Ebbeling CB, et al. Energy requirement is higher during weight-loss maintenance in adults consuming a low- compared with high-carbohydrate diet.

Online Supplementary Material

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Abbreviations:
Carb, carbohydrate
DXA, dual-energy x-ray absorptiometry
EER, estimated energy requirement
TEE, total energy expenditure measured using doubly-labeled water methodology

Supplemental Methods

Conceptual approach to current analyses

For the current study, we considered four potential reasons for imprecision and inaccuracy in the initial estimates of energy requirement used to calculate energy intake: 1) excessive variability in the START estimate used in models of change; 2) the limited time frame (using dietary data only from the days when we assessed TEE) for evaluating energy intake during the Test phase; 3) unaddressed factors, including provision of unit bars and additional *ad libitum* snacks to some individuals to assist with weight-loss maintenance (as explained in Supplemental Methods) and 4) change in body composition affecting energy balance calculations.

To begin our exploration of these issues, we reviewed food production sheets (which listed the provided amount of each individual food item) and extracted data for calculating total daily energy provided to each participant throughout the Test phase. Visual inspection revealed large changes (>500 kcal/d) in dietary energy provided for many participants in all 3 diet groups from the weight stabilization period at the end of the Run-in phase through the first few weeks of the Test phase, demonstrating that our initial estimates of energy requirement were imprecise. By MID (week 10 of the Test phase), estimates of energy requirement stabilized, with relatively few participants requiring major adjustments in dietary energy to maintain weight loss through END (week 20). This initial imprecision would erode power for detecting group differences using the change models originally reported (1, 2).

As an alternative approach to the inherent limitations of an imprecise baseline (START value) in measurement of a change variable, we examined estimated energy requirement (EER) with general linear models adjusted for baseline covariates that could plausibly influence EER (ANCOVA). We focused on the energy provided from 10 to 20 weeks, averaged over 70 days, as our most accurate measure of EER, with primary interest in the High- *vs* Low-Carb diet comparison in the PP analysis to maximize precision. Consistent with the approach used with our original TEE outcome, we calculated EER per kg and normalized the results as kcal/d using the average START weight of our participants (82 kg). We examined diet group differences in EER at START and during weeks 10 through 20 of the Test phase, with and without adjustment for the START value. In sensitivity analyses, we explored how changes in body fat mass and possible non-adherence to energy prescription might influence EER.

Meal supervision

Participants were asked to eat at least 1 meal per day, Monday through Friday, in a supervised dining area. Other weekday meals and all weekend meals were packaged for take-out.

Estimating and adjusting Run-in and Test diet energy levels

Individualized energy levels were estimated and then adjusted when necessary, but not more frequently than every two weeks. To inform adjustments, body weight was measured daily using Wi-Fi scales (Withings Inc., Cambridge, MA) synced with a study-specific online portal (SetPoint Health, Needham, MA). At the beginning of the Run-in phase (PRE), energy levels were set at 60% of estimated needs (3), and then adjusted to achieve targeted weight loss. Energy levels for weight stabilization at the end of the Run-in phase were estimated based on rate of weight loss over 20 days: energy intake during weight loss (kcal/day) + rate of weight loss (kg/day × 7700 kcal/kg). During the Test phase, energy levels were adjusted when deviation from the START anchor weight exceeded ±2 kg and/or the slope of weight regressed on time was ≥15 g per day over 14 days.

Some participants received unit bars (100 kcal per bar with diet-specific carbohydrate-to-fat ratio) and/or *ad libitum* snacks, in addition to the meals and snacks listed on food production sheets. The purpose of providing unit bars was to: 1) replace some of the meal calories, when large portions were a barrier to consuming all provided food and 2) immediately adjust energy levels, before meal adjustments could be implemented according to established production cycles, to achieve weight-loss maintenance (±2 kg of START anchor weight). The purpose of providing foods for *ad libitum* snacks (n=11) was to halt continued weight loss in participants who were already consuming large meals. Examples of snack foods (for each diet) included: banana, skim milk (High-Carb); bagel chips, chocolate chips, apple, banana, nut butters (Moderate-Carb); nuts, nut butters, dark chocolate, whole milk (Low-Carb). We conservatively estimated energy content of *ad libitum* snacks at 200 kcal per day, for the days when participants (n=11) received snacks. In sensitivity analyses, we noted similar study outcomes with energy content estimated at 500 kcal per day (data not presented).

Quantifying unconsumed energy

Data on food consumption recorded in the online portal were used to calculate daily unconsumed energy. The median and mean values for each diet group were <3% and <4%, respectively, of total energy provided during weeks 10 through 20 of the Test phase. For supervised meals, unconsumed menu items were weighed, and gram amounts were entered into the portal by food service staff. Menu data exported from the ESHA Food Processor to Excel were used to create a "food library," interfaced with the portal, for converting gram amounts to kcal. For unsupervised take-out meals, percentages of menu items consumed were recorded by participants, using a form in the online portal that was prepopulated with daily menus from food production sheets, so that unconsumed energy could be calculated as follows: energy provided – (energy provided × percentage consumed). Unconsumed energy during supervised and unsupervised meals was summed to obtain a total for each day. Food consumption data for calculating unconsumed energy were not available for cohort 1 (n=25 in ITT, n=18 in PP), prior to developing the online portal, and assumed to be 0 (this methodological limitation is addressed in a sensitivity analysis).

Quality control

We weighed menu items within narrow tolerance limits: ±0.1 g of the target weight for items ≤10 g, ±0.5 g for items >10 g). For assembled meals selected at random, we compared actual vs. target weights (spot weight checks, 3 days per week, 2 to 4 meals per day depending on cohort size). In addition, for take-out meals, we confirmed content (packaged menu item checks, 3 days per week, 5 to 7 meals per day depending on cohort size). Data from the final cohort indicated completion of 95% and 97% of the intended spot weight checks and packaged menu item checks, respectively. Spot weight checks indicated that 67% of the menu items were within the specified narrow tolerance limits and 98% were within ±5 g (a level of deviation that would not compromise macronutrient differentiation). Packaged menu item checks indicated that 99% of the take-out meals contained all of the intended menu items. Infrequent quality control issues were addressed immediately.

References

1. Van Breukelen GJ. ANCOVA versus change from baseline: more power in randomized studies, more bias in nonrandomized studies [corrected]. J Clin Epidemiol. 2006;59(9):920-5.
2. Vickers AJ. The use of percentage change from baseline as an outcome in a controlled trial is statistically inefficient: a simulation study. BMC Med Res Methodol. 2001;1:6.
3. Mifflin MD, St Jeor ST, Hill LA, Scott BJ, Daugherty SA, Koh YO. A new predictive equation for resting energy expenditure in healthy individuals. Am J Clin Nutr. 1990;51(2):241-7.

SUPPLEMENTAL TABLE 1 Effects of Test diets on body composition by DXA and isotope dilution during weight-loss maintenance in the Framingham State Food Study

Diet[1]				Linear Trend[2]	
Low-Carb	**Moderate-Carb**	**High-Carb**	***P*** [3]	**(Low-Carb) – (High-Carb)**	***P*** [4]
Intention-to-Treat [5]					
Percentage body fat by DXA					
PRE–START–END 39.8 – 36.0 – 35.7	PRE–START–END 40.9 – 37.0 – 36.7	PRE–START–END 41.6 – 37.9 – 37.4	0.72	0.24 (-0.35, 0.84)	0.42
Percentage body fat by isotope dilution					
PRE–START–MID–END 39.6 – 36.1 – 34.9 – 36.0	PRE–START–MID–END 41.2 – 37.5 – 36.8 – 37.0	PRE–START–MID–END 42.2 – 37.8 – 36.8 – 36.9	0.76	-0.30 (-1.5, 0.95)	0.64
Per Protocol [6]					
Percentage body fat by DXA					
PRE–START–END 39.7 – 35.9 – 35.7	PRE–START–END 40.3 – 36.4 – 36.3	PRE–START–END 42.2 – 38.5 – 38.4	0.97	-0.048 (-0.58, 0.48)	0.86
Percentage body fat by isotope dilution					
PRE–START–MID–END 39.0 – 35.9 – 35.0 – 35.8	PRE–START–MID–END 40.9 – 36.5 – 36.2 – 36.7	PRE–START–MID–END 42.3 – 37.9 – 37.6 – 38.2	0.57	-0.62 (-2.1, 0.89)	0.42

1 Values are means across time points for DXA (PRE–START–END) and isotope dilution (PRE–START–MID–END). DXA, dual-energy x-ray absorptiometry; END, end of Test phase; MID, midpoint of Test phase; PRE, pre-weight loss; START, start of randomized trial (post-weight loss, pre-randomization); TEE, total energy expenditure measured using doubly-labeled water methodology.

2 Values are differences between Low-Carb and High-Carb for changes over time: END – START for DXA, Av(MID, END) – START for isotope dilution.

3 P-value is for the overall diet group effect during the Test phase. Statistical models were minimally adjusted for cohort; adjustment for other baseline covariates did not materially affect the results.

4 P-value for (Low-Carb) – (High-Carb) contrast is equivalent to a test for linear trend across diet groups (with equal, 20% increments in the contribution of carbohydrate to total energy intake from Low-Carb to Moderate-Carb and from Moderate-Carb to High-Carb). Statistical models were minimally adjusted for cohort; adjustment for other baseline covariates did not materially affect the results.

5 N=148 (DXA), N=146 (isotope dilution). One participant (ITT only) had unusable isotope dilution data at START. One participant (ITT and PP) had unusable isotope dilution data at MID and END.

6 N=110 (DXA), N=109 (isotope dilution). One participant (ITT and PP) had unusable isotope dilution data at MID and END.

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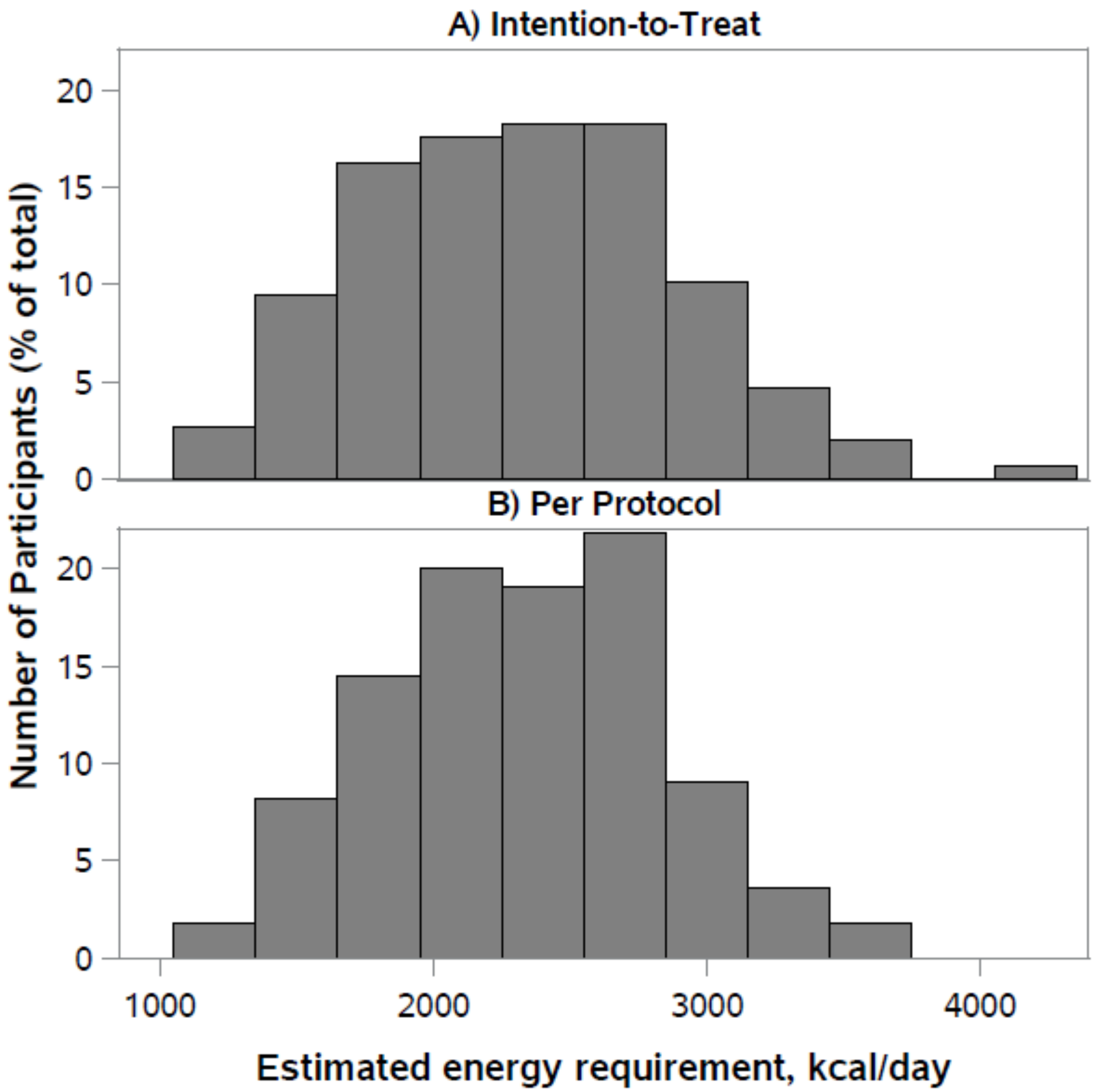
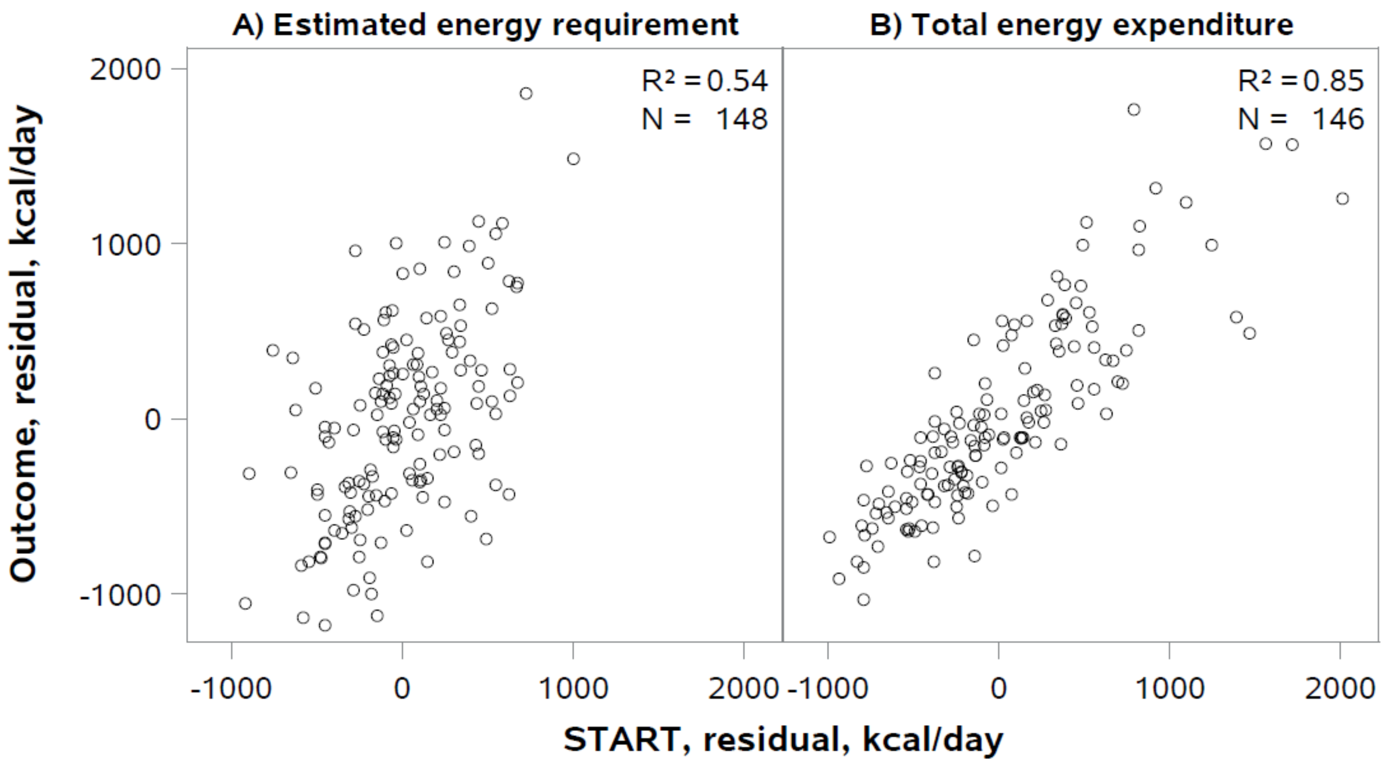
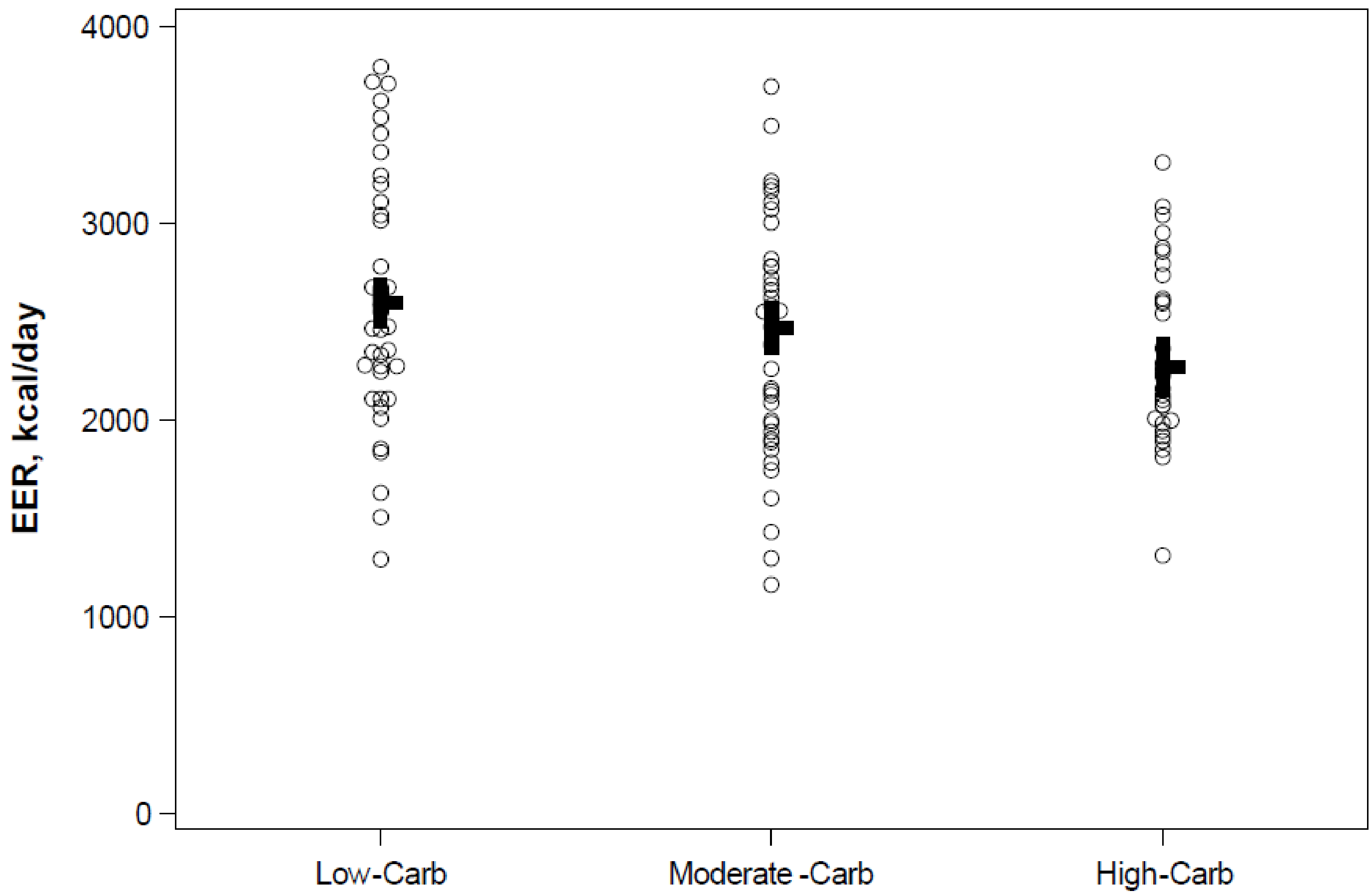
SUPPLEMENTAL FIGURE 1 Frequency distributions of EER during the Test phase in Intention-to-Treat and Per Protocol analyses in the Framingham State Food Study (Panel A, Intention-to-Treat analysis, N=148; Panel B, Per Protocol analysis, N=110). Frequencies are expressed as percentages of the total number of participants. EER, estimated energy requirement.



SUPPLEMENTAL FIGURE 2 Scatter plots showing variability in EER and TEE in the Framingham State Food Study. Controlling for diet group, variability was evaluated using partial correlation of the residuals from models comparing EER at START with EER during the Test phase (MID through END), and TEE at START with TEE during the Test Phase (average of MID and END). The correlation between START and Test phase measurements was substantially lower for EER (Panel A, R^2=0.54, N=148) compared to TEE (Panel B, R^2=0.85, N=146), providing rationale for using ANCOVA rather than change models for EER. ANCOVA, analysis of covariance; EER, estimated energy requirement; END, end of Test phase; MID, midpoint of Test phase; START, start of randomized trial (post-weight loss, pre-randomization); TEE, total energy expenditure measured using doubly-labeled water methodology.



SUPPLEMENTAL FIGURE 3 Diet effect on EER with individual data by to diet group (Low-Carb, Moderate-Carb, High-Carb) in the Framingham State Food Study. Data were analyzed using a GLM framework and are from Model 4 of the Per Protocol analysis (N=109), presented in Table 2 of the manuscript. The overall group effect was significant (P=0.008): Low-Carb, 2594 (2465, 2723); Moderate-Carb 2467 (2331, 2602); High-Carb 2271 (2120, 2422). Horizontal bars, group means; Vertical bars, 95% CI. Carb, carbohydrate; EER, estimated energy requirement; GLM, general linear model.



SUPPLEMENTAL FIGURE 4 EER-to-TEE ratio during the Test phase as a measure of non-adherence in the Framingham State Food Study. Data were analyzed using a GLM framework. Differences by diet group were not significant (Panel A, Intention-to-Treat analysis, P=0.42, N=147; Panel B, Per Protocol analysis, P=0.86, N=109), suggesting no systematic bias. EER-to-TEE ratio in Low-Carb, Moderate-Carb, and High-Carb were, respectively: 0.88, 0.91, and 0.85 in the Intention-to-Treat analysis; and 0.88, 0.89, and 0.87 in the Per Protocol analysis. Diamond symbols, mean; Horizontal lines, median; Gray shaded area, interquartile range (IQR, 25^{th} to 75^{th} percentile); Bars, range (minimum observation greater than 1.5×IQR below 25^{th} percentile to maximum observation less than 1.5×IQR above 75^{th} percentile). EER, estimated energy requirement; GLM, general linear model; TEE, total energy expenditure measured using doubly-labeled water methodology.