PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Risks for comorbidity in atopic children: an observational study in Dutch general practices
AUTHORS	Pols, David; Bohnen, Arthur; Nielen, Markus MJ; Korevaar, J; Bindels, Patrick

VERSION 1 – REVIEW

REVIEWER	Aaron Drucker, MD, ScM Assistant Professor of Dermatology Brown University, USA
REVIEW RETURNED	09-Jun-2017

GENERAL COMMENTS	This is a study of comorbidities associated with atopic disorders conducted in a large primary care database. The sample size is large and population based. The authors have described a number of significant associations with atopic conditions. My main concern is a lack of a hypothesis-driven approach. The inclusion of all possible diagnoses in the database as potential outcomes leads to: (1) false positives from multiple testing, as the authors point out; (2) The inclusion of positive associations that are not meaningful as they are likely part and parcel with the disease in question such as the associations between atopic eczema and "pruritus," and "rash, localized;" (3) findings that are not meaningful as they are very non-specific (e.g., association between eczema and "stomach function disorder"); and (4) results that are likely due to confounding by frequency of health service utilization. I suspect a large amount of this sort of confounding. Evidence for this is that all associations reported in the tables are positive, none negative. Other minor comments: Line 48: Please change the word "proven" to "demonstrated" or something else less definitive Line 60: The question "Are children with one atopic disorder at risk to be underdiagnosed with another atopic disorder?" is not answerable with this data. I am confused by the terminology "episodes" and "moments" in the methods. Please clarify these terms. Why did the authors exclude trauma diagnoses and social problems? Both traumatic injury and psychosocial problems have been associated with atopic disorders and would be worth studying with specific hypotheses in mind.

	Have any studies been done on validity of ICPC diagnostic codes, specifically for atopic disorders? Please provide more detail on the matching process. How closely did ages have to match, etc. Please clarify whether those with a single diagnosis of an atopic disorder (as opposed to those with 2 or more visits for atopic disorders) were excluded from being controls. It seems that they were but this should be explicitly stated. The significant association with psoriasis among those with atopic eczema suggests misclassification among these 2 chronic skin diseases that are often confused for one another. Line 194: I disagree with the conclusion that the inclusion of symptoms such as wheeze for atopic eczema patients suggests underdiagnosis of asthma and a lack of knowledge of atopic comorbidities among GPs. I would suspect that most GPs are aware of these associations. There are other reasons for this association, such as including the symptom "wheeze" in addition to the diagnosis "asthma" or a recognition of early signs of asthma but a lack of chronicity up to that point to make a definitive diagnosis. It was not examined whether those reporting wheeze did or did not also report asthma.

REVIEWER	Karel Kostev QuintilesIMS, Epidemiology, Frankfurt, Germany Fresenius University, Medical Sciences, Idstein, Germany
REVIEW RETURNED	11-Jun-2017

GENERAL COMMENTS	This is interesting and clinically important article. Big number of patients were investigated and methods were appropriate. I have some minor comments: 1) Table 2; this is better than first column shows ICPC code and second column ICPC description, and not when ICPC description is shown in the last column. 2) Introduction/Discussion. I think that this article is very relevant: “Jacob L., Keil T. & Kostev K. Comorbid disorders associated with asthma in children in Germany- national analysis of pediatric primary care data Pediatr Allergy Immunol. 2016 Sep 10. doi: 10.1111/pai.12656”, but it was not cited. 3) The term “atopic children” seems to be a little strange; maybe ‘children with atopic ….”?

REVIEWER	Sinead Langan London School of Hygiene and Tropical Medicine
REVIEW RETURNED	24-Aug-2017

GENERAL COMMENTS	The authors have addressed an important question, the associated morbidity with atopic disorders. Major comments My first comment relates to the validity of the ICPC codes for atopic disorders. Has this been assessed? Do we know anything about the validity of the codes? The strong association observed between eczema and psoriasis strongly suggests misclassification as these disorders are not known to coexist frequently. I wondered if requiring practices to have "sufficient coding" >70% was a good idea in the context of EHR data. In administrative systems, physicians are required to capture codes for each consultation but this is not usually the case in EHR settings. This could lead to a non-representative group of practices being included. Has this been assessed? I wondered why the authors had chosen their study design. Why not just do a cross-sectional study? The methods used don't seem typical of the usual case control study where we start with the outcome (atopic disorder) and look back to the exposure. It seemed as if the analysis was more analogous to a cross-sectional study. What was the advantage of matching rather than adjusting for age and gender? It was not clear in the study during what time period the various diagnoses could have been recorded. The study was in 2014, but could the diagnoses of either the atopic disorder or the potential associated disorders be ever? It would be useful to have greater clarification. It would be worth discussing the requirement to be followed up for 3 years, as this automatically excludes young children. Why was this chosen? Was there any adjustment for confounders? Did they use 99% confidence levels or 95% and what happens if they use 99% CIs? I wondered why they decided social problems were not relevant to children? I didn't quite follow the results "After selecting….and with a higher probability". Can the authors clarify? In terms of associations with symptoms of other atopic disorders, this could be for two reasons (1) the children might be too young and may not have received a diagnosis yet or (2) the GPs may have recorded symptoms without a code but may still have treated appropriately. Might be worth exploring. The authors should present a table of baseline characteristics.

	I thought that the authors should have a table showing all associations (even if not significant). If this is too large for the journal, could be in supplementary material. It allows the reader to see how many associations were observed so they can assess the probability of chance associations. Some of those displayed are not significant. The authors should discuss their lack of power to detect some associations. Minor issues The definition of atopy is not the usual one. ICPC codes are not defined when first used. I would be careful about saying “proven associations”- say “repeated associations”

VERSION 1 – AUTHOR RESPONSE

Reviewer 1:
Comment 1. There is a lack of hypothesis-driven approach.

RESPONSE: The reviewer makes a good point. This study is indeed not ‘hypothesis-driven’. In this explorative study, we chose a ‘hypothesis-generating’ approach. This might not have been very clear from the introduction, so we added the next sentence: The design of this study allows new hypotheses to be generated, providing valuable input for future research.

Comment 1.1. Multiple testing.

RESPONSE: An important limitation regarding this type of explorative study is the unavoidable multiple testing. We recognize this risk, as pointed out in our discussion. In order to reduce this risk, we used very low p-values of 0.001.

Comment 1.2. The inclusion of positive associations that are not meaningful .

RESPONSE: One of our hypothesis is: GPs are not always fully aware of relevant atopic comorbidity, or at least do not label it correctly. We added an example in the ‘main results’-paragraph to make this more clear: First of all, a child diagnosed with atopic eczema is also diagnosed with pruritus, suggesting possible misclassification.

Comment 1.3. Findings that are not meaningful as they are very non-specific.

RESPONSE: The reviewer points out the association between eczema and stomach function. In the discussion of the article (line 242), we discuss these gastrointestinal-related symptoms that were frequently diagnosed in our study. We believe that these GI-related symptoms could be related to IgE-mediated food allergies and we think it is therefore of interest to discuss them.

Commment 1.4. Results that are likely due to confounding by frequency of health service utilization. The evidence to support this, is that all associations reported in the table are positive, none negative

RESPONSE: The reviewer is right, but we discussed this point already in the discussion as follows: Fourthly, atopic children might visit the GP more frequently than non-atopic children. And although this may be more representative of parental fears, rather than an indication of morbidity, it can result in more detected morbidity in atopic children and could partly explain some of the associations found. In future research, the number of consultations might need to be taken into account in the analyses.

Comment 2. Line 48: Please change the word "proven" to "demonstrated" or something else less definitive.

RESPONSE: we changed the word to ‘demonstrated’.

Comment 3. Line 60: The question "Are children with one atopic disorder at risk to be underdiagnosed with another atopic disorder?" is not answerable with this data.

RESPONSE: We removed this research questions from the introduction, since we believe it causes confusion. This study can generate hypothesis, it cannot test hypothesis. We made this more clear in the introduction: The design of this study allows new hypotheses to be generated, providing valuable input for future research.
We rephrased the other research question from “Are atopic children at increased risk for specific non-atopic symptoms or diseases, that general practitioners (GPs) should be aware in order to reduce the risk of underdiagnosing relevant comorbidity?” in “Are atopic children at increased risk for non-atopic symptoms or diseases? Awareness by GPs of these risks may reduce the probability that relevant comorbidity is not diagnosed.”

Comment 4. I am confused by the terminology "episodes" and "moments" in the methods.

RESPONSE: The term ‘moments’ is removed from the manuscript, to make it more clear. “Episodes” are now described in the methods section: Primary care physicians (gatekeepers for the Dutch healthcare system) recorded morbidity using the International Classification of Primary Care (ICPC), a classification method for primary care that is accepted by the WHO (23). Dutch GPs cluster relevant consultations, prescriptions and referrals, in ICPC classified “episodes of care”. An episode of care is a health problem or disease from its first presentation to the GP to the last presentation for the same problem.

Comment 5. Why did the authors exclude trauma diagnoses and social problems?

RESPONSE: The registration of ‘social problems’ in EHRs are not very reliable. For example, alcohol abuses of one of the parents, might not be registered in the EHR of a child, but only in the EHR of the parent. Still it could have potential influence on the wellbeing of the child. Because of this possible registration bias, we did not focus on social problems.
Regarding trauma related diagnoses, we are not aware of any study that specifically relates atopic disorders with a specific trauma-related diagnosis (e.g. broken leg). Since there are many trauma-related ICPC-codes, the risk for a type-1 error would be substantial.

Comment 6. Have any studies been done on validity of ICPC diagnostic codes, specifically for atopic disorders?

RESPONSE: Regarding the validity of atopic disorders: We tried to increase the validity of the atopic diagnoses by correcting atopic-related episodes of care. In practice, an atopic episode of care was only maintained if (between 2002-2014) the child had at least contacted the GP twice in that episode of care and had received at least two relevant prescriptions. Furthermore we added some background to the method paragraph to prove the validity of ICPC diagnostic codes: Primary care physicians (gatekeepers for the Dutch healthcare system) recorded morbidity using the International Classification of Primary Care (ICPC), a classification method for primary care that is accepted by the WHO (23). It has been translated in 22 languages and is now widely used for the routine collection of data on episodes of care, but also in encounter studies (24). Routinely collected general practice computer data, aggregated into large databases, is used for epidemiological research(25). Hippisley-Cox et al. illustrates how routine clinical data, in selected high recording practices (this selection criteria was also applied in the present study), are now reaching reasonable levels of accuracy and completeness for a range of key variables (26). According to Britt et al., morbidity data, actively collected by GPs, provide a reliable overview of morbidity managed in general practice (27).

Comment 7. Please provide more detail on the matching process.

RESPONSE: For each atopic child, one matched control patient was selected. We added the next sentence in order to make this more clear: Controls were only matched if a 100% match on age, gender and general practice with an atopic child was determined.

Comment 8. Please clarify whether those with a single diagnosis of an atopic disorder (as opposed to those with 2 or more visits for atopic disorders) were excluded from being controls.

RESPONSE: If a child was diagnosed with an atopic disorder, but later excluded in the study because he or she didn't meet the criteria (e.g. 2 consultations and 2 related prescriptions), this child could not become a control. We added the following sentence in the text: … and was excluded from the study (this child could not be used as a control patient, to make sure that controls did not have any atopic disorder).

Comment 9. The significant association with psoriasis among those with atopic eczema suggests misclassification among these 2 chronic skin diseases that are often confused for one another.

RESPONSE: The reviewer mentions an important explanation for this observation. We added the following sentence to the manuscript: Although the clinical pictures of these two diseases can be very different, the observed association could also suggests misclassification among these two chronic skin diseases that are often confused for one another.

Comment 10. I disagree with the conclusion that the inclusion of symptoms such as wheeze for atopic eczema patients suggests underdiagnosis of asthma and a lack of knowledge of atopic comorbidities among GPs.

RESPONSE: The reviewer is right. There may be reasons why GPs would use symptom diagnoses. We added this to the discussion: However, a GP could also use symptom-related ICPC-codes deliberately when the purpose is to record a provisional diagnosis (e.g. wheeze as the provisional diagnosis of asthma).

Reviewer 2

Comment 11. Table 2; this is better than first column shows ICPC code and second column ICPC description, and not when ICPC description is shown in the last column.

RESPONSE: we changed the order of the columns in the tables 2-5. It makes the tables indeed easier to read. (We didn't use 'track-changes' in order to present a normal lay-out of the tables for the editor and reviewers.)

Comment 12. Introduction/Discussion. I think that this article is very relevant.

RESPONSE: The reviewer provides us with a very relevant reference. We used the reference in both the introduction as well as in the discussion section of this article.

Comment 13. The term "atopic children" seems to be a little strange; maybe 'children with atopic …."?

RESPONSE: To our knowledge, the term 'atopic children' is widely used in international literature. We did not change it, but will do so if the BMJ Open prefers another phrasing.

Reviewer 3

Comment 14. My first comment relates to the validity of the ICPC codes for atopic disorders.

RESPONSE: The reviewer addresses the same concern as reviewer 1. We would like to refer to point 6 of this rebuttal letter.

Comment 15. I wondered if requiring practices to have "sufficient coding" >70% was a good idea in the context of EHR data.

RESPONSE: On average, Dutch GPs code >95% of their consultations with an ICPC-code. A financial incentive stimulates GPs to do this. Therefore the 70% criteria is still quite conservative. We therefore do not expect serious selection bias. We addressed this now in the article by mentioning the average of >95%.

Comment 16. I wondered why the authors had chosen their study design.

RESPONSE: We might have not described the study design clearly in the manuscript. The first sentence under 'design' is therefore changed in: An observational study design was used in which cases with one atopic disorder were matched with controls without any atopic disorder.

If we would have used all available children and if we would have adjusted for age, gender and GP, there would have been a substantial risk that everything would become statistically significant as a result of very large control groups. By matching, we avoid this problem, studying the effect of age, gender and GP more reliable.

Comment 17. It was not clear in the study during what time period the various diagnoses could have been recorded.

RESPONSE: The atopic disorder should have been diagnosed (if the data was available) between 2002-2014. For each child (0-18 years), a minimum follow-up of 3 years was required (e.g. data had to be available for 2012-2014) for the present study to reduce the risk of registration bias. Therefore, if a child had the diagnosis of an atopic disorder somewhere between 2002-2014, we consider the child to have the atopic disorder also in 2014. We clarified this in the manuscript by including the following: … and was considered to be a chronic problem.

Regarding comorbidity, this is different. A child was considered prevalent for a specific symptom or disease if the child had at least one active episode of care for that symptom or disorder in the full year 2014. We clarified this in the manuscript by including the following: After establishing which child had an atopic disorder (see above), a child was considered prevalent for a specific symptom or disease if the child had at least one active episode of care for that symptom or disorder between January and December of 2014.

Comment 18. It would be worth discussing the requirement to be followed up for 3 years, as this automatically excludes young children. Why was this chosen?

RESPONSE: For each child (0-18 years), a minimum follow-up of 3 years was required (e.g. data had to be available for 2012-2014) for the present study to reduce the risk of registration bias. For this reason, only data for children aged ≥ 2 years are presented here. In the Netherlands, GPs see about 72% of their patient population at least once a year. We considered a 3-year follow-up period to be sufficient time for a GP to diagnose a child with (atopic) disorders. We clarified this in the Method section.

Comment 19. Was there any adjustment for confounders?

RESPONSE: We matched for age, gender and general practice.

Comment 20. Did they use 99% confidence levels or 95% and what happens if they use 99% CIs?

RESPONSE: For our study we used a p-value of 0.001 as level of significance. However we presented 95%-CI in the tables, since most readers are used to these confidence intervals instead of 99.9%-CI.

Comment 21. I wondered why they decided social problems were not relevant to children?

RESPONSE: We would like to refer to point 5 of this rebuttal letter.

Comment 22. I didn't quite follow the results "After selecting….and with a higher probability". Can the authors clarify?

RESPONSE: The reviewer is right. We are repeating the methods here. We removed this sentence, since it doesn't contribute to a better understanding of the results.

Comment 23. In terms of associations with symptoms of other atopic disorders, this could be for two reasons…

RESPONSE: The reviewer is correct. For more details we refer to point 10 of this rebuttal letter.

Comment 24. The authors should present a table of baseline characteristics.

RESPONSE: This data is presented in table 1.

Comment 25. I thought that the authors should have a table showing all associations (even if not significant).

RESPONSE: In appendix 1, we present all the ICPC-codes that we have tested.

Comment 26. The authors should discuss their lack of power to detect some associations.

RESPONSE: On page 15 of the manuscript, we changed the sentence to: The prevalences of some of these disorders are low and a cross-sectional design (as used in the present study), might not have enough power to prove these relationships.

Comment 27. The definition of atopy is not the usual one.

RESPONSE: We changed the definition to: In the present study we refer to atopy as a (genetic) predisposition toward developing certain allergic hypersensitivity. Therefore the clinical manifestation of atopy is allergy. However, not all allergies are based on atopy. In this study the word 'atopic' refers to this genetically mediated predisposition, which did result in the clinical diagnosis by a GP of eczema, asthma and allergic rhinitis

Comment 28. ICPC codes are not defined when first used.

RESPONSE: In the methods paragraph ICPC-codes are defined when first used. To further improve the tables, we put the definition of an ICPC-code in the column next to the ICPC-code.

Comment 29. I would be careful about saying "proven associations"- say "repeated associations".

RESPONSE: We changed the word 'proven' to 'demonstrated'.

We confirm that the submitted material is still original and has not been published elsewhere. This is the first resubmission to BMJ Open.

All (co-) authors have reviewed and approved the final manuscript. All (co-) authors declare that they have no conflicting (financial) interest in relation to this article.

We hope you will find our manuscript suitable for publication.

VERSION 2 – REVIEW

REVIEWER	Karel Kostev QuintilesIMS; University Clinic of Marburg
REVIEW RETURNED	19-Sep-2017

GENERAL COMMENTS	no further comments