Author's response to reviews

Title: Comparison of a Low Carbohydrate and Low Fat Diet for Weight Maintenance in Overweight or Obese Adults Enrolled in a Clinical Weight Management Program

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Author's response to reviews: see over

Reviewer 1 report:

General:
The purpose of the current study was to examine two diets, a low-carbohydrate and a low-fat diet, on weight loss maintenance. As weight loss maintenance continues to be a challenge, studies investigating ways to improve methods for weight loss maintenance are very important. The results of the study found that weight loss maintenance was equivalent between the two diets over a 6-month follow-up.

This manuscript was very clearly written, and comments about this manuscript predominantly are regarding methodology.

1)In the Weight Management Clinic section, the authors indicated that if attendance fell below 75% - participants were terminated * does that mean participants could never come to groups again * or that they were considered terminated for analyses purposes? If they were no longer allowed to come to sessions * had they been informed of this (and was this a fee-for-service clinic)?

Author Response: Thank you for the comment. Participants were informed of the 75% attendance requirement at recruitment. A reduced fee (ie. 2/3 reduction) was given to all participants for their participation. Participants falling below 75% attendance no longer came to meetings…from the beginning, they were informed of our need for the data and without compliance their data was not of value. We attempted to better address your question under the section "weight management clinics" in the methods.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

1) For the diets * what occurred in the gradual refeeding stage * was refeeding based upon the dietary prescription they would be aiming for (so for example, did they low-carbohydrate group aim to start consuming foods lower in carbohydrate as soon as they started refeeding)?

Author Response: Yes, re-feeding was based on their assigned diet. We have attempted to clarify the re-feeding diet under the section, "Weight Maintenance Diet" in the methods.

2)Also once participants were in month 4 and following their diet * were they recording caloric intake and grams of fat or carbohydrate and aiming for their specific goals based upon the HB equation? No mention was made of recording caloric intake.

Author Response: Very good comment. Participants received a maintenance kcal level and the number of grams of either fat or carbohydrate based on a percentage of their total kcals; however, they only recorded their fat/CHO grams but not their kcals. We have attempted to clarify this point in the methods under the section "weight maintenance diet".

3) Most importantly, the authors describe this study as an efficacy study * thereby stressing internal validity * and providing this as a reason for why an intent-to-treat analysis was not conducted. However, it seems for an efficacy study * a better check of actually consuming the diet that was prescribed is needed other than self-report. Thus, perhaps food should have been provided to participants that met the prescription or structured menus that informed participants on exactly what to eat to meet the prescription should have been provided. Other methods to document internal validity might have been to measure ketones *thus if the dietary prescription of the low-carbohydrate diet expected to produce ketones * then they should have been measured. Since the attrition rate was so high (almost 50%) and there really was no way to determine how well participants followed the diet * this reviewer would propose that this is really not an efficacy study * and therefore intent-to-treat analyses should be conducted.

Author Response:

We appreciate your suggestions regarding methodology for this study. We recognize the weaknesses with almost every form of dietary assessment strategy to ensure compliance and therefore, efficacy. It is true that there are weaknesses with self-reported diets and we list this as a limitation of the study in the discussion section. Other recent studies assessing a low carbohydrate or low fat diet have utilized food records and food recalls as a measure of compliance to the diet and it is generally accepted as a valid assessment tool. For example, Gardner et al used 3-day food records in a recent study of 4 popular diets, including the Atkins and Ornish diets (JAMA 2007; 297: 969-977); Brehm et al used 3-day food records (J clin Endocrinol Metab 88: 1617-1623, 2003); and Yancy et al used 4-day food records (Nutr Metab (Lond). 2005; 2: 34). Further, as this study was conducted in an ongoing weight management clinic, the 9-month duration makes diet verification difficult logistically and financially.

Our original intent, from the inception of this study, was to report only those participants who met compliance regulations and completed the study. Our reference to this study as an efficacy study was used to clarify that only those completing the study were included in the analysis. In light of the argument that our assessment methodology was not sensitive enough for this study to be called an efficacy study, we have removed the term "efficacy" from the manuscript and instead use the term "per protocol" to refer to those who meet compliance regulations.

Your suggestion that, "*perhaps food should have been provided …or structured menus should have been provided*" is warranted. For our study, we did not give them exactly what to eat or provide them the acutal food they should eat. Rather, participants were given a carbohydrate or fat gram daily budget and they were allowed to self-select their foods to stay within their fat or carbohydrate budget. Instead of specific menus, there was discussion at virtually every group meeting of appropriate low carb or low fat foods, correct portions, recipes, meals, and discussion of their difficulties adhering to their specific diet. In addition, by our participants keeping track of their carbohydrate or fat gram intake every single day during the weight maintenance period, reporting their grams every week, and by periodic administration of detailed food records, we felt we had a good handle of their compliance to their diet.

We have attempted to address your concern where we can and provide more detail about the study diets in the methods of the paper. We have also included under the "attrition and adherence" section the results of the self-reported average daily carbohydrate and fat gram consumption in order to provide additional evidence to the 3-day food records of compliance to the diet.

Regarding your mention of attrition rate, it is unfortunate that attrition was so high in our study; however, these rates are comparable to other behavioral weight loss clinic studies and other studies comparing a low carbohydrate and low fat diet. For example, a recent meta-analysis of 5 low carbohydrate vs. low fat trials reported by Nordmann et al, showed attrition rates to be 30% and 43% for a low carbohydrate and low fat diet, respectively, after 6 months and 38% and 46%, respectively, after 12 months (Normdann AJ, Arch intern Med 2006; 166:285-293). **We have added to our discussion of this point under "weight maintenance" in the discussion section.**

4) Additionally, it is not clear why the analyses were not conducted with a nested design * as clinics were how dietary prescriptions were chosen (or randomized? * it is not clear how clinic assignment was made and this information should be provided) * to more correctly account for that the fact that participants were not randomized to a diet.

In the discussion, we mentioned that we chose to not randomize participants due to our concern at that time (Atkins diet was at its height) that there would be contamination among participants if they were randomized within group; therefore we randomly selected clinic site as either low carbohydrate or low fat and exclusively recruited participants for the specific site…hence the quasi experimental design.

Please note that there was no difference between cohorts at baseline for body weight. Further, within each group, there was no difference between cohorts.

5) Percent weight loss should be controlled for in all subsequent analyses of weight loss maintenance.

Author Response: We controlled for weight in our analyses and mention this in the results.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Discretionary Revisions (which the author can choose to ignore)

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions Level of interest: An article whose findings are important to those with closely related research interests Quality of written English: Acceptable Statistical review: Yes, and I have assessed the statistics in my report.

Reviewer 2 report:

Summary. Subjects in this study all lost a significant amount of weight during a 3 mo standardized very low calorie liquid meal program. The primary aim of this study was to compare body weight responses after this weight loss phase in subjects counseled to consume either a low fat or low carbohydrate diet. Despite regular meetings and interaction with subjects, a large number of subjects withdrew from the study for different reasons. In subjects who completed the study the major finding was that on average, both groups were equally successful at maintaining body weight over the 6 months weight maintenance period.

Comments. The logic for the experiment is not entirely clear. The preponderance of evidence shows that in ab libitum experiments where the macronutrient composition is tightly controlled very low carbohydrate diets consistently do better than low fat diets on weight loss. The question posed here is whether low carbohydrate and low fat diets have a different response during a period following rapid weight loss. In the introduction it is stated **significant questions remain regarding the long-term impact of this [low carb] diet for the prevention of weight re-gain (i.e., weight maintenance).*, yet the authors do not explain what these significant questions are. The authors state that **a low carbohydrate diet may produce greater weight loss than a low fat diet in the short term but there may be no difference beyond 6 months.*, citing studies by Brehm et al. 2003; Foster et al. 2003; Samaha et al. 2003; and Yancy et al. 2004. Each of these studies actually shows greater weight loss at 6 months with a low carbohydrate diet. The Foster study showed no statistical difference in weight loss at one year, but the protocol allowed increases in carbohydrate consumption as the trial progressed indicating that it is likely that reintroduction of carbohydrate that predisposes to long-term regain in weight. Most notable is that a significant improvement in lipid profile persisted. It is surprising given the strong evidence supporting low carbohydrate diets and the general failure of low fat diets that the paper is written such that low fat diets are given a free pass whereas the burden of proof is on low carbohydrate diets.

Author Response: We have attempted to make it more clear in the introduction the purpose of this study - that this is a weight maintenance study and that there is currently limited data comparing a low carb and low fat to prevent weight regain.

The reviewer mentions that the logic for this study is not entirely clear. NHLBI guidelines suggest, at a minimum, to prevent further weight regain. As current data indicate that those who lose weight, regardless of method, are likely to regain a large portion…any possible strategy to prevent this, we

believe, is warranted. As recent data have shown benefits of a low carbohydrate diet compared to a low fat diet; we find it very reasonable to ask the question, "can weight re-gain be prevented or attenuated after rapid weight loss by manipulating fat and carbohydrate content and if so…which is superior?" Previous studies have primarily been for weight loss and have not followed a period of weight loss; therefore, we believe the design of this study is simple and novel.

We have changed our wording in the "Introduction" to address the reviewer's comment of "not explaining what these significant questions are."

It appears that the reviewer misunderstood or misread the sentence we wrote that "…there may be no difference in the diets beyond 6 months". Our intent for that sentence was to convey precisely the same thing that the reviewer argued for in comments to us. It is true that studies comparing low carb and low fat show superior results for weight loss over 6 months. However, just like the comment about the Foster study…these studies do not show a difference for body weight at 12-months. This is what we wrote in our introduction. We have adjusted our wording to make it more clear.

The reviewer comments that the paper is written in such a way that "…low fat diets are given a free pass whereas the burden of proof is on low carbohydrate diets." We do not fully understand this comment as we tested both diets against each other and reported results for both diets. We did not intend to present any bias; however, we have attempted to improve the paper as reduce any possible bias.

Overall, a near 50% attrition rate is suggestive of methodological deficiencies. No data is shown on compliance to guidelines of the subjects who finished the study. The authors refer to this as an efficacy study meaning data for all participants who completed all clinic and laboratory measures were analyzed. The issue of efficacy can only be made if there is a measure of compliance. In fact, on page 15) the authors say compliance was different between weight losers and weight gainers on low carbohydrate. In the end, the authors have not made a compelling reason for this being a biologic study that truly addresses the effects of low carbohydrate diets.

Author Response: Regarding attrition rate, it is unfortunate that attrition was so high in our study but these rates are comparable to other behavioral weight loss clinic studies and other studies comparing a low carbohydrate and low fat diet. For example, a recent meta-analysis of 5 low carbohydrate vs. low fat trials reported by Nordmann et al, showed attrition rates to be 30% and 43% for a low carbohydrate and low fat diet, respectively, after 6 months and 38% and 46%, respectively, after 12 months (Normdann AJ, Arch intern Med 2006; 166:285-293).

Regarding compliance, we have reported the results of 3-day food records. Keep in mind, other recent studies assessing a low carbohydrate or low fat diet have utilized food records and food recalls as a measure of compliance to the diet and it is generally accepted as a valid assessment tool. For example, Gardner et al used 3-day food records in a recent study of 4 popular diets, including the Atkins and Ornish diets (JAMA 2007; 297: 969-977); Brehm et al used 3-day food records (J clin Endocrinol Metab 88: 1617-1623, 2003); and Yancy et al used 4-day food records (Nutr Metab (Lond). 2005; 2: 34).

In addition, we also collected self-reported daily consumption of carbohydrate and fat grams during the entire weight maintenance period. These data were NOT reported in the previous version of this manuscript. Thus, to provide increased dietary evidence of compliance to the protocol we have revised the methodology and included this in the methods under the section "weight maintenance diet". Also, we have included the average daily self-reported grams of carbohydrate or fat grams under the "attrition and adherence" of the results section.

Our original intent, from the inception of this study, was to report only those participants who met compliance regulations and completed the study. Our reference to this study as an efficacy study was used to clarify that only those completing the study were included in the analysis. In light of the argument that our assessment methodology was not sensitive enough for this study to be called an efficacy study, we have removed the term "efficacy" from the manuscript and instead use the term "per protocol" to refer to those who meet compliance regulations. Ultimately, we can analyze for intent to treat if required, but it was our intent, from the beginning to analyze those that completed participation in the study.

We appreciate the points the reviewer brings up about weight losers and gainers in the discussion section. Please note that the difference in carbohydrate and fat grams between the weight gainers and weight losers of both groups was not statistically significant. Our wording that, "These results suggest the possibility of a difference in compliance…", may have been over-stated, as the differences were not significant; therefore, we have removed that comment from the manuscript and developed that section of the discussion to a greater extent.

There are, in fact, many reasons why macronutrient composition would produce different effects on body weight. This has been reviewed by Feinman and Fine, and compelling evidence for inefficiency with biological mechanisms recently shown in mice (Kennedy et al. AJP Feb 13, 07). These are not discussed by the authors nor is the experiment set up to address any of these mechanisms to enlighten the biology of low carbohydrate diets. Low carbohydrate and low fat diets elicit very different metabolic responses independent of weight loss, but again these measures were not done limiting the impact of the study. Given the expertise and publication record of the authors, it is surprising they do not address these critical issues. Without reporting metabolic health markers for the different diets, a finding that a prescribed calorie weight maintenance diet results in a stable body weight has little scientific or practical novelty.

Author Response: We appreciate your comments. As this study was conducted in the context of a behavioral weight management clinic our aim was not to assess the biological mechanisms; rather, to provide data showing the utility of adding either a low carbohydrate or low fat diet as part of a comprehensive weight management program. Therefore, we cannot fully address your concerns about metabolic markers. However, weight gain after weight loss is a huge issue. Many biologic outcomes are already known to vary with weight. Thus, for clinical purposes, measurement of these outcomes may not be necessary.

Given the state of the science it is also odd that no measure of body composition was performed. An excellent meta-analysis has shown that diets

lower in carbohydrate and higher in protein are associated with greater reductions in fat mass and increases in lean body mass independent of energy intake (Krieger et al. AJCN. 2006).

Author Response: We do not argue the value of a body composition assessment. However, as our clinics were conducted at various sites; there were logistical problems with assessing body composition using a gold standard instrument, such as the DEXA. We felt it would be better to assess body weight, BMI, and waist circumference as measures of health risk as opposed to a problematic portable body composition instruments such as bioelectrical impedance or skinfolds. Further, as mentioned earlier, this is a study using a clinical weight loss program and these things are rarely used.

Although the authors state there are no differences between diets in body weight, it is doubtful all subjects maintained weight during the 6 months of study. The real value in this study may be the individual responses. A plot showing each subject response would provide a clear picture of the variability and range of responses on each diet to better responders and nonresponders, and more important, open the way to identify reasons for such variability.

Author Response: We have incorporated this suggestion.

Figure 1 should be plotted after zeroing each subject. The mean value for low carbohydrate at the end of the study (86.5 kg) does not match that presented in the results (86.0 kg)?

We'd be happy to apply your suggestion…please clarify what you mean by "…zeroing each subject". We cannot find in the paper where we used 86.5 kg for the low carbohydrate group. Data from Table 4 and data in the results section are consistent. However, in table 4 we rounded to 1 decimal point to be consistent with the written results section.

Body weight is the primary dependent variable yet this sensitive measurement was carried out with subjects in clothes. This is not standard procedure in controlled experiments.

A valid point. As this was a multiple site clinic…changing rooms were not always available.

The discussion could be enhanced rather than providing a simple recount of results. A discussion on what constitutes a low carbohydrate diet using an opinion from a hostile critic is not a good place to find a definition (Page 14). On Page 15 (first paragraph), an attempt is made to discuss explanations for variability in weight loss. This could be an important point of the paper and should be probed further. Linking compliance and weight response begins to sort out what factors are important in determining a positive response. Additional analyses on this could be presented in the results and discussed.

We have enhanced our discussion for this point.

Minor

Composition of the 3 month weight loss formula should be included.

We added this in the methods.

Page 7, line 233 - blood pressure

The authors say there were no differences between groups, but the data should be shown including breakdown of percent in each group on potentially confounding factors as medications, gender, etc.

We appreciate the suggestion. We have added blood pressure data over the duration of the study in the results section consistent with the presentation of other outcome data in the manuscript.

Page 11 lines 323 and 326. Why are different units used for activity

(min/week and steps)?

They are 2 separate physical activity outcomes. Minutes per week was a self-reported measure and steps was via pedometer counts.