Author's response to reviews

Title: Dietary intake of n-3 long-chain polyunsaturated fatty acids and risk of myocardial infarction in coronary artery disease patients with or without diabetes mellitus: a prospective cohort study

Authors:

Elin Strand (Elin.Strand@med.uib.no)  
Eva R Pedersen (Eva.Pedersen@k2.uib.no)  
Gard FT Svingen (gard.frodahl.svingen@helse-bergen.no)  
Hall Schartum-Hansen (hall.schartum-hansen@helse-bergen.no)  
Eirik W Rebnord (eirik.wilberg.rebnord@helse-bergen.no)  
Bodil Bjørndal (Bodil.Bjorndal@med.uib.no)  
Reinhard Seifert (reinhard.seifert@helse-bergen.no)  
Pavol Bohov (Pavol.Bohov@med.uib.no)  
Klaus Meyer (klaus.meyer@farm.uib.no)  
J Kalervo Hiltunen (kahiltun@sun3.oulu.fi)  
Jan E Nordrehaug (jan.nordrehaug@helse-bergen.no)  
Dennis WT Nilsen (dnilsen1@getmail.no)  
Rolf K Berge (Rolf.Berge@med.uib.no)  
Ottar Nygård (ottar.kjell.nygard@helse-bergen.no)

Version: 2 Date: 9 September 2013

Author's response to reviews: see over
Dear Editor,

Attached, please find our manuscript with revisions according to the reviewers’ suggestions. We thank the reviewers for their time spent on reading and evaluating our manuscript. We have tried to address their concerns in detail and made changes accordingly, believing this has resulted in an improved manuscript. The responses and changes to the reviewers’ comments are as follows:

Dear Dr Strand,

Your manuscript has now been peer reviewed and the comments are accessible in PDF format from the links below. Do let us know if you have any problems opening the files.

Referee 1:
http://www.biomedcentral.com/imedia/7282258231053167_comment.pdf

Referee 2:
http://www.biomedcentral.com/imedia/1674577046105383_comment.pdf

Referee 3:
http://www.biomedcentral.com/imedia/7756582231060524_comment.pdf

As you will see, the reviewers are generally positive about your study, however each suggest some changes to help improve your manuscript. We would particularly like you to make a
Response: We realize that it would be appropriate to make this clear. Thus, the following sentence has been added to the limitations section of the manuscript on page 14, lines 283-285: “Our study had limited power to detect significant effects due to the smaller sample size of sub-groups and the low event rate primarily in the non-diabetes group.”

We would be grateful if you could address the comments in a revised manuscript clearly indicating any changes made, and provide a cover letter giving a point-by-point response to the concerns.

Please also ensure that your revised manuscript conforms to the journal style (http://www.biomedcentral.com/info/ifora/medicine_journals). It is important that your files are correctly formatted.

We look forward to receiving your revised manuscript by 10 September 2013. If you imagine that it will take longer to prepare please give us some estimate of when we can expect it.

You should upload your cover letter and revised manuscript through http://www.biomedcentral.com/manuscript/login/man.asp?txt_nav=man&txt_man_id=8155102911028416. You will find more detailed instructions at the base of this email.

Please don't hesitate to contact me if you have any problems or questions regarding your manuscript.

With best wishes,
Joanna Denyer, PhD
Assistant Editor
BMC Medicine

REVIEWER 1:
Reviewer's report

Title: Dietary intake of n-3 long-chain polyunsaturated fatty acids and risk of myocardial infarction in coronary artery disease patients with or without diabetes mellitus: a prospective cohort study

Version: 1 Date: 9 August 2013

Reviewer: Philip Calder
Reviewer's report: There remains significant interest in the cardiovascular impact of omega-3 fatty acids. Recent large studies show no mortality advantage in contrast to earlier studies, some of which were also large. However some of these recent studies do suggest that there may be sub-groups who benefit. Hence neutral findings of large studies may be due to a heterogeneous mix of patients/subjects, some of whom benefit and some of whom do not. Here data from a prospective study are used to examine the association between omega-3 intake at study entry and MI in patients with coronary artery disease with and without diabetes. Sample size was about 2300 and follow up was 4.8 years. In diabetics a high intake of omega-3 fatty acids was associated with lower risk of MI (hazard ratio 0.38). Conversely in non-diabetics a high intake was associated with increased MI risk (HR 1.45). The study seems to be carefully done and the manuscript is well written. There will be interest in the findings.

Specific comments:
1. Line 34. “coronary heart disease” should read “myocardial infarction”.
Response: The article of which this sentence refers to states that a high omega-3 intake is recommended in patients with coronary heart disease. Thus, the sentence remains unchanged in the manuscript.
2. Line 44. “are” should read “is”.
Response: We agree. Change has been made in the manuscript.
3. Line 47. 12.536 should read 12,536
Response: We agree. Change has been made in the manuscript.
4. Line 64. I think it would be better if “might” read” would”.
Response: We agree. Change has been made in the manuscript.
5. Line 97. “were” should read “was”.
Response: We agree. Change has been made in the manuscript.
6. Lines 151-152. Recommendations for EPA and DHA are given in mg/day, yet data are analysed and presented as % total energy. If the analysis is repeated expressing data as mg/day are the findings the same?
Response: Yes, the findings based on mg/day are very similar and do not introduce any material changes to the percentage of total energy findings. A comment on this has been added on page 12, lines 240-242: “Estimates based on mg/day amounts of n-3 LCPUFAs were very similar and did not introduce any material changes to the percentage of total energy findings (data not shown).” Risk estimates based on mg amounts are shown in the following table:
Table. Risk of total acute myocardial infarction by dietary n-3 LCPUFA (mg/day) tertiles

<table>
<thead>
<tr>
<th></th>
<th>Non-diabetes (HbA1c &lt;5.7%, n=1012)</th>
<th>Pre-diabetes (HbA1c ≥5.7%, n=1049)</th>
<th>Diabetes (n=317)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age/sex adjusted</td>
<td>Multivariate</td>
<td>Age/sex adjusted</td>
</tr>
<tr>
<td>Number of events</td>
<td>77</td>
<td></td>
<td>88</td>
</tr>
<tr>
<td>n-3 LCPUFA</td>
<td>43</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tertile 1</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>(1.00)</td>
<td>(1.00)</td>
<td>(1.00)</td>
</tr>
<tr>
<td>Tertile 2</td>
<td>1.06 (0.59 to 1.89)</td>
<td>0.95 (0.50 to 1.79)</td>
<td>1.01 (0.60 to 1.71)</td>
</tr>
<tr>
<td></td>
<td>0.36 (0.17 to 0.76)</td>
<td>0.44 (0.20 to 0.97)</td>
<td></td>
</tr>
<tr>
<td>Tertile 3</td>
<td>1.48 (0.86 to 2.55)</td>
<td>1.56 (0.88 to 2.75)</td>
<td>1.10 (0.66 to 1.84)</td>
</tr>
<tr>
<td></td>
<td>0.36 (0.17 to 0.76)</td>
<td>0.37 (0.17 to 0.82)</td>
<td></td>
</tr>
<tr>
<td><em>P</em> for trend</td>
<td>0.16</td>
<td>0.12</td>
<td>0.72</td>
</tr>
<tr>
<td></td>
<td>0.004</td>
<td>0.01</td>
<td></td>
</tr>
</tbody>
</table>

7. Lines 207-218. Are the serum fatty acid data actually of any use in this manuscript. To my mind they do not add anything. I would recommend to remove them. Alternatively you could analyse the relation between omega-3 status and disease outcome.

**Response:** Serum fatty acids are included here because we believe this to be relevant baseline data in relation to the estimated dietary intakes. These currently presented data indicates that serum fatty acids do not necessarily reflect the corresponding dietary intake. To illustrate, serum saturated fatty acids were higher, while omega-6 fatty acids were lower in diabetes patients, compared to the other patients. There was, however, no difference in dietary intake of saturated fat between the sub-groups. In addition, diabetes patients had a borderline significantly higher intake of total PUFAs.

Since serum fatty acids were analyzed in only 723 (30%) of the patients, we did not perform any risk assessments. This would, however, be valuable if we had complete data on all 2378 participants. Believing that fatty acid composition may be of interest to the readers, we suggest that these data remains as originally presented.

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:** I declare that I have no competing interests

**Reviewer's report**

**Title:** Dietary intake of n-3 long-chain polyunsaturated fatty acids and risk of myocardial infarction in coronary artery disease patients with or without diabetes mellitus: a prospective cohort study
This is a well written and conducted study. The study's major and inherent limitation is that it
is not randomised. Epidemiological studies like this one representing an important
contribution to our body of knowledge in omega-3 intake and their effects on cardiovascular
health. They serve to provide impetus for randomised trial. This is what is clearly needed. As
the authors themselves have outlined, there is significant controversy on the role of omega-3
in diabetics with mixed clinical results. A well designed randomised trial targeting the patient
group as outlined by the present results is what is needed.

Response: As we are aware of the clear limitations by doing a prospective cohort study
and the outermost advantages by randomized trials, the current prospective study was
done in a cohort with extensive data collection and follow-up, reducing the
confounding/selection bias to a minimum. Since a high intake of omega-3 may be
disadvantageous in certain patients as indicated here, we believe it would not be ethical
to perform a randomized study targeting this specific sub-group. Instead, it would be
very interesting to study if the current results could be reproduced by dividing previous
larger prospective cohorts or randomized trials into similar sub-groups.

A randomized trial in diabetes patients would be appropriate, although the
recent Origin study in dysglycemic patients did not reveal an effect. In our opinion, the
population represented by the Origin study clearly differed from our diabetes patients
as thoroughly discussed in the manuscript. Thus, it would be interesting to study the
effects through a randomized trial in a diabetic population more similar to the diabetes
group in the current study.

Quality of written English: Acceptable
Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

REVIEWER 3:

Reviewer's report
Title: Dietary intake of n-3 long-chain polyunsaturated fatty acids and risk of myocardial
infarction in coronary artery disease patients with or without diabetes mellitus: a prospective
cohort study

Version: 1 Date: 19 August 2013
Reviewer: Michel de Lorgeril
Reviewer's report: The statistics used in that work are simple and there is no problem with. The problem is in the interpretation because the sample size is rather small, the numbers of endpoints are small and we are in the context of post-hoc observational study with no "a priori" hypothesis ... The data should therefore be taken with precaution; what the authors do well! The study raises interesting questions: 1) the lack of parallel between the omega-3 and fish data, for instance, and 2) the suggestion of different effects in function of the doses and background disease ... In view of the Methods limits, it is difficult to interpret! In fact, these data need confirmation; the best way would be a meta-analysis pooling several studies with same limitations ...

Response: We have added a comment on sample size in the limitations section as previously indicated. In this setting we believe it is appropriate to present the results in this hypothesis generating manner. As discussed above we strongly agree that these findings need confirmation. We suggest a strategy of studying a larger, similar cohort by stratifying into the same sub-groups. A meta-analysis could also be appropriate, depending on studies holding enough clinical data to be able to study the specific sub-group effects.

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests: I receive research grants from The European Communit and from some Food industry, all managed through the School of medicine of the Grenoble university, none of them in direct relation with the present article

We hope that we have addressed all concerns satisfactory and thank you for reconsidering our manuscript.

Sincerely,
Elin Strand (on behalf of the Authors)

Correspondence in relation to the manuscript can be addressed to:
Elin Strand
Institute of Medicine
University of Bergen
Laboratory Building 8th floor
Haukeland University Hospital
N-5021 Bergen
Norway
phone: +4795773587
fax: +4755975890
e-mail: Elin.Strand@med.uib.no