PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

Title (Provisional)

Validation of the Adult Asthma Epidemiological Score: a secondary analysis of the EPI-ASTHMA population-based study

Authors

Laranjeira, Catarina; Jácome, Cristina; Amaral, Rita; Bernardo, Filipa; Correia-de-Sousa, Jaime; Fonseca, Joao A.

VERSION 1 - REVIEW

Reviewer	**1**
Name	**Gardiner, Michael**
Affiliation	**University of California San Diego, Pediatrics**
Date	**16-Apr-2024**
COI	**n/a**

Please note: As requested by the editor, this review is focused solely on the methodology of the manuscript.

I appreciate the opportunity to review the original manuscript entitled “Validation of the Adult Asthma Epidemiological Score: a secondary analysis of EPI-ASTHMA.” This study aims to validate the A2 score to rule-in or rule-out asthma utilizing a sample of 1283 adults with a gold standard of GP diagnosis of asthma. The authors note an AUROC of 0.829 and determine rule-in and rule-out cutoffs with 83.1% specificity (PPV 62.4%) and 92.7% specificity (NPV 93.7%) respectively. This is a well written manuscript with no glaring grammatical or methodological flaws.

I have a few minor comments.

1) When reading through the referenced EPI-ASTHMA protocol, the authors seem to employ rigorous and sound methods to diagnose asthma (the reference standard). However, it is not specifically stated how this diagnosis is made other than “clinical assessment.” I defer to the content expert reviewers to determine whether this is an appropriate means of diagnosing adult asthma, or whether more specific guidelines (GINA?) should be utilized.

2) On page 9 when describing prior studies of A2, I believe the authors mean that the prior study showed a 93.1 sensitivity, not specificity.

3) The authors employ appropriate measures for analysis of diagnostic tests (Cronbach alpha, ROC, sensitivity, specificity, youden's index).

4) The authors state to use ROC and youden's index to determine their cutpoints, though I do not have an appreciation for how this was done, and the chosen cutpoints feel somewhat arbitrary. The statement "the two cut-off points were validated by analyzing the ROC curve performance, which included calculating the Youden index" is nonspecific and does not adequately describe how this was done. The authors could define an acceptable measure such as a goal sensitivity and specificity for the respective cutoffs. On my evaluation of table II and the ROC curve I feel that the "rule-out" score is appropriate (strong sensitivity/PPV, located at an inflection point on the ROC curve, however I feel that the "rule-in" score of >= 4 is somewhat arbitrary with a weaker specificity/PPV. I feel that a score of 5 appears to be a better performing cutoff, though this goes against the previously published score cutoff (I am unsure if this was factored into the cutoff decision).

5) The authors completed the STARD checklist that was submitted though there are many fields marked as "not applicable" referring to this being a secondary analysis. Regardless of where the source data was acquired, these checklist items could be determined by the methods employed in the parent study. In particular there is no reason that the author could not include items 21a and 21b (distribution of severity of asthma in those diagnosed, distribution of alternative diagnoses if any in those without asthma).

Reviewer **2**

Name **Mroueh, Salman**

Affiliation **American University of Beirut, Pediatrics and Adolescent Medicine**

Date **12-Aug-2024**

COI **None**

The manuscript says "This secondary analysis included part of the patients included in the EPI-ASTHMA study". It is not clear to me how this part of the patients was selected.

Reviewer **3**

Name **Sibanda, Elopy**

Affiliation **National University of Science and Technology Faculty of Medicine, Faculty of Medicine**

Date 31-Aug-2024

COI no competing interesting

This work addresses an important knowledge gap in the assessment of asthma. This has worldwide implications particularly in research limited settings.

VERSION 1 - AUTHOR RESPONSE

bmjopen-2024-086493 - "Validation of the Adult Asthma Epidemiological Score: a secondary analysis of EPI-ASTHMA"

Reviewer Reports:

Reviewer: 1

Prof. Michael Gardiner, University of California San Diego

Comments to the Author:

Please note: As requested by the editor, this review is focused solely on the methodology of the manuscript.

I appreciate the opportunity to review the original manuscript entitled “Validation of the Adult Asthma Epidemiological Score: a secondary analysis of EPI-ASTHMA.” This study aims to validate the A2 score to rule-in or rule-out asthma utilizing a sample of 1283 adults with a gold standard of GP diagnosis of asthma. The authors note an AUROC of 0.829 and determine rule-in and rule-out cutoffs with 83.1% specificity (PPV 62.4%) and 92.7% specificity (NPV 93.7%) respectively. This is a well written manuscript with no glaring grammatical or methodological flaws.

R: Thank you for your feedback.

I have a few minor comments.

1) When reading through the referenced EPI-ASTHMA protocol, the authors seem to employ rigorous and sound methods to diagnose asthma (the reference standard). However, it is not specifically stated how this diagnosis is made other than “clinical assessment.” I defer to the content expert reviewers to determine whether this is an appropriate means of diagnosing adult asthma, or whether more specific guidelines (GINA?) should be utilized.

R: A better description of how the diagnosis was made at stage 2 has now been added in the Methods section.

Please see page 8, lines 16-20: “Diagnosis of asthma followed GINA recommendations[1], relying primarily on the presence and pattern of respiratory symptoms (wheeze, shortness of breath, chest tightness, or cough) and supported by objective lung function findings such variable expiratory airflow limitation and high FeNO levels and other objective collected data (eosinophil).”

2) On page 9 when describing prior studies of A2, I believe the authors mean that the prior study showed a 93.1 sensitivity, not specificity.

R: You are right. This has now been corrected in the manuscript.

Please see page 8, lines 7-10: “The original authors suggested that asthma presence could be ruled in for scores of 4 or more (PPV of 93.3%, with 99.2% specificity and 89.4% accuracy) and ruled out for scores of 0 to 1 (NPV of 98.2%, with 93.1% sensitivity and 89.4% accuracy).[12]”

3) The authors employ appropriate measures for analysis of diagnostic tests (Cronbach alpha, ROC, sensitivity, specificity, youden’s index).

R: Thank you for your feedback.

4) The authors state to use ROC and youden’s index to determine their cutpoints, though I do not have an appreciation for how this was done, and the chosen cutpoints feel somewhat arbitrary. The statement “the two cut-off points were validated by analyzing the ROC curve performance, which included calculating the Youden index” is nonspecific and does not adequately describe how this was done. The authors could define an acceptable measure such as a goal sensitivity and specificity for the respective cutoffs. On my evaluation of table II and the ROC curve I feel that the “rule-out” score is appropriate (strong sensitivity/PPV, located at an inflection point on the ROC curve, however I feel that the “rule-in” score of >= 4 is somewhat arbitrary with a weaker specificity/PPV. I feel that a score of 5 appears to be a better performing cutoff, though this goes against the previously published score cutoff (I am unsure if this was factored into the cutoff decision).

R: We understand your point, indeed we made a selection of cut-offs based on those metrics but also considering previous knowledge (previous cut-offs defined and previous PPV cut-of). We had some doubts when deciding between the cut-offs 4 and 5 to rule-in asthma; and we ended in deciding 4 based on previous cut-off defined and also based on the reasonable PPV cut-off of at least 50%. We are now explaining in more detail how these cut-offs were

selected in the Methods section. In addition, we changed the way we presented the cut-offs selected.

Methods, page 7, lines 7-9: ". Additionally, we considered the combination of PPV, NPV, sensitivity, and specificity that best suited the purpose of this score for each case (rule-in/rule-out), also taking into account the previous cut-offs suggested [12]."

Results, page 12, lines 17-20: "Both cut-offs ≥4 or ≥5 could be appropriate to rule in asthma based on their accuracy in identifying asthma cases. Nevertheless, a cut-off of 4 or higher, with a PPV of 62.4%, and a specificity of 83.1%, was selected as being reasonable accurate in identifying asthma cases (78%) (Table 2)."

5) The authors completed the STARD checklist that was submitted though there are many fields marked as "not applicable" referring to this being a secondary analysis. Regardless of where the source data was acquired, these checklist items could be determined by the methods employed in the parent study. In particular there is no reason that the author could not include items 21a and 21b (distribution of severity of asthma in those diagnosed, distribution of alternative diagnoses if any in those without asthma).

R. Thank you for your relevant inputs. We have now made an effort in better completing the STARD checklist. Regarding 21a and 21b, unfortunately we did not had access to asthma severity nor alternative diagnosis from the participants.

Reviewer: 2

Dr. Salman Mroueh, American University of Beirut

Comments to the Author:

The manuscript says "This secondary analysis included part of the patients included in the EPI-ASTHMA study". It is not clear to me how this part of the patients was selected.

R: When this secondary analysis was performed, data collection was still ongoing. Furthermore, the authors aimed to use the same distribution of cases/no cases as in the primary study developing and validating the A2 score as it is known that accuracy measurements such as PPV and NPV are highly dependent on prevalence. This has now been better clarified in the Methods section, subheading Participants.

Please see page 7, lines 22-27: "This secondary analysis included part of the patients included in the EPI-ASTHMA study as data collection for EPI-ASTHMA study was still ongoing. All subjects diagnosed with asthma at stage 2 from the 34 participating primary care centers were included and those without asthma were randomly selected, in order to have a final sample of ~30% with asthma and ~70% without. This distribution, similar to the used in the

A2 score original study, was chosen as it is known that accuracy measurements such as PPV and NPV are highly dependent on prevalence [12].”

Reviewer: 3

Prof. Elopy Sibanda, National University of Science and Technology Faculty of Medicine, Medical University of Vienna

Comments to the Author:

This work addresses an important knowledge gap in the assessment of asthma. This has worldwide implications particularly in research limited settings.

R: Thank you for your feedback.

VERSION 2 - REVIEW

Reviewer	**1**
Name	**Gardiner, Michael**
Affiliation	**University of California San Diego, Pediatrics**
Date	**25-Sep-2024**
COI	

My prior comments have all been adequately addressed in the author's responses.