Author’s response to reviews

Title: Effect of omega-3 fatty acid supplementation on cancer incidence, non-vascular death, and total mortality: a meta-analysis of randomized controlled trials

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Author’s response to reviews:

Dear editor,

Thanks for your kind reply, and thanks for the reviewers’ beneficial comments. We have revised the manuscript according to the reviewers’ comments and the point to point response is enclosed to this file. The reply was noted in RED.

Response to editor:

Q1. This is a relevant Meta analysis. Many meta analysis has evaluate effect of omega 3 fatty acid however end these endpoint to my knowledge have not been explored.

R1. It is pleasing to have acknowledged our diligence in conducting and writing up this systematic review. And we appreciate the referee’s constructive suggestions. The details of responses to the referees’ comments regarding the content of the manuscript are listed as follows:

Q2. Authors included works of Singh RB and al in lancet 2002. This team has been suspected of fraud. Unless the suspicion as been lifted it should this paper should be excluded from the meta analysis.

R2. We agree with reviewer’s opinion that works if Singh RB should be excluded from our meta-analysis. We have already made this change in the revised manuscript.

Q3. Results for cancer and non cardiovascular mortality are clearly non significant results. In my opinion this is the main finding of the meta analysis.

R3. Thanks for your kind reply, the main purpose of this study was to conduct a meta-analysis to evaluate the effect of omega-3 fatty acid on the risk of cancer incidence, nonvascular death, and total mortality.

Q4. Results for total mortality are less clear and should be explore further. The forest plot suggests that stronger effects are observed in smaller studies suggesting publication bias. This should be further explored and discuss. Funnel plot should be presented even if egger test is not significant because this
test has little power (funnel plot should be also presented in supplemental figure for cancer and non cardiovascular mortality).

Size of the study should be also included in the meta regression. There is discrepancy between meta-regression and conclusions leaded by table 2. No moderators are significant in meta-regression conversely mean age, sex and duration of follow up seems to modulate the association in table 2. Test for the effect of moderator should be ad in table 2 to help resolved this discrepancy. Futhermore meta-regression should help to identify independent effect of moderator and lead to a unique conclusion. Using class variable may also be on of the explanation for the discrepancy. This should be explore and discuss by the authors.

Finally as intervention differs widely between studies the heterogeneity is not surprising. It would be hard to include this variable in the meta regression however this point should be discussed.

R4. We appreciated this good suggestion and conducted the calculation of additional subgroup analysis for total mortality to address your attention. Furthermore, we also performed additional analysis for publication bias listed in Figure S5. Finally, Size of the study also included in the meta regression, and found that sample size did not seem to be important factors contributing to the association between omega-3 fatty acid supplementation and total mortality risk.

Q5. Table 2: P value for moderator and number of studies in each group should be ad in table 2. Analysis should be stratified by alpha-linolenic acid and long-chain n-3 PUFA as suggest by reviewer 1.

R5. We thanks this beneficial suggestion and added the number of studies in Table 2. We also conducted additional analysis based on intervention (alpha-linolenic acid and long-chain n-3 PUFA). The details of these change are listed in Table 2.

Q6. The conclusion should not emphasis results of subgroup analysis for mortality. These positive results are isolated and may not be strong results (see comment on meta regression).

R6. We had followed this beneficial suggestion and removed the results of subgroup analysis in Conclusion section.

Q7. Please make the following formatting changes during the revision of your manuscript. Ensuring that the manuscript meets the journal's manuscript structure will help to speed the production process if your manuscript is accepted for publication:

1) Please note that Research articles require the following sections:

Abstract sections
- Background
- Methods
- Results
- Conclusions
Article sections
-Background
-Methods
-Results
-Discussion (Results and Discussion may be combined)
-Conclusions
-List of abbreviations used (if any)
-Competing interests
-Authors? contributions
-Acknowledgements
-References
-Figure legends

Please ensure that these sections are present and clearly labelled as described above. Please do check the instructions for authors on the journal website to ensure that your manuscript follows the correct structure for this journal and article type, and to ensure that you are aware of additional recommendations for formatting that will facilitate handling of your manuscript.

2) For manuscripts with more than one author, all BMC Series journals require an Authors’ Contributions section to be placed after the Competing Interests section. An 'author' is generally considered to be someone who has made substantive intellectual contributions to a published study. To qualify as an author one should 1) have made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) have been involved in drafting the manuscript or revising it critically for important intellectual content; and 3) have given final approval of the version to be published. Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content. Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.

We suggest the following format (please use initials to refer to each author’s contribution): AB carried out the molecular genetic studies, participated in the sequence alignment and drafted the manuscript. JY carried out the immunoassays. MT participated in the sequence alignment. ES participated in the design of the study and performed the statistical analysis. FG conceived of the study, and participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

Contributors who do not meet the criteria for authorship should be listed in an acknowledgements section. Examples of those who might be acknowledged include a person who provided purely technical help, writing assistance, or a department chair who provided only general support.

R7. Thanks for this suggestion. We have already made these change according to Journal formatting.
Response to reviewer 1:

Q1. BMC Public health 00492309 reports a meta-analysis of randomized controlled trials to evaluate the effect of omega-3 fatty acids on the risk of cancer incidence, nonvascular death and total mortality. I have some comments about the study:

R1. Thanks for your kind reply, and thanks for the reviewers’ beneficial comments. We have revised the manuscript according to the reviewers’ comments and listed as follows:

Q2. Authors did not separate alpha-linolenic acid and long-chain n-3 PUFA (from marine source, such as EPA and DHA), they have different biological functions, they should be analyzed separately.

R2. We appreciated this good suggestion and followed it. The details of these change are listed in Table 2. These findings also updated in the revised manuscript and marked “Red”

Q3. A sensitivity analysis should be conducted for each disease (or mortality).

R3. We had followed this beneficial suggestion and conducted sensitivity analyses in the revised manuscript. We added several sentence in Results section: “A sensitivity analysis indicated that the results were not affected by sequential exclusion of any particular trial from all pooled analysis.”; “After sequential exclusion of each trial from all pooled analysis, the results were not affected by exclusion of any specific trial” and “Heterogeneity was observed in the magnitude of the effect across the trials (I²=46.3%; P = 0.02). However, after sequential exclusion of each trial from all pooled analysis, the conclusion was not affected by the exclusion of any specific trial.”

Q4. A bias analysis should be conducted for each disease (or mortality).

R4. We have adopted this beneficial suggestion and conducted funnel plots for cancer incidence, nonvascular death, and total mortality in Figure S5.

Response to reviewer 2:

Q1. This is an interesting and clinical relevant meta-analysis, evaluating the effect of omega-3 supplementation on: 1. cancer incidence, 2. non-vascular death and 3. total mortality. The authors have based their report on 20 randomized, controlled studies after scrutinizing the literature for clinical omega-3 studies. The selected trials are frequently cited and include 69,954 subjects, receiving treatment for either primary or secondary prevention. Follow-up time and dosages differ between studies.

The authors have also evaluated the effect of omega-3 supplementation in subgroups from the studies included: 1. those published before and those after 2000, 2. those with >1000 and those with <1000 included subjects, 3. those with more than 80% and those with less than 80% males, 4. those with a mean age >64 and those with a mean age <64 years, 5. those with primary and secondary prevention, respectively, 6. those with a duration >36 and those < 36 months, and finally 7. according to Jadad score >4 and < 4.
Their data would suggest that omega-3 fatty acids have no significant effects on cancer incidence, non-vascular mortality, or total mortality. Their subgroup analyses would suggest that omega-3 supplementation might play an important role in total mortality in men and if the duration of follow-up is less than 36 months.

R1. Thanks for your kind reply, and thanks for the reviewers' beneficial comments.

Q2. The authors correctly state in their limitations that the trials included were designed to evaluate the effects of omega-3 on cardiovascular outcomes, and not cancer-outcomes. In the total patient population they found a 6%, statistically non-significant reduction in total mortality, and refer to a review paper by Leon et al. (BMJ 2009; 338:a2931) in which the authors conclude that omega-3 supplementation might play an important role in reducing the risk of total mortality due to the improved effects on cardiac death. Other reviews in which this opinion is not shared, should also be mentioned, and the reason for this difference in opinion should be stated. As several of the included studies have an open, controlled design, this may have introduced behavioral differences which may have had an impact on the development of cancer. Were there overall differences in smoking habits between the groups?

R2. We appreciate this good suggestion and we have already added several sentence in Discussion section listed as follows: “Finally, studies with an open, controlled design may have introduced behavioral differences which may have had an impact on the development of cancer. “ and ” We noted that omega-3 fatty acid supplementation reduced the risk of total mortality only when we included trials published before 2000, the sample size was less than 1000, the proportion of men in the population was more than 80%, or participants received alpha-linolenic acid. The reason for these findings could be that several factors might affect the efficacy of treatment, which happened to occur more frequently in male patients, such as smoking status.”

Q3. In the Introduction and Discussion sections the authors claim that cardiac death was reduced in numerous large-scale, randomized, controlled trials for primary and secondary prevention of cardiovascular outcomes. This would not apply to ORIGIN and Alpha Omega Trial which are large randomized, placebo-controlled trials. This issue should be discussed and referenced, as the authors suggest that omega-3 supplementation may play an important role if the duration of follow-up is less than 36 months, claiming that these findings may be related to the early occurrence of sudden cardiac death.

R3. Many thanks for reviewer’s useful comment, and we have already made this change in the revised manuscript according to your suggestion.

Q4. In Table 2 the authors should also state the number of patients in each subgroup.

R4. We thanks this beneficial suggestion and added the number of studies in Table 2. The details of these change are listed in Table 2.

Q5. The third sentence in the second paragraph of the Introduction section lacks
fluency and should be revised.
R5. Thanks for this suggestion and we have already made this change in the revised manuscript.