Author’s response to reviews

Title: Development of a questionnaire weighted scoring system to target diagnostic examinations for asthma in adults: a modelling study

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Author’s response to reviews: see over
Covering Letter

The points made by the reviewers are shown one by one in bolded italics, with the author's response and actions immediately following.

Reviewer 1 Maritta Kilpelainen

Point 1 Lines 1-2. “In the results section, the age ranges and mean ages of the respondents in the clinical review could be shown”

Author response: Insert this information in the Results section as follows:
(i) Results section, paragraph 1, line 5. After “…was incomplete” insert “The ages of the 180 respondents ……male.”
(ii) Results section, paragraph 4, subheading ‘Phase 3’, line . After “…end 200.” insert “In total, 145 ……40.7% were male.”

Point 2 Lines 3. “What was the percentage of mixed disease of all cases at different score levels?”

Author response: Insert this information as follows:
(i) Insert columns 4 and 5 in table 3.
(ii) Results, paragraph 4, subheading ‘Phase 3’. Line 11 After “…mixed disease” insert “(53 asthma, 10 mixed disease)”
(iii) Line 13 After “… mixed disease” insert “(77 asthma, 19 mixed disease)”

Point 3 Lines 4-5 “In the results section, you could possibly show the results of non-weighted scores and weighted scores (now shown shortly in Discussion)”

Author response: Insert this information as follows:
(i) Insert Table 4
(ii) Original table 4 now table 5
(iii) Results, paragraph 4, subheading ‘Phase 3’ after last line “…physician opinion.” Insert new paragraph “Table 4 shows the percentage ….. weighted score ranking”
(iv) Discussion Original final sentence in penultimate paragraph “There was less correlation …. weighted scoring”. Replace by “Hence, ranking according to the number of ‘yes’ answers may not produce the required probability ordering. This is illustrated by the small differences in proportions of clinical asthmatics associated with the various simple score thresholds shown in table 4.”
Point 4 Lines 6-7 “Tables: The age ranges could also be shown in Table 3. In table 4 the last three columns may not open to the reader”.

Author response: Insert this information as follows:
(i) Insert age ranges in column 3 in table 3
(ii) Expand column headings in original table 4 (new table 5)

Point 5 Lines 8-10 “In discussion …….. what else?” This point asks about reasons for wheezing/respiratory symptoms other than asthma in older people and smokers.

Author response: Insert this information as follows:
(i) Discussion, paragraph 2, line 4 after “….other than asthma” insert “for example, heart disease, malignant lung disease or one of the chronic obstructive lung conditions collectively referred to as COPD”
(ii) Discussion paragraph 2, last line after “…. other than asthma” insert “for example malignant lung disease, COPD, or heart disease”.

Point 6 Lines 11 – 14 “In the discussion ……..highlighted” This point asks for comparisons with other studies, including using simple scoring based on ‘yes’ answers, and the importance of this study

Author response: Insert this information as follows:
(i) Discussion. After end of original paragraph 1 “….taken into account” insert new paragraph 2 “Developing a model which uses ….greater than 0.5 were designated ‘asthmatic’”.

Point 7 Lines 15-18 Discretionary Revision “Although the use of PPV ….. risk factor analyses”. This point asks about standard epidemiological measures eg sensitivity, specificity etc.

Author response: Epidemiological measures such as these are of interest, but require assessment based on the whole population range. This is beyond the remit of the present study which aimed to investigate only the high probability individuals deemed of most interest in a screening situation (along with a small number of low probability individuals who were included only to demonstrate the diagnostic discrimination of the experts).

Reviewer 2: Raoul Wolf

Point 1 Lines 1 – 4 “While the statistical model ….clinical standard” This point asks for clarification of how the third phase determined validity.

Author response: Extend / amend the ‘Methods’ section to provide further clarification, as follows:
(i) Methods subheading ‘Phase 3’ Sentence 2 re-written and now reads “The weighted scoring system is valid if it can be shown to retain this property when applied to a new data set, and this was tested by comparing scores with clinical diagnosis of asthma in a subset of data collected in 2001.”
(ii) Methods subheading ‘Phase 3’ end of original paragraph 1 is “… designated clinically asthmatic”. Original paragraph 2 reads “Weighted scores ….”
probability of asthma”. Replace original paragraph 2 with new paragraph 2 to read

“As part of the 2001 population survey, each reviewed individual had already completed a postal questionnaire, and a weighted score was calculated based on questionnaire responses. For each possible score, the proportion of reviewed individuals with that score or higher, who had been designated ‘clinically asthmatic’ was calculated. These percentages reflect the association between score and probability of asthma and were used as an indication of the validity of the postal questionnaire and scoring system.”

Point 2  Lines 5 – 13 “How did the … issue”. The points made here relate to the fact that the 1995 modelling data were selected by different methods than those used for the test data.

Author response: This was intentional and necessary to provide the conditions, including independence, between data used for modelling and data used for testing / validation. Provide further clarification in Discussion, as follows:
(i) Discussion. After the new paragraph 2 inserted in response to Reviewer 1’s point 6, which ends …… greater than 0.5 were designated ‘asthmatic’” insert a new paragraph 3 “Since the aim of a screening system ….. scoring system in phase 3”.

Point 3 Lines 14 – 21 “It is surprising that criteria …..clinical suspicion of asthma”. This point asks why factors known to be associated with asthma have a low or zero weighting in the scoring system.

Author response: The weighted scoring model is based on a multivariate technique (logistic regression). As such, the separate question weights cannot be viewed simplistically in isolation, rather it is how they work together to produce the final weighted score which is relevant. The interpretation of the low weighting given to respiratory symptoms other than wheeze, for example, night cough or shortness of breath, is that these symptoms are highly correlated with wheezing, and as such provide no additional information over an above the high ‘wheeze’ weighting. Whereas any of these symptoms viewed in isolation would be highly correlated with a diagnosis of asthma, when viewed in the context of a multivariate model such as this weighted scoring system, it is the interaction between the variables which defines the final model.

Include clarification of this as follows:
(i) Results. Paragraph 2. Line 7. After “… found to be zero weighted” insert “and therefore, when used in combination with this set of questions did not contribute further to the overall weighted score”.

(ii) Discussion. Original paragraph 2, now paragraph 4, line 4. After .. reasons other than asthma, for example, heart disease or one of the chronic obstructive lung conditions collectively referred to as COPD” insert “The interpretation of the low weighting …..defines the model.”
**Point 4** Lines 21 – 31. “How frequently did the physicians ..... as opposed to COPD” The points covered here relate to agreement/disagreement between the experts and the differences in methodology when combining 3 expert opinions into a diagnosis for the modelling set, and combining these opinions in the test validation set

Author response: Insert this information as follows:

(i) Methods. Paragraph 2 subheading Phase 1. Line 17. After … for each individual [13]. Add new sentence “In order to ensure the independence ..... criteria or guidelines.”

(ii) Methods subheading ‘Phase 3’ Paragraph 1 line 11 Replace “Each physician classified” with “The method of combining the three independent physician opinions differed from that used in phase 1. This time, the aim was not to produce diagnoses as the basis of a mathematical model, but rather to emulate as far as possible diagnosis in a clinical setting. Each physician was therefore asked, on the basis of the clinical review information, to classify”

(iii) Results. Subheading ‘Phase 3’ Paragraph 1 Line 7. After “… not in the top 10%” insert “In general, agreement between the experts ….. one low probability.”

**Point 5** Lines 32 – 37. “The authors do not ..... differs from that taken by others” This point asks for comparisons with other studies, and the importance of this study

Author response: Developing a model which uses a questionnaire to identify likely asthmatics in the general population crucially depends on having a subset of questionnaires from respondents reliably classified as ‘asthmatic’ or ‘non-asthmatic’ on which to build the model. In a condition such as asthma there is inherent uncertainty in the diagnosis, and even detailed clinical review information inevitably produces disagreement between experts as to the diagnostic category for some of the reviewed individuals. Other studies have produced questionnaire models for predicting high risk asthmatics and these studies have either used a single expert or resolved the problem of disagreement between experts using methods such as ‘majority verdict’ or designated diagnostic rules. The importance of this present study lies in the rigorous methods used to capture the uncertainty inherent in asthma diagnosis by combining the opinions of three experts using probabilistic techniques, resulting in a reliable diagnosis for each individual in the phase 1 subset of questionnaires on which the weighted scoring model was built.

In addition, we had available the neural network model which allowed us to identify all the high probability asthmatics from the new 2001 survey – this provided us with the test set of likely asthmatics we required to validate the weighted scoring system.

(i) Provide further explanations of the methods used to combine experts for the modelling data in Discussion. After end of paragraph 1 “…taken into account” insert new paragraph 2 “Developing a model which uses …greater than 0.5 were designated ‘asthmatic’”.

(ii) The point about the high probability, independent validation set is already covered in the paper.