06-Feb-2018

Dear Dr. Silverwood

Manuscript ID BMJ.2017.042874 entitled "Severe and predominantly active atopic eczema in adulthood is a risk factor for cardiovascular disease: a UK population-based cohort study, 1998–2015"

Thank you for sending us your paper. We sent it for external peer review and discussed it at our manuscript committee meeting. We recognise its potential importance and relevance to general medical readers, but I am afraid that we have not yet been able to reach a final decision on it because several important aspects of the work still need clarifying.

We hope very much that you will be willing and able to revise your paper as explained below in the report from the manuscript meeting, so that we will be in a better position to understand your study and decide whether the BMJ is the right journal for it. We are looking forward to reading the revised version and, we hope, reaching a decision.

Please remember that the author list and order were finalised upon initial submission, and reviewers and editors judged the paper in light of this information, particularly regarding any competing interests. If authors are later added to a paper this process is subverted. In that case, we reserve the right to rescind any previous decision or return the paper to the review process. Please also remember that we reserve the right to require formation of an authorship group when there are a large number of authors.

Thanks!

Tiago Villanueva
Associate Editor
tvillanueva@bmj.com

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Report from The BMJ's manuscript committee meeting

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript.

Members of the committee were: Elizabeth Loder (chair), Julie Morris (statistician), Georg Roggla, John Fletcher, Wim Weber, Jose Merino, Tiago Villanueva, Robin Baddeley

Decision: Put points

Detailed comments from the meeting:

First, please revise your paper to respond to all of the comments by the reviewers. Their reports are available at the end of this letter, below.

Please also respond to these additional comments by the committee:

- Our statistician made the following comments:
• Subjects were matched for age within a 15-year time frame. This seems excessively wide. Why was this age gap chosen?

• The statistical analysis of the data excluded a rather large percentage (20%) of subjects with missing values. The potential bias is acknowledged in the Discussion. Why was this rather simplistic method used to deal with missing values? Why, for example, was a multiple imputation procedure not used?
• The estimated absolute cardiovascular rates should be presented. This is important to enable a careful consideration of the impact of the estimated risk estimates, given that many of the relative risks are rather low.
• The median follow-up period was only just over 5 years. Is this a long enough follow-up period, particularly as results for cardiovascular mortality changed in the sensitivity analysis using subjects with at least 5-years follow-up ?

- One editor liked the research question and thinks that there is a lot that is well done. However, there are limitations:

1. There are confounders that are not measured. Diet, exercise and medication use are all pretty important for cardiovasculr outcomes.

2. You "matched" for age within 15 years but in fact there are more elderly people in the eczema cohort (eg 12.4% vs 9.0% over 70) and fewer young people (18.1% vs 20.6% 30to39) except in the 18-19 age group who probably don't contribute many events anyway.

3. The completeness and accuracy of codes in CPRD is not great for some things such as alcohol and BMI. You should report this and discuss for all covariates.

4. The treatment of missing data is poor. To simple exclude 20% in this day and age and not make any attempt at including via imputation or other methods is verging on unacceptable.

5. The fully adjusted associations are pretty small and many of them don't reach statistical significance (even though you have used 99% CIs).

Table numbering has gone astray.

- Another editor said this was an interesting research question, and while not novel, surely the largest study until now. He saw no info on medication, and steroid use might be an important variable.

- Another editor said that these statements don’t seem supported by data and should be revised and toned down: “The results support targeted screening and focus on primary prevention strategies to reduce cardiovascular disease among patients with severe or predominantly active atopic eczema.” He also said that you need to emphasise that the effect size is small, and the effect size should be mentioned in the abstract.

- Another editor was supportive given that the study addresses a relevant research question.

- Another editor was in favour but said the title should not announce the findings.

In your response please provide, point by point, your replies to the comments made by the reviewers and the editors, explaining how you have dealt with them in the paper.

Comments from Reviewers

Reviewer: 1

Recommendation:

Comments:
Thank you for the opportunity to review this manuscript, which describes a study of the association between eczema and CV risk. This is an important and interesting topic, and the authors aim to increase understand of the impact of eczema on CV risk.

I understand that a requirement for all manuscripts submitted to The BMJ is a statement regarding patient involvement - I could not see this, so please add. As this was a non-interventional study, the authors did not have the opportunity to involve the patients whose data they used in the study. Nevertheless, it would be useful to know if they discussed the study design and the chosen outcomes with a group of patients with atopic eczema (and if not, why not).

In the Discussion, the authors state that "it is not possible to disentangle the effects of therapy and severity, but this was not an objective of the present paper." However, this is an extremely important distinction for patients. I feel strongly that The BMJ has engaged patient reviewers like myself in order to encourage authors not to make such statements without really considering the impact on patients. Many patients with atopic eczema remain distrustful of long-term topical steroid and/or immunosuppressant use. Would it have been possible to disentangle the effects of therapy from the effects of disease when assessing CV risk with an altered study design? If so, please discuss why it was not done. If it was not possible, some discussion of this impact that this has on the usefulness of the study, particularly the practical impact for PCPs and their patients, would be good.

Another point I wanted to raise was a potential limitation that has not been covered in the Discussion. In my experience, patients who suffer long-term from eczema often do not adhere to therapy, or have episodes of adherence alternating with non-adherence. This means that many patients in the study who actually have active disease may not be classified as such, because they may not have had a CPRD/HES record within the last 12 months. This potentially could confound the results.

A couple of specific points:
The median follow up seems quite low to me, given the time period of the study and the fact that eczema is a long-term disease. Could the authors comment?

In the supplementary tables, I think it is clearer to describe the groups as With atopic eczema/Without atopic eczema as in Table 2, rather than as Exposed/Unexposed. Either way, I think the tables should be consistent in this regard.

Thanks again for this opportunity and good luck with your future research.

Additional Questions:
Please enter your name: Charlotte Cookson

Job Title: Patient reviewer

Institution: NA

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

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Reviewer: 2

Recommendation:

Comments:
Interesting paper and a large population base. I would have some questions to the authors:
1. Page 10, second paragraph: I did not quite understand the sentence: Any patients with an atopic eczema diagnosis...., could you please clarify why they were put into the group of unexposed individuals
2. Page 11, second paragraph the classification of patients into moderate or severe disease. You can have a severe disease and still use only topical treatment. If the patients would have been seen and classified by a dermatologist it would have been more reliable, but I understand the difficulty when the population base is so large. This is still a limitation of the study which could me mensioned in the discussion.
This is a paper which brings new information about the comorbidities of atopic dermatitis and I recommend it for publication

Additional Questions:
Please enter your name: Anita Remitz

Job Title: Senior lecturer, specialist in dermatology

Institution: Helsinki University Central Hospital

Reimbursement for attending a symposium?: Yes

A fee for speaking?: Yes

A fee for organising education?: Yes

Funds for research?: Yes

Funds for a member of staff?: No

Fees for consulting?: Yes

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Reviewer: 3

Recommendation:

Comments:
Silvergood et al. have produced a manuscript with the aim of describing atopic dermatitis as a possible risk factor for cardiovascular disease, using routine data arising mainly from UK primary care.

The manuscript is well written and has many positive aspects:
Population based
Use of a validated case definition
A very good and illustrative example of the use of acyclic graphs to identify mediators and confounders, including multivariable analysis that includes mediators (showing a reduction in adjusted risk that confirms this role).
Control for relevant confounders and availability of measures of disease activity and severity.
Excellent use of sensitivy analysis to take into account sources of uncertainty.

My comments on specific sections follow:

The abstract makes a good summary of the overall paper.

Introduction

The study question and background are clearly described. I found that the literature review is adequate and unbiased.

Methods

My main concerns about the methods are:

I suggest a statistical reviewer to check that Cox regression stratified for matched set is a good method to take matching into account, and that the simple methods used for missing data are adequate.

I do not agree with the sentence (page 10, lines 30-4)" Any patients with and atopic eczema diagnosis….this ensured greater certainty that the pool of unexposed patients did not have atopic eczema. " I think that including atopic eczema patients before their diagnosis in the unexposed pool does not ensure that this pool does not have eczema patients. It might lead to some differential misclassification (patients having eczema among the unexposed group) that would lead to a result biased towards the null effect. This does not compromise the study, but I think that authors should consider modifying this sentence.

Both the diagnosis definition and the measures of severity are probably associated with more frequent interaction with health providers, that might also lead to a higher probability of being diagnosed with the outcome. This might be more relevant for "softer" outcomes (atrial fibrillation?) and should be discussed.

Results

I suggest adding in table 2 a category of patients without classic risk factors for CVD (DM, hypertension, hyperlipidemia, smoking, overweight-obese). This are the patients that might specially benefit from the results of this paper.

Discussion

I miss a few points in the results and discussion:

Figure 2 and 3 seem to show a dose-effect response between eczema severity and outcome, and less clear for activity. This might be included in the models (assuming a linear relationship) and be further discussed, as it strengthens the argument of the paper.

If we assume a causal association, there are several practical consequences that might be highlighted in the paper:

*I suggest that authors clearly indicate how many of the atopic dermatitis patients do not have classic risk factors for CVD. This would be the patients that might benefit for additional counseling (exercise and diet prescription, increased screening for risk factors, etc.)

I also suggest that authors should discuss the expected impact of their findings. Assuming a cause-effect relationship, what are the attributable risk and population attributable risks of atopic dermatitis?

Kind regards,

Additional Questions:
Please enter your name: Ignacio Garcia-Doval

Job Title: Research Unit Director

Institution: Fundación Piel Sana Academia Española de Dermatología y Venereologia.

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

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HREF='http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/declaration-competing-interests'target='_new'> (please see BMJ policy) please declare them here: I declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work."

Reviewer: 4

Recommendation:

Comments:
This is a fascinating and important study, and the authors should be commended for their excellent methodological approach. Similar findings in psoriasis (some based on the GPRD) have sparked a vast research enterprise on the association between psoriasis and heart disease.

Using use of immunosuppressants to (partially) define severe atopic eczema may be slightly problematic, as these drugs could represent confounders. This is acknowledged by the authors on page 18. Were they controlled for in the analyses?

It may be helpful to tease out the use of immunosuppressants. This could be done in several ways, by either controlling for immunosuppressant use as a covariate, analyzing those with severe eczema excluding those on immunosuppressants, or including patients on immunosuppressants who do not have eczema (i.e. those using these drugs for other indications). Another question would be duration of therapy on immunosuppressants, as extensive data have suggested a dose-response relationship for important clinical outcomes such as cancer risk.

Table 1 could possibly be changed to a supplemental table, unless required per BMJ style.

Line 26: Why was the age matching performed so broadly (+/-15 years)?

Additional Questions:
Please enter your name: Jonathan Kantor

Job Title: Adjunct Assistant Professor

Institution: Univ. of Pennsylvania

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

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