PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Association between nut intake and Non-alcoholic fatty liver disease risk: a retrospective case-control study in a sample of Chinese Han adults
AUTHORS	Chen, Bing bing; Han, Ying; Pan, Xinting; Yan, Jianhui; Liu, Wenjuan; li, yangfan; lin, xu; xu, shanghua; Peng, Xian-E

VERSION 1 – REVIEW

REVIEWER	Marc Saez University of Girona Spain
REVIEW RETURNED	27-Jan-2019

GENERAL COMMENTS	The authors tried to analyzed the association between nut intake and non-alcoholic fatty liver disease risk and the interactions between nut intake and other established risk factors in a large case-control study with a sample of Han adults in China. The authors have been quite successful in achieving their objectives. In fact, I only have minor comments. Minor comments - Although the authors have discussed the information bias, it is not clear to me whether this has been differential or non-differential. In addition, it is not clear in all cases, what they did to control it.

REVIEWER	Stefano Bellentani Clinica Santa Chiara - Locarno (Switzerland)
REVIEW RETURNED	19-Feb-2019

GENERAL COMMENTS	This paper is essentially a negative paper. The authors investigated with a case-control study the possible inverse association between NUts consumption and NAFLD. They did not find any association unless in men in the highest quartile. They used a semi-quantitative food questionnaire that was not illustrated and reported well in the paper, and, most important, it was not validated by other groups. They used a very weak statistical test and they claim to have corrected for the major confounding factors (such as the ones reported in Table 3), but they did not correct for either other food intake that could contain nuts or for coffee or fructose consumption. The paper, to my opinion does not deserve publication in BMJ Open

REVIEWER	Mohammad Ali Mansournia Tehran University of Medical Sciences, Iran

REVIEW RETURNED	02-Mar-2019

GENERAL COMMENTS	1) All analyses should adjust for the matching variables as they were used in the matching process; otherwise the results are subject to selection bias. So adjustment (or stratification) based on gender, ethnicity, and region is necessary. Also adjustment for age should match the matching protocol. Please read and cite the following paper: https://link.springer.com/article/10.1007/s10654-017-0325-0 2) Sample size should be justified especially for the negative results. 3) The controls should be described in more details. In particular, the controls should not have a disease for which the exposure of interest is a known risk factor. 4) Pages 6-7 say that selection of covariates was based on clinical significance, results of previous studies, and strength of correlation with exposure. The latter item is vague. How did the authors assess this correlation and how did they use it for the selection process? As a technical point, the term correlation is incorrect here and should be replaced with association. Moreover, association with exposure can only increase variance without decreasing bias if the variable is not a risk factor of outcome. In general, potential confounders including known risk factors of the outcome should be included the model and change in estimate criterion can be used for variable selection. 5) Categorization of continuous exposure variables in quartiles can lead to bias and inefficiency. This is indeed a type of measurement error and should be at least acknowledged as a limitation in the paper. 6) Table 3: The cutpoints for Q1-Q4 should be mentioned in the footnote. 7) Tables 1 and 3: Please report exact P-value unless it is less than 0.001. The latter should be written as P<0.001. P=0.00 doesn't make sense.

REVIEWER	Mohammad Ali Mansournia Tehran University of Medical Sciences, Iran
REVIEW RETURNED	02-Mar-2019

GENERAL COMMENTS	1) All analyses should adjust for the matching variables as they were used in the matching process; otherwise the results are subject to selection bias. So adjustment (or stratification) based on gender, ethnicity, and region is necessary. Also adjustment for age should match the matching protocol. Please read and cite the following paper: https://link.springer.com/article/10.1007/s10654-017-0325-0 2) Sample size should be justified especially for the negative results. 3) The controls should be described in more details. In particular, the controls should not have a disease for which the exposure of interest is a known risk factor.

	4) Pages 6-7 say that selection of covariates was based on clinical significance, results of previous studies, and strength of correlation with exposure. The latter item is vague. How did the authors assess this correlation and how did they use it for the selection process? As a technical point, the term correlation is incorrect here and should be replaced with association. Moreover, association with exposure can only increase variance without decreasing bias if the variable is not a risk factor of outcome. In general, potential confounders including known risk factors of the outcome should be included the model and change in estimate criterion can be used for variable selection. 5) Categorization of continuous exposure variables in quartiles can lead to bias and inefficiency. This is indeed a type of measurement error and should be at least acknowledged as a limitation in the paper. 6) Table 3: The cutpoints for Q1-Q4 should be mentioned in the footnote. 7) Tables 1 and 3: Please report exact P-value unless it is less than 0.001. The latter should be written as P<0.001. P=0.00 doesn't make sense.

REVIEWER	Marilyn Cyr New York State Psychiatric Institute, USA
REVIEW RETURNED	08-Apr-2019

GENERAL COMMENTS	The present paper reports on the association between nut consumption and NAFLD in a large sample of patients and controls from a Chinese Han population. The authors employed logistic regression models to estimate odds rations. The statistical approach is sound but some clarifications are required to fully evaluate the validity of the analyses conducted. There are also some concerns regarding the inflated risk for type I error in the absence of measures to correct for the multiple tests conducted. Below are specific comments: 1. The last paragraph of the introduction (Patient and Public Involvement) and the first paragraph of the Methods section (Participants and study design) are both redundant and inconsistent. The information reported therein is best suited for the Methods section. The dates during which the study was conducted should be fixed (i.e., 10/2015-09/2017 vs 04/2015-08/2017). Past tense rather than future tense should be used given that the study in now completed. 2. In the Methods section, the subsection title "Statistical analysis" (p.6) should be pluralized to be "Statistical analyses", given that more than one analysis was conducted. 3. In the Statistical analysis section (p.6), it is unclear what the difference is, if any, between potential confounders, risk factors, and modifying factors. 4. P.6: It appears that a sentence defining MET was inserted in the middle of the enumeration of potential confounders (covariates included in the model). The enumeration begins with age, income,

	… then continues two sentences later with history of diabetes, hypertension, and hyperlipidemia. 5. P.7: “We tested for linear trends across categories of nut intake by assigning each participant the median value for each category and modeling this value as a continuous variable”. This sentence is unclear and I’m unable to determine the validity of these analyses without understanding what was done precisely. 6. Results section, under “Stratified Analsyes”: It seems that the stratified analyses were conducted for each covariate regardless of whether there was a significant interaction between nut intake and that covariate in predicting NAFDL. Is this correct? How do the authors justify this decision? Were there any significant interaction? Did any of the covariate have a significant effect on NAFLD, either on their own or over and above nut consumption? Finally, how many stratified analyses were conducted in total? Was there any correction for multiple test applied? If not, this would substantially inflate the risk for type I error and should at the very least be acknowledge anywhere these results are reported and discussed. 7. A careful proofread should be conducted as there are many grammatical sentences and typos.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Marc Saez
The authors tried to analyzed the association between nut intake and non-alcoholic fatty liver disease risk and the interactions between nut intake and other established risk factors in a large case-control study with a sample of Han adults in China. The authors have been quite successful in achieving their objectives. In fact, I only have minor comments.
Minor comments
Q1- Although the authors have discussed the information bias, it is not clear to me whether this has been differential or non-differential. In addition, it is not clear in all cases, what they did to control it.
A1: Many thanks for reviewer’s suggestion. The final logistic regression models adjusted for potential confounders, including age, income, smoking status, educational level, and tea-drinking status, occupational status, marital status, body mass index (BMI), physical activity, and history of diabetes, hypertension, and hyperlipidemia, MUFA and PUFA intake to control for the information bias. The inverse association between total-nut consumption and NAFLD risk was differential (please see Table 3) .

Reviewer: 2
Reviewer Name: Stefano Bellentani
Institution and Country: Clinica Santa Chiara - Locarno (Switzerland)
Please leave your comments for the authors below
This paper is essentially a negative paper. The authors investigated with a case-control study the possible inverse association between NUts consumption and NAFLD. They did not find any association unless in men in the highest quartile. They used a semi-quantitative food questionnaire that was not illustrated and reported well in the paper, and, most important, it was not validated by other groups. They used a very weak statistical test and they claim to have corrected for the major confounding factors (such as the ones reported in Table 3), but they did not correct for either other

food intake that could contain nuts or for coffee or fructose consumption. The paper, to my opinion does not deserve publication in BMJ Open

A: Many thanks for reviewer's comment. Indeed, as a exploratory research, there were some limitation in the present study, and we have discussed this limitation in the discussion section in the revised manuscript (page 14). However, there are several statements we have to mention. First, the semi-quantitative food questionnaire was developed and validated in a sample from southern China according to the prior study (Ke L, Toshiro T, Fengyan S, et al. Relative validity of a semi-quantitative food frequency questionnaire versus 3 day weighed diet records in middle-aged inhabitants in Chaoshan area, China. Asian Pac J Cancer Prev 2005;6(3):376-81). Second, our stratified analysis, the inverse association between total-nut consumption and NAFLD risk was consistent across strata of age, sex, BMI, educational level, income, physical activity, smoking, tea drinking, and history of diabetes, hypertension, and hyperlipidemia, although these were not statistically significant unless in men (Fiture 1). Third, we cannot exclude the effects of all confounding variables or residual confounding (such as coffee or fructose consumption) which might have influenced the observed associations. However, the associations persisted even after controlling for known and suspected predictors of NAFLD.

Reviewer: 3

Reviewer Name: Mohammad Ali Mansournia

Institution and Country: Tehran University of Medical Sciences, Iran

Q1- All analyses should adjust for the matching variables as they were used in the matching process; otherwise the results are subject to selection bias. So adjustment (or stratification) based on gender, ethnicity, and region is necessary. Also adjustment for age should match the matching protocol. Please read and cite the following paper:

https://link.springer.com/article/10.1007/s10654-017-0325-0

A1：We have read the paper . Because the cases and controls are all Han ethnicity and resident of Nanping, so we did not adjust these two matching variables, and we have adjust sex and age in all analyses of our manuscript.

Q2- Sample size should be justified especially for the negative results.

A2:We agree with the reviewer's concerns and suggestion. We have added the description about the calculation of sample size in the method section of the revised manuscript (please see page 5).

Q3- The controls should be described in more details. In particular, the controls should not have a disease for which the exposure of interest is a known risk factor.

A3：Thank you very much for your valuable comments.The controls were randomly selected from the same center during the study period. Their eligibility criteria were identical to those of the cases. The exclusion criteria were as follows: (a) daily alcohol intake of >40 g (men) and >20 g (women), (b) a history of other liver diseases including drug-induced liver disease, viral hepatitis, autoimmune hepatitis, total parenteral nutrition, and hepatolenticular degeneration, (c) taking hypolipidemic or weight reduction drugs, (d) age <18 or >70 years, (e) non-resident of Nanping, or (f) not of Han ethnicity. We have added this description in the revised manuscript.

Q4- Pages 6-7 say that selection of covariates was based on clinical significance, results of previous studies, and strength of correlation with exposure. The latter item is vague. How did the authors assess this correlation and how did they use it for the selection process? As a technical point, the term correlation is incorrect here and should be replaced with association. Moreover, association with exposure can only increase variance without decreasing bias if the variable is not a risk factor of outcome. In general, potential confounders including known risk factors of the outcome should be included the model and change in estimate criterion can be used for variable selection.

A4: Sorry for our carelessness and many for reviewer's suggestion. We have deleted the ' strength of correlation with exposure ' in the method section (page 7) of the revised manuscript.

Q5-Categorization of continuous exposure variables in quartiles can lead to bias and inefficiency. This is indeed a type of measurement error and should be at least acknowledged as a limitation in the paper.

A5：Many thanks for reviewer’s suggestion. We have discussed this limitation in the discussion section in the revised manuscript (page 14).
Q6-Table 3: The cutpoints for Q1-Q4 should be mentioned in the footnote.
A6：Many thanks for reviewer’s suggestion. We have mentioned the cutpoints for Q1-Q4 in the footnote (Table 3).
Q7- Tables 1 and 3: Please report exact P-value unless it is less than 0.001. The latter should be written as P<0.001. P=0.00 doesn’t make sense.
A7: Many for reviewer’s suggestion. We have amended the ' P=0.00 ' to ' P<0.001' in the discussion section (Table 1 and Table 3) of the revised manuscript.

Reviewer: 4
Reviewer Name: Marilyn Cyr
Institution and Country: New York State Psychiatric Institute, USA
The present paper reports on the association between nut consumption and NAFLD in a large sample of patients and controls from a Chinese Han population. The authors employed logistic regression models to estimate odds rations. The statistical approach is sound but some clarifications are required to fully evaluate the validity of the analyses conducted. There are also some concerns regarding the inflated risk for type I error in the absence of measures to correct for the multiple tests conducted. Below are specific comments:

Q1-The last paragraph of the introduction (Patient and Public Involvement) and the first paragraph of the Methods section (Participants and study design) are both redundant and inconsistent. The information reported therein is best suited for the Methods section. The dates during which the study was conducted should be fixed (i.e., 10/2015-09/2017 vs 04/2015-08/2017). Past tense rather than future tense should be used given that the study in now completed.
A1: Sorry for our carelessness and many for reviewer’s suggestion. We have move the patient and public involvement statement to the end of the methods section, and removing duplicate information in the revised manuscript (page 7).
Q2.-In the Methods section, the subsection title “Statistical analysis” (p.6) should be pluralized to be “Statistical analyses”, given that more than one analysis was conducted.
A2: Many for reviewer’s suggestion. We have amended the ' Statistical analysis ' to 'Statistical analyses' in the methods section (page 6) of the revised manuscript.
Q3-In the Statistical analysis section (p.6), it is unclear what the difference is, if any, between potential confounders, risk factors, and modifying factors.
A3: Apologies for the confusion and many for reviewer’s suggestion. We have unified the expression in the revised manuscript (page 6-7).
Q4-P.6: It appears that a sentence defining MET was inserted in the middle of the enumeration of potential confounders (covariates included in the model). The enumeration begins with age, income, … then continues two sentences later with history of diabetes, hypertension, and hyperlipidemia.
A4: Sorry for our carelessness and many for reviewer’s suggestion. We have corrected this sentences in the revised manuscript (page 7).
Q5- P.7: “We tested for linear trends across categories of nut intake by assigning each participant the median value for each category and modeling this value as a continuous variable”. This sentence is unclear and I’m unable to determine the validity of these analyses without understanding what was done precisely.
A5: We appreciate the reviewer’s comment, and have updated our references for this analyse (page 7). These analyses were referred to prior studies (.Nut Consumption and Survival in Patients With Stage III Colon Cancer: Results From CALGB 89803 (Alliance). Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2018;36(11):1112-20. doi: 10.1200/JCO.2017.75.5413; Sugar-sweetened beverage intake and cancer recurrence and survival in CALGB 89803 (Alliance). PloS one 2014;9(6):e99816. doi: 10.1371/journal.pone.0099816; Dietary glycemic load and cancer recurrence and survival in patients with stage III colon cancer: findings from

CALGB 89803. Journal of the National Cancer Institute 2012;104(22):1702-11. doi: 10.1093/jnci/djs399).
Q6- Results section, under “Stratified Analsyes”: It seems that the stratified analyses were conducted for each covariate regardless of whether there was a significant interaction between nut intake and that covariate in predicting NAFDL. Is this correct? How do the authors justify this decision? Were there any significant interaction? Did any of the covariate have a significant effect on NAFLD, either on their own or over and above nut consumption? Finally, how many stratified analyses were conducted in total? Was there any correction for multiple test applied? If not, this would substantially inflate the risk for type I error and should at the very least be acknowledge anywhere these results are reported and discussed.
A6: Many thanks for reviewer’s suggestion. This is a exploratory analysis. We were referred to prior study (.Nut Consumption and Survival in Patients With Stage III Colon Cancer: Results From CALGB 89803 (Alliance). Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2018;36(11):1112-20. doi: 10.1200/JCO.2017.75.5413). No significant interactions of total nut consumption and the potentially confounding effects of NAFLD risk factors were identified. All covariate have a significant effect on NAFLD based on clinical significance, results of previous studies. We did not correct for multiple test applied, and we have discussed this limitation in the discussion section in the revised manuscript (page 14).

Q7-A careful proofread should be conducted as there are many grammatical sentences and typos.
A7: We appreciate the reviewer’s comment.We have carefully proofread grammatical sentences and typos in the revised manuscript.

VERSION 2 – REVIEW

REVIEWER	Mohammad Ali Mansournia Tehran University of Medical Sciences
REVIEW RETURNED	29-Apr-2019

GENERAL COMMENTS	The authors didn’t address my previous first concern: All analyses should adjust for the matching variables as they were used in the matching process; otherwise the results are subject to selection bias. So adjustment (or stratification) based on gender, ethnicity, and region is necessary. Also adjustment for age should match the matching protocol. Please read and cite the following paper: https://link.springer.com/article/10.1007/s10654-017-0325-0 A1：We have read the paper . Because the cases and controls are all Han ethnicity and resident of Nanping, so we did not adjust these two matching variables, and we have adjust sex and age in all analyses of our manuscript. As said above, adjustment for age shoud reflect the matching protocol; otherwise bias can occur. Please carefully read and cite the paper I suggested before.

REVIEWER	MARILYN CYR New York State Psychiatric Institute, USA
REVIEW RETURNED	14-May-2019

GENERAL COMMENTS	Q1- The sample size calculation (page 5) is not sufficiently described. What formula (or specific function in a software calculator) was used and what were the variables & values input

	(with sufficient details to allow one to replicate these analyses)? Importantly, were all the covariates included in the analyses taken into account in the power analyses? If they were not, they should absolutely be, especially given that the authors state on Pages 1 and 14 that “the study had sufficient power to investigate interactions between nut intake and other risk factors…”. Q2- Relatedly, the expected OR (0.74) used in this power analyses was taken from a single study reporting the association between physical activity and NAFLD. A) What is the justification for expecting a similar effect from nut consumption than from physical activity? B) If justified, it should be clearly mentioned that the power calculation was based on a prior study (Katsagoni et al., 2017) reporting an association between physical activity (not nut consumption) and NAFLD. Otherwise, as it currently reads, the citation is misleading.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 3

Reviewer Name: Mohammad Ali Mansournia

The authors didn’t address my previous first concern:

Q1: All analyses should adjust for the matching variables as they were used in the matching process; otherwise the results are subject to selection bias. So adjustment (or stratification) based on gender, ethnicity, and region is necessary. Also adjustment for age should match the matching protocol. Please read and cite the following paper:

https://link.springer.com/article/10.1007/s10654-017-0325-0.

A1：Many thanks for reviewer’s suggestion. We have carefully read the paper and cited it in the revised manuscript. In the present study , the subjects are all Han ethnicity and resident of Nanping, so we did not adjust these two matching variables. However, according to the matching protocol, we have adjust sex and age in all analyses of the revised manuscript.

Q2:As said above, adjustment for age shoud reflect the matching protocol; otherwise bias can occur. Please carefully read and cite the paper I suggested before.

A2：Many thanks for reviewer’s suggestion.We have read and cite the paper. In order to reflect the matching protocol, when adjusted for age, we entered a term for residual age into the regression analysis (page 7 and 11). Because we input age as a classified variables rather than continuous variables in the previous analysis, so the result was similar after entered a term for residual age into the regression.

Reviewer: 4

Reviewer Name: MARILYN CYR

Q1- The sample size calculation (page 5) is not sufficiently described. What formula (or specific function in a software calculator) was used and what were the variables & values input (with sufficient details to allow one to replicate these analyses)? Importantly, were all the covariates included in the analyses taken into account in the power analyses? If they were not, they should absolutely be, especially given that the authors state on Pages 1 and 14 that “the study had sufficient power to investigate interactions between nut intake and other risk factors…”.

A1: Many thanks for reviewer’s suggestion. We have added the information about the sample size calculation (formula, variables & values input).(page 5) in the revised manuscript. The covariates did not included in the analyses taken into account in the power analyses. Therefore, we have revised the related sentences in the revised manuscript (page 2 and 15).

Q2- Relatedly, the expected OR (0.74) used in this power analyses was taken from a single study reporting the association between physical activity and NAFLD.

A) What is the justification for expecting a similar effect from nut consumption than from physical activity?

B) If justified, it should be clearly mentioned that the power calculation was based on a prior study (Katsagoni et al., 2017) reporting an association between physical activity (not nut consumption) and NAFLD. Otherwise, as it currently reads, the citation is misleading.

A2: Sorry for our carelessness and many for reviewer’s suggestion. Actually, in the present study,the sample size calculation was based on a prior study (Table3, Katsagoni et al., 2017) reporting an association between nut consumption(not physical activity) and NAFLD (OR = 0.72). However, because of our carelessness, we wrote 0.72 as 0.74, and we have corrected it in the revised manuscript (page 5).

TABLE 3. LOGISTIC REGRESSION ANALYSIS MODELS, EXPLORING THE ASSOCIATION BETWEEN LIFESTYLE CHARACTERISTICS AND THE LIKELIHOOD OF THE PRESENCE OF NONALCOHOLIC FATTY LIVER DISEASE (N=100 CASES AND 55 CONTROLS)

	Model 1[a]			*Model 2*[b]			*Model 3*[c]		
	OR	*95% CI*	P	*OR*	*95% CI*	P	*OR*	*95% CI*	P
Physical activity (per 100 MET-min)	0.78	0.67–0.91	**0.001**	0.77	0.66–0.91	**0.002**	0.74	0.61–0.89	**0.002**
Optimal sleep duration[d]	0.50	0.15–0.97	**0.04**	0.52	0.22–1.24	0.14	0.38	0.14–1.01	**0.05**
Nuts (servings/day)	0.56	0.33–0.94	**0.03**	0.61	0.38–0.98	**0.04**	0.72	0.41–1.25	0.24
Vegetables (servings/day)	0.94	0.77–1.15	0.57	0.95	0.77–1.18	0.64	1.01	0.79–1.29	0.96
Sweets (serving/day)	2.13	1.30–3.48	**0.003**	2.24	1.33–3.78	**0.003**	2.13	1.22–3.71	**0.008**
Coffee (times/day)	0.67	0.48–0.93	**0.01**	0.68	0.49–0.94	**0.02**	0.72	0.49–1.04	0.07

Figures in *bold* are statistically significant.
[a]Model 1: adjusted for age, sex.
[b]Model 2: adjusted for age, sex, waist circumference, HOMA-IR.
[c]Model 3: adjusted for age, sex, waist circumference, HOMA-IR, adiponectin, and TNF-a.
[d]Optimal sleep duration: ≥7 and ≤9 hr sleep per day.
CI, confidence interval; OR, odds ratio.

VERSION 3 – REVIEW

REVIEWER	Mohammad Ali Mansournia Tehran University of Medical Sciences, Iran
REVIEW RETURNED	25-Jun-2019

GENERAL COMMENTS	The authors' revisions are adequate. As a very minor point, I noticed that the names of authors in references 19-23 are abbreviated and need revisions.

REVIEWER	Marilyn Cyr New York State Psychiatric Institute
REVIEW RETURNED	12-Jul-2019

GENERAL COMMENTS	The authors have answered my comments. I still believe the paper would be stronger if the power analyses included the relevant covariates included in the main analyses. It is not very useful to know that the sample is large enough to detect an association between nut consumption and NAFLD in the absence of other factors, if that's not what ends up being tested. In conclusion, these power analyses are inconclusive as to whether the sample size was sufficient to detect the association when other confounds are taken into account. The authors removed the statements about having sufficient power to investigate interactions between nut intake and other risk factors, but they have not added a statement noting that this potential lack of power is a major limitation. What is unfortunate, is that they may very well be sufficiently powered. We just don't know because this was not assessed.

VERSION 3 – AUTHOR RESPONSE

Reviewer: 3
Reviewer Name: Mohammad Ali Mansournia
Institution and Country: Tehran University of Medical Sciences, Iran
Q: The authors' revisions are adequate.
As a very minor point, I noticed that the names of authors in references 19-23 are abbreviated and need revisions.
A:Sorry for our carelessness and many for reviewer's suggestion. We have amended the names of authors in references 19-23 in the revised manuscript (please see page 19-20).
Reviewer: 4
Reviewer Name: Marilyn Cyr
Institution and Country: New York State Psychiatric Institute
Q: The authors have answered my comments. I still believe the paper would be stronger if the power analyses included the relevant covariates included in the main analyses. It is not very useful to know that the sample is large enough to detect an association between nut consumption and NAFLD in the absence of other factors, if that's not what ends up being tested. In conclusion, these power analyses are inconclusive as to whether the sample size was sufficient to detect the association when other confounds are taken into account.
The authors removed the statements about having sufficient power to investigate interactions between nut intake and other risk factors, but they have not added a statement noting that this potential lack of power is a major limitation. What is unfortunate, is that they may very well be sufficiently powered. We just don't know because this was not assessed.
A: Many thanks for reviewer's comment. We absolutely agree with your suggestion, and we have added a statement noting that this potential lack of power is a major limitation in the discussion section of the revised manuscript (page 15).