Symptom outcome measures in the ECRHS

There has been considerable variation in the use of the symptom questions in the ECRHS. Many papers have reported results based on individual questions.\textsuperscript{1-17} Some of these have additionally reported results for symptom combinations,\textsuperscript{2,3,6,9,14,16,17} some have only reported symptom combinations,\textsuperscript{18-22} and some have included bronchial responsiveness in a definition of asthma.\textsuperscript{2,3,5,19} This discussion paper considers the pros and cons of each approach in order to stimulate debate.

**Individual questions\textsuperscript{1-17}**

**Pros.** Promotes comparison with results of other studies that asked the same question(s) and also gave individual results.\textsuperscript{23,24} Interpretation simple, although limited for some questions. Allows readers of papers to form own summary. Youden’s index (sensitivity+specificity-1), assessed for prediction of physician-diagnosed asthma, high for some questions.

**Cons.** Many outcomes, with all the problems of multiple comparison of correlated outcomes. Sensitivity of some individual questions for ‘asthma’ may be low.

Repeatability measured by kappa statistic for agreement between stage 1 and 2 questionnaires, and validity as assessed by sensitivity and specificity for bronchial responsiveness, varies between questions.\textsuperscript{25} However, kappa, sensitivity and specificity are affected by prevalence of a positive response. Kappa should not be compared across questions with different prevalence. Sensitivity is likely to increase and specificity decrease as the prevalence increases. A study carried out prior to the ECRHS assessed repeatability using the average ‘correct’ classification rate, and found wheeze and asthma in last 12 months to have high repeatability, but that it varied between centres in the study.\textsuperscript{26} Repeatability of other questions tended to be lower.

**Combination of two questions to define ‘diagnosed asthma’\textsuperscript{6,9,17,20}**

**Pros.** Combination of ‘attack of asthma in the last 12 months’ with ‘current medication for asthma’ (positive response to either) is uncontroversial, increases sensitivity, and it is possible to compare with results of other studies.

**Cons.** All the drawbacks of the limitations of ‘diagnosed asthma’ as an outcome.

**Combination of ‘diagnosed asthma’ with ‘woken by attack of shortness of breath’, positive response to any of the three questions\textsuperscript{2,14,21,22}**

**Pros.** Sensitivity will be increased further. May be less affected by variation in diagnosis.

**Cons.** Specificity reduced. Less possibility of comparison with results of other studies than with above outcomes as specific combination may not be reported elsewhere.
Bronchial responsiveness (BHR)

Pros. Objective. Can (and should) be analysed as a continuous outcome variable. Specificity (when dichotomised) high for physician diagnosed asthma.

Cons. Increased BHR strongly associated with asthma, but not synonymous. Comparison with results of other studies affected by differences in protocol for measurement and/or cut-off point to define positive BHR. Reduced sample size in analysis. Sensitivity lower than symptom questions for physician diagnosed asthma.

Combination of any of above definitions of ‘asthma’ with ‘bronchial responsiveness’ (positive to both).\(^{2,3,5,19}\)

Pros. Specificity greater than question combinations.

Cons. Sensitivity less than question combinations. Also as for bronchial responsiveness alone. Cannot study relation of asthma with BHR if BHR included in definition.

Combination of several symptom/other questions into a composite score.

There are several methods for selecting and weighting the questions. The pros and cons overlap, but are not identical, so the methods are considered separately.

a) Number of positive responses to several questions.

Pros. Simple. May be little loss of information over differential weighting of questions. With sufficient questions the outcome can be treated as a quantitative variable. Avoids multiple outcomes. A positive response to several questions may maximise positive predictive value for BHR.\(^{27}\)

Cons. Equal weighting of questions may be questioned. Results, either in terms of sum, or a dichotomised variable,\(^{3,16}\) are difficult to interpret or compare with other studies. A positive response to several questions has low prevalence and sensitivity.\(^{26}\) A continuous score that combines questions on symptoms and asthma diagnosis may have greater power for some comparisons,\(^{27}\) but if incidence of symptoms is related mainly to smoking while incidence of asthma is independent of smoking (results of paper in preparation suggest this) then change in score will be misleading. A positive response to any 6 or more of 8 questions did not have greater predictive power than all 3 ‘ECRHS definition’ questions.\(^{27}\)

b) Question selection and weighting to form score determined by discriminant analysis.

This was attempted in a forerunner of the ECRHS.\(^{28}\) Questions were selected on their ability to predict BHR (dichotomised) by logistic regression. The weighting was chosen to maximise Youden’s index (sensitivity+specificity-1), but other indices could be maximised.
Pros. Avoids multiple outcomes. Selection of questions and weighting has rationale. Correlation of questions taken into account. Linear discriminant analysis could be used to predict continuous outcome.

Cons. Requires ‘gold standard’, both for selection of questions and determining weighting (see further discussion below). Sensitivity and specificity of score may differ between populations, so selection and weighting may not be generalisable.\textsuperscript{28} Results difficult to interpret or compare with other studies. Cannot study relation of derived score to gold standard.

c) Question selection and weighting determined by factor analysis.

A factor analysis was carried out on ECRHS main questionnaire data, to study internal consistency of questions.\textsuperscript{29} This identified factors labelled as wheezing/shortness of breath, cough, phlegm, asthma. A factor analysis of the screening data in the Italian centres suggested a single dimension for these questions after omission of the questions on ‘woken at night with an attack of coughing’ and ‘nasal allergies’.\textsuperscript{30} Sensitivity and specificity for diagnosis of asthma by a clinician (from the ECRHS data) was assessed.

Pros. Selection of questions and weighting has rationale. Reduces number of outcomes. Outcome not limited to one score. Does not require a ‘gold standard’.

Cons. Results difficult to interpret or compare with other studies. Factors may not be the same for different populations.

The problem of a ‘gold standard’.

Most of the difficulties arise because there is no agreed definition of asthma. If there were then either it could be used directly, or the best predictor could be determined. BHR is known to be raised in COPD patients and strongly associated with smoking, as well as increased in asthma patients. Physician-diagnosed asthma has the problem that diagnostic criteria and access to services may differ between populations, the very reasons that symptom questions and/or BHR are preferred. Hence neither is ideal as a gold standard. It can be argued that a proposed scale or symptom combination should be highly correlated or associated with BHR and physician diagnosed asthma, and so they can be used to assess construct validity, as was done by Pekkanen \textit{et al},\textsuperscript{27} and Grassi \textit{et al},\textsuperscript{30} but this is of limited value.\textsuperscript{31} Imperfect reproducibility of BHR and physician diagnosed asthma also limit their value as proxy gold standards. The intraclass correlation coefficient for short-term repeatability of BHR was reported as 0.85 to 0.89,\textsuperscript{32} depending on the summary statistic used, and a kappa statistic of 0.71 for physician diagnosed asthma.\textsuperscript{33}

Bronchial responsiveness

Toelle \textit{et al} proposed that for epidemiological studies asthma should be defined as wheeze in the last 12 months plus positive BHR.\textsuperscript{34} Pearce \textit{et al} considered the role of BHR in studies of asthma prevalence,\textsuperscript{35} concluding that BHR should be used as a supplementary measurement, and not combined with symptoms, endorsing the early
conclusion of Pekkanen and Pearce. They considered that BHR had no greater validity than symptom questions for comparison of asthma prevalence across populations that share the same language, symptom perception, labelling and diagnostic practice. This seems to beg the question of whether this can ever be assumed in an international study. More convincingly, they argued that if asthma symptoms are combined with BHR, the possibility is lost of studying the separate contributions of these factors to asthma prevalence. Pekkanen and Pearce showed that sensitivity and specificity of BHR to detect a self-report of physician-diagnosed asthma varies with cut-point to define positive BHR. The variation in protocols for BHR testing is therefore a problem for comparison between studies.

**General**

Pekkanen and Pearce considered the problem of defining asthma in epidemiological studies. They stated that the ‘validity of an instrument depends not only on its agreement with the gold standard but also on its intended use’. When a difference in prevalence between populations is required maximising Youden’s index minimises bias. Bias in relative risk is dependent on positive predictive value, which is largely determined by specificity. Definitions of asthma that have high specificity tend to have low Youden’s index. Positive predictive value also depends on prevalence.

**Incidence, remission and net change**

The above notes largely refer to risk factor comparisons in a cross-sectional study, but most comments are relevant to longitudinal analyses. In addition considerations of repeatability are more crucial, as it has been shown that incidence and remission are over-estimated (Chinn, unpublished), and relative risks for incidence can be biased towards or away from one (Pekkanen, unpublished) when symptoms are not fully repeatable. Net change is less biased, but knowledge of the differential false positive and false negative rates would be necessary to ascertain bias.

In favour of net change are that it is interpretable for any symptom, has public health interpretation, and (probably) low bias. Problems are that generalised estimating equations, required to estimate adjusted net change, may not converge when several factors are included. When follow-up varies, as in the ECRHS, net change per year (or 10 years of follow-up) can be estimated, but main effects of risk factors must be included as interactions with length of follow-up. Interactions of interest are difficult to test, and analysis lacks power.

Incidence analysis is more straightforward, as models converge, although not all parameters are necessarily estimated, and interaction terms can be included. However, except for first attack of asthma, no age of onset is likely to be recalled. Age of first attack in those who had asthma onset before ECRHS I, did not show good agreement between the two surveys. Limits of agreement were -10.8 to 11.2 years. Incidence analysis is less powerful than net change to detect risk factors that increase incidence and decrease remission (or vice-versa). If a risk factor increases or decreases both incidence and remission then it would not be detected by net change analysis.
Conclusion

The conclusion of Pekkanen and Pearce that selection of the instrument should depend on its intended use can be endorsed. However, they also recommended that the chosen method should be validated, although what constitutes acceptable validity was not defined. As discussed above, ‘validation’ against BHR or physician diagnosed asthma is not true validation. The pros and cons of each form of outcome can be deduced without a true gold standard, and selection should take place on the basis of the broad criteria.
References (those to ECRHS are not exhaustive)


12. Jarvis D, Chinn S, Potts J, Burney P on behalf of the European Community Respiratory Health Survey. Association of body mass index with respiratory


27. Pekkanen J, Sunyer J, Anto JM, Burney P on behalf of the European Community Respiratory Health Study (ECRHS). Operational definitions of asthma in studies on its aetiology. (ERJ in press)


