Author's response to reviews

Title: Fish Consumption and Ischemic stroke in Southern Sweden

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Version: 3 Date: 25 July 2011

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

My colleagues and I thank the reviewers, and we modified the manuscript according to most of their suggestions, see below.

Thank you again for considering our manuscript, we hope that you’ll find it in order.

Yours sincerely,

Anna Oudin

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**Answer to Reviewers comments**

**Reviewer Wing-Sze Lo**

1. The rationale of this study seems to be under-develop. It is not clear to me why the authors chose to replicate the Northern Sweden study in the first place. Is it because of the differences in SES characteristics (such as education level and birth country) and dietary patterns, including type of fish intake and cooking methods? To me, the populations from these two regions are similar. Providing overview of fish intake patterns in southern Sweden study may be useful.

*Answer:* We agree with the reviewer that in the previous version of the manuscript, it was not clear enough why we chose to compare our results from northern Sweden with a southern Sweden cohort. The reason was that we were somewhat intrigued by our results from northern Sweden [1] together with contradicting results from another Swedish cohort [2], and that we had access to an already available material from southern Sweden (which originally was created to study health effects of air pollution). In the current version of the manuscript, we’ve rephrased our formulation at page 2: “In a prospective case-control study within Northern Sweden Health and Disease Study, we observed an increased risk of stroke in men reporting fish consumption more often than three times a week, as compared to less than once a month. [1] The association was similar for lean and fat fish consumption. No statistical significant association was found in women. Recently, lean fish intake, but not intake of other types of fish, was observed to
reduce total stroke risk in Swedish women. [2] The disparities in results regarding sex-specific effects and type of fish (lean or fat) between the two Swedish studies are intriguing. We therefore aimed at studying the relationship between ischemic stroke and fish intake once again, this time in an already available data material from southern Sweden.”

2. The authors provide a good description of their methods. However, it may be useful to describe whether the study has made use of any memory aids such as colour photographs, and whether questionnaire has clearly defined what lean/fat fishes are to avoid information bias.

*Answer:* Thank you for that comment, we did as the reviewer suggested and added a sentence about the nature of the fish consumption assessment at page 3: “... Lean Fish intake, and Fat Fish intake (cod, but, pike and perch were mentioned as examples of lean fish, and herring, salmon, trout, lavaret, salmon trout and eel were mentioned as examples of fat fish).

3. It is better to include the male/female ratio of the subjects even sex-specific analyses were done.

*Answer:* Unfortunately we’re not entirely sure what the reviewer is aiming at here, could we please ask for a clarification?

4. The number of case/control in each exposure category should be reported (may be in table format).

*Answer:* We agree with the reviewer and have included a descriptive table (Table 1) with the number of cases and controls stratified for sex and lean/fat fish intake.

5. Have you checked the dose response effect, especially in fat fish intake?

*Answer:* Unfortunately we were not able to check the dose-response effect since our variable was categorical to start with and we had no way to estimate the number median number of fish intake per week in each category.

6. Report if sensitivity analysis is done to handle the recall bias.
Answer: We agree that recall bias is a serious issue in studies where retrospectively self-reported exposure data is collected and we mention recall bias in the Discussion. We did not do a sensitivity analysis specific for this study, however several of the retrospectively self-reported variables (Diabetes mellitus, Hypertension, Atrial fibrillation and Smoking) has been validated in a previous study, as we mention in the Discussion, page 5: “Information on fish intake was self-reported retrospectively in the present study. Validations of the fish-intake variables were not feasible in this setting, but validations of some of the other retrospectively self-reported variables (Hypertension, Smoking, Diabetes mellitus and Atrial fibrillation) suggested that the accordance with register data was generally fair, which can likely be generalized to other self-reported variables in the study, such as the fish intake variables. Given that fish intake is known to be beneficial; it is possible that recall bias was present, but it is less likely that recall bias differ between the effect estimates of fat and lean fish intake. In order to create recall bias away from the null (and thus explain the findings regarding lean fish intake in women) an individual’s inclination to report fish intake would have to depend both on disease status (case/control), sex and type of fish intake reported. Neither the findings regarding fat fish (similar in men and women) nor previous results from the southern Sweden data, support such a differential in recall.”

7. The authors should discuss more about the crudeness of fish consumption categories used in this study. The frequency of meal intake is not necessary the same as the amount of fish consumption.

Answer: We agree with the reviewer that the exposure measure is crude in this study. The frequency of fish consumption does not necessarily correspond to the actual weight of the fish consumed. We added a sentence at page 5 to clarify that: “Moreover, the amount, or weight of fish is not necessarily reflected by how often fish is consumed.”

8. Perhaps more details regarding the generalisability (external validity) of the study results for international interest.

Answer: We agree that external validity is important to discuss, especially in this field, where the association between fish consumption and stroke risk is inconsistent between studies. However, given that the results differ so extensively between different studies, it is hard to assess external validity of any study of this kind.

Minor Essential Revisions
1. Introduction, page 2, 1st paragraph: “life-style related factors” should be “lifestyle-related factors”.
2. Introduction, page 2, 2nd paragraph: suggest to replace “geography” with “geographic regions/areas”.
3. Material and methods, page 3, 1st paragraph: “life style factors” should be “lifestyle factors”; also “response-rate” should be “response rate”.

*Answer to all minor essential revisions:* We thank the reviewer and have changed them according to the reviewer’s suggestions.

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**Reviewer Hong-Bo Shao**

The paper has the following questions that must be answered for continuing process:

1. English expression needs major revision for the all parts of the text;  
   *Answer:* We have gone through the text carefully and improved the language.

2. Many recent ket references are missing out, especially for articles in Nutritional Journal(2005-) and other related Journals such as public health journal(2005-);  
   *Answer:* We agree with the reviewer that the references are sparse in the previous version of the manuscript, and therefore added several references to page 2. However, we had to limit the number of references since this is a short report, thus we selected the ones that seemed the most relevant to our specific aim. Of course, we welcome suggestions on relevant references that should be included.

3. References style should be corrected;  
   *Answer:* We thank the reviewer for noticing that, and we have corrected the reference style according to the style of Nutrition Journal.

4. Statistical data should be provided with detail;  
   *Answer:* We agree with the reviewer and we added a descriptive table with the number of cases and controls stratified for fish intake and sex (Table 1). However, we
were somewhat limited by the format short report, and therefore decided to only report the main results, although we mention that crude estimates and estimates from other models than the main model in the text: “The crude effects were rather similar to the adjusted estimates, although the effect estimates for both lean and fat fish intake were weakened when not adjusted for each other (data not shown). In a model similar to the one used in the northern Sweden study (including the variables Diabetes mellitus, Hypertension, BMI, Smoking, Birth year category and Sex), the fish intake effect estimates were almost identical to those presented here (data not shown).”

5. Previous reports are not introduced enough;

*Answer:* We agree and added several references to the introduction, page 2.

6. How to ensue the uniformity of the tested men in the same surviving environment?

*Answer:* We’re sorry but we’re not entirely sure we understand the question. However, we want to stress that we do adjust for a broad range of confounding factors in the analysis. Interestingly, the effect estimates did not change substantially when adjusting or not adjusting.