VALUE IN HEALTH ∎ (2017) ∎∎∎–∎∎∎

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Development of Methods for the Mapping of Utilities Using Mixture Models: Mapping the AQLQ-S to the EQ-5D-5L and the HUI3 in Patients with Asthma

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ABSTRACT

Background: Studies have shown that methods based on mixture models work well when mapping clinical to preference-based methods. **Objectives:** To develop these methods in different ways and to compare performance in a case study. **Methods:** Data from 856 patients with asthma allowed mapping between the Asthma Quality of Life Questionnaire and both the five-level EuroQol five-dimensional questionnaire (EQ-5D-5L) and the health utilities index mark 3 (HUI3). Adjusted limited dependent variable mixture models and beta-based mixture models were estimated. Optional inclusion of the gap between full health and the next value as well as a mass point at the next feasible value were explored. **Results:** In all cases, model specifications formally modeling the gap between full health and the next feasible value were an improvement on those that did not. Mapping to the HUI3 required more components in the mixture models than did mapping to the EQ-5D-5L because of its uneven distribution. The optimal beta-based mixture models mapping to the HUI3 included a probability mass at the utility value adjacent to full health. This is not the case when estimating the EQ-5D-5L, because of the low proportion of observations at this point. **Conclusions:** Beta-based mixture models marginally outperformed adjusted limited dependent variable mixture models with the same number of components in this data set. Nevertheless, they require a larger number of parameters and longer estimation time. Both mixture model types closely fit both EQ-5D-5L and HUI data. Standard mapping approaches typically lead to biased estimates of health gain. The mixture model approaches exhibit no such bias. Both can be used with confidence in applied cost-effectiveness studies. Future mapping studies in other disease areas should consider similar methods.

Keywords: EQ-5D, HUI, mapping, utility.

Introduction

Preference-based measures (PBMs) that allow the calculation of health state utilities are not always administered in studies of clinical effectiveness. Nevertheless, these outcomes are often preferred by decision makers such as the National Institute of Health and Care Excellence to estimate quality-adjusted life-years (QALYs) for use in cost-effectiveness analysis [1]. "Mapping," or "cross-walking," is commonly used to estimate health state utilities when clinical studies have not included any PBM [2].

This article develops mapping methods and illustrates their use in relation to asthma. In clinical trials that include patients with asthma, the Sydney Asthma Quality of Life Questionnaire (AQLQ-S) is routinely recorded, but these trials often record no PBM and therefore QALYs cannot be estimated [3]. Nevertheless, there is increasing interest in how asthma is influencing health-related quality of life [4,5]. For these reasons, studies have used mapping techniques to map from asthma-specific measures to PBMs [6,7].

There are two broad approaches to mapping. The direct approach models the health state utility values themselves. The indirect approach, also referred to as response mapping, models each dimension of the PBM and calculates the predicted utilities as a second, separate step. Response-mapping models require observations (preferably a sizeable number) at all levels of each dimension and this can be a problem for small data sets if there are many different levels in each dimension.

Health state utility values are characterized by unusual distributions; they are commonly skewed, multimodal, and often have a large number of observations at 1 (indicating full health) and a gap between full health and the next feasible value. By definition, they are limited between the range of best and worst health states. Basic regression models are unable to capture all these features, which leads to biased estimates of health gain.

Beta regressions can provide flexibility when modeling skewed, bounded PBMs. Basu and Manca [8] proposed the use of single and two-part beta regressions to model PBMs and QALYs. The standard beta regression assumes that the

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1098-3015$36.00 – see front matter
http://dx.doi.org/10.1016/j.jval.2017.09.017

dependent variable is defined only in the open interval (0,1) but many PBMs display negative values. Some studies have suggested that a beta regression is inappropriate in these cases [9]. Other studies have attempted to overcome this problem by converting ad hoc all negative values to 0 [7,10], not only ignoring that some health states are worse than death but also potentially distorting the distribution because of the well-known sensitivity of beta regressions to pile-ups of values at the boundaries. Nevertheless, there is a standard transformation in the literature that allows the transformation of values in any open interval into a (0,1) interval [11]. After estimation, the expected value is then transformed to its original scale to obtain the correct predictions. In the area of mapping, this is the approach followed by Kent et al. [12] and Khan et al. [13]. Beta-based regression models have been found to be more robust and outperform linear regressions [8,13,14]. One significant issue when using beta regressions is how to deal with observations on the boundaries of the feasible utility range. Different methods have been proposed and it is recommended that the sensitivity of the estimates to the different methods be assessed [11]. Even though beta regressions can deal with the bounded nature of utility data and can reproduce various shapes, multimodality is difficult to capture.

Mixture models are increasingly being used in the context of mapping because of their flexibility and the ability to capture multimodality [7–11,15,16]. Mixtures of normal distributions have been used to model different PBMs such as the health utilities index mark 3 (HUI3) [17], the three-level EuroQol five-dimensional questionnaire (EQ-5D-3L) [12,14], and the six-dimensional health state short form [14]. Some mixture models have been specifically designed for utility mapping such as the adjusted limited dependent variable mixture model (ALDVMM) [15,16,18,19]. This uses a mixture of adjusted normal distributions to account for the multimodality of PBMs and includes a number of other useful characteristics. It contains built-in features that account for the peak of observations at full health and the option of a gap in the distribution below that peak. Other mixture models used for mapping include a mixture of Tobit models censored to account for the bounded nature of PBMs with an additional degenerate distribution at perfect health [20]. One additional study [13] claims to estimate a limited dependent variable model. Nevertheless, the model described is not a finite mixture model but a two-part model with an ad hoc assumption of a normal distribution for values of the dependent variable less than 0.3 and a beta binomial for values at 0.3 or higher. The split at 0.3 is justified via visual inspection of a kernel density plot of the dependent variable. Recently, beta mixture models have also been used in utility mapping with success [12]. In general, mixture models have been found to outperform nonmixture models [18–20]. One study found some evidence to suggest that beta regressions can outperform mixture models, which might be in part related to the distributional shape of the health utility measure being used [14].

This study develops knowledge about mapping methods by comparing approaches for estimating two PBMs, the five-level EQ-5D (EQ-5D-5L) and the HUI3, from the AQLQ-S score, a clinical asthma measure using data from an international sample [21]. Two different classes of mixture models are used: the ALDVMM and extensions to a beta mixture model [12], which 1) account for the gap in the PBM distributions between full health and the next feasible value and 2) allow alternative approaches to deal with observations on the boundary of the beta distribution [12]. We provide a choice of mapping algorithms for use in economic evaluation along with advice on how best to choose between them.

All models are estimated using user-written code in Stata (StataCorp, College Station, TX) via the commands "aldvmm" [18] and "betamix" [22].

Methods

Data

We used data from the Multi-Instrument Comparison (MIC) project data set, which includes data on 7933 observations across six countries: Australia, Canada, Germany, Norway, the United Kingdom, and the United States [21]. The data include information on well-being, health state utilities, and demographic characteristics. In addition, respondents who self-reported having specific conditions were asked to answer disease-specific questionnaires. In total, 856 respondents self-reported asthma and completed the AQLQ-S. Data were available for respondents' age and sex as well as their EQ-5D-5L and HUI3 scores. After removing observations with missing values in any of the required variables, the final sample for analysis consisted of 852 observations.

Preference-Based Measures

Both the EQ-5D-5L and the HUI3 are PBMs with health state utility estimates for each feasible response to their descriptive system. The EQ-5D-5L covers the same five dimensions as the original three-level version (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), but each dimension has five response levels (no problems, slight, moderate, severe, and extreme/unable to do). It is designed for self-completion, has a low response burden, and is applicable to a range of diseases and treatments. The HUI3 is also a self-completion questionnaire with eight dimensions (vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain). The levels for each dimension vary between 5 and 6. We use the value sets in the studies by Devlin et al. [23] and Furlong et al. [24] to attach utility values to each health state in the EQ-5D-5L and the HUI3, respectively. For both instruments, a value of 1 represents full health, a value of 0 is considered equivalent to being dead, and their values can be negative, representing a state worse than death. Both instruments have a gap between full health and the next feasible health state (these next feasible health states are 0.951 in the EQ-5D-5L and 0.97258 in the HUI3). We refer to this value as the truncation point; these are the highest possible values generated for each of the PBMs that are not represented by full health. The lower limits are −0.281 and −0.36, respectively, for the EQ-5D-5L and the HUI3.

Asthma Quality of Life Questionnaire

The AQLQ-S was designed as a measure of quality of life for adult patients with asthma. The questionnaire contains 20 questions within four domains (symptoms, activity limitation, emotional function, and environmental stimuli). Each of the questions allows a response on a 0 to 4 scale, with 0 representing no problems at all. The scores for each question are averaged to produce an overall AQLQ-S score between 0 and 4. Although there are many different versions of the AQLQ, the AQLQ-S is recommended by the European Medicines Agency [25] and has been validated [26]. Nevertheless, because the scoring is not preference-based, it is not suitable for use in cost-utility analysis.

Comparison of the AQLQ-S with the EQ-5D-5L and the HUI3 is shown in Figure 2 of the study by Kaambwa et al. [7] The EQ-5D-5L has good overlap with the AQLQ-S. The only dimension of the EQ-5D-5L that is not covered directly by the AQLQ-S is pain/discomfort. The dimensions of the HUI3 have less overlap with the AQLQ-S. The social and concerns dimensions of the AQLQ-S are not represented by any dimensions of the HUI3. In addition, the vision, pain, hearing, speech, dexterity, and cognition dimensions of the HUI3 are not represented in the AQLQ-S. Nevertheless, correlations between both PBMs and the AQLQ-S are highly significant; they are