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The relationship between EQ-5D, HAQ and pain in patients with rheumatoid arthritis: further validation and development of the limited dependent variable, mixture model approach

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**The relationship between EQ-5D, HAQ and pain in patients with rheumatoid arthritis:
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Abstract

Objective

To provide robust estimates of EQ-5D as a function of the Health Assessment Questionnaire (HAQ) and pain in patients with rheumatoid arthritis.

Method

Repeated observations of patients diagnosed with RA in a US observational cohort (n=100,398 observations) who provided data on HAQ, pain on a visual analogue scale and the EQ-5D questionnaire. We use a bespoke mixture modelling approach to appropriately reflect the characteristics of the EQ-5D instrument and compare this to results from linear regression.

Results

The addition of pain alongside HAQ as an explanatory variable substantially improves explanatory power. The preferred model is a four component mixture. Unlike the linear regression it exhibits very good fit to the data, does not suffer from problems of bias or predict values outside the feasible range.

Conclusions

It is appropriate to model the relationship between HAQ and EQ-5D but only if suitable statistical methods are applied. Linear models underestimate the QALY benefits, and therefore the cost effectiveness, of therapies. The bespoke mixture model approach outlined here overcomes this problem. The addition of pain as an explanatory variable greatly improves the estimates.

Introduction

Economic evaluation of health care technologies is now a technique in widespread use across most developed health care systems and a key aid to decision makers. It provides a rational framework to consider both the cost and benefits of treatments that compete for scarce health care resources. In rheumatoid arthritis (RA), the advent of high cost biologic drugs has been a particular driver for the large number of such cost effectiveness analyses. In many jurisdictions, decision makers wish to have health benefits of treatments expressed in terms of quality adjusted life years (QALYs) so that comparisons across diverse disease areas can be made using a common metric. The QALY attaches weight to each year of survival to adjust for its perceived quality. A year in full health is scored as one and death is zero. These serve as the points around which all intermediate health states are valued.

In order for the health benefits of a therapy to be estimated in terms of QALYs gained, it is usual for an appropriate outcome measurement tool to be administered to patients as part of the clinical trial. Several “off the shelf” instruments are available including the EQ-5D(1), SF6D(2) (a derivative of the SF36) and the Health Utilities Index(3). Each of these instruments comprise of questions which ask patients to indicate their health on a range of dimensions. Pre-existing scores on the QALY scale calculated from the general populations of several different countries are then available to attach to those health states.

However, in RA many of the pivotal trials for new therapies have failed to include such preference based instruments. In this situation, analysts have attempted to estimate the relationship between clinical outcome measures that are included in trials (predominantly the Health Assessment Questionnaire – HAQ) and preference-based measures via statistical modelling (4,5,6,7,8). These are almost all simple linear regression models which is problematic because this kind of statistical model has been shown to fit badly to the data and

thereby undervalue treatment benefits. This is evident from numerous studies in varying disease settings (9) and in RA populations both when using the HAQ summary score (10) or the individual components of HAQ (4,11) as predictors. In these cases the statistical model underestimates utility values for those patients with little or no functional disability, but overestimates the utility score for those with poor function.

This linking of clinical and economic outcome measures has been referred to as “mapping” and has been subject to substantial controversy. The OMERACT network (Outcome Measures in Rheumatology) Economics Group recognised this and reported that “mapping should be better explored” (12). Scott et al. (13) go so far as to suggest that economic evaluations should not be based on HAQ transformed to EQ-5D.

We have previously developed a new statistical approach to modelling EQ-5D(14). Using a small dataset from an early RA cohort we demonstrated the appropriateness of the method using HAQ and pain to estimate EQ-5D scores. This paper refines the method and applies it to a much larger dataset in order to provide definitive results. Whilst this paper concentrates on the UK EQ-5D tariff, the issues are relevant to EQ-5D using scores from other countries populations, or for other health utility based instruments. Overall, we aim to estimate EQ-5D as a function of HAQ and pain.

Materials and Methods

Data were provided by the US National Data Bank for Rheumatic Diseases (NDB). The NDB is a not-for-profit rheumatic disease research databank in which patients complete detailed self-report questionnaires at 6 month intervals (15). Eligible patients in this study were those with RA who had completed a biannual survey for events occurring between July 1st 2002 and November 22nd 2010.

At each assessment, demographic variables were recorded including sex, age, ethnic origin, education level, current marital status, medical history and total family income. Patients also complete the Health Assessment Questionnaire Disability Index (HAQ), including pain on a visual analogue scale (VAS) scored from 0-100 and EQ-5D, amongst other items. UK EQ-5D tariff values were used. Summary statistics for the sample are provided in Table 1.

A total of 103,867 observations were included in the total dataset from 16,011 patients. 3,469 observations had missing data and were not included in the statistical models. The size of the dataset dwarfs that which is typical of most “mapping” studies. Patients spanned the full range of HAQ, pain and EQ-5D values. Nevertheless, very few observations were observed in the most extreme HAQ health state. 1244 observations (1.2%) from 528 patients had a HAQ exceeding 2.5, and just 152 observations (0.15%) from 64 patients had a HAQ of 3.

The histogram in Figure 1 displays the key features typical of EQ-5D. First, there is a substantial mass of observations at 1. There are 13,891 observations (14%) at full health. Second, there is a gap between these observations and those for any level of impairment, as is imposed by the method for calculating EQ-5D tariff scores. There are then at least two more separate components to the distribution with models around zero and 0.75. There is a very large mass of observations around 0.8. There are 50 observations in the so-called “Pits state” that is, 33333, the worst state that can be described by the EQ-5D descriptive system. These are the features of EQ-5D that raise statistical challenges and result in the poor performance of standard approaches.

Statistical methods

We aim to estimate the conditional relationship between EQ-5D, HAQ and pain on a scale of 0-100. Standard linear regression models are in widespread use for modelling EQ-5D but are clearly not appropriate in this situation given the bounded and multimodal nature of the

distribution (see Figure 1) and tend to perform poorly. A linear regression model was included to confirm this. We apply the general framework for modelling EQ-5D from Hernández et al. (14) which combines bespoke distributions in a mixture model. Full details are provided elsewhere (14), however, the key details of the two main elements of the approach are provided here. First, mixture models are formed from a number of different component distributions which are combined to form a new density. They offer an extremely flexible and convenient manner in which complex distributions (such as EQ-5D) can be analysed in a semi-parametric manner (16). Second, in this case each component is made up of a normal distribution that is limited at full health (1) and has an adjustment to reflect the gap in feasible values between 1 and 0.883. Explanatory variables may enter the model in two ways: either as predictors of the relationship with EQ-5D within each component or as predictors of component membership.

Models were estimated using maximum likelihood in GAUSS v11 (Aptech Systems Inc.). We considered models comprising different numbers of components. Comparisons were made in terms of Akaike's and Bayesian information criteria (AIC/BIC). Other measures of fit such as the mean absolute error (MAE) and the root mean squared error (RMSE) are also reported.

Many RA cost effectiveness models simulate individual patients, as opposed to averages from patient cohorts (7, 17). To reflect this use of the model results, we simulated a set of 100 modelled EQ-5D scores for each of the patients in the dataset. This further illustrated differences between the observed data and the data generated by the linear regression and the mixture model approaches.

Results

A four component mixture model was selected as the optimal model. Each of the components includes HAQ and HAQ², pain, age and age² as explanatory variables. The probability of any patient's observation being assigned to a component is based on HAQ, pain and pain². The optimal linear regression model included HAQ and HAQ², pain, age and age². However, this model suffered very poor fit particularly at the extremes of good health and poor health.

The mixture model vastly outperformed the linear model in terms of summary fit measures. AIC and BIC were both lower for the mixture model and there was a 9.6% improvement in MAE and a 3.4% improvement in RMSE. Importantly, the improvement in fit was greatest at the extremes of very poor and very good health. For those patients with a HAQ between either 0 and 1 or between 2 and 3, MAE improved by more than 11%. At pain scores of zero the MAE reduces from 0.13 to 0.08, a 35% improvement. At pain scores exceeding 95, the MAE reduces from 0.23 to 0.18, a 22% improvement. These features are evident in Figure 2, which plots the mean EQ-5D versus a) HAQ and b) pain, for the observed data, the linear regression model and the preferred mixture model. Results for this model are reported in Table 2.

Each patient observation is assigned a probability of being in each of the four components. One way of considering the size of each class is as the mean of the component probabilities.

The first class is by far the largest with a mean probability of class membership of 0.73. In this class, HAQ and pain are negatively related to EQ-5D ($p < 0.000$) (see Table 2). HAQ² is not significant. A positive relationship with age and age² is demonstrated but in the case of age² this is not statistically significant ($p = 0.23$). The average characteristics of those patients most likely to be in this class are very similar to those of the average overall dataset. Notably, these are less severely affected patients with a mean HAQ of around 1, EQ-5D of 0.67 and disease duration of 17 years. Figure 3a illustrates that this component of the model has a

peak around 0.7 that coincides with that observed in Figure 1. This component also contributes to the mass of data at EQ-5D equal to one, but does not contribute significantly to the lower end of the distribution.

The mean probability of any observation being in the second class is 0.05, making it the smallest class. This component of the model has a large spread, including both those patients in the most severe EQ-5D health states and those in full health (Figure 3b). The coefficients on HAQ and HAQ² indicate that EQ-5D decreases, by increasing amounts, as HAQ worsens. The impact of pain on EQ-5D in this group is the most pronounced of all the classes. In those patients most likely to be assigned to this group, the mean HAQ is almost 2.76 (SD 0.23), EQ-5D is 0.33 (SD 0.32) but pain is relatively mild at 10.3 (SD 11.2). Patients most likely to be in this group have an average RA duration in excess of 31 years.

Figure 3c shows that the fourth component is centred around EQ-5D of 0.2 and accounts in part for the second element of the bi-modal EQ-5D distribution. 7% of patients are most likely to be assigned to this component. HAQ is negatively associated with EQ-5D and is much greater in magnitude than the positive coefficient on HAQ². Pain is also negatively associated with EQ-5D. This is a class made up of patients with poor functional status. The mean HAQ is 2.03 (SD 0.44). These patients also have the most severe average pain score for any of the four groups at 87.8 (SD 7.4).

The 4th class shows no statistically significant relationship between EQ-5D and either age or pain. HAQ is negatively related to EQ-5D ($p < 0.05$). HAQ² is not statistically significant. This group of 14% of the dataset is made up of patients with mild or no symptoms. The mean HAQ is 0.15 (SD 0.27), pain is 2.3 (SD 2.5) and EQ-5D is 0.93 (SD 0.11). Figure 3d illustrates how this element of the model contributes predominantly to the mass of values at EQ-5D equal to one.

Figure 3e shows that the key features of the EQ-5D data distribution (Figure 1) are replicated by the bespoke mixture model: a mass of observations at 1, a gap to the next set of feasible values, tri-modal and does not predict values outside the feasible range either at the top or the bottom. The linear regression model has none of these features (see Figure 3f).

Discussion

Cost effectiveness analyses of treatments for patients with RA frequently estimate health benefits in terms of QALYs by estimating the relationship between preference-based outcome measures like EQ-5D, and clinical outcomes measures like HAQ. However, the statistical models used to do this tend to be relatively simplistic and do not account for the many idiosyncrasies of the EQ-5D instrument and valuation system. For this reason, such approaches result in systematically biased estimates which undervalue the benefits of treatments. Unsurprisingly, this has led to criticism from the rheumatology community since the methods to estimate these relationships are not merely of academic interest but form critical components of the analyses that reimbursement authorities across the world rely on in reaching funding decisions (13). These features are not limited to the UK version of the EQ-5D and many are present in other quality of life instruments used to estimate QALYS such as the SF-6D (2) and the Health Utilities Index (3). Indeed, comparisons of linear models using several of these instruments have been performed in RA using data from the NDB (10).

This study uses a very large dataset to refine a flexible statistical approach that was designed specifically to address such shortcomings.

Results show that the preferred 4 component model does indeed overcome the problems of poor fit associated with simplistic techniques. Fit is substantially better at the extremes of the distribution and there is no evidence of the systematic undervaluation of the benefits of treatment. Furthermore, the model is not capable of predicting values that lie outside the

feasible range (-0.561 to 1). Simple approaches generate such nonsensical estimates particularly when they are used to simulate individual patients and when the parameter uncertainty in the estimates is reflected in cost effectiveness models. The covariance matrix that would allow analysts to perform such analyses with this model is available online (Web appendix).

Many cost effectiveness analyses focus on changes in HAQ due to treatment. This study demonstrates that better estimates of the benefits of treatments in terms of QALYs will be gained if HAQ and pain are simultaneously considered. This is neither new (10,14), nor surprising when one considers that pain is one of the five domains in the EQ-5D instrument and contributes the greatest weight to the summary score. Yet this finding implies that economists will need to consider the decision models they use and how meta-analysis methods can capture treatment benefits appropriately.

The mixture model approach that has been reported here was implemented because it offers a flexible framework for complex distributions like EQ-5D. However, it also opens the potential for the consideration of patient subgroups: the relationship between HAQ and pain to EQ-5D are very different within the four components of the model. In some instances pain is particularly important, in others it is HAQ that is critical. The patients that are likely to form these groups are also very different in terms of age, duration and severity of disease. These implications require further investigation. It is also worth noting that in the previous implementation of this modelling approach in RA, the preferred model comprised 3 components. The additional of a fourth class here improved fit at the bottom end of the EQ-5D distribution. Data at this extreme of poor health was lacking in Hernandez et al. (14). This issue is diminished but not eliminated by using the NDB database. The only place where the mixture model does not fit extremely well is where HAQ exceeds 2.5. Whilst better model fit is achieved by fitting a greater number of components to the mixture, this would be at the

expense of generalizability. The validity of observations from patients at such extreme levels of functional impairment may also be questionable and for this reason we propose the 4 component model.

More recent clinical trials of newer biologic agents are increasingly incorporating preference based outcome measures. However, whilst it has often been claimed that direct health utility assessment is preferable to using indirect “mapping” methods (4,9) this is not necessarily the case. Here we have a dataset comprising in excess of 100,000 observations across the full spectrum of functional disability and pain combined with an appropriate method to relate these measures to EQ-5D. On the other hand, clinical studies, particularly trials, have limited patient variability and follow up. Economic evaluations therefore extrapolate well beyond these clinical studies, often over the entire patient lifetime, in order to accurately capture the impact of treatment on long term costs and health benefits. Our approach offers a means by which such extrapolations can be undertaken.

Furthermore, even if new trials include measures like EQ-5D the entirety of the evidence base remains relevant, including studies of older treatments as comparators. Hence, given that such estimates will be critical to reimbursement decisions for some time to come it is of vital importance for patients and their physicians that treatment benefits are appropriately valued. The results reported here can be used in future economic evaluations.

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Tables

Table 1: Descriptive statistics of RA patients from NDB by observation (n=100,398)

| | n | % |
|-------------------|-------------|-----------|
| Female | 79,639 | 79.3% |
| | Mean | SD |
| RA duration (yrs) | 17.17 | 11.07 |
| Age (yrs) | 62.82 | 12.24 |
| Pain | 35.32 | 26.76 |
| HAQ | 1.00 | 0.73 |
| EQ-5D | 0.66 | 0.27 |

RA = Rheumatoid Arthritis, HAQ = Health Assessment Questionnaire

Table 2: Results from 4 class Mixture Model.

| | Parameter | theta | robust se | t-value | p-value |
|-------------------------------------|-----------------------|--------------|------------------|----------------|----------------|
| class 1 | HAQ | -0.0898 | 0.0027 | -32.9151 | 0.0000 |
| | HAQ ² | 0.0005 | 0.0009 | 0.5892 | 0.5557 |
| | Pain/100 | -0.0580 | 0.0023 | -25.4275 | 0.0000 |
| | Age/10m | 0.0049 | 0.0005 | 10.1656 | 0.0000 |
| | Age/10m ² | 0.0003 | 0.0002 | 1.2111 | 0.2258 |
| class 2 | HAQ | 0.0544 | 0.0301 | 1.8043 | 0.0712 |
| | HAQ ² | -0.0509 | 0.0100 | -5.1027 | 0.0000 |
| | Pain/100 | -0.3841 | 0.0225 | -17.0781 | 0.0000 |
| | Age/10m | 0.0291 | 0.0035 | 8.2411 | 0.0000 |
| | Age/10m ² | 0.0023 | 0.0017 | 1.3532 | 0.1760 |
| class 3 | HAQ | -0.1415 | 0.0076 | -18.5781 | 0.0000 |
| | HAQ ² | 0.0155 | 0.0027 | 5.7871 | 0.0000 |
| | Pain/100 | -0.0839 | 0.0089 | -9.3978 | 0.0000 |
| | Age/10m | 0.0037 | 0.0012 | 3.2078 | 0.0013 |
| | Age/10m ² | 0.0007 | 0.0006 | 1.1702 | 0.2419 |
| class 4 | HAQ | -0.1958 | 0.0811 | -2.4137 | 0.0158 |
| | HAQ ² | 0.0347 | 0.0246 | 1.4097 | 0.1586 |
| | Pain/100 | -0.0127 | 0.0693 | -0.1839 | 0.8541 |
| | Age/10m | -0.0043 | 0.0058 | -0.7417 | 0.4583 |
| | Age/10m ² | 0.0002 | 0.0021 | 0.1106 | 0.9119 |
| Between level | Intercept1 | 0.8141 | 0.0013 | 629.4830 | 0.0000 |
| | Intercept2 | 0.4266 | 0.0164 | 25.9934 | 0.0000 |
| | Intercept3 | 0.3297 | 0.0081 | 40.6365 | 0.0000 |
| | Intercept4 | 1.0220 | 0.0327 | 31.2430 | 0.0000 |
| | Male | -0.0265 | 0.0013 | -20.9092 | 0.0000 |
| Within level | Variance1 | 0.0025 | 0.0001 | 48.7842 | 0.0000 |
| | Variance2 | 0.0240 | 0.0016 | 14.8595 | 0.0000 |
| | Variance3 | 0.0022 | 0.0002 | 10.2405 | 0.0000 |
| | Variance4 | 0.0044 | 0.0042 | 1.0374 | 0.2995 |
| Between level | Variance | 0.0026 | 0.0001 | 46.2489 | 0.0000 |
| Probability of component membership | Intercept 1 | -1.2746 | 0.0637 | -20.0245 | 0.0000 |
| | HAQ | 0.2420 | 0.4424 | 0.5471 | 0.5843 |
| | Pain/100 | 23.4673 | 0.5897 | 39.7970 | 0.0000 |
| | Pain/100 ² | -21.5513 | 0.6707 | -32.1307 | 0.0000 |
| | Intercept2 | -6.6310 | 0.2597 | -25.5366 | 0.0000 |
| | HAQ | 2.1936 | 0.4234 | 5.1808 | 0.0000 |
| | Pain/100 | 18.3719 | 1.2220 | 15.0337 | 0.0000 |
| | Pain/100 ² | -13.8001 | 0.8071 | -17.0981 | 0.0000 |
| | Intercept3 | -7.4768 | 0.2988 | -25.0242 | 0.0000 |
| | HAQ | 1.0517 | 0.4344 | 2.4209 | 0.0155 |
| | Pain/100 | 25.3396 | 1.1359 | 22.3075 | 0.0000 |
| | Pain/100 ² | -16.9622 | 0.7624 | -22.2473 | 0.0000 |

Figure 1: Distribution of EQ-5D scores from NOB cohort

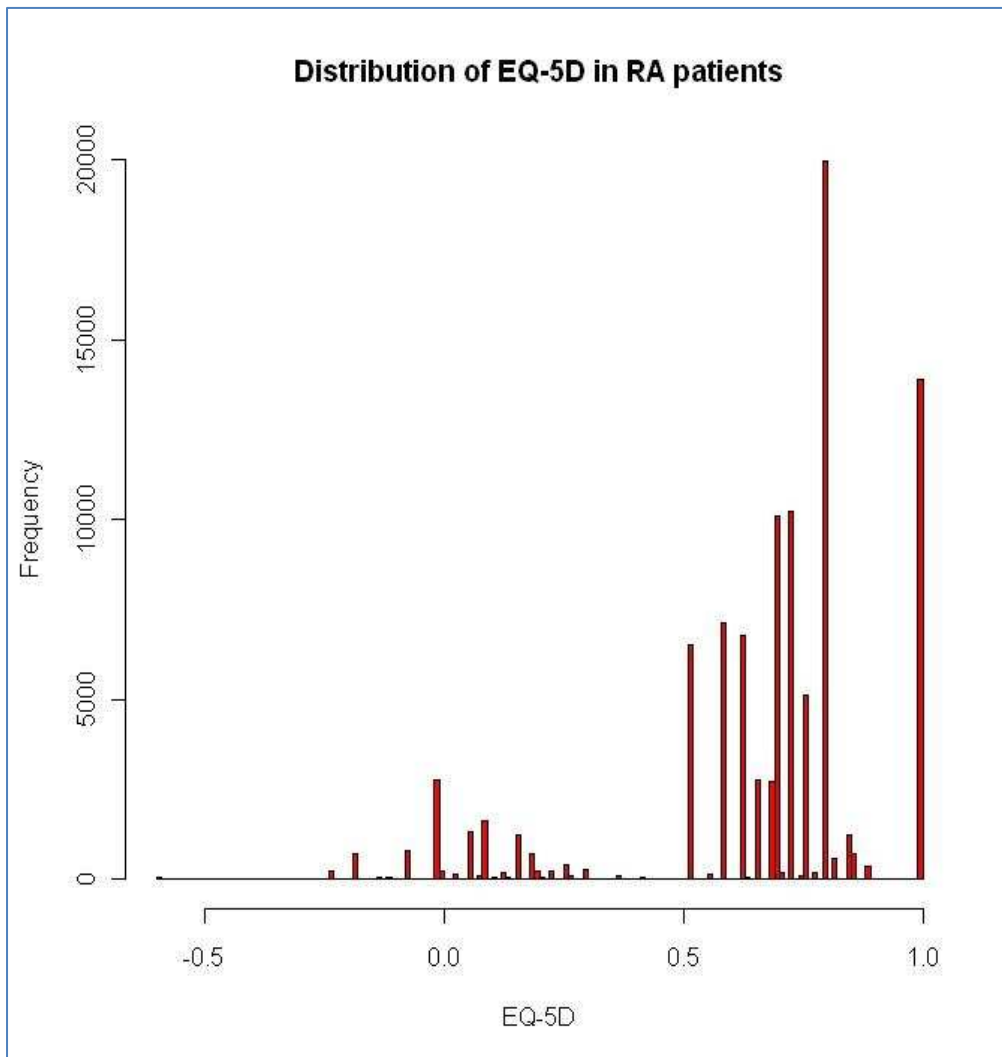


Figure 2: Mean observed and predicted values for linear and mixture model a) HAQ vs EQ-5D and b) Pain vs EQ-5D

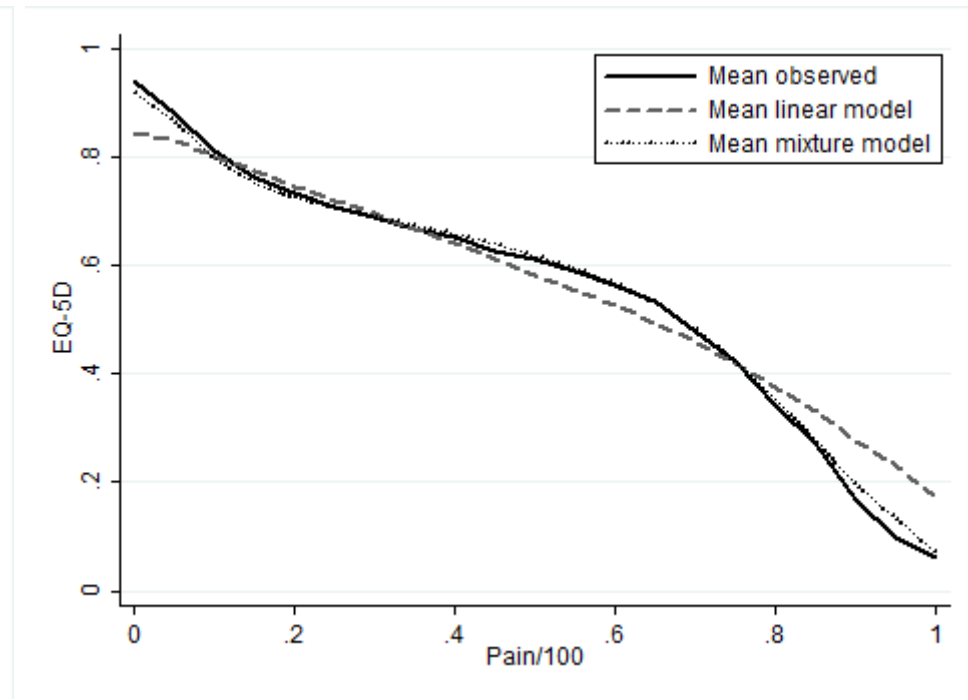
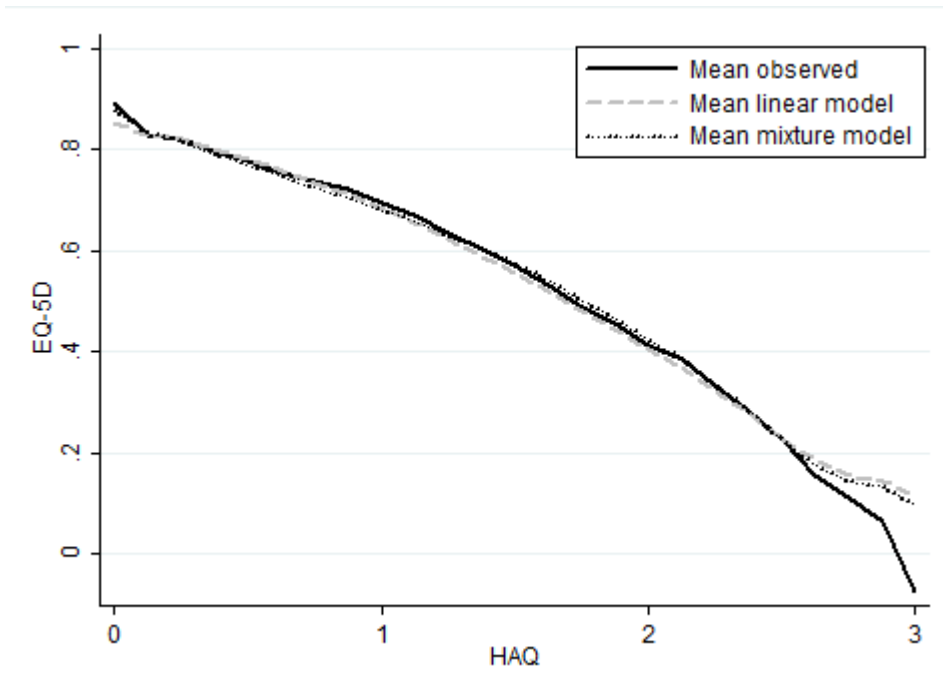


Figure 3: Distribution of simulated values from the 4 component mixtw-e and linear models. a)-d) for each component individually, e) 4 class combined and f) linear model

