18 September 2018

Dear Dr. Loder,

Thank you for the very fast review of our manuscript and encouraging initial decision. We are grateful for the opportunity to improve the manuscript in a revision.

In this submission, we address all issues on a point-by-point basis below, incorporate extensive reanalyses, and made major revisions to the text.

I believe that we have positively responded to, or have provided reassurance on, all concerns. Perhaps the only outstanding issue is Point # 1: how to address the error in our initial Clinical Trials registration. If you disagree with our proposed approach, we would be willing to proceed per your general guidelines.

For clarity, I've number all points in this Response Letter sequentially, beginning with the editorial requests and continuing through Reviewer 5 and the formatting guidelines (a total of 104 items). Page and paragraph notations to changes in the text pertain to the Clean Copy of the manuscript. The Supplement has also been extensively revised, including new material – please let me know if you'd like a Track Changes version for that document.

Regarding other matters:

i. Per my email to you on 29 August 2018, I've confirmed with The Obesity Society their continued interest in synchronizing potential publication of the full manuscript with the oral presentation of study results. They would also be happy to coordinate a press release with *BMJ*. Our oral presentation is scheduled for the Blackburn Session (in honor of one of the Society's founders, who died last year) on Wednesday Nov 14 at 10:40AM, Eastern US Time Zone. This session is expected to receive considerable attention. Here are the relevant links:

Our session: https://obesityweek.com/session/tos-asn-joint-symposium-george-l-blackburn-md-phd-nutrition-and-metabolism-symposium/
General conference info: https://obesityweek.com/

Please note that this session has several other presentations, including by Gardner of his DIETFITS study recently published in *JAMA*. In our manuscript Discussion section, we provide a rationale for reconciling the ostensibly differing results of his study and ours. Thus, I think this session will importantly help move the field toward a consensus. When you make a final decision on the manuscript (assuming it's positive), I'll work with The Obesity Society to have *BMJ* featured in the session description and elsewhere on the Conference web site as appropriate.

ii. Per my email to you 3 August 2018, Friedman and Appel published on the preprint server *BioRxiv* a reanalysis of the study by Hall et al, the chief critics of the carbohydrate-insulin model of obesity https://www.biorxiv.org/content/early/2018/08/03/383752. The reanalysis found that total energy expenditure increased by 203 to 283 kcal/d on Hall's very-low-carbohydrate diet vs standard diet – virtually identical to what we report in our manuscript. Of note, our study is much stronger, with 163 vs 17 participants; a randomized vs non-randomized design; and a 5-month vs

1-month treatment arm. We now include a citation to the reanalysis in our Discussion section.[1] (page 19, para 1)

iii. Per your email of 24 August 2018, thank you for license to structure the Discussion to be most readable and logical. We've aimed to include all guideline components.

iv. Figures 1, 3 and 5 of the original submission did not format properly in the combined pdf, perhaps contributing to some confusion among the reviewers. Please let me know if any figures in this submission require reformatting or other attention.

v. The ICMJE forms for all authors were sent under separate cover to papersadmin@bmj.com

COMMENTS FROM THE EDITORS

*1. * We were pleased to see that the trial was prospectively registered. Thank you as well for submitting the study protocol. In your revision please be guided by the following: If there are any discrepancies between outcomes specified in the protocol and those specified in the trial registration, please default to the registry-specified entries. If there have been any changes to registry-specified outcomes during the course of the study, please explain the dates and reasons for the changes and as a general rule please report BOTH the originally specified and the changed outcomes so that readers can judge for themselves the effect of any changes.*

We closely adhered to the *a priori* clinical trials and protocol plans, also as detailed in our methods paper[2] and Open Science Framework registry (https://osf.io/rvbuy/).

The only discrepancy involves a change from initial specification in the anchor used to calculate change in the primary outcome. In our original analysis plan of 2014, we had indicated the pre-weight loss (i.e., pre-Run-In, BSL in Figure 1) measurement as the anchor for determining the diet effect on total energy expenditure (TEE), but this was an error on our part. We corrected this error in the Clinical Trials registry and used an analysis for our manuscript with the post-weight loss (i.e., post-Run-In, PWL in Figure 1) measurement as the anchor. For the reasons explained below, we request an exception to your general rule of including both analyses in the Results section, and instead have provided further clarification of this issue in Methods.

- *The initial listing was clearly an error:*
  - As a general rule, anchor data should be collected as close to randomization as possible, to decrease error introduced by time-varying covariates. The pre-Run-In measurement involves a 3- to 4-month delay prior to initiation of the Test diets.
  - In addition to this delay, the pre-Run-In measurement is strongly confounded by weight loss, whereas the specific aim of the study is to examine TEE during weight maintenance. (Indeed, the title of the study in the registry is: *Dietary Composition and Energy Expenditure During Weight-Loss Maintenance.*)
  - The expressed purpose of the Run-In was to produce 12% weight loss, changing biological state (i.e., creating a predisposition to weight regain) to test the study hypotheses. Thus, it would be inconsistent with study aims and methodologically

inappropriate to use the pre-Run-In time point to establish a precise and accurate anchor for determining how the Test diets change TEE. Doing so would necessitate a substantially larger number of participants (and cost) to account for the additional imprecision, with no scientific benefit.

- *Study power (and thus participant number) was determined with use of post-Run-In measurement as the anchor.*
  - Our *a priori* power calculations defined the primary outcome as "change in total energy expenditure at week 20 of the test phase compared to week 0 (post-weight loss)."[2]
  - We did not take into account the variability between pre-Run-In and post-Run-In (Week 0) measurements, which in our case had r-values on the order of only 0.3 for the unadjusted model and 0.5 for the adjusted model.
  - Not surprisingly, doing the analysis with the pre-Run-In measurement as the anchor yielded a mean estimate in the same direction, but with substantial loss of precision and a statistically non-significant overall effect in the ITT. For example, TEE in the unadjusted model of Low vs High Carbohydrate diets was + 141 kcal/day (p=0.08, overall p=0.2).
- *The error was recognized and corrected* a priori
  - We obtained IRB approval for our final analysis plan on 06 Sept 2017, before the blind was broken (and indeed, before measurement of the primary outcome had been completed by our collaborator Bill Wong in Houston). Similarly, we corrected the Clinical Trials registry prior to breaking the blind. We provide documentation of this timeline, and additional detail, in the Supplement Protocol section.

Although we agree with the general policy of including multiple analyses where discrepancies exist, we think an exception would be warranted in this situation. For reasons suggested above, we believe that we have fulfilled the letter and spirit of an *a priori* analysis plan. Furthermore, we are 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. Rather, inclusion of the additional analysis would tend to elevate and give undue attention to an error, and therefore potentially cause confusion.

To place our study in the context of other diet trials, I reviewed the Clinical Trials registry of diet and weight loss trials published in one of the *JAMA* journals since 2015 (to obtain a collection of cross-specialty examples). Of the 13 trials identified, 8 had significant changes in the primary outcome since initial posting.[3-10] In several additional trials, the level of detail for the primary outcome was insufficient to exclude multiple statistical treatments.

Regarding this last point, our pre-analysis plan provided a comparatively great level of detail.[2] For contrast, the study by Hall et al of 2016[11] (cited in the Endocrine Society Scientific Statement as major evidence against the Carbohydrate-Insulin Model[12]) included only a 1-paragraph statistical plan (https://osf.io/9q8cu/ beginning bottom of page 23), thus providing freedom to analyze outcomes in many different ways (e.g., *post hoc* exclusion of outliers).

My intent in providing this context isn't to justify suboptimal practices, but rather to clarify that error or lack of specificity in an initial registry of major diet trials (vs industry-sponsored drug

trials which have much larger budgets, infrastructural support and standardization) is more the rule than the exception. However, we believe that our overall rigor is comparatively very high, and the proposed course of action entails no risk to the integrity of the data analyses.

To address your reasonable concerns on this point and to maintain maximum transparency, we have clarified this situation in the Methods (page 12, para 2) and provided additional detail in the Supplement Protocol section. Please also note that we have committed to post the complete data set on a publicly available server upon publication of the manuscript, so that anyone can perform additional exploratory analyses, including this one. Nevertheless, we will defer to you, and include the additional analysis, if you disagree with our proposed solution.

(N.B., for effect modification [e.g., with insulin secretion] we pre-specified use of pre-weight loss measures, as these would be most relevant to the clinician. That is, the clinician could identify individuals in the highest response groups without first having to induce weight loss.)

*2. * Please report prespecified outcomes in the paper in the order they are listed in the trial registry. Please make sure the paper (or the appendices) report all of the outcomes mentioned in the registry. If you plan to report some of these outcomes elsewhere in separate papers, please still list all of these outcomes and state that they will be published separately. Please make clear in any tables or figures whether the outcomes included are primary, secondary, or post-hoc outcomes.*

This paper presents outcomes from our registry involving: 1) all indicated components of energy expenditure, including the pre-specified primary outcome; 2) metabolic hormones potentially related to diet and energy expenditure; and 3) biomeasures of dietary compliance. Since each of these three categories was not specifically grouped in the registry, strictly following the order listed would make for a less logistical and clear presentation of the data.

In the spirit of your guideline, we now list the outcomes in this order:

- Participant flow and adverse events
- Pre-specified primary outcome (total energy expenditure)
- Pre-specified secondary outcomes related to energy expenditure
- Pre-specified secondary outcomes related to metabolic hormones
- Pre-specified secondary outcomes (biomeasures) of compliance

In the Supplemental eTable 1, we now list all pre-specified outcomes and indicate that those not presented here (e.g., related to cardiovascular disease risk factors, hunger, quality of life, cognitive function and miscellaneous hormones) will be the subject of future analyses and publication elsewhere.

In addition, we now indicate whether the outcomes are primary or secondary in the tables and figures.

*3. * If you report any non-prespecified (post-hoc) outcomes, please clearly identify them as post-hoc and refrain from undue emphasis on them in drawing conclusions about the study.*

We did not formally specify testing for effect modification by fasting insulin and glucose, as suggested by Reviewer 4 (Point #70). Thus, we label these requested tests as *post-hoc* analyses and present them in the Supplement (eFigures 2 and 3), rather than main text. We also include a *post-hoc* estimate of energy intake, as requested in Point #52. All other analyses were pre-specified (see eTable 1 in the Supplement).

*4. * Many of the points that you make in your appeal letter to JAMA are persuasive. We thought that some of these explanations should be in the paper itself.*

Thank you. We included more material from that letter, and several additional references, to counter the recent suggestion that novel effects of diet on de novo lipogenesis could substantially bias measurement of doubly-labeled water (the two paragraphs beginning bottom page 21). The newly added material should immunize us from any attack by critics.

For due diligence, I sent this section of the Discussion to several senior colleagues, including Marc Hellerstein of UC Berkeley, arguably the world's expert on de novo lipogenesis. All concurred with our treatment of the issue. Hellerstein agreed to be formally recognized in the Acknowledgement section for providing advice on this topic. Hellerstein also identified other major flaws with this attack, beyond those we discuss here, such as conflating essential with non-essential fatty acids, which resulted in wildly inflated estimates of de novo lipogenesis, but addressing these more technical aspects will probably best be left for a different venue. (Also, two of our coauthors, Robert Wolfe and William Wong, are internationally-recognized experts in doubly-labeled water methods.)

Another topic considered in the letter is addressed elsewhere, related to Point #1, above.

*5. * Can you clarify why you were looking for a difference of 237 kcal/day in TEE? Is this a clinically meaningful difference? Can you justify this choice? We also think that general doctor readers might not be used to thinking about TEE and wonder if you can explain this in an easily understandable way. You might, for example, make it clearer than you do that the study question has to do with whether the overall composition of one's diet (balance of various types of nutrients) makes a difference in maintenance of weight loss.*

We obtained the figure of 237 kcal/d for change in TEE from a detectable-difference calculation, having specified the design (3 parallel arms), the sample size (45/arm), the power (80%), the critical p-value (0.05), and the residual standard deviation (412 kcal/d, based on a prior study[13]). Further details can be found in our design paper.[2] We have clarified this point in the revision as follows (page 11, para 2): *"*... The target of 135 completers provided 80% power, with 5% Type I error, to detect a difference of 237 kcal/d in TEE change between one diet arm and the other two. This difference is somewhat smaller than the effect detected in the prior study[13] and consistent with a predicted effect of +50 kcal/d per 10% decrease in the contribution of dietary carbohydrate to total energy intake.[14]*"*

We have also aimed to make the clinical translation of these findings clear to the general doctor (e.g., on page 19, para 1) and now include a new passage on the significance of energy expenditure in the beginning of the Discussion (page 18, para 2).

*6. * Figure 4 gives the data in kcal/kg/d, which is confusing. Looking at the CIs, there is not much difference between groups.*

We realize that our presentation of the data in various ways (e.g., with and without normalization to the average weight of our participants) contributed to confusion. To be most consistent with our pre-specified analysis plan – and with the reassurance you provided in Point #12, below – we will continue to include a model that calculates TEE per kg, but we now express all results as normalized values (kcal/day, a more easily interpretable measure). As further discussed below and in our responses to Reviewer 3 (Point #63), the theoretical concerns related to calculating TEE per kg should not apply to our within-individual change values (as the relative amounts of fat mass vs fat-free mass will not meaningfully change during weight maintenance over a few months). Moreover, we arrive at similar results with all the statistical models, including one that does not include body weight.

The reviewer comments that the error bars that figure (now Figure 3) don't suggest much difference between groups. To provide information about time course, we chose to illustrate the mean change and SE for each diet at both Test Phase time points, but our pre-specified analytical approach involves the average mean change combining weeks 10 and 20. The 2-df hypothesis test for this quantity is specified in Methods. For Fig. 3A (Intention-to-Treat), the result was $F_{2,149}=6.24$, $p=0.002495$; for Fig. 3B (Per Protocol), $F_{2,108}=8.61$, $p=0.0003$. These statistics represent the definitive result. We hope that clarifications and additional detail in the revised Methods will help prevent reader confusion.

Per email correspondence, I understand that SE will be acceptable for the figures. Note that we will continue to present summary comparisons in the text, as appropriate, with CIs.

*7. * As many reviewers have commented, it is also unclear how the trial was actually done. Were participants admitted to a ward and measured daily? If they were at home, how was compliance checked, etc ? Did they use food diaries? It is difficult to find these details.*

We have extensively clarified the overall design in Methods and revised our study overview (Figure 1). We address issues related to compliance and food diaries below (Points # 33, 48, 49, 52, 55 and elsewhere).

*8. * The Abstract doesn't make clear that the results described are all prespecified, and hence more valid.*

We now indicate in the Abstract that the main outcomes were pre-specified. This issue is also considered in eTable 1.

*9. * The main results include lots of covariate adjustments that ought not to be necessary given the randomised design. Our statistician wants to see an unadjusted analysis presented first.*

Per your email of 4 September 2018, we now use the requested analysis (unadjusted, except for study site, cohort, and enrollment wave – which are design features) as our primary model. For

all outcomes, the results of this model and the fully adjusted model (including the individual-level covariates) yield similar effect estimates. We also include the fully adjusted model for our primary outcome, TEE.

*10. * Our statistician also notes that Table 3 should give the ITT results, not PP – as they stand the ITT results are relegated to supplementary Table e5. Also PP results are reported before ITT results in other places. Please be sure to present ITT results first, before the per protocol results. In interpreting the findings, you need to focus on the ITT results.*

We now present the ITT first for all analyses, and focus on it as you request, with one exception: the newly requested *post hoc* analysis of estimated energy intake. This measure is germane to data interpretation only during weight stability (i.e., those individuals included in the Per Protocol analysis, comprising 74% of the total). It would be highly problematic to make inferences of energy requirements among the remaining 26% who were not weight stable, and by definition had not closely complied with Test diets (see Point #52 for additional rationale).

*11. * The analysis should include a test for trend in the % carbohydrate content, not just HI vs LO.*

At issue is a test for linear trend in TEE across diets of increasing carbohydrate content, rather than simply comparing HI with LO. If we take the three diets as forming an ordinal scale, equally spaced (HI, MOD, LO), then the test for linear trend is equivalent to the test for a difference between HI and LO; this is a consequence of the middle point in a linear regression having no leverage on the slope. (Even so, the MOD data are not without influence; they contribute to the pooled estimate of residual variance and thus to the precision with which the HI-LO difference is estimated.) Instead of the ordinal scale, we could use the actual carbohydrate content of the three diets; but this also was equally spaced (HI 60%, MOD 40%, LO 20%). Therefore, the test for linear trend is equivalent to the comparison of HI with LO, a point now clarified in a footnote in Table 3.

*12. * We acknowledge the concern of one of the reviewers that TEE was divided by weight but are not as worried about this, since you also did the alternative analysis of adjusting TEE for weight.*

To better anticipate this concern among readers in the field, we include in the revision a more detailed discussion of our reason for making this calculation and why general concern about this approach (typically involving cross-sectional comparisons between-individuals) wouldn't apply to the specifics of our trial (involving change within individuals). And as you recognize, we also provide the alternative model which yields a similar result (with and without weight adjustment; with and without dividing TEE by weight). Please see Point #63.

*13. * The example weight and height on page 17 should be in metric not imperial units.*

Done

14. In your response please provide, point by point, your replies to the comments made by the reviewers and the editors, explaining how and where (page number) you have dealt with them in the paper. Please return both a track changes and clean version of the manuscript.

Done

COMMENTS FROM REVIEWERS

REVIEWER: 1

15. Understanding why weight is frequently regained following weight loss is an important area of study. Although it is well known that energy expenditure declines with weight loss, facilitating weight regain, relatively less is understood about whether diet composition post weight loss is relevant.

The authors invoke the Carbohydrate-Insulin Model (CIM) which they have proposed is a mechanism which helps explain the burgeoning of obesity in the past decades. However, the approach taken is to test whether this theoretical model may alter energetics post weight loss rather than during weight gain. Hence, although the experimental work is interesting and valuable, the premise is not necessarily supported by this study design.
In my view, had there been less emphasis on the Model per se and perhaps a broader discourse on various models of obesity including the CIM, the paper would be more complete.

For example the authors dismiss discussion of other models (refs 8-12) except in the context that these dispute CIM due to lack of controlled feeding studies. A very recent review of body weight homeostasis https://urldefense.proofpoint.com/v2/url?u=https-3A__www.ncbi.nlm.nih.gov_pmc_articles_PMC6039924_&d=DwIFaQ&c=qS4goWBT7poplM69zy_3xhKwEW14JZMSdioCoppxeFU&r=HzbHdpS-3grwpLx9r6E-9VusIayHmpyiieQcL7MXKaNp4MapU5y_XVbBHBTjdVvH&m=h60T0aiAqeBwsLEQ-27_G74mLdu_BIYYSCkyH82XO9A&s=-s5AyXA5ILJC8QqbYp3EPHUOCHGQ3hQhz0eIASlEZB8&e= provides a comprehensive overview of this area and confirms that indeed energy expenditure is a critically important area of investigation in relation to obesity. In this regard, the study by Ebbeling and co-authors is important, notwithstanding divergent views on mechanisms of obesity. Indeed one of the strengths of this paper is the direct measurement of TEE using doubly labeled water methodology rather than indirect methods.

We thank the reviewer for this perspective.

A primary motivation for this study was to test a specific prediction of the Carbohydrate-Insulin Model (CIM) relating to energy expenditure. We designed a protocol of longer duration than any previous feeding study on this subject to exclude confounding by transient adaptive processes to changes in macronutrients, as considered in our recent review.[14] Therefore, we think it appropriate to interpret the results in the context of the CIM. Nevertheless, we agree that a change in energy expenditure has clinical significance, regardless of underlying mechanisms. In

the revision, we have include a comment to this effect and cite the recent paper by Müller et al. as recommended by the Reviewer: "Regardless of the specific mechanisms involved, the study shows that dietary quality can affect energy expenditure independently of body weight, a phenomenon that may be key to obesity treatment, as recently reviewed." (page 18, para 2).

16. The paper provides valuable insights into post weight loss regain rather than the development of obesity per se. That regain is following what is a high protein energy restricted diet followed by one of three dietary patterns that vary carbohydrate and fat only with a stable protein composition. It is unclear why this particular pattern was selected.

The post-weight loss state has been used to study mechanisms predisposing to weight regain, and the difficulty for most people of successful long-term weight loss maintenance.[15] We agree that our study does not directly test a hypothesis related to development of the obesity epidemic, and for that reason have focused our conclusions on treatment, not prevention.

We chose to control for protein in the test diets, to highlight potentially novel effects of macronutrients. Protein is recognized to have a higher thermic effect than carbohydrate or fat; thus, controlling for it provides a more rigorous test of the CIM.[16] We now include a comment to this effect in the revision (page 10, para 1).

As further discussed below (Point #21), the Run-In diet is not especially high in protein, considering the overall energy deficit. On an absolute basis (grams), the Test diets have higher protein content than the Run-In diet.

Nevertheless, we are aware of the Reviewer's important work on high protein diets, and agree that higher protein intake might provide metabolic benefits through mechanisms consistent with the CIM, a possibility that warrants additional research.

My specific comments are as follows:
17. Abstract
I believe the abstract should describe the composition of the energy restricted diet as well as specify the timeline of the run in and intervention for greater clarity for the reader.

With the tight space constraints of the abstract, we're not sure whether this additional detail of the Run-In diet justifies eliminating other material. We have no reason to think that the method by which individuals arrived at the pre-specified weight loss target would affect the primary hypothesis; and if any such effect existed, it would have been controlled for in the randomization scheme.

18. Also important is to describe that TEE was measured by doubly labelled water.

Done

19. For clarity suggest state: 164 were randomized to ONE OF THREE test diets.

Done

20. It is not clear to me what "scaled to average post-weight loss body weight (82 kg) for reporting in kcal/d." actually means and why actual post-weight loss body weight wasn't used.

Our primary prespecified outcome was TEE per kilogram – an approach that should improve precision and not cause bias for these within subject comparisons during weight-loss maintenance (see Point #63, below). These results are then scaled to the mean weight of the participants, 82 kg. Of note, we achieve similar outcomes with alternative methods (i.e., expressing results without dividing by weight; and with and without adjustment for weight-related variables). We have clarified this point in Methods and revised the Abstract to achieve consistency and avoid confusion.

21 The conclusion in the abstract states: "Lowering dietary carbohydrate increased energy expenditure independently of body weight. This metabolic effect may facilitate weight-loss maintenance, especially among individuals with high insulin secretion."I believe this is not entirely an accurate conclusion based on the study. My interpretation would be as follows: "Following a 12% weight loss on a higher protein energy restricted diet, lowering dietary carbohydrate/fat ratio increased energy expenditure in energy balance. This metabolic effect may facilitate weight-loss maintenance especially among individuals with high insulin secretion."

The Run-In diet (with 25% protein and 60% of estimated energy needs) would provide an absolute amount of protein consistent with prevailing intakes and lower than the Test diets (at 20% protein and 100% of energy needs).

Consider a theoretical participate with TEE of 2500 kcal/day prior to weight loss. The Run-In Diet would have provided 94 g protein/day, below typical high-protein diets. For this reason, and as considered in Point #17 above, we don't think an emphasis on the Run-In diet composition is warranted for the Abstract.

22. Introduction
Glycaemic load can be varied not only by exchanging carbohydrate for fat but also for protein. Is there a rational for focusing specifically on fat/carbohydrate ratio alone?

We focused on the exchange of carbohydrate and fat for reasons considered above (Point #16).

23. Methodology
It would assist the reader in knowing this was a free living intervention or tightly controlled in a research institution. As such, no information is provided in the dietary methodology and how energy requirements were assessed. Assume it was based on the TEE data but this is not clear. It would also be useful to have TEE data prior to weight loss if this was performed as this would provide a useful reference point.

We extensively revised Methods to provide a clearer understanding of study design and procedures.

We did not base energy requirements on TEE, as measured by doubly-labeled water, due to the lag between the assessment (collection of spot urine samples following administration of doubly-labeled water) and availability of results from Gas-Isotope-Ratio Mass Spectrometry. The following methods were deemed acceptable given that our protocol allowed for adjustments in energy intake to achieve weight loss (Run-In Phase) and weight-loss maintenance (Test Phase).

- For the Run-In Phase, we determined individual energy needs based on resting requirements, estimated using a regression equation,[17 18] with a physical activity factor of 1.5 (page 9, para 2).
- At the end of the Run-In Phase, we adjusted energy level to stabilize body weight based on recent rate of weight loss for each participant (energy intake during weight loss [kcal/day] + (rate of weight loss [kg/day] × 7,700 kcal/kg) (page 9, para 2).

Because the initial level of calorie intake was established before randomization, and intakes were individually adjusted according to objective criteria, no systematic bias would have been likely (as confirmed by the lack of difference in body weight by group assignment throughout the Test Phase, p=0.43).

TEE, measured at baseline (pre-weight-loss), is presented in Table 2.

24. It would also very much assist the reader if the diagram that shows the study design also was annotated to show when and which measures were taken over the course of the study.

We modified Figure 1 slightly and extensively revised the Methods for improved clarity.

25. Why are not the actual diet compositions provided rather than a standard?

In Table 1, we present dietary composition of the Test diets (expressed per 2,000 kcal), as determined using the ESHA Food Processor software. We scaled the diets based on the energy requirement of each participant. We now present estimates of energy intake in the manuscript (see also Point #52, below).

We recognize that some degree of non-compliance occurred, especially among individuals whose weights deviated beyond ±2 kg relative to the post weight-loss anchor (i.e., not in the Per Protocol group). However, methods for dietary assessment of non-compliance on an outpatient basis are inherently inaccurate and imprecise. We consider the issue of non-compliance extensively in the manuscript and below (Points #33, 48, 49, 52, 55 and elsewhere).

26. How was GL measured?

GL was calculated as the product of the glycaemic index and net carbohydrate: (glycaemic index/100 × net carbohydrate), as now described in the footnote of Table 1.

27. The change in TEE is adjusted for body weight but not adjusted for exercise? Would not that have been appropriate as there were subtle differences in exercise?

Our primary hypothesis focused on TEE, as the sum total of all the individual components of energy expenditure. Adjustment for physical activity would over-correct our models, with bias to the null hypothesis. In other words, it is possible that changes in macronutrients might increase TEE through increased physical activity level, if individuals had better access to metabolic fuels, felt more energetic and spontaneously moved more. Indeed, there is evidence that physical activity level is controlled by biological factors related to weight gain.[19 20] In summary, the TEE effect would remain clinical significant (and scientifically interesting) regardless of which individual component of energy expenditure changed. Additional research will be needed to better characterize these mechanisms, as we now state in the concluding paragraph of the Discussion.

28. Results
Why is there no data on weight trajectory, and why adjustment per kg with a standard 82kg as per comment above?

We now provide data on weight trajectory during the Test Phase (page 15, para 2). Overall, there was very high consistency (correlations ≥0.99), a very small overall change in weight (< 1 kg), and no differences by diet group (p=0.43). Moreover, most individuals remained with ±2 kg of the post weight-loss anchor weight (the 120 comprising the Per Protocol analysis). Furthermore, taking weight and weight change into account in our fully adjusted model had no significant impact on outcomes.

We discuss weight adjustment of TEE below (Point #63) and express data normalized to mean weight of participants in kcal/day as a term more easily understood by the general practitioners.

29. Can the actual intervention diet compositions provided rather than a standard?

See response to Point #25, above.

30. Similarly, can the run in period diet information be provided as this is also part of the overall intervention?

The target macronutrient composition of the Run-In diet is included in the text (page 9, para 2). There will be some uncertainly in dietary composition of the Run-In diet as actually consumed, due to possible non-compliance, as considered elsewhere. However, substantial compliance – to the extent that participants had to achieve the pre-specified weight loss – was a prerequisite to randomization; any variation during this pre-randomization phase should not bias evaluation of the Test diets.

31. Conclusion
The statement "In conclusion, dietary composition appears to affect energy expenditure independently of body weight. A low-glycemic load, high-fat diet may facilitate weight loss maintenance beyond the conventional focus on restricting calorie intake and encouraging physical activity." Requires revision. In my view, a statement based on the methods and results should be the same as per the abstract : In conclusion, following a 12% weight loss on a higher protein energy restricted diet, lowering dietary carbohydrate/fat ratio increased energy

expenditure in energy balance. This metabolic effect may facilitate weight-loss maintenance especially among individuals with high insulin secretion."

We address this issue above (Points #17 and 21)

REVIEWER: 2

This is an important and excellently written MS indicating the potential benefits of restricting carb intake for weight maintenance after weight loss. The Authors thesis is that it is diet (lifestyle) not genetic change that is associated with the rise in body weight in Western populations. They demonstrate the value of lower carbohydrate diets at 20% and 40% versus 60% in maintaining weight lost.

32. The change from 60% to 40% carbohydrate diets would be unlikely to increase ketone body levels, probably the same applies for 20%. Did you contemplate 24h urine collections for β-OHB outputs? Even blood levels could have been useful if you have them. Possibly your spot urines might have been interesting if creatinine adjusted.

We thank the reviewer for the encouraging feedback.

We did not anticipate clinically significant nutritional ketosis on a 60% fat diet, based on essentially negative measurement of ketones from a prior study of ours with the same fat level.[13] For this reason, we did not obtain suitable samples for these volatile substances.

Especially among individuals with a high BMI (such as those we recruited) who tend to be relatively hypoketotic, fat intake above 70% is typically necessary to predictably obtain nutritional ketosis. We aim to study such a diet in an ongoing protocol: https://clinicaltrials.gov/ct2/show/NCT03394664

33. You may have published your methodology but it would be helpful to know more about the diets used. Was it weighed and eaten in a cafeteria. Were meals supervised (how many)? Were leftovers weighed and recorded? Were meals packed for weekends? Etc

We've included additional detail concerning the dietary intervention methodology in the revision (see especially Supplemental Methods). In brief, all menu items were weighed within narrow tolerance limits (±0.1g of the target weight for items ≤10g and ±0.5g for items >10g). Participants were asked to eat at least one supervised meal per day, Monday through Friday, in a dining area at FSU or AV under the supervision of research staff. Other meals (including weekend meals) were packaged for take-out. For supervised meals, weights of leftover menu items were recorded in an online study portal; for take-out meals, participants were asked to record the proportion of each provided menu item consumed using a form on the portal that was pre-populated with daily menus.

34. Do we have any idea if the participants preferred one carb level that might have influenced diet compliance

We designed the diets to be as similar as possible, using the same high protein foods and gradients of high carbohydrate vs high fat foods across the diets to achieve nutrient targets (as described in the Supplemental Methods and exemplified in eTable 3). It's possible that subtle differences in preference could have influenced compliance to some degree, but we have no way of making a definitive determination on that question. We have limited, unvalidated data on palatability, which we have not yet analyzed; and these data have unclear relevance to a feeding study focused on mechanisms. Our most objective measure of compliance, body weight, did not differ between diet groups (p=0.43). Moreover, our multiple analytic models (ITT, Per Protocol, covariate adjustments and sensitivity analyses) address the issue of non-compliance, as considered below (Points #48, 49, 52, 55 and elsewhere).

35. The SFA was fixed, what were the MUFA and PUFA intakes as a % of calories

We now include information on saturated fat, monounsaturated fat, and polyunsaturated fat (as a percentage of total energy) in Table 1.

37. The protein level was fixed. What was the nature of the protein foods? Were they the same across treatments? What was the % of animal, dairy and plant protein contribution to the total protein.

We used the same amounts and types of protein-rich foods across diets, including a variety of plant-based, dairy, eggs, fish and meats. We included plant-based proteins such as soy products in view of their perceived health benefits. The sample meals now shown in eTable 3 demonstrate how we achieved gradients in carbohydrate and fat across Test diets while controlling sources of protein. However, it would take considerable time to calculate accurate distributions of protein types; since this information would not directly alter study interpretation, we prefer to present these data in a future publication.

38. We have the glycemic load of the diets in Table 1, can we have the GI values also?

The glycaemic index values of the Test diets are now included in Table 1.

39. The ratio of carbohydrate/fiber differ between treatments. What was the nature of the carbohydrate foods used on the 3 treatments, did they differ?

Non-starchy vegetables, which are generally low in carbohydrate and high in fiber, were similar across diets. Total fiber content was consistent with recommendations from the Institute of Medicine and reflected a gradient across the three diets, as would be expected on diets with these carbohydrate proportions, as shown in Table 1.

40. Did you have a 3 or 7 day rotating menu? It would be helpful to see a day's menu plan for each treatment (2000 kcal)

We included information regarding cycle menus to the revision (Supplemental Methods). There were 42 meals (14 breakfasts, 14 lunches, 14 dinners), and 14 snacks incorporated into three 1-

week cycle menus during the Run-In phase. Another 42 meals and 14 snacks for each of the different Test diets, totaling 126 meals and 42 snacks, were incorporated into six 1-week cycle menus during the test phase. eTable 3 provides a sample menu for the Test diets.

Minor points
41. You need not qualify glycemic load with "carbohydrate" ("as in high glycemic load carbohydrate"). The carb is already implied. For GI, "high GI carbohydrates" would be correct.

Agree, and done (e.g., Introduction, para 2).

42. With your detailed stratification did you have difficulty filling all your cells. Apart from center, some statisticians caution against too much stratification. Presumably in your case it worked?

We verified that the randomized sample included at least one participant in 24 of the 32 combinations of strata (site × gender × age × obesity × Hispanic ethnicity). Most importantly, the stratified randomization succeeded in balancing each stratification factor across the three diet arms according to Fisher's exact test, with non-significant tests for gender (p=0.29); study site (p=0.54); Hispanic ethnicity (p=0.83); age under 40 yr (p=0.96); and baseline BMI under 30 kg/m^2 (p=0.65). The continuous distributions of BMI (p=0.13) and age (p=0.55) were confirmed to be the same in the three diet arms by one-way analysis of variance. We now comment on this point in the text (page 14 bottom to 15 top).

43. Lines 31 to 50 I understand that you were using a repeated means ANOVA "spanning 3 time points" but you also state that for the change between PWL and weeks 10 & 20, the latter two (were) averaged. Am I missing something?

The reviewer's reading is correct, that the repeated-measures model employed three time points: PWL, MID, and END. After the three-point model was fitted, we combine its fitted parameters – namely diet-specific mean values for PWL, MID, and END – to construct a secondary parameter of particular interest, which we call the "mean test phase change in TEE;" in other words, the "change between PWL and weeks 10 and 20, the latter two averaged" (page 12, para 2). Symbolically, this would be:

$$(\text{MeanMID} + \text{MeanEND})/2 - \text{MeanPWL}.$$

We have clarified that the Test Phase change in TEE is for each diet group (page 12, para 2).

44. You log transformed hormones. Were they the only outcomes with a skewed distribution? Was this determination an iterative process (assessing outcomes) or was it determined on baseline values or predetermined?

We performed log transformation only when the raw data showed severe skew, either overall or within time strata. To avert bias, we made the decision to transform before analyzing the outcome and without separating the data by diet arm. Of the measures reported here, only the hormones (ghrelin, leptin) and triglycerides showed enough skew to warrant log transformation.

To make the results readily interpretable, we re-transformed the adjusted mean logs to natural units and expressed changes as percentage.

45. You comment in Discussion on "consuming sugary beverages". Is the high glycemic load the problem or the inability to be satisfied by liquid calories?

We speculate that the high glycaemic load is mechanistically causal, a possibility consistent with the genetic study by Qi et al;[21] but we cannot exclude an independent effect with regard to food form (liquid vs solid calories). Additional research will be needed to explore this issue.

46. Page 20 line 3 (your line 8) "opposite to what"

We deleted the confusing clause.

REVIEWER: 3

Differences in total energy expenditure (TEE) estimated using an indirect technique were found during periods in which diets differing in macronutrient content were consumed. The authors conclusion was that a diet high in fat could translate into long-term weight loss.

47. The study protocol needs to be more fully detailed in the Methods section. It is not until the Discussion that we find out that participants were provided meals to take home. Was it the intention that participants only ate study-provided food? What about beverages?

We thank the reviewer for the thoughtful comments.

We agree that our initial methods were not sufficiently detailed. That section has been extensively revised in the resubmission.

48. Describe the strategies you used to promote dietary compliance.

We added detail on strategies to encourage adherence in the Supplement. These strategies included monthly group workshops, weekly educational handouts posted in the dining area, personalized notes, and special activities during major holidays or events. Participants also received individualized quarterly progress reports indicating weight loss or weight-loss maintenance, depending on study phase. The presence of study dietitians in the dining area allowed for frequent communication and direct observation of dietary intake during on-site meals. Individual counseling sessions to address adherence issues were conducted in-person in a private space at FSU or AV, or by telephone.

49. I would have expected food records to be kept by the participants. If these were taken then the data need to be presented with statistical comparisons among diets. If not, then the lack of intake data should be discussed as a limitation.

Food records are typically used in behavioral weight loss trials, but their imprecision and inaccuracy has been well recognized, especially when energy intake is compared with the gold standard doubly labeled water.[22] Because we conducted a feeding study, the value of food records is dubious. With our metabolic kitchen and trained staff, we would have a much greater ability to quantify diet than our participants.

Thus, the main issue is to what degree our participants did not comply, either by not fully consuming provided foods or by consuming non-study foods. We address our methods for promoting and monitoring compliance above (Point #48) and in the Supplement; we used change in body weight as another method for assessing compliance (pertaining to total energy intake); and we conducted sensitivity analyses to examine how varying degrees of non-compliance could affect the primary outcome. The strengthening of the findings in the Per Protocol vs the ITT may provide additional reassurance on this point. Also, see Point #52, below.

50. Page 5 Line 22 and 33. Describe what you mean by high glycemic load carbohydrates. Any carbohydrate-containing food has variable glycemic load dependent on the amount eaten.

As suggested above (Point #41), we now use the term high glycaemic load foods or meals. Glycaemic load is by definition expressed relative to typical portion size, providing a method to unambiguously distinguish among foods. We have included references on glycaemic load methodology for the interested reader.[23 24]

51. Note that the diets will differ in aspects other than glycemic load so it would not be appropriate to attribute differences to glycemic load alone as implied in various places.

We aimed to make the diets as similar as possible across groups (e.g., similar protein amount and type, distribution of fat types, amounts of non-starchy vegetables), as considered in the Supplemental Methods and shown in eTable 3. Although the outcomes are consistent with the CIM (and important regardless of mechanism, as discussed in Point #15, above), we agree that this study cannot be definitively attributed to carbohydrate-to-fat ratio alone. We now include this limitation in the Discussion: "Furthermore, our study cannot prove that changes in carbohydrate-to-fat ratio alone mediate study findings. Although we constructed Test diets as similar as possible (e.g., controlling for protein content, amount of non-starchy vegetables, the ratio of saturated to total fat), unrecognized dietary factors could have contributed to the observed effects. This possibility, of relevance to translation, requires exploration in future mechanistically-oriented research." (page 23, para 2).

52. Present the data for the number of people who required energy intake adjustment to keep within 2kg of the anchor weight. This is important data to present and to statistically compare among treatments.

We thank the reviewer for this suggestion. We made frequent adjustments to energy intake throughout the study, based on an algorithm, to promote weight-loss maintenance; therefore, comparing the number of people requiring adjustment would not be ideal to address this issue.

We did monitor total energy intake, based on our knowledge of food provided, measurement of any unconsumed foods, and reports of non-study food consumption. These *post hoc* estimates of total energy are expressly not accurate or precise,[22] and would be likely to underestimate consumption for individuals with high energy expenditure for reasons considered in the revision (see Supplemental Methods). That is, individuals losing weight (due to high energy expenditure) were in some cases instructed to consume additional study-provided snacks consistent with Test diet macronutrient targets, and we did not consistently receive accurate reports on how many such snacks were consumed. Because of the inherent difficulties in accurately and precisely assessing energy intake among outpatients, estimated energy expenditure derived using doubly-labeled water methodology during weight stability is the gold standard for determining energy intake.[25 26]

Recognizing these inherent limitations, we now include data on estimated energy intake in the Per Protocol analysis in the text (page 17, para 1). Numerically, energy intake increased least in the high-carbohydrate group and most in the low-carbohydrate group:

- High-carbohydrate: + 139 kcal/d, (95% CI: -4 to 282)
- Medium-carbohydrate: +175 kcal/d (42 to 308)
- Low-carbohydrate: + 269 kcal/d (143 to 396)
- The overall ANOVA for group difference was not significant (p=0.36)

Interesting, these group differences strengthened in the high insulin-30 tertile, consistent with the observed effect modification of TEE:

- High-carbohydrate: +37 kcal/d (-249 to 323)
- Medium-carbohydrate: -24 kcal/d (-293 to 245)
- Low-carbohydrate: +340 kcal/d (132 to 548)
- Overall ANOVA, p= 0.05

Thus, our estimates of energy intake, though underpowered and likely underestimated, are consistent with the primary findings of the study.

NB, consistent with the Reviewer's request, we used the Per Protocol analysis for this outcome (including only those individuals who remained within ±2 kg of the post weight-loss anchor weight), as estimates of energy intake – and its comparison with TEE – would be severely confounded during weight change.

53. Present the LDL, total and total/HDL ratio data with statistical comparisons among treatments as these have been found to be influenced by macronutrient composition.

We included triglycerides and HDL-cholesterol as process measures, as these have been previously shown to be sensitive markers of total carbohydrate intake and glycaemic load. LDL-cholesterol is less sensitive to changes in dietary carbohydrate. As now delineated in eTable 1, we plan to analyze LDL-cholesterol as part of a future study on CVD risk factors.

54. In the discussion on translation to public health you mention poor long-term compliance, surely that would also apply to any diet that you might advocate?

We agree that long-term compliance can be problematic for dietary changes of all sorts. While a feeding study such as ours provides a more rigorous test of efficacy, the results are one step removed from translation, compared to diet studies relying on nutrition education and dietary counseling.

55. There is a substantial body of literature in which it has been found that compliance to diet is the predominant predictor of weight loss/maintenance independent of macronutrient composition. Please discuss.

We agree that compliance is a major issue in determining long-term successful weight loss maintenance. Compliance can be influenced by environmental, behavioral and psychological factors not studied here (but necessary for successful translation of any long-term diet.) Nevertheless, biological factors may also influence long-term success. A significantly higher energy expenditure would allow for either the same degree of weight loss with greater energy intake or greater weight loss with the same energy intake. Please also see the new passage we've added in response to Point #15: "Regardless of the specific mechanisms involved, the study shows that dietary quality can affect energy expenditure independently of body weight, a phenomenon that may be key to obesity treatment, as recently reviewed." (See page 18, para 2).

56. Using data from the NHANES survey, a positive relationship was found between the proportion of dietary fat and categories of body mass index (Yancy et al. Trends in energy and macronutrient intakes by weight status over four decades. Public Health Nutrition: 17(2), 256–265). Discuss in relation to your suggestion (page 17) that lowering the proportion of dietary energy intake from carbohydrates by increasing fat would result in weight loss.

This series of cross-sectional studies found that, consistent with many other reports, the proportion of energy intake as carbohydrate increased substantially since the early 1970s for all BMI groups (an absolute increase of 5.3% in men and 5.2% in women). Also reported was a slightly lower intake of carbohydrate in the highest vs. lowest BMI categories (-1.1% for men, -0.4% women), but the significance of this finding is unclear, and it may be due to selective under-reporting associated with obesity status. Because the theoretical background for the CIM has been recently reviewed,[14] this manuscript on study findings may not be the best format to speculate on interpretation of other research not directly germane to the tested hypotheses.

57. Observationally, traditional Asian diets with carbohydrate contents providing up to 80% of dietary energy have been associated at a population level with normal weight, discuss how this aligns with the concept of encouraging more fat in the diet.

We discuss this specific case in our recent review of the CIM.[14] As above, we are not certain that this manuscript is the right format for a general discussion of such issues.

58. Comment on the male to female ratios among treatment groups and whether this could have had an influence on the outcomes.

The sex ratios by diet groups are presented in Table 2. Variability across groups was non-significant by Fisher's exact test, p=0.28 (page 14 bottom to 15 top). Any discrepancy in balance

among groups was therefore unlikely to affect the outcome, either in theory or in fact, as the results were insensitive to covariate adjustment (including sex among the other demographic variables).

59. Discuss whether there are specific limitations to the doubly labelled water technique when used in overweight humans and any implication of this to the present work (eg: Ravussin et al. Energy expenditure by doubly labeled water: validation in lean and obese subjects. Am J Physiol. 1991 Sep;261(3 Pt 1):E402-9).

The Ravussin study, involving 12 male subjects across a wide range of body fatness, suggested that doubly-labeled water "is a suitable and accurate method to measure energy expenditure in free-living conditions but might provide a slightly underestimated figure in fatter subjects" relative to a respiratory chamber. However, this minor effect, if real, would not impose systematic bias in our study, as we focus on change within individuals during weight-loss maintenance (from randomization to end of the Test diet periods) rather than cross-sectional comparisons between individuals of differing adiposity. Furthermore, randomization should protect against any bias for or against any Test diet, as would our additional analyses adjusting for body weight. See Point # 63 for more on this methodological issue.

60. Page 8, line 24. Randomization was done in an at Boston Children's Hospital

Thank you, we have corrected this typographical error.

REVIEWER: 4

Major comments
61. The authors have not complied with the BMJ requirement:
"The BMJ expects authors of clinical trials to report their findings in accordance with the outcomes listed in the trial registry. Outcomes that were not pre-specified in the registration should be identified as such in the text of the paper and in any tables. All registered outcomes should be described in the BMJ paper. If results for any outcomes will be or have been reported in another publication this should be made clear to readers. The timing and reasons for any changes in registered outcomes should also be disclosed."
https://urldefense.proofpoint.com/v2/url?u=https-3A__clinicaltrials.gov_ct2_show_NCT02068885&d=DwIFaQ&c=qS4goWBT7poplM69zy_3xhKwEW14JZMSdioCoppxeFU&r=HzbHdpS-3grwpLx9r6E-9VusIayHmpyiieQcL7MXKaNp4MapU5y_XVbBHBTjdVvH&m=h60T0aiAqeBwsLEQ-27_G74mLdu_BIYYSCkyH82XO9A&s=prKhpQ6qboCjcNVoDInSEXd0N3ypO4_ckZBYdFq3TLI&e= *(registration document)*
In the registration document there are multiple relevant secondary end-points that are not reported in the current paper, which indeed is required for the full analyses and interpretation of the findings. All these end-points can easily be reported in supplementary online material and the relevant results reported in the results section. If the discussion section is re-organized there will be plenty of space for a full discussion of the results.

We thank the reviewer for this guidance and the expert critique of TEE methods.

Based on direction from the Editor, we now list all pre-specified outcomes (eTable 1) but focus here on those related to our primary outcome TEE (including components thereof and metabolic hormones related to diet and body weight for mechanistic insights). We have not yet analyzed all other outcomes (e.g., cardiovascular disease risk factors), and now indicate that these will be the subject of future manuscripts.

62. The primary end-point TEE (Total Energy Expenditure) data is essentially not provided in the manuscript in a way that allows other scientist to re-calculate and understand the derived figures. This is particularly problematic because it is the primary end-point, so all the raw data and derived data needs to be given in a table. Currently, only mean baseline data for the three groups are given in Table 2 (TEE, mean (SD), kcal/kg/d), and then values adjusted for weight loss are given as changes (Table 3). Please provide unadjusted and adjusted values for all groups.

As requested by the editors (Point #9, above), we now use analyses without adjustment for individual-level characteristics as our main model, an approach which yields similar results to those with full adjustment.

As considered below (Point #63), we now provide unadjusted individual-level data in eFigure 1.

As also considered below (Point #63), we believe these data will be easily reproducible with the publicly available database and general statistical skills.

63. The primary end-point TEE (Total Energy Expenditure) is normalized for body weight simply by division of TEE by body weight. This is a serious flaw and can lead to artifacts, which have been shown very elegantly by Eric Ravussin and Clifton Bogardus in AJCN 2009 in their methods paper:
This analyses need to be done correctly by adjustments by linear regression ad modem Ravussin. The changes from baseline need to be analyzed with a transparent method that can be reproduced by other scientists. Please provide individual data before and after in a spaghetti-gram.

We thank the Reviewer for identifying a point that requires further explication. We were unable to find a review by Ravussin and Bogardus in AJCN 2009, but perhaps he had the 1989 review in mind entitled "Relationship of genetics, age, and physical fitness to daily energy expenditure and fuel utilization."[27] In that review, the authors advise against normalization of data due to inter-individual differences in metabolically active body mass and related statistical modeling issues. However, our comparisons are within-individual; that is, change from pre-randomization through 20 weeks. Moreover, the change variable was obtained during weight-loss maintenance. We would not expect any meaningful change in the relationship between fat-free mass and fat mass during this period, nor change in body shape that would confound outcomes. For these reasons, any concerns with normalization should not apply to our study. Indeed, estimates of TEE using doubly-labeled water methodology remained "highly reproducible" in longitudinal studies over > 2.4 years.[26]

We pre-specified normalization (dividing by total weight) to take into account the small variation in weight that will inevitably occur during weight-loss maintenance among free living subjects, because TEE is strongly influenced by total weight – thereby improving the precision of our estimates. In any event, to anticipate this issue, we presented an additional model in our original submission without adjustment which yielded a similar estimate to our primary model. This model without body weight remains in our resubmission, and we now include additional discussion of this methodological issue in the revision (page 10 bottom to 11 top).

We certainly agree with the aim of achieving maximum transparency and ease of reproducibility. We constructed adjusted mean changes from the fitted parameters of a repeated-measures regression model, in which each participant's data were represented by a vector of correlated TEE values. This is a standard, widely favored method among biostatisticians and is described thoroughly in Methods and in our published design paper.[2] The findings will be reproducible by any capable analyst, following our specified methods, with the full data set that we will make publicly available on Open Science Framework.

The reviewer asks for a "spaghetti-gram" and we now provide this individual-level, raw change data in the Supplement (eFigure 1).

64. Insulin secretion based on insulin-30 is end-point number 52 in the protocol. It would be appropriate to conduct some sensitivity analyses by using other relevant biomarkers: fasting glucose, fasting insulin, AUC glucose based on OGGT, and the two secondary protocol end-points 15 and 16 hepatic and systemic insulin sensitivity assessed by frequently-sampled oral glucose tolerance test.

We plan to evaluate these secondary outcomes more systematically as part of our next study on CVD and diabetes-related outcomes, as indicated in eTable 1. We are not clear as to how these would be used for sensitivity analysis; however, we have done new analyses for effect modification, as per Point # 70, below.

65. According to the registration document the trial consists of 3 phases. Food is provided throughout the study to all 3 dietary arms, with the following phases: 1) Weight loss; 2) Weight maintenance; 3) Ad libitum. Please also report the "ad libitum" part of the trial in this paper.

The *ad libitum* phase was secondary and not directly related to the focus of this manuscript on energy expenditure. We now list this outcome in eTable 1 but will need to do substantial additional work to put these data into useable form and conduct informative analyses.

66. Please present the adverse event by diet group in a table (could be supplementary material).

Done (see eTable 5).

67. Please report ketone bodies as a biomarker of compliance.

Please see Point #32, above.

68. Figures 3 and Figure 5 are missing from the manuscript.

We apologize for the formatting problem and any ensuing confusion.

69. The authors report that the mean difference in TEE between low- and high-carbohydrate diets among individuals in the highest tertile of insulin secretion (464 kcal/day) was triple the difference for those with lower insulin secretion. This is very interesting and an important finding. Please report the weight changes in these subgroups. If the difference in TEE is not translated into a weight loss the finding is less relevant. The data is available in the study, so please present them to the reader.

One methodological point to emphasize: the study design intended to produce weight-loss maintenance in all participants by periodic adjustments in energy intake. We hope that the revision will make this key issue clear (e.g., page 8, para 2).

Consistent with the study design, we have confirmed that change in body weight did not differ significantly between diet arm during the weight maintenance period, with p=0.43 (allowing for a test of TEE unconfounded by differences in body weight). Indeed, weight from pre-randomization through 20 weeks tracked very strongly, based on within-participant correlations of ≥0.99. (page 15, para 2)

The 3 tertiles of insulin secretion differed in pre-randomization weight, but this difference did not change during the weight-loss maintenance period on the Test diets, as now noted in the legend of Figure 4.

Along the lines anticipated by the Reviewer, we did see a pattern in estimated energy intake consistent with the TEE effect, especially in the highest tertial of insulin secretion. We address this issue in Point #52, above.

70. In the recent paper by Hjorth et al (Hjorth MF, Zohar Y, Hill JO, Astrup A. Personalized Dietary Management of Overweight and Obesity Based on Measures of Insulin and Glucose. Annu Rev Nutr. 2018 Jun 1. doi:) it is suggested that normoglycemic obese individuals and pre-diabetic obese respond very differently to high versus low GI diets. Please report the distribution of pre-diabetic status for the 3 groups, and if there is an effect-modification on the TEE outcome by glycemic status.

The proportion of participants with baseline elevated fasting blood glucose (blood glucose ≥100 mg/dL) is now presented in Table 2 (with no significant difference between diet groups).

In response to this point, we looked for effect modification by baseline fasting glucose and fasting insulin. The results have a similar, though less strong, pattern compared to insulin secretion. We present these results in the Supplement (eFigures 2 and 3) and briefly refer to them in the Results. Additional research will be needed to determine whether these effect modifiers reflect similar or differing underlying mechanisms, and whether a composite index might prove even more predictive of individual response.

REVIEWER: 5

71. This is a unique study with an exceptionally strong design evaluating the effects of a low carbohydrate diet on total energy expenditure during weight maintenance following a weight loss program. However, the paper is very difficult to read. The complex study design contributes to the poor readability, but it also is poorly written. The writing style suggests that different authors wrote various sections. One author needs to edit the entire manuscript for readability and clarity.

We thank for the reviewer for these helpful comments. We have extensively revised the manuscript, with special emphasis on Methods to aid clarity.

72. The abstract needs considerable editing. The rationale for the ITT and Per Protocol analysis needs to be included. How did the sample size vary for these two approaches? What was the sample size for the insulin secretion comparison? What was the p-value for the ghrelin outcome.

We had included sample sizes for the ITT and Per Protocol analyses. We provide the rationale for the Per Protocol as including "participants who achieved weight-loss maintenance." We added "potentially providing a more precise effect estimate." We added the p-value for the diet effect on ghrelin. We have aimed to clarify several other aspects within the space constraint.

73. The final conclusion needs to be stated more clearly emphasizing that this was a post-weight loss study and that total energy expenditure was measured. Also, a rationale or mechanism for how low dietary carbohydrate increases TEE without altering body weight needs to be provided.

As above, we are under space constraint for the abstract. We now mention the CIM, to provide context (a model described in detail in the Introduction). We now also emphasize the post-weight loss aspect as follows: "Consistent with the Carbohydrate-Insulin Model, lowering dietary carbohydrate increased TEE during weight loss maintenance. This metabolic effect may improve the success of obesity treatment, especially among individuals with high insulin secretion."

Methods:
74. Page 6, line 36. How many achieved targeted weight loss.

We present the flow of participants through the trial in Results (first two paragraphs of Results, Figure 2). Of the 234 participants who were enrolled in the Run-In Phase, 164 achieved weight loss of 12±2% and were randomly assigned to different macronutrient diets for the Test Phase.

75. Page 6-7. Unclear if the description of participants is for the primary study or for those who participated in the maintenance phase.

We clarified that screening was done prior to baseline (BSL pre-weight loss) assessments (page 9, para 1). Participants who successfully completed the Run-In Phase were eligible for randomization (page 8, para 2). Table 2 indicates baseline characteristics are pre-weight loss.

76. Page 7-8. The randomization description is impossible to understand. Needs to be totally rewritten.

We apologize for some redundancy and lack of clarity in the section on randomization. We revised this section to avoid confusion (see Supplemental Methods).

77. Page 9-10. Clarify when each set of measurements was made. Are there 4 or 3 timepoints? Baseline, PWL, MID and END.

We revised Figure 1 and the study design paragraph (page 8, para 2), and added eTable 1, to clarify the time points for measurements.

78. Page 12, Line 5. What 4 comparisons were made. Not clear from the description.

We apologize for this error and have revised this passage as follows (page 12, para 2): "When this hypothesis was rejected, the principle of closed testing permitted us to make the three pairwise diet comparisons (HI vs. LO, HI vs. MOD, MOD vs. LO) with critical p=0.05 while preserving a maximum familywise 5% Type I error rate."

79, Page 12, line 31. First sentence of this paragraph is not clear.

We revised Methods to more clearly explain the reason for sensitivity analyses, examining how plausible errors in FQ could influence results (page 13, para 3).

80. Results:
Page 15, line 20. Figure 3 is missing from the paper; there were two copies of figure 4.

We apologize for the problem with formatting of several figures, and any resulting confusion.

81. Discussion:
In general, the authors do not adequately explain how a low carbohydrate diet increases TEE without any change in energy intake. This general finding is inadequately explained.

As we now clarify, energy intake was modified to maintain body weight within ±2 kg of the post weight-loss anchor during the Test Phase (page 8, para 2). We now present evidence suggesting the expected greater energy requirements in the low-carbohydrate group, consistent with the primary findings (see Point #52). We mention mechanisms in the Introduction for how a low-glycaemic load diet could alter energy expenditure consistent with the CIM, and now include a reference on the importance of energy expenditure, regardless of mechanism, on body weight.[28]

82. The discussion of the impact of a low carbohydrate diet on TEE on page 17, lines 24-54 is confusing and no potential mechanism is provided.

We hope that the clearer presentation of Methods and Results will help understanding of this paragraph on effect modification.

83, Page 16, lines 45-54. The primary outcome in this study was TEE. The link between the higher TEE on a low carbohydrate diet and the activation of brain areas is not clear.

We now include the concept of food cravings in the Introduction, with a new reference on related mechanisms.[29] A link to the findings on brain activation on the high-carbohydrate diet, including additional mechanistic discussion, is available for the interested reader.

84. The strengths and limitations of the study are adequately described. However, the discussion of the physiology and potential mechanisms is totally inadequate and confusing.

We hope that the clarification of methods, additional relevant references and discussion of mechanisms will resolve the difficulty.

Information for submitting a revision

85. Deadline: Your revised manuscript should be returned within one month.

Done

86.How to submit your revised article: Log into https://urldefense.proofpoint.com/v2/url?u=http-3A__mc.manuscriptcentral.com_bmj&d=DwIFaQ&c=qS4goWBT7poplM69zy_3xhKwEW14JZMSdioCoppxeFU&r=HzbHdpS-3grwpLx9r6E-9VusIayHmpyiieQcL7MXKaNp4MapU5y_XVbBHBTjdVvH&m=h60T0aiAqeBwsLEQ-27_G74mLdu_BIYYSCkyH82XO9A&s=loixDjoMfpogGWIDGlNCjNu7I0lkgVy2evexpgM5v7Y&e= and enter your Author Center, where you will find your manuscript title listed under "Manuscripts with Decisions." Under "Actions," click on "Create a Revision." Your manuscript number has been appended to denote a revision.

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Not applicable

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27_G74mLdu_BIYYSCkyH82XO9A&s=M5FUMoEF6MhUZ5VNbhdtj5hPGUUmRzhHl58n2IsJfsI&e=)

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96. Funding statement and statement of the independence of researchers from funders
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97. Patient involvement statement (see https://urldefense.proofpoint.com/v2/url?u=http-3A__www.bmj.com_about-2Dbmj_resources-2Dauthors_article-2Dtypes_research&d=DwIFaQ&c=qS4goWBT7poplM69zy_3xhKwEW14JZMSdioCoppxeFU&r=HzbHdpS-3grwpLx9r6E-9VusIayHmpyiieQcL7MXKaNp4MapU5y_XVbBHBTjdVvH&m=h60T0aiAqeBwsLEQ-27_G74mLdu_BIYYSCkyH82XO9A&s=rkvJ6Qicz9u24cjc4fMA6xGGPCR4EcnHwJJBA-Cr6Cc&e=).

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100. Introduction: This should cover no more than three paragraphs, focusing on the research question and your reasons for asking it now.

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101. Methods: For an intervention study the manuscript should include enough information about the intervention(s) and comparator(s) (even if this was usual care) for reviewers and readers to understand fully what happened in the study. To enable readers to replicate your work or implement the interventions in their own practice please also provide (uploaded as one or more supplemental files, including video and audio files where appropriate) any relevant detailed descriptions and materials. Alternatively, please provide in the manuscript urls to openly accessible websites where these materials can be found.

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102. Results: Please report statistical aspects of the study in line with the Statistical Analyses and Methods in the Published Literature (SAMPL) guidelines https://urldefense.proofpoint.com/v2/url?u=http-3A__www.equator-2Dnetwork.org_reporting-2Dguidelines_sampl_&d=DwIFaQ&c=qS4goWBT7poplM69zy_3xhKwEW14JZMSdioCoppxeFU&r=HzbHdpS-3grwpLx9r6E-9VusIayHmpyiieQcL7MXKaNp4MapU5y_XVbBHBTjdVvH&m=h60T0aiAqeBwsLEQ-27_G74mLdu_BIYYSCkyH82XO9A&s=xx4W_M5eedNrLzggGVAZRfYX06qMFkzsqoMZ0ODLUeQ&e=. Please include in the results section of your structured abstract (and, of course, in the article's results section) the following terms, as appropriate:

i. For a clinical trial: Absolute event rates among experimental and control groups; RRR (relative risk reduction); NNT or NNH (number needed to treat or harm) and its 95% confidence interval (or, if the trial is of a public health intervention, number helped per 1000 or 100,000.)
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iv. For a study of a diagnostic test: Sensitivity and specificity; PPV and NPV (positive and negative predictive values.)
v. For a systematic review and/or meta-analysis: Point estimates and confidence intervals for the main results; one or more references for the statistical package(s) used to analyse the data, eg RevMan for a systematic review. There is no need to provide a formal reference for a very widely used package that will be very familiar to general readers eg STATA, but please say in the text which version you used. For articles that include explicit statements of the quality of evidence and strength of recommendations, we prefer reporting using the GRADE system.

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As mentioned at the beginning of this letter, we appreciate having license to structure the Discussion in a way that we feel will be most readable and logical. We've endeavored to include all standard components per your guidelines, and would be happy to reformat/abridge this section if so requested for print publication.

104. Footnotes and statements

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2Dmodel&d=DwIFaQ&c=qS4goWBT7poplM69zy_3xhKwEW14JZMSdioCoppxeFU&r=HzbHdpS-3grwpLx9r6E-9VusIayHmpyiieQcL7MXKaNp4MapU5y_XVbBHBTjdVvH&m=h60T0aiAqeBwsLEQ-27_G74mLdu_BIYYSCkyH82XO9A&s=WSfhxHUwjIZDcHYqQ7vN-ZWLOUNythTRLvl0iOe2kaY&e=). The print and iPad BMJ will carry an abridged version of your article. This abridged version of the article is essentially an evidence abstract called BMJ pico, which we would like you to write using the template downloadable at https://urldefense.proofpoint.com/v2/url?u=http-3A__resources.bmj.com_bmj_authors_bmj-2Dpico&d=DwIFaQ&c=qS4goWBT7poplM69zy_3xhKwEW14JZMSdioCoppxeFU&r=HzbHdpS-3grwpLx9r6E-9VusIayHmpyiieQcL7MXKaNp4MapU5y_XVbBHBTjdVvH&m=h60T0aiAqeBwsLEQ-27_G74mLdu_BIYYSCkyH82XO9A&s=MSkXYLEiK7Wg6EgbC-IANk_WVLUn3RxU2X9SA49odwE&e=. Publication of research on bmj.com is definitive and is not simply interim "epublication ahead of print", so if you do not wish to abridge your article using BMJ pico, you will be able to opt for online only publication. Please let us know if you would prefer this option. If your article is accepted we will invite you to submit a video abstract, lasting no longer than 4 minutes, and based on the information in your paper's BMJ pico evidence abstract. The content and focus of the video must relate directly to the study that has been accepted for publication by The BMJ, and should not stray beyond the data.

We would be willing to work with you reformatting materials and producing a video, if deemed appropriate.

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