The Impact of Diabetes-Related Complications on Preference-Based Measures of Health-Related Quality of Life in Adults with Type I Diabetes

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Introduction. *This study estimates health-related quality of life (HRQoL) or utility decrements associated with type 1 diabetes mellitus (T1DM) using data from a UK research program on the Dose Adjustment For Normal Eating (DAFNE) education program.* ***Methods***. *A wide range of data was collected from 2341 individuals who undertook a DAFNE course in 2009–2012, at baseline and for 2 subsequent years. We use fixed- and random-effects linear models to generate utility estimates for T1DM using different instruments: EQ-5D, SF-6D, and EQ-VAS. We show models with and without controls for HbA1c and depression, which may be endogenous (if, for example, there is reverse causality in operation).* ***Results***. *We find strong evidence of an unobserved individual effect, suggesting the superiority of the fixed-effects model. Depression shows the greatest decrement across all the models in the preferred fixed-effects model. The fixed-effects EQ-5D model also finds a significant decrement from retinopathy, body mass index, and HbA1c (%). Estimating a decrement using the fixed-effects model is not possible for some conditions where there are few new cases. In the random-effects model, diabetic foot disease shows substantial utility decrements, yet these are not significant in the fixed-effects models.* ***Conclusion***. *Utility decrements have been calculated for a wide variety of health states in T1DM that can be used in economic analyses. However, despite the large data set, the low incidence of several complications leads to uncertainty in calculating the utility weights. Depression and diabetic foot disease result in a substantial loss in HRQoL for patients with T1DM. HbA1c (%) appears to have an independent negative impact on HRQoL, although concerns remain regarding the potential endogeneity of this variable.* ***Key words:*** *type 1 diabetes; T1DM; EQ-5D; SF-6D; EQ-VAS; health-related quality of life; depression; HbA1c; utility.* ***(Med Decis Making 2016;36:1020–1033)***

For affected individuals, type 1 diabetes mellitus (T1DM) has a substantial impact on health-related quality of life (HRQoL). The impact arises through 1) long-term complications, both microvascular (neuropathy [nerve damage], nephropathy [kidney disease], and vision disorders [retinopathy, glaucoma, cataracts]) and macrovascular (heart disease, stroke, peripheral vascular disease [which can lead to ulcers and amputation]); 2) acute metabolic complications such as episodes of hypoglycemia and diabetic ketoacidosis (DKA) events; 3) fear and anxiety around hypoglycemic and DKA episodes and future health prospects; and 4) restrictions on lifestyle and activities due to treatment regimen and risk of diabetes-related complications and adverse events.

Decision makers who use quality-adjusted life years (QALYs) as a metric for the value of an intervention require evidence on preference-based health-related quality of life (or utilities [the term *utility* in this context is used in a very general sense as a reflection of value or how "good" a state would be to live in]) of health states that are used within economic decision models. A number of studies have explored utility values for patients with T1DM. Hahl and others[1] considered the impact on the 15D utility instrument using Finnish data on a cross-sectional sample of n = 539. Ahola and others[2] also used the 15D but in a larger sample

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(n = 1023). Coffey and others[3] and Tabaei and others[4] both analyzed a data set from Michigan to explore the impact of health states on the Quality of Well-being (QWA) utility instrument. Lee and others[5] elicited values from a time-tradeoff (TTO) exercise for hypothetical diabetes-related states for a sample of US adults with T1DM (n = 213). The impact on the EQ-5D, which has particular relevance in the UK context, has been considered only in fairly small samples by Hart and others[6] using a patient sample from the Netherlands (n = 234) and by Solli and others[7] using a patient sample from Norway (n = 165).

Many T1DM economic models have, to date, used utilities estimated from patients with type 2 diabetes mellitus (T2DM). This is because utility decrements for patients with T2DM have been estimated based on large data sets. Clarke and others[8] and Alva and others[9] derived estimates from the United Kingdom Prospective Diabetes Study (UKPDS) cohort, and Bagust and Beale[10] derived estimates from the European CODE-2 data. It is plausible, however, that utility values for health states of T1DM might differ from those for T2DM because the conditions differ in terms of etiology, epidemiology, management, and risk of complications.[11,12] Patients with T1DM are typically younger and hence more likely to be of working age, are likely to have had diabetes for longer, are less likely to be obese, and are less likely to be socioeconomically deprived.[13] Age, for example, has been found to behave differently as a predictor of self-reported health for people with T2DM compared with T1DM.[14]

This study estimates utility decrements associated with diabetes-related health states for patients with T1DM for use in economic models using data obtained from a large UK research program focused on the Dose Adjustment For Normal Eating (DAFNE) education program. The DAFNE course is a 5-day structured education program that aims to give adults with T1DM the skills and confidence to estimate the carbohydrate content of food and adjust their insulin doses accordingly to maintain acceptable glycemic control.[15] Within the research program, observational data were collected on a wide range of clinical and HRQoL outcomes and held in the DAFNE research database.[16] The value of the database in terms of research on utilities arises, first, because it has a large sample size of patients with T1DM (n = 2470 at baseline); second, because there are 3 different utility measures available (EQ-5D, SF-6D, and EQ-VAS), which enables us to explore differences and similarities between these measures as they relate to diabetes-related health states; and third, because there is a panel of 3 time periods, which allows us to take account of unobserved individual effects within the analysis, thereby removing a key potential for bias that arises within cross-sectional data. These estimates are also compared with those that have been estimated in other studies for T1DM and T2DM.

METHOD

Description of Outcome Measures

The EQ-5D[17] and SF-6D[18] are generic HRQoL questionnaires for which preference-based scores (utility weights) have been developed for use in the calculation of QALYs.

The EQ-5D-3L instrument comprises 5 questions dealing with aspects of physical and mental health (mobility, self-care, usual activities, pain/discomfort, anxiety/depression), for which the response is 1 of 3 possible degrees of impairment. Data from the EQ-5D-3L were converted into utility values using UK preference-based utility weights.[19] EQ-5D is the recommended utility measure for cost-effectiveness analysis of health technologies in the United Kingdom.[20] The SF-12 questionnaire is a generic 12-item health status questionnaire[21] developed from the Short Form 36-item (SF-36) instrument.[22] Data from the SF-12 were converted into the SF-6D

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utility values using UK weights.[23] The EQ-VAS, usually administered alongside the EQ-5D, is a visual analog scale (VAS) used for recording an individual's rating of his or her current health. This rating is anchored at 0 at the bottom (worst imaginable health state) and at 100 at the top (best imaginable health state).

These 3 utility instruments differ in a number of key ways. SF-6D and EQ-5D use standard descriptive systems to describe a particular health state. These descriptive systems describe what the health state is like in different ways. They use different measurement periods, have different domains (e.g., the EQ-5D contains no domain for vitality), use a different number of response choices for each domain, and describe differing levels of severity.[24] The EQ-5D can describe states that are of greater severity than the SF-6D, but with only 3 response options for each domain, it is less sensitive than the SF-6D to mild changes in health states. The SF-6D tends to have a larger percentage of respondents at the floor (or worst) level for the physical dimensions than the EQ-5D,[25] making it less sensitive to changes in health at the severe end.

Both of these measures allow us to link responses to the descriptive questions to a utility score or social tariff. These tariffs were derived from preferences from the general public who valued a sample of health states described by the descriptive system using methods that allow the scale to be anchored at a point where a health state is equivalent to being dead (TTO for the EQ-5D and standard gamble [SG] for the SF-6D). These values were modeled to generate a social tariff for all health states on a scale on which zero is equivalent to dead, 1 is equivalent to full health, and states below zero are valued as worse than dead. They reflect, therefore, the average judgment of how good the general public thinks it would be to live in each health state. The EQ-VAS relies only on the individual's judgment of his or her own health state, and rather than focus on particular domains of health-related quality of life, the individual's judgment can incorporate anything the individual perceives as important. However, in generating the value, the individual has not had to face a choice or tradeoff; consequently, it is sometimes considered a less accurate measure of preferences. Although the EQ-VAS is rescaled to a 0–1 scale here, this is not directly comparable to the 0 (dead) to 1 (full health) scale used in the EQ-5D and SF-6D. The EQ-5D, SF-6D, and VAS each offer a slightly different perspective on utility; it is therefore interesting to see how they compare for T1DM states.

Data

All individuals within the DAFNE research database undertook a DAFNE course, delivered to groups of 6 to 8 patients over 5 consecutive days during 2009 to 2012.[26] Biomedical questionnaires were completed by DAFNE educators (diabetes specialist nurse or dietitian who had access to medical records), and DAFNE entrants completed a psychosocial questionnaire prior to their education program and again 1 and 2 years later. This survey canvassed demographic, behavioral, and clinical variables, as well as history of relevant clinical events. In addition, various standard instruments were used to collect HRQoL, including the EQ-5D, EQ-VAS, and the SF-12. The variables used in subsequent regression analyses are summarized in Table 1. The utility weights are positively skewed. The EQ-5D suffers from ceiling effects with about 50% of respondents in each time period reporting a health state that is valued at 1 (see Table 1).

The format of the questionnaire at baseline meant that patients report whether they are experiencing a complication at that point in time, even though the onset may be some years prior. The impact of complications on HRQoL may not be constant over time. For some degenerative conditions, longer duration may result in greater negative impact; for others, particularly where adaptation or recovery is possible, the impact may reduce with time. The follow-up data identify those who experience a new complication during the follow-up period. For the analysis, it is assumed that if a complication is reported in previous years, that complication remains present, unless they also report a greater severity. For example, if an individual reports partial blindness at baseline, this state is assumed to remain unless he or she reports full blindness at follow-up. Depression is assessed in each time period as defined by a case according to the Hospital Anxiety and Depression Score (HADS[27]).

Motivations

The initial model was determined by health states required within a cost-effectiveness model.[28] Steps to augment this model were influenced by an understanding of the relationships between the clinical outcomes and HRQoL, such as the extent to which complications were asymptomatic, whether their effect was direct, possible interactions between outcomes, and the likely duration of any impact.

Table 1 Descriptive Summary of Variables: Sample from the DAFNE Research Database

	Baseline		1 Year		2 Years	
Variable Name	**No. (n = 2469 Unless Indicated)**	**Mean (SD) or Frequency (%)**	**No. (n = 1433 Unless Indicated)**	**Mean (SD) or Frequency (%)**	**No. (n = 602 Unless Indicated)**	**Mean (SD) or Frequency (%)**
Demographic/behavioral						
Sex (male)	2467	51.4%	1431	49.9%		48.0%
Age, y		39.3 (13.8)		41.5 (13.6)		42.5 (14.0)
Duration, y	2449	16.3 (12.6)	1422	18.2 (13.1)	596	18.8 (13.2)
BMI, kg/m^2	2320	26.4 (4.9)	1169	26.6 (4.8)	458	26.7 (5.3)
Born in United Kingdom	2465	76.2%	1431	73.7%	602	89.0%
Race (white)	2443	91.5%	1415	91.5%	598	90.0%
Smoking: current	2441	19.4%	1265	18.1%	478	13.8%
Former		24.9%		24.1%		23.6%
Never		55.7%		57.8%		62.6%
Pregnant	2393	1.3%	1433	1.9%	602	1.5%
Health outcomes						
EQ-5D index	2341	0.839 (0.231)	1101	0.851 (0.236)	413	0.840 (0.234)
EQ-5D = 1		1164 (49.72%)		610 (55.40%)		210 (50.85%)
EQ-VAS	2292	69.4 (0.199)	1081	73.8 (0.181)	409	74.0 (0.186)
EQ-VAS = 100		53 (2.31%)		31 (2.87%)		14 (3.42%)
SF-6D index	2337	0.745 (0.137)	1081	0.765 (0.141)	403	0.773 (0.136)
SF-6D = 1		59 (2.52%)		41 (3.79%)		20 (4.96%)
Clinical/laboratory tests						
HbA1c (%)	2351	8.8 (1.6)	1277	8.4 (1.4)	532	8.5 (1.5)
HbA1c IFCC mmol/mol [HbA1c (%) − 2.15] × 10.929		72.8 (17.8)		68.4 (15.8)		69.3 (16.4)
SBP, mm Hg	2278	128.5 (17.4)	1124	128.3 (16.5)	434	129.0 (17.6)
DBP, mm Hg	2278	75.8 (10.3)	1123	75.3 (9.8)	434	74.4 (10.2)
Depression						
Taking antidepressant	2381	8.4%	1235	9.4%	481	10.2%
HADS score ≥11	2295	6.8%	1090	5.1%	413	5.1%
Complications (self-reported)	Ever experienced to baseline		New between baseline and follow-up		New between year 1 and year 2	
Hypertension		345 (14.0%)		11 (0.8%)		4 (0.7%)
Myocardial infarction		30 (1.2%)		1 (0.1%)		0
Coronary revascularization		23 (0.9%)		1 (0.1%)		0
Percutaneous intervention		9 (0.4%)		1 (0.1%)		0
Stroke		24 (1.0%)		3 (0.2%)		0
Painful neuropathy		118 (4.8%)		8 (0.6%)		3 (0.5%)
Painful neuropathy (only)		106 (4.29%)		6 (0.4%)		3 (0.5%)
Foot ulcer		42 (1.7%)		8 (0.6%)		4 (0.7%)
Foot ulcer, no amputation		30 (1.2%)		7 (0.5%)		4 (0.7%)
Amputation of toe(s)		14 (0.6%)		0		3 (0.3%)
Amputation above toes		8 (0.3%)		1 (0.1%)		0
Retinopathy		685 (27.7%)		28 (1.9%)		12 (1.9%)
Retinopathy (only)		554 (22.4%)		28 (1.9%)		11 (1.8%)
Proliferative		120 (4.86%)		3 (0.2%)		3 (0.5%)
Proliferative retinopathy (only)		113 (4.57%)		3 (0.2%)		3 (0.5%)
Partial blindness		20 (0.8%)		0		0
Blindness		3 (0.2%)		1 (0.1%)		0
Microalbuminuria		103 (4.2%)		5 (0.4%)		2 (0.3%)

(continued)

Table 1 (continued)

Variable Name	Baseline		1 Year		2 Years	
	No. (n = 2469 Unless Indicated)	Mean (SD) or Frequency (%)	No. (n = 1433 Unless Indicated)	Mean (SD) or Frequency (%)	No. (n = 602 Unless Indicated)	Mean (SD) or Frequency (%)
Microalbuminuria (only)		82 (3.3%)		5 (0.4%)		2 (0.3%)
Proteinuria		50 (2.0%)		6 (0.4%)		2 (0.3%)
Proteinuria (only)		48 (1.9%)		6 (0.4%)		2 (0.3%)
Dialysis (only)		3 (0.1%)		0		0
Renal transplantation		13 (0.5%)		0		0
Erectile dysfunction		132 (5.3%)		2(0.1%)		1(0.2%)
Diabetic events						
DKAs last year	2383		1291		517	
0		91.4%		97.4%		97.7%
1		6.5%		2.3%		1.9%
2		1.2%		0.2%		-
3+		0.9%		0.2%		0.4%
Severe hypos last year	2453		1273		503	
0		78.4%		89.9%		90.5%
1		9.4%		5.0%		5.4%
2		4.4%		2.0%		1.8%
3		2.2%		1.0%		1.0%
4		1.4%		0.7%		0.8%
5+		4.2%		1.4%		0.6%

The outcomes in this table do not allow for an assessment of the effectiveness of the Dose Adjustment For Normal Eating (DAFNE) intervention since no allowance is made for dropout. This can be found in Hopkins and others.[26] If individuals did not report a complication, it is assumed that they do not have one (this arose for about a third of cases that had EQ-5D data). Where uncertainties existed or inconsistencies arose in the data, missing fields were left blank. BMI, body mass index; DBP, diastolic blood pressure; DKA, diabetic ketoacidosis; HADS, Hospital Anxiety and Depression Score; IFCC, International Federation of Clinical Chemistry; SBP, systolic blood pressure.

We were particularly interested in whether HbA1c had an independent impact on utility values. Lowering HbA1c reduces the risk of microvascular complications and may in the longer term reduce the risk of cardiovascular events.[29] Some concern has been expressed that lower HbA1c levels may also be related to weight gain and increased risk of hypoglycemia.[30,31] In addition, better control may be achieved through greater commitment to self-management by an increased complexity of medical intervention and self-care, which for some individuals may itself have a negative impact on HRQoL. Analysis of DAFNE data has found that the frequency of severe hypoglycemic events reduced after DAFNE[31] and led to an increase in quality of life measured by the diabetes quality-of-life instrument, the Audit of Diabetes-Dependent Quality of Life (ADDQoL).[32] Improved glycemic control has been found to be positively related to short-term quality of life for patients with T2DM.[33] Lower HbA1c has also been associated with higher utility values in people with T1DM in Finland.[2]

The relationship between utility and HbA1c raises some interesting issues for the regression analysis. First, we may not see an independent effect of HbA1c if the benefit arises through reduced risk of complications where these are fully controlled for. Second, the benefit of a reduction in HbA1c may be overestimated if weight and the frequency of hypoglycemic events are controlled for. Third, the relationship between HbA1c and quality of life may be nonlinear.[34]

Events such as DKA and hypoglycemic episodes are likely to have a direct impact on HRQoL while they are being experienced and during the recovery period.[35] The utility measures administered at a particular point in time may not identify this trajectory of severe health shock followed by recovery. There may also be an indirect impact relating to the fear of future events (which is likely to be related to DKA and hypoglycemic event frequency[36]) and an impact from the restrictions that the risk of these complications imposes upon activities.

Statistical Methods

There are 3 key challenges for the regression analysis. The first is the bounded nature (utilities cannot go above 1) and the positive skew of the utility data, together with many values at full health. The second is the risk of bias due to omitted, unobserved variables, including the unobserved individual effect. We may identify a utility decrement from a particular comorbidity, but patients with that comorbidity may have had a lower utility value prior to developing that comorbidity. The third, related problem is that of attrition and missing data, which may generate another source of bias.

The Tobit model[37] is often recommended for bounded scales, but biased and inconsistent parameter estimators result in the presence of heteroskedastic errors.[38] When the utility data were modeled using a Tobit approach, Lagrange multiplier tests by auxiliary regressions[39] rejected the null hypothesis that the error variances were normally distributed and homoskedastic. Consequently, a linear approach was adopted, with heteroskedasticity addressed through the use of a robust Huber/White estimation of the variance-covariance matrix.[40]

The use of longitudinal data opens the possibility of addressing the problem of unobserved time-invariant individual heterogeneity. With panel data, we can consider changes in utility values over a particular time period and diabetes-related events occurring during that period. Relying only upon change at the individual level would, in effect, remove any unobserved individual effect.

$$\begin{aligned} U_{it} &= \alpha + \beta X_{it} + u_{it}. \\ u_{it} &= v_i + \varepsilon_{it}. \\ v_i &\sim \text{IDD}\ (0, \sigma_v^2). \\ \varepsilon_{it} &\sim \text{IDD}\ (0, \sigma_\varepsilon^2). \end{aligned} \quad (1)$$

For $i = 1 \ldots N$ and $t = 1, 2, 3$, where U_i are the measures of individual utility value at time t, X is a vector of independent variables at time t, and β is a vector of unknown parameters to be estimated. The model can be estimated using a within (fixed-effect) estimator that uses deviation from the individual level mean of each variable, thereby removing the unobserved time-invariant individual effect (v_i) from the model.

$$U_{it} - \overline{U}_i = \alpha_{it} - \overline{\alpha}_i + \beta(X_{it} - \overline{X}_i) + v_i - v_i + \varepsilon_{it} - \overline{\varepsilon}_i. \quad (2)$$

However, in many cases, the complications we are interested in have very few reported new cases during follow-up (see Table 1). Using a restriction of requiring at least 10 new cases during follow-up results in dropping 12 of our variables of interest. To explore a more complete model, we still rely on a random-effects generalized least squares (GLS) model, which gives weight to both the within-individual variation and the between-individual variation. The individual unobserved effect (v_i) is treated as random disturbance drawn from a specified distribution and assumed to be uncorrelated with the covariates. This uses the same model as (1) above but with the additional assumption that v and ε are mutually independent. It is important to note that bias might arise in the random-effects model if the unobserved individual effect is correlated with the covariates; for example, an unobserved individual trait such as compliance or risk aversion might be correlated with both outcomes and our covariates.

To explore the issue of attrition (both permanent dropout and nonresponse for some waves), we use a method developed by Heckman[41] and employed in a similar context by Alva and others.[9] We run 2 selection models in which the dependent variable is equal to 1 when we observe the individual responding in the second wave and zero otherwise, and similarly for the third wave, both based on covariates (including postcode area) from baseline data. From these we estimate the inverse Mills ratio, a transformation of the probability of participation for each observation, which is then included in the main model. If the coefficient on this variable is not significantly different from zero, we can assume that there is no correlation of the errors between our main model and the selection model, and hence no bias is created through attrition. We also consider the variable addition test,[42] which is simply a count of the waves an individual has data for, where again a coefficient that is not significantly different from zero suggests no attrition bias. We further test whether the coefficients derived from a balanced sample of individuals with data in all 3 waves are different from coefficients derived from an unbalanced sample in which individuals with incomplete data are included, based on a Hausman-type test.[43]

The initial model included health states required for the cost-effectiveness model[28] and then added covariates based on findings from the existing literature, clinical knowledge, and improving model

performance as judged by the Akaike information criterion (AIC). To ensure that the health states in the regression model were mutually exclusive (as required for populating economic models), individuals were only assigned the most severe reported state of progressive conditions. This applies to renal failure states (where individuals progress from microalbuminuria to proteinuria, then dialysis or transplantation), vision states (where individuals progress from retinopathy to proliferative retinopathy to being registered partially sighted or blind), and diabetic foot ulceration (where individuals progress from painful neuropathy to foot ulcer to amputation). Given that these foot states may arise on one foot and then the other and that painful neuropathy can exist on its own or in the presence of foot ulceration,[44] this progression is a simplification designed to produce values for the mutually exclusive states in economic models. Some categories were combined (blind and partially sighted, amputation above the toe and amputation of toes, dialysis and transplant) to ensure that all discrete predictor variables had frequencies of at least 10.

Squared terms for each continuous predictor variable were also considered. Where nonlinearities in relationships were identified, further consideration was given to whether the variables were best transformed (e.g., taken logs), categorized, or taken as deviation to the sample mean or relevant value.

Each of the outcome measures (EQ-5D, SF-6D, and EQ-VAS) was modeled using a linear fixed-effects and a GLS random-effects model. For each outcome, we inspected graphs of predicted v. actual values to consider how well the model performed across the range of utility values. Data were analyzed using Stata version 12 (StataCorp LP, College Station, Texas). An α value of 0.05 was used as a guideline to determine statistical significance.

RESULTS

DAFNE baseline data were available on 2470 eligible subjects with 2341 (94.7%) having fully completed the EQ-5D. Those with and without complete EQ-5D at baseline were similar in terms of background characteristics, treatment, and comorbidity profile. Twelve-month data were available on 1433 subjects (not all individuals had reached that time point at the time of data extraction from the DAFNE research database), of whom 1101 had EQ-5D values. Two-year data were available on 602 subjects, of whom 413 had EQ-5D values. For each time period, the EQ-5D gave the highest average utility, followed by the SF-6D, with the EQ-VAS giving the lowest score (see Table 1), which is in line with our expectations of these instruments.[45]

The selection models found that respondents who did not report follow-up EQ-5D for the first year (and similarly for the second year) were younger, less likely to be born in the United Kingdom, and had higher HbA1c at baseline (see Suppl. Table S1). However, no evidence of attrition bias was found based on the inclusion of the variable for number of waves of data available or the inverse Mills ratio in the full EQ-5D random-effects model, both of which were insignificant (see Suppl. Table S2). Nor were the coefficients from a balanced panel for the EQ-5D different from those from the unbalanced panel based on a Hausman test (see Suppl. Table S3). Consequently, no correction was made in the models for incomplete data.

The coefficients for the fixed-effects models are shown in Table 2 (columns 1–3). In each case, a modified Wald tests suggests heteroskedasticity, and hence robust standard errors are used. (Heteroskedasticity occurs when the variance of the error term is not constant. In panel data, we may be particularly concerned about groupwise heteroskedasticity where the variance of the error is specific to an individual. The modified Wald test adopts a null hypothesis that the variance is constant and the test statistic [estimated using the stata command xttest3[46]] will be distributed as chi-squared under this null hypothesis.) For all outcome measures, we find evidence of an individual time-invariant error term (based on modified Breusch-Pagan Lagrange multiplier tests, which adopt a null hypothesis that the variance of the unobserved, time-invariant individual effect is zero) and evidence of correlation of this individual error term with the other regressors, suggesting the superiority of a fixed-effects model (based on a Hausman test that compares the parameter estimates from the fixed- and random-effects approaches. It adopts a null hypothesis that the random effect is not correlated with the other regressors, and hence the random-effect model would be the preferred [most efficient] model. When the coefficients are found to be substantially different between the 2 models [giving us a large and significant Hausman statistic], we have reason to doubt this assumption). However, we also show the random-effects models to generate coefficients for conditions where there is little change over time (columns 4–6). The variance-covariance matrices for these models are shown in Supplemental Table S4.

Table 2 Impact of Diabetes Complications on Utilities from Dose Adjustment For Normal Eating Data on People with Type 1 Diabetes Mellitus: Ordinary Least Squares Fixed-Effects Models and Generalized Least Squares Random-Effects Models

	Fixed-Effects Models, Coefficient (SE)			Random-Effects Models, Coefficient (SE)		
	(1) EQ-5D	(2) EQ-VAS	(3) SF-6D	(4) EQ-5D	(5) EQ-VAS	(6) SF-6D
Age (/10)				–0.0214***	0.0092***	–0.0004
				(0.003)	(0.003)	(0.002)
Female				–0.0236**	–0.0270***	–0.0357***
				(0.008)	(0.007)	(0.005)
Smoker	–0.0027	–0.0432*	–0.0138	–0.0373**	–0.0466***	–0.0311***
	(0.024)	(0.025)	(0.013)	(0.012)	(0.010)	(0.006)
BMI	–0.0052**	–0.0040	–0.0008	–0.0028**	–0.0039***	–0.0013*
	(0.002)	(0.002)	(0.002)	(0.001)	(0.001)	(0.001)
Born in the United Kingdom				–0.0257**	0.0004	0.0027
				(0.008)	(0.008)	(0.006)
MI				–0.0242	–0.0876*	–0.0256
				(0.053)	(0.038)	(0.029)
Stroke				–0.0327	–0.0473	–0.0152
				(0.048)	(0.042)	(0.025)
Microalbuminuria				–0.0105	–0.0268	0.0118
				(0.028)	(0.021)	(0.015)
Proteinuria				–0.0277	–0.0334	–0.0143
				(0.032)	(0.029)	(0.014)
Transplant or dialysis				–0.0097	–0.0221	0.0029
				(0.050)	(0.030)	(0.029)
Retinopathy	–0.0544**	0.0075	–0.0111	–0.0265*	–0.0218*	–0.0116
	(0.023)	(0.033)	(0.020)	(0.011)	(0.009)	(0.006)
Proliferative retinopathy				–0.0288	–0.0113	–0.0242
				(0.026)	(0.020)	(0.012)
Blind or partially sighted				–0.0592	–0.0527	0.0220
				(0.062)	(0.029)	(0.024)
Painful neuropathy	–0.0497	–0.0997	–0.0578***	–0.2361***	–0.0835***	–0.0900***
	(0.043)	(0.073)	(0.020)	(0.032)	(0.022)	(0.012)
Foot ulcer	–0.1042	0.0316	–0.0536**	–0.1245*	–0.0995**	–0.0503**
	(0.119)	(0.093)	(0.023)	(0.052)	(0.032)	(0.019)
Amputation (any)				–0.1172*	–0.0321	–0.0592*
				(0.055)	(0.047)	(0.027)
Erectile dysfunction				–0.0310	–0.0122	–0.0179
				(0.025)	(0.018)	(0.013)
Coronary revascularization				–0.0787	–0.0021	–0.0090
				(0.071)	(0.044)	(0.035)
Percutaneous revascularization				0.0250	0.0195	–0.0186
				(0.039)	(0.035)	(0.036)
Hypertension	–0.0265	–0.0404	–0.0163	–0.0144	–0.0128	–0.0131
	(0.044)	(0.053)	(0.024)	(0.015)	(0.011)	(0.008)
Severe hypoglycemic episodes in past year	–0.0020	–0.0023	–0.0030	–0.0022*	–0.0010	–0.0017**
	(0.002)	(0.002)	(0.002)	(0.001)	(0.001)	(0.001)
DKA episodes in past year	0.0119	–0.0367**	–0.0021	–0.0091	–0.0265**	–0.0130***
	(0.011)	(0.015)	(0.007)	(0.010)	(0.010)	(0.004)
HbA1c	–0.0152***	–0.0099*	–0.0037	–0.0161***	–0.0164***	–0.0076***
	(0.006)	(0.006)	(0.004)	(0.003)	(0.002)	(0.002)
Depression (HADS depression score $\geq$11)	–0.0960***	–0.0831***	–0.0771***	–0.2520***	–0.1919***	–0.1589***
	(0.035)	(0.026)	(0.016)	(0.026)	(0.015)	(0.008)

(continued)

Table 2 (continued)

	Fixed-Effects Models, Coefficient (SE)			Random-Effects Models, Coefficient (SE)		
	(1) EQ-5D	(2) EQ-VAS	(3) SF-6D	(4) EQ-5D	(5) EQ-VAS	(6) SF-6D
Wave 2	–0.0021	0.0160**	0.0159***	0.0038	0.0218***	0.0149***
	(0.007)	(0.007)	(0.005)	(0.006)	(0.006)	(0.004)
Wave 3	–0.0019	0.0105	0.0166**	0.0052	0.0183*	0.0158*
	(0.012)	(0.011)	(0.008)	(0.011)	(0.009)	(0.007)
Constant	1.1439***	0.9276***	0.8173***	1.2261***	0.9664***	0.8960***
	(0.073)	(0.084)	(0.055)	(0.034)	(0.031)	(0.022)
Observations	2927	2895	2905	2917	2885	2895
Number of id	2044	2023	2029	2036	2015	2021
Rho	0.746	0.696	0.679	0.615	0.555	0.518
R^2 overall				0.272	0.222	0.227
R^2 within	0.042	0.052	0.057			

Robust standard errors in parentheses. Rho is the proportion of the total variance that is due to the individual effect. BMI, body mass index; DKA, diabetic ketoacidosis; HADS, Hospital Anxiety and Depression Score; MI, myocardial infarction. *$P < 0.1$. **$P < 0.05$. ***$P < 0.01$.

The impact of time-invariant covariates is shown only in the random-effects model. Across all measures, women show significantly lower levels of utility. Individuals who were not born in the United Kingdom show lower utility for the EQ-5D only. Time dummies rather than age are included in fixed-effects model, and these show some improvement in the SF-6D and EQ-VAS over time. This effect is not picked up in the EQ-5D, and indeed, in the random-effects model, age is negatively related to the EQ-5D yet positively related to the EQ-VAS score.

Being a current smoker is negatively and significantly associated with all 3 utility measures in the random-effects model and significantly so for the fixed-effects model for the EQ-VAS, where it shares a very similar effect size. BMI is negatively related to all outcome measures in the random-effects model and the fixed-effects EQ-5D (a 1-unit increase in BMI results in a 0.0052 fall in the EQ-5D, but only half that in the random-effects model).

The greatest utility decrement for both sets of models arises due to experiencing depression. At baseline, 8.4% of the sample take antidepressants and 6.8% of the sample meet the criteria of ''caseness'' based on the HADS depression score (about a third of whom are currently also taking antidepressants). In the fixed-effects models, depression reduces the EQ-5D by 0.096, the EQ-VAS by 0.0831, and the SF-6D by 0.0771. These estimates are generated through individuals who change their depression state and are less than half those from the random-effects model estimated through both within and between individuals.

A substantial decrement is identified from painful neuropathy and foot ulcers. For neuropathy in the random-effects models, the decrements are 0.2361 for the EQ-5D, 0.0835 for the EQ-VAS, and 0.0900 for the SF-6D. However, the high EQ-5D decrement is not robust to the control for the individual effect, and in the fixed-effects models, we find a decrement of only 0.0497 (and nonsignificant) for the EQ-5D, 0.0997 (and nonsignificant) for the EQ-VAS, and 0.0578 for the SF-6D. Having experienced amputation (only included in the random-effects model) reduces the EQ-5D by 0.1172 and the SF-6D by 0.0592. For the EQ-VAS, this is lower still (–0.0321 and nonsignificant). This may, again, be driven by the small number of amputees (<1%).

The negative impact of having experienced a stroke, coronary revascularization, microalbuminuria, or proteinuria; having had dialysis or a transplant; and the presence of hypertension was limited in magnitude, which may be due to the sample sizes for these comorbidities being relatively small.

For vision problems, retinopathy has a decrement of around 0.0265 in the EQ-5D in the random-effects model and 0.0544 in the fixed-effects model. The EQ-VAS showed a decrement of 0.0218 for the random-effects model, and the SF-6D was nonsignificant in both models. Proliferative retinopathy and being blind or partially sighted, only included in the random-effects models, had a roughly similar magnitude of decrement but were not significant. Again, this may arise due to having a small number of individuals at baseline (1%) that experience partial or full blindness, resulting in imprecise estimates.

The impact of severe hypoglycemic episodes is negative but only significant in the random-effects EQ-5D model (–0.0022) and random-effects SF-6D model (–0.0017). DKA events are significantly negative for the EQ-VAS (lowering utility by 0.0367 in the fixed-effects model and 0.0265 in the random-effects model) and the SF-6D (lowering utility by 0.0130 per event in the random-effects model) but are not significant for the EQ-5D.

HbA1c levels have a significant negative association with all measures in the random-effects models and the EQ-5D and EQ-VAS in the fixed-effects models. A 1-unit increase (increase by 1%) in HbA1c lowers the EQ-5D by 0.0161 in the random-effects model and, very similarly, by 0.0152 in the fixed-effects model. For the EQ-VAS, a 1% increase lowers utility by 0.0164 in the random-effects model and 0.0099 in the fixed-effects model. For the SF-6D, a 1% increase lowers utility by 0.0076 in the random-effects model and 0.0037 (and nonsignificant) in the fixed-effects model. These decrements remained virtually unchanged when the controls for weight and frequency of hypoglycemic episodes were removed. No evidence was found of nonlinearity (squared terms were not significant and reduced model performance).

For each utility instrument, we also show 4 random-effects models with the gradual addition of variables to the model (shown in Suppl. Tables S5–S7). In most cases, the coefficients remain similar following the introduction of additional covariates, and the model fit improves based on the overall R^2. For the EQ-5D, we see a slight decline in coefficient size for amputation as additional variables are included, and for foot ulcers, the inclusion of depression reduces the coefficient by at least a third for the EQ-5D and SF-6D.

DISCUSSION

We find a considerable decrement arising from the presence of depression, reducing the EQ-5D by 0.096 in the fixed-effects model. The inclusion of the depression control is slightly problematic as the HADS self-completed instrument may share unobserved measurement biases with the SF-12 and EQ-5D; for example, if the respondent was in a good mood at the time of completion, this may result in a positive bias on both the HADS and utility instruments. Furthermore, we do not know whether the depression in these cases has arisen due to the diabetes. The decrement on HRQoL of depression has also been shown for patients with T2DM in cross-sectional data, with Bagust and Beale[10] estimating a decrement of 0.202 for the EQ-5D and 9 (on 0–100 scale) for the EQ-VAS arising from a history of depression. However, with T2DM, depression may be a contributing factor to developing the disease, making reverse causality more likely.[47] The inclusion of depression improves our models, and since depression is a potential health state caused by living with diabetes, it is important to estimate the utility loss from this state.

We identify a large utility loss from diabetic foot disease. The decrement estimated here from painful neuropathy is larger than that found in the Bagust and Beale[10] T2DM data. The most severe neuropathy in their cross-sectional ordinary least squares (OLS) model has a decrement of 0.085, whereas painful neuropathy in our random-effects model is 0.2361. This may be a result of how individuals were classified in the 2 studies or due to a different degree of severity or experience of neuropathy between patients with T1DM and those with T2DM. Solli and others[7] also found that neuropathy results in the greatest decrement in the EQ-5D for a sample of patients with T1DM in Norway. This may indicate potential problems using utility decrements for painful neuropathy from patients with T2DM in T1DM cost-effectiveness models. The DAFNE cohort is considerably younger than the European cohort used by Bagust and Beale (mean age of 39 years at baseline v. 67 years) and hence contains many more individuals of working age; consequently, painful neuropathy may have more impact on their daily lives. The large decrement arising from painful neuropathy is supported by the findings by Currie and others,[48] who found a close association between the EQ-5D and the Neuropathic Total Symptom Score (NTSS-6-SA). However, the decrement estimated here is not robust to the inclusion of the individual fixed effect and hence may be an overestimate. This suggests a need to explore the impact on HRQoL of diabetic foot disease for patients with T1DM in future work.

Almost all models identified an independent impact on utility of HbA1c levels, which is slightly greater for the EQ-5D and EQ-VAS than the SF-6D. The impact on the EQ-5D in the fixed-effects model is a 0.0152 decrease per unit increase in HbA1c (%). This is greater than the decrement identified for people with T1DM by Ahola and others[2] using the 15D, who found a 1% increase to result in a 0.006 decline in the utility value using cross-sectional data. Hart and others[5] did not find HbA1c to be a

significant predictor of the EQ-5D (or of subsequent changes in the EQ-5D) in their data from the Netherlands, although their sample size was small (n = 234). However, there is reason to be concerned about potential endogeneity, given that HbA1c does not have an obvious direct impact on quality of life. HbA1c may be correlated with time-variant unobservables; for example, individuals may experience a new stressful event, which both results in a decline in their ability to control blood glucose levels and increases their probability of responding at level 2 or 3 to the anxiety/depression item on the EQ-5D. Furthermore, the direction of causality is a little unclear. Poor overall health (as picked up by the utility measures) may be contributing to the higher HbA1c.

The lower utility value for women in T1DM and T2DM is a common finding.[2,3,9,10] Regarding BMI, we expected this to show a slightly smaller impact for patients with T1DM than T2DM, partly due to existing estimates suggesting a smaller impact of BMI on the 15D[2] and QWB[3] for T1DM and since higher BMIs contribute directly to the development and progression of T2DM itself. However, the estimate for the decrement in the EQ-5D for BMI in the fixed-effects model is 0.0052 per unit of BMI and 0.0028 in the random-effects model; these are very similar to the 0.006 decrement in the EQ-5D estimated in Bagust and Beale[10] on cross-sectional data. Decrements in the VAS scale are also broadly similar.

Due to small sample sizes, it is difficult to see robust significant decrements for some long-term complications. Coefficients, such as those for stroke and myocardial infarction (MI), while mostly nonsignificant, still appear very small relative to other estimates for T2DM such as those from Alva and others.[9]

Comparisons to utility decrements estimated for T2DM and T1DM within the existing literature are problematic due to the many nonsignificant findings for complications with the DAFNE data and differences in models and covariates used across the literature. Critically, existing models that are based on cross-sectional data do not control for unobserved individual heterogeneity and hence are likely to systematically overpredict the impact of complications.[9] Our analysis finds clear support for the need to address the unobserved individual effect.

Comparing our estimates to those drawn from hypothetical TTO questions with adults with diabetes, we see much lower utility values in the TTO estimates. For example, Lee and others[5] found estimates of 0.52 for blindness, 0.47 for end-stage renal disease, 0.74 for angina, 0.34 for severe stroke, and 0.73 for amputation. It is difficult to make these comparisons for a number of reasons. First, we have limited numbers of patients with certain conditions, making precise estimates difficult. Second, our estimates control for decrements arising from other aspects (such as weight, age, other conditions, frequency of complications such as DKA). Third, our estimates also cover a range of severity and time since the condition, and we would expect certain conditions (such as stroke) to have a different impact across the severity level of strokes and time since the stroke occurred.

Estimates derived from hypothetical TTO estimates[49] identified a reduction in utility of 0.0033 for each nonsevere hypoglycemic event, broadly similar to the 0.0022 decrement identified in the EQ-5D random-effects model for severe hypoglycemic events (which is supported by a similar [0.0020] but nonsignificant fixed-effects coefficient). Some of the impact of hypoglycemic events may be mediated via fear,[50] but we do not find the coefficient to decrease following the inclusion of depression.

Aggregating categories such as partially sighted and blindness is problematic, since we would anticipate a different impact for these 2 categories. Indeed, the division should arguably be much finer after taking into consideration the deterioration in each eye. The sensitivity of these measures to vision deterioration has been questioned[51]; however, we do detect a significant negative impact of having retinopathy on both the EQ-5D (around –0.0544 in the fixed-effects model) and the EQ-VAS (–0.0218 in the random-effects model). This is broadly in line with findings from Hart and others,[6] who found new cases of retinopathy to result in a decrease in the EQ-5D of 0.048. Brown and others[52] also found a decrement for retinopathy using direct patient valuations (TTO and SG).

The comparison between the EQ-VAS, SF-6D, and EQ-5D does not show any clear patterns. We anticipated that the SF-6D would be more sensitive to mild changes in health, whereas the EQ-5D might show a greater decrement for more severe health states.[53] Indeed, the EQ-5D can give a much lower possible value to a health state than is possible with the SF-6D: the minimum value possible for the EQ-5D is –0.594, with a minimum value in this data set of –0.239, but for the SF-6D, the minimum possible value is only 0.29, with a minimum value in this data set of 0.345.[54] In almost all cases where the

SF-6D is significant, it shows a smaller decrement size, with a smaller standard error, compared with the EQ-5D. The number of DKA episodes per year is the only covariate that shows significance in the SF-6D (and EQ-VAS) but not the EQ-5D, which might suggest that the SF-6D is better at picking up episodic events. Experiencing an MI is the only covariate that shows a greater decrement on the EQ-VAS than the other instruments, which are non-significant. The instruments tell a similar story about which health consequences will be identified in utility instruments, but they are not identical (the conflicting relationship with age is a case in point). The extent to which these differences matter will depend on the importance of small changes in utility values within the cost-effectiveness model.

Will our findings generalize to other populations of people with T1DM? These findings are based on a survey, which may introduce bias, but the spread of information required for an analysis of this type is only available in a research database rather than in one used for routine clinical practice. There are incomplete data on the sample over the 3 years, with those with poor health most likely to drop out of the sample. However, the sample selection tests undertaken to explore the potential impact of attrition find that the impact on our estimates is likely to be minimal.

Although the random-effects model provides more complete estimates for the range of diabetes-related health states, it still rests on the assumption that the unobserved individual effect is not correlated with the any of the covariates. While we can be more confident in the estimates derived from the fixed-effects model, the lack of change at the individual level means we are unable to generate estimates for many important health states.

Data rely on patient completed preference-based measures (EQ-5D and SF-6D) along with patient-completed VAS. Other options include other instruments (such as HUI3, 15D, and QWB) or direct valuation (using methods such as TTO and SG) with patients, with valuation of vignettes either by patients or the general public. A key advantage of relying on preference-based measures is that we are not relying on potentially limited understanding of what it might be like to live in a hypothetical health state. Furthermore, in diabetes patients, we may expect patients to have a number of different comorbidities and complications. Relying on direct values from patients based on utility instruments reflects that more complex picture.

CONCLUSIONS

The analysis of the DAFNE research database provides utility estimates based on panel data on diabetes-related health states to populate economic models exploring the cost-effectiveness of interventions for patients with T1DM. The models improve upon existing available estimates due to the large sample size available across 3 time periods, which enables analysis using the preferred fixed-effects approach. However, even with the large data set available, it is still difficult to identify robust estimates for many complications due to the small number of patients who experience some complications.

Comparing the decrements in EQ-5D for comorbidities, complications, and diabetes-related events in people with T1DM and T2DM suggests broadly similar decrements. For complications with a low frequency (such as stroke, MI, dialysis, transplant, and blindness) where T1DM utility values from preference-based measures are not available to use in economics models, using either direct valuation of states (preferably with patients with diabetes [e.g., Lee and others[5]]) or T2DM utility values is reasonable. However, future work should look to extended T1DM panel data to allow improved estimates.

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