PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	A prospective study on maternal occupational exposure to asthmogens during pregnancy and the risk of asthma in the 7 year-old children.
AUTHORS	Schlünssen, Vivi; Christensen, Berit; Thulstrup, Ane Marie; Hougaard, Karin; Skadhauge, Lars; Frydenberg, Morten; Hansen, Kirsten

VERSION 1 - REVIEW

REVIEWER	Malcolm Sears, Professor of Medicine, McMaster University, Canada
REVIEW RETURNED	21-Dec-2012

THE STUDY	The authors have attempted to examine the effects of maternal exposure to known environmental agents related to occupational exposures during pregnancy and relate this to development of asthma in the offspring. I have a number of issues to raise concerning this study. 1) Only 42% of the mother child pairs were eventually eligible for analysis (41,725 of 100,418). The authors give reasons for this substantial reduction in the database but the relatively low response rate (questionnaires were answered by 45,687 of the eligible 78,813 mother child pairs, a 58% response rate) is worrying. 2) While the data provides knowledge of the occupation of the mother, this is not necessarily evidence of exposure. Were questions asked about actual job content and details of actual exposures assessed, either by questionnaire or objective means? 3) It is not clear whether change of occupation during pregnancy was accounted for. 4) My major concern is the definition of atopy both in the parent and in the child. Among the children, having atopic dermatitis ever was used as a proxy for atopy. There are many children who are atopic, defined by a positive skin test or elevated serum IgE, who do not have atopic dermatitis but have other manifestations of allergy or sometimes are entirely clinically asymptomatic despite their evident sensitization. Atopy does not always result in atopic dermatitis. Similarly mothers were defined as atopic based on ever reported asthma, rhinitis or atopic dermatitis. Many adults show skin sensitization defining atopy without having clinical allergic disease. 5) Outcomes of asthma and atopy in children are clearly different in boys and girls, and the data should be examined by gender rather than both sexes together. 6) Table 2 illustrates the problem I have with the definition of atopy. The prevalence of asthma in “atopic” children (i.e those with atopic dermatitis) was 23% in total, and in “non-atopic” children 14%. Epidemiologic studies with measurements of atopy, especially by age 7 years would suggest that this prevalence of asthma in allegedly non-atopic children is high. The authors should state that

	this is the prevalence of asthma in children who have not manifested atopic dermatitis rather than calling them non-atopic. 7) In the discussion, the authors add additional results e.g. second paragraph, after discussing a Swedish study, they state that “we also found that atopic boys…”. Results should be in the results section. This gender difference is important and as noted above should be provided for all exposures and outcomes within the results sections. 8) The sixth paragraph of the discussion states that they did not find convincing differences between atopic and non-atopic children for associations between maternal occupational exposures and asthma in the children. This maybe influenced by the imprecise definition of atopy, based on clinical atopic dermatitis. While the study finding is not totally invalidated by that, it is substantially weakened. 9) The discussion overall is long and difficult to follow. It could be much improved by shortening. 10) In discussing limitations of the study, the authors do reflect on the lack of objective and specific measures for atopy. They however, indicate that questions regarding atopic dermatitis have been validated against clinical investigation for atopic dermatitis and were deemed suitable for defining atopic dermatitis in epidemiologic studies. However this does not get around the fact that atopic dermatitis, no matter if highly validated, is not a substitute for a definition of atopy. 11) I am confused by the data sharing statement on page 28. Did the authors not undertake their own statistical analysis? If this was all analyzed by Statistics Denmark, without the input of the clinical investigators, I would have some concerns about understanding of the data especially the issues around atopy as already mentioned. 12) In several of the figures, the word “just” and “common” are used. Just should be replaced by "adjusted" and common by "combined".

REVIEWER	Nara Tagiyeva, research fellow, University of Aberdeen, UK. I have no competing interests to declare.
REVIEW RETURNED	23-Dec-2012

GENERAL COMMENTS	This is an interesting and well written paper on maternal occupational exposure during and after pregnancy and the risk of asthma in 7-year old children in a large birth cohort study. I have a few comments /questions to the authors: -the statement in the abstract about the associations with prenatal & postnatal exposures is misleading, as they are not significant. -as the authors mentioned, HMW & LMW categories include a wide range of agents and the child's immune system, allergy and/or asthma development may be influenced by some of these but not others -I am not comletely satisfied with the exposure categorisation (tables 2 & 3, subheadings "outcome" & "asthma" in the latter are misplaced) that groups together occupational exposures to substances and job titles -table 4 explores the association with specific occupations, however some job titles are presented as individual agents/ substances (plastic, paper, stone, wood) which is confusing, I thought at first that the table presented the relationship with agents/ substances mixed with occupations. - I do not understand the sentence that starts with "The Impact of

	offspring...." (Lines 33-36) -could the authors please explained why they chose to use atopic dermatitis, but not rhinitis as a marker of atopy? -while prenatal codes were derived from the questionnaire-based job descriptions, postnatal codes are based on the data from the Statistics Denmark. Would authors want to discuss implications of this for the results if any?

VERSION 1 – AUTHOR RESPONSE

Reviewer: Malcolm Sears, Professor of Medicine, McMaster University, Canada
1) Only 42% of the mother child pairs were eventually eligible for analysis (41,725 of 100,418). The authors give reasons for this substantial reduction in the database but the relatively low response rate (questionnaires were answered by 45,687 of the eligible 78,813 mother child pairs, a 58% response rate) is worrying.

(We agree the loss to follow up is substantial. By loss to follow up analysis we have tried to display the (minor) differences in characteristics between participants and non-participants, and furthermore we can refer to earlier publications from the DNBC cohort suggesting loss to follow-up in the cohort to have a minor impact on explored association. We have underlined this weakness in the study, please see page 27-28)

2) While the data provides knowledge of the occupation of the mother, this is not necessarily evidence of exposure. Were questions asked about actual job content and details of actual exposures assessed, either by questionnaire or objective means?

(This is a very relevant question. Unfortunately we only had information about job, and no direct information about exposures. Although it can be difficult to evaluate the quality of self-reported exposure information, it could have been of interest also to have this kind of information in this study. The limitations of the exposure assessment in our analysis are stated in the discussion, page 28)

3) It is not clear whether change of occupation during pregnancy was accounted for.

(We have used information about job from the telephone interview performed in 12-16. Week of pregnancy, and change in job during pregnancy was not accounted for. This is stated on page 7, line 2. It has been added as a limitation in the discussion page 28.)

4) My major concern is the definition of atopy both in the parent and in the child. Among the children, having atopic dermatitis ever was used as a proxy for atopy. There are many children who are atopic, defined by a positive skin test or elevated serum IgE, who do not have atopic dermatitis but have other manifestations of allergy or sometimes are entirely clinically asymptomatic despite their evident sensitization. Atopy does not always result in atopic dermatitis. Similarly mothers were defined as atopic based on ever reported asthma, rhinitis or atopic dermatitis. Many adults show skin sensitization defining atopy without having clinical allergic disease.

(We agree, this is a major limitation in this epidemiological study. We have in the discussion further underlined this limitation by adding this section, please see page 29: ” Many atopic subjects (children and adults) defined by a positive SPT or elevated serum IgE, do not have atopic dermatitis but have other manifestations of allergy, and atopy does not always result in atopic dermatitis.. It can be argued that allergic rhinitis is even closer related to IgE mediated sensitisation than atopic dermatitis, but due to the age of the children (7 year) only few have developed allergic rhinitis, and therefore allergic rhinitis was not a good predictor for atopy in this study. Still, with these weaknesses in mind, we think it is justified to use the presence of atopic dermatitis as a reasonable proxy for atopy among

young children")

5) Outcomes of asthma and atopy in children are clearly different in boys and girls, and the data should be examined by gender rather than both sexes together.

(We have added tables stratified by gender as supplemental tables, and added a short description of the results in the result section and furthermore we included the issue in the discussion section, please table E2,E3 and E5, and page 15, page 18 and page 22. The issue has been added to the discussion page 26.)

6) Table 2 illustrates the problem I have with the definition of atopy. The prevalence of asthma in "atopic" children (i.e those with atopic dermatitis) was 23% in total, and in "non-atopic" children 14%. Epidemiologic studies with measurements of atopy, especially by age 7 years would suggest that this prevalence of asthma in allegedly non-atopic children is high. The authors should state that this is the prevalence of asthma in children who have not manifested atopic dermatitis rather than calling them non-atopic.

(We have both in the title of Table 2 and in the text underlined that atopy are defined as ever atopic dermatitis, please see table 2 and page 15, line 1-2)

7) In the discussion, the authors add additional results e.g. second paragraph, after discussing a Swedish study, they state that "we also found that atopic boys…". Results should be in the results section. This gender difference is important and as noted above should be provided for all exposures and outcomes within the results sections.

(Please see above)

8) The sixth paragraph of the discussion states that they did not find convincing differences between atopic and non-atopic children for associations between maternal occupational exposures and asthma in the children. This maybe influenced by the imprecise definition of atopy, based on clinical atopic dermatitis.
While the study finding is not totally invalidated by that, it is substantially weakened

(We are aware of this, and has extended the limitation section of this issue, please see page 28-29)

9) The discussion overall is long and difficult to follow. It could be much improved by shortening

(In order to make it easier to follow the discussion subheading have been added, and the original discussion has been shortened)

10) In discussing limitations of the study, the authors do reflect on the lack of objective and specific measures for atopy. They however, indicate that questions regarding atopic dermatitis have been validated against clinical investigation for atopic dermatitis and were deemed suitable for defining atopic dermatitis in epidemiologic studies. However this does not get around the fact that atopic dermatitis, no matter if highly validated, is not a substitute for a definition of atopy.

(We are aware of this, and have extended the limitation section of this issue, please see page 28-29)

11) I am confused by the data sharing statement on page 28. Did the authors not undertake their own statistical analysis? If this was all analyzed by Statistics Denmark, without the input of the clinical investigators, I would have some concerns about understanding of the data especially the issues around atopy as already mentioned.

(We apologize for the vague wording. The authors have performed all the analysis, and the data on atopy is from the DNBC dataset, and do no origin from register data. The sentence on page 30 has been changed to: “The data has been analyzed by the authors on a data platform in Statistics Denmark, where register data and DNBC data were merged after an application on the specific register variables of interest were approved by Statistics Denmark”)

12) In several of the figures, the word “just” and “common” are used. Just should be replaced by "adjusted" and common by "combined".

(There is one Figure, which has been changed according to the reviewers’ suggestion, please see Figure 1)

Reviewer: Nara Tagiyeva, research fellow, University of Aberdeen, UK.

This is an interesting and well written paper on maternal occupational exposure during and after pregnancy and the risk of asthma in 7-year old children in a large birth cohort study.

I have a few comments /questions to the authors:
-the statement in the abstract about the associations with prenatal & postnatal exposures is misleading, as they are not significant.

(The abstract has been changed – it is now clear that some of the results are only borderline significant, please see page 2, abstract)

-as the authors mentioned, HMW & LMW categories include a wide range of agents and the child's immune system, allergy and/or asthma development may be influenced by some of these but not others -I am not comletely satisfied with the exposure categorisation
tables 2 & 3, subheadings "outcome" & "asthma" in the latter are misplaced

(has been corrected)

that groups together occupational exposures to substances and job titles -table 4 explores the association with specific occupations, however some job titles are presented as individual agents/ substances (plastic, paper, stone, wood) which is confusing,

(This is perfectly true – all has been corrected to jobs, please see table 4 and page 22, line 1-2)

I thought at first that the table presented the relationship with agents/ substances mixed with occupations.
- I do not understand the sentence that starts with "The Impact of offspring...." (Lines 33-36)

(the sentence has been rephrased, please see page 25)

-could the authors please explained why they chose to use atopic dermatitis, but not rhinitis as a marker of atopy?

(The prevalence of rhinitis was low in the cohort due to the children’s age; please see the comments to reviewer I)

-while prenatal codes were derived from the questionnaire-based job descriptions, postnatal codes

are based on the data from the Statistics Denmark. Would authors want to discuss implications of this for the results if any?

(A section in the discussion on this issue has been added to the discussion, please see page 28)

VERSION 2 – REVIEW

REVIEWER	Malcolm Sears McMaster University
REVIEW RETURNED	20-Feb-2013

THE STUDY	I have reviewed this paper again and note the many changes that the authors have made. As requested, they have modified substantially the strength of the statements regarding the association, acknowledged the concern regarding loss to follow up and addressed this adequately, discussed the lack of specific information about exposures as they only have information about occupation, addressed the lack of information regarding change of occupation which seems to be a relatively low likelihood in most individuals, and overall have improved the manuscript substantially. They have provided data for boys and girls separately, largely in the supplemental tables but this is quite satisfactory. The one remaining problem I have relates to my major concern on first review, namely the use of atopic dermatitis as a proxy for atopy in the child. I am less concerned about the use of multiple diseases (asthma, rhinitis and atopic dermatitis) in the mother as this gives a wider range and although it is still will miss some atopic mothers, the risk of misclassification is likely quite small. However as noted, and as the authors acknowledged, the risk of misclassification by using atopic dermatitis as the sole indicator of atopy in the children is substantive. Recognizing that this problem cannot be avoided, I would strongly recommend that the text be modified in a number of places to make it quite clear that the discussion relates to children who demonstrate atopic dermatitis compared with those who do not, rather than persisting using the terms atopic and non-atopic. As specific examples, on page 15, line 6, I would suggest the wording be “the overall prevalence of asthma was 16%; 23% for children with atopic dermatitis and 14% for children without atopic dermatitis”. In line 11, this could be worded “and for the children with (27-28%) and without (16-17%) atopic dermatitis”. In line 21, the statement would more accurately be “the overall prevalence of asthma was higher for children with atopic dermatitis compared to those without”. There are several other places throughout the paper where that change could be made without making the text unduly cumbersome. In the tables, the same changes should be made (e.g. Table 3, the first column should be headed “Children with atopic dermatitis” and the next column “Children without atopic dermatitis”) and this continued across different columns. If the authors are willing to make that change in the interests of clarity and specificity, then I believe this paper is as well developed as is possible given the limitation of data collection and the lack of specific measurements of skin tests or IgE to define atopy. However if the authors continue use the words “atopic” and “non-atopic” throughout even with the explanation of the definition of atopy that is provided, there is a significant likelihood of misinterpretation by the

	casual reader.

VERSION 2 – AUTHOR RESPONSE

We have now changed the manuscript according to the reviewers suggestion - i.e. throughout the manuscript and in most tables we have changed the word "atopic" with the term "atopic dermatitis", please se the revised manuscript including tables and furthermore the revised table E2, E3 and E5