Author's response to reviews

Title: Factors accounting for the association between anxiety and depression, and eczema: The Hordaland Health Study (HUSK)

Authors:

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Version: 2 Date: 20 November 2009

Author's response to reviews: see over
Dear editors and reviewers,

We are most grateful for the thorough reviews; the response to the reviewers will follow below.

On behalf of the authors

Best regards,

Marianne Klokk, MD

Response to the reviewers of the manuscript:

“Factors accounting for the association between anxiety and depression, and eczema: The Hordaland Health Study (HUSK)”.

Reviewer I:

Parker Magin

Reviewer’s comment:
The manuscript contains some interesting findings but I have some concerns with the paper as presented, particularly the focus on IgE which distracts from the findings that are of genuine interest.

Reviewer’s comment:
1) Major compulsory revision
The main problem is in the definition and measurement of eczema.
• As the authors point out, eczema (or dermatitis) includes not only atopic dermatitis but a whole range of other clinical entities that share common pathological features: Seborrhoeic dermatitis, contact dermatitis, dishyrdotic eczema etc

• Atopic eczema has been strongly associated with atopy/IgE but not other forms of eczema/dermatitis
The question “Have you had eczema (red, itching, sensitive, or fissured skin) on any occasion during the last year?” will elicit a positive response from subjects with atopic eczema, but also from those with other forms of eczema/dermatitis and quite possibly from those with other inflammatory skin diseases (such as psoriasis, tinea, and a number of less common skin diseases) – especially if the skin condition has not yet been given a diagnosis by a health professional. The problem is in disease definition – other dermatoses besides eczema may have “red, itching, sensitive, or fissured skin”.

But, equally, not all inflammatory skin conditions will be elicited – the form of the question will tend to cause subject s whose skin condition (though red, itching, sensitive or fissured) has been given a “non-eczema” diagnosis to answer negatively.

Thus, findings from the analyses presented in the manuscript relate to a population with a much broader range of dermatoses than atopic eczema. Using such a population, inferences can’t be made concerning IgE and atopic eczema. I can’t see the data regarding IgE and atopy being of relevance to what I see as the bigger picture presented in the paper (that is, the association of skin disease with depression and anxiety).

Additionally, for this research question, the relevance of conducting a sub-study only in current and ex-hairdressers is problematic. The generalisability of results to the general population is limited.

**Action taken:**

We agree that the focus on IgE in relation to a broad range of different types of eczema beyond atopic eczema is problematic, and could distract from findings that are of genuine interest in this paper. The association between IgE and anxiety/depression based on these data are also analyzed before, and the published nil finding is referenced in our manuscript [1]. In accordance with the reviewer’s comment, we have therefore omitted all analyses involving IgE from the manuscript.

As the reviewer indicates, our self-reported eczema concept relates to a much broader range of skin conditions than atopic eczema. It is not uncommon, however, to use a wider definition of eczema in large epidemiological studies, which due to resource considerations often must rely on self-reported measures, this in contrast to clinical studies that normally involve
smaller samples and can make use of doctor’s diagnoses. In a population-based study by Hanifin and Reed [2] the term “empirical eczema” was defined by several skin symptoms that resemble the skin symptoms listed in the HUSK Questionnaire concerning eczema. Further, the validity of several self-reported skin complaints against clinical signs was explored in a Norwegian, population-based, validation study [3]. They showed that self-reported skin complaints to predict clinical morbidity can be a valid tool for quantifying and exploring skin diseases at population level.

A broader use of the eczema concept has also been suggested in the revised nomenclature for allergy for global use [4]: “Since the work of the EAACI Nomenclature Task Force started, there has been increased acceptance of the basis for a term describing an aggregation of several skin diseases with certain clinical characteristics in common involving a genetically determined skin barrier defect. This genetically determined target organ sensitivity constitutes the basis for eczema, as is true for asthma and rhinitis. In children and young adults of the atopic constitution, the underlying inflammation is dominated by an IgE-antibody associated reaction, which would allow use of the term atopic eczema. As long as the immunological mechanism of eczema is unclear, the disease should be referred to as eczema”.

All these issues are discussed in more depth in the resubmitted manuscript.

**Reviewer’s comment:**

Furthermore, the authors should be careful in extrapolating validity of self-reported symptoms/diagnoses from studies of hand eczema to other body sites as examined in this study. Hand dermatitis is a singular clinical entity.

**Action taken:**

We agree with the reviewer in that hand eczema is a singular clinical entity, and that the reliability and validity of self-reported hand eczema cannot be generalized to eczema in other areas of the body. However, we have no reason to assume the validity to be poorer. But, at the same time, our analyses showed that both hand, face and body eczema had an almost equally strong association to anxiety and depression (Table 2 of the resubmitted manuscript). Further, the same pattern was repeated in analyses of pure hand, face and body eczema (that is, not co-occurring with eczema in other body areas), indicating that the association between eczema and mental health symptoms is not restricted to special sub-types of eczema, such as hand
eczema. Future studies of the validity of self-reported face and body eczema might be warranted, but while awaiting these, we have to assume that the validity of self-reported hand eczema can be generalized to other body areas. This is discussed in the revised manuscript.

**Reviewer’s comment:**

2) **Minor essential revision**

The Participants and data collection should be made clearer.

It is not altogether apparent just what is the final response rate (once completion of the valid responses on the eczema and mental health variables is accounted for). It looks as though it may be approximately 44% for the main analyses, but can’t be calculated from the material provided. And it is certainly less than the figures of 57% / 70% / 73% / 81% that are cited for separate study populations at earlier stages. This has implications for the external validity of the study. A flow chart of numbers of inclusions/exclusions at the steps prior to inclusion in the various analyses would help overcome this problem.

**Action taken:**

The Hordaland Health Study (HUSK) was conducted as collaboration between the National Health Screening Service, the University of Bergen and local health services of Hordaland County in Norway. All individuals born between 1953-57, who resided in Hordaland County on December 31, 1997, were invited to the HUSK study. The target population counted 29400 individuals [5]. A total of 18581 (8598 men and 9983 women) both answered the first questionnaire and came to clinical examination. A random sample of about 6300 individuals born 1950-1951, that participated in a previous (1992-93) health study in Hordaland, were also invited. Finally, 18581 individuals born 1953-57 (participation rate of 63%), and 4849 individuals born 1950-51 (participation rate of 77%) attended. Altogether, this amounted to about 23430 individuals. In the present study, we included only those who came to clinical examination, and returned the second self-report form, further excluding those without valid responses on eczema and HADS variables (about 33% of the participants). Thus the final population consisted of 15 715 individuals. This more detailed information is now included in the revised manuscript.

**Reviewer’s comment:**

The final paragraph of The Participants and data collection needs is also unclear,
even after reading the cited paper.
From the sentence structure, it appears that
The first, which was identical for all participants, included a self-administered
questionnaire and a health examination with blood samples where the
participants received a second form that was returned by prepaid mail.
all refers to the first stage of data collection. What was the second stage of data
collection?

**Action taken:**
Data collection in HUSK was performed over two steps: First, participants were mailed a
questionnaire (Form 1) and an invitation to a health examination (measuring blood pressure,
height, weight and hip-waist ratio) where also blood samples were taken. After handing in the
first form at the examination, the participants were given one of two versions of a second
form to be returned by prepaid mail.
This specification of the data collection is also included in the revised manuscript.

**Reviewer’s comment:**
What data was elicited at the examination and in the two
questionnaires?

**Action taken:**
The health examination is described in the paragraph above.
Form 1 included questions about general health complaints, well-being and exercise, common
somatic diagnoses such as myocardial infarction, angina pectoris, asthma, diabetes, multiple
sclerosis, stroke, eczema, smoking habits, coffee and alcohol use, socio-economical factors
and current use of medication( and what kind of condition medication was taken for). Form 2
came in two versions. In that way some questions were distributed to a sub-sample only. Form
2 included HADS, the Whiteley Index, somatic symptoms, questions about different somatic
diagnoses, sleeping problems, social contact and working and living conditions.

**Reviewer’s comment:**
3) Discretionary revision
The authors are rightly careful to claim that there data demonstrates an
association (and don’t claim to have provided evidence for causality), but more
should be made in the discussion of the fact that this is a cross-sectional study and as such is unable to make inferences regarding causality.

This of great importance in psychodermatology where stress and other psychological and psychiatric morbidity has been proposed to be causative of skin disease, as well as skin disease being proposed to be causative of anxiety, depression, stress and other psychological and psychiatric morbidity.

A major limitation of interpretation of results from the study is its cross-sectional nature and this should be made explicit.

**Action taken:**

To further underline the limitation of the cross-sectional design, the following sentence was added in the strengths and limitations section of the discussion of the resubmitted manuscript:

“Another important limitation to our study is the use of a cross-sectional design, precluding inferences regarding causality for the association between anxiety and depression, and eczema. Employing a cross-sectional design, it is not possible to determine whether psychological symptoms can result from eczema, or if such symptoms are part of the causative chain in skin disease”.

**Reviewer’s comment:**

In addition, in the wording in Page 4, paragraph 3:

The aim of the present study is therefore to examine the relevance of some proposed mechanisms

The use of the word “mechanisms” could be interpreted as implying evidence for causation. The wording could be reconsidered.

**Action taken:**

In the revised version of the current manuscript, the word “mechanisms” is replaced with “contributing factors”.

**Reviewer’s comment:**

4) Discretionary revision

Page 4, 2nd paragraph

The sentence:

On the other hand, the advantage of clinical studies is the presumed good
reliability of eczema, anxiety, and depression
I suspect this should read
is the presumed good reliability of diagnoses of eczema, anxiety, and depression

**Action taken:**
We fully agree with the reviewer, and the word “diagnoses” is added to the above-mentioned sentence in the revised version of the manuscript.

**Reviewer’s comment:**
5) Discretionary revision
Page 9, paragraph 1
Using a simple list of questions derived from the somatisation diagnostic criteria doesn’t have the same validity as employing a validated instrument, and this should be made clear as a limitation of this aspect of the study.

**Action taken:**
To the best of our knowledge, there are yet no well validated and widely used instrument for somatization. The index for somatization is also not a validated instrument, but has been used in previous publications [6, 7].

The following sentence was added in the revised version of the manuscript: “Our Index for somatization should not be compared to validated instruments for the diagnosis of somatization disorder. Our index for somatization was used as a dimensional measure (using a mean-score of the 12 items) for tendency of somatization. This dimensional measure for somatization has also been used in previous publications [6, 7].”

**Reviewer’s comment:**
6) The statistical aspects require more expert review than mine
Statistical analysis
I think expert statistical review may be of value.
Even as a non-statistician, I would have expected to have been provided with more information about the regression analyses – whether forward or backwards processes were used and criteria for inclusion and exclusion of independent variables in and from the models.
**Action taken:**
The senior author has recently been promoted professor of psychiatric epidemiology and has closely supervised all analyses.

The models used were theoretically defined and based on current psychodermatological literature. On this background, we decided to include eczema as the independent variable, and anxiety and depression as dependent variables in the analyses, but if this was the opposite way around, the analyses of mediation/confounding would still be giving the same results. We did not use any automatic procedures (as in backward or forward processes), we simply manually added one candidate mediating/confounding factor at the time in a pre-defined order. We have added “No automatic procedures for including/excluding variables in the regression model were used” in the resubmitted manuscript.

**Reviewer’s comment:**
The rationale for using logistic regression in one set of analyses and linear regression in another when the dependent variable was HADS results in both circumstances needs to be stated

**Action taken:**
Logistic regression analyses were employed for categorical dependent variables (as in case-level HADS). We have added the following to the resubmitted document: “The association of interest (including candidate confounding/mediating factors) was also analyzed applying HADS as a continuous variable, and with linear regression models. All conclusions were confirmed applying this approach.”

Further, as the IgE analysis is now omitted, we no longer apply any linear regression models in the main analyses.

**Reviewer’s comment:**
Again as a non-statistician, I’m not sure why the successive iterations of regression modelling are presented (Table 5) rather than the final models which I would have thought would convey more useful information.
**Action taken:**
The reason why we presented cumulative adjustments, and not only the final models, is that we were interested in the individual contribution of possible confounding or mediating factors for the association of interest.

In these analyses, we adjust for a new possible mediating or confounding variable at each step in the subsequent analyses. In this way, we can estimate the individual contribution of each candidate contributing factor in the association of interest [6].

**Reviewer’s comment:**

**Conclusion**
My overall assessment is that the question of IgE/atopy and it’s relation to depression and anxiety in atopic eczema is not able to be answered with the data presented here.

The paper does present data from a wider study of the association of anxiety and depression with skin disease. It also examines the role of somatisation and health anxiety in this association. This is of interest.

Thus the study adds some further insight to the existing cross-sectional literature on depression and anxiety in eczematous skin diseases. I think the paper would be best reframed as such, with its main limitation being the diagnostic validity of the self-diagnosis of eczema – this will result in a heterogeneous patient population of atopic and non-atopic eczema/dermatitis diagnoses. It is also likely that some measurement bias will be inherent in the survey question and some participants with non-eczematous inflammatory dermatoses will be included.

But, as the authors rightly state, a trade-off of diagnostic sensitivity/specificity versus power and generalisability is inherent in the psychodermatological

**Level of interest:** An article whose findings are important to those with closely related research interests

**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 II:

Ruth E Taylor

Reviewer’s comment:

General comments:
In general I thought this was an interesting and worthwhile paper and I enjoyed reading it. However I did have some specific comments which are set out below. I think one of the main problems which I would class as a major compulsory revision is that the authors need to clarify the concept of somatization which they are using and how they are defining somatization. The aims and objectives should then become clearer. I think they need to be clearer about the proposed links between the aetiological factors they set out to study. Most of the other comments are discretionary revisions where the paper could be improved.

Action taken:
In the revised manuscript we have further clarified the proposed links between possible contributing factors in the associations of interest. The concept of somatization is also discussed in more depth in the background section.

1. Major compulsory revision:

Abstract could be clearer:
Background could explain why the particular factors of interest were picked.

Action taken:
In the revised manuscript, the following was added in the background section of the abstract: “Low levels of omega-3 fatty acids and female gender have been found to be associated with both depression and eczema, whereas somatization and health anxiety are known to be associated with anxiety and depression. Further, somatization symptoms, and health anxiety has been found in several dermatological conditions. Accordingly, Levels of omega-3 fatty
acids, female gender, somatization and health anxiety are possible contributing factors in the association between anxiety and depression, and eczema”.

**Reviewer’s comment:**
Methods should make it clear that whole sample was used for all factors except IgE where only existed in female subsample. How was omega 3, health anxiety and somatisation measured.

**Action taken:**
Based on the same data, we have previously published the lack of association between IgE and anxiety/depression, and this is mentioned in this paper. On the basis of this nil finding, IgE cannot be a mediating or confounding factor in the association of interest. Therefore, we have omitted analyses of IgE from this manuscript.

The method of measurement for the possible contributing factors in the association between anxiety/depression and eczema was self-report, and therefore, the following sentence was added in the methods section of the abstract in the revised manuscript: “Information on eczema, omega-3 fatty acid supplement, female gender, somatization and health anxiety was obtained by self-report”.

**Reviewer’s comment:**
In conclusions it sounds rather muddled to say “and the associations of interest were insignificant after this adjustment” because somatization and health anxiety were two of the associations of interest. Needs to be clearer what the primary hypothesis was and which factors were then adjusted for as possible confounders.

**Action taken:**
In the revised manuscript, the conclusion section of the abstract was rephrased as follows: “We found no support for omega-3 fatty acid supplement and female gender as contributing factors in the association between anxiety/depression, and eczema. Somatization and health anxiety accounted for about half of the association between anxiety/depression, and eczema, somatization contributed most. The association between anxiety/depression, and eczema was
insignificant after adjustment for somatization and health anxiety. Biological mechanisms underlying the mediating effect of somatization are yet to be revealed”.

Reviewer’s comment:
Background
2. Discretionary revision:
Second paragraph: Would be interesting to comment on what the association is with parity.

Action taken:
Parity and gestational age has been shown to be associated with atopic disorders, and both multiparity and atopy have been shown to be associated with depression [8-10]. This makes parity a possible confounder in the association between anxiety and depression, and eczema (our measure for eczema will among others include atopic forms of eczema). These aspects are included in the text of the background section in the revised manuscript.

Reviewer’s comment:
3. Minor essential revision:
Sentence after this does not make sense: “As a substantial part etc “ there should be no full stop after excema just needs a comma and then don’t need consequently.

Action taken:
We agree with the reviewer in her remarks, this is now corrected.

Reviewer’s comment:
4. Major compulsory revision:
These two sentences not very clear.
Last sentence page 3: I don’t really understand this sentence, are the authors suggesting excema is a somatization symptom? Perhaps they are using somatization in a different sense to what I would understand. Somatised symptoms generally considered to be non organic-no underlying physical disease process. I would not put excema in this category.
I think it could be made clearer what exactly are the proposed aetiological links
between depression, IgE, Omega fatty acids, health anxiety, somatization and eczema because even after reading the introduction I am not clear about this.

**Action taken:**
In the revised manuscript, the proposed aetiological links between depression, Omega-3 fatty acids, health anxiety, somatization, and eczema are described more clearly in the background section of the paper.

Our understanding of somatization approximates the ICD-10 [11] understanding of somatization as a wide spectrum of somatic symptoms where no organic cause could be found. Psychiatric comorbidity is not included as a criterion in the ICD-10 criteria for F 45.0 somatization disorder. These aspects are now included in the background section of the paper.

Skin symptoms are listed in the research criteria for the ICD-10 F 45.0, somatization disorder. It is possible that such skin problems sometimes could be interpreted as some form of eczema (although not confirmed by a doctor) and therefore reported as eczema in our study. This could be due to selective attention to bodily symptoms (here skin symptoms), in a somatizing individual. In that way, eczema, or at least skin symptoms, could represent a symptom of somatization.

It could also be theoretically possible that somatization may lead to psychological stress reactions in the body. Psychological stress has been found to worsen or trigger outbursts of eczema [12]. This makes us speculate that at least some forms of eczema could represent a symptom of somatization, which is frequently co-morbid to anxiety and depression [13]. Following this line of thought, it is interesting that Dantzer [14] is linking stress reactions cytokines and expression of symptoms of anxiety, depression and somatization. This is especially interesting as we know that cytokines are involved in the pathophysiology of eczema. Anyhow, this is theoretical speculations that would have been interesting to examine in future research.

The issues relating to eczema as a possible symptom of somatization are now discussed in more depth in the discussion section of the manuscript, and will not be mentioned in the background section.
Reviewer’s comment:

Methods

5. Minor discretionary revision:
Top of page 5. There was obviously quite a lot of missing data on eczema and mental health variables as the sample included is much smaller than the overall sample. The extent of this missing data could be made clearer and given in percentage terms for both mental health and eczema variables.

Action taken:
In the revised manuscript, the following text was included in the methods section:
“The Hordaland Health Study (HUSK) was conducted as collaboration between the National Health Screening Service, the University of Bergen and local health services of Hordaland County in Norway. All individuals born between 1953-57, who resided in Hordaland County on December 31, 1997, were invited to the HUSK study. The target population counted 29400 individuals [5]. A total of 18581 (8598 men and 9983 women) both answered the first questionnaire and came to clinical examination. A random sample of about 6300 individuals born 1950-1951, that participated in a previous (1992-93) health study in Hordaland, were also invited. Finally, 18581 individuals born 1953-57 (participation rate of 63%), and 4849 individuals born 1950-51 (participation rate of 77%) attended. In the present study, we included only those who came to clinical examination, and returned the second self-report form, further excluding those without valid responses on eczema and HADS variables (about 33% of the participants). Thus the final population consisted of 15 715 individuals.”

Reviewer’s comment:

6. Minor discretionary revision:
The IgE substudy in females only will have an overrepresentation of hairdressers i.e. half the sample.. May or may not be relevant.

Action taken:
We agree this is a limitation. However, the IgE analyses are now omitted from the paper.

Reviewer’s comment:
7. Minor discretionary revision:

P5 para 3: sentence beginning “The first which is identical etc” is not very clear I am not sure what this means about prepaid envelope etc how was examination and bloods done?

Action taken:

Prepaid envelope means that they got an envelope with stamps on, so they did not have to by stamps to return the envelope with the questionnaire.
The blood samples were drawn from the cubital vein with the subject sitting in a chair. The samples were full-blood and they were later stored (as frozen samples) in the HUSK bio bank.

The following text was included in the resubmitted manuscript: “Data collection in HUSK was performed over two steps: First, participants were mailed a questionnaire and an invitation to a health examination (measuring blood pressure, height, weight and hip-waist ratio), where also blood samples were taken. After handing in the first form at the examination, the participants were given one of two versions of a second form to be returned by post in a prepaid envelope [5].”

Reviewer’s comment:

8. Minor discretionary revision: P11 in results. There is a comment that the gender by excema interaction may be due to multiple testing. A bonferroni correction should be applied to correct for multiple testing.

Action taken:

In the interaction analysis part of table 2, one analysis turned out to have a significant interaction, the p-value of this analysis was 0.03, which is pretty close to the chosen significance level of 0.05 for that analysis. We have added a sentence to the manuscript mentioning that this gender interaction would not be robust for a Bonferroni correction.

Reviewer’s comment:

Discussion
I thought this was good and interesting. It is clearly written and acknowledges relevant methodological problems and limitations.

Reviewer’s comment:
9. Major compulsory revision
(but is same issue as in point 4 relating to the concept of somatization). In the section discussion about somatization accounting for the relationship between anxiety and depression and excema the somatization measure is basically a measure of the tendency of an individual to experience non organic symptoms. We do not know what causes this. It could be that some individuals are aware of and attend excessively to physiological body symptoms which because of health anxiety they attribute pathologically. This possibility makes the measure of somatisation and that of health anxiety very similar. Or it could be that there are anxiety /depression driven pathophysiological processes which produce bodily symptoms for example excess gastric acid producing gastric symptoms, or bowel spasms producing pain etc. This latter mechanism would more plausibly lead to a generation of excema by some pathophysiological process. There are people who would argue that excema is not a somatization symptom. They would define somatization as experience of and help seeking for a symptom not explained by any organic disease, (but attributed by the patient to disease) in a patient who has psychological disorder. In excema there is clearly a disease process. I think the authors need to define at the outset what concept of somatization they are using and this will make their argument in the discussion clearer.

Action taken:
As the reviewer points out, somatization could be understood in different ways: It could be understood as help-seeking for unexplained organic symptoms, attribution to a somatic condition due to health anxiety, further, somatization could be viewed as comorbidity between psychological conditions and unexplained organic symptoms. Our understanding of somatization approximates the ICD-10 understanding of somatization as a wide spectrum of somatic symptoms where no organic cause could be found, and that there not necessary would be any psychiatric comorbidity (i.e. psychiatric comorbidity is not included as a criterium in the ICD-10 criteria for F 45.0 somatization disorder).

It is theoretically possible that there are anxiety /depression driven pathophysiological processes which produce bodily symptoms such as pain etc, and that this latter mechanism could lead to a generation of excema by some pathophysiological process
(for instance involving stress mechanisms?). But, is it not also possible that there could be a common unknown pathophysiological factor underlying somatization and eczema?

We were surprised by the large contributing effect of somatization in the association between anxiety/depression, and eczema, and one of the other surprising findings was that the association between eczema and somatization actually was stronger than the association between eczema and anxiety/depression. It is theoretically possible that the association between eczema and anxiety/depression is actually driven by somatization.

Concerning eczema as a symptom of somatization, this was discussed in the “major compulsory revision” section above, and the issues discussed there are incorporated in the discussion section of the revised manuscript.

All of the above mentioned issues are incorporated in the discussion section of the revised manuscript.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

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

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

References:


