Author's response to reviews

Title: A Prospective Study of Dietary Selenium Intake and Risk of Type 2 Diabetes

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Author's response to reviews: see over
Dear Dr. Hesketh,

Please find enclosed our revised manuscript which addresses the reviewers’ comments. What follows is a point-by-point response to the comments provided as part of the review process. Please be aware that in the revised manuscript we have used the yellow "highlighting" feature in Word to mark the areas that have been modified compared to the original submission.

REVIEWER 1

1. **Accuracy of FFQ to assess dietary selenium intake**

   *Re:* We have acknowledged this as one of the limitations of the present manuscript. Despite this potential issue, however we have attempted to support the validity of our intake data as detailed in the manuscript. In addition to the points discussed in the original submission, we would like to add what follows. *First,* there are studies showing good correlations between dietary selenium intake from FFQ and biomarker levels (ref. 30-31). We have further examined this issue by using the 24h-recall questionnaire from NHANES 2003-2004, and found significant correlations between serum selenium and total daily selenium intake (p = 0.0005). Specifically, for each 100 µg/day increase in dietary intake, serum selenium increases by 5 µg/L. *Second,* most of the knowledge we have accumulated, over the past 40 years, on the role of micro and macro-nutrients in chronic disease epidemiology come from dietary intake data. *Finally,* use of dietary data may convey different information than biomarkers for the reasons explained in the manuscript, and should not be merely interpreted as a surrogate measure. Please notice that we detail and comment on these limitations extensively in the Discussion, and we believe that readers get a fully informed and balanced perspective on the data with the information provided.

2. **1,290 women could not be re-contacted over the follow-up and were further excluded. The authors need to compare those who were lost during follow-up with those who remained in the cohort to see whether loss-to-follow up is likely differential or not.**
Re: Following the reviewer’s request, we have provided these additional
details in the supplementary material (table 1) enclosed with our response
letter. Indeed, participants who were lost to follow-up were significantly older
than participants who completed the follow-up. However, there was no
difference in the average dietary selenium intake between the two groups,
which reduces the likelihood of major bias in our study.

3. Why a logistic regression rather than a Cox regression?

Re: As detailed in the methods’ section, diabetes ascertainment and
verification was based on multiple sources of information (i.e. self-report of a
physician diagnosis, use of antidiabetic medication, or a hospitalization
discharge with record linkage to hospital and prescription databases).
Consequently, dates of diabetes diagnosis were not always available or
comparable, hence the use of logistic regression instead of Cox regression.

REVIEWER 2

4. Odds Ratios of the other independent variables entered in the model.

Re: Following the reviewer’s request, we have provided these additional
details in the supplementary material (table 2) enclosed with our response
letter. Results are as expected. For example, age and BMI are associated with
higher diabetes risk.

5. Could the authors enter selenium intake as a continuous variable in the
model?

Re: Indeed, selenium was used as a continuous variable as well, by computing
the odds ratios associated with a 10 µg/day increase in selenium intake in the
revised analyses.

6. Cut-offs for energy intake

Re: We would like to clarify that we have not used absolute values of energy
intake but the ratio of total energy intake (determined from the food frequency
questionnaire) to basal metabolic rate, which takes into account the individual
body weight and height, age and estimated physical activity. In addition, the
suggestion to exclude participants in the lowest and highest quintiles (40% of
the study population!) seems quite drastic in our opinion.

7. Was physical activity assessed in the health questionnaire?

Re: Unfortunately, physical activity was not assessed in the ORDET
questionnaire. We have acknowledged this issue in the revised manuscript.

8. What was the rationale of including animal proteins, saturated fat but
then not including carbohydrates (refined and unrefined)?
Re: Animal proteins are linked both to diabetes risk and selenium intake, because red meat is the main food source of selenium in the ORDET study. However, following the reviewer’s suggestion, in the revised manuscript we have included total carbohydrates as well in multivariate analyses (fully-adjusted model). Risk estimates are only slightly attenuated.

9. The discussion (5 pages) is wordy and should be more concise and simply focused on the interpretation of the results and more concisely tried to understand the potential mechanisms of the association between selenium and diabetes risk.

Re: Following this reviewer’s suggestion, we have substantially shortened the discussion in the revised manuscript.

REVIEWER 3

10. Table 4 is titled “Relative Risk” but throughout the results the estimates are referred to as odds ratios.

Re: We have amended this inconsistency and used the terminology “odds ratios” throughout the revised manuscript and tables.

11. Can the authors clarify how test for trend was performed?

Re: Tests for trend across selenium intake quintiles were derived from likelihood ratio tests comparing models with and without a variable including the median selenium intake at each quintile as a continuous variable. We have clarified this issue in the methods’ section of the revised manuscript.

12. Low cumulative incidence of diabetes

Re: The hospital and prescription databases, in Italy, virtually include the vast majority of the diabetes cases and medication, because of the universal coverage of the national health system. However, as case identification was based on self-report, underestimation of type 2 diabetes incidence in the ORDET study is likely. In addition, given the voluntary nature of the study population, we cannot rule out the potential for a ‘healthy volunteer’ bias, which is likely to produce a lower incidence of type 2 diabetes as compared to samples randomly selected from the general population. We have briefly addressed this issue in the revised manuscript.

13. In the last paragraph of the results section the authors report that the odds ratio associated with a 50ug/d increase in selenium intake is 3.51. 50ug/d seems like a large increment. What was the rationale for this amount when the mean (SD) of selenium intake was 60.9 (1.11) and 56.8(0.212) for cases and non-cases, respectively?
Re: Following this reviewer’s suggestion, in the revised analyses we have reported the odds ratios associated with a 10 µg/day increase in selenium intake [OR =1.29 (95% CI: 1.10, 1.52) in the fully-adjusted model].

14. How representative are the participants of the general population?

Re: As described in the manuscript, women were volunteers from the general population who had learned of the study at public meetings, through advertising, or at breast cancer early-diagnosis units.

15. The response rate of 79% is excellent. Were there any significant differences between those who agreed and refused to participate?

Re: We have provided these additional details in the supplementary material (table 1) enclosed with our response letter.

16. The authors cite the InterAct Study and say that it’s a collaboration of nine European countries with 500,000 subjects. They give the URL—the number of EU collaborators on the site seems to vary from eight to 10 and the number of participants they show is 350,000

Re: We have provided updated details regarding the InterAct Study in the revised manuscript.

We would like to thank you and the reviewers for thoughtful comments and suggestions. We truly appreciate your interest in our work. We believe that as a result of the review process our paper has improved and hope that it is now acceptable for publication in BMC Public Health.

Please send all correspondence to my attention.

Look forward to hearing from you.

Sincerely,

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