PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Eczema and subsequent suicide: a matched case-control study
AUTHORS	Drucker, Aaron; Thiruchelvam, Deva; Redelmeier, Donald

VERSION 1 – REVIEW

REVIEWER	Alexander Egeberg Department of Dermatology and Allergy, Herlev and Gentofte Hospital, University of Copenhagen, Denmark
REVIEW RETURNED	07-May-2018

GENERAL COMMENTS	This paper examines the association between eczema and suicide in a Northern American population. The paper is interesting and warrants publication, however, there are important issues that needs to be addressed by the authors, and the paper appears biased in its interpretation as their data (and existing literature) does not fully support their conclusions. This requires some modification. MAJOR ISSUE: The authors state in the title, abstract, and throughout the paper that this is ATOPIC dermatitis. However, based on the presented data, and the existing validations studies, I have major concerns that this study is not examining atopic dermatitis, but rather a mishmash of several different skin conditions. First of all, the validation study by Hsu et al. (reference 21) showed that ICD-9 codes are practically useless to assess atopic dermatitis compared with other types of dermatitis. To this end, you state: “To increase the specificity and to define persistent atopic dermatitis, we required five or more physician visits for the diagnosis, each separated by at least one week over the look-back interval.” The issue with this definition is, that this does not increase the specificity towards atopic dermatitis. In fact, this simply ensures that patients have had more contacts with the same diagnosis, regardless of whether this was atopic dermatitis or another type of eczema. In your baseline table, it is shown that 17% of all suicide victims had alcohol abuse. It is well-established that patients with alcoholism eat unhealthy more often than not these patients suffer from zink- and vitamin B deficiency, which will result in dry skin and eczema. Similarly, if a patient is referred for patch-testing e.g. due to hand eczema, this patient will have multiple visits (some within one week, and some by more than a week), and be misclassified as “persistent atopic dermatitis” in your primary analysis. From your data, regardless of how many repeated ICD-9 codes have been used, there is a high probability that your “atopic dermatitis” cohort is not at all atopic. This is emphasized by the sensitivity analyses where the addition of asthma or rhinitis to their atopic dermatitis definition showed no significant difference in risk of suicide (p=012).

	Therefore, the authors absolutely must remove the word “atopic” from the title, abstract, and throughout the paper. In their sensitivity analyses #3 (page 10), the authors excluded patients with “a history of stasis ulcers, varicose veins, lymphedema or contact dermatitis”. I would like to see the authors perform a sensitivity analyses where they, in addition, exclude patients with an ever-diagnosis of ANY other type of dermatitis or psoriasis. Please add this data. The authors state “…suggesting that atopic dermatitis is not an independent contributor to suicide risk beyond its influence on mental health risk overall”. This is a very important point; a message which unfortunately downs in the manuscript. Please add this (without the word “atopic”) in the abstract, and in the first paragraph of the discussion. There are places where the authors are cherry-picking the literature to support their hypothesis. For example, the authors write “One conducted using administrative data for adults in Denmark found that atopic dermatitis patients had a 71% increased risk of suicide attempts and a 208% increased risk of death from suicide, a more prominent association than in our study. In agreement with our findings, older adults with atopic dermatitis had a further accentuated risk. The only other past study, also from Denmark, found no association between atopic dermatitis and suicide, but had wide confidence intervals and imprecision.” Not only should this statement be modified, but I ask that the authors provide a detailed explanation of how they justify this statement. First of all: please explicitly state how reference 11 had “imprecision” and how you can assess that this was not the case for the atopic dermatitis subanalysis in reference 10. Second, please explain how you can justify choosing your arguments from a study primarily focused on psoriasis (reference 10), where the subanalysis using atopic dermatitis did not provide any characteristics about the atopic dermatitis cohort, while there is a paper (reference 11) with the primary focus of addressing the same question not finding any association. This is a concerning sign of cherry-picking your arguments. I am very interested in hearing the authors explanation of this matter. Moreover, in the introduction, please rephrase to: "A study from Denmark found no significant association between atopic dermatitis and subsequent suicide (ref 11). In contrast, in a psoriasis study from Denmark, a subanalysis using atopic dermatitis as the exposure suggested a potential association between atopic dermatitis increased suicide risk (ref 10)". And in the discussion, the statement about these studies should considerably moderated. E.g. “a 208% increased risk” is a newspaper scare-tactic designed to create headlines and tells you absolutely nothing about the absolute risk, which (in all studies I have read, including you own currently under review here) is extremely low. Indeed, since the absolute risk of association is very low, this needs to be emphasized in the first paragraph of the discussion. Methods: “Atopic dermatitis was defined using diagnosis code 691”. Were these all primary diagnoses? Or did you also include secondary diagnoses? Because this is problematic and will further decrease specificity.

	The authors used a cut-off of patients between 15-55. It is unclear to me why this cut-off was used. Studies assessing associations usually define adults as subjects >18 years. For comparison with previously published data, I ask that the authors as their primary analysis examine the risk in all subjects >= 18 years (with no upper age cut-off). Moreover, how can you use a five-year look-back when it was only required that patients were enrolled 1 year prior to index. The authors need to explain why they did not require 5 years enrollment, when the look-back period was 5 years. Preferably, a 5-year look-back would be applied in the reanalysis of the data, but as a very minimum the authors should list the average length of enrollment for suicide cases and controls, stratified by AD status in the respective groups. Lastly, in the limitation section, the authors state that misclassification of less severe skin diseases may have biased towards the null. Please explain how you know that this would be from less severe cases. As argued above, patients are more likely to be misclassified from skin diseases e.g. due to alcohol abuse/vitamin deficiency, and other skin diseases e.g. an exfoliative dermatitis would arguably be MORE severe, thereby biasing towards a false-positive association.

REVIEWER	Mu-Hong Chen Department of Psychiatry, Taipei Veterans General Hospital, Taiwan
REVIEW RETURNED	11-May-2018

GENERAL COMMENTS	I like this topic, and I only have several comments. 1. In the method part, authors use ICD-9/10 for the definition of suicide, but why they only use ICD-9 for the definition of diseases, such as AD. I think they should use both ICD-9 and ICD-10 for the definition of any variable. 2. They may test the severity of AD with the risk of suicide. The long-term oral steroid may be a possible clinical marker for severe AD. 3. They define the persistent AD. But, I am also curious about the timing of persistent AD. For example, does the risk differ between persistent AD in recent 1 year and before 1 year? 4. AD medication may be a confounding factor for the suicide. If authors can overcome it, please do it. If not, please mention in the limitation. 5. The association between AD and suicide is predominant in older population, but not in younger population, which needs some discussion.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

1. Affirmation of the study

The reviewer starts by affirming the importance of this area of study. We agree that the relationship between skin conditions and mental health is important, and hope our study will contribute.

2. Validation studies of atopic dermatitis codes

The reviewer expresses concern about the results of a previous validation study of ICD codes. We share the reviewer's concern about misclassification when using ICD diagnostic codes to identify patients with atopic dermatitis. We note the results of the validation study by Hsu et al, and we believe

it underestimates the true positive predictive value, and we mention in the text. Additionally, we have now added preliminary results of the Danish validation study (J Am Acad Dermatol. 2017) to the text; in that article, which focuses on autoimmune comorbidities of atopic dermatitis, the authors mention that patients identified by the ICD-10 code for atopic dermatitis were confirmed in all but two of fifty cases.

3. Occurrences to define atopic dermatitis.
The reviewer asserts that five or more occurrences of the atopic dermatitis ICD code does not guarantee specificity and might still include other chronic skin diseases (false positives). We agree that some misclassification is likely, as in most studies relying on ICD codes. Our rationale is that we likely increase specificity at the expense of decreased sensitivity by eliminating transient dermatitis. We have now expanded on the potential for misclassification (particularly of other severe skin diseases) in the limitations section.

4. Non-significant findings when requiring comorbid rhinitis or asthma.
The reviewer highlights that our sensitivity analysis requiring an additional diagnosis of rhinitis or asthma for the definition of atopic dermatitis shows results that are not statistically significant. We agree that this sensitivity analysis provides nearly the same odds ratio of 1.26, with wide 95% confidence intervals (0.94 to 1.69). We are reassured that the estimate was largely unchanged from the primary analysis, with the lack of statistical significance mostly explained by widening of confidence intervals from decreased sample size. We have now added this caution to the discussion.

5. Use of the word atopic
The reviewer similarly suggests we use a less specific term to describe the disease under study. We agree thatsome misclassification is likely due to fallible diagnoses. To provide some reassurance, we have now compared the prevalence of other atopic conditions (asthma, rhinitis) for patients in our study diagnosed with and without persistent atopic dermatitis. We found that our patients diagnosed with persistent atopic dermatitis according to our case definition were twice as likely to also have asthma and rhinitis. We have now added this corroboration in a supplementary table and in the manuscript. Further, our use of the term “atopic dermatitis” agrees with other epidemiology studies relying on ICD codes to make the diagnosis (including from Denmark).

6. Excluding other forms of dermatitis
The reviewer suggests an additional sensitivity analysis by excluding patients diagnosed with psoriasis and other forms of dermatitis. We agree that this would be useful to address potential misclassification. We have now performed a sensitivity analysis excluding patients with a diagnosis of psoriasis, seborrheic dermatitis, contact dermatitis, lymphedema or peripheral venous disease and obtained nearly the same results. The manuscript has now been revised to include this additional sensitivity analysis.

7. Mediation by traditional suicide risk factors
The reviewer proposes we emphasize the findings of our mediation analysis, which suggests the increased risk for suicide observed in our study is mediated through traditional mental health risk factors. We agree the relationship between skin disease, mental health comorbidities and ultimate suicide is important. We have now elaborated on this in the abstract and strengthened this point in the discussion.

8. Clarification of the term “imprecision”
The reviewer requests a detailed explanation of why we refer to one of his own past studies as imprecise. The reasons relate to statistical sample size, and we intended no criticism of the methodology. In that study (*Allergy*. 2018), the association of mild (HR 0.81, 95% CI 0.33-1.96) and moderate-severe (HR 0.73, 95% CI 0.27-1.97) atopic dermatitis are similar. In each case, the confidence intervals are wide, encompassing hazard ratios that could suggest a protective association or a nearly doubled risk. The other study (Br J Dermatol. 2016) also has wide confidence intervals (IRR 2.08, 95% CI 1.03–4.21, P = 0.041), but the findings suggest an increased risk. We have now amended the discussion, including deleting the word “imprecision,” given that our meaning could be misconstrued.

9. Cherry-picking literature

The reviewer cautions there are debates in the literature and that we may have favored studies that support our hypothesis. We agree the literature on the association between atopic dermatitis and suicide is uncertain. To address the reviewer's concerns, we have now edited the introduction, presenting the study focused on atopic dermatitis first.

9. Emphasizing low absolute risk
The reviewer notes the increase in absolute risk attributable to atopic dermatitis is low. We agree. We have amended the conclusions in the abstract and the first paragraph of the discussion to emphasize the low absolute risk.

10. Primary vs. secondary ICD-9 Codes
The reviewer questions whether we included secondary (as opposed to primary) diagnostic codes in our definition of atopic dermatitis. We agree this is an important distinction that should be explicitly mentioned. In Ontario, physicians may only associate each encounter with a single ICD-9 code; in our physician visit data there are no secondary codes. We have now added this point to our methods section.

11. Inclusion of patients aged 15-18
The reviewer asked why we included patients aged 15-18 in our analysis whereas most studies of adults limit the population to age ≥18. We agree that our methodology is different than previous studies because we made the decision to include youth in our study population (age 15-18) since atopic dermatitis is more common among youth and suicide is a common cause of death in this population. This is now explained in the manuscript.

12. Exclusion of adults ≥55 years old
Similarly, the reviewer asked why we excluded older adults over 55 years. We agree again this differs from previous studies. We excluded patients older than 55 due to concerns about including other forms of non-atopic dermatitis in our case definition such as xerosis and itch associated with increasing age. This is now more carefully explained in the manuscript.

13. Five-year look-back window
The reviewer points-out a disparity between our look-back window (5 years) and our requirement for insurance enrollment in the study (1 year). We agree this could lead to differential healthcare access between cases and controls in remote years of each patient's look-back window. To address this, we have calculated the percentage of cases and controls who were eligible for the provincial insurance plan over the entire five year look-back. This is now presented in Table 1, with reassuring results that strengthen our analysis.

Reviewer: 2
1. Affirmation of importance of the topic
The reviewer expresses that he enjoyed our research paper. We thank the reviewer for acknowledging this research.

2. ICD-9 to identify atopic dermatitis and covariates
The reviewer comments that we use both ICD-9 and ICD-10 to identify cases of suicide whereas our primary predictor uses only ICD-9. We agree that this is discrepant because coroners' reports utilize both ICD-9 and ICD-10 in Ontario whereas the Ontario Health Insurance Plan database that records physician visits only uses truncated ICD-9 codes. As such we are limited to using ICD-9 codes for the majority of our variables, and we have now clarified this in the manuscript.

3. Stratifying atopic dermatitis based on severity, medication use
The reviewer suggests a stratified analysis based on atopic dermatitis treatments would be beneficial. We agree that such an analysis would be very interesting. Unfortunately, public medication data is only available for patients 65 and older or with low income; as such we were unable to include medication data for our patients. This has now been added as a limitation.

4. Recency of atopic dermatitis diagnosis
The reviewer suggests there may be differences in suicide risk according to the temporal relationship of the five visits for atopic dermatitis. We agree that an analysis examining the timing of atopic dermatitis could be interesting. Unfortunately, our study is not powered to examine the relationship of

atopic dermatitis and suicide in that level of clinical detail. We have now added this as an opportunity for future research.

5. Strengthening of the association in older populations
The reviewer notes that the association between atopic dermatitis and suicide is stronger for older adults, and asks if we have a potential explanation. We agree this is an interesting finding. Our interpretation is speculative; namely the cumulative burden of living with chronic diseases. We have now added this potential explanation to the discussion.

VERSION 2 – REVIEW

REVIEWER	Alexander Egeberg Gentofte Hospital, Department of Dermatology and Allergy, Denmark
REVIEW RETURNED	11-Jun-2018

GENERAL COMMENTS	The authors have improved the manuscript and responded adequately to most of my comments. However, there are still issues which the authors have not addressed sufficiently. Importantly, their conclusions are not supported by their data. My concerns are still of methodological nature. This is an epidemiological study that will likely be used by pharmaceutical companies in presentations and for interactions with payers, and it is therefore important to have as accurate a method as possible, since we otherwise risk making people appear more sick than they really are. Keep in mind that many people (unfortunately) only read the title and abstract of a paper, and make their impression based on that alone. Following the sensitivity analyses, with exclusion of patients with psoriasis and other skin diseases, the results are now non-significant, i.e. a null-finding. However, the authors still conclude that atopic dermatitis is associated with suicide. The “sensitivity analyses” would have been more appropriate as the primary analysis, since it excludes patients e.g. with psoriasis. Thus, the conclusion of the study could rather be that eczema was not significantly associated with suicide, but that in an analysis where other skin diseases such as psoriasis and seb.dermatitis were not excluded, there was a significant association between dermatitis (believed to be atopic) and suicide. Regarding the validation studies of ICD-codes, and use of the word atopic: The authors now have added a reference for the Danish ICD-10 validation study of atopic dermatitis. However, the issue is that ICD-9 and ICD-10 differs considerably in their accuracy, which is why it is problematic to use ICD-9 codes for AD research, as emphasized by the study by Hsu et al. Referencing a study that used ICD-10 codes is not appropriate in this context, and this should be removed from the manuscript. Moreover, as indicated above; when attempting to make a more specific cohort, there was no significant association. Thus, even if there was a – very small – associated with suicide, this association is extremely weak at best, and most likely due to residual confounding. The assessment of asthma and rhinitis co-occurrence in patients with “persistent atopic dermatitis” cannot help establish that these patients (those that committed suicide) had in fact atopic dermatitis. What the authors show by their analysis, is simply that patients with

	more health care contacts have a higher chance of achieving additional diagnoses of other diseases. Moreover, while the authors find that 22% of patients with “persistent atopic dermatitis” have a diagnosis of asthma, from their data, we have no way of knowing if the true asthma prevalence in persistent AD was in fact 45%, but that the 22% prevalence was simply due to dilution of the “atopic dermatitis” cohort by non-atopic cases of dermatitis. Arguing that other studies and other countries have used a potentially misclassified terminology does not make it more accurate or appropriate to use. We should as epidemiologists always aim for the highest level of methodological accuracy, even if the findings of the study may not be as sensational as one could have hoped. Therefore, in light of these considerations, especially the low validity of the ICD-9 code, as stated in my initial review the word “atopic” dermatitis should be removed.

REVIEWER	Mu-Hong Chen Taipei Veterans General Hospital, Taiwan
REVIEW RETURNED	13-Jun-2018

GENERAL COMMENTS	I have no further comment. Authors answered my questions well.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

1. Affirmation of the revisions

The reviewer starts by acknowledging improvement in the manuscript, including addressing concerns from his original review. We thank the reviewer for this affirmation.

2. Potential for misinterpretation

The reviewer expresses concern that our findings may be taken out of context, misquoted by others or exaggerated by pharmaceutical companies. We agree that third parties sometimes sensationalize the results of research. While the interpretation of our results by third parties is largely outside of our control, we have now made further efforts to pre-empt potential misinterpretation in the conclusion of the abstract and the discussion. Naturally, the interpretation of our findings could also be the subject of an accompanying editorial if the journal judges appropriate.

3. Null findings in sensitivity analyses

The reviewer next highlights our sensitivity analysis excluding patients with psoriasis and other skin diseases, yielding results that overlap the null hypothesis. We agree this post-hoc analysis has less statistical power than the pre-specified primary analysis despite showing a similar estimated odds ratio. We now make this point in the discussion but we are hesitant to over-interpret the results of this post-hoc analysis; instead we allow readers to judge consistency for themselves.

4. Validation of atopic dermatitis codes

The reviewer summarizes the results of a previous validation study of ICD-9 codes and raises distinctions with ICD-10 codes. We agree the results of the previous study (Hsu et al.) suggest our case definition is fallible. We now raise this caveat more forcefully when discussing the limitations of the study. Additionally, we have now removed the citations of the Danish ICD-10 validation study as suggested by the reviewer.

5. Weakness of link between predictor and suicide

The reviewer emphasizes that the association between our primary predictor and suicide is

numerically small. We agree, as would be expected in a population-wide study of suicide because most cases will be unrelated to skin disease. This was our rationale for also looking at other predictors of suicide (substance use disorders, mental illness). We now emphasize the modest overall magnitude of the association more carefully in the abstract and discussion sections.

6. Atopic dermatitis combined with rhinitis and asthma
The reviewer asserts that the prevalence of asthma and rhinitis observed in our patients may not be a perfectly accurate indicator of the prevalence of the diseases. We agree because the correlation of physician encounters with disease prevalence will be imperfect even in a system of universal care without user fees. Our intention was not to perfectly estimate the association of persistent atopic dermatitis with asthma and rhinitis or to estimate their baseline prevalence. The strong associations seen between our primary predictor and asthma (odds ratio = 2.63) and rhinitis (odds ratio = 3.27) suggest the connection is not merely chance or confounding by health system access. Instead, the pattern helps validate our primary predictor with known atopic dermatitis comorbidities. We now make this point more carefully in the discussion section.

7. Terminology for primary predictor
The reviewer expresses concern that ICD-9 codes are not a diagnostically accurate definition of atopic dermatitis, and suggests that we not use the term “atopic” when referring to our primary predictor. We agree that ICD-9 codes tend to be more accurate for disorders outside of dermatology such as infectious diseases. We have continued to use the term “atopic dermatitis” in accordance with internal reviewers and the other external reviewer. Of course, such definitions are open for debate and this could also be included as a topic in an accompanying editorial.

Reviewer: 2
1. Affirmation of the manuscript
The reviewer expresses satisfaction with all prior questions being answered and offers no further comments. We are grateful for the affirmation and have endeavored to maintain the article as recommended aside from the revisions discussed above.

VERSION 3 – REVIEW

REVIEWER	Alexander Egeberg Gentofte Hospital, Denmark
REVIEW RETURNED	29-Aug-2018

GENERAL COMMENTS	I am still concerned about misclassification. If this paper is to be published stating that this is atopic dermatitis, and not unspecified eczema, then the analysis excluding other skin conditions should be used as the primary model. The authors say that this is likely to be underpowered but does not show the power calculation to support their claim. Please present this. Moreover, adding additional patients that does not have atopic dermatitis but in stead have other skin diseases (e.g. psoriasis) does not add power, but rather dilute the accuracy of the cohort. Therefore; since the authors are so determined on keeping the word "atopic", then the correct thing to do is to use the analysis excluding other skin diseases. Post hoc or not. Either remove "atopic" or use the aforementioned analyses as the primary model.

VERSION 3 – AUTHOR RESPONSE

Reviewer: 1

1. Change in Terminology

The reviewer begins by acknowledging improvement in the manuscript and reiterates a suggestion to change the specific term “atopic dermatitis” to the more general term “eczema” in the manuscript, tables, and figures. We agree the accuracy of ICD diagnostic codes is uncertain and we have now adopted the suggested change in terminology throughout. We also explain the choice of this new terminology in the methods and discussion sections.