Valuing Health-Related Quality of Life in Diabetes

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OBJECTIVE — Cost-utility analyses use information on health utilities to compare medical treatments that have different clinical outcomes and impacts on survival. The purpose of this study was to describe the health utilities associated with diabetes and its treatments, complications, and comorbidities.

RESEARCH DESIGN AND METHODS — We studied 2,048 subjects with type 1 and type 2 diabetes recruited from specialty clinics at a university medical center. We administered a questionnaire to each individual to assess demographic characteristics, type and duration of diabetes, treatments, complications, and comorbidities, and we used the Self-Administered Quality of Well Being index (QWB-SA) to calculate a health utility score. We then created regression models to fit the QWB-SA–derived health utility scores to indicator variables for type 1 and type 2 diabetes and each demographic variable, treatment, and complication. The coefficients were arranged in clinically meaningful ways to develop models to describe penalties from the health utility scores for nonobese diabetic men without additional treatments, complications, or comorbidities.

RESULTS — The utility scores for nonobese diet-controlled men and women with type 2 diabetes and no microvascular, neuropathic, or cardiovascular complications were 0.69 and 0.65, respectively. The utility scores for men and women with type 1 diabetes and no complications were slightly lower (0.67 and 0.64, respectively). Blindness, dialysis, symptomatic neuropathy, foot ulcers, amputation, debilitating stroke, and congestive heart failure were associated with lower utility scores.

CONCLUSIONS — Major diabetes complications are associated with worse health-related quality of life. The health utility scores provided should facilitate studies of the health burden of diabetes and the cost-utility of alternative strategies for the prevention and treatment of diabetes.

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Cost-utility analyses are a type of economic analysis used to compare medical treatments that have different clinical outcomes and impacts on survival (1). In cost-utility analyses, the health outcome is expressed in terms of quality-adjusted life-years (QALYs). QALYs measure length of life adjusted for quality of life. The numerical value assigned to quality of life reflects a judgment on the desirability of the outcome and is called a health utility. Health utilities are placed on a continuum where optimal health is assigned a value of 1.0 and health judged equivalent to death is assigned a value of 0.0.

To date, no one has systematically quantified the degree to which type 1 and type 2 diabetes and their treatments, complications, and comorbidities affect quality of life. In published economic analyses, empirical health utility scores were often not available. Instead, health utility scores were derived from theoretical constructs, the judgment of experienced physicians, expert panels, community surveys, and patients (2–5). The lack of standardized and consistent health utility scores for the array of treatments and the microvascular, neuropathic, and macrovascular health states associated with diabetes has constrained researchers' abilities to conduct cost-utility analyses and to credibly compare their results. This has been recognized as an important limitation of these economic analyses (1,6).

The availability of the Self-Administered Quality of Well-Being index (QWB-SA) makes it feasible to rapidly assess health utilities from large numbers of subjects in diverse health states using a standardized self-administered instrument, and is also makes if feasible to derive estimates of the general public's preferences for those health states. Our intent was to capitalize on this opportunity to develop an "off-the-shelf" catalogue of health utilities relevant to diabetes.

RESEARCH DESIGN AND METHODS

— Although conceptually straightforward, measurement of health utilities requires assessment of peoples' preferences for various health states (7). The basis for such calculations are the standard gamble and time trade-off methodologies (8). In the standard gamble, an individual is asked to choose between a chronic health state characterized by symptoms and functional limitations and a gamble offering a certain probability of a

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Abbreviations: DCP, Diabetes Care Profile; DMH, Diabetes Medical History; DSQ, Diabetes Staging Questionnaire; HUI, Health Utilities Index; QALY, quality-adjusted life-year; QWB, Quality of Well Being index; QWB-SA, Self-Administered QWB; UKPDS, U.K. Prospective Diabetes Study.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

worse health state (immediate death) or an improved health state (perfect health). The health utility score measures the point at which the individual is neutral between the two choices. The time trade-off methodology directly assesses how many years of life in perfect health are equivalent to life with a chronic health state. An individual is asked to choose between two alternatives: a chronic health state with a defined life expectancy and perfect health with a reduced life expectancy. The reduction in life expectancy is varied until the individual is indifferent between the choices. Although somewhat easier to administer than the standard gamble, the time trade-off methodology requires extensive interviewer training, careful description of the proposed health state, and substantial subject time. In addition, both methods measure how an individual, rather than the general public, value a given health state.

To simplify the assessment of health utilities and to provide health utility estimates from the perspective of the general public, multi-attribute utility models were developed (1). Such multi-attribute utility models include the EuroQol (EQ-5D), the Health Utilities Index (HUI) and the Quality of Well Being index (QWB). QWB is an extensively applied multi-attribute utility model derived from community-based preference assessments (8). The QWB has been widely used in clinical trials and studies to evaluate medical and surgical therapies (9–11). A major limitation of the QWB is that it requires a trained interviewer. Furthermore, the QWB questionnaire is long and complex and uses branching and probe questions.

To address the limitations of the QWB, Kaplan and colleagues (12–14) developed a self-administered version of the QWB (QWB-SA) that takes <10 min to complete. The QWB-SA is a comprehensive measure of health-related quality of life that includes several components. First, it includes three separate scales of patient-reported levels of functioning: mobility, physical activity, and social activity. Second, each patient identifies symptoms or problems that may have affected him or her over the past 3 days from a list of 58 items. Then, the reported levels of functioning and the subjective symptomatic complaints are weighted by the preferences of an independent sample of judges. Using this system, it is possible to place the general health status of any individual on the continuum between death and optimal functioning for any specified time. A study comparing the interviewer-administered QWB with the self-administered QWB-SA demonstrated equivalence and suggested that the quick and inexpensive QWB-SA produces data comparable to the more difficult, expensive, interviewer-administered version (15). The QWB-SA can be obtained from Dr. Robert Kaplan at the University of California at San Diego Health Outcomes Assessment Program (on-line at http://medicine.ucsd.edu/fpm/hoap/qwbsa.htm).

The protocol for this study was reviewed and approved by the University of Michigan and the Centers for Disease Control institutional review boards. Of the candidates approached, 88% participated in the study, and all subjects provided written informed consent. A total of 2,048 patients with type 1 or type 2 diabetes who attended endocrinology, diabetes, and ophthalmology clinics at the University of Michigan Health System between 29 June 1998 and 15 March 2001 were studied cross-sectionally. Because of missing values, 7 subjects were not classified by type of diabetes; therefore, analyses used a total of 2,041 subjects. Eligibility requirements included age ≥18 years, a diagnosis of type 1 or type 2 diabetes, ability to give informed consent, and ability to either self-administer the questionnaires or, if visually impaired, to respond to a research assistant reading the questionnaires.

Two questionnaires were administered: the Diabetes Staging Questionnaire (DSQ) and the QWB-SA. The DSQ was developed to stage an individual's type and duration of diabetes, treatment, complications, and comorbidities. The DSQ was adapted from two instruments available from the Michigan Diabetes Research and Training Center: the Diabetes Care Profile (DCP) and the Diabetes Medical History (DMH). The DCP includes questions about demographics, age at onset of diabetes, symptoms, and limitations on performing activities of daily living that are caused by diabetes. The DMH includes questions on type and duration of diabetes, treatment (insulin and oral medications), complications, and comorbidities.

Study candidates were approached in the clinics at the time of routinely scheduled appointments. Subjects were asked to complete the DSQ before starting the QWB-SA. All questionnaires were completed in the clinic on the day of recruitment. Participants received $10 as an incentive.

Type 1 diabetes was defined as diabetes with onset before 30 years of age with current insulin treatment. All others were classified as having type 2 diabetes. Demographic variables included age, sex, race, age at onset of diabetes, duration of diabetes, and BMI group. Subjects were classified as obese if their BMI was ≥30 kg/m^2. Disease state variables included treatments, retinopathy, nephropathy, neuropathy, stroke, cardiovascular disease, hypertension, and hypercholesterolemia. In general, disease state variables were based on the subject's report that the disease state was diagnosed by a health care provider.

Medians and 25th and 75th interquartile ranges are reported for continuous variables, and frequencies and proportions are reported for categorical variables. Statistical significance of differences between groups was assessed with Wilcoxon's rank-sum test for continuous variables and the Pearson χ^2 test for categorical variables.

The QWB-SA–derived health utility scores were fit by a multiple linear regression model to demographic and disease state variables separately for each type of diabetes. Variables with multiple categories were represented by indicator variables. In the fitting process, all variables were initially entered into the regression model. We computed the estimates of the variables, and we noted those variables with adjacent levels that were not in order of increasing severity. Adjacent inconsistently ordered levels of one variable were then combined, and the model was run again. The process was repeated in a stepwise fashion until the ordering of all variable coefficients increased in severity. Because our primary interest was to model the QWB-SA–derived health utility score as a function of a wide range of treatments and complications, all variables ordered in increasing severity were kept in the model, regardless of *P* value. The final coefficients of the indicator variables represent the penalty associated with each variable. When a coefficient was greater than zero—indicating that the complication was not associated with a penalty—the corresponding variable was omitted from the model. Penalty functions, when subtracted from the health

Table 1—*Characteristics and comparison of study population by type of diabetes*

Characteristic	Type 1 diabetes	Type 2 diabetes
N	784	1,257
Age (years)	34.5 (25.4–44.1)	57.6 (49.9–67.3)
Female sex	430 (55)	613 (49)
Race white	705 (91)	1,010 (81)
Education		
Less than high school	57 (7)	123 (10)
High school graduate	132 (17)	316 (25)
Some college	288 (37)	371 (29)
College graduate	183 (23)	197 (16)
Any postgraduate work	124 (16)	250 (20)
BMI (kg/m^2)	25.7 (22.9–29.4)	30.4 (26.2–36.0)
Duration in years	20.3 (12.0–27.8)	10.4 (4.0–17.2)
Diabetes treatment		
None or diet	0 (0)	89 (7)
Oral medication	0 (0)	487 (39)
Insulin	784 (100)	681 (54)
Retinopathy status		
Retinopathy	199 (25)	204 (16)
Blind in one eye	62 (8)	129 (10)
Blind in both eyes	90 (11)	135 (11)
Nephropathy status		
Diabetic kidney disease	184 (23)	199 (16)
Dialysis	18 (2)	21 (2)
Transplant	28 (4)	16 (1)
Neuropathy status		
Tingling and burning	72 (9)	192 (15)
Neuropathy	208 (27)	376 (30)
Sores	57 (7)	92 (7)
Amputation	24 (3)	37 (3)
Stroke status		
TIA or stroke	27 (3)	107 (9)
Stroke with residual	14 (2)	57 (5)
Cardiovascular status		
Angina	22 (3)	104 (8)
Myocardial infarction	25 (3)	140 (11)
Congestive heart failure	28 (4)	141 (11)
High blood pressure status		
Not treated	54 (7)	102 (8)
Treated with medications	222 (28)	669 (53)
Cholesterol status		
High cholesterol	108 (14)	276 (22)
Treated with medications	133 (17)	459 (37)

Data are median (interquartile range) or frequency (%). Stroke with residual: stroke with any persistent difficulty speaking, any weakness, or difficulties performing daily activities or working. TIA, transient ischemic attack.

utility scores for diet-controlled nonobese male subjects without diabetic complications, formed an additive model to explain the QWB-SA–derived health utility score for any combination of treatments and complications.

Using the final model for each type of diabetes, marginal means were obtained by subsetting subjects in each demographic, treatment, and complication group, and by calculating the mean QWB-SA–derived health utility score for all of the subjects in that group. The marginal means are interpreted as the mean QWB-SA–derived health utility score for each demographic, treatment, or complication group, not controlling for other variables.

In both models, interaction terms between variables were considered using a response surface regression procedure. This procedure simultaneously tested whether any combination of variables produced an interaction effect that added significant information to the model. Any interaction effect significant at $P \leq 0.05$ was included in the model.

The quality of the fit of the models to the QWB-SA–derived health utility scores was considered by partitioning the residual sum of squares into two components: *1*) pure error, which represents the variability between patients who have the same characteristics, and *2*) lack of fit error, which represents the need for additional terms to explain nonlinearity in the model. All statistical analyses were performed using SAS software version 6.12 (SAS Institute, Cary, NC).

RESULTS — The characteristics of the diabetic subjects are presented in Table 1. Type 1 diabetic subjects were younger, more educated, and had lower BMIs. Higher percentages of type 1 diabetic subjects were female and white. Type 1 diabetic subjects had longer durations of diabetes than type 2 diabetic subjects and had more retinopathy, diabetic kidney disease, renal transplantation, and symptomatic neuropathy. More than one-half of the subjects with type 2 diabetes were treated with insulin. Subjects with type 2 diabetes were older, had higher BMIs, and were more likely to have stroke, angina, myocardial infarction, congestive heart failure, treated high blood pressure, high cholesterol, and treated high cholesterol.

The penalty functions and marginal means associated with each demographic and complication variable are presented in Table 2. In type 2 diabetes, the intercept value of 0.689 can be interpreted as the mean health utility score for diet-controlled nonobese diabetic men without microvascular, neuropathic, or cardiovascular complications. In type 2 diabetes, obese subjects and subjects treated with oral antidiabetic agents, insulin, and antihypertensive agents had slightly lower health utility scores. Blindness, dialysis, symptomatic neuropathy, foot ulcers, amputation, stroke, and congestive heart failure were associated with more substantial reductions in quality of life (0.052–0.170). Age, race, education, age at onset of diabetes, duration of diabetes, and cholesterol status were not associated with significant reductions in

Table 2—*Penalty functions and marginal means for QWB-SA health utility scores*

Disease status	Complication level	Model for type 1 diabetic subjects		Marginal mean	Model for type 2 diabetic subjects		Marginal mean
		Penalty	SE		Penalty	SE	
	Intercept	0.672	0.007		0.689	0.014	
Sex	Female	−0.033	0.008	0.557	−0.038	0.007	0.528
BMI (kg/m^2)	Obese	−0.016	0.010	0.526	−0.021	0.007	0.534
Diabetes intervention	None or diet only	-	-	-	-	-	0.601
	Oral antidiabetic agents	-	-	-	−0.023	0.013	0.560
	Insulin	-	-	-	−0.034	0.013	0.520
Retinopathy	Blind in one eye	−0.024	0.015	0.534	−0.043	0.011	0.510
	Blind in two eyes	−0.208	0.013	0.347	−0.170	0.011	0.361
Nephropathy	Diabetic kidney disease	−0.017	0.010	0.525	−0.011	0.009	0.509
	Dialysis	−0.023	0.027	0.453	−0.078	0.026	0.404
Neuropathy	Tingling and burning	−0.067	0.014	0.545	−0.060	0.010	0.528
	Neuropathy	−0.055	0.010	0.513	−0.065	0.008	0.508
	Sores	−0.076	0.016	0.504	−0.099	0.013	0.474
	Amputation	−0.116	0.023	0.414	−0.105	0.020	0.438
Stroke	TIA or stroke	−0.018	0.022	0.482	−0.044	0.012	0.480
	Stroke with residual	−0.105	0.030	0.386	−0.072	0.016	0.420
Cardiovascular disease	Congestive heart failure	−0.058	0.022	0.401	−0.052	0.011	0.453
High blood pressure	High BP/high BP with meds (combined)	−0.032	0.010	0.507	−0.011	0.007	0.528

BP, blood pressure; TIA, transient ischemic attack.

health utility scores and were excluded from the analysis.

In type 1 diabetes, the intercept value of 0.672 can be interpreted as the mean health utility score for diabetic men without microvascular, neuropathic, or cardiovascular complications. Obese subjects, subjects with diabetic kidney disease, and those treated with antihypertensive agents had slightly lower health utility scores. Blindness, symptomatic neuropathy, foot ulcers, amputation, congestive heart failure, and debilitating stroke were associated with more substantial reductions in quality of life (0.058–0.208). Compared with having some college education, having less than a high school education was associated with a small reduction in health utility scores. Because only 7% of subjects had less than a high school education and because education was not otherwise associated with health utility scores, we elected not to include education in the analysis. Age, race, age at onset of diabetes, duration of diabetes, and cholesterol status were not associated with significant reductions in health utility scores and were also excluded from the analysis.

The marginal mean utility scores for complication states represent the mean health utility scores for individuals with specific complications, without controlling for other variables. The marginal mean health utility scores for individual complication states ranged from 0.528 (tingling and burning) to 0.361 (blind in both eyes) in type 2 diabetes and from 0.545 (tingling and burning) to 0.347 (blind in both eyes) in type 1 diabetes.

In both type 2 and type 1 diabetes, all interaction effects measured by the response surface regression had P values ≥ 0.05; therefore, none were included in the models. Both models fit the data moderately well (adjusted R^2 = 36.3 and 45.0% for type 2 and type 1 diabetes, respectively) and did not show a significant lack of fit (P = 0.643 and 0.664, respectively).

CONCLUSIONS — In this study, we derived health utility scores by systematically applying the QWB-SA to a large and diverse group of diabetic subjects with a variety of treatments, complications, and comorbidities. In type 2 and type 1 diabetes, diet-controlled nonobese diabetic men without microvascular, neuropathic, or cardiovascular complications had the highest health utility scores (0.69 for type 2 diabetes and 0.67 for type 1 diabetes). In type 2 diabetes, health utility scores were slightly lower in women and obese subjects and in those treated with oral antidiabetic agents, insulin, and antihypertensive drugs. Health utility scores were substantially lower in type 2 diabetic subjects with blindness, dialysis, symptomatic neuropathy, foot ulcers, amputation, stroke, and congestive heart failure. Similarly, in type 1 diabetes, health utility scores were slightly lower in women and obese individuals, in subjects treated with antihypertensive drugs, and in those with diabetic kidney disease. Health utility scores were substantially lower in type 1 diabetic subjects with blindness, symptomatic neuropathy, foot ulcers, amputation, debilitating stroke, and congestive heart failure.

The health utility scores for people with diabetes are generally in keeping with those for other populations. For example, the mean QWB scores were 0.81 for the general population in San Diego, CA; 0.70 for healthy adults ≥65 years of age; 0.66 for adults with chronic obstructive pulmonary disease; 0.64 for subjects with osteoarthritis; and 0.61 for AIDS patients in a clinical trial (9,16–19).

Marginal means represent the mean health utility scores for individuals in each demographic, treatment, and complication state without controlling for other variables. The marginal means derived from our study population do not reflect those for a general diabetic population because we oversampled subjects

with advanced complications. Although the reductions in health utility scores associated with dialysis were small, and they were smaller for subjects with type 1 diabetes than for subjects with type 2 diabetes (−0.023 and −0.078, respectively), the marginal mean utility scores for type 1 and type 2 diabetic subjects receiving dialysis were 0.453 and 0.404, respectively. This reflects the presence of multiple concurrent complications in these subjects. Not unexpectedly, the marginal means were <0.500 in both type 1 and type 2 diabetic subjects with other advanced chronic complications, including blindness in both eyes, amputation, stroke, and congestive heart failure.

A recent review that reported 1,000 measures of quality of life identified just one health utility score for diabetes (20,21). We found only four studies that presented empirically derived health utility scores for diabetes (22–25). However, these studies did not systematically include health utility scores for individual microvascular and macrovascular complications and comorbidities in type 1 and type 2 diabetes. In general, health utility scores were indirectly assessed, assessed with potentially less-sensitive instruments, or reported only for subgroups of diabetic patients.

Wu et al. (22) estimated health utility scores for subjects with type 1 diabetes, using health status data derived from the SF-36 and a published empirical regression equation (26), to predict QWB scores. The regression equation drew on five of eight SF-36 domains and predicted 56.9% of the observed variance in the QWB-derived health utility scores. Predicted QWB scores were stratified by age and reported for individuals with no complications, with retinopathy, and with other complications. Age was inversely correlated with predicted QWB scores. In subjects <65 years of age, health utility scores were lower in subjects without complications than in those with retinopathy. In subjects ≥65 years of age, health utility scores were higher in those without complications than in those with retinopathy.

The U.K. Prospective Diabetes Study (UKPDS) Group directly assessed health utility scores in type 2 diabetes by applying the EQ-5D questionnaire (EuroQol) (23). Subjects with microvascular complications had slightly, but not significantly, lower scores than patients without complications, and subjects with macrovascular complications had significantly lower scores than those without complications. This study differed from ours in several ways. First, subjects in the UKPDS represented a relatively homogenous incidence cohort with type 2 diabetes. Our population included type 1 and type 2 diabetic subjects with a wide range of durations of disease, treatments, complications, and comorbidities. In addition, the UKPDS group assessed health utility scores with the EQ-5D, whereas we used the QWB-SA. The EQ-5D measures only three levels of functions on five domains, whereas the QWB-SA measures multiple levels of function on three domains and 58 specific symptoms and health problems. Because of these differences, the QWB might be expected to be more sensitive to small differences in health. Finally, the UKPDS did not assess the association among individual microvascular and macrovascular complications and utility scores, whereas we created regression models to fit health utility scores to type of diabetes and each demographic variable, treatment, and complication.

Recently, Redekop et al. (24) assessed health utility scores by applying the EuroQol to a sample of Dutch type 2 diabetic subjects who participated in the Cost of Diabetes in Europe - Type 2 (CODE-2) study. Older age, obesity, female sex, insulin therapy, and presence of complications were associated with lower health utility scores. Like the UKPDS analysis, this study did not assess health utility scores for specific microvascular and macrovascular complications.

Ragnarson Tennvall and Apelqvist (25) also assessed health utility scores in diabetic patients with foot complications by applying the EuroQol questionnaire. In this subgroup of diabetic subjects, individuals with major amputations and current foot ulcers had lower health utility scores than those with primary healed ulcers.

As is apparent, there are several alternative methods for rapidly assessing health utility scores. In addition to the QWB-SA, there is the HUI (27) and the EuroQol (EQ-5D) (28). These three methods are not strictly comparable. As a result, the health utility scores obtained in this study would correlate with those obtained with the EQ-5D and HUI but may not be directly interchangeable. Studies are underway in an attempt to develop cross-walk mapping between the most popular utility-based measures.

Two limitations of our study deserve special mention. First, our decision to use diabetic subjects drawn from clinics at a tertiary care referral center was based on our desire to oversample subjects with advanced diabetic complications and to model the impact of individual complications and comorbidities. Because the QWB-SA, by its design, derives the preferences or utilities that the general public has for particular symptoms and functional states, it was not critical or even desirable that respondents to the QWB-SA be representative of the population, only that the societal judges be representative of the community. The penalty functions in Table 2 provide an additive model to calculate the health utility score for any combination of treatments, complications, and comorbidities and are not affected by the distribution of subjects with complications. The marginal mean utility scores in Table 2 are not, however, representative of those for the general diabetic population because we oversampled subjects with advanced complications, and they may not apply to the general diabetic population.

Second, we chose to define diabetes health status by self-report rather than by more objective testing. Our purpose in doing so was to reflect both the natural history of disease and to categorize complications according to the stages at which either the complication or its treatment would impact symptoms and functioning. The focus is thus on individual awareness of complications, symptoms of complications, or treatments for complications that would likely affect quality of life. Because the focus of staging is on complications that affect symptoms and functioning and not anatomy and physiology, we believe that it is indeed more appropriate to collect diabetes staging data by self-report (e.g., questionnaire) rather than by medical record review or objective testing (fundus photographs, biochemical testing, etc.).

In summary, these empirically derived health utility scores will allow researchers to calculate QALYs for studies involving subjects with type 1 and type 2 diabetes and a wide variety of treatments, complications, and comorbidities. The health utility scores provided should facilitate studies of the health burden of diabetes and the cost-utility of alternative

strategies for the prevention and treatment of diabetes.

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