(2, 3). However, despite major methodologic limitations, the results support the opposite conclusion.

According to the clinical trials registry, this study was designated a pilot, presumably with the aim of acquiring preliminary data for a future study. By definition, pilot studies are not powered to make precise estimates of effect sizes or rigorously test a hypothesis. Thus, it is surprising that the authors dismissed the importance of the primary outcome: an increase in energy expenditure on the KD on the basis of 2 independent state-of-the-art methods. A fairer interpretation would be to reject the null hypothesis (i.e., all calories are alike from a metabolic perspective)—a remarkable finding for a pilot.

The observed 151 kcal/d increase in energy expenditure when consuming the KD based on doubly labeled water is >10-fold larger than the energy gap Hall himself calculated as underlying the entire obesity epidemic (4), and evidence for a novel biological phenomenon. Moreover, the pilot study likely underestimated the true effect of the KD because of several fundamental methodologic limitations, most importantly the nonrandomized (technically observational) design. Because the baseline diet was given first to all participants, any factor that changes with time could confound outcomes. In this case, we know that the participants began the KD in a different metabolic state versus the baseline diet because they weighed significantly less (because of miscalculation of total energy intake) and probably also experienced changes in muscle mass and metabolic activity (because of the preceding 1-mo confinement to a research unit). In addition, the protocol failed to measure energy losses from ketones and fat in the breath, urine, and stool, which would have been greater when consuming the KD. Each of these potential sources of confounding easily could have biased the estimate of energy expenditure by 50 kcal/d in the same direction, suggesting a potential effect size 150 kcal/d larger than observed, and consistent with the 300-kcal/d difference in energy expenditure in our crossover feeding study (5).

The authors dismiss any sustained metabolic benefit based on linear trend analysis of energy expenditure obtained in the metabolic chamber, but this interpretation assumes precision wildly beyond the limited power of this pilot. We simply cannot know how cumulative changes in body weight or other metabolic variables might influence these pre-post comparisons, nor can the statistical adjustments involving weight or body composition compensate for the weak experimental design. Furthermore, metabolic chamber respirometry was shown to be inferior to doubly labeled water in the detection of adaptive thermogenesis, according to a comparative study involving several coauthors of the present investigation (6). Therefore, the doubly labeled water measurements collected during the final 2 wk of the assessment period flatly contradict the authors' inferences about time course.

Another concern with small pilots is that they inherently lack generalizability. For many dietary exposures, individual responses vary according to numerous biological and behavioral factors. One critical factor may be insulin secretion, which strongly predicts change in energy expenditure on low– compared with high–glycemic load diets (7, 8). We cannot know to what degree the convenience sample of 17 individuals (excluding one outlier with very high energy expenditure in the KD group) resembled the general population with regard to this and other relevant baseline covariates. Indeed, the outlier might represent an important subset of the population whose exclusion may have further biased the data against the KD (by an additional ≥60 kcal/d).

Finally, the authors overinterpret the initial reduced rate of change in fat mass after initiation of the KD. For individuals who habitually consume a high-carbohydrate diet, it may take several weeks for fat oxidation to reach steady state after they increase fat intake (9, 10). Although disregarded, their data actually support this possibility, with an apparent acceleration in fat-mass loss in the final 2 wk of the KD (as visually demonstrated in Figure 2B of the study). Measurement of change in fat balance probably also was biased against the KD by factors considered above.

The conventional "calories in, calories out" approach to obesity has been largely unsuccessful in practice throughout the last 40 y, as evidenced by the continuing high prevalence rates and the difficulty of most individuals in maintaining weight loss over the long term. The carbohydrate-insulin model proposes an alternative approach to obesity treatment that is based on considerable theoretical and clinical data. Properly controlled and adequately powered randomized controlled trials are urgently needed to test this model.

DSL has received royalties for books on nutrition and obesity. CBE reported no conflicts of interest.

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Reply to DS Ludwig and CB Ebbeling

Dear Editor:

Does the proportion of dietary carbohydrate and fat affect energy expenditure (EE) or body fat? The carbohydrate-insulin model predicts that reduced carbohydrate diets decrease insulin secretion, thereby increasing EE, fat oxidation, and body-fat loss compared with isocaloric diets with higher amounts of carbohydrate (1). Testing these predictions requires inpatient feeding studies, because diet adherence cannot be guaranteed in outpatient studies (2).

As noted in our report (3), 15 inpatient studies have compared isocaloric diets with constant protein and varying carbohydrates from 20% to 75% of total calories and found either small decreases in EE with lower carbohydrate diets or no significant differences. A recent study (by some of us) found that carbohydrate compared with isocaloric fat restriction led to significantly decreased EE, despite substantially lower insulin secretion (4). Although these results contravene predictions of the carbohydrate-insulin model, the EE effects of very low–carbohydrate diets had not been investigated before our study (3). Mathematical model simulations predicted small EE increases for such diets (4), but below the estimated 300–600 kcal/d metabolic advantage suggested by Ludwig (5) and others (6).

Our inpatient study was designed to determine the maximum EE effect of an extremely low-carbohydrate (5%) ketogenic diet with the use of metabolic chambers. The prespecified threshold representing a physiologically important EE effect was 150 kcal/d; the study was powered for an endpoint analysis that compared EE on the final pair of chamber days on each diet. We found no significant difference ($P = 0.21$). The repeated-measures mixed model used in the final analyses substantially increased the study's power; EE was increased by 57 kcal/d during the ketogenic diet ($P = 0.0004$), but the effect waned over time ($P = 0.002$).

Ludwig and Ebbeling suggest that the doubly labeled water (DLW) method used to measure EE in their study (5) is superior to metabolic chambers. However, this claim is based on a misinterpretation of a study that was conducted by some of us that concluded that these methods provide different EE estimates as a result of the environments in which they are performed (7). DLW requires many additional assumptions that can considerably bias EE, and it has substantially lower precision than metabolic chambers, which are the gold standard against which the DLW method has been validated. Our exploratory DLW measurements found a statistically nonsignificant 126 kcal/d increase in EE related to physical activity on the days outside the chamber at the end of the 2-mo inpatient stay (3). Although Ludwig and Ebbeling interpret this as a direct effect of the ketogenic diet, a likely alternative is that the subjects' behavior was affected by the time spent on the metabolic wards.

By design, we fed subjects so that they were in approximate energy balance during the metabolic chamber days. However, physical activity was higher on days spent outside the chambers, resulting in a modest overall negative energy balance and corresponding weight loss. Ludwig and Ebbeling argue that our study was biased against the ketogenic diet because it was provided second, when the subjects weighed less. However, the EE effect was still <100 kcal/d after adjusting for the weight loss, and this was likely an overestimate because the adjustment assumed that body water losses corresponded with decreased metabolically active tissue. Furthermore, providing the ketogenic diet second may have biased the results toward increased EE, because Ludwig and Ebbeling reported a greater metabolic rate during a low-carbohydrate diet when it followed a high-carbohydrate diet, as compared with the reverse order (8).

Despite the reported urinary ketone excretion being <15 kcal/d (3), Ludwig and Ebbeling suggest that our EE measurements were biased against the ketogenic diet by 150 kcal/d corresponding to additional breath and stool losses. However, the principal equations of indirect calorimetry [Supplementary Materials equation 22 (3)] demonstrate that even such overestimated losses would affect EE by <5 kcal/d.

The carbohydrate-insulin model predicts increased body fat loss with reduced carbohydrate diets. However, no inpatient feeding study has demonstrated significantly greater body fat loss with lower carbohydrate diets than with isocaloric diets with equal protein. Our study (3) and an earlier one (4) found that the rate of body fat loss was slightly lower during reduced carbohydrate diets despite rapid, substantial, and sustained decreases in daily insulin secretion. Slowing of body fat loss during the low-carbohydrate diets was unlikely to have been due to a time effect, because the relevant time scale for fat loss slowing is much longer (9). Indeed, no controlled feeding study has measured a slowing of body fat loss during a constant hypocaloric diet over a period of less than several months.

Ludwig and Ebbeling suggest that it takes several weeks for fat oxidation to reach a steady state after fat intake is increased. But when carbohydrates were simultaneously reduced during the ketogenic diet, daily fat oxidation completely adapted within the first week, as indicated by the rapid and sustained maximal drop in respiratory quotient (3). There is no evidence of a physiologic mechanism that would subsequently accelerate daily fat oxidation or body fat loss.

Compared with our inpatient study, Ludwig and Ebbeling's outpatient study reported similar negative energy balance, as calculated by subtracting EE from the energy in the food provided to the subjects (5). The corresponding weight loss in that study should have amounted to several kilograms over the 3-mo test period, and the 325 kcal/d EE increase during the 28-d low-carbohydrate, high-protein diet should have led to a difference in stored energy of $\sim$9100 kcal compared with the low fat diet. However, no significant changes in body weight or composition were observed, raising concerns about diet adherence and the accuracy of the DLW measurements (10).

The results of our study and other inpatient feeding studies demonstrate that the proportion of dietary carbohydrate and fat has a minimal effect on EE and body fat. These results should not be interpreted as "raising the bar on low-carbohydrate diets." Rather, such outpatient weight loss diets may lead to greater body fat loss because of decreased energy intake and/or increased physical activity, but probably not because of any metabolic advantages predicted by the carbohydrate-insulin model.

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