

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Effect of a Six Months Vegan Low-Carbohydrate (“Eco-Atkins”) Diet on Cardiovascular Risk Factors and Body Weight in Hyperlipidemic Adults: A Randomized Controlled Trial
AUTHORS	Jenkins, David; Wong, Julia; Kendall, Cyril; Esfahani, Amin; Ng, Vivian; Leong, Tracy; Faulkner, Dorothea; Vidgen, Ed; Paul, Gregory; Mukherjea, Ratna; Krul, Elaine; Singer, William

VERSION 1 - REVIEW

REVIEWER	William S. Yancy, Jr. MD MHS Associate Professor of Medicine VA Medical Center and Duke University USA
REVIEW RETURNED	20-Aug-2013

THE STUDY	Article refers reader to previous article for many Methods details, including entry criteria. Description of how diet counseling was delivered is needed. Several references are misinterpreted.
RESULTS & CONCLUSIONS	High attrition rate limits conclusions to those who can adhere to a very unique diet. Wording of the interpretation of prior studies needs to be changed to be more representative.
GENERAL COMMENTS	The authors report 6 months further follow-up of a trial randomizing 50 overweight adults with elevated LDL-C to a vegan, low-carbohydrate diet (Eco Atkins) versus a high carbohydrate diet (control). The Eco Atkins diet is a hybrid of 2 approaches attempting to combine the potential beneficial impacts of lowering carbohydrates and lowering saturated fats. The first month, participants were provided all foods whereas the next 6 months, participants bought and prepared their own meals; this report focuses on results from the 39 participants who continued into this latter part of the study. Participants following the vegan low-carbohydrate had mildly greater weight loss and greater LDL-C and triglyceride lowering than control participants. The study is a nice design, and the manuscript is clearly written. Major issues: 1. The discussion section misinterprets the existing literature regarding low-carbohydrate diet effects on LDL-C. The text suggests the Eco Atkins diet overcomes the detrimental effect on LDL-C seen in prior studies of low-carbohydrate diets that allowed intake of animal foods. However, LDL-C did not increase from baseline on the low-carbohydrate diet in most of the studies and when it did, the

	<p>increase was transient. Most of these studies also did not have statistically different changes in LDL-C between the diet arms. A more accurate interpretation would be that the Eco Atkins diet led to LDL-C lowering whereas prior low-carbohydrate diets typically did not lead to LDL-C lowering.</p> <p>2. The study suffered a high dropout rate, compromising interpretation of the results. Appropriate statistical methods were used to deal with missing data but with >50% dropout, concerns remain. High dropout rates in existing studies do not increase confidence in these results.</p> <p>Minor issues:</p> <ol style="list-style-type: none"> 1. It is unclear from the Methods whether the 6 month continuation was part of the original protocol or if participants were re-consented for a follow-up study upon completion of the feeding study. 2. P8, ln 48, it could be made clearer that the 11/39 participants who discontinued lipid lowering medications were the only participants taking such medications. 3. Information is needed about whether diet counseling was provided and if so, how it was delivered (eg, who delivered the counseling, how frequently, what setting, etc.). 4. It is unclear if the control diet was vegan or not. 5. The adherence goals (for the 3 vegetable proteins) could be described in more detail. 6. Ad libitum is misspelled in some places. 7. P16, line 18-it is unclear to which diet some statements in this paragraph refer.
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REVIEWER	Thomas Meinert Larsen, Associate Professor, Department of Nutrition, Exercise and Sports, University of Copenhagen, Denmark
REVIEW RETURNED	29-Aug-2013

THE STUDY	Figure 2 and 3 does not adequately present how the LDL-cholesterol and other outcomes changed from the end of the first very controlled period (at week 4), and until the end of the subsequent 5 month of free living adherence to the 2 diets (week 26). This may give the impression to the readers, that the beneficial effects on LDL-cholesterol and other outcomes that were found in the first 4 weeks were maintained or even increased during the subsequent 5 month intervention, which was not the case, as it is clear that the LDL-cholesterol increased significantly for both groups during the 5 month free living period. I would suggest that figure 2 and 3 should be redrawn, to make it clear that e.g. LDL-cholesterol increased from week 4 to week 26.
RESULTS & CONCLUSIONS	Given the high importance of dietary modification for body weight regulation and cardiovascular risk reduction, this study is of importance for the nutritional research area. The authors have evaluated whether a low-carb, vegetable diet (ECO-Atkins) is superior to a higher-carbohydrate, lacto-ovo vegetarian diet to induce weight loss and improvement in cardiovascular risk factors. This manuscript is a continuation of previously published results from the same study. During the first 4 weeks of the study (already published), all foods were provided to the study participants, whereas in the subsequent 5 month continuation, the participants had to obtain the foods themselves (free living condition). In this manuscript, the authors conclude, that the low-carb, vegetable diet – when evaluated from baseline to the end of the 6 month free living

	<p>period - improved weight loss, and several cardiovascular risk factors, including LDL cholesterol.</p> <p>However, the manuscript suffers from a number of methodological weaknesses, the most important being figure 2 and 3.</p> <p>Figure 2 and 3 does not adequately present how the LDL-cholesterol and other outcomes changed from the end of the first very controlled period (at week 4), and until the end of the subsequent 5 month of free living adherence to the 2 diets (week 26). This may give the impression to the readers, that the beneficial effects on LDL-cholesterol and other outcomes that were found in the first 4 weeks were maintained or even increased during the subsequent 5 month intervention, which was not the case, as it is clear that the LDL-cholesterol increased significantly for both groups during the 5 month free living period. I would suggest that figure 2 and 3 should be redrawn, to make it clear that e.g. LDL-cholesterol increased from week 4 to week 26.</p>
<p>GENERAL COMMENTS</p>	<p>Major comments.</p> <p>1) Figure 2 + 3 need revision Figure 2 and 3 does not adequately present how the LDL-cholesterol and other outcomes changed from the end of the first very controlled period (at week 4), and until the end of the subsequent 5 month of free living adherence to the 2 diets (week 26). This may give the impression to the readers, that the beneficial effects on LDL-cholesterol and other outcomes that were found in the first 4 weeks were maintained or even increased during the subsequent 5 month intervention, which was not the case, as it is clear that the LDL-cholesterol increased significantly for both groups during the 5 month free living period. I would suggest that figure 2 and 3 should be redrawn, to make it clear that e.g. LDL-cholesterol increased from week 4 to week 26.</p> <p>2) Results from Completer analysis comparable with results from ITT-analysis? The manuscript presents the results based on an ITT-analysis. However, as the dropout rate is quite large, it would be appropriate to carry out completer analyses for most or all outcomes (in addition to that presented for the changes in LDL-cholesterol among completers), and if these completer analyses differ significantly from the ITT-analysis, this should be reported in the manuscript. If they do not differ, then this should somehow also be reported.</p> <p>3) Drop out rate The manuscript does present the dropout rate for the 2 study diet groups, but nowhere is it mentioned whether there was a difference in drop rate. This should be added.</p> <p>4) Unclear description of the dietary intervention. The authors describe the study as “hypocaloric”, but also as “ad libitum”. This seems to me as a contradiction. It should be made more clear what and how information about caloric intake was conveyed to the study participants.</p> <p>5) Calculation of 7-day food diaries. In table 2, the nutritional composition in the “ad libitum” period is described. However, nowhere is it described when during the study, these 7-day food diaries were collected. Also, if the intake in the “ad libitum” period is calculated as mean values from several 7-day food</p>

	<p>diaries, this should be made clear.</p> <p>6) Consistent naming of the “Control diet” In the clinicaltrials.gov registration, the “Control diet” is described as the NCEP diet. Why is this term not used in this manuscript?</p> <p>7) Sample size calculation The manuscript does not describe, if any sample size calculation was performed before the study. Please describe if this was done, and if so, how.</p> <p>8) Withdrawal of study participants due to hypercholesterolemia & use of statins The manuscript describes that 3 participants in the low-carb group were withdrawn due to hypercholesterolemia. However, from figure 1, it also appears that 3 participants from the same diet were not considered as completers, as they resumed drug treatment with statins. How and why were participants experiencing hypercholesterolemia considered different from those resuming statin treatment?</p> <p>9) Diet score at baseline In table 2, the adherence to “ECO-Atkins” is presented for the ad libitum period. Why are no data presented for the high carbohydrate group, and for the ECO-Atkins group at week 0? If data are available, they should be included.</p> <p>10) Real life applicability As the authors point out, the long term adherence to the ECO-Atkins diet is sub-optimal, and a total of 3 (or 6?) participants do not achieve the expected lowering of total- and LDL-cholesterol. This raises the question whether this diet can be adapted into (most) peoples diet. The discussion should include some reflections on this very critical aspect.</p> <p>Minor comments</p> <p>a) The manuscript describes that 11/39 discontinued lipid lowering medications before inclusion. It is not clear if those 11 participants were all those that took lipid lowering medication before inclusion. That should be made clear.</p> <p>b) It is not clear what kind and amount of exercise that was prescribed in the free living period. Please describe that.</p> <p>c) In the text, it is described that the participants were prescribed to eat 60% of their energy needs, and that this would then give a stable body weight! Eating only 60% of calorie needs would clearly provide extra weight loss, also beyond the 4 week very controlled period (that achieved 4 kg weight loss). Please revise the statement that this would lead to stable body weight.</p> <p>d) It is not clear how much of the three principal components (viscous fiber, vegetable protein and nuts) that were prescribed. Please add this information.</p> <p>e) It is unclear how satiety was measured. Please make this more clear.</p> <p>f) In the discussion part, some results are mentioned (page 15, line</p>
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	<p>10 on the LDL-cholesterol changes among completers). These results should be moved to the results section.</p> <p>g) The dietary content of the “control diet” should be explained in somewhat more detail, and not only by reference to the previous publication from the study.</p>
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REVIEWER	<p>Andrew Hinde Division of Social Statistics and Demography, University of Southampton, SOUTHAMPTON SO17 1BJ, United Kingdom</p> <p>No competing Interests</p>
REVIEW RETURNED	18-Sep-2013

GENERAL COMMENTS	<p>My main concern about the analysis is the high rate of drop out from the study. The authors recognise this and try to cope with it using multiple imputation. They also seek refuge in the fact that drop out is common in studies of this type. However I think they could do more to examine the characteristics of the survey members who did drop out. They have evidence from the one-month metabolic study reported in Jenkins, Wong and Kendall (2009) which they could use to see whether those who dropped out from the ad libitum six-month study had experiences during the metabolic study which were atypical. One might even analyse whether the probability of drop-out from the ad libitum study could be predicted from the outcome of the metabolic study - a simple logistic regression analysis of drop out or not with a few covariates could be estimated. This analysis might not be possible with such small numbers. But even if not, some discussion of the characteristics of those who dropped out is important.</p> <p>The fact that on p. 10, l. 7, I think 'dairy' should be 'diary'. No saturated fats in this paper!</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer: William S. Yancy, Jr. MD MHS
Associate Professor of Medicine
VA Medical Center and Duke University
USA

Major issues:

1. The discussion section misinterprets the existing literature regarding low-carbohydrate diet effects on LDL-C. The text suggests the Eco Atkins diet overcomes the detrimental effect on LDL-C seen in prior studies of low-carbohydrate diets that allowed intake of animal foods. However, LDL-C did not increase from baseline on the low-carbohydrate diet in most of the studies and when it did, the increase was transient. Most of these studies also did not have statistically different changes in LDL-C between the diet arms. A more accurate interpretation would be that the Eco Atkins diet led to LDL-C lowering whereas prior low-carbohydrate diets typically did not lead to LDL-C lowering.

Response: We agree that the low-carbohydrate diets do not in general cause large increases in LDL-C [~2-4% for the Samaha et al., 2003; Foster et al., 2003; and Gardner et al., 2007 (references #2,3,6)] and these rises are only seen earlier or when compliance with the diet is greatest. However, Gannon and Nuttall (Diabetes, 2004) showed in type 2 diabetes, when all food was provided, that a 7.6% increase in LDL-C was seen between treatments. However, we agree that this finding contrasts

sharply with that of Shai et al. (reference #10) where no rise in LDL-C was seen on a low-carbohydrate diet. But that low-carbohydrate diet also emphasized nuts and other vegetable protein and oil sources. As suggested, we have modified our Discussion accordingly (page 16, line 8-11).

2. The study suffered a high dropout rate, compromising interpretation of the results. Appropriate statistical methods were used to deal with missing data but with >50% dropout, concerns remain. High dropout rates in existing studies do not increase confidence in these results.

Response: We agree we have 50% attrition on the low-carbohydrate and 32% attrition on the high-carbohydrate diets (overall attrition 41%) (page 13, line 15-18). However, despite this deficiency we were still able to show significant benefits in LDL-C and body weight reductions in the ITT analysis with considerably larger benefits amongst the completers.

Minor issues:

1. It is unclear from the Methods whether the 6 month continuation was part of the original protocol or if participants were re-consented for a follow-up study upon completion of the feeding study.

Response: Thank you asking for further clarification on this issue. Subjects were consented only at the start of the study. Subjects were given the option of completing only the 4-week metabolic phase or both the metabolic phase and the 6-month ad libitum phase. We have clarified this in the Methods section (page 8, line 36-39).

2. P8, In 48, it could be made clearer that the 11/39 participants who discontinued lipid lowering medications were the only participants taking such medications.

Response: Thank you for the comment. You are correct that that the 11/39 who discontinued lipid lowering medications were the only participants who reporting taking such medications. We have clarified this in the manuscript (page 8, line 51-53).

3. Information is needed about whether diet counseling was provided and if so, how it was delivered (eg, who delivered the counseling, how frequently, what setting, etc.).

Response: Additional comments regarding the study visits with the dietitian have been added to the Methods – Study Protocol section (page 9, line 27-32). Thank you for the comment.

4. It is unclear if the control diet was vegan or not.

Response: The prescribed control diet was a lacto-ovo vegetarian diet. This point is now clarified in the manuscript (page 10, line 39).

5. The adherence goals (for the 3 vegetable proteins) could be described in more detail.

Response: We have provided additional details in the Methods – Diets section - relating to the adherence goals of the 3 cholesterol lowering components of the low-carbohydrate diet (page 11, line 11-18). These components were vegetable proteins (soy and gluten), nuts, and viscous fibers. The sources of each of these components have been added in response to another Reviewer's comments (page 10, line 18-35). These amounts prescribed during the metabolic phase, were the same amounts prescribed during the ad libitum phase. Adherence was determined based on the amount prescribed in relation to the amount consumed. With regards to gluten, adherence was based on the prescribed "seitan" products and not gluten consumed from grain products which would artificially inflate the adherence to this component.

6. Ad libitum is misspelled in some places.

Response: Thank you for bringing this to our attention. We have corrected the misspellings.

7. P16, line 18-it is unclear to which diet some statements in this paragraph refer.

Response: Thank you for the comment. We have clarified statements in this paragraph to reflect the diets that are being referred to (page 17, line 46).

Reviewer: 2

Major comments.

1. Figure 2 + 3 need revision

Figure 2 and 3 does not adequately present how the LDL-cholesterol and other outcomes changed from the end of the first very controlled period (at week 4), and until the end of the subsequent 5 month of free living adherence to the 2 diets (week 26). This may give the impression to the readers, that the beneficial effects on LDL-cholesterol and other outcomes that were found in the first 4 weeks were maintained or even increased during the subsequent 5 month intervention, which was not the case, as it is clear that the LDL-cholesterol increased significantly for both groups during the 5 month free living period. I would suggest that figure 2 and 3 should be redrawn, to make it clear that e.g. LDL-cholesterol increased from week 4 to week 26.

Response: This suggestion is very helpful. We have redrawn Figures 2 and 3 accordingly. They show that although the reductions on both the low-carbohydrate and high-carbohydrate diets are greatest on the metabolic phase for LDL-C and the ratio of TC:HDL-C, the treatment differences remain fairly constant throughout.

2. Results from Completer analysis comparable with results from ITT-analysis?

The manuscript presents the results based on an ITT-analysis. However, as the dropout rate is quite large, it would be appropriate to carry out completer analyses for most or all outcomes (in addition to that presented for the changes in LDL-cholesterol among completers), and if these completer analyses differ significantly from the ITT-analysis, this should be reported in the manuscript. If they do not differ, then this should somehow also be reported.

Response: The completer analysis did not differ from the ITT-analysis with regard to statistical significance, but the magnitude of change was greater for the completers in a number of outcomes. These observations are now reported in the Results section of the manuscript (page 13, line 44-48; page 14, line 22-30, 48-51; page 15, line 18-20; and page 15, line 29-32).

3. Drop out rate

The manuscript does present the dropout rate for the 2 study diet groups, but nowhere is it mentioned whether there was a difference in drop rate. This should be added.

Response: Thank you for this comment. There were no significant differences in the dropout rate between the two diets. We have now added this point to the manuscript (page 13, line 20-22).

4. Unclear description of the dietary intervention.

The authors describe the study as "hypocaloric", but also as "ad libitum". This seems to me as a contradiction. It should be made more clear what and how information about caloric intake was conveyed to the study participants.

Response: Yes, we agree that the type of diet prescribed may not have been clearly conveyed in the manuscript. The term "ad libitum" was used for the second phase of the study to distinguish it from the metabolic phase, where all foods were provided. During the ad libitum phase, no foods were provided which meant participants were free to choose which of the recommended foods to consume.

However, as part of the study design, we recommended and counseled participants to follow the diet they were prescribed during the metabolic phase. Participants were also given a copy of the menu plans provided during the metabolic phase to refer to during the ad libitum phase. Furthermore, participants were given an exchange list to achieve the prescribed amounts of each component. The items on the exchange list were based on items on the menu plan. This exchange list allowed participants to make appropriate substitutions based on their preference with the goal of enhancing adherence. This description has been added to the manuscript (page 10, line 46-56).

5. Calculation of 7-day food diaries.

In table 2, the nutritional composition in the “ad libitum” period is described. However, nowhere is it described when during the study, these 7-day food diaries were collected. Also, if the intake in the “ad libitum” period is calculated as mean values from several 7-day food diaries, this should be made clear.

Response: In response to your comment and another from Reviewer #1, we have clarified the frequency (monthly intervals) participants completed the 7-day food diaries (page 11, line 8). Thank you for your comment about calculating the data presented in Table 2. We have added this information to the Analyses section of the manuscript (page 12, line 6-8).

6. Consistent naming of the “Control diet”

In the clinicaltrials.gov registration, the “Control diet” is described as the NCEP diet.

Why is this term not used in this manuscript?

Response: Yes, we agree that we could have used the term NCEP (National Cholesterol Education Program) Diet for the “control” as described in the clinicaltrials.gov registration, but we opted to use the term high-carbohydrate diet to contrast it with the low-carbohydrate diet. Regardless of the terminology used, the high-carbohydrate diet prescribed in the current study conforms to the macronutrient distribution recommended by NCEP ATP III.

7. Sample size calculation

The manuscript does not describe, if any sample size calculation was performed before the study.

Please describe if this was done, and if so, how.

Response: A formal sample size calculation was not performed prior to the study. However, based on previously available data, for the metabolic study we were powered to detect a -0.37 mmol/L change difference in LDL-C, with 40 participants, assuming a commonly expected SD of 0.70 (Am J Clin Nutr 2002;76:365-72) and using an ANCOVA model where r , the correlation coefficient between successive measurements, equals 0.8. For the ad libitum phase ($n=39$), with the same assumptions as above, we could detect a minimum LDL-C treatment difference of 0.38 mmol/L. With the completers ($n=23$) the minimum LDL-C treatment difference detected as significant increased to 0.49 mmol/L.

8. Withdrawal of study participants due to hypercholesterolemia & use of statins

The manuscript describes that 3 participants in the low-carb group were withdrawn due to hypercholesterolemia. However, from figure 1, it also appears that 3 participants from the same diet were not considered as completers, as they resumed drug treatment with statins. How and why were participants experiencing hypercholesterolemia considered different from those resuming statin treatment?

Response: Thank you, this point needed clarification. The participants who resumed statins were those who had prior to the study been taking statins, but dropped out to resume taking statins. The participants who were withdrawn (and would then be placed on statins) were those whose LDL-C levels were above 5.0mmol/L and TC:HDL-C ratios were also above 5.0 during the study. All completers regardless of treatment had LDL-C levels below 5.0mmol/L, except 2 participants (1 low-carbohydrate and 1 high-carbohydrate) whose baseline values were also above 5mmol/L.

9. Diet score at baseline

In table 2, the adherence to “ECO-Atkins” is presented for the ad libitum period. Why are no data presented for the high carbohydrate group, and for the ECO-Atkins group at week 0? If data are available, they should be included.

Response: Participants were instructed not to consume any soy, nuts, foods high in viscous fibers, and meat substitutes made from gluten two weeks prior to the start of the study. For this reason, adherence to the cholesterol lowering components was not assessed at week 0. If there was any intake of these components, it would have likely been minimal relative the amounts prescribed during

the study. The prescribed high-carbohydrate diet did not contain specific recommendations for components that must be consumed, rather it was based on guidelines consistent with the macronutrient distribution of the NCEP ATP III recommendations, with emphasis on consuming dairy and egg protein in place of animal protein (i.e. a lacto-ovo vegetarian diet). For this reason an “adherence score” was not established for the high-carbohydrate diet, rather assessments were based on the nutritional composition of the diet presented in Table 2 (including dietary fatty acid profiles and cholesterol content).

10. Real life applicability

As the authors point out, the long term adherence to the ECO-Atkins diet is sub-optimal, and a total of 3 (or 6?) participants do not achieve the expected lowering of total- and LDL-cholesterol. This raises the question whether this diet can be adapted into (most) peoples diet. The discussion should include some reflections on this very critical aspect.

Response: We agree with the reviewer’s comment that the results of the study raise the key next question of how dietary adherence can be increased, given the benefits observed. In the Discussion, we briefly touched upon the potential issues of food availability and preparation as possible reasons for the lower adherence and higher dropout rate during the ad libitum phase compared to the metabolic phase. Future studies will need to focus on strategies to increase and maintain adherence, especially to the cholesterol lowering components, which all bear US FDA health claims for cardiovascular disease risk reduction. Furthermore, collaboration with food industry may be helpful in addressing concerns of availability, variety, and ease of preparation. In retrospect, a simplified one page eating plan for breakfast, lunch, and dinner with a number of options and amounts for each meal, as we have used in our dietary portfolio studies, might also be helpful (JAMA, 2011). We have added this discussion to the manuscript (page 18, line 27-41).

Minor comments

a) The manuscript describes that 11/39 discontinued lipid lowering medications before inclusion. It is not clear if those 11 participants were all those that took lipid lowering medication before inclusion. That should be made clear.

Response: This comment was also brought up by Reviewer #1. We have clarified in the manuscript (page 8, line 51-53) that the 11/39 who discontinued lipid lowering medications were the only participants who reported taking such medications.

b) It is not clear what kind and amount of exercise that was prescribed in the free living period. Please describe that.

Response: During the ad libitum phase of this study, there was no prescription related to exercise. Exercise alterations were allowed. In contrast to the metabolic phase, participants were asked to hold their exercise constant. Exercise histories were recorded for 7-days prior the monthly clinic visits during the ad libitum phase. This exercise recording protocol has been clarified in the manuscript (page 9, line 37).

c) In the text, it is described that the participants were prescribed to eat 60% of their energy needs, and that this would then give a stable body weight! Eating only 60% of calorie needs would clearly provide extra weight loss, also beyond the 4 week very controlled period (that achieved 4 kg weight loss). Please revise the statement that this would lead to stable body weight.

Response: Thank you for the comment. We agree that the reduction in estimated caloric requirements would likely result in some further weight loss during the ad libitum phase. Our statement has therefore been modified (page 10, line 6-8).

d) It is not clear how much of the three principal components (viscous fiber, vegetable protein and nuts) that were prescribed. Please add this information.

Response: The exact amounts prescribed of the three principal components were described in the

original publication of the metabolic phase. We referenced our publication to stay within the word limit of the Journal. We have now added this information to the current manuscript (page 10, line 18-35).

e) It is unclear how satiety was measured. Please make this more clear.

Response: Thank you for this comment. The method used to assess satiety has now been added to the Methods – Study Protocol section (page 9, line 32-37).

f) In the discussion part, some results are mentioned (page 15, line 10 on the LDL-cholesterol changes among completers). These results should be moved to the results section.

Response: The results presented in the Discussion section related to LDL-C changes among the completers have been moved to the Results section (page 14, line 25-27). Thank you for the suggestion.

g) The dietary content of the “control diet” should be explained in somewhat more detail, and not only by reference to the previous publication from the study.

Response: We did not include details of the high-carbohydrate diet again for brevity. We are happy to add the additional details as suggested (page 10, line 39-46).

Reviewer #3: Andrew Hinde

Division of Social Statistics and Demography, University of Southampton, SOUTHAMPTON SO17 1BJ, United Kingdom

1. My main concern about the analysis is the high rate of drop out from the study. The authors recognise this and try to cope with it using multiple imputation. They also seek refuge in the fact that drop out is common in studies of this type. However I think they could do more to examine the characteristics of the survey members who did drop out. They have evidence from the one-month metabolic study reported in Jenkins, Wong and Kendall (2009) which they could use to see whether those who dropped out from the ad libitum six-month study had experiences during the metabolic study which were atypical. One might even analyse whether the probability of drop-out from the ad libitum study could be predicted from the outcome of the metabolic study - a simple logistic regression analysis of drop out or not with a few covariates could be estimated. This analysis might not be possible with such small numbers. But even if not, some discussion of the characteristics of those who dropped out is important.

Response: Thank you for this suggestion. We do have small numbers, but we looked to see if the mean baseline values for LDL-C, body weight, BMI, absolute or relative CHD risk were different between the 16 who dropped out or were withdrawn and the 23 who completed. There were no significant differences. Higher baseline LDL-C approached significance amongst the dropouts and withdrawals compared to the completers (-0.5mmol/L [95% CI: -1.1, 0.0], P=0.053). No significant differences between dropouts and completers were seen in the changes in the variables during the metabolic phase (P=0.462-0.995).

2. The fact that on p. 10, l. 7, I think 'dairy' should be 'diary'. No saturated fats in this paper!

Response: Thank you for catching this typo and bringing it to our attention. We have made the correction.

VERSION 2 – REVIEW

REVIEWER	William Yancy Durham VAMC Duke University USA
REVIEW RETURNED	24-Nov-2013

GENERAL COMMENTS	<p>This study reports results of 6 months follow-up of a subset of participants (n=39) from a 1-month feeding trial randomizing 50 overweight adults with elevated LDL-C to a low-carbohydrate vegan diet (Eco Atkins) versus a high carbohydrate lacto-ovo vegetarian diet (control). Participants in the low-carbohydrate vegan diet arm had slightly greater weight loss and LDL-C lowering than control arm participants.</p> <p>Issues:</p> <ol style="list-style-type: none"> 1. p6, ln4-remove 'only' as it confuses the message of the bullet. 2. p6, ln17-high dropout rates in other studies does not lessen the implications of the high 6-month attrition rate. These comments should be removed here and elsewhere. 3. 3 participants from the test arm were removed from analyses due to elevation in LDL-C compared with only 1 in the control arm. This pertinent issue was not noted in my prior review. It is not clear if these individuals were included in analyses. Figure 1 and/or the text should clarify the number of participants who were actually analyzed. If these individuals were not analyzed, the LDL-C results might be quite different from what is reported and then I suggest softening the conclusions to say that this diet approach 'might have lipid lowering advantages...' The potential impact of these individuals' results should be added to the limitations. If these participants' data were included in analyses up until the point they were withdrawn (i.e., their high LDL-C readings are included in analyses), then the conclusions are reasonably valid.
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REVIEWER	Thomas Meinert Larsen Department of Nutrition, Exercise and Sports (NEXS), University of Copenhagen, Denmark
REVIEW RETURNED	06-Dec-2013

GENERAL COMMENTS	<p>I realize that the revision process has added to the length of the manuscript.</p> <p>However, the added text is indeed very informative, and should therefore be kept in the manuscript if at all possible.</p>
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VERSION 2 – AUTHOR RESPONSE

Reviewer Name William Yancy
Institution and Country Durham VAMC
Duke University
USA

Please state any competing interests or state 'None declared': None declared

This study reports results of 6 months follow-up of a subset of participants (n=39) from a 1-month feeding trial randomizing 50 overweight adults with elevated LDL-C to a low-carbohydrate vegan diet (Eco Atkins) versus a high carbohydrate lacto-ovo vegetarian diet (control). Participants in the low-carbohydrate vegan diet arm had slightly greater weight loss and LDL-C lowering than control arm participants.

Issues:

1. p6, ln4-remove 'only' as it confuses the message of the bullet.

Response: We have removed "only".

2. p6, ln17-high dropout rates in other studies does not lessen the implications of the high 6-month attrition rate. These comments should be removed here and elsewhere.

Response: We have removed reference to high dropout rates in other studies in "Strengths and Limitations of this Study" after Key Messages and in the limitations paragraph in the Discussion.

3. 3 participants from the test arm were removed from analyses due to elevation in LDL-C compared with only 1 in the control arm. This pertinent issue was not noted in my prior review. It is not clear if these individuals were included in analyses. Figure 1 and/or the text should clarify the number of participants who were actually analyzed. If these individuals were not analyzed, the LDL-C results might be quite different from what is reported and then I suggest softening the conclusions to say that this diet approach 'might have lipid lowering advantages...'. The potential impact of these individuals' results should be added to the limitations. If these participants' data were included in analyses up until the point they were withdrawn (i.e., their high LDL-C readings are included in analyses), then the conclusions are reasonably valid.

Response: All data were used including the 3 low-carbohydrate diet participants with high LDL-C values who were later withdrawn from the study (i.e. the high values were included). We have mentioned that the 39 starters were included in the Methods (under "Participants"), under Statistical Analyses, and in Figure 1.

Two participants (1 low-carbohydrate diet and 1 high-carbohydrate diet) had high triglyceride values (>4.5mmol/L). Nevertheless, their LDL-C values were also calculated to give full LDL-C data. Elimination of these 2 participants did not alter the conclusion. We have made these points under "Analyses".

Reviewer Name Thomas Meinert Larsen
Institution and Country Department of Nutrition, Exercise and Sports (NEXS), University of
Copenhagen, Denmark
Please state any competing interests or state 'None declared': None declared

I realize that the revision process has added to the length of the manuscript.

However, the added text is indeed very informative, and should therefore be kept in the manuscript if

at all possible.

Would you be willing to share your data?

Response: Thank you. We are prepared to share our raw data.