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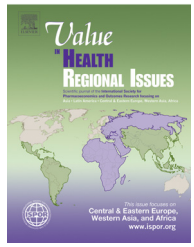

Mapping the Nottingham Health Profile onto the Preference-Based EuroQol-5D Instrument for Patients with Diabetes

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ABSTRACT

Objective: The aim of this study was to derive a function that can map the Nottingham Health Profile (NHP) questionnaire onto a utility measure, the EuroQol five-dimensional (EQ-5D) questionnaire index, for diabetic patients. **Methods:** A cross-sectional study was performed on diabetic patients in Hungary with different complications in which quality of life was measured by using both the NHP questionnaire and the EQ-5D questionnaire. Ordinary stepwise-backward least-squares regression was used to develop a mapping function. Adjusted R^2, Akaike's information criterion, and root mean square error were used to assess the performance of the model. The robustness of the models was tested using 10-fold cross-validation and bootstrapping. **Results:** The best-fitting models were those that contained all the NHP statements as predictors and a stepwise reduced version that contained only 19 statements. The latter model, however, showed considerable variability in the selection of predictors. The adjusted R^2 of the former model was 0.68, the root mean square error was 174, and the Akaike's information criterion was −559.9. **Conclusions:** The expected value of the EQ-5D questionnaire can be reasonably predicted on the basis of results of the NHP in patients with diabetes mellitus. The mapping function of the NHP onto the EQ-5D questionnaire is capable of estimating the expected EQ-5D questionnaire utility values in a group of patients with diabetes. The function's applicability for individual-level predictions, however, is limited. Further research is needed to find out whether mapping functions developed in Central-Eastern European countries are transferable to Western European countries.

Keywords: diabetes mellitus, economic models, linear models, quality of life, health profile.

Introduction

The burden of diabetes mellitus, which is already large in most countries, is steadily increasing with the epidemic of obesity, inactivity, population aging, and greater longevity in patients with diabetes [1]. An important aspect of this burden is the loss of quality of life (QOL) among patients who suffer from complications of diabetes. Therefore, many studies regularly measure the QOL of diabetic patients as an important outcome [2,3]. In these studies, QOL is usually measured by using a generic or a disease-specific instrument that does not provide utility measures. To support an efficient allocation of resources to both prevent and control diabetes, the cost-effectiveness of alternative strategies needs to be considered. Cost-effectiveness analysis requires, however, preference-based utility measures of QOL. Therefore, it would be desirable to have mapping functions that could translate the results obtained by non–preference-based instruments to utility values. Accordingly, the aim of this study was to develop a function that can map the Nottingham Health Profile (NHP) questionnaire onto the EuroQol five-dimensional (EQ-5D) questionnaire utility index.

Methods

Participants, Setting

The study was performed in 15 centers in Hungary specializing in the care of diabetic patients. Study groups were defined by the type of diabetes (type 1 or type 2), type of treatment (oral antidiabetic or insulin treatments), and the presence of complications (visual impairment, nephropathy, neuropathy, coronary

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heart disease, and/or cerebrovascular disease). Quotas were given to the centers according to these modalities, and the centers enrolled the patients consecutively. The primary objective of the study was to estimate the QOL among diabetic patients with different complications [4]. This report presents the results related to the secondary objective, which was mapping the NHP questionnaire onto the EQ-5D questionnaire. The study was approved by the institutional ethical boards and by the National Ethical Board for Medical Research (8-239/2009-1018EKU). All persons gave their informed consent before their inclusion in the study.

Instruments

All patients were asked to fill in the NHP questionnaire and the EQ-5D questionnaire [5,6]. The questionnaires were self-administered, although help was provided by the study personnel on request. The EQ-5D questionnaire consists of the EQ-5D descriptive system and the EQ visual analog scale. We used the former for this study. The EQ-5D descriptive system comprises five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has three levels: no problems, some problems, extreme problems. The respondent indicates which statement in each of the five dimensions describes his state most appropriately. A total of 243 possible health states can be defined this way. Utility values (EQ-5D questionnaire index values) were attached to these states in our analysis by using the time trade-off valuation technique from a UK study [7]. The EQ-5D questionnaire has been validated in Hungary [8].

The 38 statements of the NHP fall into six sections: energy (nine items), pain (eight items), emotional reactions (three items), sleep disturbances (five items), social isolation (five items), and physical mobility (eight items). The respondents need to consider whether each statement applies to him or her in general. For each section, a score is calculated according to the NHP scoring guidelines [9]. Individual items are scored 1 for a "yes" response and 0 for a "no" response. The score for each section represents the summation of the item scores expressed as a percentage. As such, the scores range from 0 to 100, with a higher number representing greater distress. A patient-completed index of distress from the Nottingham Health Profile (NHP-D) can be calculated as the sum of 24 items out of the total 38 statements [10]. The NHP was one of the first QOL instruments validated in Hungary [11]. As in the Hungarian validation study NHP-D showed great reliability and sensitivity, it proved to be a valuable outcome measure for trials for which carefully developed disease-specific QOL measures are unavailable.

Analysis

OLS regression models

The most common method for establishing a functional relationship between two QOL measures is ordinary least squares (OLS) regression [12–17]. There are many possible ways to obtain EQ-5D questionnaire indices from a non–preference-based instrument such as the NHP. Having a data set in which patients have responded to both instruments, empirical matching is the most straightforward method. The essence of this approach is to explore the relationship between the two instruments by using regression analyses. Because the range of the EQ-5D questionnaire is bounded, the use of OLS regression models risks predicted values outside the range [12]. Alternatives would be to use generalized linear models, tobit regression, or censored least absolute deviations to allow for censoring. A recent review, however, showed that the standard method for mapping to the EQ-5D questionnaire was OLS regression [17]. The review of 90 studies found that 80% of the studies used OLS regression. There are arguments supporting OLS. Tsuchiya et al. [15] showed that in mapping problems such as ours, performance of the generalized linear model was comparable to that of the OLS regression, but not better. They concluded that "the associated benefits of generalized linear model do not seem to outweigh its costs." In another recent study, where OLS, tobit, and censored least absolute deviation models were compared, OLS turned out to be the best-performing model because it produced the lowest RMSE and mean absolute error and the highest R^2 [18]. Taking into account the above considerations and the fact that the range of the predicted EQ-5D questionnaire values of our OLS models hardly exceeded the limits (see Table 4), we decided not to use the generalized linear model.

In our analysis, the dependent variable was the overall EQ-5D questionnaire index, while the explanatory variables were the 38 NHP items used in the different aggregation levels. The study did not attempt to predict separately the individual EQ-5D questionnaire dimensions because previous studies showed it to be no more efficient in terms of prediction [12,14,19].

First, we regressed the overall EQ-5D questionnaire index on the total NHP-D score as a start-up. Next, we refined this basic model by first using the six NHP scores and later using all 38 separate statements as dependent variables.

In each model, we looked for nonlinear dependence between the independent and the explanatory variables as a signal to put either squared or otherwise transformed terms into the model. In addition, we studied whether two-way interactions could lead to better-fitting statistics, which are commensurate with the higher complexity of a given model.

If the full models fitted reasonably well, then we looked for more parsimonious models by running stepwise backward regression. We started with the full model and set the removal criterion to $P = 0.1$ and the reentry criterion to $P = 0.05$. This means that if a predictor was not significant at the level of 0.1, it was removed from the model but it could reenter if its significance reached 0.05 after removing other predictors.

OLS regression assumptions were examined by using the following methods:

1. The variance inflation factor (VIF) index was used to test collinearity. Some of the problematic (VIF index >10) predictors were removed.
2. Nonlinearity in any of the predictors was checked with the help of augmented partial residual plots.
3. Normality assumption for regression residuals was checked by plotting the quantiles of the regression residuals against the quantiles of standard normal distribution (Q-Q plot).
4. The assumption of the homoscedasticity of the residuals was visually checked by plotting predicted values against standardized residuals because known statistical tests for homoscedasticity are very sensitive to the violation of the normality assumption and cannot be used if the normality assumption fails.

Assessment of goodness of fit

Goodness of fit and predictive power were measured with the root mean square error (RMSE), the adjusted R^2 indices, and Akaike's information criterion (AIC). AIC is an information-theoretical model selection criteria with the advantage of applicability to non-nested models. Lower AIC values indicate a better model. The range of the predicted EQ-5D questionnaire values is also reported because OLS models struggle to produce EQ-5D questionnaire indices that are negative or equal to 1.

Internal validity

Judging the internal validity of the results is of primary importance when predictive models are built. Because no external data set is available, within-sample validation was carried out with the help of replication techniques. Two tests were conducted. First, stability of model coefficients is of interest because the relatively large number of predictors may lead to an overparametrized model. Stability,

tendency to overfitting, was tested using k-fold cross-validation. Second, stepwise backward selections were validated by refitting the stepwise-backward model in 200 independent bootstrap samples of the same size as the original model had, using simple random sampling with replacement. The validity, robustness of the selection, is described in terms of what percentage of the replications retrieve each of the predictors selected in the original model.

The whole analysis was conducted by using the software package STATA 10.0 (StataCorp, College Station, TX) [20].

Results

A total of 943 diabetic patients participated in the study. Table 1 shows the main characteristics of the study population. Most of them suffered from type 2 diabetes. All major complications of diabetes mellitus were represented in the study population.

Missing Data

The rate of missing scores varied between 0.5% and 1.9%. The NHP-D index could not be calculated in 2.7% of the participants. The five dimensions of the EQ-5D questionnaire had a missing rate between 0.2% and 0.7%, resulting in a 1% missing rate regarding the overall score.

Table 2 presents the summary statistics of the scores in question. As Fig. 1 shows, the distribution of the EQ-5D questionnaire index was heavily skewed, with 21% of the indices equal to 1, 80% of the indices greater than 0.5 and only 5% below 0.

NHP-D score regression

This model was fitted on the data of 912 participants with data on the NHP-D score and the EQ-5D questionnaire index. In these participants, the NHP-D had a range of 0 to 24 and the EQ-5D questionnaire index had a range of −0.594 to 1. The predictive power of the total NHP-D score was relatively poor, with an adjusted R^2 of 0.487, AIC of −176.09, and RMSE of 0.219. For the latter, we used the Huber-White variance estimation because the residuals increased toward the higher end of the NHP-D, indicating that prediction errors were affected by poorer health. In addition, the normality assumption for the residuals did not meet perfectly, though it might have had only a marginal effect on the confidence intervals.

Table 1 – Characteristics of the study population.

Characteristic (N = 943)	% or mean ± SD
Sex: Male	54.4
Age (y)	61.0 ± 13.1
Type 2 diabetes	84.5
Time since diagnosis of diabetes (y)	14.3 ± 10.5
Visual impairment	
0.1 <= visual acuity < 1	15.6
Visual acuity < 0.1	5.5
Nephropathy	
Only laboratory finding	11.2
Symptomatic	6.8
Neuropathy*	
Sensomotoric symptoms	19.2
Ulcer or minor amputation	8.5
Autonomic neuropathy	7.4
Coronary heart disease	
Without acute event	11.5
With acute event	10.0
Cerebrovascular disease	
TIA	9.7
Stroke	5.8
Peripheral artery disease*	
Symptoms	7.7
Amputation	8.4

TIA, transient ischemic attack.
* A patient could belong to multiple categories.

Table 2 – Summary statistics of the NHP and EQ-5D questionnaire domain scores.

Dimension	N	Mean ± SD	Median
NHP1 (Energy)	936	38.82 ± 35.50	33.33
NHP2 (Pain)	931	27.40 ± 29.17	12.50
NHP3 (Emotional reactions)	925	20.00 ± 24.39	11.11
NHP4 (Sleep disturbance)	938	28.40 ± 30.21	20.00
NHP5 (Social isolation)	929	8.29 ± 18.66	0.00
NHP6 (Mobility)	926	32.17 ± 28.99	25.00
EQ-5D1 (Mobility)	940	1.62 ± 0.53	2.00
EQ-5D2 (Self-care)	936	1.24 ± 0.47	1.00
EQ-5D3 (Usual activity)	941	1.55 ± 0.68	1.00
EQ-5D4 (Pain/discomfort)	940	1.68 ± 0.58	2.00
EQ-5D5 (Anxiety/depression)	940	1.52 ± 0.60	1.00
NHP-D	918	5.06 ± 4.96	4.00
Overall EQ-5D questionnaire index	934	0.66 ± 0.31	0.73

EQ-5D, EuroQol five-dimensional; NHP, Nottingham Health Profile.

NHP Scores Regression

Next, we regressed the EQ-5D questionnaire index on the six NHP scores using 900 observations without missing values. The VIF did not indicate a high collinearity for any of the six predictors out of which four proved to be significant (energy, pain, emotional reactions, and mobility). According to the Q-Q plot, residuals were not far from being normally distributed, although a rather heteroscedastic and, thus, robust variance estimation was used in this case. There was a large progress, as the adjusted R^2 changed to 0.645, and as the AIC changed to −497.024. With RMSE being 0.183, however, there was an 11% average error in terms of the whole range of the EQ-5D questionnaire scale (−0.594 to 1). Augmented partial residual plots did not indicate that any nonlinear terms would have been beneficial as additions to the model. The stepwise backward selection retrieved only the four significant predictors. The goodness-of-fit statistics were nearly unchanged, with adjusted R^2 = 0.645, AIC = −503.414, and RMSE = 0.183. Two-way interactions could not be taken into account because of multicollinearity problems indicated by the VIF analysis.

NHP Statements Regression

The 38 individual NHP statements were entered into the model as dummy explanatory variables. Because of the heteroscedastic pattern of the residuals, a Huber-White variance estimator was used for the model calculations. The model performance showed only a marginal improvement compared with the previous model, with an adjusted R^2 of 0.680, AIC of −559.835, and RMSE of 0.174. The significant coefficients were all negative with the exception of statement EM4, "the days seem to drag," and statement SO3, "I feel there is nobody I am close to," which are counterintuitive in their sign (Table 3). Fig. 2 presents the fitted versus observed values plot.

The stepwise backward selection removed 19 of the 38 NHP statements; EM4 and SO3 both remained in the model with

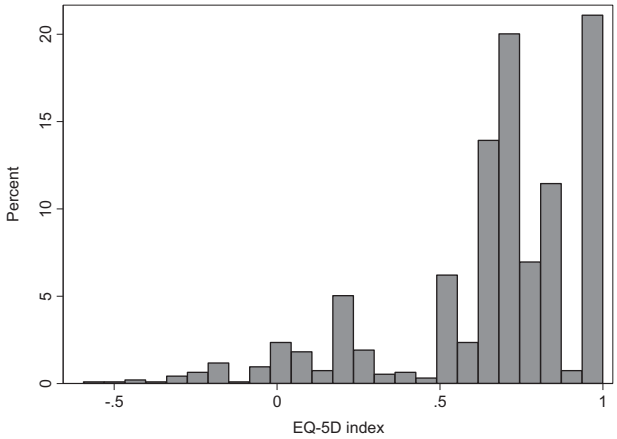

Fig. 1 – Histogram of the EQ-5D questionnaire index (N = 934). EQ-5D, EuroQol five-dimensional.

positive signs, while all other coefficients intuitively had the correct signs. The predictive power of the model was similar to that of the full model; the adjusted R^2 was 0.676, AIC was −564.655, and RMSE was 0.175. This model could have been augmented with two-way interactions, although severe multicollinearity problems were apparent among the interaction terms and were, therefore, not explored further.

Summary of Model Results

Table 4 summarizes the settings and goodness-of-fit statistics of the above models. In terms of AIC, the model with NHP statements as predictors performed the best. The predicted EQ-5D questionnaire range of the full model was slightly wider than that of the stepwise reduced model: −0.23 to 1.05 versus −0.19 to 0.99. It was still considerably narrower, however, than the range of the observed data, which was −0.594 to 1. The two models that regressed the EQ-5D questionnaire index on the NHP scores were worse than the models with NHP statements as predictors in

Table 3 – Coefficients with robust standard errors of the models with NHP statements as predictors.

Statement	Full model (N = 900)			Stepwise selection (N = 909)		
	Coefficient	P > |t|	95% CI	Coefficient	P > |t|	95% CI
EM1	−0.0937	$<10^{-3}$	−0.1385 to −0.0489	−0.0999	$<10^{-3}$	−0.1436 to −0.0562
EM2	0.0080	0.8	−0.0424 to 0.0583	–	–	–
EM3	−0.0420	0.01	−0.0750 to −0.0091	−0.0455	0.003	−0.0752 to −0.0158
EM4	0.0504	0.01	0.0105 to 0.0902	0.0497	0.01	0.0116 to 0.0877
EM5	−0.0136	0.3	−0.0404 to 0.0132	–	–	–
EM6	−0.0095	0.6	−0.0503 to 0.0314	–	–	–
EM7	−0.0348	0.2	−0.0861 to 0.0165	−0.0467	0.05	−0.0942 to 0.0008
EM8	−0.1075	0.005	−0.1821 to −0.0330	−0.1189	0.001	−0.1912 to −0.0465
EM9	−0.0084	0.7	−0.0547 to 0.0379	–	–	–
EN1	0.0080	0.6	−0.0243 to 0.0404	–	–	–
EN2	−0.0532	0.03	−0.1009 to −0.0056	−0.0598	0.01	−0.1067 to −0.0128
EN3	−0.0290	0.05	−0.0580 to −0.0001	−0.0292	0.04	−0.0566 to −0.0017
P1	−0.0352	0.03	−0.0674 to −0.0029	−0.0386	0.01	−0.0690 to −0.0082
P2	−0.1518	$<10^{-3}$	−0.2245 to −0.0791	−0.1407	$<10^{-3}$	−0.2090 to −0.0723
P3	0.0304	0.3	−0.0277 to 0.0886	–	–	–
P4	−0.0243	0.2	−0.0625 to 0.0140	–	–	–
P5	0.0280	0.1	−0.0075 to 0.0635	–	–	–
P6	−0.0600	0.01	−0.1057 to −0.0142	−0.0639	0.004	−0.1067 to −0.0210
P7	−0.0219	0.3	−0.0649 to 0.0211	–	–	–
P8	−0.0148	0.5	−0.0608 to 0.0312	–	–	–
PM1	−0.0185	0.4	−0.0654 to 0.0284	–	–	–
PM2	−0.0507	0.001	−0.0798 to −0.0217	−0.0475	0.002	−0.0774 to −0.0176
PM3	−0.0913	0.03	−0.1746 to −0.0079	−0.0893	0.03	−0.1713 to −0.0073
PM4	−0.0354	0.06	−0.0719 to 0.0011	−0.0512	$<10^{-3}$	−0.0797 to −0.0227
PM5	−0.0451	0.04	−0.0875 to −0.0028	−0.0467	0.03	−0.0891 to −0.0042
PM6	−0.0782	0.001	−0.1255 to −0.0308	−0.0829	0.001	−0.1298 to −0.0360
PM7	−0.0573	$<10^{-3}$	−0.0883 to −0.0263	−0.0543	$<10^{-3}$	−0.0831 to −0.0255
PM8	−0.1389	$<10^{-3}$	−0.1856 to −0.0922	−0.1479	$<10^{-3}$	−0.1922 to −0.1037
SL1	−0.0041	0.8	−0.0421 to 0.0339	–	–	–
SL2	−0.0056	0.7	−0.0319 to 0.0207	–	–	–
SL3	−0.0149	0.5	−0.0602 to 0.0305	–	–	–
SL4	−0.0183	0.3	−0.0506 to 0.0141	–	–	–
SL5	0.0064	0.7	−0.0316 to 0.0445	–	–	–
SO1	−0.0313	0.2	−0.0803 to 0.0176	–	–	–
SO2	0.0406	0.2	−0.0230 to 0.1042	–	–	–
SO3	0.0718	0.04	0.0051 to 0.1385	0.0651	0.03	0.0049 to 0.1253
SO4	−0.0725	0.04	−0.1404 to −0.0047	−0.0664	0.05	−0.1339 to 0.0012
SO5	−0.0127	0.8	−0.1121 to 0.0867	–	–	–
Constant	0.9326	$<10^{-3}$	0.9161 to 0.9492	0.9228	$<10^{-3}$	0.9059 to 0.9396

CI, confidence interval; EM, emotional reactions; EN, energy; P, pain; SL, sleep disturbance; SO, social isolation; M, physical mobility.

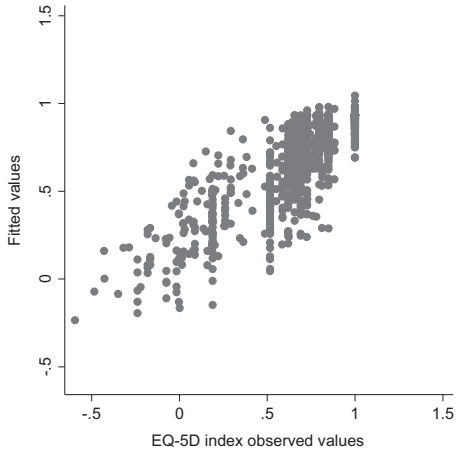

Fig. 2 – Fitted versus observed values from the full model with NHP statements as predictors (N = 900). EQ-5D, EuroQol five-dimensional; NHP, Nottingham Health Profile.

every respect. They almost entirely lacked any negative predictions for the EQ-5D questionnaire index.

When choosing between models, one must also consider internal validity tests. To test the stability of the stepwise selection, we bootstrapped the selection procedure 200 times to see how much variability was seen in the list of the selected variables. The 19 most frequently selected variables were exactly the same predictors as in the original stepwise reduced model with NHP statements as predictors. Twelve of the 19 predictors were retrieved less than 90% of the time, while 3 were retrieved less than 70% of the time. The results seem to indicate some variability in the selection.

We tested the full model against overfitting. Its RMSE was 0.174. We used 10-fold cross-validation to determine whether we would obtain a similar figure fitting the model on nine-tenth of the sample population and applied the coefficients on the remaining one-tenth of the data. The average increase in RMSE between the training set predictions and validation set predictions was small in size (0.007), while the variation across the 10 trials was 0.032.

Taking all the results into account, we prefer the full model because it fitted only marginally worse than the reduced one but was considerably better than the other three models. However, internal validation showed the full model to be more robust than the reduced one.

Discussion

Usually, mapping functions of generic or disease-specific QOL instruments to predict utility measures are developed in Western Europe or North America. There is limited evidence on the transferability of these mapping functions to emerging markets, such as Central-Eastern European countries. Our study is among the first to derive a mapping function of a generic QOL instrument in Central-Eastern Europe. Further research is needed to find out whether mapping functions developed in Central-Eastern European countries are transferable to Western European countries.

We found that the expected value of a preference-based QOL measure (EQ-5D questionnaire index) can be reasonably predicted on the basis of results of a generic QOL instrument (NHP) in patients with diabetes mellitus. NHP is a widely used instrument with proper validation to Hungary. With the mapping function developed in this study, it is possible to translate the results of both existing and future studies in which NHP is used in diabetic patients to the utility scale of the EQ-5D questionnaire and, also, to use these estimates in economic analyses.

Responsiveness of the EQ-5D questionnaire and the NHP has already been studied in elderly patients with femoral neck fractures. The authors found that both the EQ-5D questionnaire and the NHP were responsive. The findings indicated an advantage for the EQ-5D questionnaire. The empirical overlap between change scores from the two instruments was limited [21]. To our knowledge, this mapping of the NHP questionnaire onto the EQ-5D questionnaire utility scale described in this article is the first attempt to establish a direct connection between the two instruments.

Brazier et al. [12] carried out a systematic review of the literature that developed any mapping techniques between non–preference-based and preference-based instruments. Some technical problems that were found in previous studies occurred in our study, as well. The range of the predicted utility values was narrower than the range of the observed values. This finding is mainly due to the lack of data from the lower end of the EQ-5D questionnaire scale. Former studies also observed the skewness of the distribution of the EQ-5D questionnaire values, which affects the reliability of the confidence interval of the parameter estimates [12,14]. Nevertheless, this phenomenon does not limit the applicability of the mapping function. We had two explanatory variables, namely, EM4 ("the days seem to drag") and SO3 ("I feel there is nobody I am close to"), with coefficients exhibiting opposite signs from those expected in the full and the reduced models with NHP statements as predictors. Nevertheless, we did not exclude them from the function because they were statistically significantly related to the EQ-5D questionnaire index. However, our function showed divergent validity, too, because in the full model with NHP scores as predictors the two nonsignificant scores in Model 2a were "Sleep disturbance" and "Social isolation." These two scores were not covered by the five dimensions of the EQ-5D questionnaire, while the other four scores had their counterparts in the other instrument.

In all our models, the RMSE at the individual level was larger than the published minimally important differences for the EQ-5D questionnaire [22]. It nevertheless does not limit the

Table 4 – Description of the models fitted with the results of goodness of fit.

Predictor	Selection	N	Adjusted R^2	RMSE	AIC	Predicted EQ-5D questionnaire range
NHP-D score	Enter	912	0.487	0.219	−176.09	−0.16 to 0.88
NHP scores	Enter	900	0.645	0.183	−497.02	−0.08 to 0.96
NHP scores	Stepwise	905	0.645	0.183	−503.41	−0.08 to 0.95
NHP statements	Enter	900	0.680	0.174	−559.84	−0.23 to 1.05
NHP statements	Stepwise	909	0.676	0.175	−564.66	−0.19 to 0.99

AIC, Akaike's information criterion; EQ-5D, EuroQol five-dimensional; NHP, Nottingham Health Profile; NHP-D, index of distress from the Nottingham Health Profile; RMSE, root mean square error.

applicability of the mapping function because the purpose of mapping functions is to estimate differences across groups of patients or differences between treatment arms over time.

We used a UK tariff valuation of the EQ-5D questionnaire. Although it is beneficial to estimate national tariffs [23,24], Hungarian tariff values of the EQ-5D questionnaire are unfortunately unavailable. Similarly, the preferences of diabetic patients might differ across countries, which may restrict the applicability of the mapping function developed in our study. Another limitation of our study is that the order of the administration of the questionnaires was not randomized, and responses in one test might have affected the responses in the other.

Although we tested the robustness of our results using internal validation, it may be important to externally test the validation of the proposed function in a different series of diabetic patients before the function is actually used to estimate utility values for economic analysis.

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