PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Prevalence and characteristics of psoriasis in Denmark – findings from the Danish Skin Cohort
AUTHORS	Egeberg, A; Andersen, Yuki; Thyssen, Jacob

VERSION 1 - REVIEW

REVIEWER	Yochai Schonmann Department of Non-communicable Disease Epidemiology, Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London WC1E 7HT, UK. Clalit Health Services; Department of Family Medicine, Rabin Medical Center, Petah Tikva, Israel Department of Family medicine, Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel.
REVIEW RETURNED	12-Dec-2018

GENERAL COMMENTS	The authors report on a cross-sectional survey, including approximately 11,000 Danish residents. Participants were asked about their dermatological diagnoses, as well as several other clinical characteristics. The sample included three groups: A sample of the general Danish population (Sample A); People with psoriasis (Sample B); and people with atopic dermatitis (Sample C). Sample A was drawn randomly from the general Danish population (Sample A), and samples B and C were drawn from those with registered diagnoses in the Danish National Patient Register (i.e. secondary care). The authors report on the prevalence of self-reported psoriasis in the general population sample, as well as on several other clinical characteristics of the 275 psoriasis patients in this group. They go on and use the questionnaires administered to those with a known psoriasis diagnosis (Sample B) and those with atopic dermatitis (Sample C) in order to estimate the sensitivity and specificity of patient-reported psoriasis to ascertain the diagnosis of psoriasis. The methods are well-described, and several interesting conclusions are reported. Reading through the manuscript, I believe that a few issues mandate further attention. 1. The study reports on results from the Danish Skin Cohort. The general construction of this cohort and other technical aspects seem to be sufficiently described, but a few more details would be helpful: a) I could not find the time period of the study, and would be happy to know when was the data collected.

	b) It was not clear to me what was the setting of the participants' interviews. Were they conducted face-to-face? Was it a telephone interview? 2. The psoriasis and the atopic dermatitis groups were defined based on diagnoses in the Danish National Patient Register, which seems to include only secondary care data. If indeed this is the case, than this implies that the included patients in samples B and C are likely to be those with severe psoriasis and severe atopic dermatitis. I believe this point should be made clear to the reader in both the methods section, and when discussing the study results and limitations. 3. The data in figure 1 suggests that over half of those with self-reported psoriasis were diagnosed by non-dermatologists (i.e. GPs?). Does this mean that such patients would not have been captured in Sample B (the psoriasis patients sample)? Perhaps some brief elaboration on the relevant structure of the Danish health system would help to clarify which physicians usually diagnose psoriasis patients in Denmark, and whether this is captured electronically. To what extent is mild-moderate psoriasis captured in this electronic register? 4. One of the study's main conclusions is that the the self-reported psoriasis prevalence was 7.9%. The authors interpret this as evidence that register-based studies underestimate the prevalence of psoriasis. This seems reasonable, but I believe the authors should consider mentioning other potential sources of bias for this estimate a) Affected individuals (i.e. people with a skin chronic skin condition) could be more prone or willing to take part in a survey (i.e. selection bias. Especially when considering the overall participation rate of around 40%) b) Not adjusting for age: Supplementary table 1 shows that the study population was comparable to that of the source population (i.e. the entire Danish population), although "marginally skewed". However, most of the results described in the paper refer to Sample A, which is not specifically shown in Supplementary table 1. I believe it could useful to show the age- and sex-distributions of each of the 3 samples separately. If the age distribution of sample A is not similar to that of the general Danish population, this means the prevalence estimates are biased (e.g. if sample A population is older than the general population, we would expect increased psoriasis prevalence). The authors could consider presenting age-standardised estimates, or mention the potential for bias in the discussion if the sample-specific age-distribution is not similar to the general population. 5. The authors attempted to assess the validity of patient-reported psoriasis. This is an important topic, as addressing the 'gap' between register-based data and 'real patients' is important for future research. Such validation studies are very much needed, and the authors succeeded in utilising their available data to address this topic. Nonetheless, they made several assumptions that could perhaps be made more explicit. a) Sensitivity - as I mentioned above, this is probably the sensitivity to ascertain the presence of severe psoriasis. If I

	understand correctly, this is the proportion of patients diagnosed in secondary care that also reported having the diagnosis. This probably should be made explicit in the text. b) Specificity - was calculated as the proportion of atopic dermatitis patients that reported they did not have psoriasis. According to the study-design none of them had a psoriasis diagnosis. The derived 88% specificity estimate is an interesting figure, but probably not completely representative of the general population (as it was calculated from a very specific patient population, those with [probably severe] adult atopic dermatitis). I would assume that in such a specific population the accuracy of patient-report would be different than the general population (i.e. these are more 'experienced' patients). I therefore believe that the derived specificity estimate is not necessarily applicable 'as-is' to the general population. It is probably a reasonable estimate, but I think think this should be discussed to avoid confusion. c) The most critical issue, in my opinion, is that of the reported positive and negative predictive values for self-reported psoriasis to detect physician-diagnosed disease. The PPV and NPV tell us what is the probability that a given response to a questionnaire is correct, and are therefore of great interest. However, I'm afraid the calculation presented in Table 2 is a bit misleading: The PPV and NPV are dependent on the underlying population. The authors combined the psoriasis sample and the non-psoriasis AD sample to creat an artificial population (over 50% of the combined population had psoriasis). This makes the PPV spuriously high. The 88% PPV would, therefore, only be applicable to similar (not realistic) populations with ~50% psoriasis prevalence. Even if we assume that the sensitivity and specificity are not heavily biased (see my comments above), when we apply them to the general population (e.g. psoriasis prevalence of 8%), we get a much lower PPV, of less than 40%. These issues could be addressed in several ways: a) Preferably - calculate the actual sensitivity and specificity in the general population, using Sample A (if it can be linked to the Danish Patient Register, and if that data is available to the authors) b) If additional analyses cannot be done, I would suggest discussing the limitations of the sensitivity and specificity estimates, and presenting the expected PPV/NPV in the general population. c) The authors could consider presenting the positive and negative likelihood ratios instead of PPV/NPV (measures that are independent of the population prevalence and pre-test probability) 6. Discussion - The authors speculate that the female predominance among dermatologist-diagnosed psoriasis is due to sex-specific health behaviours. However, this could also be an artifact of the underlying age-distribution (i.e. the proportion of women is higher as the population ages). It is difficult to assess if this is a relevant possibility without the age-distribution of the 3 specific samples separately. Minor comments: 1. Results - second sentence - should begin with "Data on", rather than "Data one"

	2. Results - The authors write that “41 individuals (1.2%) were excluded from the study (values treated as missing)” - This is a bit unclear to me - why were they excluded (what data was missing and why). How were missing values treated? This is a small number, so it probably did not have a big influence, but it would be helpful to clarify. 3. Conclusion (and abstract?) consider clarifying that the reported 7.9% prevalence is of self-reported psoriasis. 4. Table 2 - Consider adding the absolute numbers, or at specify below that this table refers to Samples B and C, and their sample sizes. 5. Figure 1 and 2 - Consider adding the sample size and specifying which of the study samples is depicted here.

REVIEWER	Jeong Eun Kim Hanyang University College of Medicine, Korea
REVIEW RETURNED	06-Jan-2019

GENERAL COMMENTS	The authors tried a new methodological approach to overcome the limitation of the studies using nation-wide health data. Validation of this questionnaire-based results could be helpful to support drawbacks of epidemiological studies. However, I have some queries. 1. Did you survey via telephone or email? Present the patients questionnaire as a supplement data. 2. This study focuses on the psoriasis prevalence and validation. Please add more details on validation part. Clarify the 'sensitivity', 'specificity', 'PPV', 'NPV' (definitions, denominators and numerators..) and the use of data from Sample B & C. 3. In reference section, journal name should be listed as an abbreviation according to the author guideline.

VERSION 1 – AUTHOR RESPONSE

Comments from reviewer 1

General Comment:

Participants were asked about their dermatological diagnoses, as well as several other clinical

characteristics. The sample included three groups: A sample of the general Danish population (Sample A); People with psoriasis (Sample B); and people with atopic dermatitis (Sample C). Sample A was drawn randomly from the general Danish population (Sample A), and samples B and C were drawn from those with registered diagnoses in the Danish National Patient Register (i.e. secondary care).

The authors report on the prevalence of self-reported psoriasis in the general population sample, as well as on several other clinical characteristics of the 275 psoriasis patients in this group. They go on

and use the questionnaires administered to those with a known psoriasis diagnosis (Sample B) and those with atopic dermatitis (Sample C) in order to estimate the sensitivity and specificity of patient-reported psoriasis to ascertain the diagnosis of psoriasis.

The methods are well-described, and several interesting conclusions are reported. Reading through the manuscript, I believe that a few issues mandate further attention.

Reviewer 1, Comment 1:

The study reports on results from the Danish Skin Cohort. The general construction of this cohort and other technical aspects seem to be sufficiently described, but a few more details would be helpful:

a) I could not find the time period of the study, and would be happy to know when was the data

collected.

b) It was not clear to me what was the setting of the participants' interviews. Were they conducted face-to-face? Was it a telephone interview?

Our reply:

We apologize that this was not clear from the manuscript. This information has now been added to the methods section.

Reviewer 1, Comment 2:

The psoriasis and the atopic dermatitis groups were defined based on diagnoses in the Danish

National Patient Register, which seems to include only secondary care data. If indeed this is the case, then this implies that the included patients in samples B and C are likely to be those with severe psoriasis and severe atopic dermatitis. I believe this point should be made clear to the reader in both the methods section, and when discussing the study results and limitations

Our reply:

We thank the reviewer for the opportunity to clarify this matter. Among the psoriasis and atopic dermatitis groups (Samples B and C), the majority of patients had mild psoriasis or mild atopic dermatitis when assessed by body surface area or the PO-SCORAD, respectively. Indeed, distribution of psoriasis severity and atopic dermatitis severity was as would be expected on a national level. However, since this is the topic of another manuscript currently in development, we respectfully suggest not to elaborate further on this in the present manuscript. Importantly, samples B and C were defined based on dermatologists diagnoses in the Danish National Patient Register. This register contains data from hospital inpatient visits since 1977, and outpatient visits since 1995. Since 2002, data from a number of private outpatient specialty clinics (which includes private practicing dermatologists) have also been recorded in this register. This is mentioned on page 6 of the manuscript.

Reviewer 1, Comment 3:

The data in figure 1 suggests that over half of those with self-reported psoriasis were diagnosed by non-dermatologists (i.e. GPs?). Does this mean that such patients would not have been captured in Sample B (the psoriasis patients sample)? Perhaps some brief elaboration on the relevant structure of the Danish health system would help to clarify which physicians usually diagnose psoriasis patients in Denmark, and whether this is captured electronically. To what extent is mild-moderate psoriasis captured in this electronic register?

Our reply:

According to figure 1 (and as also stated in the Results section, page 8), the majority of the 221 patients with psoriasis were diagnosed by dermatologists. This has now been explicitly stated in the Results section. The National Patient Register, which served as a source for Sample B, does also contain diagnoses from non-dermatologists, however, to ensure diagnostic accuracy of Sample B and C, patients were only eligible if the diagnosis had been made by a dermatologist. Upon selecting the cohorts for the study, Sample A was selected first. Once these individuals had been drawn, then Samples B and C were extracted. This was done, to avoid the risk of a falsely-low prevalence of psoriasis (if Sample B had been extracted before Sample A, then it would appear that there were in fact 10,000 fewer patients with psoriasis in Denmark when Sample A was collected). In Denmark, patients initially consult their GP, and from there they have the are referred to a private or hospital dermatologist if the GP finds it necessary to establish a firm diagnosis or provide certain treatments, e.g. phototherapy. A referral to a dermatologist does not require that patients have severe psoriasis, and even in hospital dermatology clinics, a lot of patients with mild psoriasis or atopic dermatitis are seen (e.g. referred by rheumatologist [psoriasis] or pediatricians [atopic dermatitis]). One example could be a patient with arthritis who is referred from the rheumatologists to the dermatologists to examine whether psoriasis could be the underlying cause. These patients often have mild disease, e.g. small plaques in the hairline or nail changes. In the Danish National Patient Register, data from hospitals and a number of private clinics (including private practice dermatologists) are recorded. Visits to GPs are not recorded in this registry, but data from GP visits are available from another registry, i.e. the Health Care Statistics Registry. As suggested, we have briefly described the relevant health care setup in the revised manuscript.

Reviewer 1, Comment 4:

One of the study's main conclusions is that the self-reported psoriasis prevalence was 7.9%. The authors interpret this as evidence that register-based studies underestimate the prevalence of psoriasis. This seems reasonable, but I believe the authors should consider mentioning other potential sources of bias for this estimate

a) Affected individuals (i.e. people with a skin chronic skin condition) could be more prone or willing to take part in a survey (i.e. selection bias. Especially when considering the overall participation rate of around 40%)

b) Not adjusting for age: Supplementary table 1 shows that the study population was comparable to that of the source population (i.e. the entire Danish population), although "marginally skewed". However, most of the results described in the paper refer to Sample A, which is not specifically shown in Supplementary table 1. I believe it could useful to show the age- and sex-distributions of each of the 3 samples separately. If the age distribution of sample A is not similar to that of the general Danish population, this means the prevalence estimates are biased (e.g. if sample A population is older than the general population, we would expect increased psoriasis prevalence). The authors could consider presenting age-standardised estimates, or mention the potential for bias in the discussion if the sample-specific age-distribution is not similar to the general population.

Our reply:

The reviewer raises an important point. In epidemiological studies, particular studies estimating disease prevalence from a survey, selection bias is a risk, since patients with more severe disease are more likely to agree to participate in the survey. To specifically overcome this issue, patients were not informed about the topic of the survey initially, but were simply told that this was a survey "regarding the people in the Danish population". From this initial information, 3,490 (out of 10,000 invited) people from the general population agreed to participate. Once they had agreed, they were able to withdraw their consent to participate. In total, 41 individuals (1.2%) individuals either withdrew

consent or did participate although they had initially agreed. These were thus excluded from the study. Thus, since only 1.2% of patients declined to participate, we feel fairly confident that selection bias did not significantly affect our findings. Regarding the age distribution of Sample A compared with the general population, we have now added data for each of the 3 samples (A, B, C) in the supplementary table. Indeed it is comforting to see that characteristics of Sample A are in fact more similar to the general population than the overall group of patients that accepted to participate.

Reviewer 1, Comment 5:

The authors attempted to assess the validity of patient-reported psoriasis. This is an important topic, as addressing the 'gap' between register-based data and 'real patients' is important for future research. Such validation studies are very much needed, and the authors succeeded in utilising their available data to address this topic. Nonetheless, they made several assumptions that could perhaps be made more explicit.

a) Sensitivity - as I mentioned above, this is probably the sensitivity to ascertain the presence of

severe psoriasis. If I understand correctly, this is the proportion of patients diagnosed in secondary care that also reported having the diagnosis. This probably should be made explicit in the text.

b) Specificity - was calculated as the proportion of atopic dermatitis patients that reported they did not have psoriasis. According to the study-design none of them had a psoriasis diagnosis. The derived 88% specificity estimate is an interesting figure, but probably not completely representative of the general population (as it was calculated from a very specific patient population, those with [probably severe] adult atopic dermatitis). I would assume that in such a specific population the accuracy of patient-report would be different than the general population (i.e. these are more 'experienced' patients). I therefore believe that the derived specificity estimate is not necessarily applicable 'as-is' to the general population.

It is probably a reasonable estimate, but I think this should be discussed to avoid confusion.

c) The most critical issue, in my opinion, is that of the reported positive and negative predictive values for self-reported psoriasis to detect physician-diagnosed disease. The PPV and NPV tell us what is the probability that a given response to a questionnaire is correct, and are therefore of great interest. However, I'm afraid the calculation presented in Table 2 is a bit misleading: The PPV and NPV are dependent on the underlying population. The authors combined the psoriasis sample and the nonpsoriasis AD sample to create an artificial population (over 50% of the combined population had psoriasis). This makes the PPV spuriously high. The 88% PPV would, therefore, only be applicable to similar (not realistic) populations with ~50% psoriasis prevalence. Even if we assume that the sensitivity and specificity are not heavily biased (see my comments above), when we apply them to the general population (e.g. psoriasis prevalence of 8%), we get a much lower PPV, of less than 40%.

These issues could be addressed in several ways:

a) Preferably - calculate the actual sensitivity and specificity in the general population, using

Sample A (if it can be linked to the Danish Patient Register, and if that data is available to the authors)

b) If additional analyses cannot be done, I would suggest discussing the limitations of the sensitivity and specificity estimates, and presenting the expected PPV/NPV in the general population.

c) The authors could consider presenting the positive and negative likelihood ratios instead of

PPV/NPV (measures that are independent of the population prevalence and pre-test probability)

Our reply:

Regarding “A) Sensitivity”:

Among sample B (dermatologists diagnosed psoriasis), these patients could (as mentioned earlier) be diagnosed either in a hospital setting or by private dermatologists. As mentioned in our reply to Reviewer 1, Comment 2, the majority of patients had mild disease. We have now in the validation section of the manuscript noted that this was performed among dermatologist-diagnosed patients.

Regarding “B) Specificity”:

As indicated earlier, the majority of patients in Sample B and C had mild disease, and we therefore do not believe that use of this cohort poses any major issues. However, we have added a sentence in the limitations section to ensure that this topic is adequately addressed.

Regarding “C) PPV”:

The reviewer raises an important point. We agree, and have now removed the PPV and NPR, and focused on sensitivity and specificity in the results section. The positive and negative likelihood ratios are now shown in Table 2. Furthermore, upon updating Table 2, we discovered an unfortunate mistake regarding the sensitivity and specificity of one of the questions, which now have been corrected. We apologize for this mistake.

Reviewer 1, Comment 6:

Discussion - The authors speculate that the female predominance among dermatologist-diagnosed psoriasis is due to sex-specific health behaviours. However, this could also be an artifact of the underlying age-distribution (i.e. the proportion of women is higher as the population ages). It is difficult to assess if this is a relevant possibility without the age-distribution of the 3 specific samples separately.

Our reply:

Please see our reply to Reviewer 1, Comment 4.

Reviewer 1, Comment 7:

Results - second sentence - should begin with “Data on”, rather than “Data one”.

Our reply:

Thank you for catching this typo. This has been corrected.

Reviewer 1, Comment 8:

Results - The authors write that “41 individuals (1.2%) were excluded from the study (values treated as missing)” - This is a bit unclear to me - why were they excluded (what data was missing and why). How were missing values treated? This is a small number, so it probably did not have a big influence, but it would be helpful to clarify.

Our reply:

Please see our reply to Reviewer 1, comment 4.

Reviewer 1, Comment 9:

Conclusion (and abstract?) consider clarifying that the reported 7.9% prevalence is of self-reported psoriasis.

Our reply:

This has now been clarified in the conclusion and the abstract.

Reviewer 1, Comment 10:

Table 2 - Consider adding the absolute numbers, or at specify below that this table refers to Samples B and C, and their sample sizes.

Our reply:

This has been added to the table legend.

Reviewer 1, Comment 11:

Figure 1 and 2 - Consider adding the sample size and specifying which of the study samples is

depicted here.

Our reply:

This information has now been added to Figure 1 and 2.

Comments from reviewer 2

General Comment:

The authors tried a new methodological approach to overcome the limitation of the studies using nationwide health data. Validation of this questionnaire-based results could be helpful to support drawbacks of epidemiological studies.

However, I have some queries.

Reviewer 2, comment 1:

Did you survey via telephone or email? Present the patients questionnaire as a supplement data.

Our reply:

Please see our reply to Reviewer 1, comment 1, and the updated Methods section. The Patient questionnaire was in Danish. While many of the phrases are unambiguous in the Danish language, it is not clear that this would be the case if they were translated into English. We therefore feel that presentation of the full questionnaire would be of little value, however, we have added an overview of the data collected in the survey and presented this in the supplementary materials.

Reviewer 2, comment 2:

This study focuses on the psoriasis prevalence and validation.

Please add more details on validation part. Clarify the 'sensitivity', 'specificity', 'PPV', 'NPV' (definitions, denominators and numerators..) and the use of data from Sample B & C.

Our reply:

This has been added to the table legend.

Reviewer 2, comment 3:

In reference section, journal name should be listed as an abbreviation according to the author guideline.

Our reply:

This has now been updated.

VERSION 2 – REVIEW

REVIEWER	Yochai Schonmann London School of Hygiene & Tropical Medicine, UK. Clalit Health Services, Israel
REVIEW RETURNED	04-Feb-2019

GENERAL COMMENTS	The authors have adequately adressed my comments.