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Deriving preference-based single indices from non-preference based condition-specific instruments: Converting AQLQ into EQ5D indices

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Abstract

Suppose that one has a clinical dataset with only non-preference-based QOL data, and that one nevertheless would like to perform a cost/QALY analysis. This study reports on some efforts to establish a "mapping" relationship between AQLQ (a non-preference-based QOL instrument for asthma) and EQ5D (a preference-based generic instrument). Various methods are described in terms of associated assumptions regarding the measurement properties of the instruments. This is followed by empirical mapping, based on regressing EQ5D on AQLQ. Six main regression models and two supplementary models are identified, and the regressions carried out. Performance of each model is explored in terms of goodness of fit between observed and predicted values, and of robustness of predictions on external data. The results show that it is possible to predict mean EQ5D indices given AQLQ data. The general implications for methods of mapping non-preference-based instruments onto preference-based measures are discussed.

Key words: EQ5D, AQLQ, mapping

Abstract length: 148 words

Introduction

What can be done when only after an important clinical trial is designed and after data collection is completed (or only after the last chance to re-design the trial has been missed), researchers realise the need to carry out a cost-effectiveness analysis, preferably a cost/QALY analysis? It is very often the case that no suitable health classification instrument for deriving preference-based single indices is incorporated, and all that is available is either a condition-specific or generic quality of life instrument that does not have a preference-based value set to go with it. However, suppose there is an independent dataset in which the non-preference-based instrument used in the trial has been administered alongside a preference-based instrument to patients with comparable conditions to the trial patients, would it not be possible to derive some relationship and thus an algorithm between the two types of instruments and apply this to the trial results in order to gain some insight regarding the net change in health gain that took place?

These are the motivations that led to this paper, which deals with the derivation of a range of algorithms to convert non-preference information into preference-based- single-index-equivalents. The emphasis of the paper is mostly on practicality and feasibility, what can be done and said, rather than on the reasons why certain findings are obtained. The conversion of non-preference-based instruments to preference-based indices should be a second best to incorporating preference-based instruments in the trial in the first place. However, given that some major clinical trials take years from design to completion, and that the interest in incorporating cost/QALY studies into clinical trials is relatively recent, the kind of techniques explored here may be of great use for some time to come. These techniques should also be useful in analysing old data where no preference-based instruments were used.

The paper is based on a dataset in which a disease-specific non-preference-based instrument was administered alongside a generic preference-based instrument: these instruments were the Asthma Quality of Life Questionnaire (AQLQ) (1, 2) and the EQ5D (3) respectively. An algorithm for converting AQLQ information into EQ5D single indices are explored and compared.

The AQLQ has 32 items, and each item has 7 levels, with 1 denoting extreme problems and 7 indicating no problems. The number of possible health states that can be distinguished from each other, in theory at least, is $7^{32} = 1.1 \times 10^{27}$. The items in the AQLQ cover 4 domains (symptoms, activities, emotions, and environment). Results can be reported in terms of domain scores (average score across the items within each domain), or in terms of overall score (average across all 32 items). Neither scoring system is preference-based. There are four different versions of the instrument, two of which are relevant here: the first five items of the original "individualised" version asks respondents to list five activities that they personally find most limited by asthma and to indicate how much they are affected; the first five items of the subsequent "standardised" version specifies five types of activities instead of asking respondents to list their own particular activities. It is known that the individualised version results in higher rates of missing data for these five items (2) Appendix 1 lists the 32 items of AQLQ.

The EQ5D has five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has one item, and each item has three levels with 1 denoting no problems and 3 denoting extreme problems. The number of theoretically possible health states is $3^5 = 243$. EQ5D can be reported in terms of a 5-digit profile

indicating the level on each dimension, or in terms of a preference-based single index number. The latter is obtained by applying algorithms that link the 5-digit health state description with average valuations obtained from members of the public using the time trade-off method, or the visual analogue scale. In this study, EQ5D indices are obtained using the so-called MVH A1 value set, derived from a population survey in the UK using 10-year time trade-offs (for further details, see (4, 5)).

This paper is organised as follows. Section 1 reviews different ways in which this problem may be addressed. Then section 2 describes the regression models employed in this study and the data on which these models were applied. Section 3 reports the results of the regressions. Section 4 is for discussion, and our conclusions regarding the feasibility and desirability of this approach to this approach to deriving preference-based measures of health states.

1. Possible ways forward

There are four different ways in which to obtain indices from a non-preference-based instrument such as the AQLQ, and the following is a brief exposition of each of them.

1.1. Simple transformation

The overall AQLQ score (which runs from 1-7) could be transformed to a preference-based quality of life weight using the formula

$$Q = (A-1) / 6,$$

where *Q* represents the preference-based quality of life weight, and *A* represents the overall AQLQ score. Whilst this is the simplest approach, this is probably also the one involving the most stringent of assumptions. These are:

(a) that the AQLQ item levels can be interpreted to represent preferences on an interval scale, with 1 for worst health and 7 for best health,
(b) that the AQLQ items within a given domain carry equal weight,
(c) that the AQLQ domains cover all the domains of health of relevance to the condition and its treatment,
(d) that the 4 AQLQ domains carry equal weight,
(e) that the worst state (i.e. answering 1 to all 32 items) is equivalent to being dead and that there are no health states worse than dead, and
(f) that the best state defined by the AQLQ is equivalent to full health.

The AQLQ is designed to satisfy (c), but none of the remaining assumptions. Furthermore, there is empirical, though inconclusive, evidence indicating that different asthma symptoms cause different degrees of disutility to patients: Revicki and colleagues report that patients perceive shortness of breath as being worse than coughs and wheezes (6), while McKenzie and colleagues found that coughs and breathlessness are worse than wheezes and chest tightness (7). Thus this approach is unlikely to be empirically robust.

1.2. A valuation study of AQLQ

A second approach is to obtain preference weights for items (i.e. individual questions) of AQLQ using preference elicitation techniques, such as standard gamble or time trade-off.

This approach has been successfully undertaken in three studies, one with a condition specific measure (8) and two others involving a generic instrument, the SF-36 (9, 10). The estimation of preference weights using this approach involves three stages. The first is to derive a health state classification from the AQLQ that is amenable to valuation. Given that AQLQ has millions of millions of possible combinations (or states) in all, obtaining a valuation for every one of them is impossible. More importantly, it would be impossible for respondents to reliably differentiate health states containing 32 pieces of information. Therefore, the health state classification used may be reduced to the four dimensions, with appeal to assumption (b) above, that the items within a given domain carry equal weight. If so, since there are 7 levels on four dimensions, this reduced form will distinguish between 4^7 (=16,384) health states. An alternative may be to derive a health state classification using a sample of items considered to best represent the descriptive system of the original instrument. The second stage is to conduct a valuation survey of a subgroup of states defined by the classification, using standard gamble or time trade-off techniques. The third is to estimate a regression model to establish the value set. While a valuation study of AQLQ will be an interesting enterprise, it is unfortunately not feasible within the relevant resource constraints for our particular exercise.

1.3. A priori mapping of AQLQ to a preference-based quality of life instrument

In this approach components of AQLQ would be associated, by judgement, to specific domains and levels of another quality of life instrument for which preference-based weights exit (in this case, EQ5D). This would involve an extension of assumption (c) to

(c′): that the AQLQ and the preference-based measure both cover all the domains of relevance to the condition and its treatment.

This could be done in 2 different ways: by domains, or by items. In either case, AQLQ scores would be judged to be equivalent to a given level on a given domain of EQ5D. For instance, scores in the range 3 to 5 on the activity domain of AQLQ might be mapped to level 2 on the usual activities dimension of EQ5D, or levels 6 and 7 on item 14 might be equated to EQ5D anxiety/depression level 1. Needless to say, mapping by domains involves assumption (b), that the AQLQ items within a given domain carry equal weight, but mapping by item does not.

A variant of this would be to deal with the problem at the level of individual patients. The 32-item profile given by a specific patient would be taken as a whole and assigned a particular EQ5D profile, by judgement.

The main criticism for this approach is its arbitrariness (11). However, this could be overcome by testing empirically for the appropriateness of the judgements against real data (if there were any) to see whether or not patients who score between 3 and 5 on the AQLQ activities domain report themselves as being on level 2 for usual activities in EQ5D. This could lead to some kind of regression between peoples' self-reported AQLQ and EQ5D. Pushing this further is equivalent to the empirical mapping discussed in the following section.

1.4. Empirical matching of AQLQ with a preference-based quality of life instrument

The essence of this approach is to explore the relationship between the two instruments by regression analyses. This requires a real dataset in which patients have responded to an appropriate quality of life instrument (which will be the dependent variable in the regressions) alongside AQLQ (scores of which will be the independent variables). This is the method employed in this paper, and is explained in more detail in the following section.

2. Methods

2.1. The regression models

As summarised in table 1, there are at least six additive regression models, and two supplementary models, which could be used to estimate the relationship between AQLQ and EQ5D. Each is briefly explained. The notation used is as follows, where figures in square brackets indicate the potential range:

Q: the preference-based EQ5D index [-0.59,1]

A: the AQLQ overall score [1,7]

A_d: the score of an AQLQ domain [1,7], where *d* = *S*, *A*, *Em*, *Ev*,

A_i: the level of an AQLQ item [1,7], where *i* = 1, 2, … 32

$A_{i.x}$: a dummy variable that = 1 when the level of an AQLQ item *i* is *x*

E_d: the level of an EQ5D dimension [1,3], where *d* = *M*, *SC*, *UA*, *PD*, *AD*

All regressions are run using STATA version 6. Rather arbitrarily, "level" is used for AQLQ items and EQ5D dimensions, in other words, for discrete data; "score" is used for AQLQ

domains and overall scores, ie. for continuous data. Scores are always treated as continuous variables in the regressions, but levels can be treated as either continuous or discrete variables.

(1) $Q = a + \beta A + u$,

(2) $Q = a + \beta_1 A_S + \beta_2 A_A + \beta_3 A_{Em} + \beta_4 A_{Ev} + u$,

(3) $Q = a + \beta_1 A_1 + \beta_2 A_2 + \ldots \beta_{32} A_{32} + u$.

These 3 models are estimated using ordinary least squares (OLS), and the independent variables are treated as continuous. Model (1) requires assumptions (a) (b) (c') and (d), while model (2) requires (a) (b) and (c'), and model (3) requires (a) and (c').

(3'): $Q = a + \beta_1 A_1 + \ldots \beta_{32} A_{32} + \beta_{i.i} A_i A_i + \ldots \beta_{i.n} A_i A_n + \ldots \beta_{n.n} A_n A_n + u$,

where the subscript i.n represents item *i* and item *n* of AQLQ. This is supplementary to model (3), and additional interaction terms are included. In this study, the independent variables (*i* to *n*) used to form the interaction terms are selected according to the results of model (3) based on the criteria: (i) the sign for the estimator is positive (a positive sign is expected, since a higher AQLQ level should be associated with better quality of life and larger EQ5D indices), and (ii) its *p* value is less than 0.01. The latter criterion is arbitrary. The products of pairs of these items and squares of these items are added to the main effects model and estimated using OLS. Like model (3), this model requires assumption (a) and (c').

(4) $Q = a + \beta_{i.2} A_{i.2} + \beta_{i.3} A_{i.3} + \ldots \beta_{i.7} A_{i.7} + \ldots \beta_{n.7} A_{n.7} + u$,

where the subscript i.x represents level *x* on item *i* of AQLQ. The independent variables are a selected subset of the AQLQ items. In this study, this subset is selected according to the results of model (3) based on the criteria: (i) the sign for the estimator is positive, as expected, and (ii) its *p* value is less than 0.1. The latter criterion is arbitrarily set lower than its

counterpart in model (3'). This model continues to use OLS, but now the independent variables are treated as categorical variables. Thus, the number of independent variables will be 6 times the number of items selected (because each item has 7 levels). This model requires assumption (c') alone.

(4') $Q = a + \beta_{i.2}A_{i.2} + \beta_{i.3}A_{i.3} + \ldots \beta_{i.7}A_{i.7} + \ldots \beta_{m.7}A_{m.7} + u, \qquad m < n.$

Here, the independent variables are restricted further by applying the same criteria again. *Whole* items will be excluded, as opposed to excluding individual variables. This is because each variable represents different levels within a given item, and it becomes difficult to interpret if not all the levels of a given item were either included or excluded as one set. An alternative at this stage would be to merge levels by imposing equality constraints on the β coefficients. This was not done in this study.

(5) regress the five EQ5D dimensions on the 32 AQLQ item levels so that

$E_M = a + \beta_1 A_1 + \beta_2 A_2 + \ldots \beta_{32} A_{32} + u,$

$E_{SC} = a + \beta_1 A_1 + \beta_2 A_2 + \ldots \beta_{32} A_{32} + u,$

$E_{UA} =$

…

Again, OLS is used, and both the dependent and the independent variables are treated as continuous. Five regression functions, each for one of the EQ5D dimensions, are estimated. The required assumptions are (a) and (c'). Further, note that, while on the one hand the EQ5D algorithm for obtaining the preference-based single index is based on a series of coefficients to be applied to discrete numbers representing the level on different EQ5D dimensions, on the other hand the predictions obtained from this model for each of the EQ5D dimensions are on a continuous scale. Thus, this model cannot be used to generate predictions, and performance

in terms of goodness of fit cannot be tested. Rather, the objective of this model is to enable the selection of the independent variables used in the next model. In addition, this is the best model to explore empirically the relationship between the descriptive content of the two instruments, which is explored in section 5 below.

(6) regress the 5 EQ5D dimensions on a subset of the AQLQ item levels so that

$E_M = a + \beta_i A_i + \beta_j A_j + \ldots \beta_n A_n + u,$

$E_{SC} = a + \beta_i A_i + \beta_j A_j + \ldots \beta_n A_n + u,$

$E_{UA} =$

…

As in model (5), there is one regression function for each of the five EQ5D dimensions. Instead of OLS, multinomial logistic regressions are used where the levels within a given EQ5D dimension are treated as categorical variables (in other words, the dependent variable is now discrete). The independent variables are also treated as categorical, and are selected based on the results of model (5), while the selection criteria are the same as those used for model (4). The subset of independent variables will not necessarily be the same across the 5 EQ5D dimensions. The required assumption is (c') alone.

2.2. The goodness of fit

Given that the objective of the exercise is not to *explain* the relationship between AQLQ and EQ5D, the size of R^2 is not an indicator of much importance (although it is reported). The objective of the exercise is to *predict* the EQ5D index of a patient with a given AQLQ profile. Therefore the error of the prediction, or the goodness of the fit is taken as the criterion of performance of a model. This is reported in terms of the mean squared error (MSE): the

smaller this value, the better is the performance. Scatter plots between directly derived EQ5D indices and EQ5D indices predicted from the models will be examined (mostly not shown due to space constraints, but available from the corresponding author on request). The range of the predicted values, and Pearson's correlation coefficients between the observed and the predicted EQ5D indices are also reported.

While obtaining predicted EQ5D indices for the OLS models is straightforward, doing this for model (6) requires some explanation. The predictions generated from model (6) are the probability that a given respondent has a given level on each of the EQ5D dimensions (eg. the probability of level 1 for mobility, the probability of level 2 for mobility, etc). Based on these, there are two ways in which to calculate an EQ5D index. The first, "indirect" way, looks at these probabilities and determines the level for each of the five dimensions by choosing the level with the highest associated probability. This leads to the identification of an EQ5D profile, to which the value set can be applied. Since this approach makes no distinction between a probability distribution of 34%-33%-33% for the three levels of a given dimension and one of 90%-5%-5%, the method does not utilise all available information. The second, "direct" way, uses the probabilities for different dimensions and levels, including the interaction term for extreme problems, and combines these with the value set to calculate an expected EQ5D index. The shortcoming of this latter method is that it becomes almost impossible to have a predicted EQ5D index of 1.00. Given the observed distribution of EQ5D responses in the estimation dataset (presented below), where a substantial proportion of respondents had EQ5D of 11111, the choice was made to obtain predicted values for model (6) using the indirect method.

2.3. Robustness

The goodness of fit above is obtained for "within-sample" predictions. In other words, the dataset on which the model is estimated and the dataset on which the predictions are fitted are the same. In order to explore the robustness of the model, "out-of-sample" predictions are also obtained. Here, the data on which the predictions are fitted are not the same as the data on which the model is estimated. 75% of the whole sample is randomly selected, the regressions run, and then the predictions calculated for the remaining 25% of the sample. This is repeated three times on different splits of the whole sample, and MSE is reported for each.

2.4. The data

The data used in this study comes from a randomised controlled trial that looked into the effectiveness of computerised decision support in primary care, covering a wide range of patients with asthma. A sample of 3000 patients was identified from general practice morbidity and prescribing registers and were surveyed in three rounds roughly 12 months apart (*n* diminishes with round). Amongst other information, AQLQ and EQ5D were collected using posted questionnaires. The original AQLQ was used for round 1, and due to significant levels of item non-response to the individualised items in round 1, the standardised AQLQ was used for rounds 2 and 3. For further details, see Eccles et al (12).

There are three datasets to work on:

"R1": all responses to round 1; $n = 3059$; AQLQ items 1-5 are individualised,

"R23": all responses to rounds 2 and 3; $n = 3880$; items 1-5 are standardised, and

"R123": items 6-32 from rounds 1,2, and 3; *n* = 6939 (items 1-5 are excluded because of the lack of comparability of data from round 1 vs. rounds 2 and 3).

Across the three rounds, each EQ5D dimension has around 2-3% missing data. There are more missing data in AQLQ: 12-24% for items 1-5 of original AQLQ; and 2-11% for items 1-5 of the standardised questionnaire. For other items, 1-4% of responses are missing.

Mean EQ5D index in dataset R123 is 0.73. 27% of respondents report full health (11111). Other common states are 11121 (10%), 21222 (7%), 11112 and 11122 (6% each). 75% of respondents do not report any impairment at level 3 on any dimension. Further, some EQ5D dimensions have very few patients in level 3 (0.2% for mobility, 0.3% for self care).

Mean AQLQ overall score in dataset R123 is 4.94. Domain scores range from 4.81 (environment) to 5.10 (activities). The distribution of AQLQ responses is somewhat more uniform, so that the least frequently endorsed level (which always is the worst level) usually has over 3% responses, and at the least 1%. 91-97% of respondents (depending on dataset) have a "unique" response so that there is no other respondent sharing the same AQLQ response across all 32 items. Around 1% have one other respondent with the same response profile. 1-3% of respondents have no problems across any of the 32 AQLQ items (i.e. endorse level 7 on all 32 items).

The overall skewness of the data from both instruments is problematic. It means that data are thin regarding the more severe health states, and the ability of the model to predict with precision such states should be carefully observed. In an explanatory, or descriptive context, the skewness of the data would call for transformation of the data into a more symmetric

distribution before running the regressions. However, given that the objective of this exercise is to estimate a model for prediction, as opposed to explanation, and given also that the same skew of the AQLQ responses may not apply to the data to which the mapping algorithm is applied, data are not transformed.

2.5. The choice of regression models

There are three issues here: the inclusion of patient background characteristics, the use of generalised linear models, and the use of random or fixed effects models.

The independent variables of the regression models used are limited to AQLQ scores, and exclude patient background characteristics, such as age and sex, despite the possibility of misspecification. Preliminary analyses using dataset R1 and models (1) (2) (3) and (4) indicate that when age, age squared, and sex are included, these variables result in statistically significant coefficients. However, the other coefficients are hardly affected (maximum, minimum, and average change are: 0.010, -0.007, 0.000, and average absolute change is 0.000). Note moreover that, given that the final objective of the exercise is to apply the estimated mapping algorithm to trial data and to calculate net benefit of treatment, whatever variables included in the additive model that do not change between baseline and follow up observations will simply be cancelled out. Therefore, background characteristics are deliberately excluded from the regression models.

Given that the EQ5D indices used as the dependent variable in the OLS models are bounded to 1.00, the use of simple linear models risks the predicted values being larger that this limit. An alternative is to use a generalised linear model (GLM), wherein the dependent variable is

transformed into an *s*-shaped non-linear variable that approaches 1, but does not reach it. The obvious shortcoming of this in our context is that there are many responses with observed EQ5D index of 1.00, and the transformation will imply dropping these observations (because the transformed values approaches infinity). This can be accommodated by standardising the raw EQ5D indices to the range [0, 1], based on an artificial range, say, [-0.5, +1.1], and then transforming this. A preliminary analysis was carried out using dataset R1 and models (1) (2) (3) and (4), and applying a logit transformation to the thus standardised EQ5D indices. In terms of Pearson's correlation between the observed and predicted EQ5D indices, performance of GLM and the simple linear model are roughly the same (correlation coefficients of GLM are better by less than 1%). However, GLM for models (1) and (2) do markedly worse than the simple linear model in terms of MSE (>0.08 as opposed to <0.05), and maximum predicted value for those with EQ5D index = 1 is much smaller (around 0.65 as opposed to 1.00 ± 0.02). With models (3) and (4), GLM is comparable to the simple linear regression, but not better. Given the additional complication, the arbitrary nature of the standardisation and the transformation, and the fact that the maximum predicted EQ5D indices of the simple linear models hardly exceed 1.00, the associated benefits of GLM do not seem to outweigh its costs. Therefore the decision was made not to use GLM.

Finally, given that the datasets R23 and R123 are composed of repeated observations, there is theoretical scope to consider the use of either random or fixed effect models. Indeed, using dataset R123 and model (3), the Breusch-Pagen test indicates that there are individual effects. A subsequent Hausman test rules out the use of fixed effects model in favour of the random effects model. However, on the one hand, a requirement for the use of random effects models is that the independent variables and the individual effects are independent. On the other, the

independent variables being self-reported AQLQ, the two are unlikely to be independent. Therefore, the decision was made to not to use random or fixed effects models.

3. Results

3.1. Regression coefficients, p-values and MSE.

Model (1)

This indicates a positive correlation between EQ5D index and AQLQ overall score, and there is very little difference in the coefficients across the three datasets. Adjusted R^2 = 0.33 for all datasets, and MSE is 0.049 to 0.053.

$\beta_{overall}$ 0.12, $p < 0.01$,

Model (2):

As already outlined, AQLQ domain scores should be positively correlated to EQ5D indices (i.e. the larger the score the better the quality of life). AQLQ symptoms and activities domains have expected signs ($\beta > 0$), but emotions and environment domains have the opposite sign and $p < 0.1$, except for emotions for dataset R1 (where $\beta > 0$ but $p = 0.77$). Adjusted R^2 across the three datasets ranges from 0.35 to 0.37, and MSE ranges from 0.044 to 0.049.

$\beta_{symptom}$ 0.04 to 0.05, $p < 0.01$

$\beta_{activities}$ 0.10 to 0.11, $p < 0.01$

$\beta_{emotions}$ -0.02 to 0.00, $p = 0.01$ to 0.77

$\beta_{environment}$ -0.03, $p < 0.01$

Model (3):

There are certain AQLQ items that persistently have the reverse, or wrong sign ($\beta < 0$) with $p < 0.1$, across the three datasets. The "well behaved" items ($\beta > 0$ and $p < 0.1$ in at least two datasets) are:

Symptoms: 6, 16, 29, 30

Activities: 3, 5, 25, 28, 31, 32

Emotions: 15, 27

Environment: 26

The "badly behaved" items ($\beta < 0$ and $p < 0.1$ in at least two datasets) are:

Symptoms: none

Activities: 22, 24

Emotions: 21

Environment: 23

There are larger differences across datasets than with models (1) and (2), which is expected, due to the treatment of items 1-5. Adjusted R^2 across the three datasets is in the range 0.36 to 0.39 and MSE ranges from 0.042 to 0.048.

Model (3')

The AQLQ items selected to form the interaction terms are as follows:

dataset R1: 3, 5, 25, 27, 31

dataset R23: 2, 4, 5, 6, 16

dataset R123: 6, 16, 25, 27, 29, 31, 32

The five items selected for dataset R1 form 15 interaction independent variables (item 3 squared, item 5 squared, …; product of items 3 and 5, product of items 3 and 25, …), and similarly, there are 15 interaction terms for dataset R23, and 28 for dataset R123. Of these, six, six and 14 items respectively had regression coefficients with the expected sign ($\beta > 0$). For dataset R1 none of these had $p < 0.1$, for R23 two (product of items 2 and 4, product of items 2 and 16) had $p < 0.1$, and for R123 three (square of item 29, product of items 16 and 27, and product of items 16 and 29) had $p < 0.1$. Adjusted R^2 for the three datasets is between 0.37 and 0.40, and MSE is between 0.041 and 0.047.

Model (4):

The AQLQ items selected for this model based on model (3) are:

dataset R1: 1, 3, 5, 6, 25, 26, 27, 29, 31, 32

dataset R23: 2, 3, 4, 5, 6, 14, 16, 25, 28, 30, 31

dataset R123: 6, 16, 25, 26, 27, 28, 29, 30, 31, 32

Not many β coefficients have the wrong sign: there are five to 10 variables depending on dataset. Not all β coefficients have $p < 0.1$: coefficients with $p > 0.1$ tend to be clustered by items (eg. some AQLQ items have none or one variable with $p > 0.1$, while other items have more than four). Further, not all coefficients are "consistent within an item", in other words, ordering of coefficients within an AQLQ item do not match the ordering of the levels, so that for instance an improvement in AQLQ item (i.e. a higher level) results in an decrease in EQ5D index, other items being equal. Adjusted R^2 ranges from 0.37 to 0.40, and MSE from 0.041 to 0.048.

An additional model (4'):

Given that there remain in model (4) several items with the wrong sign, a further subset of items are selected. Selection criterion is that the number of β coefficients within the item with $p > 0.1$ is equal to or less than one. The AQLQ items used are:

dataset R1: 5, 6, 27, 31

dataset R23: 2, 5, 6, 16, 31

dataset R123: 6, 16, 27, 31, 32

This results in all coefficients having the expected sign, where most coefficients have $p < 0.1$ (one to three exceptions per dataset). Moreover, most coefficients are consistent within an item (two exceptions per dataset). Adjusted R^2 ranges from 0.37 to 0.39, and MSE is 0.043 to 0.048.

Model (5):

Given that there are three datasets (R1, R23, R123), $5 \times 3 = 15$ regressions are run. The results indicate which AQLQ items are correlated with the EQ5D dimensions, and thus are of interest. The list of well-behaved items is given below for model (6).

Model (6):

The independent variables selected from model (5) are:

R1, mobility:	3, 5, 25, 28, 29, 31, 32
R23, mobility:	2, 4, 25, 31
R123, mobility:	6, 8, 25, 27, 28, 30, 31, 32
R1, self care:	18, 25, 31, 32
R23, self care:	2, 3, 4, 11, 25, 32

R123, self care:	6, 18, 25, 28, 31, 32
R1, usual activities:	1, 2, 5, 8, 25, 27, 31, 32
R23, usual activities:	2, 3, 4, 16, 28, 30, 31, 32
R123, usual activities:	6, 8, 16, 25, 28, 29, 30, 31, 32
R1, pain/discomfort:	1, 3, 5,6, 11, 12, 14, 16, 25, 27, 29, 31
R23, pain/discomfort:	2, 4, 5, 6, 12, 14, 16
R123, pain/discomfort:	6, 8, 11, 12, 14, 16, 25, 26, 29, 31, 32
R1, anxiety/depression:	3, 6, 15, 26, 27
R23, anxiety/depression:	5, 7, 13, 14, 16, 26, 27, 31
R123, anxiety/depression:	6, 7, 13, 14, 16, 25, 26, 27, 29, 31

The sign and *p*-values of the β coefficients are mixed: not all of them have the right sign, and many of them have $p > 0.1$. The sign and *p*-values are not strongly clustered by items. This is likely to be affected by the uneven distribution of the EQ5D responses, especially the small proportion of those in level 3. MSE for the three datasets is in the range 0.072 to 0.077.

3.2. Goodness of fit

Goodness of fit is summarised in Table 2. While the OLS models (1) to (4') do better in terms of average predicted EQ5D compared to model (6), these models struggle to produce EQ5D indices that are negative. The improvement in moving down the list of OLS models can be seen in the minimum predicted EQ5D indices. The predicted individual EQ5D indices and

the observed indices have a correlation coefficient ranging from 0.56 (model 6, dataset R123) to 0.65 (model 4, dataset R1). Models (1) and (6) tend to be worse while models (3') and (4) perform better. In terms of prediction error, there is little difference between the OLS models, but models (3') and (4) perform slightly better than the others. Model (6) performs markedly worse compared to the OLS models. Figure 1 is a scatter plot between the observed and predicted EQ5D indices with model (6), using dataset R1, where the straight line drawn is the trend line through the plots. The figure illustrates the low concentration of the predicted EQ5D indices and their biased structure. Figure 2 illustrates the case of model (4), using dataset R1. Here, a higher concentration of the predicted values is observed, and the trend line coincides with the 45° diagonal, representing the unbiased nature of the prediction.

3.3. Robustness

For the OLS models, increase in error by going from within sample predictions to out of sample predictions is very small (less than 0.003), and the variation across the three trials is smaller (less than 0.002), thus implying the robustness of the models. Dataset R1 tends to have slightly smaller errors than R23 and R123. Again, model (6) does not perform well, suggesting that this is less robust than the others. Examination of scatter plots (not shown) suggests that the patterns of prediction and of errors are roughly the same between the split samples and the corresponding whole samples.

4. Discussion

This section will address three issues. The first is, given the results, which model should be recommended when EQ5D indices are to be estimated based on AQLQ data. The second is an exploration of the relationship between the two instruments given the results above. The last is the implications for mapping non-preference-based measures onto a preference-based one.

4.1. Recommended model

In terms of goodness of fit, models (3') and (4) do best. We favour model (4) for two reasons. Firstly, model (3') involves additional variables to model (3), not all of which have the expected sign or significance level, while model (4) performs only marginally worse. Secondly, model (3') requires the additional assumption (a) that the AQLQ item levels satisfy the interval property (see section 1.1 above). The regression coefficients of model (4) demonstrate that this assumption does not hold. While model (4) involves some inconsistent coefficients, accounting for these (as in model 4') does not lead to improvements in goodness of fit. Further, given that the number of items involved is not small, model (3), with fewer independent variables, may be seen as more practical. It will be advisable therefore to use model (4) for the main prediction, but to employ models (3), (4') and/or (3') as sensitivity analyses. When the AQLQ version in question is the original individualised version, then the coefficients based on R1 is recommended. When the standardised version is used, there is little to choose between the coefficients based on R23 and those based on R123.

4.2. The relationship between the two instruments

This sub-section will discuss the relationship between the descriptive content of EQ5D and AQLQ. If the relationship between EQ5D and AQLQ is stable, one would expect the same set of independent variables to be selected for model (4) across the three datasets. If on the other hand, there was no stable relationship, then the particular AQLQ items selected for one dataset may not apply to another dataset. Ignoring AQLQ items 1 to 5 (since they are not directly comparable between datasets R1 and R23 and were dropped from dataset R123), there are three AQLQ items with β coefficients that demonstrate the expected sign and good significance level across all three datasets: 6, 25, and 31. Six more items (16, 27, 28, 29, 30, and 32) are selected in two datasets, and there is only one item that is selected in one dataset alone (14). All this seems to indicate that the set of AQLQ items that are selected for model (4) is reasonably stable across the three datasets, implying a stable relationship across the two instruments.

Another way in which to explore this matter is to look at the results of model (5). While the results of this model are not expected to yield an algorithm with which to estimate EQ5D indices based on AQLQ data, it offers empirical information on the relationship between EQ5D dimensions and AQLQ items. Table 3 shows those AQLQ items where the association between the item and an EQ5D dimension is in the expected direction ($\beta > 0$) and $p < 0.1$, and Table 4 shows items with the reverse association ($\beta < 0$) and $p < 0.1$. The AQLQ items are grouped by their domains. From the first table, it can be seen that: the AQLQ items from the activities domain affect all EQ5D dimensions; the AQLQ items in the symptoms domain affect the EQ5D pain/discomfort and anxiety/depression dimensions most; and the emotions and the environment domains affect the anxiety/depression dimension.

However, Table 4 illustrates that for a number of AQLQ items the association with EQ5D dimensions is opposite to that expected, and that some of them are also persistent across the three datasets. Again, this suggests a stable relationship (albeit not in the expected direction) between the two instruments. It is not clear why AQLQ items such as 10 or 24, which are straightforward questions on asthma symptoms ("did you experience a wheeze in your chest?" "were you woken at night by your asthma?"), should result in this unexpected association. However, items 9, 17, and 23 merit some discussion. These items are worded as "did you experience asthma symptoms as a result of being exposed to cigarette smoke? / as a result of being exposed to dust? / as a result of the weather or air pollution outside?". The reason for the reverse association between EQ5D and these items may be that, if the patient (for whatever reason) has problems with mobility, self care, or usual activities, and thus does not go out, then this individual will not be exposed to cigarette smoke, outdoor dust or air pollution, and therefore as a result will not experience asthma symptoms in this way. In other words, better AQLQ levels can be associated with worse EQ5D levels. The only other AQLQ item worded similarly (item 26) has no association (expected or reverse) with EQ5D. This interpretation, if correct, throws light on the different conceptualisations of quality of life behind the two instruments. While on the one hand EQ5D targets problems in different dimensions of health regardless of their cause, on the other hand AQLQ looks into not only the experience of asthma symptoms but different causes and triggers for the symptoms, and how potential or anticipated symptoms affect patient behaviour. This relates to assumption (c').

4.3 Implications for mapping

This study has shown that it is possible to estimate a robust relationship between EQ5D indices with AQLQ. Thus, it is not impossible to obtain changes in quality of life in terms of preference-based single indices in a clinical trial where no direct observation is available. However, given that non-preference-based condition specific instruments and preference-based generic instruments are designed to measure different concepts of quality of life, one cannot substitute completely for the other, and mapping from one to the other is a second best strategy.

Given the large error associated with the prediction of EQ5D indices, none of these coefficients can be used to predict EQ5D indices of an *individual* patient. This study can be understood as a modelling exercise, where the observations are not systematically assigned to respondents, but are naturalistically determined by respondents' self-reported health. The obvious shortcoming compared to a more experimental setting is the skewed distribution of health states for which data are available. (This does not mean that the original data comes from a biased sample, but simply reflects the natural pattern of variability and skew in health status in the population of interest.) In the context of a modelling study, the ideal distribution of states would be evenly spread, with a good number of observations for each state: but the available information only covers an extremely small portion of all the possible AQLQ health states, and most respondents give the only available observation regarding the particular state they are in. This has two drawbacks: firstly, there are simply not enough data on the worst levels; and secondly, the data fed into the model is not rich enough to say what is the average EQ5D index of a group of patients with a given AQLQ response, because there are only a couple of patients at the most with any given AQLQ response.

There may be those who expect this kind of approach to replace the need to include preference-based instruments in a clinical trial altogether: if EQ5D indices can be predicted from AQLQ, or from any other instrument that is more widely accepted in the medical community, why bother arguing with medical colleagues over the necessity of burdening the patients with yet another instrument that provides information that could be derived through the instruments already included? Our findings, however, suggest that the derivation of preference values is only a poor second best: while the functional relationships are stable, the predictions have wide margin of error and the method is totally inappropriate for predicting EQ5D indices at the individual level. The costs of taking this approach (although not exactly quantified) are no doubt much larger than the marginal cost of including an EQ5D or other preference-based measure in the trial.

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Table 1: Summary of regression models

model	dependent variable	D/C †	independent variables	D/C †
(1)	EQ5D index	C	AQLQ overall score	C
(2)	EQ5D index	C	all AQLQ domain scores	C
(3)	EQ5D index	C	all AQLQ item levels	C
(3')	EQ5D index	C	all AQLQ item levels + interactions	C
(4)	EQ5D index	C	selected AQLQ item levels	D
(4')	EQ5D index	C	further selected AQLQ item levels	D
(5)	EQ5D dimension-level	C	all AQLQ item levels	C
(6)	EQ5D dimension-level	D	selected AQLQ item levels	D

† D/C indicates whether the variable is treated as Discrete or Continuous.

Table 2: Summary of regression results across the three datasets

	average	maximum	minimum	correlation ‡	MSE §
observed	0.719 to 0.734	1.000	-0.480 to -0.320	–	–
predicted (1)	0.719 to 0.736	0.940 to 0.987	0.241 to 0.292	0.57 to 0.58	0.049 to 0.051
predicted (2)	0.721 to 0.736	1.004 to 1.021	0.212 to 0.290	0.60 to 0.61	0.044 to 0.048
predicted (3)	0.732 to 0.743	0.994 to 1.029	0.178 to 0.241	0.61 to 0.63	0.042 to 0.048
predicted (3')	0.732 to 0.743	0.994 to 1.016	0.051 to 0.139	0.62 to 0.64	0.041 to 0.047
predicted (4)	0.729 to 0.740	0.931 to 0.956	-0.032 to +0.068	0.61 to 0.65	0.041 to 0.048
predicted (4')	0.724 to 0.733	0.913 to 0. 927	0.002 to 0.174	0.61 to 0.63	0.043 to 0.049
predicted (6)	0.808 to 0.814	1.000	-0.239 to -0.157	0.56 to 0.60	0.072 to 0.077

† Predicted EQ5D indices cannot be calculated for model (5).

‡ Range of Pearson's correlation coefficient between observed and predicted EQ5D indices, across the three datasets.

§ Range of mean square error across datasets.

Table 3: EQ5D dimensions and AQLQ items: AQLQ items with the expected association in model (5) (*p*<0.1, bold if across two datasets)

dimensions		M	SC	UA	PD	AD
symptoms	R1	29	**18**		**6 12 14 16 29**	
	R23		**6**	**6 30**	**6 12 14 16**	**14 16** 18
	R123	6 8 30	**6 18**	**6** 8 16 29 **30**	**6** 8 **12 14 16 29**	6 **14 16** 29
activities	R1	3 5 **25 28 31 32**	**25 31 32**	1 2 **5** 8 **25 31 32**	1 3 **5 11 25 31**	3 6
	R23	2 4 **25 31**	2 3 5 11 **25 32**	2 3 4 28 **31 32**	2 4 **5**	5 **31**
	R123	**25 28 31 32**	**25** 28 **31 32**	**25 28 31 32**	**11 25 31** 32	25 **31**
emotion	R1			27	27	15 **27**
	R23					**7 13 27**
	R123	27				**7 13 27**
environment	R1					**26**
	R23					**26**
	R123				26	**26**

Table 4: EQ5D dimensions and AQLQ items: AQLQ items with the reverse association in model (5) (*p*<0.1, bold if across two datasets)

dimensions		M	SC	UA	PD	AD
symptoms	R1	6 **24**			24	**10**
	R23			10 **24**		8 **10** 24
	R123	**24**	14	14 **24**	22	9 **10**
activities	R1	11				**11**
	R23		1			**19** 32
	R123					**11** **19**
emotion	R1	**13** **21**			**21**	
	R23		7	**15**	7	
	R123	**13** **21**		**15** 21	**21**	
environment	R1	**17**	**23**	**23**		
	R23	**17**	**9** **23**		**17**	
	R123	**17** 23	**9** 17 **23**	17 **23**	**17**	

Figure 1: The performance of model (6) dataset R1

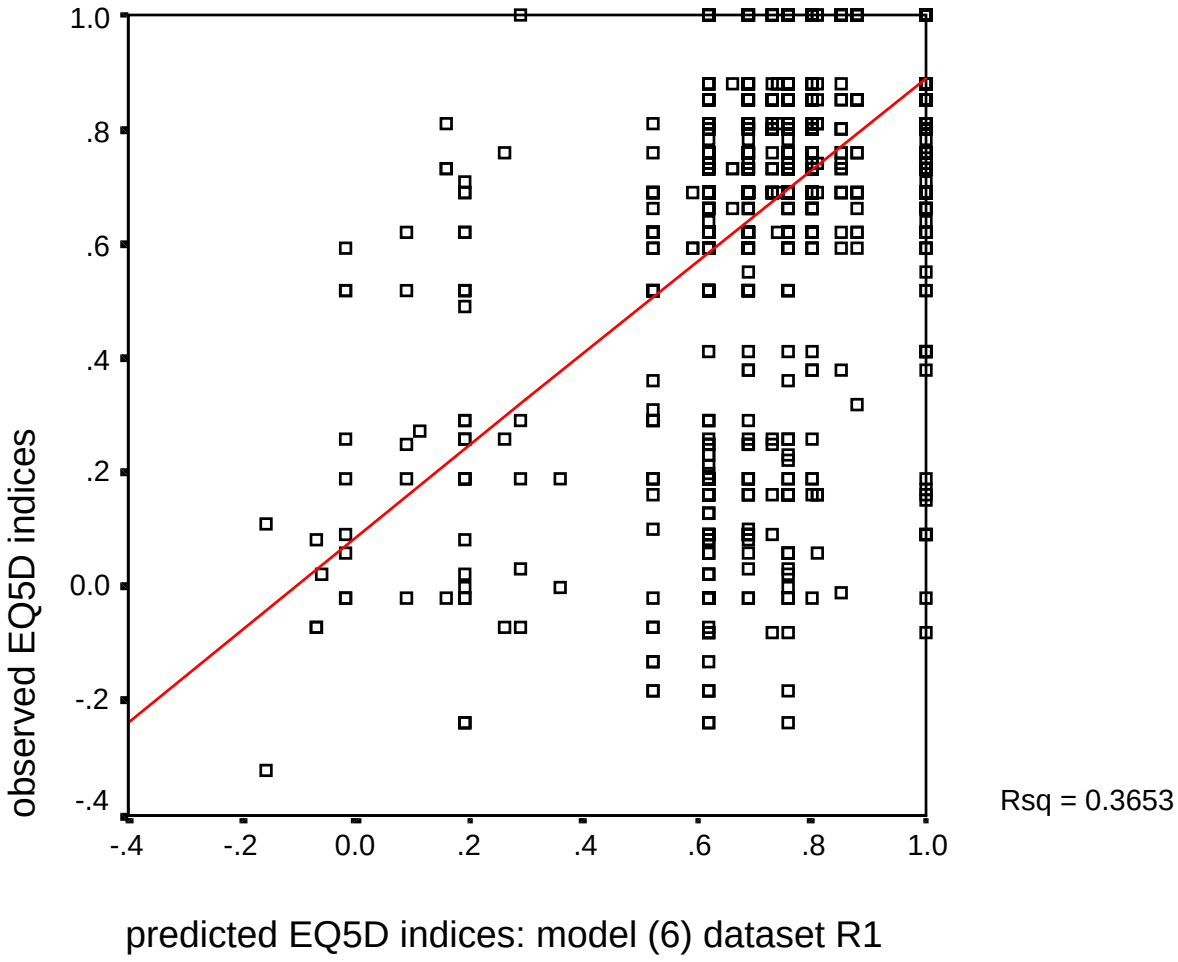
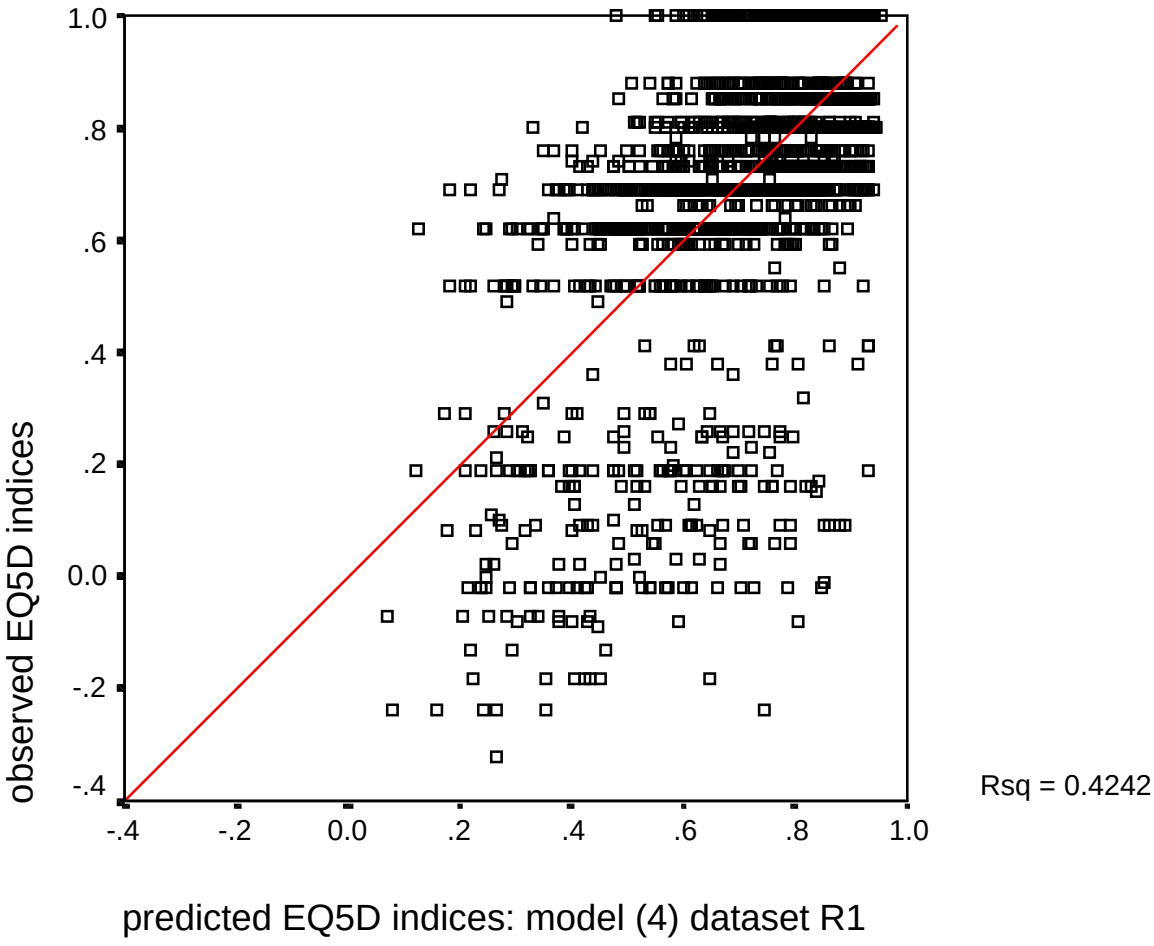


Figure 2: The performance of model (4) dataset R1



Appendix 1: The EQ5D instrument

Mobility

No problems in walking about

Some problems in walking about

Confined to bed

Self-Care

No problems with self-care

Some problems washing or dressing oneself

Unable to wash or dress oneself

Usual Activities (e.g. work, study, housework, family or leisure activities)

No problems with performing one's usual activities

Some problems with performing one's usual activities

Unable to perform one's usual activities

Pain/Discomfort

No pain or discomfort

Moderate pain or discomfort

Extreme pain or discomfort

Anxiety/Depression

Not anxious or depressed

Moderately anxious or depressed

Extremely anxious or depressed

A statement with no problems is referred to as level 1, and a statement with inability or extreme problem is referred to as level 3, so that for example, health state 21232 means:

some problems in walking about,

no problems washing and dressing oneself,

some problems with performing one’s usual activities,

extreme pain or discomfort, and

moderately anxious or depressed.

This 5-dimension descriptive system can identify 3^5=243 different health states.

Appendix 2: The Asthma Quality of Life Questionnaire (the original individualised version)

[Each of the following questions is followed by a 7-point scale with appropriate labels to do with degrees of limitation, or frequency of the problem, etc. The smaller the level, the more severe. Items are marked here with **S** (symptoms), **A** (activities), **Em** (emotions), **En** (environment), to represent the 4 domains.]

[A list of 26 activities such as bicycling, dancing, carrying out DIY, doing housework, gardening etc. is first given, and respondents are asked to write out "the **5 most important activities** in which you have been limited **by your asthma during the last 2 weeks**" on 5 spaces linked to Q1 to Q5.]

A 1-5 How **limited** have you been during the last 2 weeks in these activities?

S 6 How much **discomfort or distress** have you felt over the last 2 weeks as a result of **chest tightness**?

In general, **how much of the time** during the last 2 weeks did you:

Em 7 feel **concerned about having asthma**?

S 8 feel **short of breath** as a result of your asthma?

En 9 experience asthma symptoms as a **result of being exposed to cigarette smoke**?

S 10 experience a **wheeze** in your chest?

A 11 feel you had to **avoid a situation or environment because of cigarette smoke**?

S 12 How much **discomfort or distress** have you felt over the last 2 weeks as a result of **coughing**?

In general, **how much of the time** during the last 2 weeks did you:

Em 13 feel **frustrated** as a result of your asthma?

S 14 experience a feeling of **chest heaviness**?

Em 15 feel **concerned about the need to use medication** for your asthma?

S 16 feel the need to **clear your throat**?

En 17 experience asthma symptoms as a **result of being exposed to dust**?

S 18 experience **difficulty breathing out** as a result of your asthma?

A 19 feel you had to **avoid a situation or environment because of dust**?

S 20 **wake up in the morning with asthma symptoms**?

Em 21 feel **afraid of not having your asthma medication available**?

S 22 feel bothered by **heavy breathing**?

En 23 experience asthma symptoms as a **result of the weather or air pollution outside**?

S 24 were you **woken at night** by your asthma?

A 25 **avoid or limit going outside because of the weather or air pollution**?

En 26 experience asthma symptoms as a **result of being exposed to strong smells or perfume**?

Em 27 feel **afraid of getting out of breath**?

A 28 feel you had to **avoid a situation or environment because of strong smells or perfume**?

S 29 has your asthma **interfered with getting a good night's sleep**?

S 30 have a feeling of **fighting for air**?

How limited have you been during the past 2 weeks?

A 31 Think of the **overall range of activities** that you would have liked to have done during the last 2 weeks. How much has your range of activities been limited by your asthma?

A 32 Overall, among **all the activities** that you have done during the past 2 weeks, how limited have you been by your asthma?

[In the standardised version, the first five items (all of them **S**) are changed to:]

How **limited** have you been **during the last 2 weeks** in these activities **as a result of your asthma**?

1 **strenuous activities** (such as hurrying, exercising, running up stairs, sports)

2 **moderate activities** (such as walking, housework, gardening, shopping, climbing stairs)

3 **social activities** (such as talking, playing with pets/children, visiting friends/relatives)

4 **work related activities*** (tasks you have to do at work)

5 **sleeping**

* If you are not employed or self-employed, these should be tasks you have to do most days, for example, housework.