Brazilian valuation of EQ-5D-3L health states: Results from a saturation study.

Marisa Santos, PhD[1]; Monica A. C. T. Cintra, PhD[1]; Andrea L. Monteiro, MSc[1]; Braulio Santos, MSc[1]; Fernando Gusmão-filho, PhD[2]; Monica V. Andrade, PhD[3]; Kenya Noronha, PhD[3]; Luciane N. Cruz, PhD[4]; Suzi Camey, PhD[5]; Bernardo Tura, PhD[1]; Paul Kind, MPhil[6]

1 Instituto Nacional de Cardiologia, Rio de Janeiro, Brazil
2 Instituto de Medicina Integral Professor Fernando Figueira, Recife, Brazil
3 Departamento de Economia, Centro de Desenvolvimento e Planejamento Regional, Universidade Federal de Minas Gerais, Belo Horizonte, Brazil
4 Departamento de Epidemiologia, Programa de Pós-graduação em Epidemiologia, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil
5 Departamento de Estatística, Programa de Pós-graduação em Epidemiologia, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil
6 Academic Unit of Health Economics, Institute of Health Sciences, University of Leeds, Leeds, UK

Part of this work has been presented at the following meetings: 31st EuroQol Group Scientific Plenary, Health Technology Assessment International 2014 - 11th Annual Meeting, 21st Annual Conference of the International Society for Quality of Life Research

Grant or financial support: Brazilian Ministry of Health through the FINEP and FAPEMIG agencies

Word count: 4229

Corresponding author and person to whom reprint requests should be addressed:

Marisa da Silva Santos, MD, PhD

Instituto Nacional de Cardiologia

Rua das Laranjeiras, 374 - Laranjeiras, Rio de Janeiro - RJ, 22240-006. Brazil

Phone: +552130372421

e-mail:marisaccih@gmail.com

Financial support for this study was provided entirely by Brazilian Ministry of Health

Through FINEP and FAPEMIG agencies. The funding agreement ensured the authors' independence in designing the study, interpreting the data, writing, and publishing the report.

ABSTRACT

Background

Most EQ-5D-3L valuation studies include the same sample of health states used in the protocol of the original UK Measurement and Valuation of Health (MVH) study. Thus far, no studies using a Time Trade-off utility elicitation method have been carried out using all 243 EQ-5D health states. Values and preferences regarding health outcomes differ among countries; therefore, to enable local high-level decisions regarding resource allocation, it is essential to have country-specific data. This study aimed to develop a country-specific set of values for EQ-5D-3L health states.

Methods

A multi-centric study was conducted in four Brazilian areas. A probabilistic sample of the general population, aged from 18 years to 64 years, stratified by age and gender were interviewed. The interview protocol followed a revised version of the MVH protocol, in which all 243 health states were valued. Each respondent ranked and valued seven health states using the TTO in a home interview

Results

Data were collected from 9148 subjects. The best-fitting regression model was an individual-level mixed effects without any interaction term. The dimensions "Mobility" and "Usual Activities" were associated with higher losses in health state utility value. The "Anxiety/Depression" dimension was the domain that contributed to lower losses in health state utility value.

Conclusion

This study generated an important insight on the Brazilian's population health preferences that can be applied to health technologies assessment and economic analysis in Brazil. This information represents an advance in the decision making of Brazilian health policies.

INTRODUCTION

The EQ-5D-3L is a multi-attribute generic instrument developed by EuroQol group. Its use has significantly increased in the 25 years since its introduction (1). The instrument is based on a classification of health defined by a descriptive system with five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), with a 3-level response option for each dimension (no problems, some problems and extreme problems). In addition to the descriptive system, the EQ-5D-3L also includes a Visual Analogue Scale (EQ-VAS), in which the respondents self-rate their current health state on a 0 – 100 scale representing worst and best imaginable health.. EQ-5D-3L defines 243 theoretically possible health states, varying from 11111 (no problems in any dimension) to 33333 (severe problems in all dimensions) (1-3). Social preference weights for EQ-5D health states have been widely used in economic evaluations, specifically for use as the adjustment index used to compute quality-adjusted life years (QALYs) in cost-utility analysis.

In Brazil, the incorporation of new healthcare technologies has recently been regulated by the Ministry of Health. The law that established the Brazilian Commission for Incorporation of Technologies in the Unified Healthcare System (CONITEC), states that cost–utility analyses should be used to support decision-making, leading to the need for national valuation data based on Brazilian social preferences (4). The main intent of the creation of a Brazilian value set using the EQ-5D-3L is to provide utility weights to compute QALYs. When computing QALY estimates, the time spent on a given health state is multiplied by the utility weight correspondent to that health state. For example, if an individual spends five years in a given health state that has an associated utility of 0.5 (value obtained on a valuation study), this would correspond to 2.5 QALYs (e.g., 0.5 multiplied by 5 years).

Evidence indicates that values and preferences regarding health outcomes may differ among countries because they can be affected by the sociocultural context rather than being solely due to differences in survey methodology or in the analytic methods used (5, 6). For high-level decisions concerning resource allocation in Brazil, it is essential to obtain country-specific data. Several countries have already conducted valuation studies to develop country-specific scoring algorithms for the EQ-5D-3L, the first of which was conducted in the UK (7-9). Among Latin-America countries, Argentina (10) and Chile (11) have their own value set. Most EQ-5D-3L valuation studies have included the original set of 42 health states from the United Kingdom Measurement and Valuation of Health (MVH) study (8, 12). The 31 studies included in the systematic review performed by Xie and colleagues in 2013 (13) valued between 7 and 198 total health states, with 1 to 23 states valued per respondent. In the past, only two saturation[1] studies were conducted using the Visual Analog Scale (VAS) as the elicitation method (14-16). As the function relation between observed and predicted utility estimates is *a priori* unknown, the theoretical optimum solution to estimate a value set is to obtain direct valuation of the full set of 243 health states yielded by the EQ-5D-3L. Furthermore, the valuation of the full-set of 243 health states made it possible to test several theoretical assumptions that currently rule the health valuation field, but have never before been properly explored.

The principal aim of this study was to develop a country specific value set for the EQ-5D-3L using all 243 possible health states.

[1] The term saturation is used to describe a study in which all health states are directly valued. In general health state classification systems define too many states for all of them to be valued so that alternative strategies are adopted, either by sampling from across the severity range or constructing some type of balanced block design

METHODS

Survey design

A multi-centric cross-sectional study was conducted in four Brazilian urban areas Data were collected in two waves, the first of which was conducted in Minas Gerais state. This study involved interviews with 3,362 individuals aged 18 to 64 years conducted in 2011. Details of this survey and its design have been previously reported (Andrade et al, 2013) (16). The second wave occurred in the cities of Rio de Janeiro, Porto Alegre and Recife, with fieldwork being conducted in mid-2012.

The sampling frame in the second wave was based on data from the Brazilian 2010 census. The states in which the data collection took place represent four of the seven most populous Brazilian states and account for approximately 30% of the total population (18). According to the Brazilian Institute of Geography and Statistics in 2010, approximately 85% of the Brazilian population lived in urban area. Based on this information we recruited a geographic-based probabilistic sample of the general population from urban areas, aged 18 to 64 years and stratified by age and gender. We used area-based measures from the Brazil Census tract records to target potential participants, which included a door-to-door household recruitment strategy to identify eligible subjects. The sample size estimation was based on the desirable amount of observations for each pair of health states (at least 140 times) (19).

Each respondent ranked a set of nine health states, which included six variable and three fixed states (11111; 33333; Dead). The valuation was elicited using the Time Trade-off (TTO) face-to-face technique for seven of the nine heath states included in the individual package (six random and the worst health state possible; i.e.,-33333).

The survey protocol followed a revised version of the MVH protocol (20), in which all 243 health states (so called "saturation study") were valued. The individual valuation sets were blocked using a balanced incomplete block design (BIBD), according to the following criteria: each health state should be valued by at least 140 respondents and each individual set should contain six variable health states and each head-to-head pairwise state comparison should occur thrice. Respondents and individual valuation sets were randomly matched. As a result of this blocking strategy, half of blocks were balanced and half unbalanced. Unbalanced blocks are those that do not have at least one mild, one moderate and one severe health state. The health state severity was defined according to Kind (20).

Valuation protocol

The valuation protocol was made up of several sequential steps: 1) Firstly, respondents were asked to classify their own health state using EQ-5D questionnaire; 2) Then, respondents were asked to rank the set of nine health states, which included six randomized and three fixed states ("full health", "worst health", and "dead"); 3) In the third step, respondents were instructed to value the same set of nine health states using a 0-100 VAS; 4) After that, respondents valued seven health states (six random and the worst health state) using the TTO technique; 5) Finally, an array of socio-demographic and health questions were asked. All respondents signed the Informed Consent Form approved by the University's Institutional Review Board.

Valuation procedure

TTO comprises a succession of interactive questions in which the progression is determined by the individual responses (21, 22). A time board was used to provide a visual support to the respondents.

Respondents initially indicate whether a given health state is better or worse than being dead. If the respondent considered that the health state was better than death, the following step consisted of choosing between living in the given health state for 10 years (Life B) or full health for x years (Life A). By varying x, each respondent in an interactive process beginning at 5 years and increasing up to 10 years (if the respondent chose Life B) or decreasing to 0 years (if the respondent chose Life A). This process continued until the respondent reached the point where he was indifferent between the two alternatives offered. The responses were measured in six month intervals for a time horizon of 10 years (23).

For health states better than death, the TTO utility was calculated with the indifference point value divided by the total number of years (10 years). For states worse than death, the indifference point (x) was transformed as V= -x/ (10-x). The responses were measured in six-month intervals, producing observed TTO scores in the range from 1 to -19 (21). These were transformed using (Vt=V/(1-V)), resulting in a lower bound of -0.95(1, 3, 23).

Socio-economic component

In addition to the valuation task, the respondents also completed a questionnaire about their socioeconomic characteristics. Each respondent was asked about gender, age, religious beliefs, marital status, education level and ownership of goods.

The socio-economic classification used in this study was based on the classification proposed by ABEP - Brazilian Association of Survey Companies in 2013 (24). This approach combines data on ownership of goods and education level to create an eight level classification system, in which level A corresponds to the wealthiest class defined (with an estimated average yearly earnings of US$4,988) and the classes D/E are the poorest classes of this classification system (with an estimated yearly earnings of US$376).

Survey structure

The recruitment and data collection were conducted by an outsourced fieldwork research agency (OA). All interviewers received a 3-day intensive training programme provided by a team of experienced academic researchers. The interviewers received a map and quota structure for each census tract to be visited. Brochures containing information about the study were delivered to the residences mailboxes to ensure the public was aware of the purpose of the study. The eligible subjects that were incapable of completing an interview because of functional illiteracy or severe mental or physical impairment were not included on the survey.

Given the high complexity of the instruments and the methods applied, rigorous quality control processes were enforced. The first stage of the data quality control process occurred in the OA headquarters, where the field supervisors checked the questionnaires for missing data. The approved questionnaires were scanned and sent to the academic research team for the second stage of data quality control; this stage consisted of the evaluation of data incompletion and query reporting. If sex and age quotas were exceeded the last questionnaire collected was excluded. If there was a suspicion of fraud or incomplete responses were obtained, the relevant subset of health states was assigned to another respondent. Questionnaires were double entered in a MySQL database specifically programmed for this purpose. In the case of divergence between the two entries, an academic researcher reviewed the questionnaire. A spreadsheet was used to support quality control and to examine interviewer's individual performance. Approximately 10%, of the respondents were contacted by a member of the academic research team after their interview to ask simple questions about the interview process which were used to verify its authenticity.

Statistical analysis

The statistical analysis was conducted using R Statistical Software, version 3.0 (Foundation for Statistical Computing, Vienna, Austria 2013). The observed utilities were plotted for inconsistence checking.

The TTO utility was taken as the dependent variable in this analysis Two sets of independent variables were defined: a fixed set, composed of 10 dummy variables for each health dimension severity level (M2, M3, SC2, SC3, UA2, UA3, PD2, PD3, AD2, and AD3 respectively); and an elective set of interaction terms proposed in other valuation studies such as N2 and N3 (25). Several models were used (Ordinary Least Squares, Robust Linear Regression and Mixed Effects Model). The models were examined in terms of their coefficients, R^2 or pseudo R^2, Mean Absolute Error (MAE), AIC and BIC. Pseudo R^2 was computed using McFadden method. The choice of the best-fit model was based on goodness-of-fit statistics, coefficients and parsimony. For the mixed models, the fixed effects were based on the dummy variables for each health dimension severity level and the random effects were based on the individual values. The same modelling strategies were used to evaluate the impact of unbalanced states on individual's valuation of utilities. Other independent variables were included in the basic model to estimate the impact of the unbalanced effect. The mean observed utility values were plotted against age to investigate the association between age and valuation.

RESULTS

Data was collected from 9148 subjects and the general characteristics of the achieved sample are shown in Table 1. Porto Alegre (South Region) has a better socioeconomic status with 60.1% of the population in class A or B. In the other cities, the majority of the population (50.7%) was classified as medium class

Approximately 85% of interviewers were replaced during data collection with the consequent need to provide several training sessions. Only 4% of questionnaires were replaced, mostly due to mistakes in the completion of the TTO procedure, breaches of age/sex quotas and fraud. No replacement occurred due to inconsistent data.

Respondents, especially in the northeast region (Recife), reported difficulties with understanding the TTO procedure, specifically in their capacity to imagine themselves in the proposed health state. The overall proportion of reported difficulties in the complete sample was 23.3%.

Based on the responses to the EQ-5D-3L descriptive system dimensions “Anxiety/ Depression” (32.4%) and “Pain/ Discomfort” (48.6%) were the ones associated with a higher prevalence of problems in the sample (Figure 1). Means VAS scores were similar in all regions.

Tariffs generated from observed means showed some logically dominant states presenting worse utility values than dominated health states (i.e. 12231 obtained a mean observed value of 0.40, which was less than the value 0.42 that was obtained for the health state 12232). Figure 2 shows observed utility plotted against health states ranked by predicted utility. The continuous line represents the mean observed TTO utility values and the dashed line represents health state predicted mean utility. The “spikes” that displays a divergence between observed and predicted values. The absence of observed data smoothly ordered deters the direct use of the observed data and stresses the need for modelling.

As a result several regression models were estimated to fit TTO valuations. The best fitted models are presented in Table 2. Of all models developed, the main effects individual –level model (Table 2) showed the best fit, with lower MAE (0.044) and lower AIC and BIC. The interaction terms N2 and N3 were also used to estimate models, however they did not induce significant gains on model fit to justify their inclusion in the final model. The exclusion of the constant term did not improve the model fit. The intercept coefficient of the chosen model was 0.851. The utility value for the health state '11111', assumed to be correspondent to full health, was fixed at 1. To compute the predicted values for any health state other than '11111' the following scoring algorithm was used: 0.851+ (-0.120 *M2) + (-0.363*M3) + (-0.112*SC2) + (-0.218 *SC3) + (-0.097*UA2) + (-0.184*UA3) + (-0.064*PD2) + (-0.168 *PD3) + (-0.050*AD2) + (-0.095*AD3).

The "Mobility" and "Self-care" dimensions led to the largest decrement in the utility value (Table 2). The estimated utility value decrements for "Confined to bed" and "Unable to perform usual activities" were 0.363 and 0.218, respectively. The "Anxiety and Depression" dimension presented smaller decrements in the estimated utility value, with its most severe level associated to a 0.095 decrement. The coefficients achieved in both on main effects models and in those that included interaction terms were negative. All coefficients were statistically significant ($P< 0.001$).

The utility estimates resulted from the valuation of imbalanced sets were low. The impact of unbalanced blocks was estimated with a multivariate model including a variable "imbalanced" (Yes or No) and the coefficient obtained was 0.033.

Figure 3 displays the mean observed utility value for each age group. Utilities are presented as point estimates and 95% confidence intervals. Overall, valuations increase with respondent's age (years), wherein the mean utility value for the oldest group (60-64 years) is approximately 0.1 higher than in the youngest age group (18-19 years).

The complete table of utility values for all the health states will be made available in the appendix section.

DISCUSSION

Through the combination of two datasets, we estimate the Brazilian EQ-5D-3L value set. This value set contains utility weights for computing QALYs, which can be applied to health technologies assessment and economic appraisal in Brazil. Such information represents an advance in Brazilian health policies, enabling decision making using domestic values derived from a large population-based sample.

This study also reports the first national valuation exercise to have directly valued the full set of 243 EQ-5D-3L health states using TTO. While the essential features of previous valuation studies were replicated on our study (e.g. valuation method), a small set of methodological divergences were adopted. With that we expected to build a dataset that could provide empirical evidence to further the field of health valuation. Firstly, the valuation of the full set of health states allows comparisons between observed and predicted estimates for each health state (partially reported on table 3). Also, such data set offers the opportunity to explore several issues related to valuation that have only previously been tested on datasets including a partial selection of states. This includes the optimal number and criteria for health states selection on valuation studies using TTO, the effect of imbalanced groups of health states on individual evaluations, the minimum number of evaluations for each health state.

To the best of our knowledge, only a couple of saturation studies were performed in the past, one in a student sample and other in a general population sample, both using the only VAS as elicitation method (14, 15).Most studies directly valued a sample of the health states and estimated the remaining states. To date there is no explicit consensus on the minimal number of health states that must be directly valued. Although most EQ-5D-3L valuation studies include the original set from the MVH study, the selection of additional health states varies greatly across subsequent studies and, in most cases, the selection criteria is based on theoretical assumptions (e.g., Japan - 17 health states [24]; Argentina - 22 health states [10] and France - 25 health states [25]).

This fieldwork demonstrated that it is possible to successfully run saturation studies with EQ-5D-3L, despite high attrition rates amongst interviewers.

The valuation task is set to build a scale with the health states valuation ordered by its impact on quality of life, according to a given population values and preferences. When a valuation study is conducted using a subset of health states, the rationale for modelling is quite obvious: to estimate the value of the health states that were not directly valued. Hence, as we valued the full-set of 243 health states, theoretically we could have estimated the tariff simply using the mean observed values for each one of them. A brief exploration of logical inconsistencies showed that the health states ranking that presumably should obey a logical structure often presents inconsistent valuations (e.g. 12231 with utility lower than 12232). As it is likely that these inconsistences are due to sampling rather than to real preferences inversion, we decided to resort to modelling to correct them.

All models resulted in similar estimates, with similar utility decrements for each dimension and level. The comparison of the models suggests that a more parsimonious specification yield better fit to TTO values. Regarding AIC and BIC, the mixed effects model performs better than the remaining. In addition, the intra-class correlation estimated trough this model specification was 0.424 (95%CI 0.415- 0.433), pointing to a substantial level of aggregation, which reinforces the decision to resort to a mixed effects approach. The choice between models with and without constant was solely based on the goodness-of-fit measures.

In this study, all model specifications that included constant terms yielded coefficients for the aforementioned term considerably different from one. These findings are consistent with the literature, which often refers to this gap as capturing the effect of any move away from full health. Aspects of the valuation technique, as the inability of the health state 11111 to capture the value of “perfect health”, may also influence the occurrence of this gap. Future users of this tariff should take into consideration that due the occurrence of this gap and the consequent low values for mild health states, the sensitivity of this scale to small changes in health states might be impaired. The model specification that provides the best fit includes the constant term.

The non-inclusion of interaction terms in our estimation can partially explain the differences observed when comparing the values obtained in this study with tariffs from other countries computed with the N3-term (interaction term variable for states with at least one dimension at level three). Several studies have suggested that the inclusion of the N3-term may induce an overestimation of the decrement caused by health states with at least one dimension at level 3 (29, 30). This can be observed when comparing the estimates obtained in the Brazilian study with UK social preference weights (12). We observed major differences in the weights of the pain/discomfort (PD3: Brazil -0.168 vs UK -0.386) and anxiety/depression (AD3: Brazil -0.095 vs. UK -0.236) dimensions. These results may also indicate an adaptation to a prevalent conditions effect, although the modelling techniques applied were different. Based on the results, it seems that the Brazilian population seems to value the loss of health-related quality of life much less, as they are defined by the EQ-5D dimensions, possibly due to cultural differences compared to other countries.

The estimate effect of unbalancing was low. This finding may indicate the option to balance for severity is not nearly as crucial as it was foretold. Furthermore, by blocking the health states by severity, it is possible that we are enforcing upon the subjects an interpretation structure that can have an impact on the valuation itself. As a proxy to this evidence, we have the context bias that can be observed on the VAS valuation, where the health state set influenced the valuation exercise (28). The rationale for state blocking is stated by Dolan in the report of the MVH results on choosing the states for each respondent; the most important consideration was that they should be spread widely over the valuation space to include as many combinations of levels across the five dimensions as possible (9).

According to recent data, 20.4% of Brazilian adults are functionally illiterate (18). During the interviews, the less educated subjects struggled to complete the most complex tasks. Despite these difficulties, we decided not to exclude the respondents’ data because of inconsistences on the valuation task because we could not attribute them to miscomprehension. Furthermore, recent findings point out that exclusion by an arbitrary investigator´s choice can, through the exclusion of real preferences, result in biased estimates (31).

In this study, contrarily to what was done in other valuation studies, we chose to not include individuals aged over 64 years mainly due to the high level of illiteracy and cognitive problems that affects this age group in Brazil. According to the last Brazilian Census, approximately 26.6% of Brazilian citizens aged 64 or more are illiterate. This fact, added to the high prevalence of dementia (approximately 19%) and other cognitive impairing conditions, might have resulted in an even more difficult data collection process (32). However, there is empirical evidence that age can have an effect on the individual propensity to trade quantity for quality of life (33, 34). Therefore, the extent to which the results obtained in this study, based on adult population (aged 18-64 years) valuations can be safely generalized to the elderly remains an open question. An attempt to investigate the association between age and valuation found a positive association as is shown on Figure 3. This exploration was conducted using exclusively the valuation for the health state ‘33333’, otherwise known as pit state, as a strategy to deal with the heterogeneity of health states severity valued. While the linear association between age and valuation in older age groups may not hold, given the results obtained on our data the inclusion of elderly would likely result on a slightly higher utility tariff. Further research is needed to ensure that the values of the ever-growing Brazilian senior population are known and available to support decision-making. The non-inclusion of illiterate and elderly respondents may also imply an overestimation of the overall self-reported quality of life of the Brazilian population. Overall, our sample reported to be in a good health state.

Finally, few limitations have to be pointed to the instrument itself. The use of a measure that describes health-related quality of life with 5 dimensions and 3 levels may not capture small but important differences between health states. The recent release by the EuroQoL Group of a 5-level version of EQ-5D, may remedy this type of problem although current controversies about valuation strategies remain.

In spite of its popularity, utility estimates and cost-utility analysis are not the only tools for decision making. The Brazilian government adopted a multicriteria decision making framework that goes beyond the sole use of cost-utility analysis results and includes, for instance, budgetary impact analysis, societal issues, and implementation challenges among other criteria for technology appraisal. We therefore recommend that users consider all these issues when using and interpreting the utility values generated in this study remain.

ACKNOWLEDGMENTS

We would like to thank the team of field interviewers, academic supervisors as well the fieldwork research agency (Analysis- Soluções em Estatística) for their commitment with this project. This study received financial support of the Brazilian Ministry of Health and FINEP- Financiadora de Estudos e Projetos.

References

1. Kind P, Brooks R, Rabin R. EQ-5D concepts and methods: a developmental history: Springer; 2006.
2. Brooks R. EuroQol: the current state of play. Health Policy. 1996;37(1):53-72.
3. Rabin R, Oemar M, Oppe M. EQ-5D-3L User Guide Basic Information on How to Use the EQ-5D-3L Instrument. Rotterdam: EuroQol Group. 2011.
4. Vianna C, Caetano R, Ugá M. Diretrizes metodológicas para estudos de avaliação econômica de tecnologias em saúde. Brasília: Ministério da Saúde; 2009.
5. Badia X, Roset M, Herdman M, Kind P. A comparison of United Kingdom and Spanish general population time trade-off values for EQ-5D health states. Medical Decision Making. 2001;21(1):7-16.
6. Knies S, Evers S, Candel M, Severens J, Ament A. Utilities of the EQ-5D: transferable or not? Pharmacoeconomics. 2009;27(9):767-779.
7. Williams A. The measurement and valuation of health: a chronicle: University of York York; 1995.
8. Kind P, Dolan P, Gudex C, Williams A. Variations in population health status: results from a United Kingdom national questionnaire survey. Bmj. 1998;316(7133):736-741.
9. Dolan P. Modeling valuations for EuroQol health states. Medical Care. 1997;35(11)1095-1108.
10. Augustovski F, Irazola V, Velazquez A, Gibbons L, Craig B. Argentine valuation of the EQ-5D health states. Value in Health. 2009;12(4):587-596.
11. Zarate V, Kind P, Chuang LH. Hispanic valuation of the EQ-5D health states: a social value set for Latin Americans. Value in Health. 2008;11(7):1170-1177.
12. Dolan P. Modeling valuations for EuroQol health states. Medical Care. 1997;35(11):1095-1108.
13. Xie F, Gaebel K, Perampaladas K, Doble B, Pullenayegum E. Comparing EQ-5D valuation studies: a systematic review and methodological reporting checklist. Medical Decision Making. 2014;34(1):8-20.
14. Kind P, Macran S, Hennessy S. Measuring social preferences for EQ-5D health states: results from a saturation study. In: Prevolnik Rupel V, ed. Proceedings of the 20th Plenary Meeting of the EuroQol Group. Bled, Slovenia: Institute of Public Health of the Republic of Slovenia; 2003;153-162.
15. Busschbach J, McDonnell J, Hout B A van. Testing different parametric relations between the EuroQol health description and health valuation in students. In: Nord E, editor. EuroQol Plenary Meeting, Oslo 17-18 October 1996. Conference Proceedings. Working paper No 2/97. National Institute of Public Health, Oslo, Norway, 1997.
16. Weinstein MC, Torrance G, McGuire A. QALYs: the basics. Value in Health. 2009;12(S1):S5-S9.
17. Viegas Andrade M, Noronha K, Kind P, Maia A, Miranda de Menezes R, De Barros Reis C, et al. Societal Preferences for EQ-5D Health States from a Brazilian Population Survey. Value in Health Regional Issues. 2013;2(3):405-412..
18. IBGE. Instituto Brasileiro de Geografia e Estatística 2014 [cited 2014 June 5]. Available from: http://www.ibge.gov.br/home/.
19. Chuang L, Kind P. The effect of health state selection on the valuation of EQ-5D. Medical Decision Making. 2011;31(1):186-94.

20. P. K. A revised protocol for the valuation of health states defined by the EQ-5D-3L classification system: learning the lessons from the MVH study. New York: Centre for Health Economics, University of York; 2009.
21. Torrance GW, Thomas WH, Sackett DL. A utility maximization model for evaluation of health care programs. Health services research. 1972;7(2):118.
22. Torrance GW. Social preferences for health states: an empirical evaluation of three measurement techniques. Socio-economic planning sciences. 1976;10(3):129-36.
23. Gudex C. Time trade-off user manual: props and self-completion methods. 1994.
24. Associação Brasileira de Empresas de Pesquisa (ABEP). Critério de Classificação Econômica Brasil (CCEB) [cited 2014 November 13]. Available from: http://www.abep.org/criterioBrasil.aspx
25. Shaw JW, Johnson JA, Coons SJ. US valuation of the EQ-5D health states: development and testing of the D1 valuation model. Medical Care. 2005;43(3):203–20.
26. Tsuchiya A, Ikeda S, Ikegami N, Nishimura S, Sakai I, Fukuda T, et al. Estimating an EQ-5D population value set: the case of Japan. Health Economics. 2002;11(4):341-53.
27. Chevalier J, de Pouvourville G. Valuing EQ-5D using time trade-off in France. Eur J Health Econ. 2013;14(1):57-66.
28. Krabbe PF, Stalmeier PF, Lamers LM, Busschbach JJ. Testing the interval-level measurement property of multi-item visual analogue scales. Quality of Life Research. 2006;15(10):1651-61.
29. Rowen D, Brazier J, Roberts J. Mapping SF-36 onto the EQ-5D index: how reliable is the relationship. Health Qual Life Outcomes. 2009;7:27.
30. Parkin D, Feng Y, Devlin N, editors. What determines the shape of an EQ-5D index distribution. Health Economics Study Group meeting, Exeter University. 2013.
31. Engel L, Bansback N, Bryan S, Doyle-Waters M, Whitehurst D. Exclusion criteria in national health state valuation studies: a systematic review. Poster presented at: The 36th Annual Meeting of the Society for Medical Decision Making; 2014 October 18-22; Miami, EUA.
32. Fagundes SD, Silva MT, Thees MFRS, Pereira MG. Prevalence of dementia among elderly Brazilians: a systematic review. Sao Paulo Medical Journal. 2011;129(1):46-50.
33. Dolan P. Effect of age on health state valuations. J Health Serv Res Policy. 2000;5(1):17-21.
34. Dolan, P., & Roberts, J. (2002). To what extent can we explain time trade-off values from other information about respondents?. Social science & medicine. 2002;54(6):919-929.

Table 1. Sociodemographic characteristics of the study sample by region

	Minas Gerais	Rio de Janeiro	Porto Alegre	Recife	Total
Valid questionnaires	3363	3932	894	959	9148
Gender (%)					
Female	50.6	53.6	53.5	54.6	52.6
Male	49.4	46.4	46.5	45.4	47.4
Age (mean, SD)	36.4 (13.2)	38.6 (13.1)	39.3 (13.1)	38.2 (12.8)	37.8 (13.1)
Age Group (%)					
18-30	41.3	33.4	32.4	33.0	36.2
31-50	40.4	43.4	43.2	46.7	42.6
50-64	18.3	23.2	24.4	20.3	21.2
Marital Status					
Married (%)	51.0	49.4	52.1	54.7	50.8
Single (%)	39.2	39.5	35.1	32.8	38.2
Widower (%)	2.4	3.2	3.6	2.5	2.9
Socioeconomic Status					
A1/2 (%)	3.4	5.3	10.4	9.0	5.2
B1/2 (%)	33.6	30.4	49.7	36.2	38.4
C (%)	55.2	49.9	37.8	49.8	50.7
D (%)	8.4	4.3	2.1	4.7	5.6
E (%)	0.1	0.1	0.0	0.2	0.1
Self-rated VAS (mean,SD)	83.8	80.8	83.1	80.8	82.1

Table 2. Estimated coefficients from the alternative model specifications.

Variable	Robust Linear Model	Robust Linear Model +N2	Robust Linear Model +N3	Robust Linear Model without constant	Ordinary least Squares	Ordinary least Squares without constant
	Coef. (SD)	Coef. (SD)	Coef. (SD)	Coef. (SD)	Coef. (SD)	Coef. (SD)
Intercept	0.884 (0.007)	0.890 (0.009)	0.900 (0.007)	--	0.838 (0.007)	--
M2	-0.101 (0.005)	-0.100 (0.005)	-0.100 (0.005)	-0.136 (0.005)	-0.109 (0.005)	-0.160 (0.005)
M3	-0.384 (0.005)	-0.384 (0.005)	-0.377 (0.005)	-0.408 (0.006)	-0.359 (0.005)	-0.393 (0.005)
SC2	-0.106 (0.005)	-0.105 (0.005)	-0.106 (0.005)	-0.141 (0.005)	-0.107 (0.005)	-0.156 (0.005)
SC3	-0.224 (0.005)	-0.225 (0.005)	-0.218 (0.005)	-0.247 (0.006)	-0.214 (0.005)	-0.246 (0.005)
UA2	-0.091 (0.005)	-0.089 (0.005)	-0.089 (0.005)	-0.126 (0.005)	-0.091 (0.005)	-0.141 (0.005)
UA3	-0.189 (0.005)	-0.190 (0.005)	-0.181 (0.005)	-0.216 (0.005)	-0.180 (0.005)	-0.217 (0.005)
PD2	-0.063 (0.005)	-0.061 (0.005)	-0.061 (0.005)	-0.096 (0.005)	-0.063 (0.005)	-0.110 (0.005)
PD3	-0.176 (0.005)	-0.177 (0.005)	-0.169 (0.005)	-0.198 (0.005)	-0.169 (0.005)	-0.200 (0.005)
AD2	-0.051 (0.005)	-0.050 (0.005)	-0.050 (0.005)	-0.088 (0.005)	-0.047 (0.005)	-0.098 (0.005)
AD3	-0.101 (0.005)	-0.101 (0.005)	-0.093 (0.005)	-0.129 (0.005)	-0.092 (0.005)	-0.130 (0.005)
N2		-0.008 (0.008)				
N3			-0.040 (0.007)			
R^2	0.24	0.21	0.23	0.66	0.25	0.24
MAE	0.05	0.05	0.05	0.069	0.043	0.063
AIC	89081.23	126080.60	107013.4	102569.4	88811.45	89407.12
BIC	89189.91	126108.20	107041.0	102659.9	88911.08	89497.69

Variable	Respondent-level Mixed Effects Model	Respondent-level Mixed Effects Model without constant
	Coef. (SD)	Coef. (SD)
Intercept	0.851 (00,.006)	--
M2	-0.120 (0.004)	-0.160 (0.005)
M3	-0.363 (0.004)	-0.393 (0.005)
SC2	-0.112 (0.004)	-0.156 (0.005)
SC3	-0.218 (0.004)	-0.246 (0.005)
UA2	-0.097 (0.004)	-0.141 (0.005)
UA3	-0.184 (0.004)	-0.217 (0.005)
PD2	-0.064 (0.004)	-0.110 (0.005)
PD3	-0.168 (0.004)	-0.200 (0.005)
AD2	-0.050 (0.004)	-0.098 (0.005)
AD3	-0.095 (0.004)	-0.130 (0.005)
N2		
N3		
R^2	0.28	0.47
MAE	0.044*	0.063*
AIC	70431.87	89500.76
BIC	70549.61	89600.38

AIC, Akaike information criteria; BIC, Bayesian information criteria; *MAE was computed using the fixed coefficients of this models;

Table 3. Observed and predicted values for a selection of health states

		Observed values				Predicted Values		
Health State	Nº of Observations	Mean	SE	Median	% of negatives	Mean	SE	Prediction errors
11112	399	0.805	0.290	0.95	2.0	0.801	0.006	0.004
11113	141	0.691	0.363	0.85	2.8	0.756	0.007	-0.065
11121	397	0.828	0.266	0.95	1.8	0.787	0.006	0.041
11131	143	0.620	0.427	0.70	7.7	0.684	0.007	-0.064
11211	401	0.796	0.265	0.95	1.0	0.754	0.006	0.042
11222	401	0.687	0.350	0.85	5.2	0.640	0.006	0.048
11311	142	0.598	0.422	0.75	6.3	0.668	0.007	-0.069
11312	271	0.626	0.389	0.75	5.5	0.618	0.006	0.009
12133	140	0.388	0.500	0.50	16.4	0.477	0.007	-0.089
12232	142	0.356	0.527	0.45	16.9	0.425	0.006	-0.069
12233	139	0.336	0.526	0.45	17.3	0.380	0.007	-0.044
12333	144	0.182	0.519	0.10	28.5	0.293	0.006	-0.112
13111	144	0.578	0.401	0.70	8.3	0.634	0.007	-0.055
13112	144	0.516	0.437	0.55	8.3	0.584	0.007	-0.068
13221	141	0.404	0.462	0.50	13.5	0.472	0.006	-0.068
13222	271	0.398	0.515	0.55	18.1	0.422	0.006	-0.024
13333	143	0.172	0.564	0.05	30.1	0.188	0.006	-0.016
21111	399	0.762	0.327	0.95	3.0	0.731	0.006	0.031
21113	143	0.571	0.429	0.75	9.8	0.636	0.006	-0.065
21333	143	0.254	0.522	0.35	21.0	0.285	0.006	-0.031
22111	397	0.650	0.410	0.85	7.3	0.619	0.006	0.031
23313	266	0.208	0.535	0.55	26.7	0.235	0.006	-0.028
23321	273	0.279	0.515	0.50	24.9	0.266	0.006	0.013
23333	397	0.042	0.549	0	41.1	0.068	0.005	-0.025
31111	144	0.403	0.496	0.55	17.4	0.488	0.007	-0.084
31123	142	0.310	0.508	0.45	19.0	0.328	0.007	-0.018
31133	144	0.168	0.544	0.15	27.8	0.225	0.007	-0.057
31211	143	0.352	0.496	0.45	18.9	0.391	0.007	-0.038
31233	143	0.058	0.509	0	37.8	0.128	0.006	-0.070
32222	143	0.019	0.562	0	39.2	0.164	0.006	-0.146
33223	395	0.015	0.531	0	44.8	0.014	0.006	0.001
33313	269	0.051	0.538	0	41.3	-0.008	0.006	0.059
33323	522	-0.037	0.551	0	46.9	-0.073	0.005	0.035
33333	9056	-0.156	0.496	-0.05	54.1	-0.176	0.005	0.020

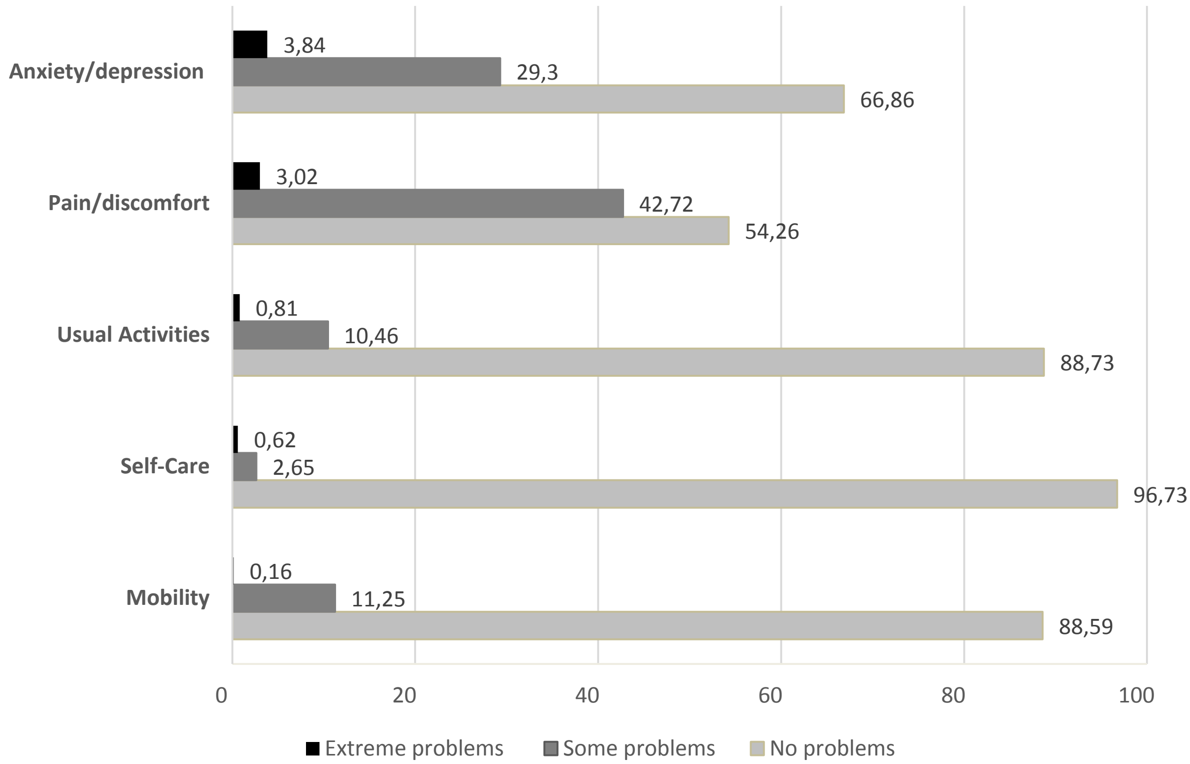

Figure 1. Population Norms

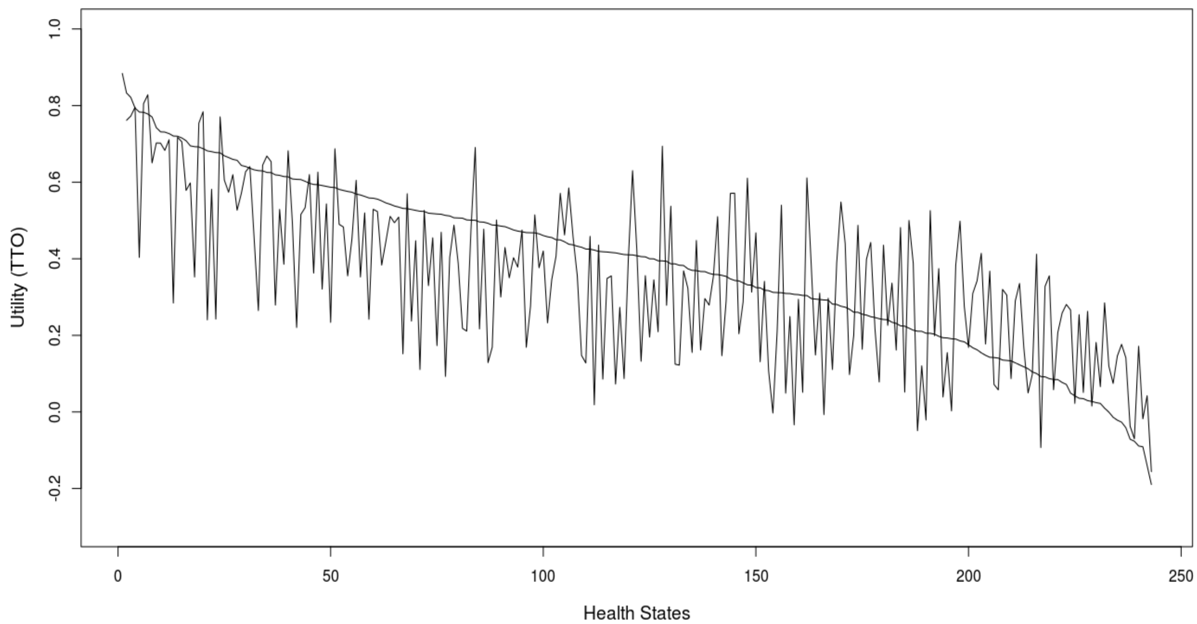

Figure 2. Utilities plotted against health states ranked by predicted utility

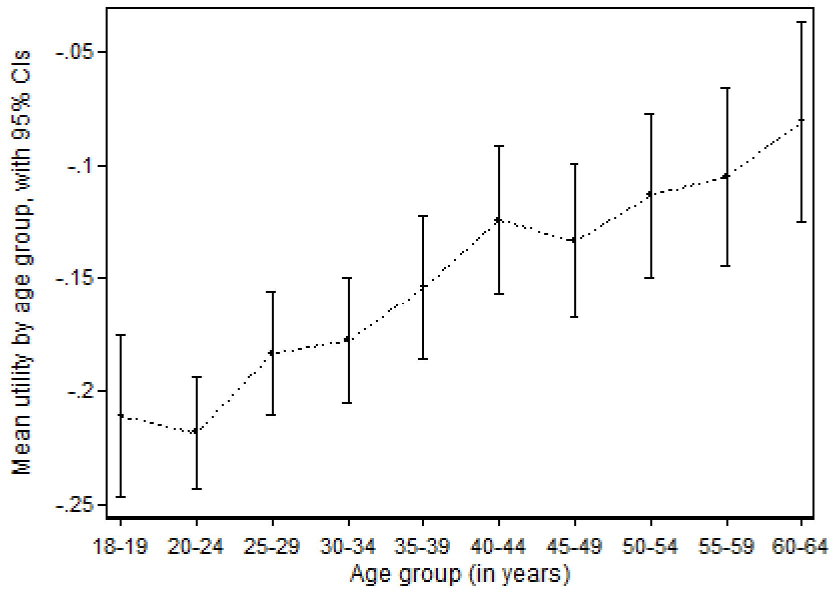

Figure 3. Mean utility value for the health state '33333' plotted against age.

Appendix 1. Brazilian predicted weights for 243 EQ-5D-3L health states based on the Mixed effects model.

Health State	Estimate	Health State	Estimate	Health State	Estimate	Health State	Estimate	Health State	Estimate
11111	**1**	11321	0,603	12231	0,475	13211	0,536	21121	0,667
11112	0,801	11322	0,553	12232	0,425	13212	0,486	21122	0,617
11113	0,756	11323	0,508	12233	0,380	13213	0,442	21123	0,572
11121	0,787	11331	0,500	12311	0,556	13221	0,472	21131	0,564
11122	0,737	11332	0,450	12312	0,506	13222	0,422	21132	0,514
11123	0,692	11333	0,405	12313	0,461	13223	0,377	21133	0,469
11131	0,684	12111	0,739	12321	0,491	13231	0,369	21211	0,634
11132	0,634	12112	0,689	12322	0,441	13232	0,319	21212	0,584
11133	0,589	12113	0,644	12323	0,396	13233	0,274	21213	0,539
11211	0,754	12121	0,675	12331	0,388	13311	0,450	21221	0,570
11212	0,704	12122	0,625	12332	0,338	13312	0,400	21222	0,520
11213	0,659	12123	0,580	12333	0,293	13313	0,355	21223	0,475
11221	0,690	12131	0,572	13111	0,634	13321	0,386	21231	0,466
11222	0,640	12132	0,522	13112	0,584	13322	0,336	21232	0,416
11223	0,595	12133	0,477	13113	0,539	13323	0,291	21233	0,371
11231	0,586	12211	0,642	13121	0,569	13331	0,283	21311	0,548
11232	0,537	12212	0,592	13122	0,519	13332	0,233	21312	0,498
11233	0,492	12213	0,547	13123	0,474	13333	0,188	21313	0,453
11311	0,668	12221	0,578	13131	0,466	21111	0,731	21321	0,483
11312	0,618	12222	0,528	13132	0,416	21112	0,681	21322	0,433

11313	0,573	12223	0,483	13133	0,371	21113	0,636	21323	0,388
Health State	Estimate	Health State	Estimate	Health State	Estimate	Health State	Estimate	Health State	Estimate
21331	0,380	22311	0,436	23221	0,352	31131	0,320	32111	0,376
21332	0,330	22312	0,386	23222	0,302	31132	0,270	32112	0,326
21333	0,285	22313	0,341	23223	0,257	31133	0,225	32113	0,281
22111	0,619	22321	0,371	23231	0,249	31211	0,391	32121	0,312
22112	0,569	22322	0,321	23232	0,199	31212	0,341	32122	0,262
22113	0,524	22323	0,276	23233	0,154	31213	0,296	32123	0,217
22121	0,555	22331	0,268	23311	0,330	31221	0,326	32131	0,208
22122	0,505	22332	0,218	23312	0,280	31222	0,276	32132	0,158
22123	0,460	22333	0,173	23313	0,235	31223	0,231	32133	0,113
22131	0,452	23111	0,514	23321	0,266	31231	0,223	32211	0,279
22132	0,402	23112	0,464	23322	0,216	31232	0,173	32212	0,229
22133	0,357	23113	0,419	23323	0,171	31233	0,128	32213	0,184
22211	0,522	23121	0,449	23331	0,163	31311	0,304	32221	0,214
22212	0,472	23122	0,399	23332	0,113	31312	0,254	32222	0,164
22213	0,427	23123	0,354	23333	0,068	31313	0,209	32223	0,119
22221	0,458	23131	0,346	31111	0,488	31321	0,240	32231	0,111
22222	0,408	23132	0,296	31112	0,438	31322	0,190	32232	0,061
22223	0,363	23133	0,251	31113	0,393	31323	0,145	32233	0,016
22231	0,355	23211	0,416	31121	0,423	31331	0,137	32311	0,192
22232	0,305	23212	0,366	31122	0,373	31332	0,087	32312	0,142
22233	0,260	23213	0,321	31123	0,328	31333	0,042	32313	0,097

Health State	Estimate	Health State	Estimate
32321	0,128	33231	0,006
32322	0,078	33232	-0,044
32323	0,033	33233	-0,089
32331	0,025	33311	0,087
32332	-0,025	33312	0,037
32333	-0,070	33313	-0,008
33111	0,270	33321	0,022
33112	0,220	33322	-0,028
33113	0,175	33323	-0,073
33121	0,206	33331	-0,081
33122	0,156	33332	-0,131
33123	0,111	33333	-0,176
33131	0,103		
33132	0,053		
33133	0,008		
33211	0,173		
33212	0,123		
33213	0,078		
33221	0,109		
33222	0,059		
33223	0,014		