Author's response to reviews

Title: Polyunsaturated fatty acid intake and prevalence of eczema and rhinoconjunctivitis in Japanese children: The Ryukyus Child Health Study

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Version: 3 Date: 28 April 2011

Author's response to reviews: see over
April 28, 2011

Melissa Norton, MD
Editor-in-Chief
BMC Public Health

Ms. No.: 5281759824990599
Title   : Polyunsaturated fatty acid intake and prevalence of eczema and rhinoconjunctivitis in Japanese children: The Ryukyus Child Health Study
First author: Miyake Y.

Dear Dr. Norton:

Thank you for your email of April 18, 2011. We are pleased that you are interested in our manuscript for possible publication as an Original Article in BMC Public Health. We appreciate the thoroughness with which the reviewers have considered our manuscript. We have addressed the comments raised by the reviewers and have carefully revised the manuscript. We hope that it is now suitable for publication in your esteemed journal. We understand that final acceptance depends on satisfactory resolution of the points raised by the reviewers.

I am sending the revised manuscript with changes highlighted in red. Description of specific revisions and responses to the reviewers are provided below.

I have checked the entire manuscript thoroughly, and it has been carefully reviewed by an experienced medical editor whose first language is English and who is specialized in the editing of papers written by physicians and scientists whose native language is not English.

We thank you in advance for your consideration. We look forward to hearing from you again.

Yours sincerely,

Yoshihiro Miyake, MD, PhD
Associate Professor of Public Health
Reviewer 1:
This is a well written report of a cross-sectional study on dietary fatty intake, with correct statistical methods and clearly presented results.

Fatty acids intake was estimate from a brief dietary food frequency questionnaire and eczema and allergic rhinoconjunctivitis in Japanese schoolchildren from Okinawa, Japan. Major limitations of the study are its cross-sectional design and the brevity and single measurement of food intake, as acknowledged and discussed by the authors. Their findings do not support a major hypothesis on food and atopic diseases related to the ratio of n-6 and n-3 fatty acids intake.

Rather, a high level of arachidonic acid intake is found to be related to lower prevalence of eczema as well as rhinoconjunctivitis.

Major Compulsory Revisions
1. In the discussion the authors should also pay attention to previous studies (with inconsistent results) for arachidonic acid, including those which measured arachidonic in blood. For instance, the results are consistent with the inverse association between arachidonic acid proportion in blood during pregnancy and risk of eczema in the child (Notenboom, Clin Exp Allergy 2011) or childhood atopic manifestations (Dirix, BrJ Nutr 2009); by contrast Kompauer (Br J Nutr 2005) found a positive association between arachidonic acid and allergic rhinitis in adults in a cross sectional study. The authors should discuss the relation between dietary intake and body status of arachidonic acid, and the timing aspects (developmental phase of the disease (pregnancy, childhood, adulthood).

Response:
We are very grateful for your careful review and insightful comments. We have carefully revised the manuscript according to your remarks.

To address the above-mentioned issue, we added the following passage to the Discussion section:

“With regard to arachidonic acid, our results are in partial agreement with those from the KOALA Birth Cohort Study, which showed that the risk of eczema in the first 12 months of life significantly decreased with increasing levels of arachidonic acid in plasma phospholipids in pregnancy, although there was no relationship between the arachidonic acid levels and eczema later in life [28]. The current results are inconsistent with those of a cross-sectional study showing a positive association between concentrations of arachidonic acid in serum phospholipids and hay fever in German adults [29]. The direction of the relationship between arachidonic acid and allergic disorders might change according to the timing of the exposure: an inverse relationship may exist starting in utero and continuing through childhood whereas a positive relationship may exist in adulthood.” (Page 9 Line 24 – Page 10 Line 7 in the revised manuscript).

The following references, mentioned in the above passage, were also added:

We did not cite the paper that you mentioned (Dirix et al, Br J Nutr 2009; 102: 387-397) because
the outcomes in that paper were not allergic disorders, but rather selected immune-related variables.

2. Discussion: please give more background information on the dietary sources of arachidonic acid (meat, eggs, dairy products?). Since some of these products may also be potential sources of trans fatty acids as well as n-3 LCPUFAs (depending on the local dietary habits, available foods, and production factors), these fatty acids could be indicators for each other and for their dietary sources. Please also indicate the levels of transfatty acids in the typical diet of Okinawa children, and whether these have changed over time.

Response:
To address this issue, we added the following passage to the Discussion section: “Eggs, meat, fish, milk, and sweets are major sources of arachidonic acid intake among Japanese people [35]. Meat, milk, and sweets are also major sources of trans fatty acid intake among Japanese people [36]. Arachidonic acid intake may be to some extent correlated with trans fatty acid intake.” (Page 11 Lines 19-22 in the revised manuscript).

The following references, mentioned in the above passage, were also added:

Unfortunately, we cannot obtain data on trans fatty acid intake in children in Okinawa.

Minor Essential Revisions
1. Please add the range of the fatty acid levels for the quintiles in table 2.

Response:
We decided not to change the formatting of Table 2 because adding the ranges would make the table appear cluttered. For example, the ranges of arachidonic acid intake in the first, second, third, fourth, and fifth quintiles were -0.325857 to 1.203576, 1.20362 to 1.44269, 1.44277 to 1.66032, 1.66037 to 1.94528, and 1.94535 to 5.35510 g/day, respectively. There is not enough room to replace the quintile medians in the original manuscript with these ranges.

2. Discussion: please pay attention to the outcome measurement (ISAAC): is ISAAC validated for Japanese children, is there independent confirmation (e.g. from medical records) of eczema and rhinoconjunctivitis?).

Response:
This issue is now discussed at the end of the sixth paragraph of the Discussion in the revised
manuscript (Page 12 Lines 7-11 in the revised manuscript). The sentence “The outcomes under study were assessed by validated core questions in the International Study of Asthma and Allergies in Childhood phase-I study” was revised to “The core questions used to assess the outcomes under study had been validated by the International Study of Asthma and Allergies in Childhood phase-I study, but validation tests of the questions had not been performed in this population. Moreover, no attempt was made to ascertain outcome status through reviews of medical records.” The ISAAC questions have been validated for Japanese children by the Research Committee on Descriptive Epidemiology of Allergic Diseases from the Ministry of Health, Labor, and Welfare, Japan, but because no academic evidence of their applicability is available, we cannot make a clear statement on this issue. In this study, no data collected through more accurate means of assessment were available.

**Discretionary Revisions**

1. It would be extremely useful to have more background information on dietary sources of fatty acids, for instance in a table with major food products or groups and fatty acids intake.

   **Response:**
   Thank you very much for this insightful comment. I think that your comment is reasonable, but other studies will have to examine the relationship between food intake and allergic disorders using data from the RYUCHS. We hope that, after being provided with some information on dietary sources of PUFAs in this paper, readers will be inspired to probe the relationships between such dietary sources and the outcomes under study. We have therefore not added any information on dietary sources of PUFAs excluding arachidonic acid. We hope you will agree that this was a reasonable decision.

2. Moreover, I would suggest that the authors add results on intake of relevant food groups and prevalence of eczema and rhinoconjunctivitis in the present paper.

   **Response:**
   Thank you very much for this insightful comment. For the aforementioned reason, we did not add results on the relationship between the intake level of any particular food and the outcomes under study. We hope you will agree that this was a reasonable decision.

3. Are the authors able to estimate the intake of transfatty acids? Based on an ecological survey in Europe, Weiland (Lancet 1999) suggested that allergies are related to high transfatty acids intake. A recent study suggested that this depends on the source of trans fatty acids: trans fatty acids from rumenic source was related with lower risk of infant eczema (Thijs, Allergy 2011). Could the authors attempt to estimate trans fatty acid intake and report the association with eczema and rhinoconjunctivitis?

   **Response:**
   We cannot estimate *trans* fatty acid intake because the Standard Tables of Food Composition in Japan do not include information on *trans* fatty acids.

   We added the following passage to the Discussion section: “In this study, data on *trans* fatty acid
intake were not available because the Standard Tables of Food Composition in Japan do not include information on \textit{trans} fatty acids. In the KOALA Birth Cohort Study, higher concentrations of \textit{trans} fatty acids from a rumenic source in human breast milk were associated with a lower risk of eczema at 2 years of age [37]. In contrast, an ecological study using data from the International Study of Asthma and Allergies in Childhood showed positive relationships between \textit{trans} fatty acid intake and the prevalences of asthma, eczema, and rhinoconjunctivitis [38].” (Page 11 Line 22 – Page 12 Line 1 in the revised manuscript).

The following references, mentioned in the above passage, were also added:

4. Discussion p. 11: here results are presented on the characteristics of excluded participants, I would prefer to see these data in a separate column in table 1 rather than reading new data in the Discussion.

Response:
This issue is addressed in the following passage, which was placed in the Discussion section in the original manuscript, but has now been moved to the beginning of the Results section (Page 7 Lines 13-23 in the revised manuscript).

“Data were incomplete for 5497 participants who were therefore subsequently excluded. Nevertheless, these excluded participants did provide information that allowed us to determine some differences between them and the participants who were included. Compared with the 5497 excluded subjects, the 23,388 included subjects were less likely to have no siblings, former smokers in the household, mothers who were less than 28 years of age at the time of the child’s birth, and mothers with a history of asthma and atopic eczema, and were more likely to be young and to have a personal history of eczema and both fathers and mothers with high educational levels. There was no statistically significant difference between the excluded participants and study subjects with regard to the prevalence of rhinoconjunctivitis, sex, paternal history of asthma, atopic eczema, and allergic rhinitis.”

Compared with the 5497 excluded participants, study subjects were more likely to have a low intake of n-3 and n-6 PUFAs. However, when 149 children with extremely low or high reported energy intake were excluded from the 5497 excluded participants, the study subjects were more likely to have a high intake of n-3 and n-6 PUFAs compared to the remaining 5348 excluded participants. To avoid confusion, we have not included data on the excluded participants in Table 1.

Instead, we addressed the issue by adding the following sentence to the Results section: “It should be noted, however, that the total of 5497 excluded participants includes 149 participants who were excluded due to extremely low or high reported energy intake; when these 149 were excluded from the excluded participants, study subjects were more likely to have a high intake of n-3 and n-6 PUFAs in comparison to the remaining 5348 excluded participants.” (Page 7 Lines 23-28 in the
5. Discussion: could the authors provide more information on pollutants in local fish?

Response:
We added the following passage to the Discussion section: “One study has found a significant correlation between fish consumption and hair mercury levels, reporting that hair mercury levels were much higher in Japanese women residing in Canada than in Canadian women [34].” (Page 11 Lines 15-18 in the revised manuscript).

The following reference, mentioned in the above passage, was also added:

Reviewer 2:
The manuscript provides useful data from a large samples for the relationship of PUFA intake and prevalence of eczema and rhinoconjunctivitis when the daily n-3 PUFA intake is not low. However there are some flaws which require to be taken into account.

Major Compulsory Revisions

Methods:
The authors have mentioned the self-administered questionnaires were completed by the junior high school students themselves and/or their parents. It should be clarified that selection bias could not be happened by different groups of replier.

Response:
Thank you very much for your careful review and insightful comments. We have carefully revised the manuscript in response to your remarks.

According to the newly added reference #39 in the revised manuscript, dietary data on children and adolescents is, in the main, prone to reporting error, and this reporting bias is not associated systematically with particular age groups or dietary survey techniques.

We added the following passage to the Discussion section: “The BDHQ was answered by parents in the case of elementary schoolchildren and by students and/or parents in the case of junior high school students. Dietary data on children and adolescents is, in the main, prone to reporting error [39]. We cannot predict whether possible selective misreporting of dietary intake would systematically deflate or inflate the estimates of these dietary variables. In any case, random misclassification in our study was likely, and it probably weakened the evidence for any true relationships.” (Page 12 Lines 21-26 in the revised manuscript).

The following reference, mentioned in the above passage, was also added:
It should be explained whether the self-reported body weight and height were validated or not. If they were not validated it can be weakness of the study.

**Response:**
To address this issue, we added the following passage to the Discussion section: “Information on self-reported body weight and height was not validated, and thus body mass index might have been biased.” (Page 12 Lines 27-28 in the revised manuscript).

**Minor Compulsory Revisions**

**Background:**
It is suggested to add some explanation about the prevalence and importance of eczema and rhinoconjunctivitis in the world and in the area of the study.

**Response:**
To address this issue, we added the following paragraph to the beginning of the Introduction section: “The prevalences of eczema and rhinoconjunctivitis have increased rapidly over the last few decades all over the world [1]. One study of Japanese elementary schoolchildren showed that the lifetime prevalence of eczema increased from 15.3% in 1985 to 24.2% in 1993 before decreasing to 16.5% in 2006, while the prevalence of rhinitis increased from 11.6% in 1983 to 24.7% in 2006 [2].” (Page 3 Lines 2-6 in the revised manuscript).

The following references, mentioned in the above passage, were also added:


**Methods:**
Finally only 61.2% of the eligible subjects were included in the current analysis. The possibility of selection bias has been inevitable. Especially according to the discussion (page11 lines2-6) those who were included and those who were excluded (14.4% of excluded subjects or the children whose questionnaires contained missing or illogical data on the variables under study) were different in some variables. It can be very important limitation of the study.

Also main variables such as prevalence of eczema and n-3 & n-6 PUFA intake should be compare between those who were included and those who were excluded.

**Response:**
In response to a comment from Reviewer 1, the following passage which addresses this issue was moved from the Discussion section to the beginning of the Results section (Page 7 Lines 13-23 in the revised manuscript).
“Data were incomplete for 5497 participants who were therefore subsequently excluded. Nevertheless, these excluded participants did provide information that allowed us to determine some differences between them and the participants who were included. Compared with the 5497 excluded subjects, the 23,388 included subjects were less likely to have no siblings, former smokers in the household, mothers who were less than 28 years of age at the time of the child’s birth, and mothers with a history of asthma and atopic eczema, and were more likely to be young and to have a personal history of eczema and both fathers and mothers with high educational levels. There was no statistically significant difference between the excluded participants and study subjects with regard to the prevalence of rhinoconjunctivitis, sex, paternal history of asthma, atopic eczema, and allergic rhinitis, or maternal history of allergic rhinitis.”

This passage mentions the difference between the excluded participants and the study subjects in terms of personal history of eczema.

We added the following sentence to the Results section: “It should be noted, however, that the total of 5497 excluded participants includes 149 participants who were excluded due to extremely low or high reported energy intake; when these 149 were excluded from the excluded participants, study subjects were more likely to have a high intake of n-3 and n-6 PUFAs in comparison to the remaining 5348 excluded participants.” (Page 7 Lines 23-28 in the revised manuscript).

We also added the following sentence to the Discussion section: “In fact, as mentioned above, there was a significant difference between the excluded participants and study subjects with regard to several factors.” (Page 13 Lines 2-4 in the revised manuscript).

**Discussion:**
Reasonable and probable cause of different results between "the relationship of PUFA intake & eczema" and "the relationship of PUFA intake & rhinoconjunctivitis" should be explained.

**Response:**
To address this issue, we added the following passage to the Conclusion section: “Because different mechanisms might be involved in the manifestation of eczema and that of rhinoconjunctivitis, there might also be differences in the detrimental effects of α-linolenic acid and linoleic acid.” (Page 14 Lines 1-3 in the revised manuscript).

**Discretionary Revisions**

**Discussion:**
For conforming to the point that mentioned in the page 10 lines 3-5, it is suggested to add the comparison of the prevalence of eczema & rhinoconjunctivitis in the area with less n-3 PUFA intake and the area of the present study.

**Response:**
Regarding the statement in the original manuscript to which you refer here, we would like to mention that inverse relationships between n-3 PUFA intake and eczema and rhinoconjunctivitis might be detected in populations whose fish intake is low, but not in Japanese people who consume large amounts of fish. The range of fish intake in the USA or UK is much narrower than that in
Japan and is likely to be entirely included in the first quintile of fish intake among Japanese people; i.e. fish intake levels that fall into both the first and fifth quintiles in the UK are likely to be included in the first quintile of fish intake in Japan. Although fish intake in the fifth quintile was significantly inversely related to eczema in contrast to fish intake in the first quintile in a UK study, it is uncertain whether such an inverse relationship might be detected in Japan. In the end, this statement is not supported by data from an ecological study. In fact, in the mainland of Japan, the prevalence of eczema is high (14.5% in Suita City as mentioned in the text). There is probably no inverse ecological association between fish intake and eczema that can be detected in all countries. We thus have not made any revision in response to this comment.

Page 10 line 22-23: Opposite of the author’s opinion it seems people with problem (eczema and rhinoconjunctivitis) might be more aware of possible ill effects of diet.

Response:
Thank you very much for this insightful comment. Certainly, people with eczema and/or rhinoconjunctivitis are likely to be aware of any possible ill effects associated with a particular diet or food allergy. Even so, they are not likely to be aware of the possible ill effects of PUFA intake. The word “diet” in the Discussion section in the original manuscript was therefore changed to “PUFA intake” (Page 12 Line 18 in the revised manuscript).

Conclusion:
It is suggested to add that explanation that the result of the study just might be replicated in communities with high n-3 PUFA intake.

Response:
The phrase “clarify these associations” in the Conclusion section of the original manuscript was changed to “ascertain whether the relationships observed in this study are replicated in other populations, especially in populations with high n-3 PUFA intake” (Page 14 Lines 6-7 in the revised manuscript).