and then conducted sensitivity analyses to examine plausible sources of bias. In addition, we have made the database with the trials publicly available to facilitate transparency and further examination.

Several limitations warrant consideration. First, many of the trials have low quality related to small size, lack of randomization, limited methodological detail (especially for the older studies), and other issues. Second, we cannot rule out the possibility of dietary nonadherence to the test diets. Participants in studies conducted at least partially outside of a metabolic ward could have underconsumed study foods or consumed foods off protocol. Dietary nonadherence would tend to inflate DLW estimation of TEE on a lower- versus higher-carbohydrate diet due to dependency of this method on estimated Food Quotient as a proxy for Respiratory Quotient. (This problem would not apply to WRC measurement of TEE, because Respiratory Quotient is determined directly.) Conversely, WRC may underestimate TEE due to suppression of nonresting energy expenditure (the component of TEE considered to be most involved in adaptive thermogenesis) (37). Reassuringly, we found no significant heterogeneity arising from the TEE measurement method after adjustment for study duration. Third, although ongoing adaptations beyond 3 wk cannot be excluded, we had insufficient power to test this possibility. To the extent that the longer studies included incompletely adapted participants, effect estimates could be underestimated. Fourth, we did not examine quantitative aspects of macronutrients that might affect insulin secretion or metabolism, such as glycemic index. According to preliminary data potentially consistent with the carbohydrate-insulin model, TEE by WRC decreased after 12 wk (by 136 kcal/d) with a diet high in sugar-sweetened beverages, whereas TEE either did not decrease or increased (by 127 kcal/d) with 2 comparison diets controlled for macronutrients that were high in either meat or fish, respectively (61). Dietary fatty acid type, specifically the relative amounts of saturated versus unsaturated fats, may also have metabolic effects of relevance to energy balance and adiposity (62). Fifth, only 1 trial examined effect modification by individual-level baseline biological characteristics (34), too few for meta-analysis. The carbohydrate-insulin model predicts that the largest increase in TEE with carbohydrate restriction will occur among individuals with the highest insulin secretion response to carbohydrate, defined as insulin concentration 30 min into a standard oral-glucose-tolerance test (63–66). Information about such subgroup susceptibility may inform a "personalized" approach to weight control, wherein a low-carbohydrate diet might be targeted to those most likely to benefit.

In view of the complexity of the physiological mechanisms and interindividual variability in response—potentially related to behavioral factors or biological factors such insulin secretion—high-quality studies with different designs will be necessary to further elucidate how macronutrients affect energy metabolism and fat storage, with attention to potentially susceptible subgroups, and translate findings to clinical interventions and public health messages. Important scientific and practical information could be obtained from trials that variously control energy intake (allowing body weight to change), control body weight (adjusting energy intake accordingly), or permit ad libitum food intake (controlling for confounding dietary and environmental factors when feasible). In addition, studies with participants habituated to a low-carbohydrate diet prior to randomization would also be of interest (the converse of most trials to date). An adequate trial duration will also be needed with this design, as consumption of a low-carbohydrate diet may protect for at least 1 mo against adverse effects of dietary carbohydrate on metabolism through persistent reduction in insulin secretion (65).

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