Author's response to reviews

Title: Weight and weight change following breast cancer: evidence from a prospective, population-based, breast cancer cohort study

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Author's response to reviews: see over
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Dr Amy Downing
Associate Editor
BMC Cancer

Dear Dr Downing

Ref: MS: 3653313851287952
Weight change following breast cancer: evidence from a prospective, population-based, breast cancer cohort study

Thank you for considering the abovementioned manuscript for publication in BMC Cancer. The authors have now incorporated the revisions, as suggested by the four reviewers, and a list of responses to each of their comments is provided below.

We trust that these revisions meet with your approval and look forward to your reply.

Yours sincerely

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1. Abstract
It is not well balanced between each part and could be improved as follows.
- At least one sentence of background should be added (only the aim is presented).
- Some major information is missing in the Methods part, such as the size of the population, type of population, how the data were collected (questionnaires, medical records, ...).
- The first sentence of the Results part is not clear (“were overweight or obese between...”).
- The beginning of the Discussion section was more clearly stated regarding this result.
- The sentence line 44 is not clear about whether the median weight gain was among all study subjects or only those who gained weight (n=?).
- The time when physical activity was assessed is missing in the results part.
We have revised the Abstract according to the above comments.

2. “Weights” and “weight changes” seem to be used in place of each other several times throughout the manuscript, which is confusing for the reader and not correct regarding the results. They should be checked carefully (e.g., first occurrence happens in the abstract line 50).
Our paper describes both “weight” and “weight change” and, as such, we have now included both terms in the title of the paper. The manuscript has been thoroughly checked to ensure the correct term is used with the corresponding result.

3. Introduction
- It is well documented (close to a complete literature review) but not appropriate for the introduction to an article. It contains too many references (some of which could be used in the Discussion section). Moreover, most references cited were probably included in recent metaanalyses or reviews, which is not obvious from the text. Therefore, the introduction should better focus on the main issues and ‘gap to fill’ for this study.
The Reviewer raises a good point; we have cited many references on the associations between body weight and mortality, morbidity, specifically breast cancer treatment-related sequelae, and risk of developing other chronic diseases. Two recent reviews and meta-analyses are also cited, exploring the incidence of co-morbidities related to obesity and overweight, and the effect of obesity on survival of women with breast cancer. However, to the best of our knowledge, there are no recent reviews or meta-analyses of observational studies focusing on weight and weight change following breast cancer. We have reworded to make clearer this aim of our study.
- Most importantly, the objective of the study is not correctly stated and not consistent with the results presented. Most of results, discussion and conclusion sections are on weight gain, not weight loss.
The title of the paper has now been altered to reflect our objective: the study describes weight and weight change. The first tables describe weight and weight change (in any direction). Through comparison with age-matched normative data, weight gain could be explored in more detail, with these findings presented in Table 2 (were previously presented in Table 4). We highlight throughout the Introduction and Discussion why describing weight and weight change (including understanding proportions of those losing and gaining weight) is important. Therefore, weight (presented as means) and proportion of those who lost or gained weight have been presented purposively because in doing so this gives a more comprehensive picture of what this cohort is experiencing.
- References are needed in the paragraph starting p3 line 31.
While the literature shows weight gain is common following diagnosis and treatment of breast cancer, none of the published studies have investigated whether these gains observed are typical of women and simply a factor of ageing (rather than associated with cancer and its treatment). Nonetheless, we’ve reworded this section to reflect what comparisons has been the focus of previous work and cited accordingly.
The last paragraph does not have the same content as the abstract. Both should be consistent with each other. The Abstract and the final paragraph of the Introduction have been amended and are now consistent with each other.

4. Methods
This section has several methodological issues that need to be checked carefully.
- The first part should start with at least one sentence presenting who the study population is (before referring to [39]). The baseline and follow-up parts should also be separated in two different paragraphs.
Revisions have been incorporated in accordance with the above comment.

- It is unclear what “clinical assessment data” are and it should be presented much clearer (what variables, assessment method ...).
This information is included in the paragraph on Data Collection; subheadings have been included to distinguish between information collected via ‘Clinical Assessment’ and ‘Self-administered Questionnaire.’

- p4 line 23: please add information on how follow-up was done (by whom, how...).
- p5 line 13-19: this paragraph should be moved to the statistical analysis part.
- The statistical analysis part should include complete definition of weight loss, maintenance and gain, which is given lower in the manuscript and arrives too late. Also, the descriptive analysis should be separated from the association analysis.
Revisions have been incorporated in accordance with the above comment.

- The Methods section should include all the description of variables included in the models (variables, categories), not only in notes to the tables. Particularly, physical activity assessment and variables should be explained.
Revision have been incorporated in accordance with the above comment (NB. categories of independent variables have been described in an added reference to Methods; however, dependent variables have been described in detail).

5. Results
- The 6-year follow-up includes data from 2002 to 2008 and more recent follow-up of the cohort could be considered.
The Pulling Through Study followed participants for a total of six years; the study has now been completed and ethical clearance closed. No further, more recent, follow-up data of the cohort are available.

- p6 line 19 and paragraph starting at line 25: it is not clear what information self-reported data on weight add compared to “clinically-assessed” weights (be more precise on this term, i.e., are these measured?). They bring confusion. Authors should consider removing self-report weights from the manuscript or explain more clearly their importance and the conclusion they draw from these results.
Self-reported weight, as well as clinically assessed weight, was collected over time. However, pre-diagnosis weight can only be assessed via self-report in the PTS (given that the study commenced six months post-surgery). Results on self-reported weight allow for comparisons with other studies which do not clinically assess weight (see details included in the Methods; page 5, paragraph 2). Information on self-reported weight also adds knowledge on issues such as changes in weight from pre-diagnosis. However, to do this, it also important to quantify the degree to which self-report and clinically measured weight agreed in our cohort. These issues have been incorporated into the Discussion (page 11, paragraph 2).
- Table 2 and paragraph starting p6 line 25: most data presented in table 2 are not useful and table 2 is too repetitive with table 1. Table 2 and the corresponding Results paragraph should be modified and present weight changes over time according to weight and/or BMI categories at baseline. Only the first header and first two lines of table 2 could be kept. Further, physical activity in table 2 should be moved and appear in table 1. Words used for number of lymph nodes should be used in table 1.

- Please define all abbreviations used in table 1.

Table 1 and Table 2 have been merged to avoid repetitiveness and results text has been updated.

- Physical activity should be defined better (e.g., using ranges of intensity). Moreover, 0 min/week of physical activity never happens. “Insufficient” physical activity level should be defined using a lower reference level. Please justify why 150 min/week was used.

Details on how physical activity was collected and scoring have now been added to the manuscript (page 5, paragraph 2). Physical activity was measured using the Active Australia survey, which defines ‘sufficient’ time to achieve health benefits of at least 150 minutes of physical activity a week. Note that this also corresponds to the standard level in the U.S. and other countries around the globe.

- Part starting p6 line 34: the results on weight, BMI changes and associations should be presented more clearly and reorganized in a consistent order.

Results in the text have been reorganized and in line with results presented in the Table.

- Table 3 and page 7: associations are not clearly presented. The text reports associations but no statistics of associations is presented. Importantly, table 3 should not present only significantly associated factors but all factors considered, with their level of significance. In the table 3 title, what does “clinically associated” mean? In table 3, time points for weight are not clear (please say clearly if weight considered as continuous variable). The content of the note to table 3 should appear in the Methods section.

One of the reasons for presenting descriptive results in Table 1 is to allow the reader to view the unadjusted data; the subsequent results included in the model take into account all relevant variables and weight over time. All variables in the final model (whether or not found to be statistically or clinically relevant) have now been included in Table 3. The content of the footnote to Table 3 now appears in the Methods section (page 7, paragraph 1). Clarifications to the Table have been included as per the suggestions above.

- The last Results paragraph should be moved up (before associations) because it contains most important descriptive results. Still avoid mix of self-reported and measured weights.

The last Results paragraph has now been moved up (before associations) and the respective Table of results have been amended accordingly. The order of the entire paper has been amended in accordance with the order of the objectives of the work, being: (i) to describe changes in body weight, (ii) compare weight with normative data, and (iii) explore whether weight changes over time are associated with a range of characteristics. All of the results for objective ii refer to clinically assessed weight, and this has been clarified in the Results section (page 8, paragraph 2).

- The structure of table 4 should be modified to present all N in the header (N does not fit with n/N). The units should appear next to their variable. Why is weight gain (>0 kg) not defined the same way as in the results section (corresponding to 1 BMI unit or 3% of baseline weight)? Also, it is not clear how the data presented in the text summarize the data presented in table 4. Finally, the notes to table 4 should appear in the Methods section.

Clinically assessed weight gain relative to normative data was assessed to two ways:
1. Gained greater than 0 kgs
2. Gained more weight than age-matched norms.

As well as over two time-periods:
1. Over a 12-month period
2. Over a 5-year period.

Table 4 (now Table 2) and associated text have been modified to clarify these results, and notes have been included in the Methods section (page 6, paragraph 3).

6. DISCUSSION
   - p9 lines 6-30: the physical activity level should be developed as physical activity is the only behavioral and modifiable factor found to be associated with weight overtime. Please develop on physical activities such as modalities, duration, type, intensity and timing.
Physical activity was assessed using a validated tool (which is now described in the Methods of the paper) and information on this variable was used to determine whether an association exists between weight and physical activity.
   - p10 line 5: on what basis (what statistical test?) can the authors say that the population was “representative”?
Information on the representativeness of the cohort has been included in the Results section (page 7, line 24-32), referencing the published paper which shows these results. Chi-square tests were conducted to assess whether there were any group differences on categorical variables between the target sample and study participants.

7. Throughout the manuscript, percentages should be presented after their numbers (e.g., 31 (15%)), not alone.
Percentages have now been added after their numbers.

Reviewer 1: Minor essential revisions

8. Style of some sentences is rather oral than written style. These sentences should be improved.
Thank you, revisions have been made throughout the paper.

9. Some paragraphs end on sentences with poor content or style. They should be improved (e.g., p3 lines 29-33, p8 lines 2-3 and 15-18, p9 line 17 “quality and quantity of life”, p9 line 22 “not surprising” …)
Revisions to language have been made throughout the paper.

10. Introduction:
   - p4 line 1: be more precise on “public health” setting and on “specific advice”.
   - p4 line 4: continue after previous paragraph.
   - p4 line 4: a study purpose is not limited to “report” data, be more specific.
   - p4 line 8: unclear what “weight status” is. Does it refer to BMI?
Revisions to the Introduction have been incorporated in accordance with the above comments.

11. Methods:
   - p4 line 18: please be more precise in “a range of outcomes”.
   - p4 line 20: The time point of “follow-up [40]…” is not clear (72 months?).
   - p4: the limits regarding inter-scale, inter-operator variability … are not discussed later in the Discussion section.
   - p4-5 data collection: this part is not well organized (jumping between weight, height and BMI).
   - p4 line 33: be consistent between terms (obesity instead of obese?). We have reviewed the use of these terms throughout the paper and have verified proper usage.
   - p5 lines 1-3: please list all variables instead of “e.g.”.
12. Statistical analysis: Either means or medians should be presented for consistency throughout the manuscript (avoid a mix of both, even if normality was the rationale behind the choice of the statistics). Means are not usually presented with range (p6 lines 27-29).
We have presented means and SD when the continuous outcome variable is normally distributed and medians and range when these conditions were not met.

13. Results:
- the subtitle “Participants” is the only subtitle. Either it should be removed or other subtitles should be added.
- Throughout the Results section, percentages should be presented with similar number of decimals across text and tables.
- p6 line 19 and line 22: please provide statistical test and level of significance in the Methods section if “similar” results are presented.
- p6 line 32: if 95% confidence intervals are used, they should be defined in the Methods section.
- p7 lines 1-6: please check the sentence for grammar and use units where necessary.
- p7 line 14: “some amount” is too vague.
Revisions to the Results have been incorporated in accordance with the above comments.

14. Discussion:
- p7 line 28: too vague. Please add references for the few studies if their number is limited.
This is the first study of its size, involving a population-based cohort, to assess weight and change in weight over a six year period, and to compare with normative data. The text has been modified to indicate this (page 9, line 13).

- p8 line 2: “unintentionally” does not sound appropriate for weight loss resulting from cachexia.
The word ‘unintentionally’ has been removed.

- p8 lines 5-7: this should be moved to the Results section.
Information has been added to the Results section.

- p8 lines 9-16: references are needed.
References have been added.

- p8 line 24: please be more precise on “magnitude of weight gain”.
“magnitude of weight” has been defined as weight gain that led to more than one unit increase in BMI (page 10, lines 8-9).

- p9 line 4: the paragraph needs to conclude by putting the results in perspective with the literature (how do they compare?).
The results of this study are summarised in the first paragraph of the Discussion highlighting key findings of this study and then subsequent paragraphs place these findings in the context of the wider literature.

- p9 line 21: what are “clinically lower body weights”? used instead of weight changes?
These results refer to weight, not weight change.
- p9 line 28: should say impact of “weight maintenance or no weight gain”, instead of “weight loss”.
Revisions have been incorporated in accordance with the above comment.

- p9 lines 33-34: please add references for recent literature.
We refer here to the PTS as being the most recent within the literature; more specifically, this current paper.

- p10 line 7: please add references for “previous work”.
References have been added.

- p10 line 10: this study does not present weight at “breast cancer diagnosis” as it starts 6 months later.
- p10 line 14: remove content on lymph nodes from the parentheses because this is not a modifiable factor.
Revisions to the Discussion have been incorporated in accordance with the above comments.

15. Notation for ranges with minus signs should be improved (e.g., -1.9--24.6kg is not easy to read). Also, signs such as 30+, >11,000 and others should be written as full text.
Revisions have been incorporated in accordance with the above comment.

16. Please check the use of hyphen in “6-months” post-diagnosis and similar words.
Revisions have been incorporated in accordance with the above comment.

Reviewer 2: Major essential revisions

1) Although the abstract states that the research explores whether weight changes over time are associated with patient, diagnosis, treatment or behaviour characteristics I think the manuscript does not address this, unless I have interpreted the mixed methods results incorrectly. Table 3, which uses mixed methods, appears to relate to measured body weight rather than weight change, and although changes in weight by patient characteristic can be seen in table 2 these changes are not described in the results or mentioned in discussion or abstract. The results in terms of patient characteristics, as described in the abstract and in the main body (2nd paragraph of the results and 4th paragraph of the discussion), appear to relate to measured body weight only and do not mention weight change. This needs addressing please. It would be useful to describe changes in weight over time by patient characteristic. For instance I noted in table 2 that although patients with 10 or more lymph nodes removed were heavier at 6 months after diagnosis than women in other categories, women in this category only gained 0.5kg by 72 months whereas on average women in other categories put on weight over this period and those who had no lymph nodes removed put on 7kg by 72 months. Women with 10 or more ‘positive’ lymph nodes actually lost weight over this period. After describing in the results section some of the weight gains and losses between 6 - 72 months in terms of patient characteristics, please make appropriate amendments to the 4th and perhaps to the final paragraphs of the discussion. Possible reasons for different patterns in weight changes for different categories of patients could be discussed along with any supporting prior research. Descriptions of patient characteristics in relation to weight status (e.g. close to diagnosis at 6 months) and weight changes between clinical measurements should be clearly distinguished.
Many of the points raised by Reviewer 2 above were also highlighted by Reviewer 1 and, as such, have already been addressed.

Results in Table 2 (now Table 1) showing weight over time by patient characteristic are bivariate analyses and subsequent mixed models showed that higher number of lymph nodes removed remained significant following adjustment for potential confounding. A strength of the modelling approach used is that the model accommodated all available weight data and tested all potential interactions with time; this information has now been explicitly included in the Methods section. Since none of the interactions were either statistically significant (p<0.05) or clinically important (<3kg difference between groups), they were subsequently
removed from the final model. All characteristics in the final model, whether retained or not, are now presented in the Table 3.

2) Ideally the weight of the patient at diagnosis should be added to table 2 (and significant differences between this and weight at 72 months calculated) if the information is available. If this information is not available perhaps weight at 6 months after diagnosis may be a close enough approximation to this, but this limitation should be mentioned in the discussion, along with the fact that you mention in the introduction that previous research has found weight gains exceeding 5Kg between diagnosis and six months - this might vary by patient characteristic. The fact that weight status at or near diagnosis is likely to be associated with type of diagnosis should also be mentioned.

See Reviewer 1, comment 5.

Reviewer 2: Minor essential revisions

1) Please alter the conclusion of the abstract so it relates more closely to the results of this study rather than background information.
Revisions have been incorporated in accordance with the above comment.

2) In table 3, please state at which time point these weight measurements were taken and whether they were clinically measured. If more than one time point is taken into account for this, as alluded to in the methods, then some additional explanation is needed to help the reader interpret this table in this respect.
The timing of assessment of characteristics in Table 3 (baseline or treatment received anytime up to 18 months post-surgery), clinically-measured weight (assessed at 6, 12, and 18 months post-surgery), and results shown for mean body weight (refers to least square means) have all been clarified with the addition of footnotes.

3) In the data collection section of methods, please state the definition of sufficient physical activity i.e. 150 minutes of moderate activity per week.
Revisions have been incorporated in accordance with the above comment.

4) In the first paragraph of the discussion it states 'At the point of breast cancer diagnosis', but I think you mean 'At 6 months after diagnosis'.
We appreciate the reviewer’s comment and have amended this paragraph accordingly.

5) Please state whether weight was clinically measured or self-reported in the normative dataset, and if it was self-reported mention this as a limitation in the discussion.
Revisions have been incorporated in accordance with the above comment.

6) Please mention as a limitation in the discussion that the follow-up periods between the PTS sample and the normative sample are close but somewhat miss-matched.
This limitation has been added to the discussion.

7) In table 4 please explain the notes to the table more clearly in relation to the age band weight gains - do these relate to the AusDiab data?
Age bands are defined within 9-year age strata and the AusDiab average rate change for the specified age range. This is defined in the footnotes of Table 2 (previously Table 4).

Reviewer 2: Discretionary revision
1) In the methods paragraph of the abstract it would be useful to add an explanation of '1 BMI unit' being a clinically relevant weight gain.
Revisions have been incorporated in accordance with the above comment.

2) A sentence in the last paragraph of the methods could be moved into Results ' of note, clinically-assessed weight was on average....
We thank the reviewer for this suggestion and have modified the text accordingly.

3) Some sections of the discussion could be condensed e.g. 3rd paragraph (background information already mentioned in the introduction), and 5th paragraph.
We have reduced the text.

4) It could be pointed out that although the sedentary group on average did not gain weight between 6-72 months they still had the highest weight 72 months post diagnosis and should be encouraged to exercise.
Table 3 shows that women who were physically sedentary had a heavier weight compared to those who were insufficiently or sufficiently active (both statistically and clinically significant). This has been highlighted in the Discussion (page 10, paragraphs 3-4). Our key message is that maintaining a healthy weight is important for all women post-breast cancer and one way to achieve this is through being regularly active.

5) The two women reporting extreme weight loss ought to be mentioned in the results first before referring to them in the discussion. Within this discussion paragraph on weight loss, it would be useful to point out that in relation to patient characteristics only women who had 10 or more positive lymph nodes and those who underwent mastectomy surgery lost weight between 6-72 months – though this may not be significant in the latter group.
Revisions have been incorporated in accordance with the above comment.

6) Women who received chemotherapy were somewhat heavier at 6 months postdiagnosis than those who did not receive chemotherapy. Those receiving chemotherapy did not, however, put on any substantial weight between 6 and 72 months, whereas women who never received chemotherapy put on about 3kg by 72 months, and were then on average a similar weight to those who had chemotherapy. This could be mentioned in the results and discussion. You mention in the introduction that the contribution of current chemotherapy regimens to weight gain is unclear, but unfortunately it is still unclear from these results because we do not know whether these women who received chemotherapy put on weight during/following chemotherapy or whether heavier women were more likely to need / be given chemotherapy.
While unadjusted results show an association between body weight and chemotherapy (i.e., those who received chemotherapy and higher body weights than those who did not receive chemotherapy), following adjustment for other characteristics outlined in Table 3, this relationship was attenuated. Further, there was no interaction between chemotherapy and time; that is, chemotherapy was also not associated with weight over time. Therefore, while the design of this study does not allow causal inferences to be made between chemotherapy and weight, our work did not show an association between the two (as highlighted in the Discussion; page 11, paragraph 2).

Reviewer 3: Major compulsory revisions

Lost to follow-up in this cohort was high. This needs to be mentioned in the limitations and the authors should address and discuss whether lost to follow-up was or may have been associated with weight?
Loss to follow-up over the six-year period was 32%; that is, 68% (195/287) of the original cohort consented to the six-year follow-up study. This is quite an achievement given the extensive testing and lengthy duration of the study. Of the original participants, only 11 withdrew from the study, 22 could not be recontacted and
36 declined participation in the follow-up study. Still, attrition was greater than 20%, which threatens the generalizability of findings and, as such, has now been mentioned and referenced as a limitation in the Discussion (page 11, lines 5-6).

Further, descriptive statistics comparing demographic and disease characteristics of women in the study sample and women excluded from analyses showed that all baseline characteristics of excluded women were similar to those observed in the total study sample, with the exception of health insurance (whereby a higher proportion of those who were excluded from analyses did not have health insurance compared with the total study sample). This information has been incorporated into the Results under the Participants section (page 7, paragraph 2).

Using 6 month post-diagnosis weight may not be the best comparison. Women’s weight may have already changed to no longer reflect her pre-diagnosis ‘normal’ weight. Perhaps the authors should considering using a pre-diagnosis weight or at least justify the use of a 6-month post diagnosis? Clinical weight was not collected pre-treatment however, based on self-reported pre-diagnosis weight, body weight did not change significantly during the treatment period. This information has been included in the Discussion (page 11, paragraph 2).

Reviewer 3: Minor essential revisions

Methods, Page 4, Data collection. Weight was measured but also self-reported. Are self-reported measurements ever used? If so, this should be more clearly stated in the statistical analysis section. This has been addressed above in response to Reviewer 1, Results.

Methods, Page 4, Data collection. If the authors have information on pre-diagnosis weight change, wouldn’t that be a more informative baseline measurement then 6 months after diagnosis? Clinical weight is the preferred method of assessment and, indeed, is a strength of the study. We found that in our sample, based on self-reported weight, body weight did not change significantly between pre-diagnosis and six months post-surgery. This information has been incorporated into the Discussion (page 11, paragraph 2).

Methods, Page 5. Statistical Analysis. More information on the predictive model building would be helpful here. List variables included in predictive model. Were there other variables that were dropped? Reviewer 1 also commented on the predictive model; additional information regarding effect modification being tested has also been included in the Statistical Analysis section.

Results, Page 6. Study Participants. ‘Demographic and clinical characteristics of the women who provided self-report and clinically-assessed data were similar to those women who provided self-reported data only (n=287)’ – Is this sample size correct? It doesn’t match with numbers in the methods. Thank you for pointing out this error. The sample is the clinical sample (n=211) and this has now been corrected in the paper.

Table 3. Clarify the definition for clinically associated in a footnote. Revisions have been incorporated in accordance with the above comment.

Reviewer 4: Minor essential revisions

1. In mathematic meaning, the sentence “those with BMI changes of >=-1 were considered to have experienced clinically relevant losses in weight” should be “those with BMI changes of <=-1 were considered to have experienced clinically relevant losses in weight” in the first paragraph of section “Statistical analysis”.


Revisions have been incorporated in accordance with the above comment.

**Reviewer 4: Major compulsory revisions**

2. In Table 4, you compare PTS data (age-based) with the mean value of AusDiab data, and give the % of weight gained. Could you do a test (like T test) between these two types of data to check whether gained weight bigger than norms is statistical significant?

While we hold raw data from the PTS cohort, we only have group data from the AusDiab study. Conducting a one sample t-test of PTS against AusDiab assumes that the AusDiab mean value is a normative value. Therefore, the most appropriate comparison between the two is not to apply statistical analyses to this, but instead to present descriptive results and interpret the potential clinical relevance.

3. **Could you give you all samples’ original weight data as a support material?**

As per the response above, raw data is available for the PTS cohort but not the AusDiab study cohort.

**Reviewer 4: Discretionary revisions**

4. We suggest to revise “between six months [19-22] and five years” as “between six months [19-22] and sixty months” in section “Introduction” second paragraph and revise “assessed prospectively between six- and 72-months” as “assessed prospectively between 6- and 72-months” in the last paragraph.

Revisions to the Introduction have been incorporated in accordance with the first suggestion; we prefer to spell-out numbers less than 10 in this section and have therefore not made changes based on the second suggestion outlined above.